FDA Briefing Document

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

October 16, 2013

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DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this supplemental application, VASCEPA (icosapent ethyl), NDA 202057/Supplement -005 to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Draft Points to Consider

In ANCHOR, 12 weeks of treatment with Vascepa 4 g/day led to an estimated median -21.5% (95% CI, -26.7% to -16.2%; P<0.0001) change in fasting triglycerides, compared with the mineral oil placebo, among statin-treated patients with mixed dyslipidemia at high cardiovascular risk. Changes in other lipid/lipoprotein parameters (selected secondary and exploratory endpoints) are summarized in the table below.

	Median % Change from Baseline to Week 12		Median % Change (95% CI)
	Placebo	Vascepa 4g/day	Treatment Difference
Fasting TG	+5.9	-17.5	-21.5 (-26.7, -16.2)
Direct LDL-C	+8.8	+1.5	-6.2 (-10.5, -1.7)
Non-HDL-C	+9.8	-5.0	-13.6 (-17.2, -9.9)
VLDL-C	+15.0	-12.1	-24.4 (-31.9, -17.0)
Apo B	+7.1	-2.2	-9.3 (-12.3, -6.1)
Tot. Chol.	+9.1	-3.2	-12.0 (-14.9, -9.2)
HDL-C	+4.8	-1.0	-4.5 (-7.4, -1.8)
Apo A-I	+3.6	-2.9	-6.9 (-8.9, -4.9)

1. Please discuss the efficacy results from the ANCHOR trial, including the clinical significance of the observed changes in lipid/lipoprotein parameters and your level of confidence that these changes will translate into a meaningful reduction in cardiovascular risk among the target population.

2. Taking into account the described efficacy and safety data for Vascepa, do you believe that its effects on the described lipid/lipoprotein parameters are sufficient to grant approval for co-administration with statin therapy for the treatment of patients with mixed dyslipidemia and CHD or CHD risk equivalent prior to the completion of REDUCE-IT? Please provide the rationale underlying your recommendation.

VASCEPA (Icosapent Ethyl)
NDA 202057

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Clinical Review
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New Drug Application 202057: AMR101 VASCEPA (icosapent ethyl)
Applicant: Amarin Pharma, Inc.
Clinical Reviewer: Mary Dunne Roberts, MD

Executive Summary

VASCEPA, herein referred to as AMR101, is a purified ethyl ester of eicosapentaenoic acid (EPA) derived from fish oil. In July 2012, AMR101 was approved as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia (defined as TG $\geq$ 500 mg/dL) at a dose of 4 grams per day. On February 21, 2013, the applicant, Amarin Pharma Inc., submitted an efficacy supplement seeking to substantially expand the treatment population of AMR101 to include patients with mixed dyslipidemia who are at high risk for coronary heart disease and who are already being treated with HMG-CoA reductase inhibitors (statins). It is estimated that approximately 21% of U.S. adults have mixed dyslipidemia, defined as the presence of high LDL-C combined with at least one other lipid abnormality.[1] Data from one pivotal efficacy trial, ANCHOR, was submitted to support the expanded treatment indication.

EPA, along with α-linolenic acid and docosahexaenoic acid (DHA), are collectively referred to as omega-3 fatty acids (FA). EPA and DHA are also the major constituents of fish oils derived from cold water fish. Over forty years ago, investigation into the dietary habits of Greenland Eskimos suggested an inverse association between the consumption of omega-3 fatty acids from fish and the incidence of ischemic heart disease.[2] Several mechanisms have been proposed to explain the putative cardioprotective effect of EPA and DHA, including triglyceride (TG) reduction, platelet aggregation inhibition, plaque stabilization, anti-inflammatory effects, and improvements in cardiac hemodynamics.[3]

There are currently two FDA-approved prescription products derived from fish oil indicated for the treatment of severe hypertriglyceridemia: (1) LOVAZA, herein referred to as omega-3 fatty acid ethyl ester (omega-3 EE), available in 1 g capsules containing, among other things, purified ethyl esters of EPA and DHA of approximately 465 mg and 375 mg, respectively; and (2) AMR101, which contains approximately 1 g per capsule of purified ethyl ester of EPA derived from fish oil and no DHA. While the dosing units for omega-3 EE and AMR101 are alike (i.e., 1 g capsule), the composition is not; the EPA

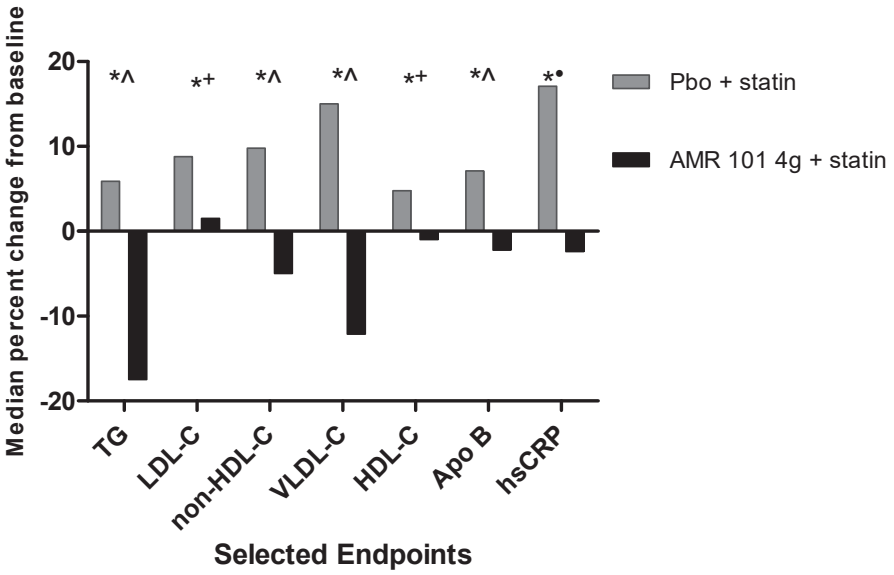
[1] Toth P et al. Prevalence of lipid abnormalities in the United States: The National Health and Nutrition Examination Survey 2003-2006. Journal of Clinical Lipidology 2012;6:325-330.
[2] Bang HO, Dyerberg J. Plasma lipids and lipoproteins in Greenlandic west coast Eskimos. Acta Med Scand 1972;192:85-94
[3] Adkins Y, Kelley DS. Mechanisms underlying the cardioprotective effects of omega-3 polyunsaturated fatty acids. Journal of Nutritional Biochemistry 2010;21:781-92

content within a 1 g AMR101 capsule is approximately twice that of a 1 g omega-3 EE capsule.

ANCHOR was a randomized, double-blind, placebo-controlled, 12-week study of AMR101 in patients with persistently high TG levels on statin background therapy. After a 6- to 8-week lead-in period for dietary instruction, washout of non-statin lipid-modulating drugs, and stabilization of statin therapy, 702 individuals still meeting lipid eligibility requirements were randomized to either placebo (mineral oil), AMR101 2 g/day, or AMR101 4 g/day. The primary endpoint was the percent change in TG levels from baseline to week 12. The treatment groups were well matched for baseline characteristics. The mean age was 61 years, most were male (61%), Caucasian (96%), and diabetic (73%); the mean HbA1c in patients with diabetes was 6.9%. Approximately one-third had a history of cardiovascular disease. The average baseline BMI was 32.9 kg/m^2. At entry into the study, 90% of subjects were taking a statin with an average treatment duration of approximately 3 years. After the lead-in and statin stabilization period, the baseline mean LDL-C was 85 mg/dL, with 21% having an LDL-C less than 70 mg/dL; mean non-HDL-C was 132 mg/dL; median TG was 259 mg/dL; mean HDL-C was 39 mg/dL, with 55% having an HDL-C less than 40 mg/dL; and 53% had a hsCRP $\geq$ 2 mg/L.

After 12 weeks of therapy, statistically significant differences were observed between placebo and AMR101 4g with respect to TG (-21.5%; $p<0.0001$) and with respect to secondary endpoints such as LDL-C (-6.2%; $p=0.007$) and non-HDL-C (-13.6%; $p=0.0001$). Notably, despite a lead-in period that is quite typical for trials with lipid parameter endpoints, within-group changes in lipid parameters and biomarkers of inflammation from baseline to 12 weeks were highly statistically significant in the mineral oil placebo group (all $p<0.001$). Although it is recognized that the effect of an intervention (e.g., mineral oil capsules) cannot be isolated when one only considers within-group changes over time, these results at least suggest the possibility that mineral oil may not be biologically inert. If true, this complicates the interpretation of between-group differences. For example, LDL-C increased a median 9% in the placebo group, despite statin therapy, and only increased a median of 1.5% in the AMR101 4g group (Figure 1), but does this reflect an LDL-lowering effect of AMR101, an LDL-raising effect of mineral oil in statin-treated individuals, or some combination?

Figure 1: Change from Baseline in Selected Endpoints



* p<0.001 for within group changes in placebo group
^ p<0.0001 between group changes
· p<0.001 between group change
+ p<0.01 between group change
Source: FDA reviewer graph of submitted data

The 702 patients exposed to at least one dose of study drug experienced relatively low and similar numbers of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuations due to adverse events. Only one adverse event led to a fatality due to a myocardial infarction (MI) in a placebo-treated patient. There were no instances of rhabdomyolysis, and CK elevations >5x ULN were infrequent and similar between treatment groups. Elevations in ALT and/or AST >3x ULN occurred in three patients (1 placebo-treated patient and 2 AMR101 4g-treated patients). No patients developed laboratory or clinical findings consistent with drug-induced liver injury defined by Hy's Law. No new safety signals were identified. The safety profile of AMR101 in ANCHOR was consistent with current labeling and post-market safety reports.

In considering the results of the ANCHOR trial, the presumption has been that improving various lipid parameters will translate into a reduction in cardiovascular risk. With rare exception, FDA has historically considered granting approval for lipid-altering drugs based on favorable changes in the lipid profile, with the assumption that these changes would translate into a benefit on clinical outcomes. Both epidemiological studies and controlled interventional trials of lipid-lowering agents, including omega-3 FA, supported the hypothesis that pharmacologically-induced improvements in the lipid profile are cardioprotective. These studies also informed professional society guidelines that promoted the consumption of EPA and DHA with the goal to reduce cardiovascular risk.[4]

[4] Kris-Etherton PM et al. American Heart Association Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 2002;106:2747-2757.

Recent clinical trials and meta-analyses have failed to confirm definitive cardiovascular benefit with EPA and DHA supplementation, however.[5,6,7]

During a pre-IND meeting with the applicant in July 2008, however, the Division noted that there was a lack of prospective, controlled clinical trial data demonstrating that pharmacological reduction of non-HDL-C (or TG) with a second drug, in patients with elevated TG levels at LDL goal on statin therapy, significantly reduces residual cardiovascular risk. The Division referenced trials ongoing at the time (e.g., AIM-HIGH, ACCORD-Lipid) that, while not able to assess the effect of specifically lowering non-HDL-C (or TG) on clinical outcomes, would be expected to provide important information on the incremental benefit of adding a second lipid-active drug to statin therapy. It was stated that before an indication would be entertained for Ethyl-EPA as add-on to statin therapy in patients with elevated TG levels, the applicant at a minimum would have to provide results from a 12-week study with lipid endpoints as well as initiate an appropriately designed cardiovascular outcomes study. This outcomes study, known as REDUCE-IT, is ongoing and is investigating whether the addition of AMR101 4 g daily ameliorates residual cardiovascular risk among patients at high CV risk who have moderate hypertriglyceridemia at LDL-C goal on statin therapy. The study designs for both ANCHOR and REDUCE-IT were agreed to by the Division under special protocol assessments.

Several cardiovascular outcome trials of non-statin lipid-modulating therapy, such as those referenced by the Division in 2008, have since completed. ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE, which were designed to target residual cardiovascular risk by improving lipid parameters other than LDL-C (e.g., HDL-C and/or TG) in patients optimally treated with statin therapy, failed to demonstrate unequivocally additional cardiovascular benefit from non-statin lipid-modulating drugs. Several hypotheses could be put forward regarding the failures of these large, carefully designed trials to demonstrate benefit on their primary endpoints, but the evidence to date certainly challenges the hypothesis that adding lipid-modulating therapies to patients optimally treated with statins will reduce residual cardiovascular risk. Although it can be argued that lipid and/or lipoprotein parameters can be used to define subpopulations of statin-treated patients who would be expected to benefit from various non-statin lipid-modulating agents, contemporary trials have not yet prospectively tested this hypothesis. Members of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) are asked to consider the results of the ANCHOR trial in the context of the available science when recommending whether to approve the proposed treatment indication for 4 grams AMR101 daily to be co-administered with statin therapy for the treatment of patients with mixed dyslipidemia and coronary heart disease (CHD) or its risk equivalent.

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[5] Kotwal S et al. Omega 3 Fatty Acids and Cardiovascular Outcomes: Systematic review and Meta-analysis. Circ Cardiovasc Qual Outcomes 2012;5:808-18.
[6] The Risk and Prevention Study Collaborative Group. N-3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors. NEJM 2013;368:1800-8.
[7] Rizos EC et al. Association between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events. JAMA 2012;308 (10):1024-33.

