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APPLICATION NUMBER:

202057Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	202057
Priority or Standard	Standard
Submit Date(s)	September 23, 2011
Received Date(s)	September 23, 2011
PDUFA Goal Date	July 26, 2012
Division / Office	Division of Metabolism and Endocrine Products/ Office of New Drugs
Reviewer Name(s)	Iffat N. Chowdhury, MD
Review Completion Date	July 25, 2012
Established Name	Icosapent ethyl
(Proposed) Trade Name	Vascepa
Therapeutic Class	Lipid-lowering Agent
Applicant	Amarin Pharmaceuticals
Formulation(s)	1 gram capsules
Dosing Regimen	Two capsules twice daily
Indication(s)	Severe hypertriglyceridemia
Intended Population(s)	Patients with TG $\geq$500 mg/dL

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The applicant, Amarin Pharmaceuticals Ireland Limited, submitted this NDA with the indication for Vascepa (icosapent ethyl) as an adjunct to diet to reduce triglycerides (TG) [redacted] (b) (4) in adult patients with very high TG (≥500 mg/dL). The applicant submitted this NDA as a 505(b)(2) with references to the literature for nonclinical toxicology data.

Vascepa, also known as AMR101, was proposed to be administered as [redacted] (b) (4) 4g per day when originally submitted on September 23, 2011. [redacted] (b) (4) reviewer would have recommended approval [redacted] (b) (4) for the 4g dose of Vascepa in patients with very high TG ≥500 mg/dL.

Vascepa is an effective TG-lowering agent; however, a more potent effect on TG was seen with the 4g dose than with the 2g dose of Vascepa.

According to the NCEP ATP III treatment guidelines, for most persons with very high TG, therapy can be considered successful if treatment reduces serum TG to <500 mg/dL.[1] The number of patients achieving therapeutic goal of TG <500 mg/dL was statistically significantly greater for Vascepa 4g as compared with placebo (p=0.0018). The number of patients reaching this threshold on Vascepa 2g was statistically similar to placebo (p=0.1395). Therefore, treatment with Vascepa 2g was less effective than treatment with Vascepa 4g.

[redacted] (b) (4)

1 Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation* 2002;106;3336.
2 Greenland P et al. 2010 ACCF/AHA Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2010; 56:e50-103.

(b) (4)

1.2 Risk Benefit Assessment

Very high TG (≥500 mg/dL) has a strong genetic component and is associated with an increasing risk for acute pancreatitis. The most frequently reported genetic defects for persons with very high TG are in the enzyme lipoprotein lipase (LPL) or in Apo C-II, a protein that activates LPL. These genetic defects result in the inability to breakdown fatty acids. Impaired catabolism of triglyceride-rich lipoproteins (TGRLP) also is induced by overproduction of Apo C-III, an inhibitor of LPL activity. Because of the danger of acute pancreatitis, persons with severely elevated TG > 2000 mg/dL should be treated as a medical urgency. [3]

According to the NCEP ATP III, the first priority for persons with very high TG is to prevent acute pancreatitis. Prevention of CHD is a secondary priority in this population. Furthermore, efficacy of drug therapy to prevent CHD in persons with very high TG has not been demonstrated by clinical cardiovascular outcomes trials.

In addition to very low-fat diets and increased physical activity, TG lowering drugs are usually required in persons with very high TG to prevent acute pancreatitis. Currently fibrates, nicotinic acid and an omega-3 fatty acid product are available to lower TG to <500 mg/dL.

This application included clinical data (both study report and datasets) from the MARINE trial. This study investigated 229 patients with TG between 500 mg/dL to 2000 mg/dL. Patients were randomized to one of three treatment arms: Placebo, Vascepa 2g, or Vascepa 4g for 12 weeks.

This application also contained a study report, but not the dataset, for the ANCHOR trial. This trial was not considered pivotal to the efficacy claims of Vascepa for this NDA. The ANCHOR trial investigated patients with TG between 200 mg/dL and 499 mg/dL despite statin therapy. The applicant was told prior to this NDA submission that data from the ANCHOR trial would not be mentioned in the Vascepa labeling until, at a minimum, 50% enrollment of a cardiovascular outcomes trial was reached.

3 Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation* 2002;106;3336.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No safety signals were noted in the marketing application which would require specific post-marketing safety evaluation other than outlined under 21 CFR 314.80.

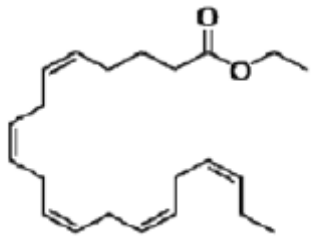
1.4 Recommendations for Postmarket Requirements and Commitments

None.

2 Introduction and Regulatory Background

2.1 Product Information

Vascepa (icosapent ethyl) is a highly purified ethyl ester of eicosapentaenoic acid (EPA; 20:5 n-3) derived from fish oil. Its molecular formula is $C_{22}H_{34}O_2$ and its molecular weight is 330.51. Its structural formula is:



The drug product, AMR101 Capsule, is a one gram, light-yellow oblong shaped soft gelatin capsule filled with pale yellow liquid.

(b) (4)

[redacted]

(b) (4)

[redacted]

2.2 Tables of Currently Available Treatments for Proposed Indications

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

Table 1: List of Products for Proposed Indication: Severe Hypertriglyceridemia

Trade Name	NDA (date of approval)	Class of Drugs
Lopid	NDA 18,422 (21 December 1981)	Gemfibrozil
Tricor (micronized)	NDA 19,304 (31 Dec 1993)	Fenofibrate
Tricor	NDA 21,656 (5 Nov 2004)	Fenofibrate
Antara	NDA 21,695 (30 Nov 2004)	Fenofibrate
Triglide	NDA 21,350 (7 May 2005)	Fenofibrate
Lipofen	NDA 21, 612 (11 January 2006)	Fenofibrate
Fenoglide	NDA 22,118 (10 Aug 2007)	Fenofibrate

Trade Name	NDA (date of approval)	Class of Drugs
Trilipix	NDA 22,224 (15 Dec 2008)	Choline fenofibrate
Fibricor	NDA 22,418 (14 August 2009)	Fenofibric acid
Niaspan	NDA 20,381 (28 July 1997)	Niacin
Simcor	NDA 22,078 (15 February 2008)	Niacin; Simvastatin
Advicor	NDA 21,249 (17 Dec 2001)	Niacin; Lovastatin
Lovaza	NDA 21,654 (10 November 2004)	Omega-3-acid Ethyl esters

Ethyl EPA has been marketed under the name Epadel Capsules (sponsor: Mochida) in Japan since 1991.

2.3 Availability of Proposed Active Ingredient in the United States

In the US, the only currently available prescription omega-3 fatty acid product is Lovaza (omega-3-acid ethyl esters). Lovaza, a mixture of ethyl esters of omega-3 fatty acids, principally EPA and docosahexaenoic acid (DHA), has been approved by the Food and Drug Administration (FDA) as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

2.4 Important Safety Issues With Consideration to Related Drugs

With regard to the only other FDA approved omega-3 fatty acid product (Lovaza), there have been four areas of potential safety concern: increases in LDL-C, liver enzymes, blood glucose, and a possible increase in bleeding risk.

The increase in LDL-C is thought to be due to the increased activity of LPL activity.[4] This increased activity enhances the conversion of very low density lipoprotein (VLDL) and intermediate –density lipoproteins (IDL) to LDL-C.

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

Historically, some studies have raised concern that omega-3 ethyl ester consumption could increase fasting plasma glucose (FPG) without corresponding increase in

4 Harris WS and Bulchandani D. Why do omega-3 fatty acids lower serum triglyceride? *Curr Opion Lipidol*.2006; 17:387-393.

HbA1C.[5] However, a recent Cochrane meta-analysis suggested that neither the FPG nor the HbA1c increased with omega-3 ethyl ester therapy.[6] Pooled data from the Lovaza NDA datasets (post-hoc) showed a slight increase in median FPG in the Lovaza treatment group (median change +6.5mg/dL) as compared to the placebo group (+2 mg/dL).

Metabolism of omega-3 fatty acids, specifically EPA, produces eicosanoids of the thromboxane A3 and leukotriene 5 series, which are associated with reduced platelet aggregation, increased vasodilation, and inhibited leukocyte chemotaxis. [7] Omega-3 acid ethyl esters have been shown *in vitro* to significantly reduce platelet aggregation by reducing production of thromboxane A2 and increasing production of thromboxane A3. The relationship of these *in vitro* findings to bleeding risk is much less clear. Currently the labeling for Lovaza includes cautionary statements with regard to bleeding risk.

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

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

With respect to effects on bleeding time, the FDA concluded that although EPA and DHA appeared to cause small, dose-related increases in bleeding time of unclear

5 Balk EM, Lichtenstein AH, Chung M, et al. Effects of omega-3 fatty acids on serum markers of cardiovascular disease risk: a systematic review. *Atherosclerosis* 2006; 189:19-30.
6 Hartweg J, Perera R, Montori VM, Dinneen SF, et al. Omega-3 polyunsaturated fatty acids (PUFA) for type 2 diabetes mellitus. Cochrane Database of Systematic Review. 2008, Issue 1. Art. No.: CD003205.DOI: 10.1002/14651858.CD003205.pub2.
7 Schmidt EB, Dyerberg J. Omega-3 fatty acids. Current status in cardiovascular medicine. *Drugs*.1994; 47:405-24.

clinical relevance, bleeding time increases associated with the use of 3g/day or less of EPA plus DHA either do not occur or are of no adverse significance.

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

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

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A preIND meeting was held on 14 July 2008. During the discussion, it was agreed that a single study could potentially suffice for the indication “as an adjunct to diet to reduce triglycerides in adult patients with very high ≥500 mg/dL triglyceride levels” provided that the results are robust. The agency defined robust results as: results that are statistically significant; results from a study with a low drop out rate; study results that are consistent across treatment centers; and results from a study with a large sample size. The Agency also confirmed requirements for NCE toxicology program.

A Special Protocol Assessment for the Phase 3, 12-Week study AMR-01-0016 (MARINE) was completed and accepted on 01 May 2009. Key agreements included raising the upper limit of TG entry criterion from 1500 mg/dL to 2000 mg/dL.

IND 102,457 was opened on 22 May 2009 with the study AMR-01-0016 (MARINE).

A Special Protocol Assessment for the Phase 3, 12-Week study AMR-01-0017 (ANCHOR) was completed and accepted on 06 July 2009. Key agreements included the enrollment of patients at high risk for cardiovascular disease (10 year risk >20%), LDL-C baseline measurements for randomization to be < 40 mg/dL and < 100 mg/dL; and TG baseline ≥200 mg/dL and <500 mg/dL and TG to remain the primary endpoint. With regard to the types and use of concomitant statin therapy, the statin must be atorvastatin, rosuvastatin or simvastatin. It was agreed that a non-inferiority test for percent change from baseline in LDL-C would be performed between AMR101 and placebo using a non-inferiority margin of 6% and a significance level at 0.05.

On 26 April 2010, the applicant requested to change ANCHOR due to low enrollment. Agreement was reached to change the HbA1C exclusion criteria from 9.0% to 9.5%; to

increase the LDL-C entry criteria upper limit by 15% to ≥40 to ≤ 155 mg/dL; and to increase the TG entry criteria to ≥170 mg/dL.

A Special Protocol Assessment for the Carcinogenicity study was completed and accepted on 16 March 2010. On 04 March 2010, the Executive CAC recommended the following treatment groups: control (water), 500, 1000, 2000, and 4600 mg/kg/day AMR101, and positive control.

A preNDA meeting was held on 16 March 2011.

A Special Protocol Assessment for the cardiovascular outcomes trial AMR-01-01-0019 (REDUCE-IT) was completed and accepted on 05 August 2011.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

In general the submission quality and integrity were satisfactory. However, the datasets for the Integrated Summary of Safety (ISS) contained .XPT files that could not be opened by GSReview. Additionally, the datasets for the MARINE study were submitted in lieu of the ANCHOR study. The actual ANCHOR study datasets were submitted on 19 July 2012.

3.2 Compliance with Good Clinical Practices

The clinical development program in Europe and US was conducted to the standards set out in the current good clinical practice (GCP) guidelines. As certified in the submission, no debarred investigators were used in the conduct of these studies.

3.3 Financial Disclosures

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

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Dr. Martin Haber's review for complete report. The following is an excerpt from the CMC review:

The drug substance, icosapent ethyl, is a long chain, poly-unsaturated omega-3 fatty acid ester derived from fish oil. Icosapent ethyl is the US Accepted Name for eicosapentaenoic acid ethyl ester (EPA-E). It is a clear, pale yellow liquid with very low water solubility. (b) (4)

(b) (4)

4.2 Clinical Microbiology

See Dr. John Metcalfe's review for full report. There were no microbiology deficiencies identified.

4.3 Preclinical Pharmacology/Toxicology

The applicant is relying on non-clinical literature references for the marketed Japanese product Epadel (ethyl EPA) to support this 505(b)(2) application.

According to the pharmacology/toxicology reviewer, Dr. Stephanie Quinn, there is reasonable evidence to conclude that Vascepa is highly similar to the marketed ethyl-EPA product Epadel for the following points:

1. The source of the ethyl-EPA before purification is fish.
2. The specifications for purity of ethyl-EPA are identical (≥96%).
3. The (b) (4) impurities for each product are similar, but not identical; however, the concentration limits for these (b) (4) are generally low, they are

intermediates in (b) (4) metabolism and are part of the complex mixture of (b) (4)

5. Nonclinical repeat dose toxicology study results were similar but not completely identical between both products for the rat (possibly due to acceptable experimental variability between studies). Similarities included for example, fur/skin changes with oily discharge, WBC changes, clotting parameter alterations, and liver enzyme increases.

Based upon scientific evidence of similar toxicologic profiles, similar (not identical) chemical profiles of highly purified icosapent-ethyl, and the well understood pharmacology of polyunsaturated fatty acids, it would be reasonable to conclude that Epadel and Vascepa are similar products.

However, from a regulatory perspective, Amarin Pharma has not conclusively demonstrated direct comparability between Epadel and Vascepa due to the absence of any direct bridging study conducted by Amarin Pharma or an acceptable PK comparison to the literature references. Therefore the 74-day letter was sent to the applicant with the following statement:

"As there is no adequate bridging information to Epadel, conduct an appropriate non-clinical study (e.g. 28-Day repeat dose toxicology study in the rat) to demonstrate at a minimum, PK comparability between Epadel and Vascepa (AMR101), so that you may rely on published Epadel literature for your 505(b)(2) application."

In their response, the applicant agreed to conduct a nonclinical study to bridge the information for Epadel to Vascepa. Subsequently, the applicant submitted a completed 4-Week rat study entitled "A 4 Week Study of AMR101 and Epadel by Oral Gavage Administration in Rats" on 17 May 2012. The pharmacology/toxicology team concluded that this study demonstrated an adequate bridge between Epadel and Vascepa. Please see the pharmacology/toxicology reviewer's report for compete details.

4.4 Clinical Pharmacology

Omega-3 fatty acids (omega-3 FA), fats commonly found in marine and plant oils, are considered "essential" fatty acids, meaning that they cannot be synthesized by the human body but are vital for normal metabolism. [8] The three most commonly known

8 Poudyal H et al., Omega-3 Fatty Acids and Metabolic Syndrome: Effects and Emerging Mechanisms of Action. *Progress in Lipid Research*. 2011; 50 (4):372-387.

omega-3 FA are eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and alpha-linolenic acid (ALA).

The drug product from Amarin contains a purified icosapent ethyl. Icosapent ethyl (ethyl eicosapentaenoic acid or ethyl-EPA) is the ethyl ester of EPA. Icosapent ethyl acts as a prodrug for EPA, as it is hydrolyzed enzymatically by esterases, particularly pancreatic lipase, to liberate the free acid EPA.

4.4.1 Mechanism of Action

A single mechanism of action to explain the effects of omega-3 FA 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

Extensive study has shown that EPA reduces TG synthesis or secretion by decreasing lipogenesis, increasing β-oxidation of fatty acids, and increasing degradation of apoB-100.[9] EPA also accelerates TG clearance by increasing lipoprotein lipase (LPL) activity which promotes removal of TG from VLDL.[10]

4.4.2 Pharmacodynamics

The relevant pharmacodynamic effect of ethyl- EPA is its TG lowering ability supported by the MARINE and ANCHOR studies.

4.4.3 Pharmacokinetics

Absorption
The proposed absorption process of EPA shown in the figure below is similar to the absorption of fatty acids from dietary lipids.

(b) (4)

9 Harris WS et al. Omega-3 fatty acids and coronary heart disease risk: Clinical and mechanistic perspectives. *Atherosclerosis* 2008; 197:12-24.
10 Khan S et al. Dietary long-chain n-3 PUFAs increase LDL gene expression in adipose tissue of subjects with an atherogenic lipoprotein phenotype. *J of Lipid Res*. 2002 Jun; 43 (6): 979-85.

(b) (4)

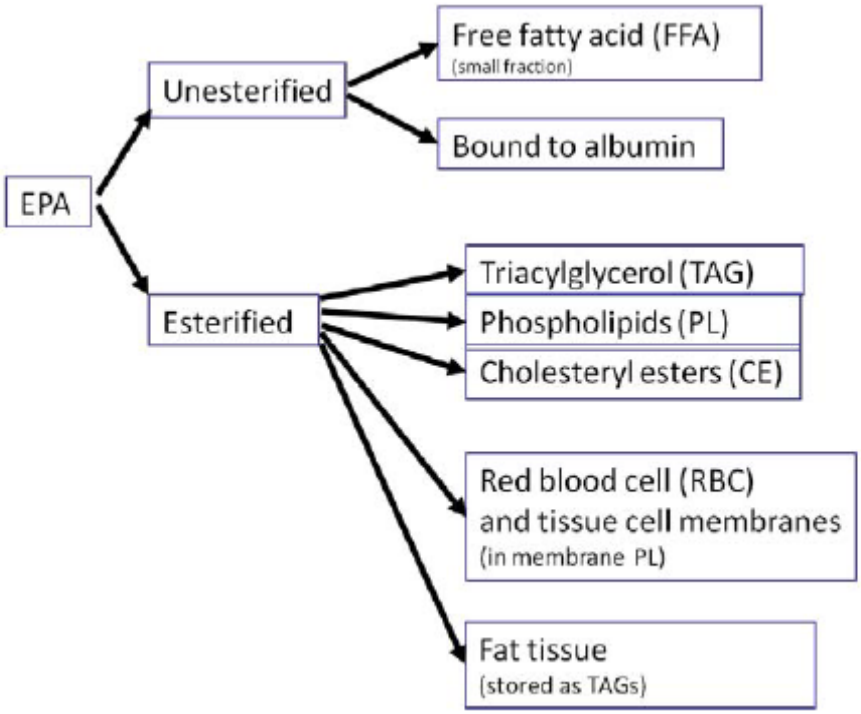
(b) (4)

Source: Applicant's Clinical Pharmacology Summary, Figure 2.7.3-3, pg. 12.

Distribution

After absorption, EPA is distributed and incorporated into circulating PL, triacylglycerol (TAG) and cholesterol esters (CE).

Figure 3: Chemical Forms of EPA in the Body

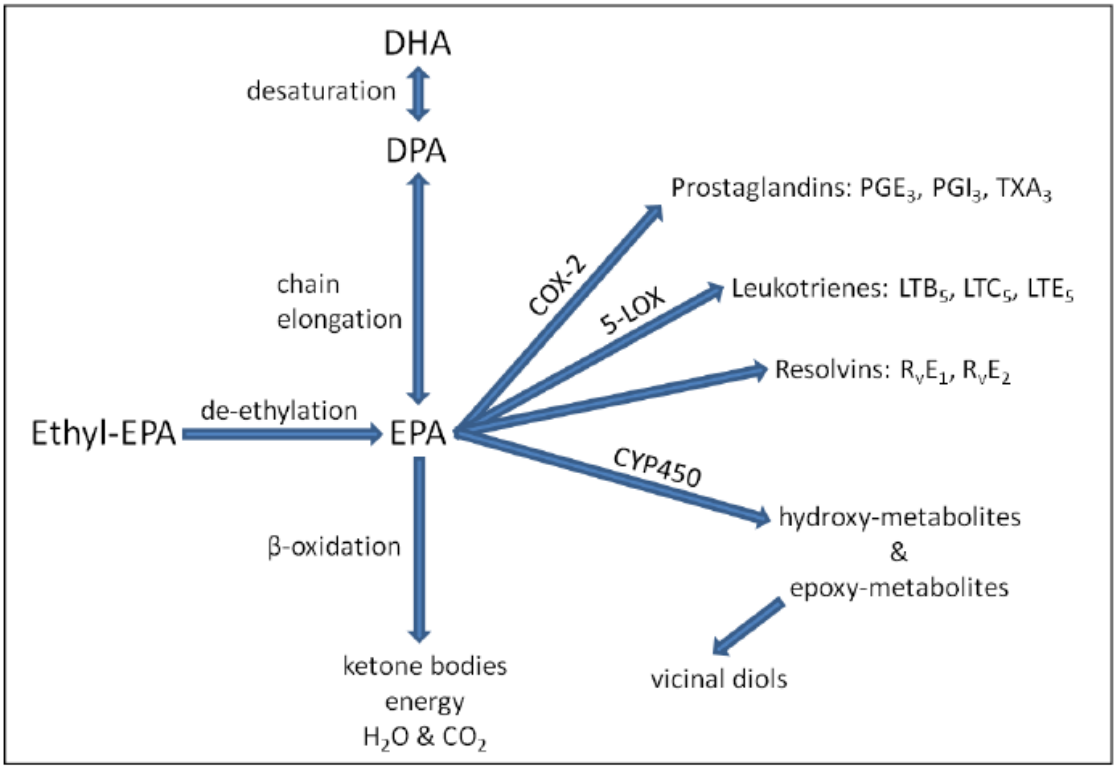


Source: Applicant's Clinical Pharmacology Summary, Figure 2.7.2-4, pg. 14.

Metabolism

The following figure shows the major pathways of metabolism of EPA.

Figure 4: Pathways for EPA Activation



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

Source: Applicant's Clinical Pharmacology Summary, pg. 17

EPA is metabolized by a number of biochemical pathways that include beta oxidation, chain elongation to docosapentaenoic acid (DPA) and desaturation to DHA, and cytochrome P450- mediated hydroxylations and oxidations.

Clinical Pharmacology Trials
A total of five clinical pharmacology trials were submitted in this NDA: two single/multiple dose PK trials and three drug-drug interaction (DDI) trials. The following is an excerpt from Dr. Li, clinical pharmacology reviewer.

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.

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 PD parameters of warfarin and their comparisons with and without ethyl-EPA were also evaluated. The ratio of the geometric means of INRmax following administration of warfarin with and without ethyl-EPA was 0.87 (90% CI: 83.7-89.5%), while the same ratio for AUCINR was 0.94 (90% CI: 92.6-95.7%). It is concluded that 4 g/day ethyl-EPA enhanced the anticoagulation effect of warfarin.

Study LA01.01.009
This was a Phase I study conducted in twenty-four men divided into two treatment groups (Treatment Group A and B). Both groups received the same total dose of Vascepa, but the dosing regimens were different.

All subjects received a single oral dose of 2g of Vascepa on Day 1. Treatment Group A received 28 continuous once daily doses of 2 g of Vascepa (Days 3 to 30). Treatment Group B received 27 continuous twice daily doses of 1g of Vascepa (Days 3 to 30) and a single dose of 2g of Vascepa on Day 30.

The patients were admitted to an in-patient unit from the evening of Day -1 to the morning of Day 3 and from the evening of Day 29 to the morning of Day 32. Blood samples for pharmacokinetic analysis were obtained during the two residential periods and samples were also obtained on Days 9, 16 and 23.

Those subjects completing the dosing period were reviewed at Day 37 (± 2 days) and samples were taken on Day 44 (± 2 days) and Day 58 (± 2 days) following the last dose. For subjects who did not complete the dosing period, a follow-up visit was performed 7± 2 days following study discontinuation.

Skin Bleeding Time
Screening, Days 1 and 30
Skin bleeding times were measured with the Simplate II device. Two small incisions were made in the skin by the device and the flow of blood was blotted at 30 second intervals until neither incision stained the filter paper with blood. The following table summarizes the bleeding times in Groups A and B on Days 1-3 and Days 30-32.

Table 2: Bleeding Times-Study LA.01.01.009

Bleeding Time (sec)	Group A n=12	Group B, n=12	All Patients, n=24
Screening			
Mean (SD)	312.9 (129)	342.5 (214)	327.7 (173)

Bleeding Time (sec)	Group A n=12	Group B, n=12	All Patients, n=24
Min, Max	150, 540	150,960	150, 960
Day 1-3 Pre-dose			
Mean (SD)	397.5 (106)	287.5 (120)	342.5 (124)
Min, Max	240, 510	150, 540	150, 540
Day 1-3 Post-dose +6 hrs			
Mean (SD)	342.5 (134)	330.0 (122)	336.2 (126)
Min, Max	150, 540	180, 480	150, 540
Day 30-32 Pre-Dose			
Mean (SD)	285.0 (135)	346.4 (138)	317.1 (137)
Min, Max	150, 540	150, 570	150, 570
Day 30-32 Post-dose +6 hrs			
Mean (SD)	288.0 (74)	343.6 (120)	317.1 (102)
Min, Max	210, 420	180, 510	180, 510

Source: Study Report LA.01.01.009, Table 15, pg.44.

Reviewer Comment: This study was conducted with a total daily dose of 2g of Vascepa in both Groups A and B. Therefore the maximum dose of 4g Vascepa was not studied. There are studies in the literature which indicate that exposure to omega-3 FA need to be in the range of several weeks and up to 52 weeks for change in bleeding times to be observed. Furthermore, a study with patients on background aspirin and clopidogrel therapy would have been useful to further evaluate a bleeding risk.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3: Clinical Trials in Development Program for Lipid-Altering Indications

Type of Study	Study ID	Study Design	Test Product; Dose	Number if Subjects	Duration	Population

Type of Study	Study ID	Study Design	Test Product; Dose	Number if Subjects	Duration	Population
Efficacy	AMR-01-01-0016 (MARINE)	Double-Blind 12 weeks, with open-label extension, placebo-controlled	AMR 101; 2 grams or 4 grams	240	12 Weeks + 40 Week open label extension	Patients with Very High Triglycerides ≥500 mg/dL
Efficacy	AMR-01-01-0017 (ANCHOR)	Double-Blind, Randomized, placebo controlled	AMR 101; 2 grams or 4 grams	648	12 Weeks	Patients with High Triglycerides, 200≥TG<500
PK	LA01.01.0009	Randomized, Open-label	AMR 101	24	30 days	Healthy men
PK	AMR-01-01-0018	Randomized, Open-label	AMR 101 2 grams or 4 grams	48	28 days	Healthy volunteers
DDI	AMR-01-01-0020	Open-label, crossover	AMR 101 4 grams; omeprazole, and rosiglitazone	30	30 days	Healthy volunteers
DDI	AMR-01-01-0021	Open-label, crossover	AMR 101 4 grams; warfarin	26	36 days	Healthy volunteers
DDI	AMR-01-01-0023	Open-label, crossover	AMR 101 4 grams; atorvastatin	30	36 days	Healthy volunteers

Source: NDA 202057

Table 4: Clinical Trials for Non-Lipid-Altering Indications for Vascepa

Type of Study	Study ID	Study Design	Test Product; Dose	Number if Subjects	Duration	Population
Efficacy	LA01.01.0005	Double-Blind, Randomized, placebo controlled	AMR 101 2 grams	135	12 months + 12 months open-label extension	Huntington's Disease
Efficacy	AN01.01.0011	Double-Blind, Randomized, placebo controlled	AMR 101 2 grams	16	6 months + 6 months open-label extension	Huntington's Disease
Efficacy	AN01.01.0012	Double-Blind,	AMR 101 2 grams	290	6 months + 6 months	Huntington's Disease

Type of Study	Study ID	Study Design	Test Product; Dose	Number if Subjects	Duration	Population
		Randomized, placebo controlled			open-label extension	
Efficacy	LA01.01.0001	Double-Blind, Randomized, placebo controlled	AMR 101 1, 2, or 4 grams	122	12 weeks	Schizophrenia
Efficacy	LA01.01.0002	Double-Blind, Randomized, placebo controlled	AMR 101 1, 2, of 4 grams	70	12 weeks	Depression
Efficacy	LA01.01.0006	Double-Blind, Randomized, placebo controlled	AMR 101 1 gram	115	12 weeks + 12 months open-label extension	Depression

Source: NDA 202057

5.2 Review Strategy

The applicant submitted a study report and dataset for the MARINE trial, the pivotal trial for the hypertriglyceridemia indication. The open-label extension of MARINE was submitted as the 120-day update.

The applicant submitted a study report for an Integrated Summary of Safety, but did not submit a dataset for the ISS. This clinical reviewer requested the datasets for the ISS to verify the conclusions in the applicant's ISS report. The applicant submitted the ISS datasets on 05 March 2012.

The applicant also submitted a study report for the ANCHOR trial; the dataset for this trial was not submitted as part of the NDA. The applicant had been told by the Agency that since the ANCHOR trial was conducted in a population different from that sought in the indication, ANCHOR would not support the indication for very high TG $\geq$500 mg/dL.

The MARINE trial is the focus of the efficacy review in Section 6, whereas the safety review focuses on both the pooled data from the MARINE and the ANCHOR trials (the Hypertriglyceridemic Placebo-Controlled Dataset).

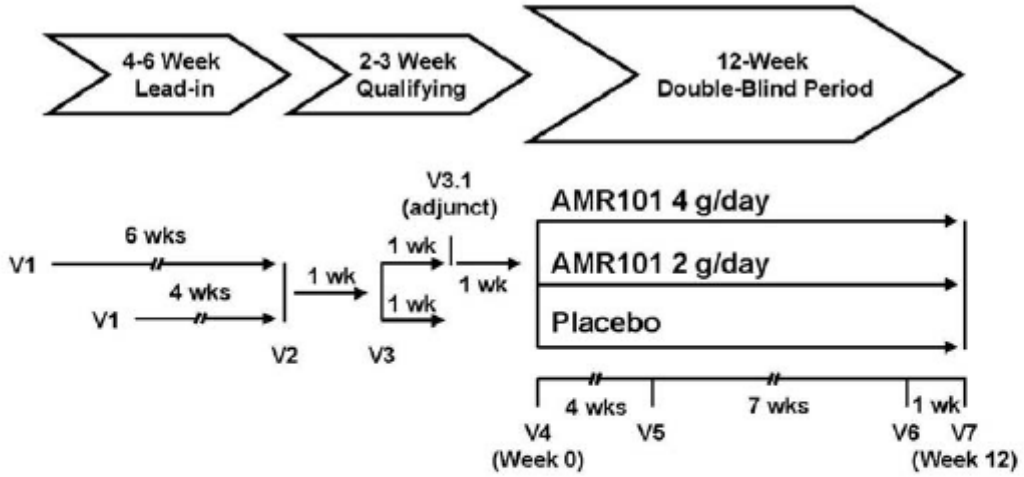
5.3 Discussion of Individual Studies/Clinical Trials

The ANCHOR Study

The primary objective of the ANCHOR study was to determine the efficacy of Vascepa, 2 g daily and 4 g daily, compared to placebo, in lowering fasting TG levels in patients with high risk for CVD and with fasting TG levels ≥200 mg/dL and <500 mg/dL, despite treatment to LDL-C goal (≥40 mg/dL and ≤115 mg/dL) on statin therapy.

The following figure shows the overall design of the ANCHOR study. The study consisted of a 6- to 8-week period for screening/washout and a 12-week double-blind, randomized, placebo-controlled treatment period.

Figure 5: ANCHOR Study Design



Eligible patients entered a 4- to 6-week lead-in period (6-week washout period for patients on lipid-altering therapy and 4 weeks for patients not on lipid-altering therapy) followed by a 2-week LDL-C and TG qualifying period (Visits 2 and 3). If a patient's LDL-C and/or TG levels from Visit 2 and Visit 3 fell outside the required range for entry into the study, an additional fasting lipid profile could have been collected 1 week later at Visit 3.1. Qualifying patients were randomized at Visit 4 and entered the 12-week double-blind efficacy and safety measurement period.
LDL-C = low-density lipoprotein cholesterol; TG = triglyceride; V = visit; wk = week.
Source: Study Protocol (see Appendix 16.1.1)

In order to enter the 12-week double-blind treatment period, patients must have had a mean fasting LDL-C level ≥40 mg/dL and ≤115 mg/dL (based on 2 qualifying visits) and fasting TG levels from 2 qualifying visits within the following ranges:

- Mean of the 2 values ≥185 mg/dL and at least 1 value ≥200 mg/dL and
- Mean of the 2 values <500 mg/dL

After confirmation of qualifying fasting LDL-C and TG values, eligible patients entered a 12-week, randomized, double-blind treatment period. At Visit 4 (Week 0), patients were randomly assigned to one of the following treatment groups:

- Vascepa 2 g daily,
- Vascepa 4 g daily, or
- Placebo.

Approximately 216 patients per treatment group were randomized in this study. Patients were stratified by type of statin (atorvastatin, rosuvastatin, or simvastatin), the presence of diabetes, and gender.

Demographics
The following table summarizes the demographics and baseline characteristics of the randomized population.

Table 5: Summary of Demographic and Baseline Characteristics-Randomized Population-ANCHOR

Characteristic	Placebo (N = 233)	AMR101 2 g daily (N = 236)	AMR101 4 g daily (N = 233)	Total (N = 702)
Age (years)				
n	233	236	233	702
Mean (SD)	61.2 (10.05)	61.8 (9.42)	61.1 (10.03)	61.4 (9.83)
Min – max	36 – 88	31 – 84	31 – 85	31 – 88
Age group (n, %)				
<65 years	146 (62.7)	141 (59.7)	142 (60.9)	429 (61.1)
≥65 years	87 (37.3)	95 (40.3)	91 (39.1)	273 (38.9)
Gender (n, %)				
Male	145 (62.2)	144 (61.0)	142 (60.9)	431 (61.4)
Female	88 (37.8)	92 (39.0)	91 (39.1)	271 (38.6)
Race (n, %)				
White	224 (96.1)	226 (95.8)	226 (97.0)	676 (96.3)
Black or African American	4 (1.7)	6 (2.5)	2 (0.9)	12 (1.7)
Asian	3 (1.3)	2 (0.8)	3 (1.3)	8 (1.1)
American Indian or Alaska Native	1 (0.4)	1 (0.4)	0 (0.0)	2 (0.3)
Other	1 (0.4)	1 (0.4)	2 (0.9)	4 (0.6)
Ethnicity (n, %)				
Not Hispanic or Latino	203 (87.1)	210 (89.0)	206 (88.4)	619 (88.2)
Hispanic or Latino	30 (12.9)	26 (11.0)	27 (11.6)	83 (11.8)
Weight [1] (kg)				
n	233	236	233	702
Mean (SD)	97.0 (19.14)	95.5 (18.29)	94.5 (18.30)	95.7 (18.58)
Min – max	58 – 145	55 – 142	54 – 153	54 – 153
Body mass index [1] (kg/m^2)				
n	233	236	233	702
Mean (SD)	33.0 (5.04)	32.9 (4.98)	32.7 (4.99)	32.9 (5.00)
Min – max	24 – 45	23 – 45	21 – 46	21 – 46
Presence of diabetes (n, %)				
Present diabetes	171 (73.4)	172 (72.9)	171 (73.4)	514 (73.2)
Past or no diabetes	62 (26.6)	64 (27.1)	62 (26.6)	188 (26.8)
Type of statin (n, %)				
Simvastatin	133 (57.1)	136 (57.6)	134 (57.5)	403 (57.4)
Rosuvastatin	55 (23.6)	57 (24.2)	55 (23.6)	167 (23.8)
Atorvastatin	45 (19.3)	43 (18.2)	44 (18.9)	132 (18.8)

1. Baseline was defined as the Visit 4 (Week 0) visit. If missing, the last valid measurement prior to dosing with study drug was used as the baseline value.
2. Defined as simvastatin 5-10 mg.
3. Defined as rosuvastatin 5-10 mg, atorvastatin 10-20 mg, simvastatin 20-40 mg, or simvastatin 10-20 mg + ezetimibe 5-10 mg.
4. Defined as rosuvastatin 20-40 mg, atorvastatin 40-80 mg, simvastatin 80 mg, or simvastatin 40-80 mg + ezetimibe 5-10 mg.
5. Baseline was defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week -1] or if it occurred, Visit 3.1) measurements. If the measurement at 1 visit was missing, the other visit was used. If the measurements at both visits were missing, the last valid measurement prior to dosing with study drug was used as the baseline value.

Apo B = apolipoprotein B; LDL-C = low-density lipoprotein cholesterol; Lp-PLA$_2$ = lipoprotein-associated phospholipase A$_2$; max = maximum; min = minimum; non-HDL-C = non-high-density lipoprotein cholesterol; SD = standard deviation; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol.
Sources: Post-text Tables 14.1.5 and 14.1.6

Source: ANCHOR study report, Table 6; pg. 66.

The randomized population in the ANCHOR study was mostly Caucasian (96%), male (61%), with a mean age of 61 years and a mean BMI of 33 kg/ m^2. Approximately 73% in each treatment group were diabetic.

Median levels of TG at baseline were 268 mg/dL in the Vascepa 4 g group, 255 mg/dL in the Vascepa 2 g group, and 258 mg/dL in the placebo group. Median levels of LDL-C at baseline were 82 mg/dL in the Vascepa 4 g group, 83 mg/dL in the Vascepa 2 g group, and 84 mg/dL in the placebo group.

Table 6: Summary of Lipid Parameters and Baseline Characteristics- Randomized Population-ANCHOR

Characteristic	Placebo (N = 233)	AMR101 2 g daily (N = 236)	AMR101 4 g daily (N = 233)	Total (N = 702)
Statin potency regimen (n, %)				
Lower [2]	15 (6.4)	17 (7.2)	16 (6.9)	48 (6.8)
Medium [3]	144 (61.8)	148 (62.7)	148 (63.5)	440 (62.7)
Higher [4]	74 (31.8)	71 (30.1)	69 (29.6)	214 (30.5)
TG [5] (mg/dL)				
n	233	236	233	702
Mean (SD)	270.6 (75.02)	270.2 (72.12)	281.1 (82.88)	274.0 (76.85)
Median	257.5	254.5	267.5	259.0
Min – max	140 – 553	152 – 503	157 – 782	140 - 782
Baseline TG category (n, %)				
<185 mg/dL	16 (6.9)	17 (7.2)	14 (6.0)	47 (6.7)
≥185 mg/dL	217 (93.1)	219 (92.8)	219 (94.0)	655 (93.3)
Baseline TG category (n, %)				
<Median	118 (50.6)	125 (53.0)	107 (45.9)	350 (49.9)
≥Median	115 (49.4)	111 (47.0)	126 (54.1)	352 (50.1)
LDL-C [1] (mg/dL)				
n	232	235	232	699
Mean (SD)	84.6 (19.12)	85.6 (18.76)	85.0 (21.97)	85.0 (19.97)
Median	84.0	83.0	82.0	83.0
Non-HDL-C [1] (mg/dL)				
n	233	236	233	702
Mean (SD)	130.8 (24.40)	131.8 (24.74)	132.2 (25.76)	131.6 (24.94)
Median	128.0	128.0	128.0	128.0
VLDL-C [1] (mg/dL)				
n	232	235	232	699
Mean (SD)	46.3 (17.33)	46.2 (18.50)	47.2 (19.00)	46.5 (18.27)
Median	42.0	43.0	44.5	43.0
Lp-PLA$_2$ [1] (ng/mL)				
n	218	226	219	663
Mean (SD)	193.8 (52.99)	194.0 (44.22)	188.9 (46.40)	192.2 (47.95)
Median	187.0	190.0	180.0	185.0
Apo B [1] (mg/dL)				
n	233	236	232	701
Mean (SD)	92.8 (16.23)	94.1 (16.46)	94.4 (17.37)	93.8 (16.68)
Median	92.0	91.0	93.0	92.0

1. Baseline was defined as the Visit 4 (Week 0) visit. If missing, the last valid measurement prior to dosing with study drug was used as the baseline value.
2. Defined as simvastatin 5-10 mg.
3. Defined as rosuvastatin 5-10 mg, atorvastatin 10-20 mg, simvastatin 20-40 mg, or simvastatin 10-20 mg + ezetimibe 5-10 mg.
4. Defined as rosuvastatin 20-40 mg, atorvastatin 40-80 mg, simvastatin 80 mg, or simvastatin 40-80 mg + ezetimibe 5-10 mg.
5. Baseline was defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week -1] or if it occurred, Visit 3.1) measurements. If the measurement at 1 visit was missing, the other visit was used. If the measurements at both visits were missing, the last valid measurement prior to dosing with study drug was used as the baseline value.

Apo B = apolipoprotein B; LDL-C = low-density lipoprotein cholesterol; Lp-PLA$_2$ = lipoprotein-associated phospholipase A$_2$; max = maximum; min = minimum; non-HDL-C = non-high-density lipoprotein cholesterol; SD = standard deviation; TG = triglyceride; VLDL-C = very low-density lipoprotein cholesterol.
Sources: Post-text Tables 14.1.5 and 14.1.6

Source: ANCHOR study report, Table 6; pg. 67.

The treatment groups were well balanced with respect to demographics and baseline characteristics in the ANCHOR study.

Statin Use
The majority of patients (n=620; 90%) were on a statin prior to screening. Of those 620 patients, 582 (85%) continued taking the same statin after screening and 571 (83%) maintained the same statin at the same dose after screening. Patients who were not on a statin prior to the screening visit (n=67; 10%) were to have been on a stable statin dose for ≥4 weeks prior to Visit 2 (Week -2).

Table 7: Summary of Statin Use – ITT Population

Category	Placebo (N = 227) n (%)	AMR101 2 g daily (N = 234) n (%)	AMR101 4 g daily (N = 226) n (%)	Total (N = 687) n (%)
Patients taking a statin prior to screening	203 (89.4)	212 (90.6)	205 (90.7)	620 (90.2)
Continued statin after screening	190 (83.7)	198 (84.6)	194 (85.8)	582 (84.7)
Continued dose after screening	187 (82.4)	194 (82.9)	190 (84.1)	571 (83.1)
Changed dose after screening	3 (1.3)	4 (1.7)	4 (1.8)	11 (1.6)
Changed statin after screening	13 (5.7)	14 (6.0)	11 (4.9)	38 (5.5)
Patients not taking a statin prior to screening	24 (10.6)	22 (9.4)	21 (9.3)	67 (9.8)
Source: Post-text Table 14.1.13				

ANCHOR study report, Table 10; pg. 71.

Of the three permitted statin medications, simvastatin was the most commonly used; at baseline, 57% of patients were on simvastatin. Rosuvastatin was used by 24% of patients at baseline and atorvastatin by 19% of patients at baseline. Overall, 63% of patients were on a medium potency statin and 31% were on a higher potency statin. Less than 10% of patients in each treatment group were on a lower potency statin.

The following table summarizes statin doses (with or without ezetimibe) at randomization by potency.

Table 8: Summary of Statin Use at Randomization by Potency-ITT Population-ANCHOR

Category	Placebo (N = 227) n (%)	AMR101 2 g daily (N = 234) n (%)	AMR101 4 g daily (N = 226) n (%)	Total (N = 687) n (%)
Lower potency				
Simvastatin 5 mg	4 (1.8)	4 (1.7)	2 (0.9)	10 (1.5)
Simvastatin 5 mg + ezetimibe	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Simvastatin 10 mg	10 (4.4)	10 (4.3)	13 (5.8)	33 (4.8)
Simvastatin 15 mg	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Total	14 (6.2)	15 (6.4)	16 (7.1)	45 (6.6)
Medium potency				
Atorvastatin 10 mg	10 (4.4)	8 (3.4)	9 (4.0)	27 (3.9)
Atorvastatin 20 mg	14 (6.2)	18 (7.7)	15 (6.6)	47 (6.8)
Rosuvastatin 5 mg	9 (4.0)	7 (3.0)	8 (3.5)	24 (3.5)
Rosuvastatin 5 mg + ezetimibe	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Rosuvastatin 10 mg	21 (9.3)	28 (12.0)	19 (8.4)	68 (9.9)
Rosuvastatin 10 mg + ezetimibe	1 (0.4)	0 (0.0)	1 (0.4)	2 (0.3)
Simvastatin 10 mg + ezetimibe	0 (0.0)	3 (1.3)	1 (0.4)	4 (0.6)
Simvastatin 20 mg	31 (13.7)	32 (13.7)	31 (13.7)	94 (13.7)
Simvastatin 20 mg + ezetimibe	5 (2.2)	3 (1.3)	4 (1.8)	12 (1.7)
Simvastatin 40 mg	47 (20.7)	48 (20.5)	53 (23.5)	148 (21.5)
Simvastatin 60 mg	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Total	140 (61.7)	147 (62.8)	141 (62.4)	428 (62.3)
Higher potency				
Atorvastatin 40 mg	16 (7.0)	9 (3.8)	12 (5.3)	37 (5.4)
Atorvastatin 40 mg + ezetimibe	1 (0.4)	2 (0.9)	0 (0.0)	3 (0.4)
Atorvastatin 60 mg	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)
Atorvastatin 80 mg	4 (1.8)	4 (1.7)	4 (1.8)	12 (1.7)
Atorvastatin 80 mg + ezetimibe	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.3)
Rosuvastatin 20 mg	20 (8.8)	15 (6.4)	21 (9.3)	56 (8.2)
Rosuvastatin 20 mg + ezetimibe	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.3)
Rosuvastatin 40 mg	2 (0.9)	3 (1.3)	5 (2.2)	10 (1.5)
Rosuvastatin 40 mg + ezetimibe	0 (0.0)	2 (0.9)	0 (0.0)	2 (0.3)
Simvastatin 40 mg + ezetimibe	10 (4.4)	10 (4.3)	6 (2.7)	26 (3.8)
Simvastatin 80 mg	20 (8.8)	19 (8.1)	18 (8.0)	57 (8.3)
Simvastatin 80 mg + ezetimibe	0 (0.0)	4 (1.7)	2 (0.9)	6 (0.9)
Total	73 (32.2)	72 (30.8)	69 (30.5)	214 (31.1)

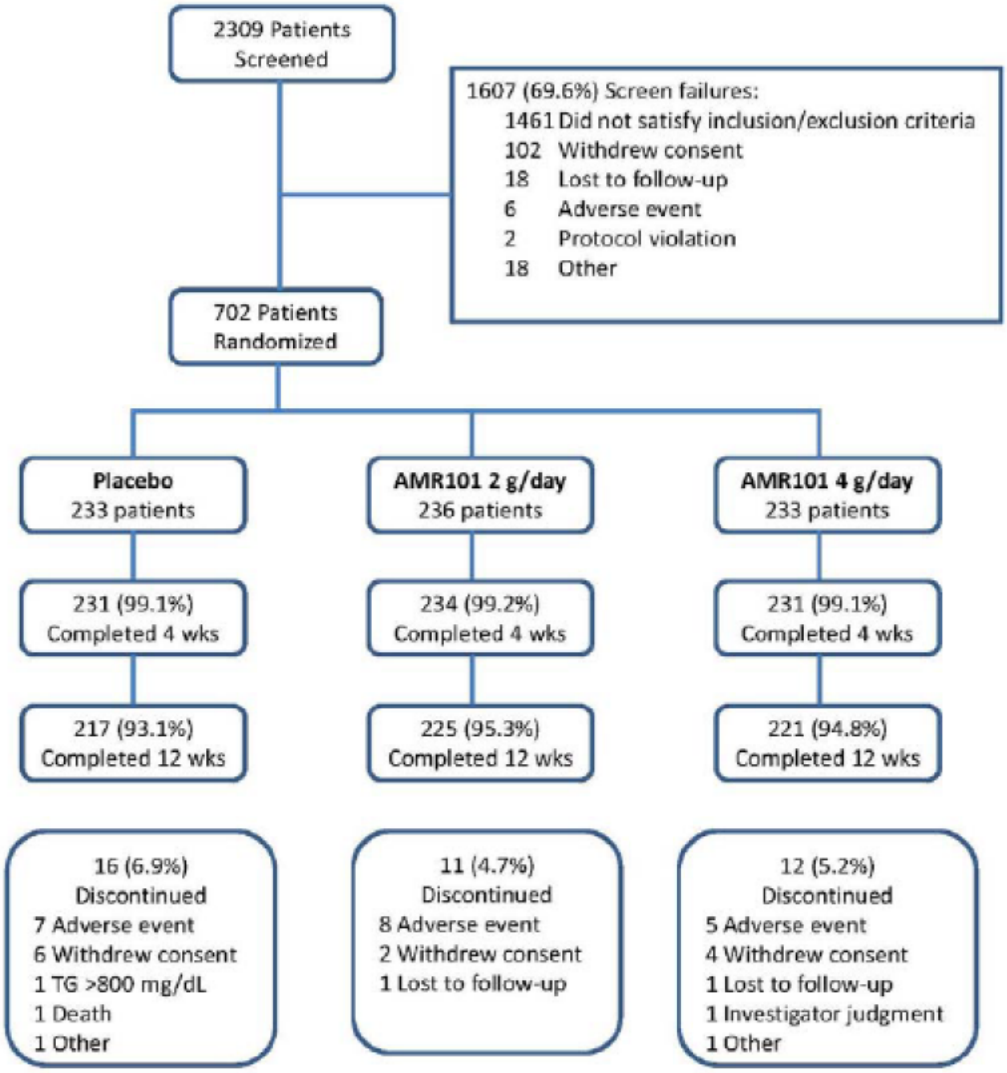
Note: Ezetimibe includes patients on 5 mg or 10 mg.
Source: Post-text Data Listing 16.2.4.4

Source: ANCHOR Study Report, Table 9; pg. 70.

Disposition- ANCHOR study

In total, 2309 patients were screened, of which 702 patients were assigned randomly to double-blind treatment and 1607 patients discontinued prior to randomization (see figure below). The most common reason for pre-randomization discontinuation was failure to satisfy inclusion/exclusion criteria for the study. Additional reasons for pre-

randomization discontinuation were withdrawal of consent, lost to follow-up, adverse event, protocol violation and reasons other than those specified above.



TG = triglyceride; wk = week.

Source: ANCHOR Study Report, Figure 2, pg.63.

The following table summarizes patient disposition during the double-blind treatment period. Thirty-nine (5.6%) patients discontinued from the double-blind treatment period: 20 (2.8%) patients due to an adverse event, 12 (1.7%) patients withdrew consent, 2 (0.3%) patients were lost to follow-up, 1 patient (0.1%) with a TG level >800 mg/dL, 1 (0.1%) patient due to investigator judgment, 1 (0.1%) patient died, and 2 (0.3%) patients withdrew for reasons other than those specified above.

Table 9: Patient Disposition –ANCHOR study

Category	Placebo (N = 233) n (%)	AMR101 2 g daily (N = 236) n (%)	AMR101 4 g daily (N = 233) n (%)	Total (N = 702) n (%)
Randomized	233 (100.0)	236 (100.0)	233 (100.0)	702 (100.0)
Without valid Week 11/Week 12 TG [1]	15 (6.4)	12 (5.1)	11 (4.7)	38 (5.4)
Completed 4 weeks in double-blind period [2]	231 (99.1)	234 (99.2)	231 (99.1)	696 (99.1)
Completed the study	217 (93.1)	225 (95.3)	221 (94.8)	663 (94.4)
Early termination from the study	16 (6.9)	11 (4.7)	12 (5.2)	39 (5.6)
Adverse event	7 (3.0)	8 (3.4)	5 (2.1)	20 (2.8)
Withdrawal of consent	6 (2.6)	2 (0.8)	4 (1.7)	12 (1.7)
Lost to follow-up	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.3)
Triglycerides >800 mg/dL	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Investigator judgment	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Death	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Other	1 (0.4)	0 (0.0)	1 (0.4)	2 (0.3)
ITT population	227 (97.4)	234 (99.2)	226 (97.0)	687 (97.9)
Per-protocol population	205 (88.0)	219 (92.8)	215 (92.3)	639 (91.0)
Safety population	233 (100.0)	236 (100.0)	233 (100.0)	702 (100.0)

See Section 9.7.1.1 for a definition of the analysis populations.
1. A patient with Week 11/Week 12 TG values was defined as a patient with valid values at Week 11, Week 12, or both time points. A TG measurement without a recorded fasting status or with a recorded non-fasting status was considered to be invalid. In addition, TG measurements taken >1 week after the last dose of study drug were also considered to be invalid.
2. Includes patients who completed Visit 5 (Week 4) of the study.

ITT = intent-to-treat; TG = triglyceride.
Sources: Post-text Tables 14.1.2 and 14.1.3

Source: ANCHOR study report, Table 5, pg. 62.

Primary Endpoint- TG

The median percent change in TG from Baseline to Week 12 Endpoint was -18% for the Vascepa 4 g group, -6% for the Vascepa 2 g group, and +6% for the placebo group. As shown in the following table, the estimate of the median of the treatment difference between the Vascepa 4g group and the placebo group was -22% (p<0.0001). The estimate of the median of the treatment difference between the Vascepa 2 g group and the placebo group was -10% (p=0.0005).

Table 10: Percent Change in Fasting TG (mg/dL) From Baseline to Week 12 Endpoint- ITT Population – ANCHOR

Treatment	n [1]	Baseline [2] Median (IQR)	Week 12 Endpoint [3] Median (IQR)	Percent Change From Baseline	
				Median (IQR)	(Q1 , Q3)
Placebo	227	259.0 (81.0)	269.5 (149.5)	5.9 (44.9)	(-13.5 , 31.3)
AMR101 2 g daily	234	254.0 (92.5)	244.3 (117.0)	-5.6 (34.5)	(-21.1 , 13.4)
AMR101 4 g daily	226	264.8 (93.0)	220.8 (92.0)	-17.5 (31.0)	(-30.5 , 0.5)

Treatment Comparison	Difference (Tmt 1 – Tmt 2)		
	Estimated Median	95% CI	P-value
AMR101 4 g daily (Tmt 1) vs. placebo (Tmt 2)	-21.5	(-26.7 , -16.2)	<0.0001
AMR101 2 g daily (Tmt 1) vs. placebo (Tmt 2)	-10.1	(-15.7 , -4.5)	0.0005

The median differences between the treatment groups and 95% CIs were estimated with the Hodges-Lehmann method. P-value is from the Wilcoxon rank-sum test.
A step-down testing procedure was followed using the fixed order: AMR101 4 g daily and then 2 g daily. The hypothesis for AMR101 2 g daily compared with placebo was tested only if the null hypothesis for AMR101 4 g daily compared with placebo was rejected. That is, the 2 g dose of AMR101 was only tested when the 4 g dose was shown to have a greater TG reduction effect compared to placebo.

1. Only patients with non-missing baseline and Week 12 endpoint values were included.
2. Baseline was defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week -1] or if it occurred, Visit 3.1) measurements. If the measurement at 1 visit was missing, the other visit was used. If the measurements at both visits were missing, the last valid measurement prior to dosing with study drug was used as the baseline value.
3. The Week 12 endpoint was defined as the average of Visit 6 (Week 11) and Visit 7 (Week 12) measurements. If the measurement at 1 visit was missing, the other visit was used. If the measurements at both visits were missing, the last valid post-baseline measurement during the double-blind treatment period was used as the endpoint measurement.

CI = confidence interval; IQR = interquartile range; Q1 = first quartile; Q3 = third quartile; TG = triglyceride; Tmt = treatment.
Source: Post-text Table 14.2.1

Source: ANCHOR study report, Table 13; pg. 74.

Secondary Endpoint -LDL-C

The median percent change in LDL-C from Baseline to Week 12 Endpoint was +1.5% for the Vascepa 4 g group, +2.4% for the Vascepa 2 g group, and +8.8% for the placebo group.

The estimate of the median of the treatment difference between the AMR101 4 g group and the placebo group was -6.2% (p=0.0067). As shown in the following table, the estimate of the median of the treatment difference between the Vascepa 2 g group and the placebo group was -3.6% (p=0.0867).

Table 11: Percent Change in LDL-C (mg/dL) From Baseline to Week 12 Endpoint- ITT Population- ANCHOR

Treatment	n [1]	Baseline [2] Median (IQR)	Week 12 Endpoint [3] Median (IQR)	Percent Change From Baseline	
				Median (IQR)	(Q1 , Q3)
Placebo	226	84.0 (27.0)	88.5 (31.0)	8.8 (31.0)	(-7.8 , 23.2)
AMR101 2 g daily	233	82.0 (24.0)	87.0 (27.0)	2.4 (26.1)	(-8.3 , 17.7)
AMR101 4 g daily	225	82.0 (25.0)	83.0 (31.0)	1.5 (26.6)	(-11.6 , 15.0)

Treatment Comparison	Difference (Tmt 1 – Tmt 2)			
	Estimated Median	95% CI	P-value	97.5% CI
AMR101 4 g daily (Tmt 1) vs. placebo (Tmt 2)	-6.2	(-10.5 , -1.7)	0.0067	(– , -1.7)
AMR101 2 g daily (Tmt 1) vs. placebo (Tmt 2)	-3.6	(-7.9 , 0.5)	0.0867	(– , 0.5)

The median differences between the treatment groups and 95% CIs were estimated with the Hodges-Lehmann method. P-value is from the Wilcoxon rank-sum test.

1. Only patients with non-missing baseline and Week 12 endpoint values were included.
2. Baseline was defined as the Visit 4 (Week 0) measurement. If missing, the last valid measurement prior to dosing with study drug was used.
3. The Week 12 endpoint was defined as the Visit 7 (Week 12) measurement. If missing, the LOCF method was used.

CI = confidence interval; IQR = interquartile range; LOCF = last observation carried forward;
Q1 = first quartile; Q3 = third quartile; Tmt = treatment.
Source: Post-text Table 14.2.7

Source: ANCHOR study report, Table 14; pg. 78.

For Vascepa 4 g and 2 g groups, the upper limit of the 97.5% confidence interval was <6% (-1.7 and 0.5, respectively), indicating both doses were non-inferior to placebo. Regarding LDL-C, Vascepa 4 g also demonstrated superiority to the placebo group.

Non-HDL-C

The median percent change in non-HDL-C from Baseline to Week 12 Endpoint was -5.0% for Vascepa 4 g group, +2.4% for the Vascepa 2 g group, and +9.8% for the placebo group.

Table 12: Percent Change in non-HDL-C (mg/dL) From Baseline to Week 12 Endpoint – ITT Population- ANCHOR

Treatment	n [1]	Baseline [2] Median (IQR)	Week 12 Endpoint [3] Median (IQR)	Percent Change From Baseline	
				Median (IQR)	(Q1 , Q3)
Placebo	227	128.0 (34.0)	138.0 (43.0)	9.8 (27.6)	(-3.5 , 24.1)
AMR101 2 g daily	234	128.0 (33.0)	134.0 (41.0)	2.4 (26.1)	(-7.0 , 19.0)
AMR101 4 g daily	226	128.0 (32.0)	122.0 (39.0)	-5.0 (21.3)	(-13.5 , 7.8)

Treatment Comparison	Difference (Tmt 1 – Tmt 2)			
	Estimated Median	95% CI	P-value	Parameter Adjusted P-value [4]
AMR101 4 g daily (Tmt 1) vs. placebo (Tmt 2)	-13.6	(-17.2 , -9.9)	<0.0001	0.0001
AMR101 2 g daily (Tmt 1) vs. placebo (Tmt 2)	-5.5	(-9.4 , -1.7)	0.0054	0.0140

The median differences between the treatment groups and 95% CIs were estimated with the Hodges-Lehmann method. P-value is from the Wilcoxon rank-sum test.

1. Only patients with non-missing baseline and Week 12 endpoint values were included.
2. Baseline was defined as the Visit 4 (Week 0) measurement. If missing, the last valid measurement prior to dosing with study drug was used.
3. The Week 12 endpoint was defined as the Visit 7 (Week 12) measurement. If missing, the LOCF method was used.
4. The adjusted p-value was obtained from applying Hommel's multiple comparison procedure to the p-value from the treatment comparison between AMR101 4 g or 2 g with placebo.

CI = confidence interval; IQR = interquartile range; LOCF = last observation carried forward;
Q1 = first quartile; Q3 = third quartile; Tmt = treatment.
Sources: Post-text Tables 14.2.9, 14.2.17, and 14.2.18

Source: ANCHOR Study Report, Table 15; pg. 79.

For non-HDL-C, the estimate of the median of the treatment difference between Vascepa 4 g group and the placebo group was -13.6% (adjusted p-value=0.0001). The estimate of the median of the treatment difference between Vascepa 2 g group and the placebo group was -5.5% (adjusted p-value=0.0140).

VLDL-C
The median percent change in VLDL-C from Baseline to Week 12 Endpoint was -12.1% for the Vascepa 4 g group, +1.6% for Vascepa 2 g group and +15% for the placebo group.

Table 13: Percent Change in VLDL-C (mg/dL) From Baseline to Week 12 Endpoint- ITT Population- ANCHOR

Treatment	n [1]	Baseline [2] Median (IQR)	Week 12 Endpoint [3] Median (IQR)	Percent Change From Baseline	
				Median (IQR)	(Q1 , Q3)
Placebo	226	42.0 (21.0)	49.0 (28.0)	15.0 (58.8)	(-10.9 , 47.8)
AMR101 2 g daily	233	43.0 (21.0)	44.0 (25.0)	1.6 (54.6)	(-20.0 , 34.5)
AMR101 4 g daily	225	44.0 (21.0)	38.0 (22.0)	-12.1 (47.9)	(-31.3 , 16.7)

Treatment Comparison	Difference (Tmt 1 – Tmt 2)			
	Estimated Median	95% CI	P-value	Parameter Adjusted P-value [4]
AMR101 4 g daily (Tmt 1) vs. placebo (Tmt 2)	-24.4	(-31.9 , -17.0)	<0.0001	0.0001
AMR101 2 g daily (Tmt 1) vs. placebo (Tmt 2)	-10.5	(-18.3 , -2.5)	0.0093	0.0170

The median differences between the treatment groups and 95% CIs were estimated with the Hodges-Lehmann method. P-value is from the Wilcoxon rank-sum test.

1. Only patients with non-missing baseline and Week 12 endpoint values were included.
2. Baseline was defined as the Visit 4 (Week 0) measurement. If missing, the last valid measurement prior to dosing with study drug was used.
3. The Week 12 endpoint was defined as the Visit 7 (Week 12) measurement. If missing, the LOCF method was used.
4. The adjusted p-value was obtained from applying Hommel's multiple comparison procedure to the p-value from the treatment comparison between AMR101 4 g or 2 g with placebo.

CI = confidence interval; IQR = interquartile range; LOCF = last observation carried forward;
Q1 = first quartile; Q3 = third quartile; Tmt = treatment.
Sources: Post-text Tables 14.2.11, 14.2.17, and 14.2.18

Source: ANCHOR study report, Table 16; pg. 80.

For VLDL-C, the estimate of the median of the treatment difference between Vascepa 4 g group and the placebo group was -24.4% (adjusted p-value=0.0001). The estimate of the median of the treatment difference between Vascepa 2 g group and the placebo group was -10.5% (adjusted p-value=0.0170).

HDL-C

The median percent change in HDL-C from Baseline to Week 12 Endpoint was -1.0% for Vascepa 4 g group, 0.0% for Vascepa 2 g group, and 4.8% for the placebo group.

Table 14: Percent Change in HDL-C (mg/dL) From Baseline to Week 12 Endpoint- ITT Population -ANCHOR

Treatment	n [1]	Baseline [2] Median (IQR)	Week 12 Endpoint [3] Median (IQR)	Percent Change From Baseline	
				Median (IQR)	(Q1 , Q3)
Placebo	227	39.0 (12.0)	40.0 (14.0)	4.8 (22.0)	(-7.7 , 14.3)
AMR101 2 g daily	234	38.0 (13.0)	38.0 (11.0)	0.0 (19.5)	(-7.7 , 11.8)
AMR101 4 g daily	226	37.0 (12.0)	37.0 (13.0)	-1.0 (18.2)	(-8.7 , 9.5)

Treatment Comparison	Difference (Tmt 1 – Tmt 2)		
	Estimated Median	95% CI	P-value
AMR101 4 g daily (Tmt 1) vs. placebo (Tmt 2)	-4.5	(-7.4 , -1.8)	0.0013
AMR101 2 g daily (Tmt 1) vs. placebo (Tmt 2)	-2.2	(-4.9 , 0.5)	0.1265

The median differences between the treatment groups and 95% CIs were estimated with the Hodges-Lehmann method. P-value is from the Wilcoxon rank-sum test.

1. Only patients with non-missing baseline and Week 12 endpoint values were included.
2. Baseline was defined as the Visit 4 (Week 0) measurement. If missing, the last valid measurement prior to dosing with study drug was used as the baseline.
3. The Week 12 endpoint was defined as the Visit 7 (Week 12) measurement. If missing, the LOCF method was used.

CI = confidence interval; IQR = interquartile range; LOCF = last observation carried forward;
Q1 = first quartile; Q3 = third quartile; Tmt = treatment.
Source: Post-text Table 14.2.21

Source: ANCHOR study report, Table 20; pg. 84.

For HDL-C, the estimate of the median of the treatment difference between Vascepa 4 g group and the placebo group was -4.5% (p=0.0013). The estimate of the median of the treatment difference between Vascepa 2 g group and the placebo group was -2.2% (p=0.1265).

6 Review of Efficacy

Efficacy Summary

The indication for Vascepa is for treatment of very high TG, ≥500 mg/dL. Patients with very high TG have a strong genetic component to their disease and have an increased risk for acute pancreatitis. Therefore, the primary goal for therapy is to lower TG to prevent this complication. Therapy is considered to be successful if TG is lowered to <500 mg/dL; often it is not possible to normalize TG in these patients. [11]

11 Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation* 2002;106;3336.

Methods recommended by the NCEP ATPIII to reduce the risk of acute pancreatitis include discontinuation of drugs that raise TG, very low-fat diets, and TG-lowering drugs such as fibrates or nicotinic acid. The NCEP guidelines also state that omega-3 fatty acids are alternatives to fibrates or nicotinic acid for the treatment of hypertriglyceridemia, particularly chyomicronemia.

Numerous studies have shown that both the major omega-3 FA, EPA and DHA, lower serum TG levels, but a study comparing the effects of EPA monotherapy to DHA monotherapy showed that DHA consistently had a more pronounced TG-lowering effect than EPA across all baseline concentrations of TG. This study also showed that DHA may be responsible for an increase in HDL-C whereas EPA may produce a small decrease in TC. [12] Thus EPA and DHA have differential effects on lipoprotein metabolism.

6.1 Indication

The applicant proposed the following indication in their draft labeling:

> "Vascepa (icosapent ethyl) is indicated as an adjunct to diet to reduce triglycerides (b) (4) levels in patients with very high (≥500 mg/dL) triglycerides."

6.1.1 Methods

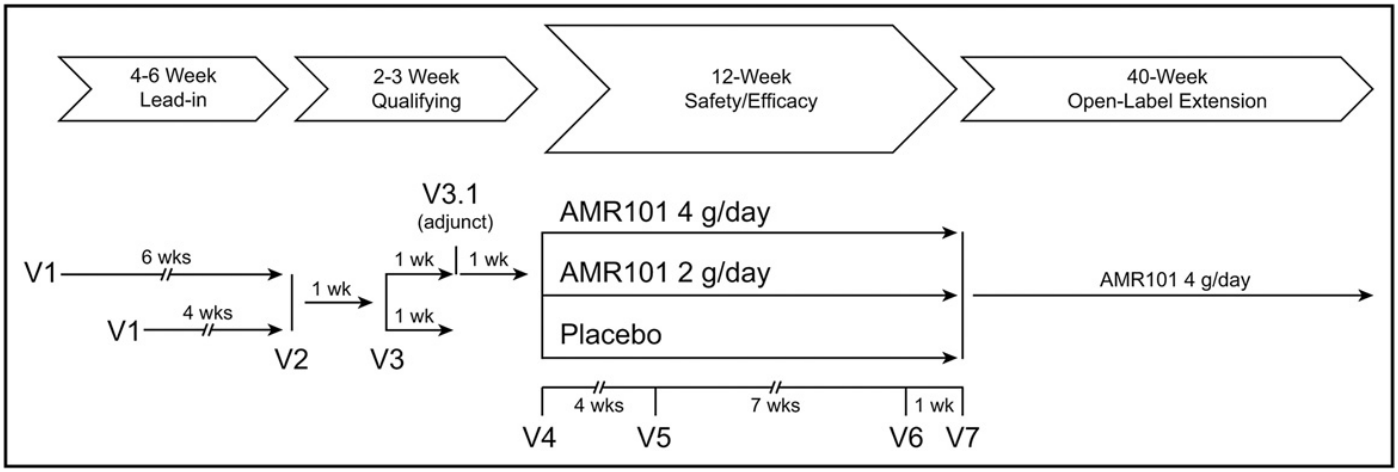
The Phase 3 clinical trial used to support the proposed indication was the MARINE study primarily because the study population in MARINE consisted of patients similar to the population described in the indication sought by the applicant, i.e., patients with very high TG ≥ 500 mg/dL.

The objective of the MARINE study was to determine the efficacy of Vascepa, 2g and 4g per day, compared with placebo, in lowering TG levels in patients with baseline TG levels ≥500 mg/dL and ≤2000 mg/dL. After a 4- to 6-week diet and lifestyle stabilization period, patients entered a 2-week TG qualifying period, where eligible patients were randomized to either placebo, 2g Vascepa or 4 g Vascepa for 12-weeks.

Stratification was by baseline TG level (≥750 mg/dL or <750 mg/dL), gender, and the use of statin therapy (treated or not treated with statin therapy at baseline) at randomization. The following figure is a schematic of the MARINE study design.

12 Grimsgaard S. et al, Highly puified eicosapentaenoic acid and docosahexaenoic acid in human have similar triacylglycerol-lowering effects but divergent effects on serum fatty acids. *American Journal of Clinical Nutrition* 1997;66:649-59.

Figure 6: MARINE Study Design



Patients who completed the 12-week double-blind treatment period were eligible to enter a 40-week, open-label extension period, in which all patients were to receive open-label 4 g/day Vascepa.

There were three analysis populations used in the efficacy analyses for the double-blind portion of MARINE. The randomized population included all patients who signed the informed consent form and were assigned a randomization number at Visit 4 (Week 0). The applicant used the randomized population for its baseline and demographic analyses.

The intent-to-treat (ITT) population consisted of all randomized patients who took at least 1 dose of any study drug, had a valid baseline efficacy measurement, and had at least 1 valid post-randomization efficacy measurement of any type. The applicant used the ITT population for its efficacy analyses.

The per-protocol (PP) population included all ITT patients without any major protocol deviations. The per-protocol population was used to assess robustness of the primary analysis results. The applicant excluded identified patients in the PP population prior to unblinding the randomization code for analyses. Patients were excluded from the per-protocol population for the following reasons:

- Major violations of eligibility criteria for randomization;
- Missing fasting TG measurements at baseline or Week 12 endpoint (Week 11 and/or Week 12 TG measurements);
- Overall study medication compliance <80%;
- Prohibited medication(s) (as defined in the protocols) taken during the double-blind treatment period; or
- Any other major protocol deviation that was thought to interfere with the assessment of drug efficacy

The following table summarizes the number of patients by treatment arm in each of the analysis populations.

Table 15: Efficacy Analysis Population-MARINE

Category	Placebo N=76 n (%)	Vascepa 2 g N=76 n (%)	Vascepa 4g N=77 n (%)	Total N=229 n (%)
Randomized Population	76 (100.0)	76 (100.0)	77 (100.0)	229 (100.0)
ITT Population	75 (98.7)	73 (96.1)	76 (98.7)	224 (97.8)
Per-protocol Population	71 (93.4)	67 (88.2)	71 (92.2)	201 (91.3)

Source: Clinical Summary of Efficacy, Table 2.7.3-4, pg. 17.

6.1.2 Demographics

The randomized population in the MARINE study was mostly Caucasian (88%), male (76%), with a mean age of 53 years and a mean BMI of 31 kg/m^2. Approximately 75% of patients were not on a statin at randomization. Twenty-eight percent of the population had a history of diabetes mellitus. There were no statistically significant differences in demographics and baseline characteristics between the treatment arms.

Table 16: Demographic and Baseline Characteristics- Randomized Population- MARINE

Characteristic	Placebo N=76	Vascepa 2 g N=76	Vascepa 4g N=77	Total N=229	P-Value
Age (years)	76	76	77	229	p=0.511
Mean (SD)	53.4 (8.34)	53.4 (9.34)	51.9 (10.27)	52.9 (9.34)	
Min-max	35-72	30-79	27-74	27-79	
Age group (n,%)					p=0.846
≤65 years	71 (93.4)	70 (92.1)	70 (90.9)	211 (92.1)	
>65 years	5 (6.6)	6 (7.9)	7 (9.1)	18 (7.9)	
Gender					p=0.998
Male	58 (76.3)	58 (76.3)	59 (76.6)	175 (76.4)	
Female	18 (23.7)	18 (23.7)	18 (23.4)	54 (23.6)	
Race n(%)					p=0.464
White	68 (89.5)	67 (88.2)	67 (87.0)	202 (88.2)	
African American	0	3 (3.9)	2 (2.6)	5 (2.2)	
Asian	5 (6.6)	4 (5.3)	7 (9.1)	16 (7.0)	
Multiple	1 (1.3)	2 (2.6)	0	3 (1.3)	
Other	2 (2.6)	0	1 (1.3)	3 (1.3)	
Weight (kg)					p=0.990
Mean (SD)	93 (16.9)	92.1 (15.6)	93.2 (18.3)	92.8 (16.9)	
Min-max	61-157	59-144	61-160	59-160	

Characteristic	Placebo N=76	Vascepa 2 g N=76	Vascepa 4g N=77	Total N=229	P-Value
BMI (kg/m2)					p=0.656
Mean (SD)	31 (4.3)	30.8 (4.2)	30.4 (4.3)	30.8 (4.3)	
Min-max	23-44	22-43	22-43	22-44	
Statin Use n (%)					p=0.947
No	58 (76.3)	57 (75.0)	57 (74.0)	172 (75.1)	
Yes	18 (23.7)	19 (25.0)	20 (26.0)	57 (24.9)	
Diabetes mellitus (%)					p=0.952
No	55 (72.4)	56 (73.7)	55 (71.4)	166 (72.5)	
Yes	21 (27.6)	20 (26.3)	22 (28.6)	63 (27.5)	

Source: MARINE CSR, Post-Text Table 14.1.7 and 14.1.8

In the MARINE trial, mean baseline TG was 783 mg/dL, with approximately 40% of the randomized population having a TG >750 mg/dL. The following table summarizes some lipid parameters.

Table 17: Baseline Lipid Parameters- Randomized Population- MARINE

Characteristic	Placebo N=76	Vascepa 4g N=77	Vascepa 2 g N=76	Total N=229	P-value
TG mg/dL					p=0.664
Mean (SD)	813.4 (390.92)	792.6 (400.58)	741.4 (310.37)	782.5 (369.27)	
Median	696.5	679.5	654.5	679.5	
TG group (n,%)					p=0.8274
≤750 mg/dL	44 (57.9)	48 (62.3)	47 (61.8)	139 (60.7)	
>750 mg/dL	32 (42.1)	29 (37.7)	29 (38.2)	90 (39.3)	
VLDL mg/dL					p=0.698
Mean	144.1 (81.32)	149.7 (105.28)	128.8 (60.75)	140.9 (84.63)	
Median	122.0	122.0	29 (38.2)	90 (39.3)	
ApoB (mg/dL)					p=0.8467
Mean (SD)	120.4 (31.78)	123.1 (30.17)	121.0 (28.54)	121.5 (30.08)	
Median	119.0	121.0	118.5	120.0	
LDL-C (mg/dL)					
Mean (SD)					
Median					
HDL-C (mg/dL)					
Mean (SD)					
Median					

Source: MARINE CSR, Post-Text Table 14.1.7 and 14.1.8

Reviewer Comment: There were no statistically significant differences in baseline demographic characteristics and lipid parameters among the three treatment arms.

Drug Exposure

In the MARINE study, the duration of exposure was similar for the 2g Vascepa treatment group and the 4g Vascepa treatment group as summarized in the table below.