1. INTRODUCTION

Over a decade ago, the National Cholesterol Education Program's (NCEP) Third Adult Treatment Panel (ATP III) recognized the relationship between elevated TG and coronary heart disease (CHD) observed in epidemiological studies and meta-analyses from the late 1990s.[8] A high TG level (≥200 to <500 mg/dL) is considered a biomarker of atherogenic potential due to its association with increased levels of cholesterol-enriched lipoproteins, such as very-low-density lipoprotein cholesterol (VLDL-C). Collectively, atherogenic lipoprotein cholesterol is a secondary target of therapy, referred to as non-HDL-C and calculated as total cholesterol minus HDL-C. The NCEP ATP III guidelines recommend statin therapy as initial pharmacotherapy for lowering LDL-C and non-HDL-C in patients with high TG levels. If elevated TG persists, the guidelines discuss further intervention such as fibrates, niacin, and dietary intake of omega-3 FA (although no specific level of intake is recommended). In 2002, the American Heart Association made recommendations that were more explicit: patients with elevated TG could be considered for additional treatment with EPA plus DHA at a dose of 2 to 4 g per day.[9]

Despite treatment recommendations based on robust clinical data and acceptance of statins as first-line standard-of-care for cardiovascular risk reduction, substantial risk for major adverse cardiovascular events still exists for many patients optimally treated with statins.[10] Therefore, several investigators have hypothesized that favorably altering other lipid, lipoprotein, or inflammatory biomarkers in addition to optimizing LDL-C may further reduce CV risk. Recent cardiovascular outcome trials testing these hypotheses, however, have failed to establish that improvements in secondary lipid targets such as HDL-C and/or TG translate into cardiovascular benefit, causing further controversy regarding effective cardioprotective lipid management. Within this context, AMR101, an FDA-approved, commercially available EPA prescription product, seeks an expanded treatment indication as add-on to statin therapy in high risk cardiovascular patients with mixed dyslipidemia based on a 12-week lipid-altering trial.

2. VASCEPA (Icosapent Ethyl)

2.1. VASCEPA

VASCEPA (icosapent ethyl), referred to as AMR101 in this review, is a purified ethyl ester of eicosapentaenoic acid (EPA) derived from fish oil. In July 2012, AMR101 was approved as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia (defined as triglycerides ≥ 500 mg/dL) at the recommended dose of 4 grams per day. The clinical rationale underlying the support of approval based on TG levels for patients with severe hypertriglyceridemia is the expected reduction in the risk for acute pancreatitis.

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[8] Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the 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). JAMA 2001;285:2486-97.

[9] Kris-Etherton PM et al. American Heart Association Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease [published correction appears in Circulation. 2003;107:512]. Circulation. 2002;106:2747-2757.

[10] Sampson UK et al. Residual cardiovascular risk despite optimal LDL cholesterol reduction with statins: the evidence, etiology, and therapeutic challenges. Curr Atheroscler Rep 2012;14:1-10.

2.2. VASCEPA Development Program

The clinical development program for AMR101 includes studies designed to assess effects on the lipid profile of patients with severe hypertriglyceridemia (TG ≥ 500 mg/dL) as well as in patients with persistent hypertriglyceridemia (TG ≥200 to <500 mg/dL) despite LDL-C control on statin therapy, and a cardiovascular outcomes trial in patients at high risk for cardiovascular disease.

FDA approval of AMR101 for the treatment of severe hypertriglyceridemia was based on **MARINE**, a Phase 3, international, double-blind, randomized, placebo (mineral oil)-controlled trial. Following diet stabilization, 229 patients with very high TG defined as (TG ≥ 500 mg/dL and ≤2000 mg/dL) with or without background statin therapy were randomized to placebo, AMR101 2g/day, or AMR101 4g/day for 12 weeks of therapy. The primary endpoint was median percent change in TG from baseline. The following table summarizes the lipid changes across the three treatment arms in MARINE. Compared with placebo, AMR101 4g/day reduced TG levels by an estimated median of 33%. Although the reduction in fasting TG levels was statistically significant in the AMR101 2g/day group compared with the placebo group, TG reduction was more substantial in the AMR101 4g/day group, and the magnitude of effects on other lipid parameters was consistently lower in the AMR101 2g/day group. During the review, the applicant submitted a formal request to remove the 2g/day dose from the proposed indication, and the request was granted.

Table 1: Median percent change from baseline to week 12 endpoint – MARINE ITT population

	Median [Q1, Q3] % Change from Baseline to Wk 12			AMR101 4g/d vs. Placebo	
	AMR101 2g/d (n=73)	AMR101 4g/d (n=76)	Placebo (n=75)	Estimated Median Difference (95% CI)	P
TG	-7.0 [-30.1, 18.6]	-26.6 [-41.1, 0.0]	+9.7 [-19.2, 42.3]	-33.1 (-46.6, -21.5)	<0.0001
LDL-C	-2.5 [-9.8, 23.5]	-4.5 [-23.3, 17.2]	-3.0 [-21.3, 23.3]	-2.3 (-12.9, 8.1)	0.68
Non-HDL-C	0.0 [-9.0, 14.1]	-7.7 [-21.6, -0.1]	+7.8 [-4.1, 26.6]	-17.7 (-25.0, -11.3)	<0.0001
VLDL-C	0.0 [-22.5, 29.2]	-19.5 [-35.7, 19.6]	+13.7 [-13.5, 55.3]	-28.6 (-43.4, -13.9)	0.0002
ApoB	+2.1 [-4.7, 7.6]	-3.8 [-11.9, 3.8]	+4.3 [-4.5, 17.5]	-8.5 (-13.5, -3.2)	0.002
HDL-C	0.0 [-11.8, 14.8]	-3.5 [-13.2, 9.1]	0.0 [-10.0, 11.5]	-3.6 (-9.1, 2.0)	0.22
Tot. chol.	+0.7 [-8.5, 10.8]	-7.3 [-17.7, 0.5]	+7.7 [-3.6, 24.2]	-16.3 (-22.4, -11.0)	<0.0001

Source: NDA 202057 MARINE Clinical Study Report, Tables 8, 10, 12-16. 95% CI estimated with the Hodges-Lehmann method; P values from Wilcoxon rank-sum.

During the review of the MARINE data, the Division noted that several lipid parameters (including TG) increased from baseline to week 12 in the placebo group, treated with mineral oil. The available literature regarding potential effects of mineral oil was considered. Similar increases in TG levels observed in the placebo groups from the Lovaza (omega-3 EE) clinical trials of hypertriglyceridemic patients were noted, and these trials did not use a mineral oil

placebo. Because no strong evidence for biological activity of mineral oil was identified, ultimately it was concluded that the between-group differences likely provided the most appropriate descriptions of the treatment effect of AMR101 and that whatever factor(s) led to the within-group changes over time in the placebo group were likely randomly distributed to all treatment groups. Taken together, along with the statistical robustness in primary and sensitivity analyses of AMR101 4g/day on TG lowering, the Division concluded that AMR101 4g/day is an effective TG-lowering agent for patients with severe hypertriglyceridemia. AMR101 was approved for the following treatment indication on July 26, 2012:

- **Treatment of Severe Hypertriglyceridemia**
  VASCEPA™ (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

A special protocol assessment (SPA) for **ANCHOR** was completed and accepted on July 6, 2009. Key agreements included the enrollment of patients at high risk for cardiovascular disease (10 year risk >20%), with baseline LDL-C for randomization to be ≥40 mg/dL and <100 mg/dL, and baseline TG to be ≥200 mg/dL and <500 mg/dL. Serum TG was the primary endpoint. Concomitant statin therapy was limited to atorvastatin, rosuvastatin, or simvastatin. To demonstrate that AMR101 does not adversely increase LDL-C, 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 1-sided significance level at 0.025. On April 26, 2010, the applicant requested to amend the ANCHOR protocol as a result of low enrollment. The HbA1C exclusion threshold was changed from 9.0% to 9.5%, the upper limit of the LDL-C criterion was increased by 15% from 100 to 115 mg/dL, and the lower bound of the TG criterion was reduced to ≥185 mg/dL.

The applicant now seeks the following indication:

- **Co-administration Therapy with Statins for the Treatment of Mixed Dyslipidemia**
  VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet and in combination with a statin to reduce TG, non-HDL-C, Apo-B, LDL-C, TC, and VLDL-C in adult patients with mixed dyslipidemia and CHD or a CHD risk equivalent.

  CHD risk equivalents comprise:
  - Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease);
  - Diabetes;
  - Multiple risk factors that confer a 10-year risk for CHD > 20%.

REDUCE-IT is an ongoing, event-driven, randomized, placebo (mineral oil)-controlled, international study designed to evaluate the effect of AMR101 4g/day in patients at LDL-C goal on statin therapy who have high triglycerides (TG ≥200 mg/dL to <500 mg/dL) and either CVD or at high risk for CVD. The primary endpoint is time to first occurrence of a cardiovascular composite of cardiovascular death, non-fatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. It is expected that a minimum of 1612 primary efficacy endpoint events and approximately 6990 patients are needed to detect a

15% relative risk reduction in the primary CV endpoint with 90% power and a placebo event rate of 5.9% per year during a median follow-up of 4 years. (b) (4) A SPA agreement was reached with the FDA on August 5, 2011.

3. ANCHOR RATIONALE AND DESIGN/CONDUCT

3.1. Rationale for ANCHOR

ANCHOR was designed to investigate the effects of AMR101 on lipid parameters in a high-risk patient population with low LDL-C levels but moderate hypertriglyceridemia on statin therapy. Rationale supporting the ANCHOR protocol at the time of the SPA agreement in 2009 included data from epidemiological studies that supported a positive association between elevated levels of TG and risk of cardiovascular events,[11] evidence of an inverse relationship between omega-3 fatty acid consumption and cardiovascular risk,[12] the precedent of the COMBOS trial (a randomized, placebo (corn oil)-controlled trial of Lovaza [omega-3 EE] that demonstrated statistically significant TG lowering in statin-treated patients),[13] and recognition that cardiovascular events still contribute substantially to the morbidity and mortality of adults treated with statins, and the possibility that abnormal atherogenic lipoproteins, reflected by high TG or non-HDL-C, may independently contribute to this residual vascular risk. [14]

3.2. Study Design

ANCHOR was designed, sponsored, and funded by Amarin Pharma. Medpace, Inc., a contract research organization performed project management, clinical monitoring, data management, statistical analysis, and study report preparation.

Table 2 lists milestone dates of the ANCHOR trial.

Table 2: ANCHOR Milestones

Original protocol date:	19 May 2009
Study initiation date:	16 December 2009
First patient randomized:	27 January 2010
Protocol Amendment 1:	10 March 2010
Protocol Amendment 2:	27 May 2010
Statistical analysis plan finalized:	2 February 2011
Last scheduled subject study visit:	21 February 2011
Statistical analysis plan Amendment 1:	2 March 2011

[11] Sarwar N et al. Triglycerides and the risk of coronary heart disease: 10158 incident cases among 262525 participants in 29 Western prospective studies. Circulation. 2007;115:450-8.
[12] He K et al. Accumulated Evidence on Fish Consumption and Coronary Heart Disease Mortality: A Meta-analysis of Cohort Studies. Circulation. 2004;109:2705-2711.
[13] Lovaza label
[14] Miller M et al. Impact of Triglyceride Levels beyond Low-Density Lipoprotein Cholesterol after Acute Coronary Syndrome in the PROVE IT-TIMI 22 trial. JACC 2008;51:724-30.

Statistical analysis plan Amendment 2:	23 March 2011
Study database lock:	23 March 2011
Study database unblinding:	29 March 2011

3.2.1. Objectives

Primary objective: ANCHOR's primary objective was to determine the efficacy of AMR101 2g daily and 4g daily, compared to placebo, in lowering fasting TG levels in patients at high risk for cardiovascular disease and with fasting TG levels ≥ 200 mg/dL and <500 mg/dL, despite treatment to LDL-C to ≥40 mg/dL and ≤115 mg/dL on statin therapy

Secondary and exploratory objectives:

1. Safety and tolerability of AMR101 2g and 4g daily
2. Effect of AMR101 on lipid profiles (TC, non-HDL-C, LDL-C, HDL-C, VLDL-C)
3. Effect of AMR101 on:
    a. VLDL-TG, apoA-I, apo-B, apo-B/apoA-1 ratio, Lp(a), Lp-PLA_2, oxidized LDL, remnant-like particle cholesterol (RLP-C),
    b. LDL particle concentration and size
    c. fasting plasma glucose (FPG), HbA1c, insulin resistance
    d. hsCRP, ICAM-1, IL-6, PAI-1
    e. fatty acid concentrations (including EPA) in plasma and RBC membranes
4. Explore the relationship between baseline fasting TG levels and the reduction in fasting TG levels; and
5. Explore the relationship between changes in fatty acid concentrations (including EPA) in plasma and RBC membranes and the reduction in fasting TG levels

3.2.2. Study Design

ANCHOR, conducted at 97 sites in the United States, was a double-blind, placebo-controlled, parallel-group trial that randomly assigned patients after a 6- to 9-week screening period to one of the following 3 treatment arms for 12 weeks: 4 mL mineral oil (placebo), 2 g AMR101, or 4 g AMR101 daily as add-on therapy to a stable dose of simvastatin, atorvastatin, or rosuvastatin with or without ezetimibe (Figure 2). The trial intended to randomize approximately 648 patients.