Table 18: Summary of Study Drug Exposure in Double-Blind Treatment Period- MARINE

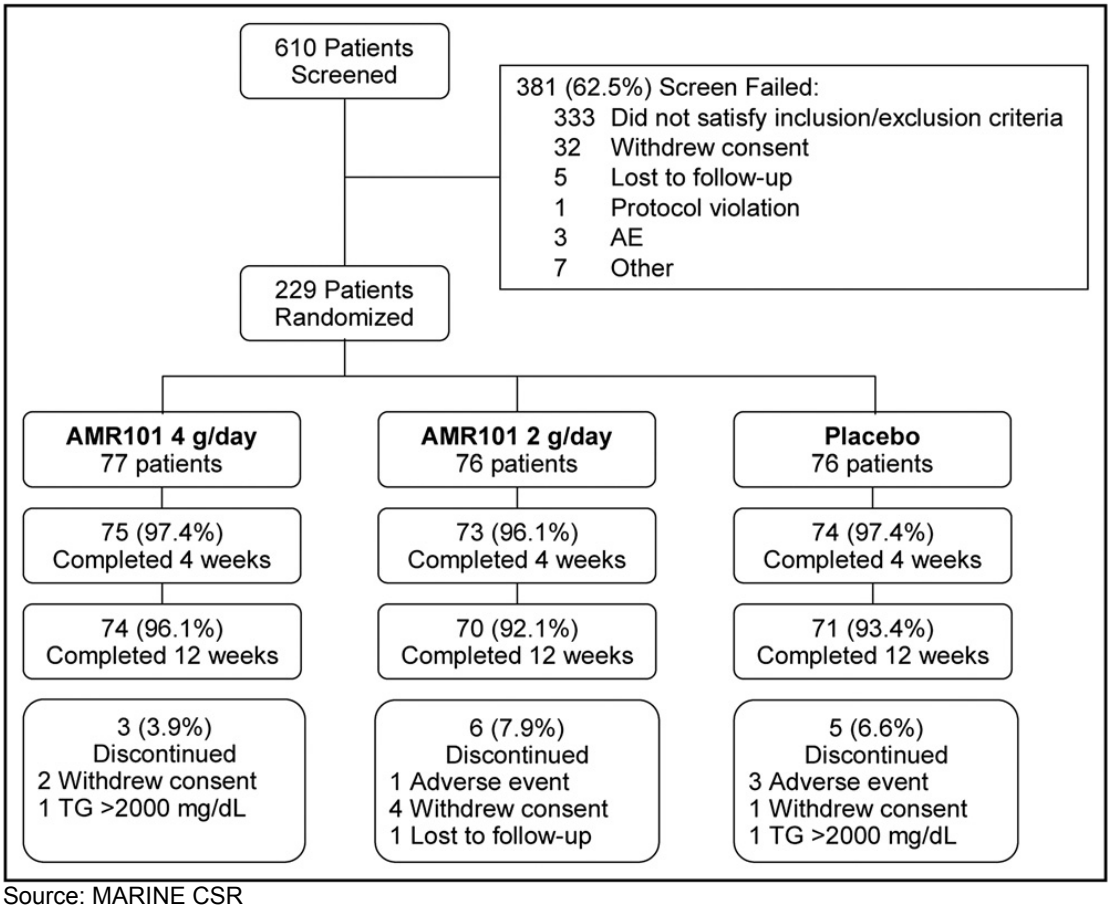
Exposure (days)	Placebo n=76	Vascepa 2 g n=76	Vascepa 4 g n=77	Total n=229
Mean	82.6	81.3	82.6	82.2
SD	13.52	16.31	12.24	14.07
Median	84	84	84	84
Minimum	3	1	10	1
Maximum	94	100	98	100

Source: CSR for MARINE, Post-Text Table 14.1.19, pg. 211.

6.1.3 Subject Disposition

The following figure shows the overall disposition if the 610 patients screened and the 229 patients who were ultimately randomized. Most of the patients who failed screening had a TG level out of the specified range.

Figure 7: Overall Patient Disposition-MARINE



Source: MARINE CSR

Approximately 1.3% of patients on Vascepa 2g and 0% on Vascepa 4g discontinued the MARINE study due to an AE. In comparison, 3.9% of patients on placebo discontinued due to an AE.

Table 19: Patient Disposition-Randomized Population- MARINE

Category	Placebo (N = 76) n (%)	Vascepa 2 g/day (N = 76) n (%)	Vascepa 4 g/day (N = 77) n (%)	Total (N = 229) n (%)
Randomized	76 (100.0)	76 (100.0)	77 (100.0)	229 (100.0)
Without valid Week 11/Week 12 TG	1 (1.3)	3 (3.9)	1 (1.3)	5 (2.2)
Completed 4 weeks in double-blind period	74 (97.4)	73 (96.1)	75 (97.4)	222 (96.9)
Completed 12-week double-blind period	71 (93.4)	70 (92.1)	74 (96.1)	215 (93.9)
Early termination from double-blind period	5 (6.6)	6 (7.9)	3 (3.9)	14 (6.1)
Withdrawal of consent	1 (1.3)	4 (5.3)	2 (2.6)	7 (3.1)
Adverse event	3 (3.9)	1 (1.3)	0 (0.0)	4 (1.7)
Triglycerides >2000 mg/dL	1 (1.3)	0 (0.0)	1 (1.3)	2 (0.9)
Lost to follow-up	0 (0.0)	1 (1.3)	0 (0.0)	1 (0.4)

TG = triglyceride
A patient with Week 11/Week 12 TG values was defined as a patient with valid values at Week 11, Week 12, or both time points.
Sources: MARINE CSR Post-Text Tables 14.1.2 and 14.1.3

As shown in the table above, a total of seven patients (six from the Vascepa treatment arms and one from the Placebo treatment arm) withdrew from the MARINE trial due to "Withdrawal of Consent". This clinical reviewer requested further information from the applicant for these withdrawals in order to ensure the reason was not actually due to an AE. The applicant submitted the following table for the patients' reason for discontinuation:

Table 20: Verbatim Reason for Withdrawal of Consent- MARINE

Pt	Reason for DC	Details
16-011-006	WD consent	hired for a civilian military job and deployed
16-577-034	WD consent	will not be able to complete the study due to personal issues and travelling
16-577-015	WD consent	relocating to taking care of new grandson, no time
16-577-035	WD consent	This subject is a driver and will be on business trips rather often, so he will not be able to follow the protocol requirements.
16-018-004	WD consent	demanding traveling work schedule
16-526-005	WD consent	subj did not want to participate anymore
16-529-009	WD consent	Subject had visited the site today and informed the site that he is facing problems in swallowing the capsule and is difficult for him to continue in the study

Source: Applicant email, 1.31.2012.

Reviewer Comment: According to the verbatim reason for withdrawal, Patient 16-529-009 gave the reason that he had "problems in swallowing the capsule". The medical term for difficulty swallowing is dysphagia and in this case the withdrawal from the study should be categorized as due to an AE.

6.1.4 Analysis of Primary Endpoint(s)

The ability of Vascepa to reduce TG compared to placebo was tested with the following hypotheses:

Hypothesis 1:
$H1_{null}$: There is no significant difference between Vascepa 4 g/day and placebo in percent change in fasting TG from baseline to Week 12 endpoint: [$\mu P = \mu 4$],
$H1_{alternative}$: Compared to placebo, Vascepa 4 g/day group has greater TG reduction at Week 12 endpoint: [$\mu P \neq \mu 4$].

Hypothesis 2:
$H2_{null}$: There is no significant difference between Vascepa 2 g/day and placebo in percent change in fasting TG from baseline to Week 12 endpoint: [$\mu P = \mu 2$],
$H2_{alternative}$: Compared to placebo, Vascepa 2 g/day group has greater TG reduction at Week 12 endpoint: [$\mu P \neq \mu 2$].

In the above hypotheses, μP was defined as the main effect of percent change in TG for the placebo group, μ4 was defined as the main effect of percent change in TG for 4 g/day Vascepa, and μ2 was defined as the main effect for 2 g/day Vascepa group.

The applicant used a fixed-sequence testing procedure (first hypothesis 1, then hypothesis 2) for their analysis. Only in the case where 4g Vascepa was shown to be more potent than placebo in reducing TG, would the 2g Vascepa be tested as a primary endpoint.

The primary efficacy endpoint was the percent change in fasting TG levels from baseline to Week 12. Baseline was defined as the average of two measurements obtained during the TG qualifying period and the during the first study visit of the 12-week treatment period prior to dosing. The Week 12 endpoint was defined as the average of two measurements obtained at the end of the 12-week double-blind treatment period, approximately one week apart.

The secondary efficacy endpoints included the percent change in VLDL-C, Lp-PLA2, and apoB. The applicant identifies parameters such as LDL-C, TC, HDL-C, and non-HDL-C as "exploratory endpoints", but the protocol for the MARINE study lists these endpoints as secondary endpoints.

Efficacy- Lipid Parameters- MARINE

The following table summarizes the lipid changes across the three treatment arms.

Table 21: Median Percent Change from Baseline to Week 12 Endpoint Across Treatment Arms for Lipid Parameters- MARINE-ITT Population

Median Percent Change (Interquartile Range)	**Vascepa 2 g n=73**	**Vascepa 4 g n=76**	**Placebo n=75**	**Difference Vascepa 4g -Placebo**	**P-Value (Vascepa 4g vs. Placebo)**
Triglyceride	-7.0%	-26.6%	+9.7%	-33.1	<0.0001
LDL-C	-2.5%	-4.5%	-3.0%	-2.3	0.6768
Non-HDL-C	0.0%	-7.7%	+7.8%	-17.7	<0.0001
VLDL	0.0%	-19.5%	+13.7%	-28.6	0.0002
ApoB	+2.1%	-3.8%	+4.3%	-8.5	0.0019
HDL-C	0.0%	-3.5%	0.0%	-3.6	0.2174
Total Cholesterol	+0.7%	-7.3%	+7.7%	-16.3	<0.0001

Source: MARINE CSR, pg.71, 77, 79, 80, 82, 83.

As shown in the table above, both Vascepa 2 g and 4 g doses decreased TG without a concomitant increase in LDL-C. Relative to placebo, treatment with Vascepa 4 g decreased non-HDL-C, VLDL, ApoB, TC, and HDL-C

Relative to placebo, treatment with Vascepa 2 g resulted in neutral or increased levels of non-HDL-C, VLDL, ApoB, HDL-C and TC.

Triglycerides
The effect of Vascepa (AMR101) treatment on TG levels is summarized in the following table.

Table 22: Median Baseline and Percent Change from Baseline in TG Across Treatment Arms (ITT population)- MARINE

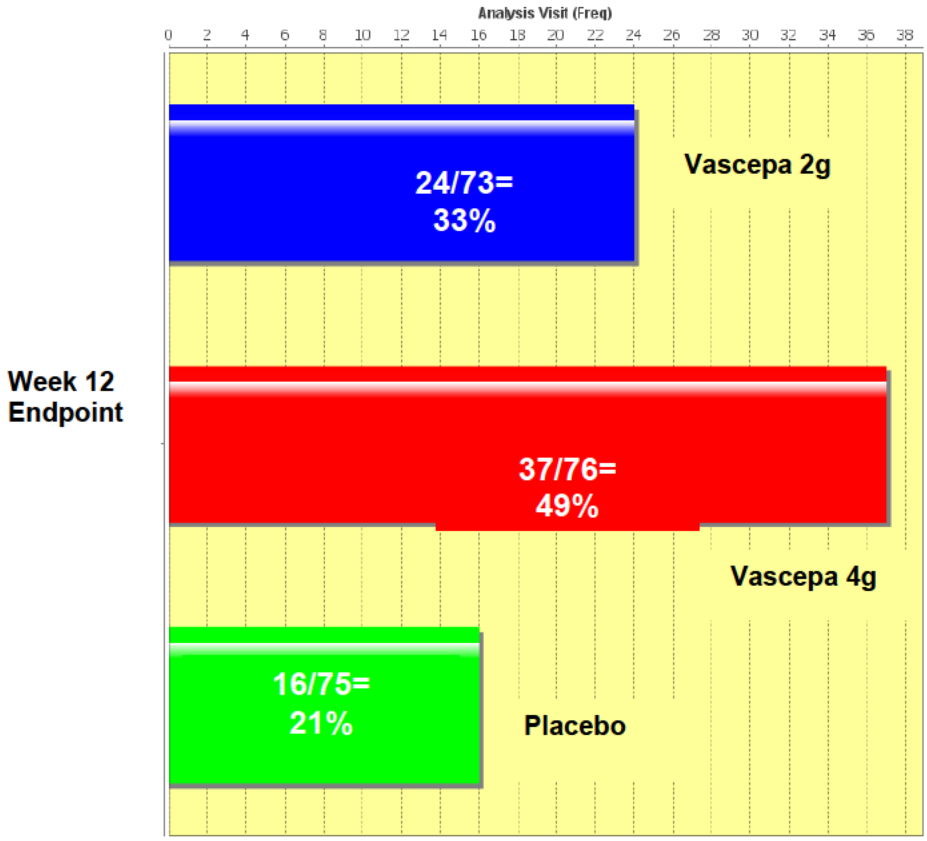
	Placebo n=75	**2 grams Vascepa n=73**	**4 grams Vascepa n=76**
Median Baseline TG	703 mg/dL	657 mg/dL	680 mg/dL
Median Week 12 Endpoint TG	746 mg/dL	606 mg/dL	502 mg/dL
Median Percent Change from Baseline	9.7%	-7.0%	-26.6%
Treatment Comparisons			
		Estimated Median	P-value
Vascepa 4g- Placebo		-33.1	<0.0001
Vascepa 2g- Placebo		-19.7	0.0051

Source: MARINE study report, Table 8, pg. 71.

Vascepa 4g was efficacious in reducing TG. The median percent change in TG from baseline to Week 12 endpoint was approximately -27% for the Vascepa 4g group, -7% for the Vascepa 2g group, and +10% for the Placebo group.

Although both the 2g and 4g doses of Vascepa reduced TG, the NCEP ATPIII treatment guidelines define treatment success as TG less than 500 mg/dL for patients with very high TG. The figure below shows the number of patients in the MARINE study who achieved a TG less than 500 mg/dL at Week 12 Endpoint.

Figure 8: Number of Patients at TG <500 mg/dL at Week 12 Endpoint by Treatment Arm-MARINE



The figure above shows the number of patients per treatment arm who achieved an endpoint TG of <500 mg/dL. By treatment arm, the numbers of patients achieving this level of TG were: 16 (21%) patients in the Placebo group; 24 (33%) patients in Vascepa 2g group, and 37 (49%) patients in the Vascepa 4g group.

The numbers of patients achieving this threshold TG was statistically similar between Vascepa 2g and Placebo (p=0.1395). However, in comparison to Placebo, Vascepa 4g had a statistically significant greater number of patients with TG <500 mg/dL (p=0018).

As shown in the following two figures, TG levels fluctuated in the Vascepa 2g and Placebo treatment arms, but after a maximum reduction at Week 4, were consistent in the Vascepa 4g treatment arm.

Figure 9: Mean Change from Baseline at Various Timepoints for TG (mg/dL) –ITT Population-MARINE

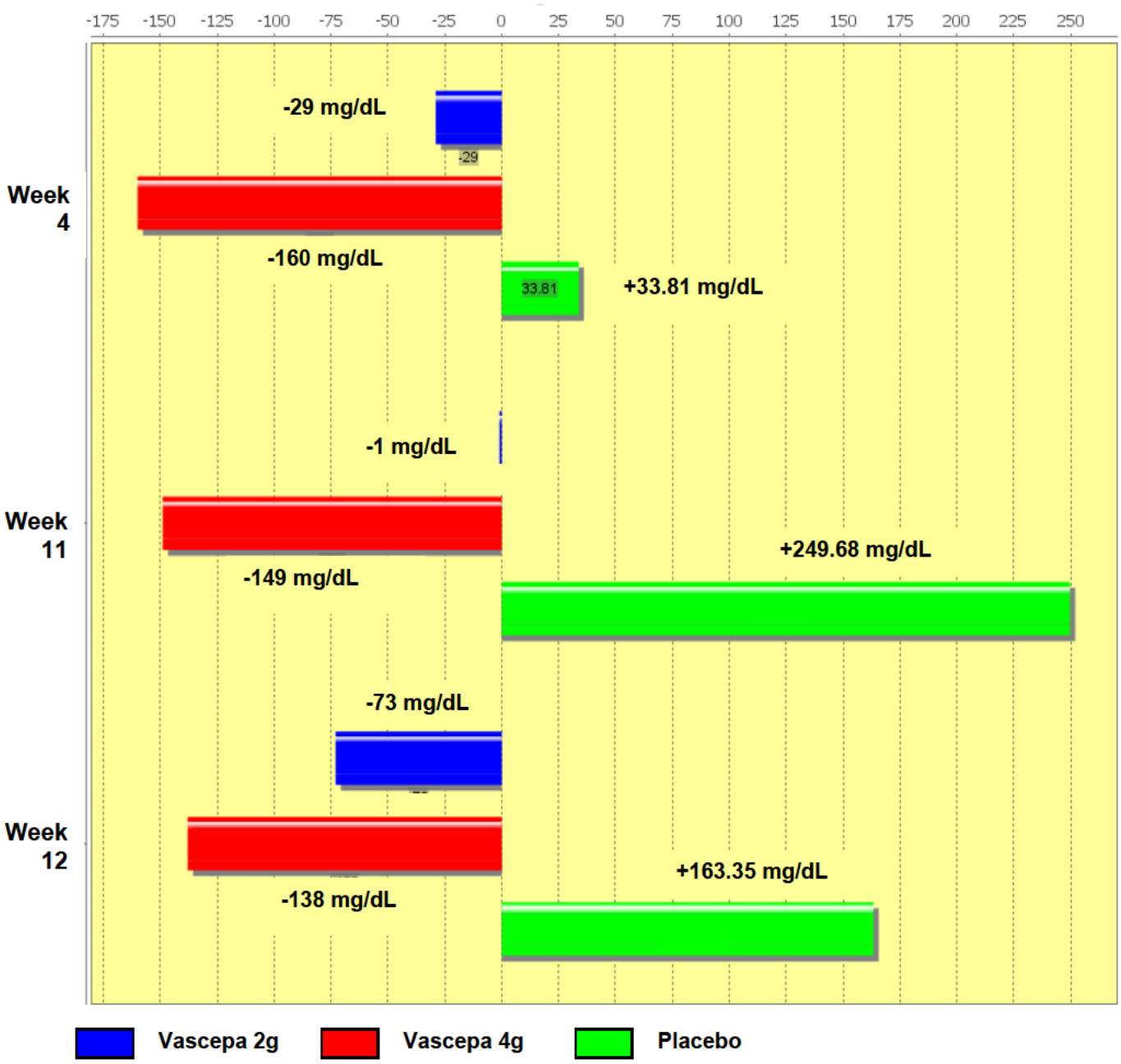
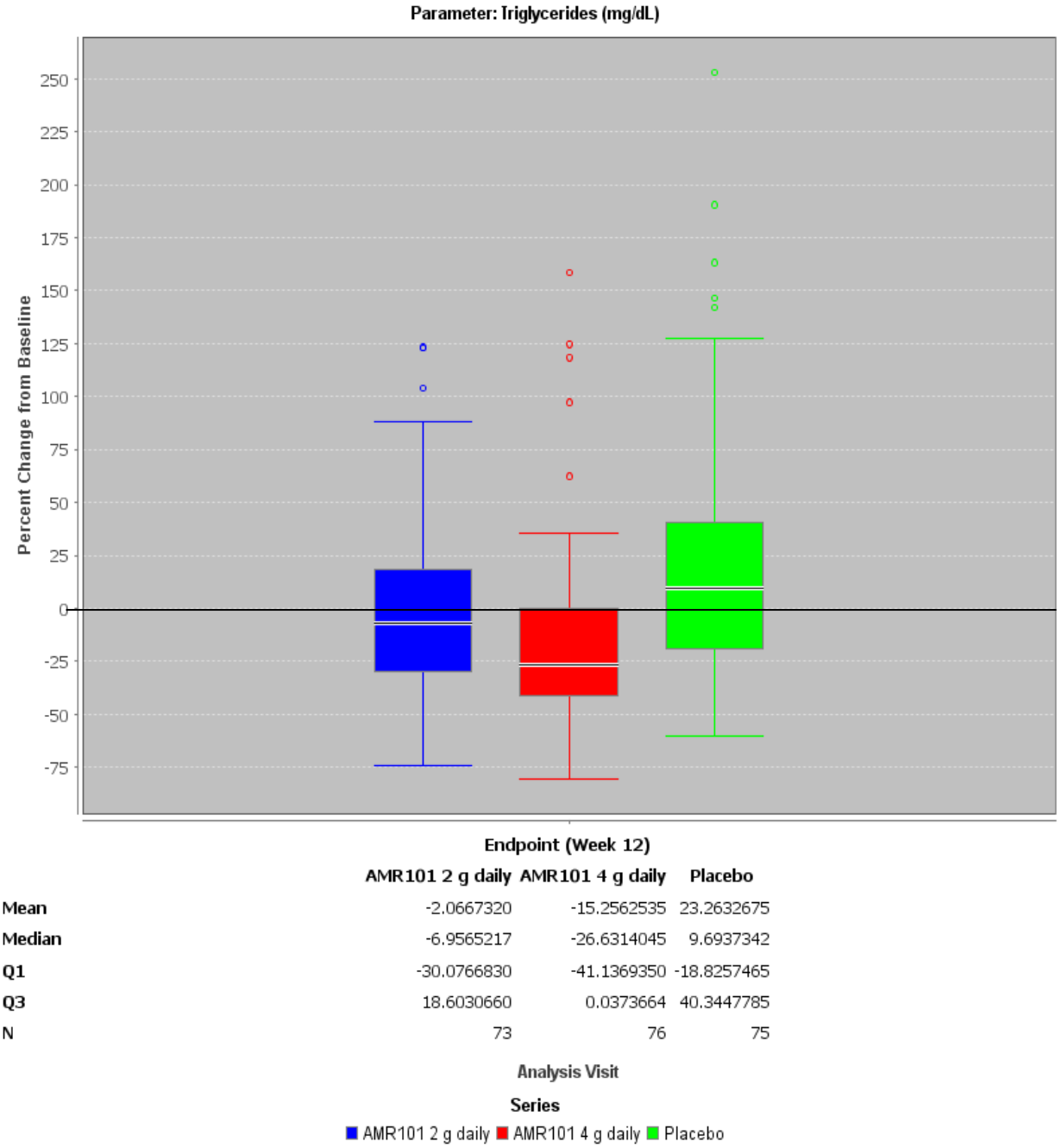
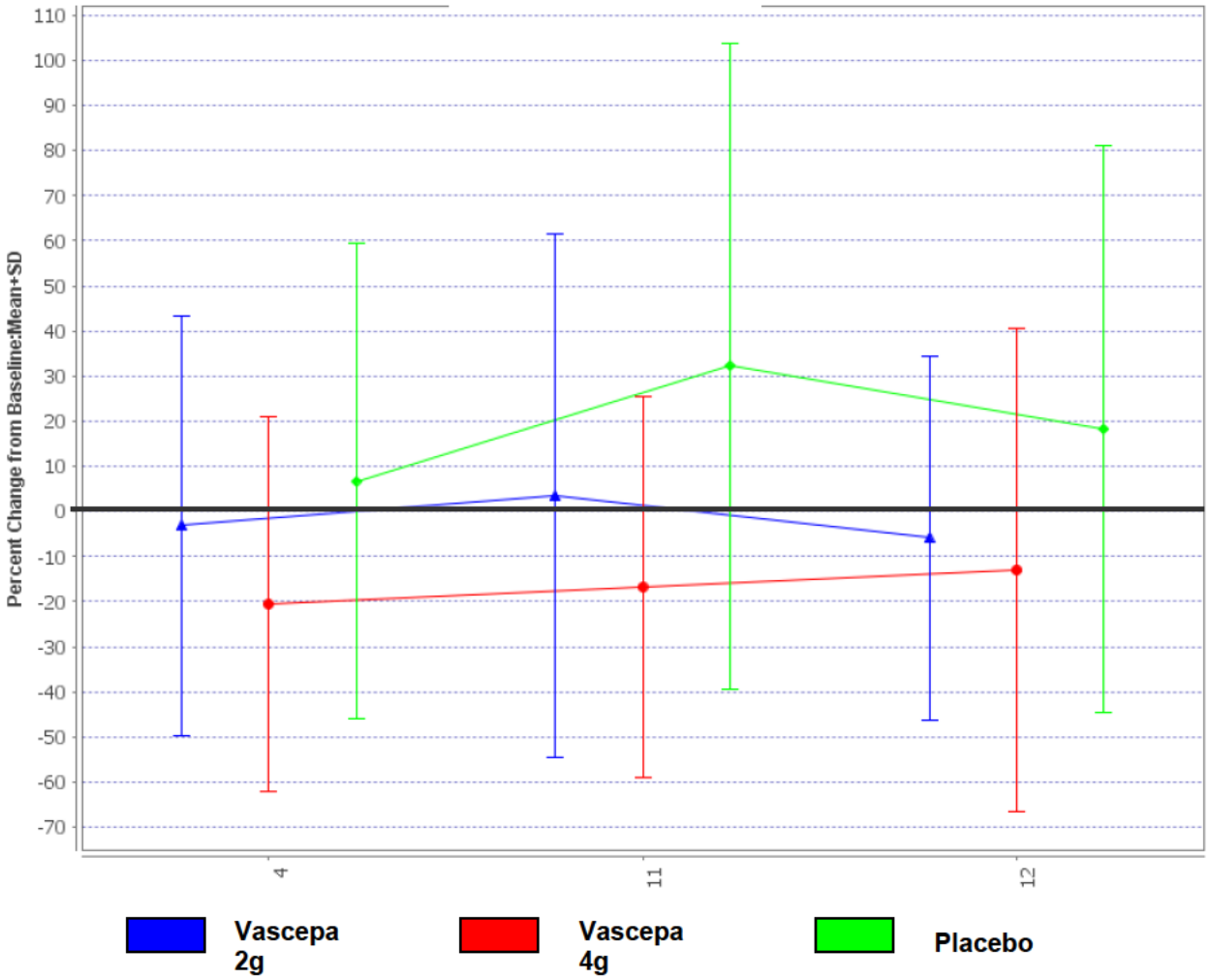


Figure 10: Mean and Median Percent Change in TG from Baseline to Endpoint-ITT Population-MARINE



	AMR101 2 g daily	AMR101 4 g daily	Placebo
Mean	-2.0667320	-15.2562535	23.2632675
Median	-6.9565217	-26.6314045	9.6937342
Q1	-30.0766830	-41.1369350	-18.8257465
Q3	18.6030660	0.0373664	40.3447785
N	73	76	75

Figure 11: Mean Percent Change From Baseline at Various Time points in TG- ITT Population- MARINE



In the following table, the mean percent change in TG from Baseline at Week 4, 11, and 12 are summarized by treatment arm.

Table 23: Mean Percent Change in TG at Various Time Intervals- ITT Population- MARINE

	Placebo N=75	Vascepa 2g N=73	Vascepa 4g N=76
Week 4	n=74	n=73	n=75
	+6.7%	-3.2%	-20.5%
Week 11	n=71	n=68	n=74
	+30.8%	+0.20%	-19.3%

	Placebo N=75	Vascepa 2g N=73	Vascepa 4g N=76
Week 12	n=69	n=70	n=73
	+20.0%	-9.8%	-17.8%

Reviewer Comment: Although the Vascepa 2g dose reduced TG, the potency of the dose was such that there were wide fluctuations in TG levels. By Week 11, the slight improvements in TG levels achieved at Week 4 were reduced back to almost the Baseline TG. Within one week (from Week 11 to Week 12) the mean percent change in TG changed from 0.20% to -9.78%. Wide fluctuations in TG were also observed in the Placebo group.

The Vascepa 4g dose reached maximum effectiveness by Week 4 and despite a slight decrease at Week 11 and Week 12, showed none of the wide fluctuations seen in Vascepa 2g or Placebo. This reviewer interprets this as a more potent effect of the Vascepa 4 g dose; i.e. the ability to eliminate the wide TG fluctuations seen in the Placebo group.

Because of the increase in TG seen with the Placebo group, this reviewer requested information from the applicant regarding the composition of the Placebo capsule and information as to the effect of the Placebo on TG levels.

The applicant responded in an email dated 21 March 2012 that the Placebo capsule used in all nonclinical and clinical studies was a light mineral oil. Light mineral oil is also referred to as ‘paraffin light liquid’. The sponsor submitted reference material that asserted light paraffin is inert because it contains hydrocarbon chains without functional groups (not fats, no carboxylic acid groups as in fatty acids). According to the applicant, light paraffin oil does not increase TG.

This reviewer examined the placebo results in Lovaza (NDA 22-363). The placebo results were similar to the ones seen in the current Vascepa NDA.

6.1.5 Analysis of Secondary Endpoints(s)

LDL-C
The effect of Vascepa (AMR101) treatment on LDL-C level is summarized in the following table.

Table 24: Median Baseline and Percent Change from Baseline in LDL-C Across Treatment Arms (ITT population)- MARINE

	Placebo n=75	2 grams Vascepa n=73	4 grams Vascepa n=76
Median Baseline LDL-C	86 mg/dL	84 mg/dL	91 mg/dL

	Placebo n=75	2 grams Vascepa n=73	4 grams Vascepa n=76
Median Week 12 Endpoint LDL-C	78 mg/dL	94 mg/dL	86 mg/dL
Median Percent Change from Baseline	-3.0%	-2.5%	-4.5%
Treatment Comparisons			
		Estimated Median, 95% CI	**P-value**
Vascepa 4g - Placebo		-2.3 (-12.9, 8.1)	0.677
Vascepa 2g - Placebo		+5.2 (-5.4, 15.6)	0.302

Source: MARINE CSR, Table 15, pg. 82.

Although the actual median Week 12 Endpoint LDL-C was higher (94 mg/dL) than Baseline (84 mg/dL), the applicant calculated the median percent change in LDL-C as -2.5% for the Vascepa 2g group.

Figure 12: Mean Change from Baseline at Various Intervals for LDL-C (mg/dL)- ITT Population-MARINE

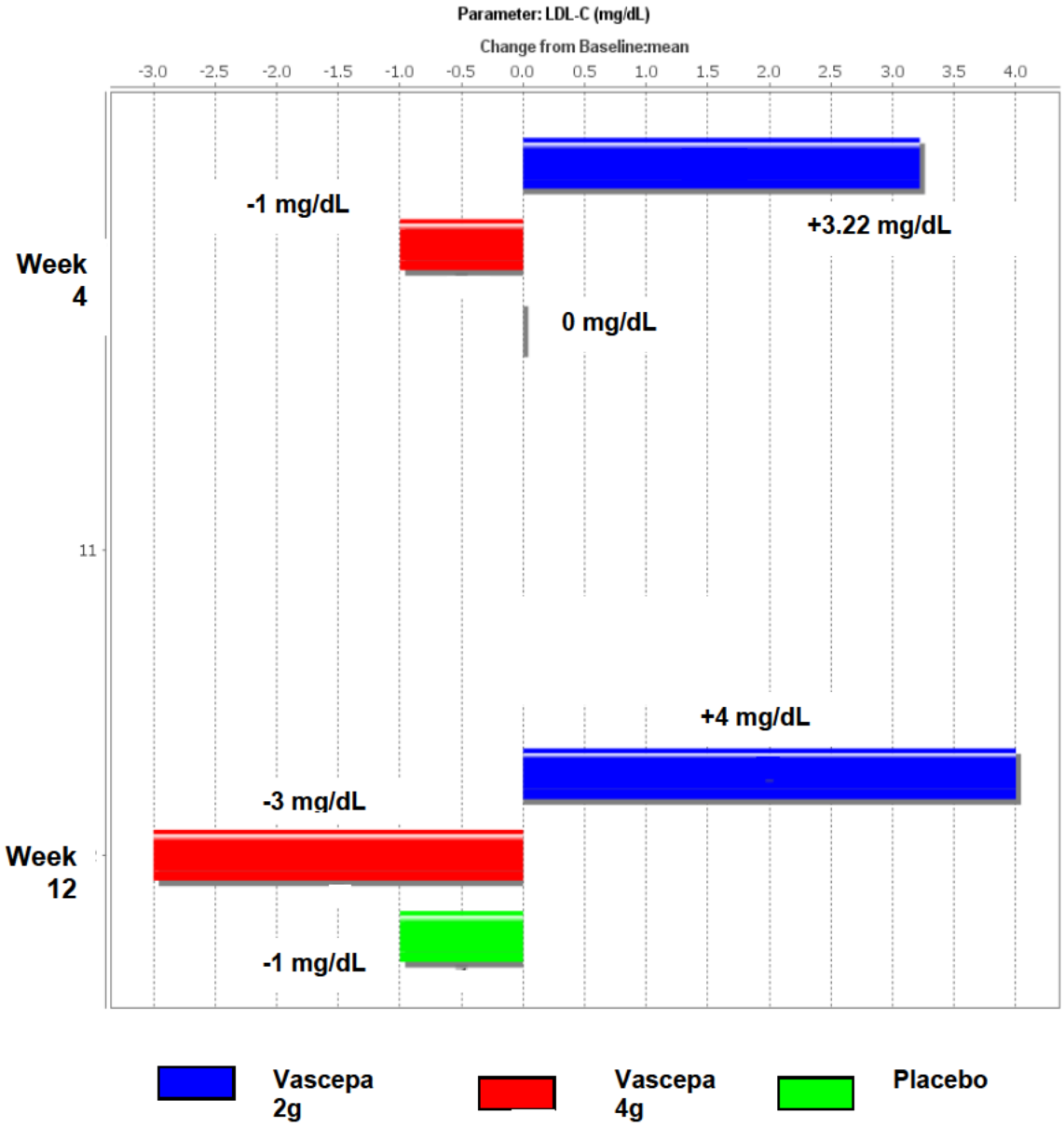


Table 25: Mean Percent Change in LDL-C at Various Intervals-ITT Population- MARINE

	Placebo N=75	Vascepa 2g N=73	Vascepa 4g N=76
Week 4	n=75	n=73	n=76
	+0.7%	+5.5%	+0.7%
Week 12	n=69	n=70	n=73
	+2.9%	+7.5%	-0.4%

Reviewer Comment: Vascepa 4g did not increase LDL-C levels, while Vascepa 2g increased LDL-C by 7.5%. The changes in LDL-C are not statistically significant compared to placebo.

LDL-C Particle Number

The median percent change in LDL particle number from baseline to Week 12 endpoint was -0.1% for the Vascepa 4 g group, 12.6% for the Vascepa 2 g group, and 14.4% for the Placebo group.

The estimate of the median of the treatment difference between the Vascepa 4g group and the Placebo group was -16.3%. This treatment difference was statistically significant (p=0.0006). The estimate of the median of the treatment difference between the Vascepa 2g group and the Placebo group was -1.1%. This treatment difference was not statistically significant.

Table 26: Comparison of LDL-C Particle Number (nmol/L) Across Treatment Arms from Baseline to Week 12 Endpoint- MARINE (ITT Population)

	Placebo n=53	**Vascepa 2g n=63**	**Vascepa 4g n=61**
Median Baseline LDL-C Particle Number	1310	1374	1418
Median Week 12 Endpoint LDL-C Particle Number	1452	1464	1419
Median Percent Change from Baseline (IQR)	14.4	12.6	-0.1
Treatment Comparisons			
		Estimated Median 95%CI	**p-value**
Vascepa 4g -Placebo		-16.3 (-25.3, -7.0)	0.0006
Vascepa 2g -Placebo		-1.1 (-10.5, +7.4)	0.8202

Source: MARINE CSR, Table 18, pg. 86.

Reviewer Comment: According to the calculations summarized in the table above, Vascepa 4g reduced the number of LDL-C particles compared to treatment with Placebo. Vascepa 2g did not show favorable changes.

LDL-C Particle Size

The following table shows the results of the changes in LDL-C particle size (nm) across the three treatment arms from Baseline to Week 12 Endpoint.

Table 27: Comparison of LDL-C Particle-Size (nm) Across Treatment Arms from Baseline to Week 12 Endpoint- MARINE- (ITT Population)

	Placebo n=53	**Vascepa 2g n=63**	**Vascepa 4g n=61**
Median Baseline LDL-C Particle Size	19.6	19.6	19.6
Median Week 12 Endpoint LDL-C Particle Size	19.6	19.6	19.7
Median Percent Change from Baseline	0	0	0
Treatment Comparison			
		Estimated Median, 95% CI	**p-value**
Vascepa 4g -Placebo		0.5 (-0.51, 1.03)	0.422
Vascepa 2g -Placebo		0 (-0.51, 0.51)	0.869

Reviewer Comment: Treatment comparisons between the two doses of Vascepa and Placebo did not show a statistical difference in LDL-C particle size.

Apo B

Table 28: Percent Change in Apo B (mg/dL) From Baseline to Week 12 Endpoint- MARINE- ITT Population

	Placebo n=73	**2 grams AMR101 n=70**	**4 grams AMR101 n=75**
Median Baseline ApoB	118 mg/dL	118 mg/dL	121 mg/dL
Median Week 12 Endpoint ApoB	122 mg/dL	117 mg/dL	117 mg/dL
Median Percent Change from Baseline	+4.3	+2.1	-3.8
Treatment Comparisons			
		Estimated Median, 95% CI	**P-value**
Vascepa 4g -Placebo		-8.5 (-13.5, -3.2)	0.0019

	Placebo n=73	2 grams AMR101 n=70	4 grams AMR101 n=75
Vascepa 2g- Placebo		-2.6 (-7.8, 1.9)	0.2367

Reviewer Comment: Treatment comparisons showed a statistically significant difference with Vascepa 4g and Placebo in reducing Apo B levels, but not with Vascepa 2g dose.