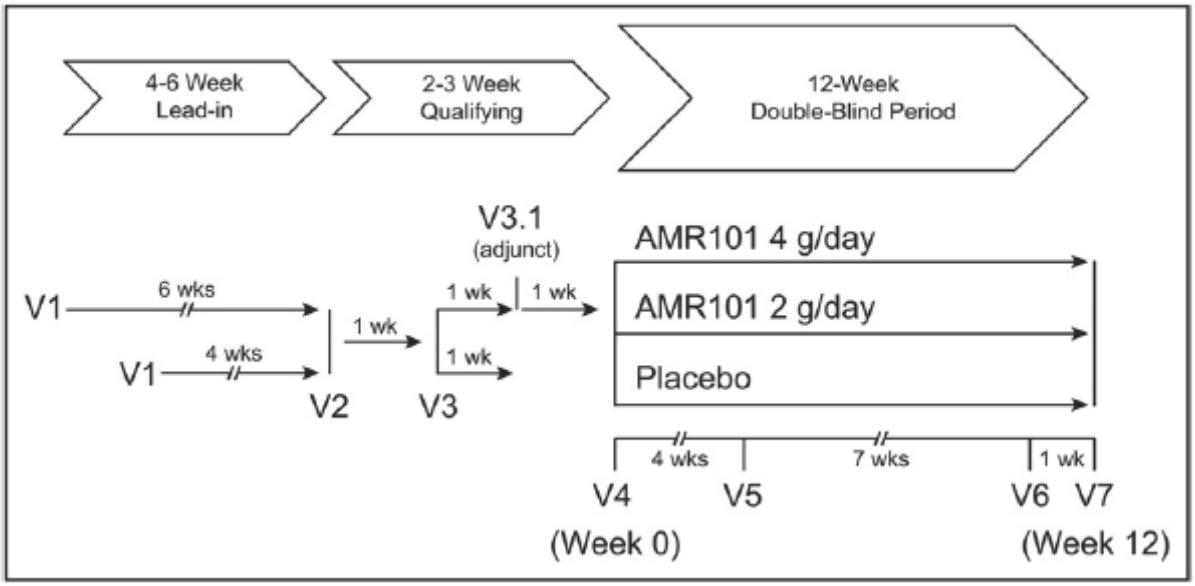
After dietary counseling, eligible patients entered a 4- or 6-week lead-in period, with the duration of this period depending on whether a washout of non-statin therapy or an adjustment to statin therapy was necessary; this was followed by a 2- or 3-week LDL-C and TG qualifying period (Visits 2 and 3, and if necessary, Visit 3.1 as described below). Qualifying patients were randomized at Visit 4 and entered the 12-week double-blind efficacy and safety measurement period.

Reviewer comment: The study design of ANCHOR is similar to other trials designed to evaluate a study drug's effect on TG. The majority of TG-lowering trials have included a dietary lead-in of at least 6 weeks to limit the effect of a recent change in diet on TG during the treatment phase of the trial.

The requirements for statin stabilization and washout of non-statin lipid therapy are also common design elements of add-on to statin therapy trials. Peak changes in LDL-C are generally achieved within 4 to 6 weeks of statin therapy. In ANCHOR, at least 4 weeks of stable statin therapy and 6 weeks of non-statin washout were required before the first qualifying TG and LDL-C values were obtained.

Based on the pharmacokinetic/pharmacodynamics effects of AMR101, a 12-week treatment period should be sufficient to establish the effect of AMR101 on lipid parameters.

Figure 2: ANCHOR Study Design



Source: ANCHOR CSR

Patients meeting the following criteria were eligible to participate in the ANCHOR study, according to the final, amended protocol.

Inclusion criteria

1. Men or women>18 yo
2. High risk for CVD: clinical CHD **OR** clinical CHD risk equivalents (10-year risk ≥20%)
    a. History of coronary artery disease: (needed one to qualify)
        i. History of MI
        ii. History of unstable or stable angina
        iii. Previous coronary artery procedures (e.g. PTCA)
        iv. Evidence of clinically significant myocardial ischemia

    OR

    b. CHD risk equivalents: (needed one to qualify)
        i. Non-coronary atherosclerotic disease: peripheral arterial disease, abdominal aortic aneurysm, or carotid artery disease (TIA or carotid stroke, or >50% obstruction of carotid artery)
        ii. Diabetes mellitus (type 1 or 2)

3. On a stable dose of statin therapy (with or without ezetimibe).
    a. Statins allowed: simvastatin, atorvastatin, or rosuvastatin
    b. Dose stable for ≥4 weeks prior to Visit 2 (Week -2)
    c. Same statin at the same dose was to be continued until the end of the study
4. TG levels based on Visit 2 (Week -2) and Visit 3 (Week -1) values*
    a. Mean of the two values ≥ 185 mg/dL and <500 mg/dL, AND
    b. One of the values must have been ≥ 200 mg/dL
5. LDL-C levels (calculated with Friedewald equation) based on Visit 2 (Week -2) and Visit 3 (Week-1) values*
    a. Mean ≥ 40 mg and ≤ 115 mg/dL

*If the TG or LDL-C values based on the Visit 2 and Visit 3 values fell outside the required range for entry, an additional fasting lipid profile could have been collected 1 week later at Visit 3.1. Entry into the study was then based on the average of the Visit 3 and Visit 3.1 values.

Exclusion criteria

1. BMI >45 kg/m^2 at Visit 1
2. Weight change >3 kg between Visit 1 (Week -8 or Week -6) and Visit 2 (Week -2)
3. Mean non-HDL-C levels <100 mg/dL from the last 2 visits before randomization
4. HbA1c >9.5% at Visit 1
5. Use of any non-statin lipid-altering medication after Visit 1, including:
    a. Niacin >200 mg/day;
    b. Fibrates;
    c. Omega-3-fatty acid medications
    d. Dietary supplements containing omega-3 FA or fish oil
    e. Supplements (e.g. flaxseed) or foods enriched with omega-3 FA (consumption of up to 2 servings per week of fish was acceptable)
    f. Sterol/stanol products
    g. Dietary fiber supplements, including >2 teaspoons of Metamucil or psyllium-containing supplements
    h. Red yeast rice supplements, garlic supplements, or soy isoflavones supplements
6. Use of any statin other than atorvastatin, rosuvastatin, or simvastatin after Visit 1 (Week -8 or Week -6). Switching between statins was prohibited.
7. Percutaneous coronary intervention within 4 weeks prior to screening
8. Known nephrotic-range (>3 g/day) proteinuria at Visit 1
9. Hospitalization for acute coronary syndrome and discharge within 4 weeks prior to screening
10. Uncontrolled hypertension (SBP >160 mmHg and/or DBP >100 mmHg)
11. Treatment with chronic prescription pharmacotherapy for metabolic or CVD management or risk factor modification (antihypertensives, antidiabetics) that had not been stable for ≥4 weeks prior to Visit 1
12. ALT or AST >3x ULN at Visit 1
13. Unexplained creatine kinase concentration >3x ULN or CK elevation due to known muscle disease at Visit 1
14. Ongoing treatment with weight loss drugs (including over the counter)

15. Treatment with tamoxifen, estrogens, or progestins that has not been stable for ≥ 4 weeks prior to Visit 1
16. TSH >1.5 xULN, clinical evidence of hypothyroidism, or thyroid hormone therapy that has not been stable for ≥6 weeks prior to Visit 1
17. Blood donation of ≥1 pint (0.5 L) within 30 days or plasma donation within 7 days prior to Visit 1
18. Consumption of >2 alcoholic beverages per day following Visit 1
19. Known familial lipoprotein lipase deficiency, apo C-II deficiency, or familial dysbetalipoproteinemia
20. History of bariatric surgery
21. History of malignancy, except patients who have been disease-free for >5 years, or whose only malignancy was basal or squamous cell skin carcinoma
22. Child-bearing potential (i.e., premenopausal woman not using a reliable method of contraception)

Protocol Amendments Related to Trial Population
There were two amendments during the course of ANCHOR.

The first amendment on March 10, 2010 included the following:
1. The definition of CHD risk equivalents was updated to a 10-year risk ≥20%
2. Exclusion criteria were modified to exclude patients with known familial lipoprotein lipase deficiency and to exclude patients with ALT or AST levels >3x ULN.

The second amendment on May 27, 2010, after 236 patients (~34% of the study population) had been randomized, included the following:
1. LDL-C and TG eligibility criteria were changed to allow for a larger degree of within-patient variability in TG and LDL-C values.
   - The upper limit for LDL-C was increased by 15% (upper limit of LDL-C changed from ≤ 100 mg/dL to ≤ 115 mg/dL). The lower limit of the required TG range for randomization was lowered from a mean of the two qualifying values having to be ≥ 200 mg/dL to ≥185 mg/dL with at least one of the two values needing to be ≥200 mg/dL.
2. During the 2 weeks following Visit 1, a patient's statin dose could be changed; this would be followed by a ≥4-week stabilization period before Visit 2 as previously described.
3. At Visit 1, at the discretion of the investigator, patients could be switched from a non-study statin to a statin allowed in the study.
4. HbA1c exclusion criterion was changed from >9.0% to >9.5%

Data Management: An electronic data capture (EDC) system was used to collect ANCHOR study data. Information was recorded at study sites on electronic case report forms (eCRFs) and reviewed by a clinical research associate (CRA). The CRA was to verify data recorded in the EDC system with source documents. All corrections or changes made to study data had to be tracked in an audit trail in the EDC system.

Source Documents: Source data was defined as all information in original records and certified copies of original records of clinical findings or other study observations.

Schedule of Visits
Table 4 includes a summary of activities performed at each study visit.

Screening (Visit 1/Week -8 or Week -6)
The screening period was divided into a 4- or 6-week lead-in phase and a 2- or 3-week LDL-C and TG qualifying phase before randomization could occur.

Eligible patients who wished to participate provided written informed consent, underwent a fasting blood draw, received dietary counseling on implementing the NCEP Therapeutic Lifestyle Changes diet, and initiated either a 4- or 6-week lead-in period depending on whether either a washout of a non-statin lipid-lowering therapy or an adjustment to the background statin was necessary.

Patients who did *not* require washout of non-statin lipid-lowering therapy: The screening visit occurred at Visit 1 (Week -6). Eligible patients entered a 4-week diet lead-in period and continued on their current dose of statin before the first TG/LDL-C qualifying visit (Visit 2/Week-2). Patients who required a change in their statin dose during the 2 weeks following Visit 1 entered a statin stabilization period so that the statin dose was stable for at least 4 weeks before the first TG/LDL-C qualifying visit (Visit 2/Week -2). At the discretion of the investigator, patients could be switched from a non-study statin to an allowed statin at Visit 1.

Approved dose ranges for the allowed statins included the following:
Atorvastatin 10 mg to 80 mg,
Rosuvastatin 5 mg to 40 mg, and
Simvastatin: 5 mg to 80 mg

Patients who required washout of non-statin lipid-lowering therapy: The screening visit occurred at Visit 1 (Week -8). Eligible patients began a 6-week washout period before the first TG/LDL-C qualifying visit (Visit 2/Week-2).

Qualifying period: At the end of either the 4-week or 6-week lead-in period, eligible patients had fasting LDL-C (calculated with Friedewald equation) and TG levels measured at Visit 2 (Week -2) and Visit 3 (Week -1). In order to enter the 12-week double-blind treatment period, the following levels were required:

Table 3: Lipid Eligibility Requirements

LDL-C	• Mean of 2 values ≥ 40 mg/dL and ≤ 115 mg/dL
TG	• Mean of the 2 values ≥185 mg/dL and at least 1 value ≥ 200 mg/dL • Mean of the 2 values <500 mg/dL

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 double-blind phase, an additional fasting lipid profile could be collected 1 week later at Visit 3.1. Entry into the study was then based on the values from Visit 3 and Visit 3.1.

Randomization Visit (Week 0)
After confirmation of the qualifying fasting LDL-C and TG values, eligible patients had fasting blood samples drawn, obtained a randomization number, and received the first dose of study drug with food.

Randomization Method: At Visit 4 (Week 0), investigators contacted Medpace ClinTrak Interactive Voice Response (CTIVRS) to acquire a randomization number for each patient. Patients were randomly assigned 1:1:1 to AMR101 2g, AMR101 4g, or placebo daily. Randomization was stratified by type of statin (atorvastatin, rosuvastatin, or simvastatin), presence of diabetes, and gender.

Blinding: AMR 101 was provided in 1 g liquid-filled, oblong, gelatin capsules. The matching placebo capsule was filled with mineral oil, also known as light liquid paraffin (LLP), and contained 0 g of AMR101. Patients took 2 capsules (AMR101 and/or matching placebo) in the morning and 2 capsules in the evening for a total of 4 capsules per day. Patients were instructed to take study drug with food. Patients were provided with 5 blister cards (4 weeks of study drug plus 1 extra week) at Visit 4 (Week 0) and 9 blister cards (8 weeks of study drug plus 1 extra week) at Visit 5 (Week 4). Each blister card contained study drug for 7 days of dosing (4 capsules per day).

Post-Randomization Follow-up (Visit 5/Week 4, Visit 6/Week 11)
At each follow-up appointment, study personnel assessed and recorded adverse events and vital signs, obtained a fasting blood sample for a lipid profile, collected all unused study drug, and dispensed study drug.

Week 12 endpoint/Early Termination
At the final study visit, study personnel assessed and recorded adverse events, vital signs, weight, 12-lead ECG, obtained a fasting blood sample for a lipid profile as well as other biochemical endpoints, and collected all unused study drug.

Compliance Control: Study medication was dispensed in amounts exceeding the amount required for the period of time until the next visit. Patients were instructed to return all unused study medication at the next visit. Compliance to the study medication regimen was evaluated by counting unused capsules. During the active treatment period, if compliance was not between 80% and 120% inclusive, the patient was counseled about the importance of compliance to the regimen.

Table 4: Schedule of Procedures

	Diet Stabilization/Washout Period	LDL-C and TG Qualifying Period [2]		Double-Blind Treatment Period				
Study Week	**-8 or-6 [1]**	**-2**	**-1**	**0**	**4**	**11**	**12**	**Early**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**Termination**
Study Procedures								
Informed consent	X							
Medical, surgical, family history, and demographics	X							
Concomitant medication(s)	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X	X	X	X				
Vital signs (blood pressure and heart rate)	X	X	X	X	X	X	X	X
Height [3] and weight	X	X		X			X	X
Electrocardiogram (12-lead)		X					X	X
Chemistry, hematology, and urinalysis	X			X			X	X
Hepatitis B and C [4]	X							
TSH and FSH [5]	X							
Serum pregnancy test for women of childbearing potential	X						X	X
Fasting lipid profile [6]	X	X	X	X	X	X	X	X
Contact ClinTrak Interactive Voice Response System	X			X				X
Withdraw non-statin lipid-altering medication(s), if applicable	X							
Physical examination and waist circumference				X			X	X
Assess for and record adverse events		X	X	X	X	X	X	X
Apolipoprotein A-I and B				X			X	X
LDL particle number and size				X			X	X
Lp(a), Lp-PLA_2, and oxidized LDL				X			X	X
Remnant-like particle cholesterol				X			X	X
Fasting plasma glucose, hemoglobin A_{1c}, and insulin	X [11]			X			X	X
High-sensitivity C-reactive protein				X			X	X
Plasma concentrations & RBC content of fatty acids [7]				X			X	X
ICAM-1, IL-6, and PAI-1 [8]				X			X	X
Blood sample for archiving (optional for patient) [9]				X			X	X
Dispense or redispense study drug as appropriate [10]				X	X			
Study drug compliance check					X	X	X	X
Collect study drug					X		X	X

1. Visit 1 for patients who require a washout and for patients whose statin dose is changed within 2 weeks after Visit 1 will be at Week -8. Visit 1 for patients who do not require a washout and with no statin dose changes after Visit 1 will be at Week -6.
2. Triglyceride and LDL-C levels will be based on the Visit 2 (Week -2) and Visit 3 (Week -1) values. If a patient's LDL-C and/or TG levels from Visit 2 and Visit 3 fall outside the required range for entry into the study, an additional fasting lipid profile can be collected (Visit 3.1). If a third sample is collected, entry into the study will be based on the values from Visit 3 and Visit 3.1.
3. Height will be measured at Visit 1 (Week -8 or Week -6) only.
4. If a patient is positive for hepatitis C, a hepatitis C recombinant immunoblot assay (RIBA) follow-up screen will be performed. If a hepatitis C RIBA is indeterminate, a follow-up hepatitis C RNA test will be performed.
5. Follicle-stimulating hormone in peri-menopausal women who have not had a menstrual period for <12 months at screening.
6. Includes TG, total cholesterol, high-density lipoprotein cholesterol, LDL-C, calculated non-high-density lipoprotein cholesterol, and very low-density lipoprotein cholesterol. Very low-density lipoprotein triglycerides will be measured at Visit 4 (Week 0), Visit 5 (Week 4), and Visit 7 (Week 12) or Early Termination. Low-density lipoprotein cholesterol will be calculated with the Friedewald equation for all patients at all visits. Low-density lipoprotein cholesterol will be measured by ultracentrifugation (Beta Quant) at Visit 4 (Week 0), Visit 5 (Week 4), and Visit 7 (Week 12) or Early Termination.
7. Includes eicosapentaenoic acid, docosapentaenoic acid, docosahexaenoic acid, arachidonic acid, dihomo-γ-linolenic acid, and other omega-3, omega-6, and omega-9 fatty acids.
8. PAI-I will only be collected at sites with proper storage conditions.
9. Used at the Sponsor's discretion to perform repeat analyses described in the protocol or to perform other tests related to cardiovascular health.
10. Study drug should be administered with food following all fasting blood samples.
11. Fasting plasma glucose and insulin are not drawn at screening (Visit 1 [Week -8 or Week -6]).

FSH = follicle-stimulating hormone; ICAM-1 = intracellular adhesion molecule-1; IL-6 = interleukin-6; LDL = low-density lipoprotein; Lp-PLA_2 = lipoprotein-associated phospholipase A_2; PAI-1 = plasminogen activator inhibitor-1; RBC = red blood cell; TSH = thyroid-stimulating hormone.

Source: ANCHOR Protocol V2; May 2010

3.2.3. Clinical Endpoint Assessment and Analyses

This section describes the assessments of outcomes specified in both the ANCHOR protocol and in the statistical analysis plan (SAP), which was finalized February 2011 and had two SAP amendments (March 2 and March 23, 2011) of minor significance (clarified text for determination of treatment-emergent adverse events, clarified text for statin intensity subgroups, added waist circumference as exploratory endpoint).

Primary efficacy outcome
Percent change in fasting TG from baseline to Week 12 in patients assigned to placebo vs. AMR 101.

Secondary efficacy outcomes: Percent changes in LDL-C (measured by ultracentrifugation [Beta Quant]), calculated non-HDL-C, VLDL-C, Lp-PLA_2, and apo B from baseline to Week 12 in patients assigned to placebo vs. AMR 101

Exploratory efficacy outcomes: Placebo vs. AMR 101

- Percent changes in total cholesterol (TC) from baseline to Week 12
- Percent changes in HDL-C from baseline to Week 12
- Percent change in VLDL-TG from baseline to Week 12
- Percent changes in apo A-I and apo B/apo A-I ratio from baseline to Week 12
- Percent change in Lp(a) from baseline to Week 12
- Percent changes in LDL particle concentration and size, measured by NMR, from baseline to Week 12
- Percent change in remnant lipoprotein cholesterol (RLP-C) from baseline to Week 12
- Percent change in oxidized LDL from baseline to Week 12
- Changes in fasting plasma glucose (FPG) and HbA1c from baseline to Week 12
- Change in insulin resistance, as assessed by HOMA-IR, from baseline to Week 12
- Change in ICAM-1 from baseline to Week 12
- Change in IL-6 from baseline to Week 12
- Change in PAI-1 from baseline to Week 12
- Change in hsCRP from baseline to Week 12
- Change in plasma and red blood cell EPA concentrations from baseline to Week 12
- Change in plasma and red blood cell concentrations of 28 fatty acids, including EPA, docosapentaenoic acid (n-3) (DPAN-3), DHA, and the arachidonic acid (AA)/EPA ratio from baseline to Week 12

Definition of baseline and endpoint for primary efficacy outcome
For TG, baseline was defined as the average of Visit 4 (Week 0/randomization) and the preceding lipid qualifying visit (either Visit 3 [Week -1] or, if it occurred, Visit 3.1). Note, therefore, that the qualifying TG level was not the same as the baseline value. The "Week 12" value was defined as the average of the TG values at Visit 6 (Week 11) and Visit 7 (Week 12). In the case of missing baseline or primary outcome values, the last valid measurement prior to

dosing was used as the baseline measurement and the last post-baseline measurement during the double-blind treatment period was carried forward as the endpoint measurement.

Definition of baseline and endpoint for secondary and exploratory efficacy outcomes
For values other than TG, baseline was defined as Visit 4 (Week 0/randomization) and the endpoint measurements only included the Visit 7 (Week 12) values. Unlike the Friedewald-estimated LDL-C levels used for trial eligibility, the LDL-C levels used in the efficacy analysis were measured by ultracentrifugation.

Safety outcomes
- Adverse events
- Physical examination
- Vital signs
- Clinical laboratory data (chemistry, hematology, urinalysis)
- 12-lead ECG

Subgroup analyses: The following subgroup analyses of the primary efficacy outcome by treatment were pre-specified in the protocol and/or SAP to be conducted using the ITT population.
- Age group (<65 years, ≥65 years)
- Race (white, non-white)
- Gender (male, female)
- Type of statin used (atorvastatin, simvastatin, rosuvastatin)
- Diabetes [present (includes type 1 and type 2), absent]
- Baseline TG value ≥185 mg/dL
- Baseline TG value ≥200 mg/dL
- Baseline TG median (<overall median baseline TG, ≥overall median baseline TG
- Baseline TG tertiles (<T1, T1-<T2, ≥T2)
- Statin potency (The applicant describes the following categories as differing in "potency," although this is a misnomer in the pharmacological sense of the term. In the remainder of this document, these categories will be referred to as regimens of different intensity.)
    - Lower intensity (simvastatin 5-10 mg)
    - Medium intensity (rosuvastatin 5-10 mg, atorvastatin 10-20 mg, simvastatin 20-40 mg, simvastatin 10-20 mg + ezetimibe 5-10 mg
    - Higher intensity (rosuvastatin 20-40 mg, atorvastatin 40-80 mg, simvastatin 80 mg, simvastatin 40-80 mg + ezetimibe 5-10 mg

In the subgroup of patients with diabetes (both type 1 and type 2) the following sub-subgroup analysis was pre-specified in the protocol and SAP.
- Proportion of patients that reached the treatment goal of TG <150 mg/dL

Analysis populations:
- Randomized population: All patients who signed the informed consent and were assigned a randomization number at Visit 4 (Week 0)

- Intent-to-Treat population: All randomized patients who took at least 1 dose of any study drug, had a valid baseline laboratory efficacy measurement, and had at least 1 valid post-randomization laboratory efficacy measurement of any type. This was the primary population for the primary efficacy analysis.

Reviewer comment: This population is more appropriately considered a modified ITT population since it excludes patients who were randomized but were missing certain data. Thus, this review refers to the applicant's "ITT" population as modified ITT (MITT) throughout.

- Per-Protocol population: All MITT patients without any major protocol deviations, which included:
    - Major violations of eligibility criteria for randomization
    - Missing fasting TG measurements at baseline or Week 12 endpoint
    - Overall study drug compliance <80%
    - Prohibited medication(s) taken during the double-blind treatment period, or
    - Any other major protocol deviation that may have interfered with the assessment of drug efficacy

All patients excluded from the per-protocol population were identified prior to unblinding. A blinded pre-analysis data review was conducted by the Medpace and Amarin clinical and statistical study teams to determine which patients were to be excluded from the per-protocol population.

- Safety population: All randomized patients who received at least 1 dose of any study drug. This was the primary population for safety analyses.

Primary efficacy analyses: The primary efficacy analysis was performed using the MITT population and an analysis of covariance (ANCOVA) model with treatment, gender, type of statin, and presence of diabetes as factors and baseline TG as a covariate. Because significant modeling departures from normality were observed when the modeling assumptions were examined, the alternative nonparametric analysis was performed. Estimates for the median of the treatment differences and Hodges-Lehmann 2-tailed 95% confidence interval were provided for each treatment comparison, and P values were determined using the Wilcoxon rank-sum test for treatment comparisons.

A step-down testing procedure was followed using the fixed testing order of comparing 4 g/day of AMR 101 versus placebo and establishing a pre-specified statistically significant level of 0.05 before comparing 2 g/day of AMR 101 versus placebo.

Supportive analyses of the primary efficacy outcome included an analysis in the per-protocol population, an ANCOVA model analysis of the primary efficacy variable repeated without gender, type of statin, and/or presence of diabetes as factors, and an analysis using a modified definition for baseline TG: the average of three TG measurements, i.e., the Visit 4 (Week 0) value and the two immediately preceding values.

Secondary efficacy analyses: Similar procedures were used as for the primary efficacy analyses. Significant departures from normality were observed when the modeling assumptions were examined, so nonparametric analyses were performed as described above.

Non-inferiority tests for percent change from baseline in LDL-C were performed between AMR101 doses and placebo using a non-inferiority margin of 6% and a significance level at 0.025 with the ANCOVA model specified above. The least-squares mean, standard error, and 1-tailed 97.5% confidence interval were provided for the comparisons between AMR101 and placebo.

Because nonparametric analyses were performed for the secondary efficacy parameters, a step-down procedure was used to control the type 1 error rate within each parameter (i.e., comparing 4g/day AMR 101 vs. placebo before comparing 2 g/day vs. placebo). Hommel's procedure was used to test the adequate control of Type 1 error for multiple secondary endpoints (excluding LDL-C).

Exploratory endpoint analysis used an ANCOVA model with treatment as a factor and the baseline value as a covariate. No statistical procedures were used to control for multiple comparisons and therefore these analyses are considered descriptive only.

Sample size determination

A sample size of 194 completed patients per treatment group was estimated to provide 90% power to detect a difference of 15% between AMR 101 4 g daily and placebo in percent change from baseline in fasting TG levels, assuming a standard deviation of 45% in TG measurements and a significance level of $p < 0.05$.

In the sample size calculation for the LDL-C endpoint, a difference in percent change from baseline of 1.7% was assumed, with a standard deviation of 15%, between study drug and placebo. A sample size of 194 completed patients per treatment group was estimated to provide 80% power to demonstrate non inferiority ($p < 0.025$, one-sided) of the LDL-C response between AMR101 4 g daily and placebo, within a 6% margin.

To accommodate a 10% drop-out rate from randomization to completion of the double-blind treatment period, a total of 648 randomized patients was planned (216 patients per treatment group).