Non-HDL-C

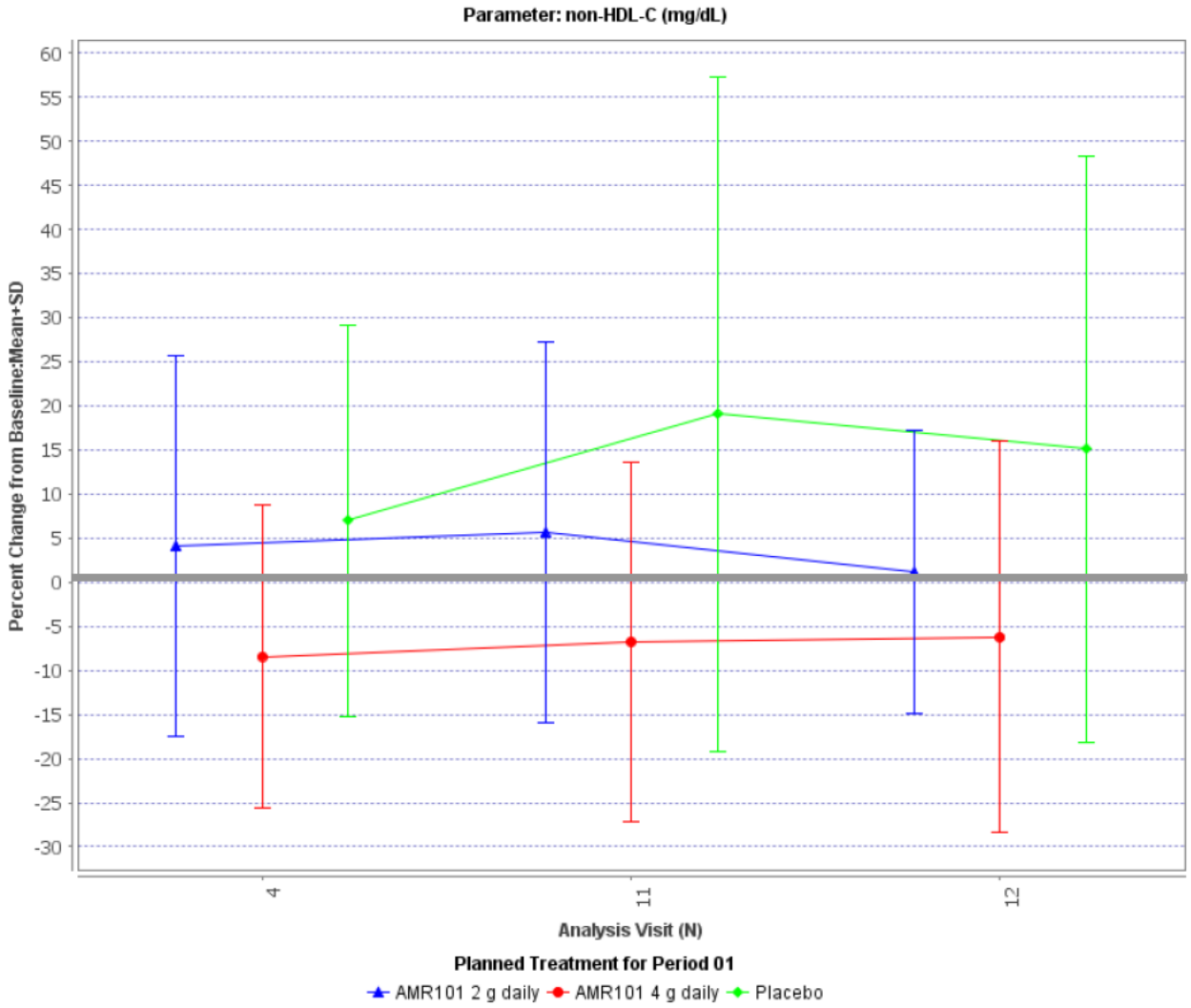
The following table summarizes the results for changes in non-HDL-C from Baseline to Week 12 Endpoint for the ITT population in MARINE. The median percent change in non-HDL-C from baseline to Week 12 endpoint was -7.7% for the Vascepa 4 g group, 0.0% for the Vascepa 2 g group, and 7.8% for the Placebo group.

Table 29: Percent Change in non-HDL-C (mg/dL) From Baseline to Week 12 Endpoint –ITT Population- MARINE

	Placebo n=75	2 grams Vascepa n=73	4 grams Vascepa n=76
Median Baseline non-HDL-C	229 mg/dL	210 mg/dL	225 mg/dL
Median Week 12 Endpoint non-HDL-C	243 mg/dL	214 mg/dL	206 mg/dL
Median Percent Change from Baseline	**7.8**	**0.0**	**-7.7**
Treatment Comparison			
	Estimated Median, 95% CI		**P-value**
Vascepa 4g - Placebo	**-17.7 (-25.0, -11.3)**		**<0.0001**
Vascepa 2g - Placebo	**-8.1 (-15.1, -1.4)**		**0.0182**

The following figure shows the mean percent change from Baseline in non-HDL-C for the three treatment arms. Vascepa 2 g increases non-HDL-C from Baseline at Week 4, but non-HDL-C levels decreases to Baseline at Week 12.

Figure 13: Mean Percent Change From Baseline at Various Timepoints in non-HDL-C – ITT Population- MARINE



HDL-C

The following table summarizes the results for percent change from Baseline to Week 12 Endpoint in HDL-C for the ITT population. Median baseline HDL-C levels were similar in the treatment groups. The median percent change in HDL-C from baseline to Week 12 endpoint was -3.5% for the Vascepa 4g group, 0.0% for the Vascepa 2g group, and 0.0% for the Placebo group.

Table 30: Median Percent Change in HDL-C (mg/dL) From Baseline to Week 12 Endpoint – ITT Population- MARINE

	Placebo n= 75	Vascepa 2 g n=73	Vascepa 4 g n=76
Median Baseline HDL-C	27 mg/dL	26 mg/dL	27 mg/dL
Median Week 12 Endpoint HDL-C	27 mg/dL	29 mg/dL	26 mg/dL
Median Percent Change from Baseline(IQR)	0% (21.54)	0% (26.58)	-3.5% (22.34)
		Treatment Comparison	
		Estimated Median, 95% CI	**p-value**
Vascepa 4g-Placebo		-3.6 (-9.1, 2.0)	0.2174
Vascepa 2g-Placebo		1.5 (-3.8, 7.8)	0.5225

Source: MARINE study report, Table 14; pg. 81.

Reviewer Comment: Neither Vascepa 4g or 2g dose resulted in favorable changes in HDL-C compared with Placebo.

6.1.6 Other Endpoints

hsCRP
The sponsor identified the change from Baseline to Week 12 in high sensitivity C-reactive protein (hsCRP) as an exploratory endpoint.

Median baseline hsCRP levels were 2.2 mg/L for the Vascepa 4g group, 2.0 mg/L for the Vascepa 2g group and 1.8 mg/L for the Placebo group. The median change in hsCRP from Baseline to Week 12 endpoint was -0.1 mg/L for the Vascepa 4g group, 0.4 mg/L for the Vascepa 2g group, and 0.5 mg/L for the Placebo group.

The estimate of the median of the treatment difference between the Vascepa 4 g group and the Placebo group was -0.7 mg/L. This treatment difference was statistically significant (p=0.0012). The estimate of the median of the treatment difference between the Vascepa 2g group and the Placebo group was -0.1 mg/L. This treatment difference was not statistically significant.

Fasting Plasma Glucose and HbA1c
Fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) were also identified by the sponsor as exploratory endpoints. The following table summarizes the changes in FPG from Baseline to Endpoint.

Table 31: Mean Change in Fasting Plasma Glucose (mg/dL) From Baseline to Week 12 Endpoint – ITT Population- MARINE

	Placebo N= 75	Vascepa 2 g N=73	Vascepa 4 g N=76
Number of Subjects	73	70	74
Mean Baseline Fasting Plasma Glucose (SD)	119.1 (38.4)	122.0 (41.0)	117.8 (32.5)
Mean Week 12 Endpoint Fasting Plasma Glucose (SD)	119.4 (31.5)	120.7 (36.2)	120.2 (29.3)
Change from Baseline	0.1 (-4.7, 5.0)	-0.4 (-5.4, 4.5)	1.8 (-3.0, 6.6)
Treatment Comparison			
		LS Mean, 95%CI	**P-Value**
Vascepa 4g-Placebo		1.6 (-5.2, 8.5)	0.6371
Vascepa 2g-Placebo		-0.6 (-7.5, 6.3)	0.8668

Source: MARINE CSR, Post-Text Table 14.2.39, pg. 336.

Table 32: Mean Change in Hemoglobin A1C (%) From Baseline to Week 12 Endpoint – ITT Population- MARINE

	Placebo N= 75	Vascepa 2 g N=73	Vascepa 4 g N=76
Number of Subjects	72	70	74
Mean Baseline HbA1c (SD)	6.13 (0.9)	6.25 (1.1)	6.21 (0.9)
Mean Week 12 Endpoint HbA1c (SD)	6.16 (0.9)	6.31 (1.2)	6.29 (0.9)
Change from Baseline			
Treatment Comparison			
		LS Mean, 95%CI	**P-Value**
Vascepa 4g-Placebo		0.03 (-0.09, 0.15)	0.605
Vascepa 2g-Placebo		0.04 (-0.07, 0.16)	0.456

Source: MARINE CSR, Post-Text Table 14.2.41, pg. 338.

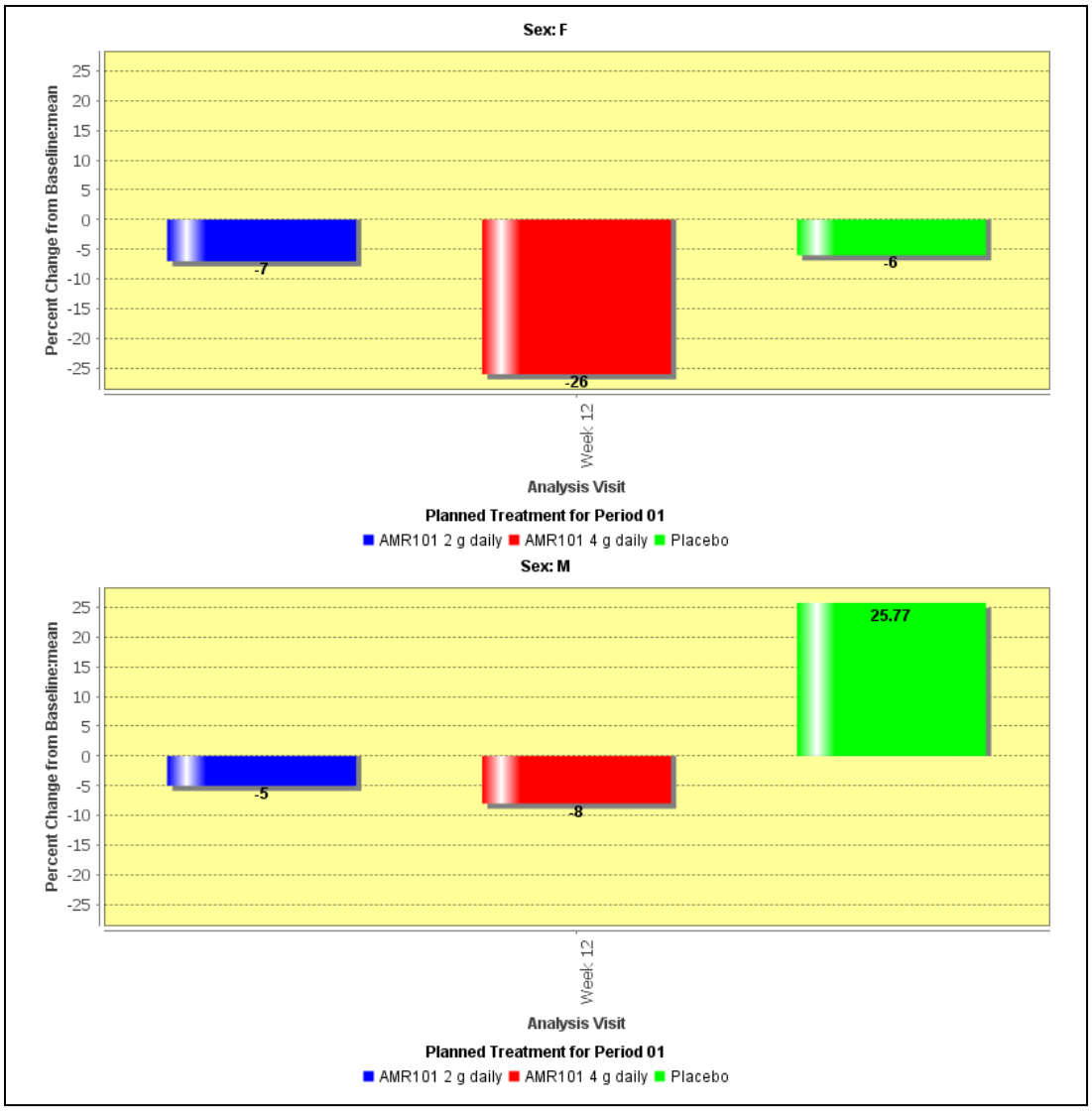
There were no statistically significant differences in FPG or HbA1c with Vascepa compared to Placebo.

6.1.7 Subpopulations

The statistical reviewer will conduct complete subgroup analyses. This clinical reviewer has limited the subgroup analysis to gender and race for the MARINE study.

Subgroup Analysis by Gender
The following figure shows the mean percent change in TG in men and women from Baseline to Endpoint.

Figure 14: Mean Percent Change in TG from Baseline to Endpoint by Gender- ITT Population-MARINE



Reviewer Comment: According to our analyses, the mean percent change in TG with Vascepa 4g was 26% in women as compared to 8% in men. However, the placebo subtracted treatment difference with Vascepa 4 g was -34% in men and -20% in women. The interaction P-value was 0.511 for the gender subgroup; thus, this difference was not statistically significant.

The applicant also conducted subgroup analyses by gender; the following is a table from the applicant's study report.

Table 33: Median Percent Change in TG (mg/dL) from Baseline to Week 12 Endpoint-by Gender –ITT Population- MARINE

Subgroup Statistics	Placebo	AMR101 2 g	AMR101 4 g
Males			
n [1]	57	56	58
Baseline [2]			
Median (IQR)	740.0 (427.0)	654.5 (289.3)	673.8 (262.5)
Week 12 endpoint [3]			
Median (IQR)	950.0 (946.0)	608.8 (462.0)	512.0 (383.0)
Percent change from baseline			
Median (IQR)	17.9 (56.2)	-3.4 (52.1)	-26.5 (46.7)
Q1 , Q3	-11.2 , 45.0	-30.7 , 21.4	-39.1 , 7.6
P-value for comparison to placebo [4]		0.0021	<0.0001
Females			
n [1]	18	17	18
Baseline [2]			
Median (IQR)	550.3 (148.0)	681.0 (287.5)	732.5 (257.0)
Week 12 endpoint [3]			
Median (IQR)	584.8 (251.5)	545.0 (257.0)	432.5 (303.0)
Percent change from baseline			
Median (IQR)	-8.6 (53.9)	-10.4 (38.5)	-27.4 (38.6)
Q1 , Q3	-28.2 , 25.7	-21.3 , 17.2	-49.3 , -10.7
P-value for comparison to placebo [4]		0.8560	0.0327

The median differences between the treatment groups were estimated with the Hodges-Lehmann method.

1. Only patients with non-missing baseline and Week 12 endpoint values are included.
2. Baseline was defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week -1] or if it occurred, Visit 3.1) measurements. If the measurement at 1 visit was missing, the other visit was used. If the measurements at both visits were missing, the last valid measurement prior to dosing with study drug was used as the baseline value.
3. The Week 12 endpoint was defined as the average of Visit 6 (Week 11) and Visit 7 (Week 12) measurements. If the measurement at 1 visit was missing, the other visit was used. If the measurements at both visits were missing, the last valid post-baseline measurement during the double-blind treatment period was used as the endpoint measurement.
4. P-value is from the Wilcoxon rank-sum test.

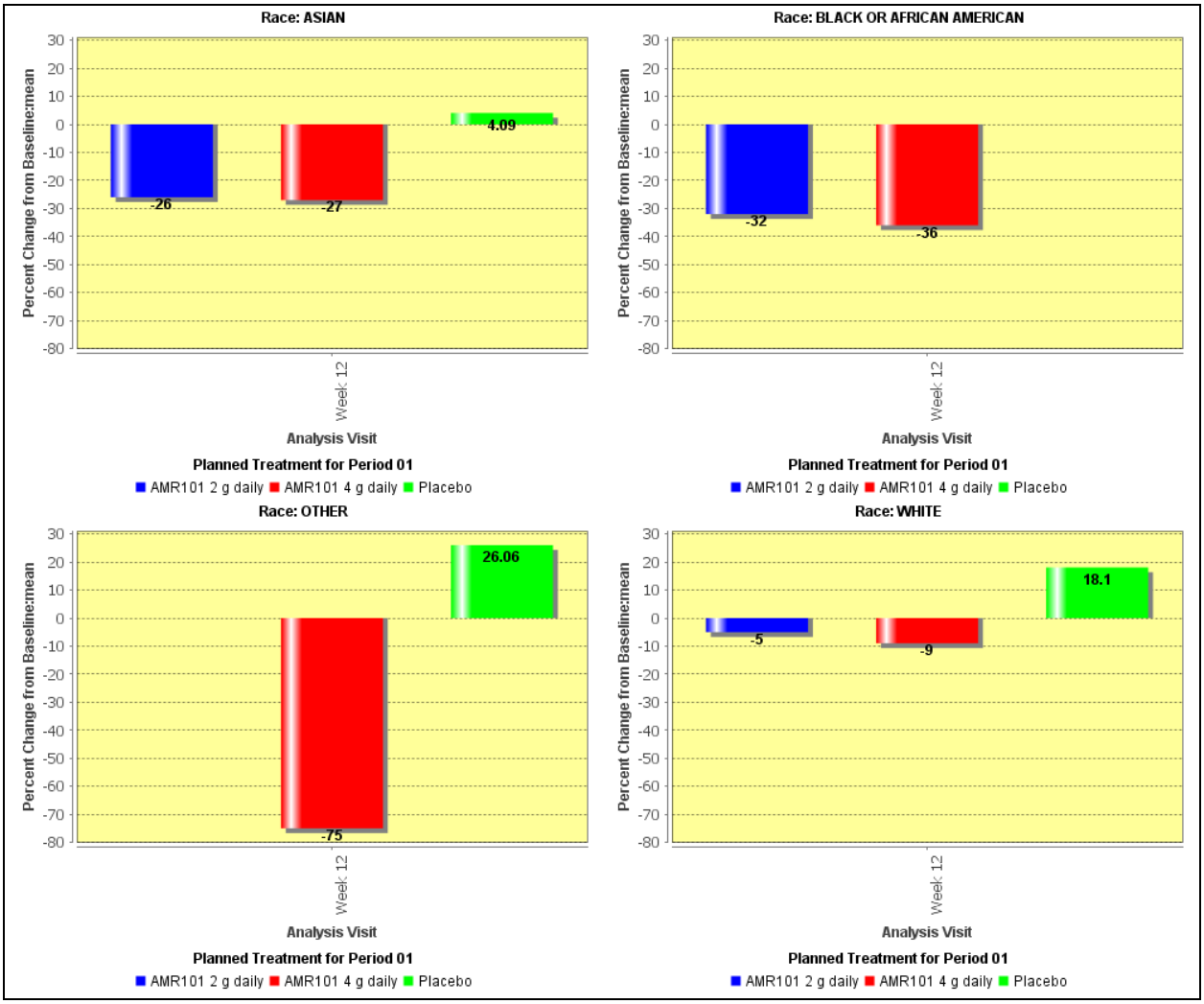
IQR = interquartile range; Q1 = first quartile; Q3 = third quartile.
Sources: Post-text Tables 14.2.84 and 14.2.85

Source: MARINE study report, Table 23, pg. 99.

Reviewer Comment: Median percent change from Baseline to Endpoint shows similar results for men and women with Vascepa 4 g. The small number of participants in the study precludes definitive conclusions.

Subgroup Analysis by Race

Figure 15: Percent Change in TG from Baseline to Endpoint by Race- ITT Population- MARINE



Reviewer Comment: The Asian and African American populations had numerically more favorable responses to Vascepa than the Caucasian population. Because of the small numbers of patients in the non-white subgroups, the results are not statistically significant.

Subgroup Analysis by Disease Severity
In the target population for this NDA (MARINE study), the applicant examined the dose response of Vascepa by disease severity. Patients were stratified by TG level, ≤ 750 mg/dL and > 750 mg/dL on enrollment into MARINE. Tables 39 and 40 below show the dose response of 2 g and 4 g Vascepa compared to Placebo based on disease severity.

In patients with baseline TG levels ≤750 mg/dL, median baseline TG levels were 565 mg/dL in the Placebo group, 568 mg/dL in the Vascepa 2 g group, and 614 mg/dL in the Vascepa 4 g group. The median percent change in TG from baseline to Week 12 was -27% for Vascepa 4 mg group, -7% for Vascepa 2 g group and +2.2% for the Placebo group.

The treatment difference between the Vascepa 4 g group and the Placebo group was -25.1% (p=0.0006). The treatment difference between the Vascepa 2 g group and the Placebo group was -9.1%. This treatment difference was not statistically significant (p=0.2816).

In patients with baseline TG levels >750 mg/dL, median baseline TG levels were 1052 mg/dL in the placebo group, 948 mg/dL in the Vascepa 2 g group, and 902 mg/dL in the Vascepa 4 g group. The median percent change in TG from baseline to Week 12 endpoint was -27% for the Vascepa 4 g group, -7% for the Vascepa 2 g group, and 19% for the Placebo group.

The treatment difference between the Vascepa 4 g group and the Placebo group was -45% (p=0.0001). The estimate of the median of the treatment difference between the Vascepa 2 g group and the Placebo group was -33% (p=0.0016).

Table 34: Median Percent Change in TG from Baseline to Week 12 Endpoint- ITT Population – Subgroup TG ≤750 mg/dL - MARINE

	Placebo N=75	**Vascepa 2g N=73**	**Vascepa 4g N=76**
	n=43	n=45	n=48
Baseline TG	565 mg/dL	568 mg/dL	614 mg/dL
Week 12 Endpoint	593 mg/dL	512 mg/dL	455 mg/dL
Median Percent Change from Baseline	+2%	-7%	-27%
Median Treatment Differences			
	Estimate, 95% CI	P-value	
Vascepa 4g-Placebo	-25%(-40, -11)	0.0006	
Vascepa 2g - Placebo	-9%(-29, 7.7)	0.2816	

Source: MARINE CSR, Post-Text Table 14.2.75, pg.387.

Table 35: Median Percent Change in TG from Baseline to Week 12 Endpoint- ITT Population -Subgroup > 750 mg/dL- MARINE

	Placebo N=75	**Vascepa 2g N=73**	**Vascepa 4g N=76**
	n=32	n=28	n=28
Baseline TG	1052 mg/dL	948 mg/dL	902 mg/dL
Week 12 Endpoint	1423 mg/dL	865 mg/dL	681 mg/dL
Median Percent Change from Baseline	+19%	-7%	-27%
Median Treatment Differences			
	Estimate, 95%CI	P-value	
Vascepa 4g-Placebo	-45%(-66, -25)	0.0016	
Vascepa 2g - Placebo	-33% (-55, -11)	0.0001	

Source: MARINE CSR, Post-Text Table 14.2.76, pg.387.

Reviewer Comment: The decrease in TG in the Vascepa 2g treatment arm was approximately 7% reduction from Baseline to Week 12 Endpoint in both the ≤750 mg/dL and >750 mg/dL TG subgroups.

The patients on Placebo in the ≤750 mg/dL and >750 mg/dL TG subgroups had very different TG changes. Those with TG ≤750 had a 2% increase in TG, while those in the >750 mg/dL group had a 19% increase in TG from Baseline to Week 12.

The decrease in TG in the Vascepa 4g treatment arm was approximately 27% from Baseline to Week 12 Endpoint in both the ≤750 mg/dL and >750 mg/dL TG subgroups.

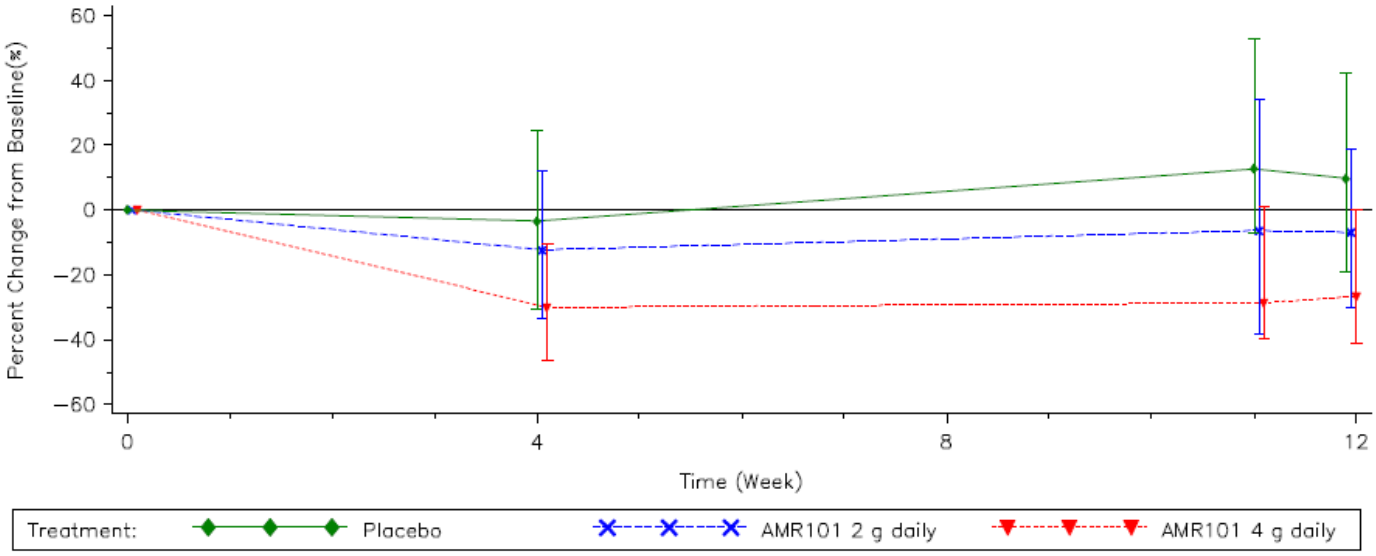
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Not applicable.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The open-label extension of MARINE with data up to 40 weeks was submitted as part of the 120 day update. However, as shown in the figure below, the maximum TG-lowering effect of 4 g Vascepa occurred by Week 4 and the effects were maintained throughout the study. The TG levels fluctuated with Vascepa 2g group and increased in the Placebo group.

Figure 16: Median Percent Change in Fasting TG from Baseline to Week 12 Endpoint- ITT Population



Vertical lines represent interquartile range (IQR).
Week 0 represents baseline. Baseline was defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week -1] or if it occurred, Visit 3.1) measurements. If the measurement at 1 visit was missing, the other visit was used. If the measurements at both visits were missing, the last valid measurement prior to dosing with study drug was used as the baseline value. The Week 12 endpoint was defined as the average of Visit 6 (Week 11) and Visit 7 (Week 12) measurements. If the measurement at 1 visit was missing, the other visit was used. If the measurements at both visits were missing, the last valid post-baseline measurement during the double-blind treatment period was used as the endpoint measurement.
Source: MARINE CSR Post-text Figure 14.2.2

6.1.10 Additional Efficacy Issues/Analyses

As part of the 74-Day Filing Letter, the applicant was requested to provide a rationale for assuming the applicability of foreign data in the submission to the US population.

The company responded by comparing the baseline demographic variables, study compliance, and efficacy results of the non-US and US populations in the MARINE study. The following table summarizes the baseline demographic variables in these populations.

Table 36: Comparison of Baseline Demographic Characteristics- US vs. Non-US (Randomized Population)- MARINE study

Characteristic	US (N = 77)	Non-US (N = 152)	Total (N = 229)	P-value [3]
Age (years)				
Mean (SD)	52.9 (9.56)	52.9 (9.26)	52.9 (9.34)	0.9711
Min – Max	27 – 72	30 – 79	27 – 79	
Age group (n, %)				
≤65 years	69 (89.6)	142 (93.4)	211 (92.1)	
>65 years	8 (10.4)	10 (6.6)	18 (7.9)	
Gender (n, %)				
Male	60 (77.9)	115 (75.7)	175 (76.4)	
Female	17 (22.1)	37 (24.3)	54 (23.6)	
Race (n, %)				
White	69 (89.6)	133 (87.5)	202 (88.2)	
Non-White	8 (10.4)	19 (12.5)	27 (11.8)	
Ethnicity (n, %)				
Not Hispanic or Latino	71 (92.2)	150 (98.7)	221 (96.5)	
Hispanic or Latino	6 (7.8)	2 (1.3)	8 (3.5)	
Use of statins at randomization (n, %)				
Not currently treated with statin therapy	58 (75.3)	114 (75.0)	172 (75.1)	
Currently treated with statin therapy	19 (24.7)	38 (25.0)	57 (24.9)	
Presence of diabetes (n, %)				
Present diabetes	20 (26.0)	43 (28.3)	63 (27.5)	
Past or no diabetes	57 (74.0)	109 (71.7)	166 (72.5)	
TG [1] (mg/dL)				
Mean (SD)	784.0 (328.8)	781.7 (389.2)	782.5 (369.3)	0.9653
Median	724.5	655.0	679.5	
TG group (n, %)				
≤750 mg/dL	44 (57.1)	95 (62.5)	139 (60.7)	
>750 mg/dL	33 (42.9)	57 (37.5)	90 (39.3)	
Apo B [2] (mg/dL)				
Mean (SD)	116.1 (26.4)	124.2 (31.5)	121.5 (30.1)	0.0533
Median	113.0	125.0	120.0	
Weight [2] (kg)				
Mean (SD)	94.6 (17.8)	91.9 (16.4)	92.8 (16.9)	0.2421
Min – Max	59.9 – 160.2	59.3 – 157.1	59.3 – 157.1	
Body mass index [2] (kg/m^2)				
Mean (SD)	31.3 (4.6)	30.5 (4.1)	30.8 (4.3)	0.1423
Min – Max	22.6 – 43.0	21.9 – 44.0	21.9 – 44.0	

1. Baseline was defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit (either Visit 3 [Week -1] or if it occurred, Visit 3.1) measurements. If the measurement at 1 visit was missing, the other visit was used. If the measurements at both visits were missing, the last valid measurement prior to dosing with study drug was used as the baseline value.
2. Baseline was defined as the Visit 4 (Week 0) visit. If missing, the last valid measurement prior to dosing with study drug was used as the baseline value.
3. two-sample t-test

Apo B = apolipoprotein B; Max = maximum; Min = minimum; SD = standard deviation; TG = triglyceride

In general, all variables listed are similar between the US and non-US patient subgroups. According to the applicant, the differences in age, baseline TG, baseline Apo B, and body mass index (BMI) were compared between both patient subgroups and were not significantly different in all tests performed (p>0.05).

Patient compliance was summarized using descriptive statistics in the table below.

Table 37: Comparison of Study Compliance- US vs. Non-US (Randomized Population)- MARINE

	US (N = 77)	Non-US (N = 152)	Total (N = 229)
Compliance (%)			
Mean (SD)	94.9 (15.3)	97.8 (7.9)	96.8 (11.0)
Median	99.0	100.0	100.0
Compliance Categories – n (%)			
<80%	8 (10.4)	5 (3.3)	13 (5.7)
80-120%	68 (88.3)	147 (96.7)	215 (93.9)
>120%	1 (1.3)	0 (0.0)	1 (0.4)

Compliance = 100 x (total no. of capsules dispensed - total no. of capsules returned)/(4 x (last visit date during double-blind period - first dose date). No. of capsules returned was imputed as 0 for subjects who did not return medication kits.

Table 38: Percent Change in TG (mg/dL) from Baseline to Week 12 Endpoint- Intent to Treat Population- US Patients

Treatment	n [1]	Baseline [2] Median (IQR)	Week 12 Endpoint [3] Median (IQR)	Percent Change From Baseline	
				Median (IQR)	(Q1 , Q3)
Placebo	25	816 (365)	1067 (803)	7.5 (49.6)	(-11 , 38)
Vascepa 2 g daily	25	614 (264)	545 (366)	0.2 (64.3)	(-31 , 33)
Vascepa 4 g daily	26	723 (252)	478 (419)	-26.1 (45.7)	(-44 , 1.4)

Treatment Comparison	Difference (Tmt 1 – Tmt 2)		
	Estimated Median	95% CI	p-value
Vascepa 4 g daily (Tmt 1) vs. placebo (Tmt 2)	-34.3	(-57 , -15)	0.0012
Vascepa 2 g daily (Tmt 1) vs. placebo (Tmt 2)	-12.4	(-41 , 11)	0.3224

The median differences between the treatment groups and 95% CIs were estimated with the Hodges-Lehmann method. P-value is from the Wilcoxon rank-sum test.
1. Only patients with non-missing baseline and Week 12 endpoint values were included.
Baseline was defined as the Visit 4 (Week 0) measurement. If missing, the last valid measurement prior to dosing with study drug was used as the baseline.
The Week 12 endpoint was defined as the Visit 7 (Week 12) measurement. If missing, the LOCF method was used.
CI = confidence interval; IQR = interquartile range; LOCF = last observation carried forward; Q1 = first quartile; Q3 = third quartile; Tmt = treatment.

Table 39: Percent Change in TG (mg/dL) from Baseline to Week 12 Endpoint- Intent to Treat Population -Non-US Population

Treatment	n [1]	Baseline [2] Median (IQR)	Week 12 Endpoint [3] Median (IQR)	Percent Change From Baseline	
				Median (IQR)	(Q1 , Q3)
Placebo	50	625 (310)	705 (853)	15.9 (63.5)	(-21 , 42)
Vascepa 2 g daily	48	669 (389)	616 (493)	-10.4 (45.2)	(-30 , 16)
Vascepa 4 g daily	50	664 (281)	510 (284)	-26.6 (39.8)	(-41 , -1.3)

Treatment Comparison	Difference (Tmt 1 – Tmt 2)		
	Estimated Median	95% CI	p-value
Vascepa 4 g daily (Tmt 1) vs. placebo (Tmt 2)	-31.9	(-49 , -16)	<0.0001
Vascepa 2 g daily (Tmt 1) vs. placebo (Tmt 2)	-22.2	(-39 , -5.1)	0.0096

The median differences between the treatment groups and 95% CIs were estimated with the Hodges-Lehmann method. P-value is from the Wilcoxon rank-sum test.
1. Only patients with non-missing baseline and Week 12 endpoint values were included.
Baseline was defined as the Visit 4 (Week 0) measurement. If missing, the last valid measurement prior to dosing with study drug was used as the baseline.
The Week 12 endpoint was defined as the Visit 7 (Week 12) measurement. If missing, the LOCF method was used.
CI = confidence interval; IQR = interquartile range; LOCF = last observation carried forward; Q1 = first quartile; Q3 = third quartile; Tmt = treatment.

7 Review of Safety

7.1 Methods

The applicant separated the safety data into four datasets:

- Healthy subjects
- Hypertriglyceridemic, Placebo-Controlled
- CNS Placebo-Controlled
- Overall AMR101 Integrated Dataset

The Healthy Subjects dataset included two clinical pharmacology studies, LA01.01.0009 and AMR—01-01-0018.

The Hypertriglyceridemic Placebo-Controlled dataset included the two trials (MARINE and ANCHOR) with hypertriglyceridemic/hyperlipidemic patient populations. Both trials were similar in design and duration. There were approximately 622 patients on Vascepa and 309 patients on Placebo in this dataset.

The CNS Placebo-Controlled dataset included information from the double-blind phases of the eight trials of patients with CNS disorders. There were approximately 700 patients on Vascepa and 519 patients on Placebo in this dataset.

The Overall AMR101 Integrated dataset included safety information obtained from all patients exposed to any dose of Vascepa in the Hypertriglyceridemic Placebo-Controlled dataset and the open-label and double-blind phases of the CNS Placebo-Controlled dataset. There were approximately 2,411 patients were in this dataset.