4. ANCHOR STUDY POPULATION

4.1. Baseline Characteristics of the Study Population

A total of 2309 patients were screened for participation in the ANCHOR trial. At the end of the screening period, 702 subjects were randomized into the double-blind treatment phase.

Of the 702 randomized patients, the majority were male (61.4%) and white (96.3%). Less than 2% of patients identified as Black or African American and approximately 12% identified as Hispanic. The mean age was 61.4 years; 38.9% were ≥65 years of age. Mean weight was 95.7 kg and mean BMI was 32.9 kg/m^2. The average duration of previous statin use was 3 years and was similar across treatment groups. Approximately 73% were diabetic, 83% were hypertensive, and 68% were obese. One-third had metabolic syndrome as defined by the American Heart Association and the National Heart, Lung, and Blood Institute. Nearly 40% of all randomized

patients had HDL-C <40 mg/dL at baseline. There were no statistically significant differences between treatment groups regarding baseline characteristics. The baseline characteristics of the randomized population and MITT population were similar.

See Table 5 below for a summary of the demographic and baseline characteristics in the ANCHOR trial.

Table 5: Summary of Demographic and Baseline Characteristics – Randomized Population

Characteristic	Placebo N=233	AMR101 2g daily N=236	AMR101 4g daily N=233
Age (y)			
Mean (SD)	61.2 (10.05)	61.8 (9.42)	61.1 (10.03)
Min-max	36-88	31-84	31-85
Age group (n,%)			
≥65 years	87 (37.3)	95 (40.3)	91 (39.1)
Gender (n,%)			
Male	145 (62.2)	144 (61.0)	142 (60.9)
Race (n,%)			
White	224 (96.1)	226 (95.8)	226 (97.0)
Black	4 (1.7)	6 (2.5)	2 (0.9)
Asian	3 (1.3)	2 (0.8)	3 (1.3)
American Indian or Alaska Native	1 (0.4)	1 (0.4)	0 (0.0)
Other	1 (0.4)	1 (0.4)	2 (0.9)
Ethnicity (n,%)			
Not Hispanic or Latino	203 (87.1)	210 (89.0)	206 (88.4)
Hispanic or Latino	30 (12.9)	26 (11.0)	27 (11.6)
Weight (kg) [1]			
Mean (SD)	97.0 (19.14)	95.5 (18.29)	94.5 (18.30)
Min-max	58-145	55-142	54-153
Body mass index (kg/m^2) [1]			
Mean (SD)	33.0 (5.04)	32.9 (4.98)	32.7 (4.99)
Min-max	24-45	23-45	21-46
MEDICAL HISTORY			
Presence of diabetes (n,%)			
Present diabetes	171 (73.4)	172 (72.9)	171 (73.4)
Past or no diabetes	62 (26.6)	64 (27.1)	62 (26.6)
Myocardial infarction			
Past/Present	46 (19.7)	34 (14.4)	31 (13.3)
Unstable angina			
Past/Present	32 (13.7)	17 (7.2)	18 (7.7)
Angioplasty			

Characteristic	Placebo N=233	AMR101 2g daily N=236	AMR101 4g daily N=233
Past/Present	55 (23.6)	40 (16.9)	40 (17.2)
Bypass surgery			
Past/Present	21 (9.0)	24 (10.2)	21 (9.0)
Peripheral arterial disease			
Past/Present	8 (3.4)	10 (4.2)	10 (4.3)
Transient ischemic attack			
Past/Present	9 (3.9)	17 (7.2)	10 (4.3)
Stroke of carotid origin			
Past/Present	6 (2.6)	9 (3.8)	7 (3.0)
Obstruction of carotid artery (>50%)			
Past/Present	15 (6.4)	12 (5.1)	11 (4.7)
Hypertension (BP≥140/90)			
Past/Present	199 (85.4)	202 (85.6)	197 (84.5)
Metabolic Syndrome			
Past/Present	88 (37.8)	80 (33.9)	85 (36.5)
LABS			
TG (mg/dL) [2]			
Mean (SD)	270.6 (75.02)	270.2 (72.12)	281.1 (82.88)
Median	257.5	254.5	267.5
Min-max	140-553	152-503	157-782
Baseline TG category (n,%)			
<185 mg/dL	16 (6.9)	17 (7.2)	14 (6.0)
≥185 mg/dL	217 (93.1)	219 (92.8)	219 (94.0)
LDL-C (mg/dL) [1]			
n	232	235	232
Mean (SD)	84.6 (19.12)	85.6 (18.76)	85.0 (21.97)
Median	84.0	83.0	82.0
Min-max	40-131	44-144	23-177
Non-HDL-C (mg/dL) [1]			
Mean (SD)	130.8 (24.40)	131.8 (24.74)	132.2 (25.76)
Median	128.0	128.0	128.0
Min-max	81-228	80-213	83-200
HDL-C (mg/dL) [1]			
Mean (SD)	39.8 (10.0)	39.1 (8.8)	38.8 (9.9)
Median	39.0	38.0	37.0
VLDL-C (mg/dL) [1]			
n	232	235	232
Mean (SD)	46.3 (17.33)	46.2 (18.50)	47.2 (19.00)
Median	42.0	43.0	44.5
Min-max	12-136	6-118	13-137
Low HDL-C (<40 mg/dL)			

Characteristic	Placebo N=233	AMR101 2g daily N=236	AMR101 4g daily N=233
Present	83 (35.6)	90 (38.1)	99 (42.5)
Lp-PLA$_2$ (ng/mL) [1]			
n	218	226	219
Mean (SD)	193.8 (52.99)	194.0 (44.22)	188.9 (46.40)
Median	187.0	190.0	180.0
Min-max	100-610	101-387	100-388
Apo B (mg/dL) [1]			
n	233	236	232
Mean (SD)	92.8 (16.23)	94.1 (16.46)	94.4 (17.37)
Median	92.0	91.0	93.0
Min-max	43-134	50-141	61-173
STATIN			
Type of statin (n,%)			
Simvastatin	133 (57.1)	136 (57.6)	134 (57.5)
Rosuvastatin	55 (23.6)	57 (24.2)	55 (23.6)
Atorvastatin	45 (19.3)	43 (18.2)	44 (18.9)
Statin regimen intensity (n,%)			
Low [3]	15 (6.4)	17 (7.2)	16 (6.9)
Medium [4]	144 (61.8)	148 (62.7)	148 (63.5)
High [5]	74 (31.8)	71 (30.1)	69 (29.6)

Source: Post-text Table 14.1.5, 14.1.6 ANCHOR CSR
[1] Baseline was defined as the Visit 4 (Week 0) visit.
[2] Baseline was defined as the average of Visit 4 (Week 0) and the preceding lipid qualifying visit
[3] Defined as simvastatin 5-10 mg
[4] Defined as rosuvastatin 5-10 mg, atorvastatin10-20 mg, simvastatin 20-40 mg, or simvastatin 10-20 mg + ezetimibe 5-10 mg
[5] Defined as rosuvastatin 20-40 mg, atorvastatin 40-80 mg, simvastatin 80 mg, or simvastatin 40-80 mg + ezetimibe 5-10 mg

The majority of patients in the MITT population of ANCHOR did not have coronary heart disease. The inclusion criteria required either history of coronary heart disease OR a CHD risk equivalent, one of which was presence of type 1 or type 2 diabetes. The majority of patients qualified for the ANCHOR trial because of their diabetic condition. (Table 6).

Table 6. Summary of Diabetes and Cardiovascular Disease – ANCHOR MITT population

	Placebo **N=227** **n(%)**	**AMR101** **2g/d** **N=234** **n(%)**	**AMR101** **4g/d** **N=226** **n(%)**	**Total** **N=687** **n(%)**
Patients with history of diabetes and CVD	52 (22.9)	49 (20.9)	42 (18.6)	143 (20.8)
Patients with history of diabetes and no CVD	113 (49.8)	122 (52.1)	123 (54.4)	358 (52.1)
Patients with no history diabetes	62 (27.3)	63 (26.9)	61 (27.0)	186 (27.1)

CVD defined as history of any of the following: MI, unstable angina, stable angina, angioplasty, bypass surgery, clinically significant myocardial ischemia, peripheral arterial disease, abdominal aortic aneurysm, TIA, stroke of carotid origin, or obstruction of carotid artery (>50%)
Source: ANCHOR CSR: Table 7

Concomitant medication use

The most commonly used concomitant medication in the ANCHOR trial was, as designed, HMG-CoA reductase inhibitor therapy. More than half of all patients were using a platelet aggregation inhibitor, primarily aspirin (398 [56.7%] patients). Of the approximately 60% of subjects taking an anti-diabetic medication, the most common was metformin (310 [44.2%]). The most commonly used anti-hypertensive medications were ACE inhibitors (253 [36%]) and selective beta-blockers (233 [33.2%]).

Table 7: Summary of Selected Concomitant Medications – Safety Population

	Placebo N=233 n (%)	**AMR101 2g/d N=236 n (%)**	**AMR101 4g/d N=233 n (%)**
HMG-CoA reductase inhibitors	233 (100.0)	236 (100.0)	232 (99.6)
Anti-hypertensive agents	190 (81.5)	200 (84.7)	199 (85.4)
Anti-platelet agent (excluding heparin)	141 (60.5)	135 (57.2)	138 (59.2)
Aspirin	135 (57.9)	130 (55.1)	133 (57.1)
Clopidogrel	26 (11.2)	20 (8.5)	18 (7.7)
Asasantin	2 (0.9)	0	1 (0.4)
Cilostazol	1 (0.4)	0	0
Anti-diabetic agents	139 (59.7)	138 (58.5)	141 (60.5)

Source: Table 11,12, Post-text Table 14.1.12, ANCHOR CSR
Concomitant medications were defined as those used during the double-blind treatment period.
1. In addition, 41 patients were on an HMG-CoA reductase inhibitor in combination with another medication.
2. Patient 057-061 (in the AMR101 4 g group) was not on a statin at randomization and did not inform site personnel until Visit 5 (Week 4) that he had stopped taking his statin 1 week prior to randomization. Patient 057-061 continued in the study; however, because the patient was not on a statin at the time baseline lipid measurements were drawn at Visit 4 (Week 0), the statin was not restarted following Visit 5.

Statin use

The majority of patients in the MITT population at randomization were on a medium-intensity statin regimen (62.3%) (Table 8). The most common dose was simvastatin 40 mg taken by 21.5% of the population. Less than 10% (n=61) of patients were on a statin plus ezetimibe combination at randomization.

Table 8: Summary of Statin Use at Randomization by Intensity – MITT population

	Placebo N=227 n(%)	**AMR101 2g/d N=234 n(%)**	**AMR101 4g/d N=226 n(%)**
Lower intensity	**14 (6.2)**	**15 (6.4)**	**16 (7.1)**
Simvastatin 5 mg	4 (1.8)	4 (1.7)	2 (0.9)
Simvastatin 5 mg + eze*	0	1 (0.4)	0
Simvastatin 10 mg	10 (4.4)	10 (4.3)	13 (5.8)
Simvastatin 15 mg	0	0	1 (0.4)

	Placebo N=227 n(%)	AMR101 2g/d N=234 n(%)	AMR101 4g/d N=226 n(%)
Medium intensity	**140 (61.7)**	**147 (62.8)**	**141 (62.4)**
Atorvastatin 10 mg	10 (4.4)	8 (3.4)	9 (4.0)
Atorvastatin 20 mg	14 (6.2)	18 (7.7)	15 (6.6)
Rosuvastatin 5 mg	9 (4.0)	7 (3.0)	8 (3.5)
Rosuvastatin 5 mg + eze	1 (0.4)	0	0
Rosuvastatin 10 mg	21 (9.3)	28 (12.0)	19 (8.4)
Rosuvastatin 10 mg + eze	1 (0.4)	0	1 (0.4)
Simvastatin 10 mg + eze	0	3 (1.3)	1 (0.4)
Simvastatin 20 mg	31 (13.7)	32 (13.7)	31 (13.7)
Simvastatin 20 mg + eze	5 (2.2)	3 (1.3)	4 (1.8)
Simvastatin 40 mg	47 (20.7)	48 (20.5)	53 (23.5)
Simvastatin 60 mg	1 (0.4)	0	0
Higher intensity	**73 (32.2)**	**72 (30.8)**	**69 (30.5)**
Atorvastatin 40 mg	16 (7.0)	9 (3.8)	12 (5.3)
Atorvastatin 40 mg + eze	1 (0.4)	2 (0.9)	0
Atorvastatin 60 mg	0	1 (0.4)	0
Atorvastatin 80 mg	4 (1.8)	4 (1.7)	4 (1.8)
Atorvastatin 80 mg + eze	0	1 (0.4)	1 (0.4)
Rosuvastatin 20 mg	20 (8.8)	15 (6.4)	21 (9.3)
Rosuvastatin 20 mg + eze	0	2 (0.9)	0
Rosuvastatin 40 mg	2 (0.9)	3 (1.3)	5 (2.2)
Rosuvastatin 40 mg + eze	0	2 (0.9)	0
Simvastatn 40 mg + eze	10 (4.4)	10 (4.3)	6 (2.7)
Simvastatin 80 mg + eze	0	4 (1.7)	2 (0.9)

*Note: Ezetimibe includes patients on 5 mg or 10 mg
Source: Table 9 ANCHOR CSR

The majority of patients (n=620; 90.2%) were on a statin prior to screening (Table 9). Of those 620 patients, 582 (84.7%) continued taking the same statin after screening and 571 (83.1%) maintained the same statin at the same dose after screening. Patients who were not on a statin prior to the screening visit (n=67 [9.8%]) were placed on a permitted statin at the discretion of the investigator and maintained a stable statin dose for ≥4 weeks prior to the first qualifying LDL-C/TG blood draw at Visit 2 (Week -2). The majority (n=44) of these patients were placed on simvastatin, all but one of whom were started on a medium-intensity regimen.