This safety review will focus on the Hypertriglyceridemia Placebo-Controlled dataset because the patient population of this dataset is most similar to the indication sought by the applicant.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 40: Clinical Trials Included in Integrated Summary of Safety

Study	Dose (g/day)	No. of Subjects	Key Inclusion Criteria	Dataset
AMR-01-01-0016 (MARINE): A Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study With an Open-Label Extension to Evaluate the Efficacy and Safety of Vascepa in Patients With Triglycerides ≥500 mg/dL and ≤2000 mg/dL	Vascepa 2 g Vascepa 4 g Placebo	76 77 76	Men or women >18 yrs and BMI ≤45 kg/m^2; Average fasting TG level ≥500 mg/dL and ≤2000 mg/dL at randomization; Patients on statin therapy (with or without ezetimibe) on stable dose for at least 4 weeks prior to randomization.	Hypertriglyceridemia Placebo-Controlled; Overall AMR101 Integrated
AMR 01-01-0017 (ANCHOR): A Phase 3, Multi-Center, Placebo-Controlled, Randomized, Double-Blind, 12-Week Study to Evaluate the Effect of Two Doses of AMR101 on Fasting Serum Triglyceride Levels in Patients With Persistent High Triglyceride Levels (≥200 mg/dL and <500 mg/dL) Despite Statin Therapy	Vascepa 2 g Vascepa 4 g Placebo	236 233 233	Men or women >18 yrs and BMI ≤45 kg/m2; High risk for CVD with fasting TG levels ≥200mg/dL and <500 mg/dL at randomization;. Patients on stable dose of statin therapy (with or without ezetimibe) at an optimal dose as evidenced by LDL-C ≥40 mg/dL and ≤115 mg/dL at randomization.	Hypertriglyceridemia Placebo-Controlled; Overall AMR101 Integrated
LA.01.01.001: A Multicentre, Double-Blind, Randomized, Parallel Group, Placebo Controlled, Dose Ranging Pilot Study of Ethyl	Vascepa 1 g Vascepa 2 g Vascepa 4 g Placebo	32 32 27 31	Men or women aged 18 - 65 yrs, inpatient or outpatient; Diagnosis of schizophrenia (DSM IV criteria) with minimum duration of 12 weeks after diagnosis, maximum duration of 20 years after diagnosis.	CNS Placebo-Controlled, Overall AMR101 Integrated

Study	Dose (g/day)	No. of Subjects	Key Inclusion Criteria	Dataset
Eicosapentaenoate (ETHYL-EPA) in Patients with Schizophrenia			Maintained on same neuroleptic for ≥12 weeks, at stable dose for ≥4 weeks.	
LA01.01.0002: A Multicentre, Double-Blind, Randomized, Parallel Group, Placebo-Controlled, Dose Ranging Pilot Study of Ethyl Eicosapentaenoate as Adjunct Therapy in Patients who Remain Depressed Following Treatment with Standard Antidepressant Therapy	Vascepa 1 g Vascepa 2 g Vascepa 4 g Placebo	17 18 17 18	Men or women 18 - 65 yrs with major depressive disorder resistant to standard antidepressant medication. Hamilton Depression Rating Score of at least 14 and received treatment with 1 or more standard antidepressant medications for at least 8 weeks with no change in therapy for at least 4 weeks prior to entry.	CNS Placebo-Controlled, Overall AMR101 Integrated
LA01.01.0005: A Multicentre, Multinational, Double-Blind, Randomized, Parallel Group, Placebo Controlled Study of Ethyl Eicosapentaenoate in Patients with Huntington's Disease	Vascepa 2 g Placebo	67 68	Men or women 30 - 70 yrs with Stage I or II Huntington's disease confirmed by either family history or genetic analysis.	CNS Placebo-Controlled, Overall AMR101 Integrated
LA01.01.0006: A Multicentre, Double-Blind, Randomized, Parallel Group, Placebo Controlled Trial of LAX-101 (ethyl eicosapentaenoate) as Adjunct Therapy in Patients who Remain Depressed Following Treatment with Standard Antidepressant Therapy	Vascepa 1 g Placebo	57 58	Men or women 18 - 75 yrs with major depressive disorder. Hamilton Depression Rating Score of at least 16 and received treatment with 1 or more standard antidepressant medications for at least 8 weeks with no change in therapy for at least 3 weeks prior to entry.	CNS Placebo-Controlled, Overall AMR101 Integrated
LA01.01.0008A: A Multicentre, Double-Blind, Randomized, Parallel Group, Placebo-Controlled, Dose Ranging Pilot Study of LAX-101 (ethyl-icosapentaenoate)	Vascepa 0.5g Vascepa 1 g Vascepa 2 g Placebo	19 20 18 20	Men or women 18 - 75 yrs with a major depressive disorder and Hamilton Depression Rating Score between 18 and 75, inclusive. No antidepressant medication in the12 weeks prior to screening	CNS Placebo-Controlled, Overall AMR101 Integrated

Study	Dose (g/day)	No. of Subjects	Key Inclusion Criteria	Dataset
in Patients with a New or Recurrent Episode of Depression				
AN01.01.0011: A Multi-Center, Double-Blind, Randomized, Parallel Group, Placebo-Controlled Trial of Ethyl-EPA (Miraxion™) in Subjects with Mild to Moderate Huntington's Disease (HD)	Vascepa 2 g Placebo	158 158	Men or women ≥35 yrs with family history and clinical features of Huntington's disease	CNS Placebo-Controlled, Overall AMR101 Integrated
AN01.01.0012: A Multicentre, Multinational, Double-Blind, Randomized, Parallel-Group, Placebo- Controlled Trial of Ethyl-EPA (Ethyl-Icosapent) in Patients with Huntington's Disease	Vascepa 2 g Placebo	147 143	Male or female patients ≥35 yrs with family history and clinical features of Huntington's disease	CNS Placebo-Controlled, Overall AMR101 Integrated
AN01.01.0014: A Single Centre, Double-Blind, Randomized, Parallel Group, Placebo Controlled Dose-Ranging Pilot Study of Ethyl-EPA in Subjects with Age Associated Memory Impairment (AAMI)	Vascepa 1 g Vascepa 2 g Vascepa 4 g Placebo	23 24 24 23	Men or women aged 50 - 70 yrs, BMI <29.5 mg/kg2, with self-reported complaints of memory loss, subjective and objective cognitive impairment with a score at least 1 SD below that of the mean for age-matched elderly population on the Paired Associated Learning subset of the Weschler Memory Scale. Diagnosis of major depressive disorder, Alzheimer's or vascular dementia as defined according to the MINI / DSM-IV Text Revision criteria.	CNS Placebo-Controlled, Overall AMR101 Integrated

7.1.2 Categorization of Adverse Events

This reviewer compared the reported AE term with the preferred terms used in the categorization of adverse events. In general the reported adverse event term was appropriately mapped to a reasonable preferred term. Coding for similar AEs, such as "Edema face" and "Edema in hands", was consistent (both mapped to "Oedema peripheral".

Table 41: Comparison of Reported Term for Adverse Event with the Dictionary- Derived Term -(MARINE)

Unique Subject Identifier	Reported Term for the Adverse Event	Dictionary-Derived Term
AMR-01-01-0016-255-005	WORSENING MENIERE'S DISEASE	MENIERE'S DISEASE
AMR-01-01-0016-255-006	BLISTER RIGHT HALLUX	BLISTER
AMR-01-01-0016-255-006	CYSTITIS	CYSTITIS
AMR-01-01-0016-255-006	CYSTITIS	CYSTITIS
AMR-01-01-0016-255-006	EDEMA FACE	FACE OEDEMA
AMR-01-01-0016-255-006	EDEMA FEET	OEDEMA PERIPHERAL
AMR-01-01-0016-255-006	EDEMA IN HANDS	OEDEMA PERIPHERAL
AMR-01-01-0016-255-006	ERYTHEMA RIGHT LEG	ERYTHEMA
AMR-01-01-0016-255-006	PRESSING FEELING ON THE CHEST	CHEST DISCOMFORT
AMR-01-01-0016-255-008	MUSCLEPAIN IN UPPERLEG AND BACK	MYALGIA
AMR-01-01-0016-255-008	SOFTENING FAECES	DIARRHOEA
AMR-01-01-0016-327-002	INCREASED PROPENSITY FOR BLEEDING DUE TO A SMALL CUT	HAEMORRHAGIC DIATHESIS
AMR-01-01-0016-327-002	NAUSEA	NAUSEA
AMR-01-01-0016-327-005	ANKLE PAIN	ARTHRALGIA
AMR-01-01-0016-327-005	BLEEDING IN THE MOUTH	MOUTH HAEMORRHAGE
AMR-01-01-0016-327-005	CONJUCTIVITIS	CONJUNCTIVITIS
AMR-01-01-0016-327-005	CONJUNCTIVITIS	CONJUNCTIVITIS
AMR-01-01-0016-327-005	CUT IN LEFT III FINGER	SKIN LACERATION
AMR-01-01-0016-327-005	FIRST DEGREE ATRIOVENTRICULAR BLOCK	ATRIOVENTRICULAR BLOCK FIRST DEGR
AMR-01-01-0016-327-005	NAUSEA	NAUSEA
AMR-01-01-0016-327-005	OVARIAN CYST (LEFT)	OVARIAN CYST
AMR-01-01-0016-327-005	SUNSTROKE	HEAT STROKE
AMR-01-01-0016-327-005	URINARY TRACT INFECTION	URINARY TRACT INFECTION
AMR-01-01-0016-327-005	VAGINITIS	VAGINAL INFECTION
AMR-01-01-0016-327-005	WORSENING OF TENDINITIS OF LEFT SHOULDER (WORSENING OF EXISTING CONDITION)	TENDONITIS
AMR-01-01-0016-327-006	UPPER RESPIRATORY TRACT INFECTION	UPPER RESPIRATORY TRACT INFECTION
AMR-01-01-0016-356-019	INCREASE OF CK	BLOOD CREATINE PHOSPHOKINASE INCR
AMR-01-01-0016-500-007	RAISED TRIGLYCERIDES LEVELS / HYPERTRIGLYCEREMIA	HYPERTRIGLYCERIDAEMIA
AMR-01-01-0016-500-014	SWOLLEN LEFT CHEEK	SWELLING FACE
AMR-01-01-0016-500-020	SPRAINED WRIST	JOINT SPRAIN
AMR-01-01-0016-501-003	TOOTH ABSCESS	TOOTH ABSCESS
AMR-01-01-0016-501-004	UPPER RESPIRATORY TRACT INFECTION	UPPER RESPIRATORY TRACT INFECTION
AMR-01-01-0016-501-007	INFLUENZA	INFLUENZA

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

This reviewer chose the Hypertriglyceridemia, Placebo-Controlled dataset to estimate the incidence of AEs for labeling purposes because it consisted of patients with lipid disorders.

However, the Overall AMR101 Integrated dataset was also reviewed because it consisted of all patients exposed to Vascepa, including the double-blind and open-label phases of the CNS trials.

7.2 Adequacy of Safety Assessments

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

Extent of exposure to study drug for the Hypertriglyceridemia, Placebo-Controlled dataset is summarized in the following table. The mean duration of exposure was 82 days for both the 2 g and 4 g Vascepa doses. Mean exposure for the placebo group was also similar at 82 days.

Table 42: Study Drug Exposure- Hypertriglyceridemic Placebo-Controlled Dataset (Safety)

	Placebo N=309	Vascepa Pooled N=622	Vascepa Daily Dose 2 g N=312	Vascepa Daily Dose 4 g N=310
Overall Exposure (days)				
Mean	81.6	82.1	82.0	82.2
Median	84.0	84.0	84.0	84.0
SD	13.9	13.2	12.6	13.8
Minimum	3	1	1	1
Maximum	98	100	100	98
Subject Years	69.0	139.8	70.0	69.8
Duration of treatment administration (n, %)				
1 to 28 days	8.(2.6)	16 (2.6)	7 (2.2)	9 (2.9)
29 to 42 days	7 (2.3)	5 (0.8)	3 (1.0)	2 (0.6)
43 to 84 days	184 (59.5)	381 (61.3)	199 (63.8)	182 (58.7)
85 to 112 days	110 (35.6)	220 (35.4)	103 (33.0)	117 (37.7)

SD = standard deviation
The Safety Analysis Set includes all enrolled patients who were administered at least one dose of study drug.
Overall exposure was calculated as (Date of last dose – Date of first dose) + 1.
Subject-years of exposure was defined as the sum of days of exposure/365.25.
Duration is based on maximum exposure; subjects appear in 1 category only.
Source: ISS Summary Table ISS.HT.5-1

Source: Clinical Summary of Safety, Table 2.7.4-2, pg. 23.

In the Overall AMR101 Integrated dataset, a total 1,683 patients were exposed to Vascepa and of these patients approximately 1,478 were either on the 2g or 4g doses of Vascepa (the to-be-marketed doses).

Table 43: Study Drug Exposure- Overall AMR101 Integrated Dataset

Overall Exposure (days)	Vascepa Pooled N=1683	Vascepa Daily Dose 0.5 g N=19	1 g N=186	2 g N=1100	4 g N=378
n	1683	19	186	1100	378
Mean	190.2	36.0	203.4	228.8	79.0
Median	88.0	42.0	88.0	176.0	84.0
SD	169.2	14.3	173.3	180.2	17.2
Minimum	1	5	9	1	1
Maximum	768	50	494	768	98
Subject Years	876.4	1.9	103.6	689.2	81.7
Duration of Treatment (n, %)					
1 to 28 days	43 (2.6)	4 (21.1)	8 (4.3)	22 (2.0)	9 (2.4)
29 to 42 days	110 (6.5)	8 (42.1)	34 (18.3)	38 (3.5)	30 (7.9)
43 to 84 days	465 (27.6)	7 (36.8)	30 (16.1)	234 (21.3)	194 (51.3)
85 to 112 days	368 (21.9)	0	35 (18.8)	188 (17.1)	145 (38.4)
113 to 140 days	14 (0.8)	0	0	14 (1.3)	0
141 to 168 days	39 (2.3)	0	0	39 (3.5)	0
169 to 196 days	110 (6.5)	0	2 (1.1)	108 (9.8)	0
197 to 224 days	34 (2.0)	0	2 (1.1)	32 (2.9)	0
225 to 252 days	8 (0.5)	0	0	8 (0.7)	0
253 to 280 days	15 (0.9)	0	2 (1.1)	13 (1.2)	0
281 to 308 days	23 (1.4)	0	2 (1.1)	21 (1.9)	0
309 to 336 days	33 (2.0)	0	1 (0.5)	32 (2.9)	0
337 to 364 days	84 (5.0)	0	11 (5.9)	73 (6.6)	0
> 364 days	337 (20.0)	0	59 (31.7)	278 (25.3)	0

SD = standard deviation
The Safety Analysis Set includes all enrolled patients who were administered at least one dose of study drug.
Overall exposure was calculated as: (Date of last dose – Date of first dose) + 1.
Subject-years of exposure was defined as the sum of days of exposure/365.25.
Duration is based on maximum exposure; subjects appear in 1 category only.
Source: ISS Summary Table ISS.0.5-1

Source: ISS, Table 4-4, pg. 33.

The mean duration of exposure to Vascepa (all doses) was 190.2 days. Patients on 2g of Vascepa had a mean duration of 229 days and those on 4g of Vascepa had a mean duration of 79 days. Approximately 337 patients exposed to Vascepa were on the drug for greater than 364 days (on the 1 mg dose).

Demographics

The following table summarizes the demographic characteristics of the patients in the Hypertriglyceridemia, Placebo-Controlled Dataset.

Table 44: Baseline Demographic, Hypertriglyceridemia Placebo-Controlled Integrated Dataset

Characteristic	Placebo N=309	Vascepa All Doses N=622	Vascepa 2 g N=312	Vascepa 4 g N=310	Total N=931
Age (years)					
Mean (SD)	59.3 (10.2)	59.3 (10.5)	59.7 (10.1)	58.8 (10.8)	59.3 (10.4)
Min-max	35-88	27-85	30-84	27-85	27-88
Age group (n,%)					
≤65 years	214 (69.3%)	418 (67.2%)	208 (66.7%)	210 (67.7%)	632 (67.9%)
>65 years	95 (30.7%)	204 (32.8%)	104 (33.3%)	100 (32.3%)	299 (32.1%)
Gender					
Male	203 (65.7%)	403 (64.8%)	202 (64.7%)	201 (64.8%)	606 (65.1%)
Female	106 (34.3%)	219 (35.25)	110 (35.3%)	109 (35.25%)	325 (34.9%)
Race n(%)					
White	292 (94.5%)	586 (94.2%)	293 (93.9%)	293 (94.5%)	878 (94.35)
African American	4 (1.3%)	13 (2.1%)	9 (2.9%)	4 (1.3%)	17 (1.8%)
Asian	8 (2.6%)	16 (2.6%)	6 (1.9%)	10 (3.2%)	24 (2.6%)
American Indian or Alaska Native	1 (0.35)	1 (0.2%)	1 (0.3%)	0	2 (0.2%)
Multiple	1 (0.3%)	2 (0.3%)	2 (0.6%)	0	3 (0.3%)
Other	3 (1.0%)	4 (0.6%)	1 (0.3%)	3 (1.0%)	7 (0.8%)
Weight (kg)					
Mean (SD)	96.02 (18.8)	94.42 (18.0)	94.66 (17.7)	94.18(18.3)	94.95 (18.2)
Min-max	58-157	54-160	55-144	54-160	54-160
BMI (kg/m2)					
Mean (SD)	32.5 (4.9)	32.3 (4.9)	32.4 (4.9)	32.1 (4.9)	32.3 (4.9)
Min-max	23-45	21-46	22- 45	21-46	21-46

Source: ISS, Table 5-2, pg. 37.

Mean age overall was 59 years, with a similar age distribution among the groups. Approximately 33% of patients in “Vascepa All Doses” were ≥65 years. Overall, the majority of patients were white (94.3%) and male (65.1%). The percentage of men was similar among the Vascepa and placebo groups, ranging from 64.7% to 65.7%. Racial distribution also was similar among the Vascepa and Placebo group.

The following table summarizes the demographic characteristics for patients included in the Overall AMR101 Integrated dataset.

Table 45: Baseline Demographics, Overall AMR101 Integrated Dataset

Characteristic	Vascepa All Doses N=1683	Vascepa 0.5g N=19	Vascepa 1 g N=186	Vascepa 2 g N=1100	Vascepa 4g N=378
Age (years)					
Mean (SD)	53.4 (12.2)	38.4 (11.8)	47.7 (13.4)	53.5 (11.4)	56.6 (12.2)
Min-max	18-85	18-59	18-72	19-84	20-85
Age group (n,%)					
≤65 years	1366 (81.2%)	19 (100%)	166 (89.2%)	908 (82.5%)	273 (72.2%)

Characteristic	Vascepa All Doses N=1683	Vascepa 0.5g N=19	Vascepa 1 g N=186	Vascepa 2 g N=1100	Vascepa 4g N=378
>65 years	317 (18.8%)	0	20 (10.8%)	192 (17.5%)	105 (27.8%)
Gender					
Male	896 (53.2%)	5 (26.3%)	64 (34.4%)	599 (54.5%)	228 (60.3%)
Female	787 (46.8%)	14 (73.7%)	122 (65.6%)	501 (45.5%)	150 (39.7%)
Race n(%)					
White	1605 (95.4%)	19 (100%)	179 (96.2%)	1049 (95.4%)	358 (94.7%)
African American	32 (1.9%)	0	2 (1.1%)	25 (2.3%)	5 (1.3%)
Asian	23 (1.4%)	0	3 (1.6%)	10 (0.9%)	10 (2.6%)
American Indian or Alaska Native	5 (0.3%)	0	0	5 (0.5%)	0
Multiple	4 (0.2%)	0	0	4 (0.4%)	0
Other	12 (0.7%)	0	2 (1.1%)	5 (0.5%)	5 (1.3%)
Weight (kg)					
Mean (SD)	81.5 (19.6)	76.9 (16.5)	77.6 (18.6)	78.4 (18.8)	91.4 (18.7)
Min-max	39-160	51-112	47-137	39-144	51-160
BMI (kg/m2)					
Mean (SD)	29.48 (6.7)	28.43 (7.7)	28.01 (6.7)	28.75 (7.2)	31.26 (5.2)
Min-max	15-139	19-43	17-49	15-139	19-46

Source: ISS, Table 5-5, pg. 44.

In the “Vascepa All Doses” category, approximately 53% of patients were men. The racial distribution was similar among the Vascepa pooled and the individual dose groups (95.4% of the pooled Vascepa patients were White).

7.2.2 Explorations for Dose Response

The applicant did not conduct dose response trials outside of their Phase 3 trial, the MARINE study.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

In the Hypertriglyceridemia Placebo-Controlled dataset, routine clinical testing was conducted at screening (week -8 to -6), week 0 (randomization), week 12 (end of treatment) and at any early termination visit. The tests conducted at these visits are summarized in the following table.

Table 46: Routine clinical tests- Hypertriglyceridemia Placebo-Controlled Dataset

Chemistry	
Alkaline phosphatase	Lactate dehydrogenase
ALT	Sodium
AST	Potassium
Total, direct, and indirect bilirubin	Albumin
Blood urea nitrogen	Total protein
Creatinine	Calcium
Creatine phosphokinase	Chloride
Bicarbonate	
Hematology	
Hemoglobin	Platelets
Hematocrit	Mean corpuscular volume
Red blood cell count	Mean corpuscular hemoglobin
White blood cell count and differential	Mean corpuscular hemoglobin concentration
Urinalysis	
pH	Bilirubin
Specific gravity	Blood
Protein	Nitrite
Glucose	Urobilinogen
Ketones	Leukocyte esterase

Source: Sponsor email, 2/24/2012.

In the Overall AMR101 Integrated Dataset, the following CNS studies had collection visits as described in the table below:

Table 47: Frequency of Clinical Testing CNS Trials- Overall AMR101 Integrated Dataset

Study	Collection visits	Open-label Extension
AN01.01.0011	Screening, Baseline, Month 6, Month 12	Month 24
AN01.01.0012	Baseline, Month 6	Month 12
AN01.01.0014	Screening	NA
LA01.01.0001	Baseline, Week 12 (termination)	NA
LA01.01.0002	Baseline, Week 12 (termination)	NA
LA01.01.0005	Baseline, Month 6, Month 12 (Termination)	NA
LA01.01.0006	Screening, Week 12 (termination)	NA
LA01.01.0008A	Baseline, Week 6 (termination)	NA

Source: Sponsor email, 2/24/2012.

Table 48: Routine Clinical Tests - CNS Trials of Overall AMR101 Integrated Dataset

	AN01.01.0011	AN01.01.0012	AN01.01.0014	LA01.01.0001	LA01.01.0002	LA01.01.0005	LA01.01.0006	LA01.01.0008
Red blood cell count	X	X	X	X	X	X	X	X
White blood cell (WBC) count	X	X	X	X	X	X	X	X
Packed cell volume (PCV)				X	X	X	X	X
Mean corpuscular volume (MCV)	X	X	X	X	X	X	X	X
Mean corpuscular hemoglobin (MCH)	X	X	X	X	X	X		X
Mean corpuscular hemoglobin concentration (MCHC)	X	X	X	X	X	X	X	X
Hematocrit	X							
Hemoglobin	X	X	X	X	X	X	X	X
Platelet count	X	X	X	X	X	X	X	X
Neutrophils (absolute value)	X	X	X	X	X	X	X	X
Lymphocytes (absolute value)	X	X	X	X	X	X	X	X
Monocytes (absolute value)	X	X	X	X	X	X	X	X
Eosinophils (absolute value)	X	X	X	X	X	X	X	X
Basophils	X	X	X	X	X	X	X	X

Source: Sponsor email, 2/24/2012.

Table 49: Routine Clinical Tests- CNS Trials of AMR101 Integrated Dataset

	AN01.01.0011	AN01.01.0012	AN01.01.0014	LA01.01.0001	LA01.01.0002	LA01.01.0005	LA01.01.0006	LA01.01.0008
Albumin	X	X	X	X		X	X	
Alkaline phosphatase (ALP)	X	X		X		X		
Alanine aminotransferase (ALT)	X	X	X	X	X	X	X	X
Aspartate aminotransferase (AST)	X	X	X	X	X	X	X	X
Gamma-Glutamyl transferase (GGT)	X	X		X	X	X	X	X
Creatinine	X		X	X	X	X	X	X
Glucose	X	X	X	X	X	X	X	X
HbA_{1c}	X	X		X	X	X	X	X
Total Cholesterol	X	X		X	X	X	X	X
Triglycerides	X	X		X	X	X	X	X
Sodium	X	X	X	X	X	X	X	X
Potassium	X	X	X	X	X	X	X	X
Bicarbonate			X					
Chloride	X							
Calcium	X	X						X
Magnesium	X	X						X
Total Bilirubin	X	X	X	X	X	X	X	X
Total Protein	X	X	X	X		X		X
Urea	X	X	X	X	X	X	X	X
C-reactive protein (CRP)	X	X						
Thyroid Stimulating Hormone (TSH) (Screening	X	X		X	X	X	X	X

Source: Sponsor email, 2/24/2012.

The applicant used the following laboratory threshold values to determine clinically significant highs and lows:

Table 50: Potentially Clinically Significant Chemistry and Hematology Threshold Values

Parameter	PCS Low	PCS High
Albumin	≤3.3 g/dL	≥5.8 g/dL
Alkaline Phosphatase	NA	>1 x ULN to 2 x ULN >2 x ULN to 3 x ULN >3 x ULN
ALT	NA	>1 x ULN to 2 x ULN >2 x ULN to 3 x ULN >3 x ULN)
AST	NA	>1 x ULN to 2 x ULN >2 x ULN to 3 x ULN >3 x ULN
Bilirubin	NA	>1 x ULN to 2 x ULN >2 x ULN to 3 x ULN >3 x ULN
ALT + Bilirubin	NA	>3 x ULN (ALT) + 2 x ULN (Bilirubin)
AST + Bilirubin	NA	>3 x ULN (AST) + 2 x ULN (Bilirubin)
Calcium	≤7 mg/dL	≥12 mg/dL
Creatinine	<0.5 mg/dL (Female) <0.65 mg/dL (Male)	>1.6 mg/dL (Female) >2.0 mg/dL (Male)
Creatine Kinase	NA	>1 x ULN to 5 x ULN >5 x ULN to 10 x ULN >10 x ULN
Glucose (fasting)	≤36 mg/dL	≥130 mg/dL
Magnesium	<1.5 mg/dL	>2.7 mg/dL
Potassium (K)	≤3.0 mEq/L	≥5.5 mEq/L
Sodium (Na)	≤130 mEq/L	≥150 mEq/L
Total Protein	<5.0 g/dL	≥9.5 g/dL
Blood urea nitrogen (BUN)	NA	≥31 mg/dL

Note: Values are given in terms of conventional units.
ALT = alanine aminotransferase; AST = aspartate aminotransferase; g/dL = grams per deciliter; mEq/L = milliequivalents per liter; mg/dL = milligrams per deciliter; NA = Not applicable; PCS = potentially clinically significant, ULN = upper limit of normal

Parameter	PCS Low	PCS High
Hemoglobin (Hb)	≤10.0 g/dL (Female) ≤10.0 g/dL (Male)	>16.5 g/dL >18.0 g/dL
Erythrocytes	≤3.5 x 10^6/µL (Female) ≤3.8 x 10^6/µL (Male)	>5.5 x 10^6/µL (Female) >6.0 x 10^6/µL (Male)
Leukocytes	≤1.5 x 10^3/µL	NA
Platelet count	≤100 x 10^3/µL	>500 x 10^3/µL

Note: Values are given in terms of SI units.
Abbreviations: g/dL = grams per deciliter; NA = Not Applicable; PCS = potentially clinically significant; µL = microliter

Source: ISS, Table 8-1 and 8-2. pg. 117.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to the Clinical Pharmacology review for the adequacy assessment of the in vitro and in vivo metabolism, excretion and drug-drug interaction testing.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Hemorrhagic diathesis
Omega-3 FA such as EPA and DHA can inhibit cyclo-oxygenase and thereby decrease platelet aggregation. [13] Platelet derived growth factor–like protein and syntheses of the platelet activation factor are also decreased with omega-3 FA.[14] Theoretically, it is possible that long-term dietary enrichment with omega-3 FA can increase the risk for bleeding.

Current prescribing information for Lovaza states:
"Some studies with omega-3-acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Clinical studies have not been done to thoroughly examine the effect of Lovaza and concomitant anticoagulants. Patients receiving treatment with Lovaza and an anticoagulant or other drug affecting coagulation should be monitored periodically (e.g., aspirin, NDAIDS, warfarin, coumarin)."

Post-marketing reports for Lovaza have identified bleeding complications or a "hemorrhagic diathesis" with the use of Lovaza.

The applicant conducted a 28-day study with 2g dose of Vascepa on healthy subjects. There was no statistically significant change in bleeding time in this study. However, it is questionable whether the study was long enough to see changes in bleeding time. According to case reports with Lovaza, the onset of apparent bleeding related AEs occur after several weeks to longer than one year of exposure.[15]

A clinical study to investigate the effect of Vascepa and concomitant aspirin therapy would have been helpful to ascertain bleeding risk.

13 Thorngren M et al. Effects of Acetylsalicylic Acid and Dietary Intervention on Primary Hemostasis. *Am J of Medicine* 1983; June 14: 66-71.
14 Bays HE et al, Safety Considerations with Omega-3 Fatty Acid Therapy. *Am J Cardiol* 2007; 99[supp]: 35C-43C.
15 GlaxoSmithKline, submission to FDA. Global Clinical Safety and Pharmacovigilance, Safety Evaluation and Risk Management: Lovaza-Hemorrhagic Diathesis 2008, pg. 7.

7.3 Major Safety Results

7.3.1 Deaths

A total of 3 deaths were reported in the studies submitted with this NDA. One death each occurred in a patient in the ANCHOR study, a Huntington's disease study, and in a Schizophrenia study (see table below).

Table 51: Listing of Deaths in Overall AMR101 Integrated Dataset

System Organ Class/ Preferred Term	Subject ID#/Study	Age/Gender	Treatment Group	Date of Onset of Event	Time since Start of Study
Cardiac Disorders/ Myocardial Infarction	AMR01.01.0017-057-046 (ANCHOR Study)	64 yo man	Placebo	25-Nov-2010	80 Days
Psychiatric Disorders/ Completed Suicide	AN01.01.0011-0028-3655/ Huntington Disease Study	54 yo man	2 g/day Vascepa	09-May-2006	139 Days
Injury, Poisoning and Procedural Complications/ Overdose (dothiepin)	LA01.01.0001-0004-4003/ Schizophrenia Study	48 yo man	1 g/day Vascepa	02-Jul-1999	39 Days (patients stopped drug 10 days prior to event)

Source: ISS, Table 7-20, pg. 97.

Subject: AMR01.01.0017-057-046
Study: ANCHOR (Hyperlipidemia Study)
Treatment: Placebo
Patient 057-046/JCR, a 65-year-old white male with a history of hypertriglyceridemia signed informed consent on 23-Jul-2010 and was randomized to Placebo on 07-Sep-2010. On [redacted] (b) (6) the patient's death notice was found in the newspaper by the site. It was noted that the patient had passed away [redacted] (b) (6) [redacted]). The death certificate noted myocardial infarction as the immediate cause of death and coronary artery disease, dyslipidemia, and type 2 diabetes mellitus as underlying conditions leading to the cause of death. The patient's medical history included alcohol use, type 2 diabetes, hypertension, metabolic syndrome, myopia,

tonsillitis, emphysema, basal cell cancer left side of neck with removal, pilonidal cyst with removal, obesity, bleeding gastric ulcer, chronic back pain, fractured left arm, insomnia, depression, anemia, blood transfusion, and tonsillectomy. Concomitant medications included sertraline, Advair, tiotropium bromide, omeprazole, metformin, aspirin, simvastatin, ferrous sulphate, lisinopril, and furosemide. The investigational medication was discontinued on an unknown date. The Investigator considered the event of myocardial infarction as severe and unrelated to investigational medication.

Subject: AN01.01.0011-0028-3655
Study: AN01.01.0011 (Huntington's Disease Study)
Treatment: 2 g/day Vascepa
[redacted] (b) (6) this 55-year-old Caucasian male committed suicide by shooting himself. The patient had been taking 2 g/day Vascepa since 22-Dec-2005 for a total of [redacted] (b) (6) The day before his death, his wife, during a counseling session, accused him of marital infidelity. That day, he wrote a suicide note detailing how he was going to kill his wife, his dog, and himself. At 19:45, he held his wife at gunpoint for approximately 12 hours. Once she had been released [redacted] (b) (6) the police were called and he committed suicide by shooting himself. It was noted that he had no known previous history of psychiatric problems or history of substance abuse. An autopsy was performed which showed evidence of Huntington's disease with no other underlying pathology. The event was considered serious since it resulted in a fatality. The patient had a history of difficulties with anger. At the time of the event he suffered from hypercholesterolemia. He also had a 3- to 5-week history of impaired concentration, becoming progressively withdrawn and expression of suicidal and homicidal ideations. Concomitant medications taken 2 weeks before the start of this event were haloperidol and atorvastatin calcium.

The Investigator considered this event to be possibly related to the study medication. Consequently, the Sponsor determined that the event was serious, unexpected (not in the Investigator's Brochure), and possibly related to the drug therapy (suspected unexpected serious adverse reaction [SUSAR]), requiring a 15-day unblinded report to the Food and Drug Administration (FDA), Health Canada and all other concerned Regulatory Authorities worldwide, plus a blinded SUSAR notification to all participating Investigators alerting them of this event. A follow-up report was later provided to Regulatory Authorities and all Investigators describing the autopsy results, which confirmed Huntington's disease.

Subject: LA01.01.0001-0004-4003
Study: LA01.01.0001 (Schizophrenia Study)
Treatment: 1 g/day Vascepa
This patient with a history of schizophrenia received study medication (1 g/day Vascepa) over a period of four weeks. As a result of changes to his psychotropic medication, the study drug was stopped. Ten days after stopping the study drug, the patient was admitted to the emergency department for an unknown reason. The patient

died that morning. Relevant concomitant medications at the time of the event were olanzapine, trifluoperazine, zopiclone, and dothiepin. An autopsy was performed, and a toxicology examination indicated a fatal dothiepin overdose. The Investigator considered the patient's death was unlikely to be related to the study medication.

Reviewer Comment: Based on review of the case narratives, the reported causes of death appear accurate.

7.3.2 Nonfatal Serious Adverse Events

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

Serious Adverse Events in the Hypertriglyceridemic Placebo-Controlled Dataset

The incidence of nonfatal SAEs was 2.9% in the "Vascepa Pooled" group and 1.6% in the Placebo group. There was no clear association with the dose of Vascepa and the development of any SAE. The following table includes all the nonfatal SAEs in the Hypertriglyceridemia Placebo-Controlled Integrated Dataset.

Table 52: All Treatment-Emergent SAEs, Hypertriglyceridemia Placebo-Controlled Integrated Dataset

SOC/PT	Placebo N=309 n (%)	Vascepa Pooled N=622 n (%)	Vascepa 2g N=312 n (%)	Vascepa 4 g N=310 n (%)
Any SOC	5 (1.6%)	18 (2.9%)	9 (2.9%)	9 (2.9%)
Cardiac Disorders	2 (0.6%)	5 (0.8%)	2 (0.6%)	3 (1.0%)
Coronary Artery Disease	1 (0.3%)	2 (0.3%)	1 (0.3%)	1 (0.3%)
Angina Unstable	0	1 (0.2%)	1 (0.3%)	0
Atrioventricular Block Complete	0	1 (0.2%)	0	1 (0.3%)
Cardiac Failure Congestive	0	1 (0.2%)	0	1 (.3%)
Bradycardia	1 (0.3%)	0	0	0
Myocardial Infarction	2 (0.6%)	0	0	00
General Disorders and Administration Site Conditions	0	5 (0.8%)	3 (1.0%)	2 (0.6%)
Non-Cardiac Chest Pain	0	5 (0.8%)	3 (1.0%)	2 (0.6%)

SOC/PT	Placebo N=309 n (%)	Vascepa Pooled N=622 n (%)	Vascepa 2g N=312 n (%)	Vascepa 4 g N=310 n (%)
Nervous System Disorders	1 (0.3%)	3 (0.5%)	1 (0.3%)	2 (0.6%)
Subarachnoid Haemorrhage	0	2 (0.3%)	1 (0.3%)	1 (0.3%)
Presyncope	0	1 (0.2%)	0	1 (0.3%)
Ruptured Cerebral Aneurysm	0	1 (0.2%)	0	1 (0.3%)
Syncope	0	1 (0.2%)	1 (0.3%)	0
Lumbar Radiculopathy	1 (0.3%)	0	0	0
Gastrointestinal Disorders	0	1 (0.2%)	1 (0.3%)	0
Abdominal Pain Upper	0	1 (0.2%)	1 (0.3%)	0
Infections and Infestations	1 (0.3%)	1 (0.2%)	0	1 (0.3%)
Herpes Zoster	0	1 (0.2%)	0	1 (0.3%)
Clostridium Difficile Colitis	1 (0.3%)	0	0	0
Injury, Poisoning and Procedural Complications	0	1 (0.2%)	1 (0.3%)	0
Subdural Haematoma	0	1 (0.2%)	1 (0.3%)	0
Metabolism and Nutrition Disorders	0	1 (0.2%)	1 (0.3%)	0
Diabetes Mellitus	0	1 (0.2%)	1 (0.3%)	0
Musculoskeletal and Connective Tissue Disorder	1 (0.3%)	1 (0.2%)	1 (0.3%)	0
Arthralgia	0	1 (0.2%)	1 (0.3%)	0
Spondylolosthesis	1 (0.3%)	0	0	0
Neoplasms Benign, Malignant and Unspecified	1 (0.3%)	1 (0.2%)	1 (0.3%)	0
Breast Cancer In Situ	0	1 (0.2%)	1 (0.3%)	0
Multiple Myeloma	1 (0.3%)	0	0	0
Respiratory, Thoracic and Mediastinal Disorders	0	1 (0.2%)	0	1 (0.3%)

SOC/PT	Placebo N=309 n (%)	Vascepa Pooled N=622 n (%)	Vascepa 2g N=312 n (%)	Vascepa 4 g N=310 n (%)
Chronic Obstructive Pulmonary Disease	0	1 (0.2%)	0	1 (0.3%)

Source: ISS Table.HT.6.2-1, pg.690.

SAEs which occurred in ≥ 2 patients in the Vascepa Pooled group as compared to Placebo are summarized in the following table.

Table 53: Serious Adverse Events Which Occurred in ≥ 2 More Patients in the Vascepa (AMR101) Overall Group than Placebo by SOC

SOC/PT	Placebo N=309 n (%)	Vascepa Pooled N=622 n (%)
Cardiac Disorders	2 (0.6%)	5 (0.8%)
Coronary Artery Disease	1 (0.3%)	2 (0.3%)
General Disorders and Administration Site Conditions	0	5 (0.8%)
Non-cardiac Chest Pain	0	5 (0.8%)
Nervous System Disorders	1 (0.3%)	3 (0.5%)
Subarachnoid Hemorrhage	0	2 (0.3%)

As summarized in the above table, the most frequent SAEs occurred in the Cardiovascular, General Disorders and Administrative Site Conditions, and Nervous System Disorders. The most frequent preferred terms under these three SOCs were coronary artery disease (0.3%), non-cardiac chest pain (0.8%), and subarachnoid hemorrhage (0.3%).

Reviewer Comment: All individual SAEs occurred infrequently. The complete study report for the MARINE and ANCHOR trials were searched for additional cases of coronary artery disease, non-cardiac chest pain and subarachnoid hemorrhage and none were found. In addition to the two SAEs of subarachnoid hemorrhage, a search of the literature elicited no reports of subarachnoid hemorrhage in patients taking fish oil products. Bleeding-related AEs are discussed further in Section 7.3.5.

Narratives for SAEs related to coronary artery disease, non-cardiac chest pain, and subarachnoid hemorrhage

This reviewer examined the case narratives for coronary artery disease, non-cardiac chest pain, and subarachnoid hemorrhage.

Patient 533-006/RSR: coronary artery disease – single vessel disease (diffuse LAD disease)- MARINE study

Patient 533-006/RSR, a 51-year-old Asian male with a history of hypertriglyceridemia, signed informed consent on 13-Apr-2010 and was **randomized to AMR101 4 g daily** 14-Jun-2010. On (b) (6) (22-Aug-2010), the patient developed dyspnea and exertional angina. (b) (6) (23-Aug-2010), an echocardiogram revealed mild concentric left ventricular hypertrophy, normal left ventricular systolic function, a left ventricular ejection fraction of 57%, trivial mitral regurgitation, and mild aortic regurgitation. On that same date, the patient underwent a cardiac stress test, which was positive at "5." On (b) (6) the patient was admitted to the hospital for evaluation and treatment. On (b) (6) a coronary angiography revealed plaque in the proximal left anterior descending (LAD) coronary artery, 60-70% stenosis of the middle LAD coronary artery, 60% stenosis of the distal LAD coronary artery, 30% stenosis of the proximal and middle right coronary artery, and left ventricular ejection fraction of 60%. Treatment of the event included isosorbide dinitrate, lisinopril, isosorbide mononitrate, and clopidogrel at the time of discharge. The patient's medical history includes hypertension, type 2 diabetes mellitus, low level of high density lipoprotein cholesterol, triglyceride level >2000 mg/dL, and diabetic neuropathy. Concomitant medications included amlodipine besylate, metoprolol tartrate, metoprolol succinate, aspirin, metformin, glibenclamide, 30% soluble insulin and 70% isophane insulin, pregabalin, and atorvastatin. The investigational medication was continued. The patient recovered with sequelae from the event of coronary artery disease-single vessel disease (diffuse LAD disease) and was discharged from the hospital (b) (6) The Investigator considered the event of coronary artery disease-single vessel disease (diffuse LAD disease) as moderate and unrelated to investigational medication.

Patient 057-007/BAC: worsening coronary artery disease, myocardial infarction-ANCHOR study

Patient 057-007/BAC, a 66-year-old white male with a history of hypertriglyceridemia and coronary artery disease, signed informed consent on 05-Feb-2010 and was **randomized to Placebo** on 22-Mar-2010. (b) (6) the patient developed shortness of breath with exertion and cardiac chest pain. The patient completed investigational medication dosing per protocol on (b) (6) , at the final study visit, the patient reported a worsening of

shortness of breath and chest pain and was referred and admitted to the hospital for evaluation and treatment. The patient was initially ruled out for an acute myocardial infarction and underwent stress testing which was **suggestive of ischemia** on the electrocardiogram (ECG) portion. Cardiology was consulted and the patient underwent a cardiac catheterization which revealed **coronary artery disease in the left main coronary artery and saphenous vein graft to second obtuse marginal coronary artery which needed stenting**. The patient was diagnosed with a worsening of coronary artery disease. [redacted] (b) (6) the patient was discharged and recommended to return for a follow-up cardiac catheterization with stent placement. On [redacted] (b) (6) the patient presented to the hospital with continuing exertional chest pain. Laboratory testing revealed an elevated troponin level (value unknown) and the patient was subsequently diagnosed with a **non ST segment elevation myocardial infarction**. [redacted] (b) (6), the patient was admitted to the hospital and underwent a coronary angiogram with angioplasty and stent placement to the left anterior descending artery (LAD), proximal LAD, and saphenous vein graft to circumflex artery. The patient tolerated the procedure well. [redacted] (b) (6), a follow up echocardiogram revealed that the basal inferior wall and mid posterior wall were akinetic (findings consistent with coronary artery disease) and an ejection fraction of 55%. The patient's medical history included asymptomatic bradycardia, stable angina, bypass surgery, hypertension, metabolic syndrome, myopia, presbyopia, tinnitus, tonsillitis, heart murmur, leaking aortic valve with replacement (multiple episodes), pilonidal cyst with cystectomy (multiple episodes), gastroesophageal reflux disease, intermittent constipation, arthritis of the right knee, fractured left leg, depression, restless leg syndrome, insomnia, seizure, appendicitis with appendectomy, tonsillectomy, dyslipidemia, and allergy to sulfa. Concomitant medications included aspirin, metoprolol, dipyridamole/aspirin, baclofen, temazepam, simvastatin, vitamin C, Vicodin, ropinirole, omeprazole, lamotrigine, hydrochlorothiazide, etodolac, docusate, and bupropion HCL. The patient recovered from the events of worsening coronary artery disease and myocardial infarction [redacted] (b) (6) was discharged from the second hospitalization [redacted] (b) (6). The Investigator considered the events of worsening coronary artery disease and myocardial infarction as moderate and unrelated to investigational medication.

<u>Patient 047-019/SAE: worsening coronary artery disease- ANCHOR study</u>

Patient 047-019/SAE, a 53-year-old white female with a history of hypertriglyceridemia and coronary artery disease, signed informed consent on 15-Apr-2010. On 24-May-2010, the patient presented to the primary care physician's office with complaints of increasing cardiac chest pain and shortness of breath. The patient was **randomized to AMR101 2 g daily** on 01-Jun-2010. [redacted] (b) (6) a LEXISCAN (regadenoson) was performed and revealed ST-T changes in the inferior lead as well as lateral lead and ST depressions noted in V4-V6. The patient was diagnosed with **lateral wall ischemia** and a recommendation was made for diagnostic catheterization with percutaneous transluminal coronary angioplasty and stenting. On [redacted] (b) (6)

[redacted] (b) (6) the patient underwent an outpatient cardiac catheterization which revealed severe stenosis in the left proximal circumflex coronary artery. Treatment included placement of a Xience drug-eluting stent. The post-procedural period was unremarkable. The patient's medical history included angioplasty, type 2 diabetes mellitus, low high-density lipoprotein cholesterol, metabolic syndrome, anemia, gastroesophageal reflux disease, chronic renal failure, hiatal hernia, carpal tunnel syndrome, ovarian cyst with excision, appendicitis with appendectomy, hemorrhoids, obesity, and post menopausal status. Concomitant medications included glimepiride, furosemide, vitamin D, calcium, ferrous sulphate, simvastatin, metoprolol ER, lisinopril, clopidogrel, aspirin, metformin, and pioglitazone. The investigational medication was continued. The patient recovered with sequelae from the event of worsening coronary artery disease on [redacted] (b) (6)). The patient was discharged from the hospital on [redacted] (b) (6) The Investigator considered the event of worsening coronary artery disease as moderate and unrelated to investigational medication.

Patient 255-004/A-D: non-cardiac chest pain radiating intrascapular- MARINE study

Patient 255-004/A-D, a 51-year-old White male with a history of hypertriglyceridemia and unstable angina, signed informed consent on 26-Feb-2010 and was **randomized to AMR101 2 g daily** on 29-Apr-2010. On [redacted] (b) (6) (14-May-2010), the patient experienced chest pain that worsened, radiating to the intrascapular area [redacted] (b) (6) The patient was subsequently admitted to the hospital for treatment on that same date. Upon admission, physical examination revealed a blood pressure of 110/70 mmHg and pulse of 68 beats per minute (bpm). An electrocardiogram (ECG) showed a sinus rhythm of 66/minute and laboratory testing revealed negative cardiac enzymes (values not provided). A bicycle ergometry was performed and revealed no ischemia and non-significant minimal ST segment deviation. An x-ray of the thorax showed no peculiarities. **The patient was subsequently diagnosed with non-specific thoracic pain complaints with multiple risk factors with indications for cardiac ischemia.** Treatment medications included dalteparin and nitroglycerin infusion. The patient's medical history also includes angioplasty, peripheral arterial disease, hypertension, low HDL cholesterol, triglycerides >2000 mg/dL, gout, hypertensive nephropathy, steatosis hepatis, premature atherosclerosis, complaints of abdominal pain, and a period with alopecia. Concomitant medications included carbasalate calcium, omeprazole, metoprolol, allopurinol, irbesartan, and rosuvastatin. The investigational medication was continued throughout the hospitilization. [redacted] (b) (6) the symptoms of chest pain improved and the patient was discharged from the hospital on that same date. It was reported the patient still experiences some pain but was considered not significant according to the cardiologist. The patient has recovered with sequelae from the event of non-cardiac chest pain radiating intrascapular [redacted] (b) (6) . The Investigator considered the event of non-cardiac chest pain radiating intrascapular as severe and unrelated to investigational medication.

Patient 065-017/MAS: chest pain, non-cardiac- ANCHOR study

Patient 065-017/MAS, a 58-year-old white female with a history of hypertriglyceridemia, signed informed consent on 06-Apr-2010 and was **randomized to AMR101 2 g daily** on 26-May-2010. The patient administered the last dose of investigational medication on Study Day 84 (17-Aug-2010), and completed the study on 18-Aug-2010. (b) (6) the patient developed extreme chest pressure and self medicated with nitroglycerin which seemed to help her symptoms. On the same date, the patient presented to her physician's office and was subsequently referred and admitted to the hospital for evaluation and treatment of possible acute coronary syndrome. During hospitalization, the patient had recurrent nausea, vague chest discomfort, and denied shortness of breath or diaphoresis. An electrocardiogram, cardiac enzymes, resting stress test, and chest x-ray revealed normal results. (b) (6)**, a consultation reported that the patient's symptoms were most likely gastrointestinal in etiology and the patient was diagnosed with non-cardiac chest pain.** There was no treatment reported for the event. The patient's medical history included family history of premature coronary heart disease (CHD), bilateral nystagmus, lower lumbar back pain, transient ischemic attack, type 2 diabetes mellitus, hypertension, postmenopausal status, depression, equilibrium balance disorder, bilateral perilymphatic ear leaks with surgery, Menieres disease, seasonal allergies, gastroesophageal reflux disease, esophageal stricture, esophageal stretching and tightening ×2, intermittent lower lumbar pain of disc 3 and 4, lower lumbar fusion of disc 3 and 4, lumbardiscectomy, blood clot lower lumbar back, non-alcoholic steatohepatitis with 1+ portal and 2+ pericellular fibrosis, liver biopsy, back surgery with 4 cm blood clot removed, uvula surgery due to snoring, tonsillectomy, tonsillitis, hysterectomy, hernia above the navel with repair, cholecystitis, cholecystectomy, pancreatitis, bladder incontinence, surgical lift of bladder ×2, bowel lift, bowel weakness, arthritis of the right knee, lateral release surgery of the right knee, surgical scope of the right knee, generalized arthritis, elective breast reduction, intermittent dizziness, hyperlipidemia, snoring, and vaginal bleeding. Concomitant medications included nitroglycerin, loratadine, amlodipine, ursodiol, transdermal estradiol patch, calcium, topical estradiol, aspirin, alprazolam, rabeprazole, metformin, lisinopril hydrochlorothiazide, venlafaxine hydrochloride, and rosuvastatin. The patient was discharged from the hospital (b) (6) and recovered from the event of non-cardiac chest pain on 12-Sep-2010. The Investigator considered the event of chest pain, non-cardiac as moderate and unrelated to investigational medication.

Patient 095-006/KRH: non-anginal chest pain- ANCHOR study

Patient 095-006/KRH, a 54-year-old white male with a history of hypertriglyceridemia and coronary artery disease, signed informed consent on 12-Jul-2010 and was **randomized to AMR101 2 g daily** on 31-Aug-2010. (b) (6)), the patient experienced a near syncopal episode at home and a sudden onset of dull, pressure-like pain underneath the left breast, which was 4 out of 10 in intensity, and not associated with diaphoresis, dyspnea, or dizziness. At that time, the patient presented

to the hospital and was admitted for further evaluation and treatment. (b) (6) an electrocardiogram revealed normal sinus rhythm with a possible old inferior myocardial infarction and no ST changes suggestive of ischemia. (b) (6) , physical examination revealed a blood pressure of 115/61 mmHg and a heart rate of 56 beats per minute. Laboratory testing revealed negative cardiac enzymes ×3. On the same date, a cardiolite stress test revealed no signs of acute ischemia or reversible ischemia. The **patient was diagnosed with non-anginal chest pain.** There was no treatment given for the event. The patient was advised to quit smoking. The patient's medical history included myocardial infarction (multiple episodes), stable angina, coronary angioplasty, coronary artery bypass surgery, peripheral arterial disease, >50% obstruction of carotid artery, hypertension, low high-density lipoprotein cholesterol, family history of premature coronary heart disease, hyperlipidemia, chronic obstructive pulmonary disease, valvular heart disease, benign prostatic hyperplasia, parotid gland cancer, Warthin's benign tumor, inactive lung granulomatous disease, hiatal hernia, depression, gastroesophageal reflux disease, femoral artery stent, abdominal pain, right hemicolectomy, appendicitis, appendectomy, right-carotid endarterectomy, carbon monoxide poisoning, insomnia, current smoker, abdominal adhesions, and an allergy to codeine. Concomitant medications included mirtazapine, zaleplon, ranitidine, metoprolol, lisinopril, atorvastatin, aspirin, amlodipine, and albuterol. The investigational medication was continued. The patient has recovered from the event of non-anginal chest pain and was discharged from the hospital (b) (6) . The Investigator considered the event of non-anginal chest pain as moderate and unrelated to investigational medication.

<u>Patient 043-003/RGC: atypical chest pain, non-cardiac- ANCHOR study</u>

Patient 043-003/RGC, a 75-year-old white male with a history of hypertriglyceridemia signed informed consent on 29-Mar-2010 and was **randomized to AMR101 4 g daily** on 08-Jun-2010. On Study Day 57 (03-Aug-2010), laboratory testing revealed a blood urea nitrogen (BUN) of 24 mg/dL (normal range [NR] 7-18 mg/dL), a creatinine of 1.3 mg/dL (NR 0.6-1.3 mg/dL), and a **sodium of 127 mmol/L (NR 135-145 mmol/L)**. (b) (6) the patient experienced **weakness, stumbling, and two falls while mowing the lawn on a hot day**. The patient was subsequently admitted to the hospital for evaluation and treatment. The patient stated that he did not experience any chest pain but felt very tired and symptoms were similar to the symptoms he had experienced at the time of his first myocardial infarction. Physical examination revealed a blood pressure of 147/77 mmHg, a pulse of 71 beats per minute, a respiratory rate of 16 breaths per minute, an oxygen saturation of 99%, and he was alert and oriented to person, place, and time. Laboratory testing revealed a troponin of less than 0.1, **a sodium of 125**, a BUN of 24, and a creatinine of 1.3 (units and NR not provided). An electrocardiogram and chest x-ray were normal and an echocardiogram and stress test were reported to be within normal limits. The patient was diagnosed with atypical chest pain, non cardiac. Treatment of the event was unknown. The patient's medical history included family history of coronary heart disease, paroxysmal atrial fibrillation, coronary

artery disease, pedal edema, stroke of carotid origin, alcohol use, myocardial infarction, angioplasty, abdominal aortic aneurysm, transient ischemic attack, hypertension, low high-density lipoprotein cholesterol, Barrett's esophagus, spinal stenosis, benign prostatic hypertrophy, infrarenal aneurysm, hyperlipidemia, small vessel lacunar disease, degenerative joint disease with ulnar deviation of the fingers, and eczema. Concomitant medications included gabapentin, aspirin, clopidogrel, metoprolol, Caduet, and irbesartan. The investigational medication was interrupted on [redacted] (b) (6) (b) (6). The patient re-started the investigational medication on [redacted] and completed dosing per protocol on the same date. The patient recovered from the event of atypical chest pain, non cardiac and was discharged from the hospital [redacted] (b) (6) The Investigator considered the event of atypical chest pain, non cardiac as moderate and unrelated to investigational medication.

Patient 019-016/CMR: Grade 3 subarachnoid hemorrhage, ruptured anterior communicating artery- ANCHOR study

Patient 019-016/CMR, a 49-year-old white female with a history of hypertriglyceridemia, signed informed consent on 07-May-2010 and was **randomized to AMR101 4 g daily** on 22-Jun-2010. On [redacted] (b) (6) (26-Aug-2010), the patient developed a severe headache and hypertension (value unknown) associated with hearing loss, pain radiating to the back of the neck, and a low grade fever (value unknown). The patient presented to the emergency room for evaluation and treatment [redacted] (b) (6). At that time, a computed tomography (CT) angiogram of the brain revealed a **Grade 3 subarachnoid hemorrhage with a ruptured anterior communicating artery aneurysm**. On [redacted] (b) (6), the patient was transferred and admitted to another hospital for neurosurgical consultation and intervention. On admission, the patient presented with a continuing headache, a temperature of 100.6°F, a pulse of 91 beats per minute, a respiratory rate of 22 breaths per minute, an oxygen saturation of 92% on 2 liters of oxygen, and a blood pressure of 116/58 mmHg. A neurological examination was reported as normal. [redacted] (b) (6) a follow-up CT scan of the head without contrast revealed dense blood in the region of the anterior communicating artery with subarachnoid blood seen anteriorly in the interhemispheric fissure, as well as over the left convexity and in the sylvian fissures bilaterally, left greater than right, no cortical infarct, mild generalized cortical edema, as well as ventricular prominence, left greater than right, with likely a trace amount of intraventricular blood on the left side. On the same date, the patient underwent a coil embolization of the anterior communicating artery aneurysm without complication. A transcranial Doppler was satisfactory and negative for spasms. On [redacted] (b) (6), the patient was noted to have **cerebral edema** related to the Grade 3 subarachnoid hemorrhage (non-serious event). Additional treatment included dexamethasone,
nimodipine, and physical therapy. The patient's medical history included type 2 diabetes mellitus; hypertension; metabolic syndrome; postmenopausal status; hypercholesterolemia; sinus allergies; sinus problems; hyperthyroidism; and allergies to

morphine, codeine, and promethazine. Concomitant medications included Exforge, rosuvastatin, furosemide, Novolin 70/30 insulin, Janumet, and Diovan/ Hydrochlorothiazide. The investigational medication was discontinued due to the event on [redacted] (b) (6)). The patient recovered with the sequelae of minimal right sided weakness from the events of Grade 3 subarachnoid hemorrhage and ruptured anterior communicating artery aneurysm and was discharged from the hospital [redacted] (b) (6). The event of cerebral edema related to the Grade 3 subarachnoid hemorrhage was considered resolved on 13-Sep-2010 and the patient was withdrawn from the study on 15-Sep-2010. The Investigator considered the events of Grade 3 subarachnoid hemorrhage and ruptured anterior communicating artery aneurysm as severe, the event of cerebral edema related to the grade 3 subarachnoid hemorrhage as moderate, and all events as unrelated to investigational medication.

Patient 010-017/RML: subarachnoid hemorrhage, subdural hematoma, syncopal episode- ANCHOR study

Patient 010-017/RML, a 72-year-old white female with a history of hypertriglyceridemia, signed informed consent on 28-Jun-2010 and was **randomized to AMR101 2 g daily** on 12-Aug-2010. The patient's last dose of investigational medication was administered on Study Day 81 (31-Oct-2010) and the patient completed the study on 01-Nov-2010. On [redacted] (b) (6), the patient experienced a syncopal episode at home, hit her head, and was subsequently transported to the emergency room. The patient was admitted to the hospital for evaluation and treatment on the same date. On admission, physical examination revealed no neurologic deficits and a computed tomography (CT) scan of the brain revealed a small subarachnoid bleed in the cortical sulci of the vertex bilaterally and no evidence of mass effect or herniation. A neurosurgery consult determined that the hemorrhage was non-operative in nature and recommended stopping anti-coagulation therapy. Subsequently, a neurology consult was obtained and determined that the subarachnoid bleed developed as a result of trauma to the head. On [redacted] (b) (6), magnetic resonance imaging (MRI) of the brain revealed a moderate amount of subarachnoid hemorrhage and a small subdural hematoma. Laboratory testing revealed an elevated blood alcohol level (value unknown) indicating near alcohol intoxication. An electrocardiogram revealed sinus rhythm and an echocardiogram was performed (results unknown). It was noted that the syncopal episode was likely due to orthostatic hypotension versus a vasovagal episode. Treatment of the events included two units of fresh frozen plasma, vitamin K, and the withholding of warfarin, enalapril/hydrochlorothiazide, and metoprolol. The patient’s medical history included type 2 diabetes mellitus, hypertension, dyslipidemia, cholecystitis, tonsillitis, appendicitis, benign tumor distal pancreas, atrial fibrillation, depression, distal pancreatectomy, splenectomy, cholecystectomy, vaginal hysterectomy, left oophorectomy, perennial rhinitis, osteoarthritis, irritable bowel syndrome, chronic urticaria, valvular heart disease involving multiple valves, mitral regurgitation, aortic insufficiency, left forearm abrasion, fibrocystic left breast lump or mass, left breast pain, incipient bilateral cataracts, type 2 diabetic nephropathy without complications,

gastroesophageal reflux disease, appendectomy, tonsillectomy, urinary tract infection, benign tumor of the spleen, mild bilateral upper extremity tremor, ¾ systolic murmur, benign dysfunctional uterine bleeding, alcohol use, mild intermittent orthostatic lightheadedness, orthostatic hypotension, tricuspid regurgitation, diastolic dysfunction, and postmenopausal status. Concomitant medications included enalapril/ hydrochlorothiazide, warfarin sodium, metoprolol succinate, acetaminophen/diphenhydramine, psyllium, trazodone hydrochloride, simvastatin, sertraline hydrochloride, omeprazole, multivitamin, metformin, glyburide, fexofenadine, and raloxifene. The patient recovered from the event of syncopal episode on (b) (6). The patient was discharged from the hospital on (b) (6), and subsequently recovered from the events of subarachnoid hemorrhage and subdural hematoma on 07-Dec-2010. The Investigator considered the event of subdural hematoma as mild, the events of syncopal episode and subarachnoid hemorrhage as moderate, and all the events as unrelated to investigational medication.

Reviewer Comment: This clinical reviewer read the SAE narratives to assess for accuracy of event term assignment and to search for additional serious events. For the majority of narratives, I concur with the assigned event term and no additional AEs were found within the narrative. The following table lists only cases where I did not concur with the assigned event term or where an additional serious event that had not been reported elsewhere was noted in the narrative.

Table 54: Serious Adverse Events: Narrative Cases Consistent with a Different Event Term or an Additional Serious Adverse Event Noted within Narrative-Hypertriglyceridemic Placebo-Controlled Dataset

Patient ID/Study	Treatment Group	Applicant's SAE Term	Clinical Reviewer's SAE Term	Additional SAE within Narrative
043-033/RGC/ ANCHOR study	Vascepa 4g	Atypical chest pain, non-cardiac	same	Hyponatremia
019-016/CMR ANCHOR study	Vascepa 4g	Grade 3 subarachnoid hemorrhage, ruptured anterior communicating artery	same	Cerebral edema

Serious Adverse Events in the Overall AMR101 Integrated Dataset

In the Overall AMR101 Integrated Dataset, the most frequently reported SAEs were in "Psychiatric Disorders" with approximately 1.1% or 19/1683 patients reporting to the SOC, followed by "Injury, Poisoning, and Procedural Complications (0.8%) and "General

Disorders and Administration Site Conditions" (0.7%). Because this dataset included open-label trials, no comparison to placebo could be generated.

The most commonly reported SAEs for patients on Vascepa were non-cardiac chest pain (0.3%), coronary artery disease (0.2%), aggression (0.2%), depression (0.2%), psychotic disorder (0.2%), overdose (0.2%) and irritability (0.2%). The psychiatric-related SAEs primarily occurred in the CNS studies.

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Table 55: Treatment Emergent SAEs by SOC and PT, Overall AMR101 Integrated Dataset

System Organ Class Preferred Term	Vascepa Pooled N=1683 n (%)	Vascepa Daily Dose 0.5 g N=19 n (%)	1 g N=186 n (%)	2 g N=1100 n (%)	4 g N=378 n (%)
Any System Organ Class	75 (4.5)	0	8 (4.3)	56 (5.1)	11 (2.9)
Psychiatric Disorders	19 (1.1)	0	1 (0.5)	16 (1.5)	2 (0.5)
Aggression	3 (0.2)	0	0	3 (0.3)	0
Depression	3 (0.2)	0	0	3 (0.3)	0
Psychotic Disorder	3 (0.2)	0	1 (0.5)	2 (0.2)	0
Paranoia	2 (0.1)	0	0	2 (0.2)	0
Suicidal Ideation	2 (0.1)	0	0	2 (0.2)	0
Affective Disorder	1 (0.1)	0	0	1 (0.1)	0
Completed Suicide	1 (0.1)	0	0	1 (0.1)	0
Depressive Symptom	1 (0.1)	0	0	0	1 (0.3)
Disturbance in Social Behavior	1 (0.1)	0	0	0	1 (0.3)
Impulse-Control Disorder	1 (0.1)	0	0	1 (0.1)	0
Intermittent Explosive Disorder	1 (0.1)	0	0	1 (0.1)	0
Major Depression	1 (0.1)	0	0	1 (0.1)	0
Mental Disorder	1 (0.1)	0	0	1 (0.1)	0
Mood Altered	1 (0.1)	0	0	1 (0.1)	0
Injury, Poisoning and Procedural Complications	13 (0.8)	0	3 (1.6)	10 (0.9)	0
Overdose	3 (0.2)	0	2 (1.1)	1 (0.1)	0
Fall	2 (0.1)	0	0	2 (0.2)	0
Subdural Hematoma	2 (0.1)	0	0	2 (0.2)	0
Ankle Fracture	1 (0.1)	0	0	1 (0.1)	0
Comminuted Fracture	1 (0.1)	0	1 (0.5)	0	0
Femoral Neck Fracture	1 (0.1)	0	0	1 (0.1)	0
Road Traffic Accident	1 (0.1)	0	0	1 (0.1)	0
Subdural Hemorrhage	1 (0.1)	0	0	1 (0.1)	0
Wrist Fracture	1 (0.1)	0	0	1 (0.1)	0
General Disorders and Administration Site Condition	11 (0.7)	0	0	9 (0.8)	2 (0.5)
Non-Cardiac Chest Pain	5 (0.3)	0	0	3 (0.3)	2 (0.5)
Irritability	3 (0.2)	0	0	3 (0.3)	0
Condition Aggravated	1 (0.1)	0	0	1 (0.1)	0
Drug Withdrawal Syndrome	1 (0.1)	0	0	1 (0.1)	0
Pyrexia	1 (0.1)	0	0	1 (0.1)	0
Nervous System Disorders	9 (0.5)	0	0	7 (0.6)	2 (0.5)
Subarachnoid Hemorrhage	2 (0.1)	0	0	1 (0.1)	1 (0.3)
Cerebrovascular Accident	1 (0.1)	0	0	1 (0.1)	0
Extrapyramidal Disorder	1 (0.1)	0	0	1 (0.1)	0
Grand Mal Convulsion	1 (0.1)	0	0	1 (0.1)	0
Ischemic Stroke	1 (0.1)	0	0	1 (0.1)	0
Migraine	1 (0.1)	0	0	1 (0.1)	0
Motor Dysfunction	1 (0.1)	0	0	1 (0.1)	0
Presyncope	1 (0.1)	0	0	0	1 (0.3)
Ruptured Cerebral Aneurysm	1 (0.1)	0	0	0	1 (0.3)
Syncope	1 (0.1)	0	0	1 (0.1)	0

System Organ Class Preferred Term	Vascepa Pooled N=1683 n (%)	Vascepa Daily Dose			
		0.5 g N=19 n (%)	1 g N=186 n (%)	2 g N=1100 n (%)	4 g N=378 n (%)
Cardiac Disorders	7 (0.4)	0	0	4 (0.4)	3 (0.8)
Coronary Artery Disease	3 (0.2)	0	0	2 (0.2)	1 (0.3)
Angina Unstable	1 (0.1)	0	0	1 (0.1)	0
Atrioventricular Block Complete	1 (0.1)	0	0	0	1 (0.3)
Cardiac Failure Congestive	1 (0.1)	0	0	0	1 (0.3)
Myocardial Infarction	1 (0.1)	0	0	1 (0.1)	0
Infections and Infestations	4 (0.2)	0	0	3 (0.3)	1 (0.3)
Bacterial Infection	1 (0.1)	0	0	1 (0.1)	0
Helicobacter Gastritis	1 (0.1)	0	0	1 (0.1)	0
Herpes Zoster	1 (0.1)	0	0	0	1 (0.3)
Pneumonia	1 (0.1)	0	0	1 (0.1)	0
Metabolism and Nutrition Disorders	4 (0.2)	0	1 (0.5)	3 (0.3)	0
Cachexia	1 (0.1)	0	0	1 (0.1)	0
Decreased Appetite	1 (0.1)	0	1 (0.5)	0	0
Diabetes Mellitus	1 (0.1)	0	0	1 (0.1)	0
Water Intoxication	1 (0.1)	0	0	1 (0.1)	0
Musculoskeletal and Connective Tissue Disorders	4 (0.2)	0	3 (1.6)	1 (0.1)	0
Arthralgia	2 (0.1)	0	1 (0.5)	1 (0.1)	0
Back Pain	1 (0.1)	0	1 (0.5)	0	0
Neck Pain	1 (0.1)	0	1 (0.5)	0	0
Gastrointestinal Disorders	2 (0.1)	0	0	2 (0.2)	0
Abdominal Pain Upper	1 (0.1)	0	0	1 (0.1)	0
Fecaloma	1 (0.1)	0	0	1 (0.1)	0
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	2 (0.1)	0	0	2 (0.2)	0
Breast Cancer in Situ	1 (0.1)	0	0	1 (0.1)	0
Lung Neoplasm Malignant	1 (0.1)	0	0	1 (0.1)	0
Reproductive System and Breast Disorders	2 (0.1)	0	0	2 (0.2)	0
Benign Prostatic Hyperplasia	1 (0.1)	0	0	1 (0.1)	0
Prostatomegaly	1 (0.1)	0	0	1 (0.1)	0
Blood and Lymphatic System Disorders	1 (0.1)	0	0	1 (0.1)	0
Iron Deficiency Anemia	1 (0.1)	0	0	1 (0.1)	0
Hepatobiliary Disorders	1 (0.1)	0	0	1 (0.1)	0
Cholelithiasis	1 (0.1)	0	0	1 (0.1)	0
Immune System Disorders	1 (0.1)	0	0	1 (0.1)	0
Allergy to Arthropod Sting	1 (0.1)	0	0	1 (0.1)	0
Investigations	1 (0.1)	0	0	1 (0.1)	0
Endoscopy	1 (0.1)	0	0	1 (0.1)	0
Renal and Urinary Disorders	1 (0.1)	0	0	1 (0.1)	0
Urinary Retention	1 (0.1)	0	0	1 (0.1)	0
Respiratory, Thoracic and Mediastinal Disorders	1 (0.1)	0	0	0	1 (0.3)
Chronic Obstructive Pulmonary Disease	1 (0.1)	0	0	0	1 (0.3)
Vascular Disorders	1 (0.1)	0	0	1 (0.1)	0

System Organ Class Preferred Term	Vascepa Pooled N=1683 n (%)	Vascepa Daily Dose			
		0.5 g N=19 n (%)	1 g N=186 n (%)	2 g N=1100 n (%)	4 g N=378 n (%)
Arterial Occlusive Disease	1 (0.1)	0	0	1 (0.1)	0

AEs = adverse events; SAEs = serious adverse events; SOC = system organ class.
The Safety Analysis Set includes all enrolled patients who were administered at least one dose of study drug.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE preferred term for that treatment.
A patient with multiple AEs within a primary SOC is counted only once in the total row.
Treatment-emergent SAEs include those that first occurred or worsened after the first dose of study drug and occurred within 30 days of study drug discontinuation.
Source: ISS Summary Table ISS.O.6.2-1

Source: ISS, Table 7-24, pg. 106.

7.3.3 Dropouts and/or Discontinuations

The following table summarizes the disposition of patients in the Hypertriglyceridemia Placebo-Controlled dataset (consisting of both the MARINE and ANCHOR trials).

Table 56: Patient Disposition, Hypertriglyceridemia Placebo-Controlled Dataset

	Placebo N=309 n (%)	Vascepa Pooled N=622 n (%)	Vascepa Daily Dose	
			2 g N=312 n (%)	4 g N=310 n (%)
Categories				
Completed the study	288 (93.2%)	590 (94.9%)	295 (94.6%)	295 (95.2%)
Withdrew from the study	21 (6.8%)	32 (5.1%)	17 (5.4%)	15 (4.8%)
Main reason for withdrawal				
Adverse event	10 (3.2%)	14 (2.3%)	9 (2.9%)	5 (1.6%)
Lost to follow-up	0	3 (0.5%)	2 (0.6%)	1 (0.3%)
Death	1 (0.3%)	0	0	0
Withdrawal by patient	7 (2.3%)	12 (1.9%)	6 (1.9%)	6 (1.9%)
Protocol violation	0	0	0	0
Pregnancy	0	0	0	0
Study terminated by sponsor	0	0	0	0
Lack of efficacy	2 (0.6%)	1 (0.2%)	0	1 (0.3%)
Physician decision	0	1 (0.2%)	0	1 (0.3%)
Did not tolerate study drug	0	0	0	0
Informant/caregiver decision	0	0	0	0
Investigator decision	0	0	0	0
Other	1 (0.3%)	1 (0.2%)	0	1 (0.3%)

All enrolled patients includes patients who met all eligibility criteria and were successfully enrolled.
Source: ISS Summary Table ISS.HT.2-1

Source: ISS, Table 6-4, pg. 48.

The pooled data from the hypertriglyceridemic patients indicate that slightly fewer patients withdrew from the trial secondary to an AE in the Vascepa Pooled group (2.3%) than in the Placebo group (3.2%).

This clinical reviewer requested the submission of the verbatim reasons for “Withdrawal by Patient” on March 12, 2012. The applicant submitted the following table for the verbatim reasons given by the patient for discontinuation from the ANCHOR study (the verbatim reasons for withdrawal from the MARINE study are given in Section 6).

Table 57: Verbatim reasons for "Withdrawal by Patient"-ANCHOR

Pt	Reason for Withdrawl of Consent
17-058-016	have been transferred to another site, but I believe she was moving to the Nashville area and there were no sites local to her.
17-039-010	He just said that he didn't want to participate in the trial anymore. Handed me the medication and said that he just didn't want to do it. He agreed to come back to the site for the follow up. But refused to do most of the procedures involved in the study.
17-088-002	The subject had a family emergency and she went out of town.
17-050-038	Subject's PCP instructed her to D/C from the study due to her TGs
17-017-014	Did not provide a reason for dc
17-066-019	He had call and spoke with Dr.toth in Aug because he had an episode in which Dr. Toth deemed as him becoming overheated and possible dehydration. Subject stop study medication until he could speak with Dr. Toth but then was going to restart. Then he just showed up and tried to turn in his study medication with the secretary. He had never
17-034-009	unknown
17-045-006	Patient called to let us know about difficulties times with his job
17-086-031	The patient learned on the day of visit 6/early termination that he has interstitial fibrosis, likely related to prior asbestos exposure. He knows many former co-workers who also have been given similar diagnosis (Maine has the highest rate of asbestosis. due to this new dx the pt w/d consent due to numerous dr. appts ahead.
17-036-041	Time constraints
17-049-051	The subject was hospitalized and is having GI follow-up. She decided to withdraw consent so that she can focus on her health issues. Subject stated that until the GI concerns are resolved she doesn't want to take any medication that is not required.
17-105-003	Patient changed jobs and is no longer able to complete visits.

Sponsor email dated March 13, 2012.

Reviewer Comments: This reviewer determined that the patients giving the "Withdrawal of Consent" as a reason for discontinuation did not need to be included in the discontinuation due to an AE category.

7.3.4 Significant Adverse Events

Please see the following Section 7.3.5.

7.3.5 Submission Specific Primary Safety Concerns

A 1997 Agency report linked doses of omega-3 FA in excess of 3g/day with an increase in bleeding time. [16] However, the risk of bleeding remains unclear since some human studies have not demonstrated clinically significant bleeding in patients taking daily fish oil.

16 FDA. Substances Affirmed as Generally Recognized as Safe: Menhaden Oil. Final Rule. 21 CFR Part 184. Federal Register Volume 62, Number 108, pg. 30751-30757.

In vitro studies have shown that omega-3 FA competitively inhibit cyclo-oxygenase and decrease the synthesis of thromboxane A2 which leads to decreased platelet aggregation. Platelet derived, growth factor–like protein is decreased, and synthesis of the platelet activation factor is decreased as well, all potentially contributing to a decrease in clinical atherothrombosis.[17]

Omega-3 FA also have been shown to have anticoagulant effects. Animal studies previously demonstrated reductions in prothrombin and factor VII with fish oil supplementation. Evidence from human trials now shows that omega-3 FA appears to reduce levels of coagulation factors V, VII, VIII, and X along with fibrinogen and von Willebrand factor. Factors VII and X are implicated in thrombin production, and both of these factors require vitamin K–dependent carboxylation for coagulation activity. This supports the theory that fish oil can interfere with vitamin K activity. Therefore, it appears that fish oil anticoagulant effects are both vitamin K dependent and independent. [18]

In addition to *in vitro* and clinical studies showing reduction of coagulation factors, it has been suggested that omega-3 FA can slightly increase the risk for hemorrhagic stroke.[19]

In a systematic review by Desai et al, the potential interactions between dietary supplements and anti-platelet drugs were evaluated. Effects on bleeding time were evaluated with the combination of omega-3 FA and acetylsalicylic acid. Compared to baseline, significant increase ($p<0.05$) in bleeding time of 13-42% and 55-82% were observed with omega-3 FA alone or in combination with acetylsalicylic acid, respectively. In three trials the additional 19-44% increases in bleeding time with combination therapy over acetylsalicylic acid were significant ($p<0.05$). The studies evaluated in the review were conducted with treatment durations of omega-3 FA and acetylsalicylic acid between 2 and 25 weeks.[20]

Harris (2007) summarized clinical trials with omega-3 FA and findings related to bleeding complications (see table below). According to that author, the risk for clinically significant bleeding is “virtually nonexistent”.

17 Bays HE. Safety Considerations with Omega-3 Fatty Acid Therapy. Am J Cardiol 2007; 99[suppl]:35C-43C.
18 McClaskey EM. et al. Subdural Hematoma After a Fall in an Elderly Patient Taking High-Dose Omega-3 G=Fatty Acids with Warfarin an Aspirin: Case Report and Review of the Literature. Pharmacotherapy 2007;27(1):152-160.
19 Bays HE. Safety Considerations with Omega-3 Fatty Acid Therapy. Am J Cardiol 2007; 99[suppl]:35C-43C.
20 Desai D. et al. Effects of Dietary Supplements on Acetylsalicylic acid and Other Anti-platelet Agents: An Evidence- Based Approach. Thrombosis Research 2005; 117:87-101.

Table 58: Summary of Reports of the Effects of Omega-3 FA on Bleeding Complications (Am J Cardiol 2007;99[suppl]:44C-46C.)

Study LA01.01.0009 in Healthy Subjects and Bleeding Times

The applicant conducted study LA01.01.009 with Vascepa 2g for 28 days to assess effects on bleeding time. This study is reviewed in Section 4.4.3.

In brief, this was a Phase 1, multiple-dose, clinical pharmacology/PK study in healthy male volunteer subjects. An investigation of skin bleeding time was performed pre-dose and 6 hours after dosing on Days 1 - 3 and Days 30 – 32.