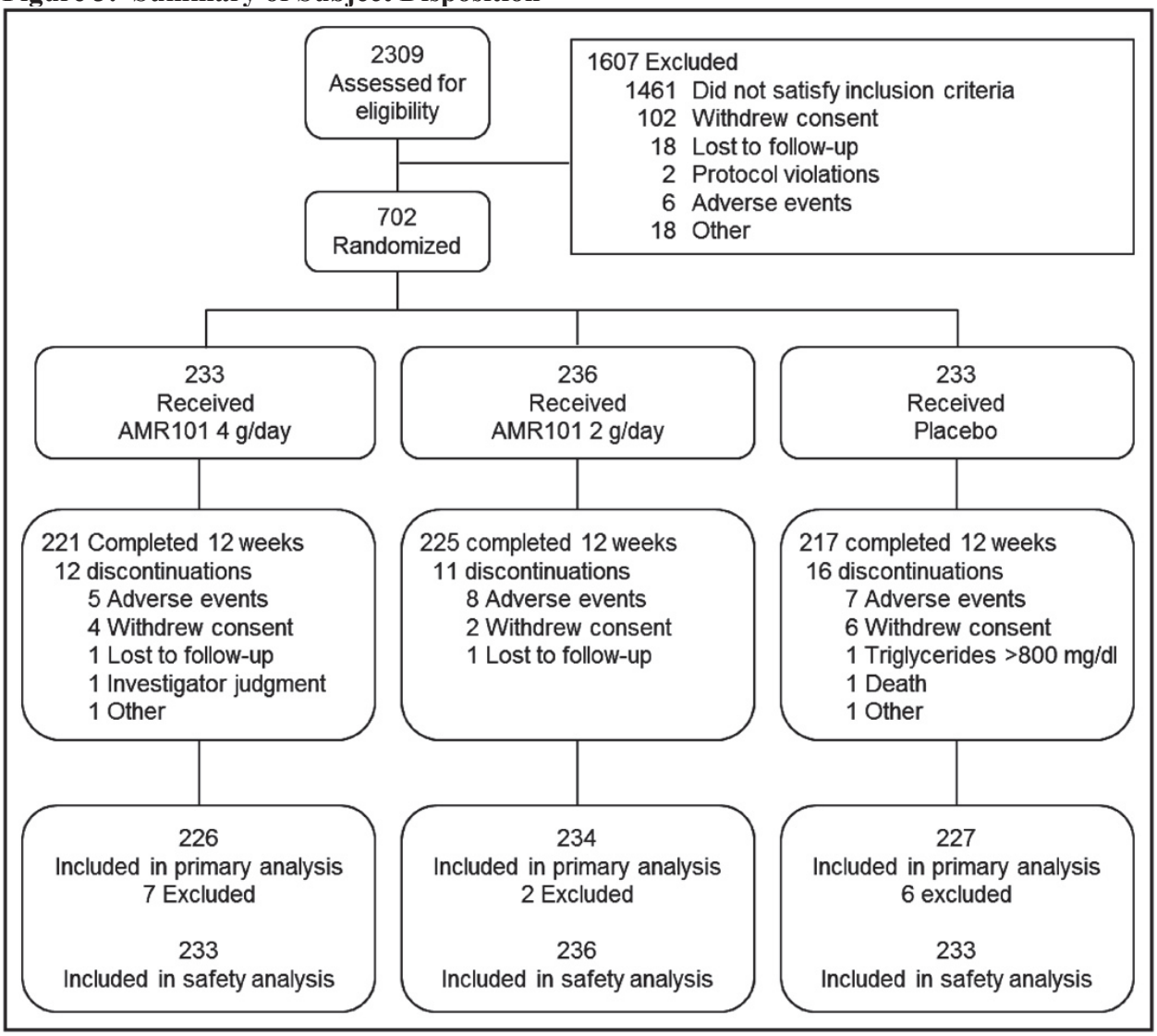
Table 9: Summary of Statin Use – MITT population

Category	Placebo N=227 n(%)	AMR101 2g/d N=234 n(%)	AMR101 4g/d 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	187 (82.4)	194 (82.9)	190 (84.1)	571 (83.1)
Changed dose	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: Table 10 ANCHOR CSR				

4.2. Patient Disposition and Compliance

The ANCHOR trial involved 97 study sites in the United States. The first patient was screened on 16 December 2009, and the first patient was randomized on 27 January 2010. Figure 3 summarizes the disposition of subjects from screening to study termination.

Figure 3: Summary of Subject Disposition



Source: Ballantyne CM et al. Am J Cardiol 2012; 110:984-992

Of the 2309 subjects assessed for eligibility, 1607 (69.6%) were excluded prior to randomization. Of this group, 1011 (43.8%) were not randomized due to lipid values outside the eligibility requirements; 813 (35.2%) subjects had TG out of range, 143 (6.1%) subjects had LDL-C out of range, 55 subjects had non-HDL-C out of range (3.4%). Other less common reasons for exclusion included HbA1c values out of range (6.4%) and not qualifying as high risk for CVD (3.7%). Of the 1607 who were screened but not randomized, 754 were excluded at the first screening visit. See Table 10 for further details.

Table 10: Reasons Screened Patients Were Not Randomized

Reason for pre-randomization discontinuation	N(%)
SCREENED	**2309 (100.0%)**
Did not satisfy inclusion/exclusion criteria	1461 (63.4%)
o TG levels out of range	813 (35.2%)

o HbA1c out of range	150 (6.4%)
o LDL-C levels out of range	143 (6.1%)
o Not at high risk for CVD	59 (3.7%)
o Mean non-HDL-C out of range	55 (3.4%)
o TSH out of range/hypothyroidism/thyroid hormone therapy not stable	46 (2.0%)
o Positive test for Hep B/C antibody	21 (0.9%)
o Statin therapy not stable	20 (0.9%)
o BMI out of range	17 (0.7%)
o AST/ALT out of range	16 (0.7%)
o Uncontrolled hypertension	13 (0.6%
o Unstable treatment for metabolic/CV disease	13 (0.6%)
o Condition/therapy posing risk to patient	12 (0.5%)
o Unexplained CK concentration/elevation due to muscle disease	12 (0.5%)
o Use of non-study drug related/non-statin/lipid-altering medications or supplements	11 (0.5%)
o History of malignancy	10 (0.4%)
o Participation in another trial	10 (0.4%)
o History/evidence of disease that would interfere with study	9 (0.4%)
o Weight change out of range	8 (0.3%)
o Poor mental function/other reason to expect difficulty in compliance	4 (0.2%)
o Routine/anticipated use of systemic corticosteroids	4 (0.2%)
o No informed consent	4 (0.2%)
o Anticipation of major surgery	3 (0.1%)
o History of bariatric surgery	3 (0.1%)
o Use of statin other than atorvastatin/rosuvastatin/simvastatin	2 (0.09%)
o Blood donation out of range/plasma donation	1 (0.04%)
o Consumption of alcoholic beverages/day out of range	1 (0.04%)
o PCI within 4 weeks of screening	1 (0.04%)
Withdrawal of consent	102 (4.4%)
Lost to follow-up	18 (0.8%)
Adverse event	6 (0.3%)
Protocol violation	2 (0.09%)
Other	18 (0.8%)
SCREENED, NOT RANDOMIZED	**1607 (69.6%)**

Source: CSR Post-text Table 14.1.1

Reviewer comment: The proportion of subjects excluded during the screening period is similar to Lovaza's add-on to statin therapy trial, COMBOS. In the COMBOS trial, of the 690 subjects assessed for eligibility; 434 (62.8%) were excluded prior to randomization; the majority (n=379) for not meeting the inclusion criteria. No further details were provided regarding which specific inclusion criteria (lipid values, HbA1c etc.) these patients did not meet.

Of the 1011 screened patients in ANCHOR who failed for lipid reasons, only 609 patients had potential qualifying lipid levels at the end of the qualifying phase (Visits 2/3 or Visits 3/3.1) of

the run-in period. The remaining 402 patients screened failed after Visit 1 or Visit 2 and therefore never made it through the entire qualifying phase of the run-in period.

The following tables provide the descriptive statistics for the qualification levels of LDL-C, TG, and non-HDL-C for the following groups: (a) the 609 subjects who were not randomized because they did not meet lipid-related eligibility criteria at the end of the qualifying phase (Visit 2 and Visit 3 or Visit 3 or Visit 3.1), and (b) the 702 randomized subjects.

Table 11: Summary of Lipid Values at the End of the Qualifying Phase of Run-in Period

	Not randomized due to lipid values at the end of the qualifying phase	**Randomized**
TOTAL subjects	**609**	**702**
TG (mg/dL) [1]		
Median	176.0	254.5
Mean (SE)	234.9 (7.62)	273.9 (2.58)
LDL-C (mg/dL) [2]		
N	599 [3]	702
Median	74.0	75.0
Mean (SE)	78.6 (1.52)	75.9 (0.63)
Non-HDL-C (mg/dL)		
Median	111.0	130.0
Mean (SE)	123.1 (1.77)	130.6 (0.72)

Source: Response to FDA IR Submitted April 17, 2013 DARRTS SD #89
[1] Lipid levels mean of Visits 2/3 or Visits 3/3.1
[2] LDL-C calculated by Friedewald formula
[3] 10 patients with negative LDL-C values excluded (screen failed for either TG or non-HDL-C)

Reviewer comment: While LDL-C levels between these two groups are similar, the TG levels and non-HDL-C levels were lower in this subset of screen failures than in the randomized group. This is to be expected based on the lipid requirements for randomization.

Table 12: Patients Not Randomized at End of Screening Period due to Lipid Levels - Classified by LDL-C and TG Category

	TG too low	TG in range	TG too high	**Total**
LDL-C too low	68	73	5	**146**
LDL-C in range	318	34*	14	**366**
LDL-C too high	10	51	26	**87**
LDL-C not available†	0	1*	9	**10**
Total	**396**	**159**	**54**	**609**

* Patients screen failed for non-HDL-C too low
† Negative LDL-C values were excluded. These patients screen failed for either TG (9 patients with TG too high) or non-HDL-C too low (1 patient)

Source: Response to FDA IR supporting document:

Reviewer comment: Most patients screened failed for TG too low while their LDL-C values were in range.

Of the 702 subjects who were randomized, 233 were assigned to the AMR101 4 g group, 236 were assigned to the AMR101 2 g group, and 233 were assigned to the placebo group. Thirty-nine (5.6%) patients discontinued early from the trial during the double-blind treatment period (Table 13). In total, 663 (94.4%) patients completed the double-blind treatment period of the study.

Table 13: Patient Disposition During the Double-Blind Treatment Period – Randomized Population

Category	Placebo N=233 n(%)	AMR101 2g/d N=236 n(%)	AMR101 4g/d N=233 n(%)	Total N=702 n(%)
Randomized	233 (100.0)	236 (100.0)	233 (100.0)	702 (100.0)
Completed 4 weeks in double-blind period	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 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	1 (0.4)	1 (0.4)	2 (0.3)
TG >800 mg/dL	1 (0.4)	0	0	1 (0.1)
Investigator judgment	0	0	1 (0.4)	1 (0.1)
Death	1 (0.4)	0	0	1 (0.1)
Other	1 (0.4)	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)

Source: Table 5 ANCHOR CSR

Compliance with therapy

At each follow-up visit, compliance with treatment was reviewed with the patient by assessing the unused capsule count. Percent compliance to study treatment was calculated as the total number of tablets taken divided by the presumed number of tablets taken in the period multiplied by 100. Less than 80% prompted a discussion of ways to improve adherence to therapy.

A slightly smaller proportion of patients treated with 4g AMR101 remained ≥80% compliant with study treatment than patients treated with placebo or 2g AMR101.

Table 14: Compliance with therapy – ANCHOR

Reported compliance ≥ 80%		
Placebo	**AMR101 2g/d**	**AMR101 4g/d**
220/233 (94.4%)	227/236 (96.2%)	216/233 (92.7%)

Reported compliance ≥ 80%		
Placebo	**AMR101 2g/d**	**AMR101 4g/d**
Source: Post-text Table 14.1.11, ANCHOR CSR		

The following table shows patient compliance for the 80% cut-off at each visit by treatment group. Over 95% of patients treated with AMR101 4g demonstrated 80% compliance at each clinic visit. The placebo group had the lowest proportion of patients with ≥80% compliance at each visit, but even so, at each visit more than 90% of these subjects met this degree of compliance.