All subjects had values within the reference range of 150 to 570 seconds, and there were no important differences between the two active treatment groups. Overall, there was no clinically important effect of Vascepa treatment on skin bleeding time.

Bleeding-Related AEs Identified in the Safety Dataset

The following table presents the incidence of patients with TEAEs that may be related to bleeding or bruising (as identified by the sponsor) in the CNS, Hypertriglyceridemia Placebo-controlled integrated datasets, and in the Overall AMR101 Integrated Dataset. The CNS and hypertriglyceridemia dataset includes TEAEs that occurred during double-blind treatment, and the Overall AMR101 integrated dataset includes TEAEs that occurred during both double-blind and open-label treatment during these studies.

TEAE Preferred Term Studies	CNS Placebo-Controlled Integrated Dataset Double-Blind		Hypertriglyceridemia Placebo-Controlled Integrated Dataset Double-Blind		Overall AMR101 Integrated Dataset Double-Blind and Open-Label
	Placebo N=519 n(%)	Vascepa Pooled N=700 n(%)	Placebo N=309 n(%)	Vascepa Pooled N=622 n(%)	Vascepa Pooled N=1683 n(%)
Anemia	0	3 (0.4)	0	5 (0.8)	11 (0.7)
Bleeding Time Prolonged	0	1 (0.1)	0	0	1 (0.1)
Conjunctival Hemorrhage	0	1 (0.1)	0	0	1 (0.1)
Contusion	3 (0.6)	5 (0.7)	2 (0.6)	4 (0.6)	11 (0.7)
Dysfunctional Uterine Bleeding	0	0	0	0	1 (0.1)
Ecchymosis	0	1 (0.1)	0	0	1 (0.1)
Epistaxis	1 (0.2)	0	0	0	1 (0.1)
Hematochezia	0	0	1 (0.3)	1 (0.2)	2 (0.1)
Hematocrit Abnormal	0	0	0	0	1 (0.1)
Hematoma	1 (0.2)	0	0	1 (0.2)	3 (0.2)
Hematoma Infection	0	0	0	0	1 (0.1)
Hematuria	1 (0.2)	0	0	0	1 (0.1)
Hemoglobin Decreased	2 (0.4)	0	0	0	2 (0.1)
Hemorrhagic Diathesis	0	0	0	1 (0.2)	1 (0.1)
Hemorrhage	0	0	0	0	1 (0.1)
Hemorrhoidal Hemorrhage	1 (0.2)	0	0	0	0
Increased Tendency to Bruise	0	0	1 (0.3)	1 (0.2)	2 (0.1)
Infusion Site Hematoma	0	0	1 (0.3)	0	0
Iron Deficiency Anemia	0	1 (0.1)	0	0	2 (0.1)
Mouth Hemorrhage	0	0	1 (0.3)	0	0
Post Procedural	0	1 (0.1)	0	0	1 (0.1)

TEAE Preferred Term Studies	CNS Placebo-Controlled Integrated Dataset Double-Blind		Hypertriglyceridemia Placebo-Controlled Integrated Dataset Double-Blind		Overall AMR101 Integrated Dataset Double-Blind and Open-Label
	Placebo N=519 n(%)	Vascepa Pooled N=700 n(%)	Placebo N=309 n(%)	Vascepa Pooled N=622 n(%)	Vascepa Pooled N=1683 n(%)
Hemorrhage					
Postmenopausal Hemorrhage	1 (0.2)	1 (0.1)	0	0	1 (0.1)
Rectal Hemorrhage	1 (0.2)	0	0	0	0
Spontaneous Hematoma	0	0	0	1 (0.2)	1 (0.1)
Subarachnoid Hemorrhage	0	0	0	2 (0.3)	2 (0.1)
Subdural Hematoma	1 (0.2)	1 (0.1)	0	1 (0.2)	2 (0.1)
Subdural Hemorrhage	0	1 (0.1)	0	0	1 (0.1)
Traumatic Hematoma	0	0	0	3 (0.5)	3 (0.2)
Uterine Hemorrhage	0	0	0	1 (0.2)	1 (0.1)
Vaginal Hemorrhage	1 (0.2)	2 (0.3)	0	0	4 (0.2)

AE = adverse event; TEAE = treatment emergent adverse event.
The Safety Analysis Set includes all enrolled patients who were administered at least one dose of study drug.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE preferred term for that treatment.
Source: ISS Summary Tables ISS.CNS.6.1-1, ISS.HT.6.1-1, and ISS.O.6.1-1

Source: ISS, Table 7-14, pg. 85.

In the Hypertriglyceridemia, Placebo-Controlled dataset, there were 3.4% bleeding-related TEAEs in patients on Vascepa compared to 1.9% of patients on Placebo. The percentage of bleeding-related TEAEs was similar for patients on Vascepa (2.5%) as compared to Placebo (2.5%) in the CNS Placebo-Controlled Integrated Dataset.

This reviewer reviewed the narratives of the six cases of subdural hematoma, subdural hemorrhage, and subarachnoid hemorrhage reported in the NDA.

Patient: AMR01.01.0017-010-017
Study: ANCHOR
Treatment: 2 g/day Vascepa
Events: subarachnoid hemorrhage, subdural hematoma, syncopal episode

The patient was a 72-year-old white female with a history of hypertriglyceridemia, randomized to 2 g/day Vascepa on 12-Aug-2010. The patient's last dose of investigational medication was administered on Study Day 81 (31-Oct-2010) and the patient completed the study on 01-Nov-2010. On [redacted] (b) (6), the patient experienced a syncopal episode at home, hit her head, and was admitted to the hospital where physical examination revealed no neurologic deficits. A computed tomography (CT) scan of the brain revealed a small subarachnoid bleed in the cortical sulci of the vertex

bilaterally and no evidence of mass effect or herniation. A neurosurgery consult determined that the hemorrhage was non-operative in nature and recommended stopping anti-coagulation therapy. Subsequently, a neurology consult was obtained and determined that the subarachnoid bleed developed as a result of trauma to the head. On [redacted] (b) (6), magnetic resonance imaging (MRI) of the brain revealed a moderate amount of subarachnoid hemorrhage and a small subdural hematoma. Laboratory testing revealed an elevated blood alcohol level (value unknown) indicating near alcohol intoxication. An ECG revealed sinus rhythm and an echocardiogram was performed (results unknown). It was noted that the syncopal episode was likely due to orthostatic hypotension. The patient recovered from the event of syncopal episode on [redacted] (b) (6). The patient was discharged from the hospital on [redacted] (b) (6), and subsequently recovered from the events of subarachnoid hemorrhage and subdural hematoma on 07-Dec-2010. The Investigator considered the event of subdural hematoma as mild, the events of syncopal episode and subarachnoid hemorrhage as moderate, and all the events as unrelated to investigational medication.

Treatment of the events included two units of fresh frozen plasma, vitamin K, and the withholding of warfarin, enalapril/hydrochlorothiazide, and metoprolol. The patient's medical history included type 2 diabetes mellitus and nephropathy, hypertension, dyslipidemia, atrial fibrillation, distal pancreatectomy, splenectomy, cholecystectomy, vaginal hysterectomy, left oophorectomy, mitral regurgitation, aortic insufficiency, benign tumor of the spleen, benign dysfunctional uterine bleeding, alcohol use, mild intermittent orthostatic lightheadedness, orthostatic hypotension, tricuspid regurgitation, diastolic dysfunction, and postmenopausal status.
Concomitant medications included enalapril/hydrochlorothiazide, warfarin sodium, metoprolol succinate, acetaminophen/diphenhydramine, psyllium, trazodone hydrochloride, simvastatin, sertraline hydrochloride, omeprazole, multivitamin, metformin, glyburide, fexofenadine, and raloxifene.

Patient: AMR01.01.0017-019-016
Study: ANCHOR
Treatment: 4 g/day Vascepa
Events: grade 3 subarachnoid hemorrhage

The patient was a 49-year-old white female with a history of hypertriglyceridemia. On Study Day 66 (26-Aug-2010), the patient developed a severe headache and hypertension (value unknown) associated with hearing loss, pain radiating to the back of the neck, and a low grade fever (value unknown). Treatment was discontinued. The patient presented to the emergency room for evaluation and treatment on [redacted] (b) (6). At that time, a CT angiogram of the brain revealed a grade 3 subarachnoid hemorrhage with a ruptured anterior communicating artery aneurysm. On [redacted] (b) (6), the patient was transferred and admitted to another hospital. On [redacted] (b) (6), a follow-up CT scan of the head without contrast revealed dense blood in the region of the anterior communicating artery. No cortical infarct was observed. On the same date, the patient

underwent a coil embolization of the anterior communicating artery aneurysm without complication. The patient recovered with the sequelae of minimal right-sided weakness from the grade 3 subarachnoid hemorrhage and was discharged from the hospital on [redacted] (b) (6). The event of cerebral edema related to the grade 3 subarachnoid hemorrhage was considered resolved on 13-Sep-2010 and the patient was withdrawn from the study on 15-Sep-2010. The Investigator considered the events of grade 3 subarachnoid hemorrhage and ruptured anterior communicating artery aneurysm as severe, the event of cerebral edema related to the grade 3 subarachnoid hemorrhage as moderate, and all events as unrelated to investigational medication.

Additional treatment included dexamethasone, nimodipine, and physical therapy.
The patient's medical history included type 2 diabetes mellitus, hypertension, metabolic syndrome, postmenopausal status, hypercholesterolemia, and hyperthyroidism.

Concomitant medications included Exforge, rosuvastatin, furosemide, insulin, Janumet, and Diovan/Hydrochlorothiazide.

Patient: AN01.01.0012-0016-400
Study: AN01.01.0012
Treatment: 2 g/day Vascepa
Events: subdural (hemorrhage) hematoma

In January of 2006, after giving consent [25-Jan-2006] but prior to the start of study medication, this 35-year-old Caucasian male with Huntington's disease fell during a skiing holiday. No apparent injury was sustained at that time, but on return from holiday he developed a headache. A skull X-ray showed no evidence of fracture and there were no localizing neurological features. The patient had no relevant medical and surgical history. The patient commenced study medication at the dose of 1000 mg twice daily on 07-Feb-2006. Ibuprofen was administered between 06 and 10-Feb-2006. On the weekend prior to admission to hospital he became aggressive and complained of headache. He was admitted to hospital on [redacted] (b) (6) where a brain scan revealed a subdural hemorrhage (hematoma), which was considered severe in intensity. He was treated with paracetamol and dihydrocodeine and underwent aspiration of the hematoma on [redacted] (b) (6) when the event resolved. In the Principal Investigator's opinion, the subdural hemorrhage was not related to study medication, which was temporarily interrupted [redacted] (b) (6) in response to this event. Study medication was subsequently restarted on 09-Jun-2006. The patient had received no concomitant medications within two weeks of the onset of this event.

Patient: AN01.01.011-0048-4305
Study: AN01.01.0011
Treatment: 2 g/day Vascepa
Events: subdural hematoma

A 73-year-old Caucasian male with Huntington's disease complained of a headache and stated that his eyes hurt 160 days after starting icosapent ethyl therapy on 09-May-2006. On 19-Oct-2006, he felt shaky and his balance had worsened. He developed a headache and was admitted to the hospital on [redacted] (b) (6) prior to the hospitalization, he had fallen, hitting his head, fracturing his wrist and suffering a laceration above his right eyebrow. On admission to the hospital, a CT scan revealed a subdural hematoma, which was considered to be secondary to the fall, and severe in nature. Concurrent aspirin was discontinued at that time. Shunts were placed in the right posterior and left anterior skull for drainage, and the event was considered to be resolved at that time. Three days after surgery [redacted] (b) (6), the patient was mobilizing with a walking frame. Study medication was permanently discontinued due this event. His shunts were removed on [redacted] (b) (6), and the patient was subsequently discharged from the hospital the next day. In the Principal Investigator's opinion, the subdural hematoma was possibly related to the study medication and possibly related to aspirin.

Concomitant medications taken two weeks before the start of the event were ibuprofen, irbesartan, atorvastatin calcium, felodipine, atenolol, loperamide hydrochloride, aspirin and alfuzosin hydrochloride. The patient had a history of right lentiform nucleus lacunar cerebrovascular accident (1999), CV stenting (2003), left internal carotid artery stenting (2005), and near syncope (2006). He concurrently suffered from decreased hearing in his left ear, hypertension, chronic sinusitis and a pituitary adenoma.

Patient: AN01.01.011-0098-4858
Study: AN01.01.0011
Treatment: Placebo
Events: subdural hematoma

This 47-year-old Caucasian male with Huntington's disease received his first dose of double-blind study medication on 07-Mar-2006. He fell and sustained a head injury on 09-Apr-2006 [redacted] (b) (6). Several days after the fall, the patient developed right-sided paresis.

On [redacted] (b) (6), the patient was taken to the Emergency Room and was subsequently admitted to the hospital. A CT scan revealed a subdural hematoma, which was considered to be severe in nature. Laboratory investigations were unremarkable. A diagnosis of subdural hematoma was made and the patient underwent bilateral drainage, during which 33 cc were removed from the right side and 70 cc from the left. Due to this event, together with the following event of herpes simplex, study drug was permanently discontinued. The event resolved on [redacted] (b) (6) and he was discharged from the hospital on [redacted] (b) (6). The Investigator considered the subdural hematoma to be unrelated to the study medication. The patient concurrently suffered from seasonal allergies, intermittent headaches and urticaria. He had a history of depression (1999)

and asthma (1982). Concomitant medications taken within two weeks of start of this event included valproic acid and acetaminophen.

Patient: LA01.01.0005-0002-2127
Study: LA01.01.0005
Treatment: 2 g/day Vascepa
Events: fall resulting in subdural hematoma

This 53-year-old male patient with Huntington's disease commenced study medication (icosapent ethyl) on 17-Jul-2001. Approximately (b) (6) months after the start of study medication the patient suffered a subdural hematoma following a fall. Study medication was interrupted and surgical drainage of the hematoma was undertaken. (b) (6) days later the patient developed severe, generalized tonic-clonic seizures which were considered to be of a disabling/incapacitating nature. He received treatment with lorazepam and phenytoin and was intubated. Further treatment with haloperidol and lorazepam was given. He was transferred to a rehabilitation center for further management. The tonic-clonic seizures resolved after eight days. Medication was restarted, but was later stopped and the patient withdrew from the study. Both SAEs were considered unlikely related to the study medication.

Reviewer Comment: There is no definitive answer as to whether omega-3 FA increases the risk for bleeding. Regulatory recommendations with Vascepa and concomitant anticoagulants should convey caution.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The following table lists those AEs by SOC and PT for which the incidence of AEs was ≥0.3% (corresponding to two or more patients) higher for the Vascepa Pooled group than for the Placebo group.

Table 59: Treatment Emergent Adverse Events ≥ 0.3% and More for AMR Pooled than Placebo- Hypertriglyceridemia Placebo-Controlled Integrated Dataset

SOC/PT	Placebo N=309 n(%)	Vascepa Pooled N=622 n(%)	Vascepa 2 grams N=312 n(%)	Vascepa 4 grams N= 310 n(%)
Any SOC	151 (48.9%)	285 (45.8%)	142 (45.5%)	143 (46.1%)
Musculoskeletal and Connective Tissue Disorders	17 (5.5%)	49 (7.9%)	24 (7.7%)	25 (8.1%)
Arthralgia	4 (1.3%)	16 (2.6%)	11 (3.5%)	5 (1.6%)
Osteoarthritis	0	5 (0.8%)	3 (1.0%)	2 (0.6%)
Myalgia	1 (0.3%)	3 (0.5%)	1 (0.3%)	2 (0.6%)

SOC/PT	Placebo N=309 n(%)	Vascepa Pooled N=622 n(%)	Vascepa 2 grams N=312 n(%)	Vascepa 4 grams N= 310 n(%)
Muscular Weakness	0	2 (0.3%)	0	2 (0.6%)
Neck Pain	0	2 (0.3%)	0	2 (0.6%)
Plantar Fasciitis	0	2 (0.3%)	1 (0.3%)	1 (0.3%)
Trigger Finger	0	2 (0.3%)	1 (0.3%)	1 (0.3%)
Respiratory, Thoracic and Mediastinal Disorders	13 (4.2%)	30 (4.8%)	14 (4.5%)	16 (5.2%)
Oropharyngeal Pain	1 (0.3%)	8 (1.3%)	2 (0.6%)	6 (1.9%)
Cough	0	3 (0.5%)	2 (0.6%)	1 (0.3%)
Chronic Obstructive Pulmonary Disease	0	2 (0.3%)		
General Disorders and Administration Site Conditions	12 (3.9%)	29 (4.7%)	19 (6.1%)	10 (3.2%)
Oedema Peripheral	3 (1.0%)	10 (1.6%)	7 (2.2%)	3 (1.0%)
Fatigue	5 (1.6%)	7 (1.1%)	2 (0.6%)	5 (1.6%)
Non-cardiac Chest Pain	1 (0.3%)	7 (1.1%)	4 (1.3%)	3 (1.0%)
Pain	0	5 (0.8%)	4 (1.3%)	1 (0.3%)
Injury, Poisoning and Procedural Complications	10 (3.2%)	28 (4.5%)	15 (4.8%)	13 (4.2%)
Procedural Pain	0	3 (0.5%)	3 (1.0%)	0
Traumatic Haematoma	0	3 (0.5%)	1 (0.3%)	2 (0.6%)
Arthropod Bite	0	2 (0.3%)	2 (0.6%)	0
Excoriation	0	2 (0.3%)	2 (0.6%)	0
Muscle Strain	0	2 (0.3%)	2 (0.6%)	0
Thermal Burn	0	2 (0.3%)	2 (0.6%)	0
Investigations	5 (1.6%)	27 (4.3%)	11 (3.5%)	16 (5.2%)
Blood Creatine Phosphokinase Increased	1 (0.3%)	6 (1.0%)	2 (0.6%)	4 (1.3%)
Bacterial Test Positive	0	3 (0.5%)	1 (0.3%)	2 (0.6%)
Blood Lactate Dehydrogenase Increased	0	2 (0.3%)	0	2 (0.6%)
Cardiac Murmur	0	2 (0.3%)	1 (0.3%)	1 (0.3%)
Vascular Disorders	6 (1.9%)	18 (2.9%)	12 (3.8%)	6 (1.9%)
Hypertension	3 (1.0%)	9 (1.4%)	7 (2.2%)	2 (0.6%)
Psychiatric Disorders				
Depression	0	4 (0.6%)	2 (0.6%)	2 (0.6%)
Anxiety	0	2 (0.3%)	0	2 (0.6%)
Blood and Lymphatic System	0	9 (1.4%)	6 (1.9%)	3 (1.0%)

SOC/PT	Placebo N=309 n(%)	Vascepa Pooled N=622 n(%)	Vascepa 2 grams N=312 n(%)	Vascepa 4 grams N= 310 n(%)
Disorders				
Anaemia	0	5 (0.8%)	3 (1.0%)	2 (0.6%)
Ear and Labyrinth Disorders	3 (1.0%)	7 (1.1%)	6 (1.9%)	1 (0.3%)
Tinnitus	0	2 (0.3%)	2 (0.6%)	0
Reproductive System and Breast Disorders	3 (1.0%)	7 (1.1%)	3 (1.0%)	4 (1.3%)
Erectile Disorders	0	2 (0.3%)	1 (0.3%)	1 (0.3%)

Only two reported AEs occurred at least 1% more in the Vascepa Pooled group than Placebo: “Arthralgia” and “Oropharyngeal Pain”.

7.4.2 Laboratory Findings

Generally a full chemistry, hematology, and urinalysis were examined prior to the start of treatment phase (Week 0) and at the end of treatment (Week 12) or upon early termination for the MARINE and ANCHOR trials.

Analyses focused on outliers or shifts

The following table summarizes a few laboratory results above certain thresholds.

Liver enzymes
There were numerically more patients on Vascepa with mild elevations of ALT (up to 2XULN) than Placebo, 12.8% vs. 10.3%, respectively. The elevations seemed to be dose-related with more patients on Vascepa 4g (14.4%) with elevated ALT than Vascepa 2g (11.3%).

One 68-year-old male patient (AMR01.01.0017-097-009) treated with 4 g/day Vascepa had an ALT value >3 x ULN. This patient’s ALT was 36 U/L at randomization. On Study Day 87 (one day after the last dose of study treatment), the ALT value was 163 U/L. The ALT decreased to 73 U/L 12 days later. His concomitant medications included simvastatin and lisinopril/hydrochlorothiazide.

As summarized in the shift table below, more patients on Vascepa with “Baseline Normal ALT” shifted to “Endpoint High ALT” than patients on Placebo (8.4% vs. 5.5%).

Glucose
The number of patients with blood glucose ≥ 130 mg/dL was similar in the Placebo group (3.3%) and the Vascepa Pooled group (2.7%). As summarized in the glucose shift table below, slightly more patients on Placebo with a “Baseline Normal Glucose”

shifted to “Endpoint High Glucose” as compared to the Vascepa Pooled group (10.6% vs. 9.0%)

Table 60: Treatment-Emergent Laboratory Results at any Time Post-Baseline, Hypertriglyceridemia, Placebo-Controlled Integrated Dataset

Parameter	Placebo N=309 n/N (%)	Vascepa Pooled N=622 n/N (%)	Vascepa 2g N=312 n/N (%)	Vascepa 4g N=310 n/N (%)
ALT				
>1x ULN to 2x ULN	**24/234 (10.3)**	**60/467 (12.8)**	**26/231 (11.3)**	**34/236 (14.4)**
>3 x ULN	0/234	1/467 (0.2)	0/231	1/236 (0.4)
AST				
>1x ULN to 2x ULN	31/256 (12.1)	61/506 (12.1)	29/256 (11.3)	32/250 (12.8)
>3 x ULN	0/256	0/506	0/256	0/250
ALP				
>1x ULN to 2x ULN	13/288 (4.5)	10/576 (1.7)	6/291 (2.1)	4/285 (1.4)
Bilirubin				
>1x ULN to 2x ULN	1/294 (0.3)	9/595 (1.5)	7/300 (2.3)	2/295 (0.7)
BUN				
≥31 mg/dL	2/301 (0.7)	2/607 (0.3)	2/304 (0.7)	0/303
Calcium				
≤7 mg/dL	0/301	1/607 (0.2)	1/304 (0.3)	0/303
Creatine Kinase				
1x ULN to 5x ULN	22/241 (9.1)	43/510 (8.4)	18/255 (7.1)	25/255 (9.8)
Creatinine				
Female: <0.5 mg/dL	2/103 (1.9)	10/213 (4.7)	6/106 (5.7)	4/107 (3.7)
Male: <0.65 mg/dL	8/198 (4.0)	23/394 (5.8)	18/198 (9.1)	5/196 (2.6)
Glucose				
≥130 mg/dL	10/301 (3.3)	16/603 (2.7)	4/302 (1.3)	12/301 (4.0)
Potassium				
≥5.5 mEq/L	4/301 (1.3)	0/603	0/303	0/300
Sodium				
≤130 mEq/L	1/301 (0.3)	4/607 (0.7)	2/304 (0.7)	2/303 (0.7)

Source: ISS, Table 8-5, pg. 122.

The percentage of patients who had normal ALT values at baseline and abnormal at Week 12 Endpoint was higher for the pooled Vascepa group than for Placebo: 8.4% and 5.5%, respectively (see table below).

Table 61: Shift Table For ALT From Baseline to Endpoint- Hypertriglyceridemia Placebo-Controlled Integrated Dataset

Parameter: ALT	**Vascepa Pooled N=622 n (%)**			
	Baseline Low	Baseline Normal	Baseline High	Missing
Endpoint Low	1 (0.2%)	0	0	0
Endpoint Normal	0	404 (68.1%)	41 (6.9%)	0
Endpoint High	0	50 (8.4%)	97 (16.4%)	0
Endpoint Missing	0	24	5	0
Parameter: ALT	**Vascepa 2g N=312 n(%)**			
	Baseline Low	Baseline Normal	Baseline High	Missing
Endpoint Low	1 (0.3%)	0	0	0
Endpoint Normal	0	203 (68.1%)	25 (8.4%)	0
Endpoint High	0	22 (7.4%)	47 (15.8%)	0
Endpoint Missing	0	11	3	0
Parameter ALT	**Vascepa 4g N=310 n(%)**			
	Baseline Low	Baseline Normal	Baseline High	Missing
Endpoint Low	0	0	0	0
Endpoint Normal	0	201 (68.1%)	16 (5.4%)	0
Endpoint High	0	28 (9.5%)	50 (16.9%)	0
Endpoint Missing	0	13	2	0
Parameter: ALT	**Placebo N= 309 n(%)**			
	Baseline Low	Baseline Normal	Baseline High	Missing
Endpoint Low	0	0	0	0
Endpoint Normal	0	211 (72.3%)	24 (8.2%)	0
Endpoint High	0	16 (5.5%)	41 (14.0%)	0
Endpoint Missing	0	12	5	0

Source: ISS, Table ISS.HT.7.1-5.

For AST, BUN, and CK, the percentage of patients with shifts from normal at baseline to high at endpoint were similar for the pooled Vascepa and Placebo groups

The percentage of patients who had normal glucose values at Baseline that were abnormal at Week 12 Endpoint was higher for the Placebo group than for the pooled Vascepa group, 10.6% vs. 9.0%, respectively (see table below).

Table 62: Shift Table for Glucose From Baseline to Endpoint- Hypertriglyceridemia Placebo-Controlled Integrated Dataset

Parameter: Glucose	**Vascepa Pooled N=622 n (%)**			
	Baseline Low	Baseline Normal	Baseline High	Missing

Parameter: Glucose	**Vascepa Pooled N=622 n (%)**			
Endpoint Low	0	1 (0.2%)	0	0
Endpoint Normal	0	214 (36.3%)	36 (6.1%)	2
Endpoint High	0	53 (9.0%)	285 (48.4%)	0
Endpoint Missing	0	17	14	0
Parameter: Glucose	**Vascepa 2g N=312 n(%)**			
	Baseline Low	Baseline Normal	Baseline High	Missing
Endpoint Low	0	1 (0.3%)	0	0
Endpoint Normal	0	112 (37.8%)	21 (7.1%)	0
Endpoint High	0	21 (7.1%)	141(47.6%)	0
Endpoint Missing	0	8	8	0
Parameter Glucose	**Vascepa 4g N=310 n(%)**			
	Baseline Low	Baseline Normal	Baseline High	Missing
Endpoint Low	0	0	0	0
Endpoint Normal	0	102 (34.8%)	15 (5.1%)	0
Endpoint High	0	32 (10.9%)	144 (49.1%)	0
Endpoint Missing	0	9	6	0
Parameter: Glucose	**Placebo N= 309 n(%)**			
	Baseline Low	Baseline Normal	Baseline High	Missing
Endpoint Low	0	0	0	0
Endpoint Normal	0	108 (37.0%)	20 (6.8%)	0
Endpoint High	0	31 (10.6%)	133 (45.5%)	0
Endpoint Missing	0	4	13	0

Source: ISS, Table ISS.HT.7.1-5.

Analyses Focused On Measures of Central Tendency

The following table summarizes the mean changes in different laboratory tests from Baseline to Week 12 Endpoint. Over the course of the 12 week period, there were small numerical differences between the Vascepa Pooled group and Placebo of unknown clinical significance.

Table 63: Mean Changes in Various Laboratory Parameters from Baseline to Endpoint-Hypertriglyceridemic Placebo-controlled Dataset

Laboratory Parameter	Placebo N=309	Vascepa Pooled N=622	Vascepa 2g N=312	Vascepa 4g N=310
ALT (U/L)				
n	292	592	297	295
Baseline mean (SD)	32.5 (15.3)	33.6 (15.7)	33.7 (15.6)	33.6 (15.7)
Week 12 Endpoint mean (SD)	32.5 (17.6)	34.1 (16.8)	33.3 (15.9)	35.0 (17.6)
Mean Change (SD)	0.0 (11.8)	0.5 (11.7)	-0.3 (11.3)	1.4 (12.1)
AST (U/L)				
n	292	593	298	295
Baseline mean (SD)	27.3 (10.4)	27.9 (10.6)	27.7 (10.8)	28.1 (10.4)
Week 12 Endpoint mean (SD)	27.0 (11.6)	28.0 (10.4)	27.4 (10.4)	28.5 (10.3)
Mean Change (SD)	-0.3 (7.9)	0.1 (8.1)	-0.2 (8.4)	0.4 (7.9)
Creatine Kinase (U/L)				
n	292	593	298	295
Baseline mean (SD)	160.5 (133.3)	146.1 (126.2)	140.8 (106.2)	151.5 (143.6)
Week 12 Endpoint mean (SD)	153.3 (136.1)	140.7 (111.5)	136.2 (119.4)	145.3 (102.9)
Mean Change (SD)	-7.2 (95.4)	-5.4 (114.7)	4.6 (95.9)	-6.2 (131.2)
Glucose (mg/dL)				
n	292	589	296	293
Baseline mean (SD)	126.4 (36.2)	130.4 (39.6)	131.8 (42.5)	129.1 (36.4)
Week 12 Endpoint mean (SD)	130.1 (37.3)	135.1 (45.4)	133.9 (43.6)	136.3 (47.3)
Mean Change (SD)	3.7 (26.0)	4.7 (32.4)	2.2 (32.0)	7.2 (32.6)
Creatinine (mg/dL)				
n	292	593	298	295
Baseline mean (SD)	0.89 (0.2)	0.87 (0.2)	0.87 (0.2)	0.87 (0.2)
Week 12 Endpoint mean (SD)	0.85 (0.2)	0.84 (0.2)	0.84 (0.2)	0.85 (0.2)
Mean Change (SD)	-0.03 (0.1)	-0.03 (0.1)	-0.03 (0.1)	-0.03 (0.1)

7.4.3 Vital Signs

Generally vital signs were assessed prior to the start of treatment phase (Week 0) and at the end of treatment (Week 12) or upon early termination for the MARINE and ANCHOR trials (Hypertriglyceridemic Placebo-Controlled Dataset).

There were no differences between the treatment groups and no changes over time in mean vitals signs (SBP, DBP, pulse rate, and body weight) for these two trials.

7.4.4 Electrocardiograms (ECGs)

For the two trials in the Hypertriglyceridemic Placebo-Controlled Dataset, a 12-lead ECG was conducted prior to the start of treatment phase (Week 0) and/or at screening or during placebo or dietary run-ins, and at the end of treatment (Week 12) or upon early termination. There were no clinically significant changes in ECG parameters in the Vascepa versus the placebo groups.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See the following analysis in Section 7.5.2.

7.5.2 Time Dependency for Adverse Events

TEAEs are summarized by the date of onset in the following table. The highest incidence of TEAEs was reported in the first week after randomization for all three treatment arms. The incidence of TEAEs was similar between Vascepa 2g and Vascepa 4g during the weeks of the double-blind period and was numerically not different from Placebo.

Table 64: Incidence of any TEAE of any SOC by Week of Onset of AE-Hypertriglyceridemia, Placebo-Controlled Integrated Dataset

	Week 1 n(%)	Week 2 n(%)	Week 3 n(%)	Week 4 n(%)	Week 5 n(%)	Week 6 n(%)	Week 7 n(%)	Week 8 n(%)	Week 9 n(%)	Week 10 n(%)	Week 11 n(%)	Week 12 n(%)	>Week 13 n(%)	Over-all n(%)
Placebo														
n	309	309	309	309	309	307	305	303	302	298	296	293	293	309
TEAE in any SOC	49 (15.9)	15 (4.9)	13 (4.2)	8 (2.6)	8 (2.6)	6 (2.0)	8 (2.6)	4 (1.3)	9 (3.0)	9 (3.0)	6 (2.0)	6 (2.0)	10 (3.4)	151 (48.9)
Vascepa Pooled														
N	622	622	622	622	622	615	611	611	609	604	602	600	597	622
TEAE in any SOC	84 (13.5)	22 (3.5)	22 (3.5)	28 (4.5)	14 (2.3)	7 (1.1)	10 (1.6)	8 (1.3)	14 (2.3)	20 (3.3)	16 (2.7)	16 (2.7)	24 (4.0)	285 (45.8)
Vascepa 2 g/day														
n	312	312	312	312	312	310	308	308	307	303	303	301	298	312
TEAE in any SOC	42 (13.5)	13 (4.2)	8 (2.6)	16 (5.1)	9 (2.9)	4 (1.3)	4 (1.3)	3 (1.0)	10 (3.3)	11 (3.6)	6 (2.0)	6 (2.0)	10 (3.4)	142 (45.5)
Vascepa 4 g/day														
n	310	310	310	310	310	305	303	303	302	301	299	299	299	310
TEAE in any SOC	42 (13.5)	9 (2.9)	14 (4.5)	12 (3.9)	5 (1.6)	3 (1.0)	6 (2.0)	5 (1.7)	4 (1.3)	9 (3.0)	10 (3.3)	10 (3.3)	14 (4.7)	143 (46.1)

AE = adverse event; TEAE = treatment-emergent adverse event; SOC = system organ class.
The Safety Analysis Set includes all enrolled subjects who were administered at least one dose of study drug.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE preferred term for that treatment.
A patient with multiple AEs within a primary SOC is counted only once in the total row.
Source: ISS Summary Table ISS.HT.6.1-9

Source: ISS, Table 7-11, pg. 76.

7.5.3 Drug-Demographic Interactions

Gender

The applicant conducted analyses of TEAEs by gender for the Hypertriglyceridemic, Placebo-Controlled Integrated Dataset. In this population, there were 403 males and 219 females treated with Vascepa. The incidence of Vascepa patients reporting TEAEs was similar for males (44.7%) and females (47.9%). The overall AE profile also was similar for males and females.

Age

The applicant conducted analyses of TEAEs by age for the Hypertriglyceridemia Placebo-Controlled Integrated Dataset. In this population, there were 418 Vascepa patients aged 18-64 years and 204 Vascepa patients aged greater than 65 years. The incidence of patients reporting TEAEs in the Vascepa pooled group was similar for those aged 18-64 years (45.0%) and those aged 65 years or older (47.5%). The overall AE profile was similar for the 18-64 year olds compared to those aged 65 years or older.

Race

The applicant conducted analyses of TEAEs by race (white versus other) for the Hypertriglyceridemia Placebo-Controlled Integrated Dataset. In this population, there

were 586 white patients and 36 patients of other races. Despite the disparity in the number of patients per race category, the incidence of patients reporting TEAEs in the Vascepa pooled group was generally similar for white patients (45.6%) and those of other races (50.0%). The overall AE profile was generally similar for the two categories of race.

7.5.4 Drug-Disease Interactions

The applicant conducted analyses of TEAEs and diabetes status. In the Hypertriglyceridemia Placebo-Controlled Integrated Dataset, there was one patient with type 1 diabetes, 386 patients with type 2 diabetes, and 235 patients with no diagnosis of diabetes.

The patient with type 1 diabetes did not report any TEAEs. The rate of TEAEs for type 2 diabetics treated with Vascepa (49%) was less than that of type 2 diabetics treated with placebo (54%). However, diabetics, in general tended to report higher incidence of AEs than non-diabetics (see following table).

Table 65: TEAEs in ≥2% or More Patients in Any Diabetes Category- Hypertriglyceridemia Placebo-Controlled Integrated Dataset

System Organ Class Preferred Term	Placebo N=309[1]		Vascepa Pooled N=622[1]	
	Type 2 n=194	Non-Diabetics n=115	Type 2 n=386	Non-Diabetics n=235
Any System Organ Class	105 (54.1)	46 (40.0)	189 (49.0)	96 (40.9)
Infections and Infestations	36 (18.6)	15 (13.0)	58 (15.0)	18 (7.7)
Urinary Tract Infection	9 (4.6)	3 (2.6)	12 (3.1)	2 (0.9)
Upper Respiratory Tract Infection	4 (2.1)	2 (1.7)	10 (2.6)	3 (1.3)
Bronchitis	5 (2.6)	3 (2.6)	5 (1.3)	3 (1.3)
Nasopharyngitis	5 (2.6)	3 (2.6)	7 (1.8)	0
Gastrointestinal Disorders	41 (21.1)	19 (16.5)	49 (12.7)	26 (11.1)
Diarrhea	12 (6.2)	5 (4.3)	16 (4.1)	7 (3.0)
Nausea	10 (5.2)	2 (1.7)	9 (2.3)	7 (3.0)
Abdominal Pain	5 (2.6)	0	3 (0.8)	1 (0.4)
Constipation	4 (2.1)	0	3 (0.8)	1 (0.4)
Eructation	2 (1.0)	6 (5.2)	3 (0.8)	1 (0.4)
Musculoskeletal and Connective Tissue Disorders	12 (6.2)	5 (4.3)	31 (8.0)	18 (7.7)
Arthralgia	3 (1.5)	1 (0.9)	8 (2.1)	8 (3.4)
Pain in Extremity	1 (0.5)	3 (2.6)	6 (1.6)	2 (0.9)
Muscle Spasm	4 (2.1)	1 (0.9)	2 (0.5)	0
General Disorders and Administration Site Conditions	7 (3.6)	5 (4.3)	14 (3.6)	15 (6.4)
Fatigue	4 (2.1)	1 (0.9)	4 (1.0)	3 (1.3)
Nervous System Disorders	12 (6.2)	4 (3.5)	21 (5.4)	7 (3.0)
Headache	4 (2.1)	0	1 (0.3)	2 (0.9)
Skin and Subcutaneous Tissue Disorders	13 (6.7)	3 (2.6)	12 (3.1)	12 (5.1)
Pruritus	4 (2.1)	1 (0.9)	1 (0.3)	2 (0.9)
Metabolism and Nutrition Disorders	8 (4.1)	4 (3.5)	18 (4.7)	4 (1.7)
Diabetes Mellitus	5 (2.6)	0	6 (1.6)	0
Vascular Disorders	6 (3.1)	0	9 (2.3)	9 (3.8)
Hypertension	3 (1.5)	0	4 (1.0)	5 (2.1)

1 There were no type 1 diabetics in the placebo group and one type 1 diabetic in the Vascepa pooled group; there were no TEAEs reported for the type 1 diabetic in the Vascepa pooled group.
AEs = adverse events; SOC = system organ class.
The Safety Analysis Set includes all enrolled patients who were administered at least one dose of study drug.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE preferred term for that treatment.
A patient with multiple AEs within a primary SOC is counted only once in the total row.
Source: ISS Summary Table ISS.HT.SGP.1-7

Source: ISS, Table 7-13, pg. 83.

7.5.5 Drug-Drug Interactions

Concomitant Statin Use
The applicant conducted analyses of TEAEs by patients receiving concomitant statins compared to those not receiving concomitant statins for the Hypertriglyceridemia Placebo-Controlled Integrated Dataset. A total of 481 patients received concomitant statin treatment with Vascepa treatment in this population, and 141 patients did not receive concomitant statin treatment. The incidence of patients reporting TEAEs was greater in patients receiving concomitant statins (47.6%) compared to those not taking concomitant statins (39.7%). The overall AE profile was generally similar for these groups.

The applicant conducted analyses of TEAEs by patients receiving concomitant statins compared to those not receiving concomitant statins for the Overall AMR101 Integrated Dataset. A total of 555 patients received statin treatment with Vascepa treatment and 128 patients did not receive concomitant statins. The incidence of patients reporting TEAEs was slightly lower in patients receiving concomitant statins (50.5%) compared to those not taking concomitant statins (58.0%). The overall AE profile was generally similar for these groups

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please see the pharmacology/toxicology report by Dr. Stephanie Leuenroth-Quinn. The following is an excerpt from the pharmacology/toxicology proposed labeling for Vascepa.

In 2-year rat carcinogenicity study with oral gavage doses of 0.09, 0.27, and 0.91 g/kg/day icosapent ethyl respectively, males did not exhibit drug-related neoplasms. Hemangiomas and hemangiosarcomas of the mesenteric lymph node, the site of drug absorption were observed in females at clinically relevant exposures based on body surface area comparisons across species relative to the maximum clinical dose of 4g/day. Overall incidence of hemangiomas and hemangiosarcomas in all vascular tissues did not increase with treatment.

In a 6-month carcinogenicity study in Tg.rasH2 transgenic mice with oral gavage doses of 0.5, 1.2, and 4.6 g/kg/day icosapent ethyl, drug-related incidences of benign squamous cell papiloma in the ski and subcutis of the tail was observed in high dose male mice. The papilomas were considered to develop secondary to chronic irritation of the proximal tail associated with fecal excretion of oil. Drug-related neoplasms were not observed in female mice.

Icosapent ethyl was not mutagenic with or without metabolic activation in the bacterial mutagenesis (Ames) assay or in the *in vivo* mouse micronucleus assay. A chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells was positive for clastogenicity with and without metabolic activation.

In an oral gavage rat fertility study, ethyl-EPA was administered at doses of 0.3, 1, and 3 g/kg/day to male rats for 9 weeks before mating and to female rats for 14 days before mating through day 7 of gestation increased anogenital distance in female pups and increased cervical ribs were observed at 3 g/kg/day (7 times human systemic exposure with 4 g/day clinical dose based on a body surface area comparison).

Reviewer Comment: Although female rats in the high dose group (exposure margin 7X the 4g/day clinical dose) had increased incidence of combined hemangiomas/ hemangiosarcomas at the mesenteric lymph node, the incidence of these vascular tumors at all anatomical sites combined was not statistically significant. Additionally, male rats did not exhibit an imbalance in vascular tumors at any anatomical site. These findings combined with the lack of imbalance in vascular tumors in mice suggest that the finding of increased hemangiomas/ hemangiosarcomas is of limited clinical significance.

7.6.2 Human Reproduction and Pregnancy Data

The following is an excerpt from the sponsor's proposed labeling:

(b) (4)

7.6.3 Pediatrics and Assessment of Effects on Growth

Safety and effectiveness in pediatric patients have not been established.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The applicant conducted a literature search for publications on overdose or withdrawal effects with Lovaza, Omacor, or Epadel. The search terms used were abuse, recreation, and overdose, over-dose, high dose AND toxic, poison, and risk hazard. The following databases were searched: Biological Abstracts, Embase, Int. Pharmaceuticals Abstracts, Life Sciences Collection, Medline, Medline Preprints, Inside Conferences, Chemical Business News, and Food Science & Technology. The literature search did not yield any citations on this topic.

7.7 Additional Submissions / Safety Issues

Case report forms for SAEs and discontinuations due to AEs that occurred in the open-label extension of AMR-01-01-0016 (MARINE) were submitted as part of the 120 Day Safety Update. All patients received 4 g daily of Vascepa in the open-label period, regardless of their initial dosing. The table below lists the patients with SAEs during the open-label extension of AMR-01-01-0016.

Table 66: List of Patients with SAEs During Open-Label Extension of AMR-01-01-0016 (MARINE) According to Initial Treatment Group

Double-Blind Treatment Group Patient No.	Adverse Event Preferred Term	Related to Study Drug	Resulted in Discontinuation
Placebo			
16-254-004	hyperparathyroidism [1]	no	no
16-255-005	osteoarthritis	no	no
16-354-010	hypertensive crisis	no	no
AMR101 2 g daily			
16-012-007	type 2 diabetes mellitus	no	no
16-254-001	arthralgia	no	no
16-553-002	diabetes mellitus	no	no
16-580-009	prostate cancer	no	no
AMR101 4 g daily			
16-354-009	ischemic stroke	no	no
16-356-019	angina pectoris	no	yes
	pharyngeal neoplasm benign	no	no
	renal failure acute	no	no
	atrial fibrillation	no	no
	post procedural hemorrhage	no	no
	respiratory failure	no	no
	impaired healing	no	no
	thrombosis	no	no
16-506-003	cardiac failure congestive	no	no
16-552-003	cholecystitis acute	no	no

1. The SAE of hyperparathyroidism started during the double-blind treatment period when the patient was on placebo. The patient recovered from the event during the open-label extension period.

Source: Applicant's 120 day safety update, Table 1, pg2.

The following table lists the patients who discontinued study during the open-label period of study AMR-01-01-0016.

Table 67: List of Patients Who Discontinued Study During Open-Label Study AMR-01-01-0016 According to Initial Treatment Group

Double-Blind Treatment Group Patient No.	Adverse Event Preferred Term	Related to Study Drug	Serious Adverse Event
Placebo			
16-017-001	bone pain arthralgia myalgia	yes yes yes	no no no
AMR101 2 g daily			
16-255-008	diarrhea	yes	no
AMR101 4 g daily			
16-013-001	tension headache	yes	no
16-356-019	angina pectoris	no	yes
16-580-009	erythema nodosum	no	no
Note: Patient 580-009 discontinued study drug but completed the open-label extension period. Patients 017-001, 255-008, 013-001, and 356-019 discontinued from the open-label extension period due to their adverse event(s).			

Source: Applicant's 120 Day Safety Update, Table 2 pg. 2.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

The applicant conducted a literature search for publications related to the safety of icosapent ethyl as part of the 120 Day Safety Update. The search covered the period from May through December 2011 and used the terms icosapent ethyl, Lovaza, Omacor, or Epadel. The abstracts are listed below:

Billman, George E; Harris, William S. Effect of dietary omega-3 fatty acids on the heart rate and the heart rate variability responses to myocardial ischemia or submaximal exercise. Am J Physiol Heart Circ Physiol 300: 6, Jun 2011

The consumption of omega-3 polyunsaturated fatty acids (n-3 PUFAs) has been reported to decrease resting heart rate (HR) and increase heart rate variability (HRV). However, the effects of n-3 PUFAs on these variables in response to a physiological

stress (e.g., exercise or acute myocardial ischemia), particularly in post myocardial infarction (MI) patients, are unknown.

Therefore, HR and HRV (high frequency and total R-R interval variability) were evaluated at rest, during sub-maximal exercise, and during a 2-min coronary artery occlusion at rest and before and 3 mo after n-3 PUFA treatment in dogs with healed MI (n = 59). The dogs were randomly assigned to either placebo (1 g/day corn oil, n = 19) or n-3 PUFA supplement (docosahexaenoic acid + eicosapentaenoic acid ethyl esters; 1 g/day, n = 6; 2 g/day, n = 12; or 4 g/day, n = 22) groups. The treatment elicited significant (P < 0.01) dose-dependent increases in right atrial n-3 PUFA levels but dose-independent reductions in resting HR and increases in resting HRV. In contrast, n-3 PUFAs did not attenuate the large changes in HR or HRV induced by either the coronary occlusion or sub-maximal exercise. These data demonstrate that dietary n-3 PUFA decreased resting (i.e., pre-exercise or pre-occlusion) HR and increased resting HRV but did not alter the cardiac response to physiologic challenges.

Bays, Harold E; Ballantyne, Christie M. Eicosapentaenoic Acid Ethyl Ester (AMR101) Therapy in Patients With Very High Triglyceride Levels (from the Multi-center, placebo controlled, Randomized, double-blind, 12-week study with an open-label Extension MARINE Trial). Am J Cardiol 108: 5, Sep 2011

AMR101 is an omega-3 fatty acid agent containing 96% eicosapentaenoic acid ethyl ester and no docosahexaenoic acid. Previous smaller studies suggested that highly purified eicosapentaenoic acid lowered triglyceride (TG) levels without increasing low-density lipoprotein (LDL) cholesterol levels. TG-lowering therapies such as fibrates, and fish oils containing both eicosapentaenoic acid and docosahexaenoic acid, can substantially increase LDL cholesterol levels when administered to patients with very high TG levels (500 mg/dl). The present double-blind study randomized 229 diet-stable patients with fasting TG 500 mg/dl and a 2,000 mg/dl (with or without background statin therapy) to AMR101 4 g/day, AMR101 2 g/day, or placebo. The primary end point was the placebo-corrected median percentage of change in TG from baseline to week 12.

The baseline TG level was 680, 657, and 703 mg/dl for AMR101 4 g/day, AMR101 2 g/ day, and placebo. AMR101 4 g/day reduced the placebo-corrected TG levels by 33.1% (n = 76, p <0.0001) and AMR101 2 g/day by 19.7% (n = 73, p = 0.0051). For a baseline TG level >750 mg/dl, AMR101 4 g/day reduced the placebo-corrected TG levels by 45.4% (n = 28, p = 0.0001) and AMR101 2 g/day by 32.9% (n = 28, p = 0.0016). AMR101 did not significantly increase the placebo-corrected median LDL cholesterol levels at 4 g/day (-2.3%) or 2 g/day (+5.2%; both p = NS). AMR101 significantly reduced non-high-density lipoprotein cholesterol, apolipoprotein B, lipoprotein-associated phospholipase A(2), very low-density lipoprotein cholesterol, and total cholesterol. AMR101 was generally well tolerated, with a safety profile similar to that of the placebo. In conclusion, the present randomized, double-blind trial of patients with very high TG levels demonstrated that AMR101 significantly reduced the TG levels

and improved other lipid parameters without significantly increasing the LDL cholesterol levels.

Watanabe, Eiichi; Sobue, Yoshihiro. Eicosapentaenoic acid for the prevention of recurrent atrial fibrillation. Ann. Noninvasive Electrocardiol 16: 4, 373-378, October 2011
Background: n-3 polyunsaturated fatty acids, primarily eicosapentaenoic acid (EPA), has been reported to have anti-arrhythmic and anti-inflammatory effects. The aim of the present study was to examine whether the combination of anti-arrhythmic drugs and EPA reduced the frequency of atrial fibrillation (AF) in patients with paroxysmal AF. Methods: We studied 50 patients with paroxysmal AF (age, 54 +- 9 years) after excluding the clinical conditions associated with an increased risk of AF. Patients were initially treated with anti-arrhythmic drugs for 6 months (the observation period), and thereafter, EPA was added at a dose of 1.8 g/day for 6 months (the intervention period). During a one-year period, patients obtained an ECG recording using a portable device each morning and when arrhythmia-related symptom occurred. The end point was the difference of the AF burden (defined by the days of AF per month) between observation period and intervention period. Plasma EPA and C-reactive protein (CRP) levels were also determined. Results: There was no significant difference in the AF burden before and after intervention (2.6 +- 2.2 days/months vs. 2.5 +- 2.2 days/months, P = 0.45). Although EPA level was significantly increased (42 +- 15 mu/mL to 120 +- 47 mu/mL, P < 0.001), CRP level was unchanged (1.04 +- 0.69 mg/L to 0.96 +- 0.56 mg/L, P = 0.24) following EPA treatment.

Conclusions: Treatment of EPA in combination with antiarrhythmic drugs did not reduce the AF burden or the CRP levels in paroxysmal AF patients who had no evidence of substantial structural heart disease.

Okabe, Naohiko; Nakamura, Takehiro. Eicosapentaenoic acid prevents memory impairment after ischemia by inhibiting inflammatory response and oxidative damage. Journal of Stroke and Cerebrovascular Diseases 20: 3, 188-195, May-June 2011

Previous studies have demonstrated that the generation of reactive oxygen species and an excessive inflammatory reaction are involved in the progression of neural damage following brain ischemia. In this study, we focused on the anti-inflammatory and antioxidant properties of eicosapentaenoic acid (EPA). Gerbils were treated intra-peritoneally with 500 mg/kg of EPA ethyl for 4 weeks until the day of forebrain ischemia, which was induced by occluding the bilateral common carotid artery for 5 minutes. In the first part of the 2-part experiment, the effect of EPA treatment was evaluated using hematoxylin and eosin staining and deoxynucleotidyl transferase-mediated dUTP nick-end labeling as a marker of cell death (n = 3 per group). The inflammatory reaction was evaluated using anti-Iba1 immunohistochemistry, a marker of microglial activation (n = 3 per group), and detection of 8-hydroxyl-2(prime)-deoxyguanosine, a marker of oxidative DNA damage (n = 4 per group). In the second part of the experiment, the effect of EPA treatment on memory function was examined

using an 8-arm radial maze (n = 6 per group). EPA treatment significantly inhibited DNA oxidative damage (P < .05) and accumulation of Iba1-positive cells in the CA1 area at 12 and 72 hours after the induction of ischemia, and also decreased apoptotic neurons and neuronal death (P < .001) at 72 hours after ischemia. EPA treatment also significantly improved memory function (P < .05). These findings suggest that EPA inhibits the inflammatory reaction and oxidative damage occurring after ischemic brain injury, and also may contribute to the prevention of neural damage and memory impairment following such injury.

Nanjwade, Basavaraj K; Patel, Didhija J. Functions of lipids for enhancement of oral bioavailability of poorly water-soluble drugs. Scientia Pharmaceutica 79: 4, 705-727, 2011.

Lipid-based formulations encompass a diverse group of formulations with very different physical appearance, ranging from simple triglyceride vehicles to more sophisticated formulations such as self-emulsifying drug delivery systems (SEDDS). Lipid-based drug delivery systems may contain a broad range of oils, surfactants, and co-solvents. They represent one of the most popular approaches to overcome the absorption barriers and to improve the bioavailability of poorly water-soluble drugs. Diversity and versatility of pharmaceutical grade lipid excipients and drug formulations as well as their compatibility with liquid, semi-solid and solid dosage forms make lipid systems most complex. Digestion of triglyceride lipids, physicochemical characteristics and solubilization of lipid digestion products as well as intestinal permeability are some of the variable parameters of such formulations. Furthermore, among the factors affecting the bioavailability of the drug from lipid-based formulations are the digestion of lipid, the mean emulsion droplet diameter, the lipophilicity of the drug and the type of lipids. The solubility of the Active Pharmaceutical Ingredient in the Lipid System, the desorption isotherm and the digestibility of lipid vehicle are important issues to be considered for formulations of isotropic lipid formulations.

This review also describes the fate of lipid formulations in the gut and the factors influencing the bioavailability from lipid-based formulations. Novel formulation systems and currently marketed products conclude this review.

Inoue, Nobuhiro; Fukuda, Shingo. Highly purified eicosapentaenoic acid improves cerebral vasomotor-reactivity in patients with chronic cerebral ischemia. Therapeutic Research 32: 10, 1325-1332, October 2011

Background: Eicosapentaenoic acid (EPA) was reported to significantly reduce the recurrence of stroke in a cohort of hypercholesterolemic Japanese patients receiving low dose statin therapy. We measured the cerebral blood flow to assess how EPA contributes to decreasing the incidence of recurrent stroke in patients with chronic cerebral ischemia. Methods: Eight patients (mean age 64 +- 10.3 years) with chronic cerebral ischemia were administrated 1800 mg of EPA daily. At entry into the study and

3 months later we measured the patients' serum level of fatty acids, assessed their depressive state using the Japan Stroke Scale-Depression Scale (JSS-D), and determined the cerebral blood flow (CBF) at rest and after acetazolamide challenge. Lastly, we calculated cerebral vasomotor reactivity (CVR). Results: After 3 months of EPA administration serum EPA and the EPA/arachidonic acid ratio were significantly increased (p=0.002 and p=0.003, respectively). Comparison of the pre- and post-administration JSS-D showed that depression tended to be ameliorated. At 3 months CVR (%) was significantly increased in the left occipital- (p = 0.004) and right tempore-parietal cortex (p=0.043). Comparison of the EPA concentration and CVR (%) at entry and after 3-month treatment revealed a positive correlation in the left occipital- (r=0.512, p=0.043) and right temporo-parietal cortex (r=0.552, p=0.02).

Conclusion: In patients treated with EPA, the significant increase in CVR (%) in the left occipital- and right temporo-parietal cortex correlated with the increase in the plasma EPA level and depression amelioration. Our findings suggest that EPA contributes to amelioration of cerebral artery remodeling in patients with chronic cerebral ischemia and inhibits its recurrence.

Davidson, Michael H; Kling, Douglas. Novel developments in omega-3 fatty acid-based strategies. Curr Opin Lipidol 22: 6, 437-44, Dec 2011.

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) have been attributed with several health benefits, including triglyceride lowering and cardiovascular disease risk reduction. This review focuses on new prescription omega-3 fatty acid products in development and recently published data regarding omega-3 fatty acid effects on arrhythmias, heart failure, and platelet inactivation.

A free fatty acid form of n-3 PUFA was found to produce a four-fold higher area under the plasma n-3 PUFA curve than prescription omega-3-acid ethyl esters in patients on a low-fat diet. Eicosapentaenoic acid ethyl esters reduced triglyceride without significantly elevating LDL cholesterol in patients with severe hypertriglyceridemia and in those with mixed dyslipidemia. Recent investigations of n-3 PUFA effects on ventricular and atrial arrhythmias, including studies in patients with implanted defibrillators, failed to demonstrate a significant benefit. However, increased fatty fish or n-3 PUFA consumption was associated with a lower rate of hospitalization in heart failure patients. A further important finding was potentiation of the anti-platelet response when n-3 PUFAs were added to aspirin+clopidogrel. Although n-3 PUFA therapy continues to show promise in the prevention and management of cardiovascular diseases, further research is necessary to more fully elucidate its role in specific disorders.

Bot, Mariska; Pouwer, Franocois. Supplementation with eicosapentaenoic omega-3 Fatty Acid does not influence serum brain-derived neurotrophic factor in diabetes mellitus patients with major depression: a randomized controlled pilot study. Neuropsychobiology 63: 4, 219-23, 2011.

Background: Low brain-derived neurotrophic factor (BDNF) levels are observed in both depressed and diabetes patients. Animal research has shown that omega-3 polyunsaturated fatty acids increase BDNF levels. In this exploratory randomized double-blind placebo-controlled study in diabetes patients with major depression, we tested whether (a) omega- 3 ethyl eicosapentaenoic acid (E-EPA) leads to increased serum BDNF levels and (b) whether changes in BDNF levels are associated with corresponding changes in depression. Methods: Patients received 1 g/day E-EPA (n = 13) or placebo (n = 12) for 12 weeks, in addition to ongoing antidepressant therapy. At baseline and 12-week follow-up, we determined serum BDNF levels and depression severity, using the Montgomery-osberg Depression Rating Scale. Results: We found no effect of E-EPA on BDNF levels (t = -0.144, p = 0.887), and changes in BDNF levels and depression severity were not significantly associated (Spearman's = -0.115, p = 0.593).

Conclusion: Our study does not provide evidence that supplementation with E-EPA improves BDNF levels in depressed diabetes patients already using antidepressants.

Mizia-Stec, Katarzyna; Haberka, Maciej. N-3 polyunsaturated fatty acid therapy improves endothelial function and affects adiponectin and resistin balance in the first month after myocardial infarction. Archives of Medical Science 7: 5, 788-795, 2011 Introduction: N-3 Polyunsaturated fatty acids (n-3 PUFA) exert clinical beneficial effects in patients after acute myocardial infarction (AMI). However, their exact mechanisms of action are not well recognized yet. Our aim was to evaluate effects of early introduced n-3 PUFA supplementation on endothelial function and serum adipokine concentrations in patients with AMI. Material and methods: Thirty-eight patients with AMI and successful coronary stent implantation were randomized to the study group (PUFA group: n = 19; standard therapy + PUFA 1 g daily) and the control group (control group: n = 19; standard therapy). The study group patients were given n-3 PUFA (Omacor 1 g daily) starting from the 3rd day of AMI. Ultrasound vascular indexes (flow-mediated dilatation [FMD], nitroglycerine-mediated dilation [NMD]) and serum concentrations of adiponectin and resistin (ELISA) were evaluated before and after 30 days of pharmacotherapy.

Results: Comparison of the mean delta values (baseline/after 30 days of therapy) between groups revealed significant differences for delta FMD (PUFA 7.6 +-12.4% vs. control -1.7 +-10.5%, p = 0.019) and delta resistin concentrations (PUFA 1.0 +-3.8 pg/ml vs. control -1.6 +-2.9 pg/ml, p = 0.028). Multiple linear regression analysis for all subjects revealed the n-3 PUFA supplementation (r = 10.933, p = 0.004) and waist circumference (r = -0.467, p = 0.01) as independent factors associated with delta FMD values (R-adjusted 0.29; p = 0.002). Conclusions: Early and short-term n-3 PUFA supplementation in AMI with successful primary PCI and optimal pharmacotherapy improves endothelial function. However, increased resistin

serum levels observed after 1-month n-3 PUFA supplementation merits further investigations. Copyright (c) 2011 Termedia & Banach.

Kar S. Omacor and Omega-3 Fatty Acids for Treatment of Coronary Artery Disease and the Pleiotropic Effects. Am J Ther. Oct 4, 2011

Omega-3 polyunsaturated fatty acids are found in fish oil and they have been shown to mitigate the risk of cardiovascular disease. Omega-3 fatty acids are essential fatty acids because they cannot be synthesized de novo and must be consumed from dietary sources such as marine fish. It reduces fatal and nonfatal myocardial infarction, stroke, coronary artery disease, sudden cardiac death, and all-cause mortality. It also has beneficial effects in mortality reduction after a myocardial infarction. Omacor is a highly potent form of Omega-3 fatty acids that lowers plasma triglycerides. In patients with severe hypertriglyceridemia who are refractory to statins, it helps augment triglyceride reduction. Omacor also increases high-density lipoprotein and decreases low-density lipoprotein levels. It is well tolerated with minimal adverse effects and no known interactions causing rhabdomyolysis. In high doses, Omacor has pronounced cardiovascular benefits with improvement of triglycerides and various lipid parameters. Omega-3 fatty acids have also been shown to have beneficial effects on arrhythmias, inflammation, and heart failure. It may also decrease platelet aggregation and induce vasodilation. Omega-3 fatty acids also reduce atherosclerotic plaque formation and stabilize plaques preventing plaque rupture leading to acute coronary syndrome. Moreover, omega-3 fatty acids may have antioxidant properties that improve endothelial function and may contribute to its anti-atherosclerotic benefits. In this review, we sought to provide the current literature on the use of omega-3 fatty acids and the potent formulation Omacor in the treatment of coronary artery disease.

Christian, Jennifer B; Juneja, Maneesh X. Prevalence, characteristics, and risk factors of elevated triglyceride levels in US children. Clin Pediatr (Phila) 50: 12, 1103-9, Dec 2011

Limited information is available on the epidemiology of hypertriglyceridemia (HTG; 150-499 mg/dL) and severe HTG (SHTG; >500 mg/dL) in children. This study estimates the prevalence of HTG and SHTG, evaluates factors that may be associated with these conditions, and describes the use of dyslipidemic agents in children. The sample included children 12 to 19 years old who participated in National Health and Nutrition Examination Survey (NHANES) 2001-2008 (n = 3248) and children 5 to 19 years of age who were part of a large managed-care claims database in the United States (n = 65 258). Results from NHANES confirm the rarity of SHTG in the US pediatric population (ie, 0.2%). Factors statistically significantly associated with having HTG or SHTG in the claims database were being male, 12 to 19 years old, having high low-density lipoprotein (LDL), having low high-density lipoprotein (HDL), diabetes, and psychological disorders. Fibrates were the most commonly prescribed triglyceride-lowering agent among children with SHTG, followed by statins and Lovaza.

Salm, Paul; Taylor, Paul J. Simultaneous quantification of total eicosapentaenoic acid, docosahexaenoic acid and arachidonic acid in plasma by high-performance liquid chromatography-tandem mass spectrometry. Biomed Chromatogr 25: 6, 652-9, Jun 2011.

A method for the simultaneous quantification of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and arachidonic acid (AA) in human plasma by HPLC-tandem mass spectrometry (HPLC-MS/MS) was developed and validated. Free and etherified forms of fatty acids were hydrolyzed from plasma samples in the presence of an internal standard and subjected to liquid-liquid extraction. The chromatographic run time was 3.5 min per sample. The assay was linear from 0.5 to 300 mg/L (r(2) > 0.997, n = 18). Based on matrix addition, accuracy deviation was <15%, except for AA at 10 mg/L (30-90%), whereas precision was <8% for all fatty acids studied. The method was applied to the measurement of these omega-3 fatty acids in a fish oil supplement study with healthy volunteers. Healthy males (n = 4) were administered a supplement containing 465 mg EPA and 375 mg DHA per capsule (Omacor). A dose of two capsules was given daily over a 4 week period. Pre-treatment concentrations varied between subjects for EPA (17-68 mg/L), DHA (36-63 mg/L) and AA (121-248 mg/L). During the dosing period EPA increased 460-480% from the baseline concentration, while DHA increased 150- 160%. The EPA-AA ratio increased from 0.07-0.56 to 0.3-3.1 after 4 weeks of dosing. In conclusion, the method described could be suitable for monitoring EPA, DHA and AA in clinical studies that may aid in achieving optimal concentrations of these fatty acids in patients who could be at risk of sudden cardiac death. Copyright e 2010 John Wiley & Sons, Ltd.

DeDea, Larissa. When to take statins; Lovaza versus OTC fish oil supplements. JAAPA 24: 5, 23, May 2011.

Salisbury, Adam C.; Harris, William S. Relation Between Red Blood Cell Omega-3 Fatty Acid Index and Bleeding During Acute Myocardial Infarction. Am J Cardiol 109: 13–18, 2012.

Omega-3 fatty acids have multiple cardiovascular benefits but may also inhibit platelet aggregation and increase bleeding risk. If this platelet inhibition is clinically meaningful, patients with the highest omega-3 indexes (red blood cell eicosapentaenoic acid plus docosahexaenoic acid), which reflect long-term omega-3 fatty acid intake, should be at the risk for bleeding. In this study, 1,523 patients from 24 United States centers who had their omega-3 indexes assessed at the time of acute myocardial infarction were studied. The rates of serious bleeding (Thrombolysis In Myocardial Infarction [TIMI] major or minor) and mild to moderate bleeding (TIMI minimal) were identified in patients with low (<4%), intermediate (4% to 8%), and high (>8%) omega-3 indices. There were no differences in bleeding across omega-3 index categories. After multivariate adjustment, there remained no association between the omega-3 index and either

serious (per 2% increase, relative risk 1.03, 95% confidence interval 0.90 to 1.19) or mild to moderate bleeding (per 2% increase, relative risk 1.02, 95% confidence interval 0.85 to 1.23). In conclusion, no relation was found between the omega-3 index and bleeding in this large, multicenter cohort of patients with acute myocardial infarction, suggesting that concerns about bleeding should not preclude the use of omega-3 supplements or increased fish consumption when clinically indicated.

9.2 Labeling Recommendations

See final approved labeling.

9.3 Advisory Committee Meeting

An Advisory Committee meeting was not considered necessary given that there were no major safety issues identified with Vascepa.

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/s/

IFFAT N CHOWDHURY
07/25/2012

ERIC C COLMAN
07/26/2012

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA 20-2057
Vacepa 1 gram capsules
(icosapent ethyl)
Applicant: Amarin Pharma, Inc.
Reviewer: Iffat N. Chowdhury, MD

Filing Meeting: November 9, 2011
Letter date: September 23, 2011
Date Received: September 26, 2011
PDUFA date: July 26, 2012

The applicant, Amarin Pharma, Inc., has submitted NDA 202057 as a 505(b)(2) for the following indication:

VASCEPA (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) (b) (4) (b) (4) levels in adult patients with very high (≥ 500 mg/dL) triglycerides.

According to the applicant, Vascepa is a single active ingredient moiety comprised of 96-99% pure icosapent ethyl.

Efficacy Data: This NDA is comprised of a total of 15 clinical trials:

- two Phase 3 studies
  - MARINE- (AMR-01-01-0016), for patients with very high (≥500 mg/dL) fasting TG levels
  - ANCHOR- (AMR-01-01-0017), for patients at high risk for CVD with persistent high fasting TG levels (≥200-499 mg/dL), despite statin treatment to LDL-C goal
- two Phase 1 studies in healthy subjects
- three drug-drug interaction trials
- eight clinical trials in patients with CNS disorders (supportive

The applicant submitted the study report (but not the data sets) for the ANCHOR trial, despite being told that it would not support the severe hypertriglyceridemia (≥500 mg/dL) indication.

Pivotal Phase 3 trial- MARINE-
MARINE was a Phase 3, randomized, double-blind, placebo-controlled, multi-center study designed to assess the efficacy and safety of Vascepa for the treatment of patients with very high TG levels in combination with a low fat, low cholesterol diet and existing stabilized statin therapy, if applicable. The primary objective of this study was to determine the efficacy of 2 and 4 g/day Vascepa, compared with placebo, in lowering fasting TG levels in patients with fasting TG levels ≥500 mg/dL and ≤2000 mg/dL. After a 4- to 6-week diet and lifestyle stabilization period, patients entered a 2-week TG qualifying period, where eligible patients were to have an average fasting TG level of ≥500 mg/dL to enter the 12-week double-blind treatment period.

A total of 229 patients were randomized to receive 4 g/day Vascepa, 2 g/day Vascepa, or placebo for the 12-week double-blind treatment period. Stratification was by baseline TG level (≤750 mg/dL or >750 mg/dL), gender, and the use of statin therapy (treated or not treated with statin therapy at baseline) at randomization. Patients who completed the 12-week double-blind treatment period were eligible to enter a 40-week, open-label

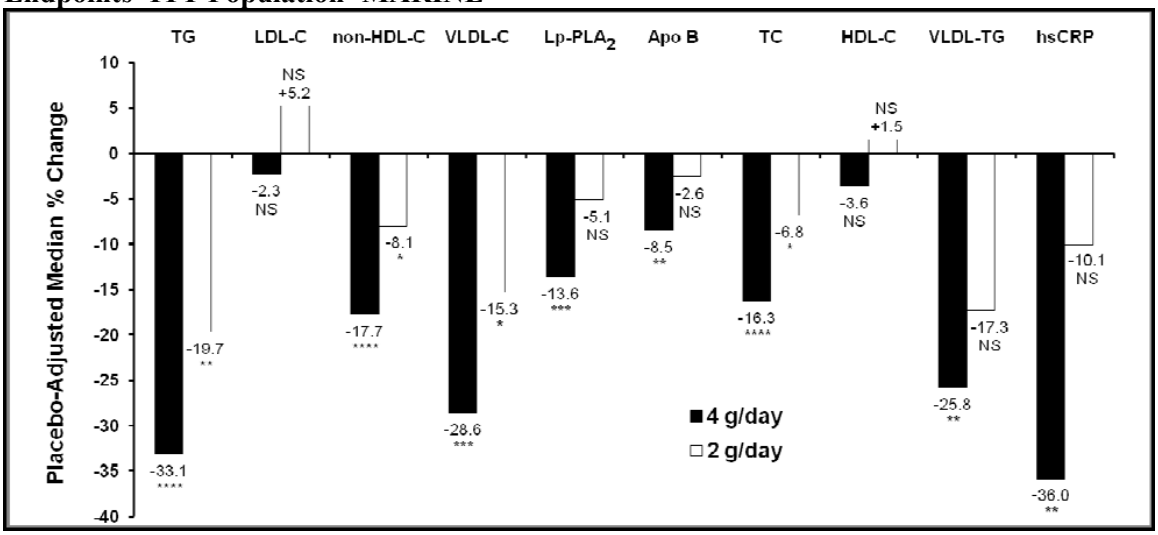
extension period, in which all patients were to receive open-label 4 g/day Vascepa and attend study visits every 12 weeks.

While the protocol prohibited the use of concomitant lipid-altering therapies, patients who could not be safely discontinued from statin therapy (e.g., having a high risk for CVD) were permitted to enroll in the study provided the statin dose was stable for ≥4 weeks prior to the baseline TG qualifying period and all other lipid and biochemical criteria were met. Enrolling patients on stable statin doses enabled the study to be consistent with current medical practice and representative of the real world disease population.

Because the open-label extension period of MARINE is ongoing, data are summarized only for the double-blind period of this study in this document.

In the Pre-NDA meeting discussion, the Agency stated that the ANCHOR study would not support the proposed indication.

Placebo-Adjusted Median Percent Change From Baseline to Week 12 in Key Lipid Endpoints- ITT Population- MARINE



****** p<0.0001; *** p<0.001; ** p<0.01; * p<0.05; NS = Not Significant (p≥0.05)**

Median Baseline TG: 703 (placebo, n=75), 680 (4 g/day, n=76), 657 (2 g/day, n=73) mg/dL
Median Baseline LDL-C: 86 (placebo, n=75), 91 (4 g/day, n=76), 84 (2 g/day, n=73) mg/dL
Median Baseline apoB: 118 (placebo; n=73), 121 (4 g/day; n=75); 118 (2 g/day; n=70) mg/dL
Medians are Hodges-Lehmann medians; p-values are from the Wilcoxon rank-sum test.

Table 3-10 Median Baseline and Percent Change From Baseline to Week 12 in Lipid Parameters-Intent-to-Treat Population (MARINE)

Parameter	Placebo (N=76)		Vascepa 4 g/day (N=77)		Vascepa 2 g/day (N=76)		Median		p-value	
	BL	% Change	BL	% Change	BL	% Change	Vascepa 4 g/day vs. Placebo	Vascepa 2 g/day vs. Placebo	Vascepa 4 g/day vs. Placebo	Vascepa 2 g/day vs. Placebo
TG[a] (mg/dL)	703.0	9.7	679.5	-26.6	656.5	-7.0	-33.1	-19.7	<0.0001	0.0051
Baseline >750 mg/dL	1052.0	19.0	902.0	-26.6	947.5	-7.3	-45.4	-32.9	0.0001	0.0016
Baseline ≤750 mg/dL	564.5	2.2	613.8	-26.6	568.0	-7.0	-25.1	-9.1	0.0006	0.2816
LDL-C (mg/dL)	86.0	-3.0	90.5	-4.5	84.0	-2.5	-2.3	5.2	0.6768	0.3022
Non-HDL-C (mg/dL)	229.0	7.8	225.0	-7.7	210.0	0.0	-17.7	-8.1	<0.0001	0.0182
VLDL-C[b] (mg/dL)	124.0	13.7	122.5	-19.5	119.0	0.0	-28.6	-15.3	0.0005[b]	0.1152[b]
Lp-PLA$_2$[b] (ng/mL)	253.0	-2.4	246.0	-17.1	235.0	-5.1	-13.6	-5.1	0.0006[b]	0.2367[b]
Apo B[b] (mg/dL)	118.0	4.3	121.0	-3.8	117.5	2.1	-8.5	-2.6	0.0019[b]	0.2367[b]
hsCRP (mg/L)	1.8	33.3	2.2	-2.5	2.0	25.1	-36.0	-10.1	0.0012	0.4028
TC (mg/dL)	256.0	7.7	253.5	-7.3	236.0	0.7	-16.3	-6.8	<0.0001	0.0148
HDL-C (mg/dL)	27.0	0.0	26.5	-3.5	26.0	0.0	-3.6	1.5	0.2174	0.5225
VLDL-TG (mg/dL)	543.0	7.8	522.5	-25.2	488.0	-6.4	-25.8	-17.3	0.0023	0.0733

% Change = Median Percent Change from Baseline; Apo B = apolipoprotein B; BL = Baseline (mg/dL); HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp-PLA$_2$ = lipoprotein-associated phospholipase A$_2$; non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; VLDL-C = very low density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides.
Medians are Hodges-Lehmann medians; p-values are from the Wilcoxon rank-sum test.
a Fasting TG level was the primary efficacy endpoint
b VLDL-C, Lp-PLA$_2$, and Apo B were secondary efficacy endpoints and adjusted p-values from applying Hommel's multiple comparison procedure to the p-value from the treatment comparison between 4 or 2 g/day Vascepa with placebo are reported.
Source: MARINE CSR Post-text Tables 14.2.1, 14.2.6, 14.2.8, 14.2.10, 14.2.7.5, 14.2.7.6, 14.2.13, 14.2.14, 14.2.15, 14.2.17, 14.2.19, 14.2.21, and 14.2.23

Exclusivity
Applicant is requesting 5 years of exclusivity: "Vasecpa does not contain the same active moiety as in any drug product approved under FDC Act § 505(b) and therefore Vascepa is eligible for five-year NCE exclusivity."

Pediatric Use
The applicant has submitted a request for waiver for pediatric studies for patients aged 0-10 years and a request for deferral for patients aged 11-18 years.

Assessment
From a clinical standpoint, the NDA is fileable, but pharmacology-toxicology team has a Refuse-to-File Issue. Specifically, pharm-tox does not have adequate bridging information (for reproductive toxicology) to Epadel to support the 505(b)(2) application.

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			Originally submitted as a 505(b)(1); applicant changed to 505(b)(2) status on its own accord
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 MARINE (0016) Pivotal Study #2 Indication:	X			Efficacy data from one Phase 3 study with hypertriglyceridemic patients for 12 weeks, plus extension phase up to 40 weeks.
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?				
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?		X		
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X		Re: pharm-tox studies
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Applicant submitted a waiver for ped population 0-10 years and a deferral for ages 11-18.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _Yes_____

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

74-Day Letter Request- Please submit a rationale for assuming the applicability of foreign data in the submission to the U.S. population.

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

/s/

IFFAT N CHOWDHURY
11/15/2011

ERIC C COLMAN
11/15/2011