Table 15: Summary of study medication compliance categories by visit and incidence of subjects with compliance <80% at one or more visits – Randomized population

Visit	Compliance Category	Placebo (N=233) n (%)	AMR101 2 g/day (N=236) n (%)	AMR101 4 g/day (N=233) n (%)	Overall (N=702) n (%)
Week 4		(N'=233)	(N'=236)	(N'=233)	(N'=702)
	<80%	10 (4.3)	7 (3.0)	11 (4.7)	28 (4.0)
	≥80%	223 (95.7)	229 (97.0)	222 (95.3)	674 (96.0)
Week 11		(N'=226)	(N'=229)	(N'=226)	(N'=681)
	<80%	16 (7.1)	11 (4.8)	7 (3.1)	34 (5.0)
	≥80%	210 (92.9)	218 (95.2)	219 (96.9)	647 (95.0)
Week 12		(N'=212)	(N'=224)	(N'=213)	(N'=649)
	<80%	19 (9.0)	16 (7.1)	8 (3.8)	43 (6.6)
	≥80%	193 (91.0)	208 (92.9)	205 (96.2)	606 (93.4)
Overall		(N'=233)	(N'=236)	(N'=233)	(N'=702)
	At least one visit with compliance <80%	41 (17.6)	30 (12.7)	24 (10.3)	95 (13.5)

N' is the number of subjects with non-missing data for the specified Visit. n is the number of subjects in the compliance category. % = 100 x n/N'.
Compliance % = 100 x capsules consumed/capsules prescribed.
Capsules consumed = number of capsules dispensed at previous visit - number of capsules returned at specified Visit. Capsules dispensed and/or returned at unscheduled visits are also taken into account.
Capsules prescribed = 4 x (specified Visit date - previous visit date).
When the specified Visit date is missing and no subsequent visits are recorded, the date of study completion is imputed.

Source: Response to FDA IR submitted 19 July 2013 DARRTS SD #109

Compliance with background statin therapy was not assessed with pill counts. Compliance with statin therapy during the lead-in period was assessed indirectly by ensuring patients took an adequate dose of a permitted statin to achieve their LDL-C goal before the qualifying visits prior to randomization. No measurements of statin plasma exposure were made during the study.

5. ANCHOR EFFICACY RESULTS

5.1. Primary Endpoint Results: Reduction in Triglycerides

All standard lipid laboratory tests were performed by a certified clinical pathology laboratory (Medpace Reference Laboratories, Cincinnati, Ohio). Blood samples were obtained under fasting conditions (nothing by mouth except water and essential medications for ≥10 hours).

The ITT population, referred to in this document as the modified ITT (MITT), was the primary analysis population. This group of 687 individuals took at least 1 dose of study drug, had a baseline laboratory efficacy measurement, and had at least 1 post-randomization laboratory efficacy measurement. The per-protocol population was supportive of the MITT analysis and will not be further described.

There were a total of 38 subjects without a valid Week 11/Week 12 TG value (placebo n=15, AMR101 2g n=12, AMR101 4g n=11). Of these, 15 did not have any post-baseline values, and were excluded from the primary analysis. The remaining 23 patients' last post-baseline TG values (17 from Week 4 visits and 6 from early termination visits ranging from 2 to 9 weeks after randomization) were carried forward for the primary TG analysis.

Median baseline TG levels were similar across the treatment groups. The median percent change in TG from baseline to Week 12 was -17.5% for the AMR101 4g group, -5.6% for the AMR101 2g group and +5.9% for the placebo group (Table 16). The estimate of the median of the treatment difference between AMR101 4g and placebo was -21.5% ($p<0.0001$) and between AMR101 2g and placebo was -10.1% ($p=0.0005$). The results from the per-protocol and completer populations were similar in direction and magnitude to those observed in the MITT population.

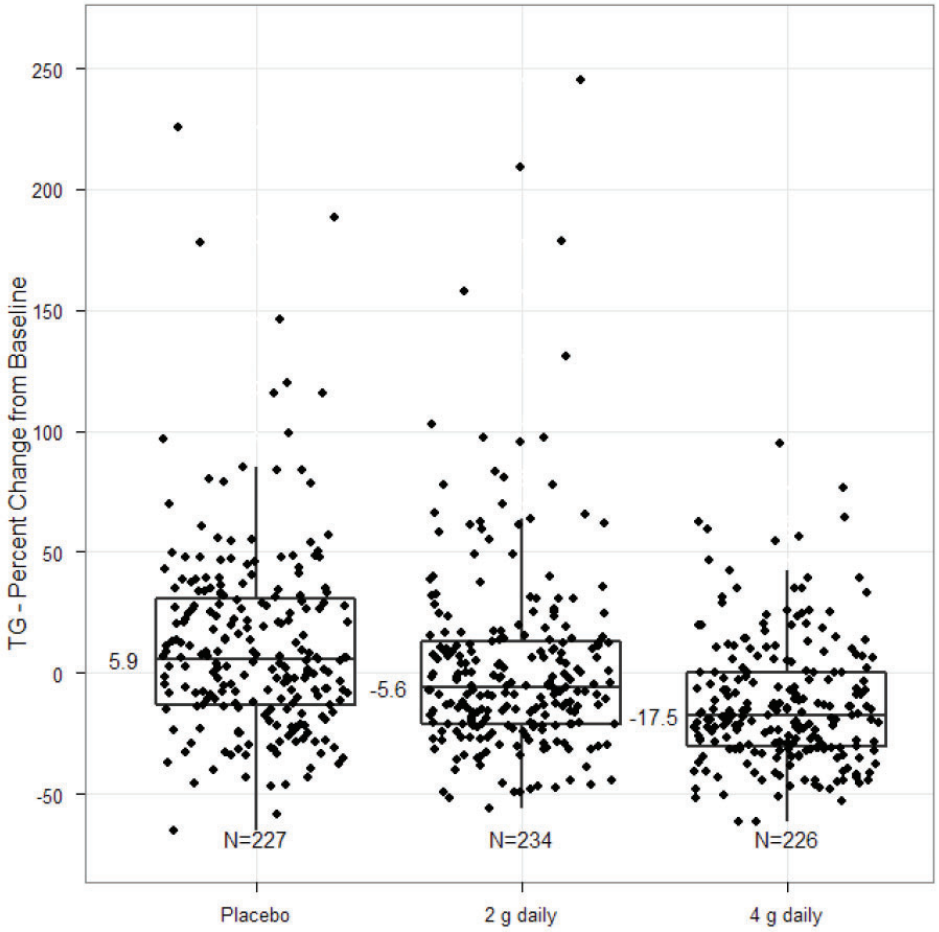
Table 16: Percent Change in Fasting TG (mg/dL) from Baseline to Week 12 Endpoint and Difference From Placebo– MITT Population

Treatment + Statin	n [1]	Baseline[2] Median (IQR)	Week 12 EP [3] Median (IQR)	Percent change from Baseline			Difference from placebo		
				Median (IQR)	(Q1, Q3)	p-value	Estimated median	95% CI	p-value
Placebo	227	259.0 (81.0)	269.5 (149.5)	5.9 (44.9)	(-13.5, 31.3)	0.0002	--	--	--
AMR101 2g/d	234	254.0 (92.5)	244.3 (117.0)	-5.6 (34.5)	(-21.1, 13.4)	0.1111	-10.1	(-15.7, -4.5)	0.0005
AMR101 4g/d	226	264.8 (93.0)	220.8 (92.0)	-17.5 (31.0)	(-30.5, 0.5)	<0.0001	-21.5	(-26.7, -16.2)	<0.0001

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; EP = endpoint; IQR = interquartile range; Q1 = first quartile; Q3 = third quartile
Source: Table 13 ANCHOR CSR

Figure 4 shows the individual data points, except for one value of 564% in the AMR101 4g/day group, for the percent changes in fasting TG from baseline to Week 12.

Figure 4: Box-and-Whisker Plot of Median Percent Change in Fasting TG From Baseline to Week 12 Endpoint – MITT Population



Each dot represents the percent change from baseline in TG for each patient. The horizontal line within each box and corresponding value represent the median percent change in TG from baseline to Week 12 endpoint. The bottom edge of each box represents Q1; the top edge of each box represents Q3. The whiskers extend to ≤1.5 × IQR from the box. One value in the AMR101 4 g/day treatment group (564%) is not shown as it was an outlier and is outside of the y-axis range shown in the figure.
IQR = interquartile range; N = number of patients per treatment group; Q1 = first quartile; Q3 = third quartile; TG = triglyceride.
Source: Post-text Data Listing 16.2.6.1 (Note: This figure was provided by the Sponsor.)

An exploratory categorical analysis of patients reaching fasting triglyceride treatment goals (<150 mg/dL) at the Week 12 endpoint was performed. A slightly higher proportion of AMR101 4g-treated patients achieved their TG goal compared to the 2g and placebo-treated patients. Overall, the numbers were very small with less than 10% of patients in each group achieving a TG <150 mg/dL.

Table 17: Percentage of Patients Achieving TG Treatment Goal (<150 mg/dL) at Week 12 Endpoint

Achieved TG < 150 mg/dL		
Placebo	**AMR101 2g/d**	**AMR101 4g/d**

Achieved TG < 150 mg/dL		
Placebo	**AMR101 2g/d**	**AMR101 4g/d**
13/227 (5.7%)	9/234 (3.8%)	16/226 (7.1%)
Source: Post-text Table 14.2.6, ANCHOR CSR		

Reviewer comment: The reviewer recognizes that the proportion of patients achieving certain lipid thresholds is dependent on baseline levels; therefore, this exploratory analysis provides little additional information. Nevertheless, it does highlight that given a population with typical TG levels in the mid-200's (mg/dL), few will achieve what many consider a treatment goal for serum triglycerides, and the between-group comparisons to placebo are not impressive in this regard.

5.2 Secondary Endpoint Results

Median LDL-C increased from baseline to Week 12 in all treatment groups despite stable statin therapy, with the placebo group exhibiting the largest increase. The median percent change in LDL-C from baseline to Week 12 was +8.8% for the placebo group, +2.4% for the AMR101 2g group, and +1.5% for the AMR101 4g group. These changes resulted in estimated median treatment differences of -6.2% for AMR101 4g and -3.6% for AMR101 2g compared with placebo. Because omega-3 FA are not typically expected to be LDL-lowering therapies, the goal of these comparisons was to rule out an unacceptable increase in LDL-C compared with placebo. The pre-specified non-inferiority margin was 6%. Both the 2g and 4g doses of AMR101 demonstrated non-inferiority compared to placebo group, with the latter demonstrating superiority; the upper limits of the 97.5% confidence interval of the treatment differences were +0.5% and -1.7% for AMR101 2g/day and 4 g/day, respectively.

Median non-HDL-C levels increased from baseline to Week 12 in the placebo and AMR101 2g groups and decreased by 5% in the AMR101 4g group. These changes resulted in estimated median treatment differences of -13.6% for AMR101 4g and -5.5% for AMR101 2g compared with placebo. The other pre-specified secondary endpoints also demonstrated statistically significant treatment differences between the placebo group and the AMR 101 4g group, even with statistical adjustment for multiple comparisons.

Reviewer comments: Whether these changes will translate into cardiovascular risk reduction, which is the ultimate goal of therapy for the proposed target population, requires confidence that the changes presented for these lipid and lipoprotein parameters will be cardioprotective.

Also, note that for each of these parameters, with the exception of HDL-C and apo A1, the placebo group demonstrated nominally statistically significant changes from baseline in an adverse direction, while on background statin therapy. If these within-group changes were the result of factors that were randomly distributed across treatment groups, the comparisons to placebo should represent the best estimates of the treatment effect. If it is possible, however, that the mineral oil placebo was not biologically inert (e.g., could it have partially inhibited statin absorption if concomitantly ingested?), then the comparisons with placebo could produce biased treatment effects. This possibility that the placebo may not be inert is further discussed in Section 5.5.

Table 18: Percent Change from Baseline and Difference from Placebo- Secondary Endpoints – MITT Population

Treatment + Statin	n [1]	Baseline[2] Median (IQR)	Week 12 EP [2] Median (IQR)	Percent change from Baseline			Difference from placebo		
				Median (IQR)	(Q1, Q3)	p-value	Estimated median	95% CI	Adjusted p-value [4]
LDL-C (mg/dL)									
Placebo	226	84.0 (27.0)	88.5 (31.0)	8.8 (31.0)	(-7.8, 23.2)	<0.0001	--	--	--
AMR101 2g/d	234	82.0 (24.0)	87.0 (27.0)	2.4 (26.1)	(-8.3, 17.7)	0.0010	-3.6	(-7.9, 0.5)	0.0867
AMR101 4g/d	225	82.0 (25.0)	83.0 (31.0)	1.5 (26.6)	(-11.6, 15.0)	0.1733	-6.2	(-10.5, -1.7)	0.0067
non-HDL-C (mg/dL									
Placebo	227	128.0 (34.0)	138.0 (43.0)	9.8 (27.6)	(-3.5, 24.1)	<0.0001	--	--	--
AMR101 2g/d	234	128.0 (33.0)	134.0 (41.0)	2.4 (26.1)	(-7.0, 19.0)	0.0001	-5.5	(-9.4, -1.7)	0.0140
AMR101 4g/d	226	128.0 (32.0)	122.0 (39.0)	-5.0 (21.3)	(-13.5, 7.8)	0.0106	-13.6	(-17.2, -9.9)	0.0001
Apo B (mg/dL)									
Placebo	219	91.0 (24.0)	98.0 (25.0)	7.1 (23.2)	(-4.7, 18.6)	<0.0001	--	--	--
AMR101 2g/d	227	91.0 (22.0)	95.0 (24.0)	1.6 (20.7)	(-6.4, 14.3)	0.0001	-3.8	(-6.9, -0.7)	0.0170
AMR101 4g/d	217	93.0 (23.0)	90.0 (25.0)	-2.2 (16.4)	(-10.2, 6.2)	0.0759	-9.3	(-12.3, -6.1)	0.0001
VLDL-C (mg/dL)									
Placebo	226	42.0 (21.0)	49.0 (28.0)	15.0 (58.8)	(-10.9, 47.8)	<0.0001	--	--	--
AMR101 2g/d	233	43.0 (21.0)	44.0 (25.0)	1.6 (54.6)	(-20.0, 34.5)	0.0287	-10.5	(-18.3, -2.5)	0.0170
AMR101 4g/d	225	44.0 (21.0)	38.0 (22.0)	-12.1 (47.9)	(-31.3, 16.7)	0.0043	-24.4	(-31.9, -17.0)	0.0001
Lp-PLA$_2$ (ng/mL)									
Placebo	213	185.0 (58.0)	200.0 (71.0)	6.7 (24.0)	(-6.4, 17.6)	<0.0001	--	--	--
AMR101 2g/d	224	190.0 (55.5)	183.5 (57.5)	-1.8 (23.1)	(-12.7, 10.4)	0.2686	-8.0	(-11.6, -4.5)	0.0004
AMR101 4g/d	217	180.0 (56.0)	160.0 (57.0)	-12.8 (18.5)	(-22.1, -3.6)	<0.0001	-19.0	(-22.2, -15.7)	0.0001

				Percent change from Baseline			Difference from placebo		
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 4g or 2g with placebo with exception of LDL-C CI = confidence interval; EP = endpoint; IQR = interquartile range; Q1 = first quartile; Q3 = third quartile Source: Table 14-18 ANCHOR CSR									

5.3 Exploratory Endpoints

The following tables describe the changes from baseline and treatment comparisons for pre-specified exploratory endpoints. Per the SAP, these analyses are not controlled for type 1 error and should be considered descriptive.

Table 19 describes additional lipid parameters of interest. The placebo group demonstrated unfavorable changes from baseline for total cholesterol (+9%), VLDL-TG (+9%), and ApoB/ApoA1 (+2%); AMR101 4g demonstrated numerical reductions from baseline. There appears to be a dose-related reduction in HDL-C when comparing AMR101 to placebo, with a median percent change in HDL-C of +4.8% in the placebo group versus a 1% decrease in the AMR101 4g group, producing a between-group treatment estimate that was nominally statistically significant (p=0.0013).

Reviewer comment: The absolute changes in median HDL-C were small (no change versus +1 mg/dL). The clinical significance of these changes is probably minimal.

Table 19: Percent Change from Baseline and Difference from Placebo- Lipid Exploratory Endpoints – MITT Population

Treatment + Statin	n [1]	Baseline[2] Median (IQR)	Week 12 EP [2] Median (IQR)	Percent change from Baseline			Difference from placebo		
				Median (IQR)	(Q1, Q3)	p-value	Estimated median	95% CI	p-value
Total cholesterol (mg/dL)									
Placebo	227	168.0 (38.0)	181.0 (46.0)	9.1 (20.8)	(-1.4, 19.4)	<0.0001	--	--	--
AMR101 2g/d	234	169.0 (34.0)	175.0 (44.0)	2.1 (19.6)	(-4.4, 15.2)	<0.0001	-4.8	(-7.8, -1.8)	0.0019
AMR101 4g/d	226	167.0 (38.0)	162.0 (38.0)	-3.2 (16.8)	(-11.3, 5.5)	0.0023	-12.0	(-14.9, -9.2)	<0.0001

				Percent change from Baseline			Difference from placebo		
HDL-C (mg/dL									
Placebo	227	39.0 (12.0)	40.0 (14.0)	4.8 (22.0)	(-7.7, 14.3)	<0.0001	--	--	--
AMR101 2g/d	234	38.0 (13.0)	38.0 (11.0)	0 (19.5)	(-7.7, 11.8)	0.0164	-2.2	(-4.9, 0.5)	0.1265
AMR101 4g/d	226	37.0 (12.0)	37.0 (13.0)	-1.0 (18.2)	(-8.7, 9.5)	0.8474	-4.5	(-7.4, -1.8)	0.0013
VLDL-TG (mg/dL)									
Placebo	226	183.0 (94.0)	196.0 (136.0)	8.9 (63.8)	(-19.3, 44.5)	<0.0001	--	--	--
AMR101 2g/d	233	185.0 (86.0)	168.0 (98.0)	-2.1 (48.9)	(-26.3, 22.6)	0.8897	-11.3	(-19.4, -3.4)	0.0049
AMR101 4g/d	225	190.0 (99.0)	147.0 (88.0)	-19.2 (46.2)	(-39.2, 7.0)	<0.0001	-26.5	(-33.9, -19.0)	<0.0001
Apo A1 (mg/dL)									
Placebo	219	140.0 (35.0)	145.0 (34.0)	3.6 (14.9)	(-2.1, 12.1)	<0.0001	--	--	--
AMR101 2g/d	227	140.0 (26.0)	141.0 (26.0)	2.0 (13.0)	(-4.0, 9.0)	0.0007	-1.7	(-3.7, 0.3)	0.0943
AMR101 4g/d	217	141.0 (31.0)	137.0 (29.0)	-2.9 (12.6)	(-9.6, 3.1)	<0.0001	-6.9	(-8.9, -4.9)	<0.0001
Apo B/ApoA1 ratio									
Placebo	219	0.7 (0.2)	0.7 (0.2)	2.4 (21.7)	(-7.8, 13.9)	0.0028	--	--	--
AMR101 2g/d	227	0.7 (0.2)	0.7 (0.2)	0.1 (18.3)	(-7.9, 10.4)	0.2523	-2.0	(-5.0, 0.9)	0.1886
AMR101 4g/d	217	0.7 (0.2)	0.7 (0.2)	-0.7 (20.3)	(-8.1, 12.2)	0.4097	-2.4	(-5.4,0.8)	0.1333
Lp(a) (mg/dL)									
Placebo	83	12.0 (31.0)	12.0 (37.0)	0.0 (35.0)	(-8.3, 26.7)	0.0452	--	--	--
AMR101 2g/d	83	11.0 (33.0)	12.0 (33.0)	0.0 (24.9)	(-2.5, 22.4)	0.0011	0.0	(-2.5, 8.3)	0.5466
AMR101 4g/d	81	7.0 (33.0)	9.0 (31.0)	0.0 (10.0)	(-6.5, 3.4)	0.4722	0.0	(-8.3, 0.0)	0.3626
RLP-C (mg/dL)									
Placebo	86	14.0 (7.0)	13.0 (9.0)	8.0 (66.9)	(-29.4, 37.5)	0.1316	--	--	--
AMR101 2g/d	84	15.0 (7.0)	11.0 (7.0)	-11.1 (40.0)	(-30.0, 10.0)	0.0124	-16.7	(-30.0, 10.0)	0.0153

				Percent change from Baseline			Difference from placebo		
AMR101 4g/d	82	13.5 (6.0)	10.0 (6.0)	-24.0 (45.5)	(-45.5, 0.0)	0.0002	-25.8	(-39.9, -12.4)	0.0001
Oxidized LDL (U/L)									
Placebo	84	51.8 (16.8)	59.7 (18.1)	11.6 (28.1)	(-4.0, 24.1)	<0.0001	--	--	--
AMR101 2g/d	75	54.0 (17.8)	55.8 (22.8)	2.6 (18.3)	(-4.5, 13.8)	0.0245	-5.8	(-11.9, 0.9)	0.0946
AMR101 4g/d	78	54.0 (14.6)	51.4 (17.5)	-4.8 (19.6)	(-11.5, 8.1)	0.0610	-13.3	(-19.3, -7.5)	<0.0001

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; EP = endpoint; IQR = interquartile range; Q1 = first quartile; Q3 = third quartile
Source: Table 19-21, Post-text table 14.2.25- 29, 35-37 ANCHOR CSR

LDL particle concentration and size were measured by nuclear magnetic resonance from baseline to Week 12. Based on the Multi-Ethnic Study of Atherosclerosis (MESA) population, LDL particle concentrations <1000 nmol/L correspond to the 20th percentile and >1600 correspond to the 80th percentile and higher.[15] Individuals with elevated TG or low HDL-C have been found to have higher LDL-P concentrations, on average, at a given level of LDL-C. Treatment with statins in general lowers LDL-C to a greater degree than LDL-P. All groups demonstrated an increase from baseline in LDL-P concentration, but AMR101-treated groups increased to a lesser degree (without evidence of a dose-response).

Table 20: Change from Baseline and Difference from Placebo - LDL Particle Concentration and Size - Exploratory Endpoints – MITT Population

Treatment + Statin	n [1]	Baseline[2] Median (IQR)	Week 12 EP [2] Median (IQR)	Percent change from Baseline			Difference from placebo		
				Median (IQR)	(Q1, Q3)	p-value	Estimated median	95% CI	p-value
LDL Particle Concentration (nmol/L)									
Placebo	211	1152.0 (353.0)	1287.0 (456.0)	11.9 (31.6)	(-3.0, 28.6)	<0.0001	--	--	--

[15] Cromwell WC et al. Heterogeneity of low-density lipoprotein particle number in patients with type 2 diabetes mellitus and low-density lipoprotein cholesterol <100 mg/dL. Am J Cardiol 2006; 98:1599-1602

				Percent change from Baseline			Difference from placebo		
AMR101 2g/d	222	1170.5 (349.0)	1215.0 (355.0)	4.7 (29.2)	(-10.3, 18.9)	0.0008	-7.5	(-12.1, -2.9)	0.0013
AMR101 4g/d	216	1130.5 (369.5)	1190.5 (512.0)	3.8 (31.8)	(-11.0, 20.8)	0.0016	-7.7	(-12.3, -2.8)	0.0017
LDL Particle Size (nm)									
Placebo	211	19.8 (0.6)	19.9 (0.5)	0.0 (2.5)	(-1.0, 1.5)	0.3037	--	--	--
AMR101 2g/d	221	19.8 (0.5)	20.0 (0.6)	0.5 (2.5)	(-0.5, 2.0)	<0.0001	0.5	(0.5, 1.0)	0.0007
AMR101 4g/d	215	19.8 (0.5)	20.0 (0.6)	0.5 (2.5)	(-0.5, 2.0)	<0.0001	0.5	(0.0, 1.0)	0.0031

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.
Median differences between treatment groups and 95% CI were estimated with the Hodges-Lehmann method. P-value is form the Wilcoxon rank-sum test
CI = confidence interval; EP = endpoint; IQR = interquartile range; Q1 = first quartile; Q3 = third quartile
Source: Table 22-23 ANCHOR CSR

Fasting plasma glucose and HbA1c increased in all treatment groups during the 12 weeks of study treatment. The AMR101 4g group exhibited a 4.7 mg/dL and 0.1 percentage point increase in fasting plasma glucose and HbA1c over placebo, respectively, but these changes did not achieve nominal statistical significance.

Table 21: Percent Change from Baseline and Difference from Placebo - Glucose Metabolism Exploratory Endpoints – MITT Population

Treatment + Statin	n [1]	Baseline[2] Mean (SD)	Week 12 EP [2] Mean (SD)	Mean Change from Baseline			Difference from placebo		
				LS Mean (SE)	(95% CI)	p-value	LS Mean (SE)	95% CI	p-value
Fasting plasma glucose (mg/dL)									
Placebo	219	128.9 (35.2)	133.7 (38.5)	4.2 (2.1)	(0.0, 8.4)	0.0032	--	--	--
AMR101 2g/d	226	134.8 (42.6)	138.0 (44.9)	3.6 (2.1)	(-0.5, 7.7)	0.0042	-0.6 (3.0)	(-6.5, 5.3)	0.8408
AMR101 4g/d	217	133.1 (37.0)	141.9 (51.1)	8.9 (2.1)	(4.7, 13.1)	0.0007	4.7 (3.0)	(-1.2, 10.6)	0.1200
HbA1c (%)									
Placebo	218	6.5 (0.9)	6.7 (1.1)	0.2 (0.04)	(0.1, 0.2)	<0.0001	--	--	--

				Mean Change from Baseline			Difference from placebo		
AMR101 2g/d	228	6.7 (1.1)	6.8 (1.2)	0.2 (0.04)	(0.1, 0.2)	<0.0001	-0.0 (0.05)	(-0.1, 0.1)	0.9392
AMR101 4g/d	220	6.6 (0.9)	6.9 (1.1)	0.3 (0.04)	(0.2, 0.3)	<0.0001	0.1 (0.05)	(-0.0, 0.3)	0.0899
Insulin (µIU/mL)									
Placebo	215	23.0 (33.1)	20.1 (17.5)	-1.2 (0.9)	(-2.9, 0.6)	0.1568	--	--	--
AMR101 2g/d	217	18.6 (11.5)	18.6 (11.0)	-1.2 (0.9)	(-3.0, 0.5)	0.5685	-0.1 (1.3)	(-2.6, 2.4)	0.9567
AMR101 4g/d	215	19.6 (16.0)	19.0 (16.2)	-1.1 (0.9)	(-2.9, 0.6)	0.9601	0.0 (1.3)	(-2.5, 2.5)	0.9874
HOMA-IR									
Placebo	215	8.1 (16.4)	6.9 (6.9)	-0.4 (0.4)	(-1.2, 0.3)	0.4806	--	--	--
AMR101 2g/d	217	6.4 (4.8)	6.4 (4.5)	-0.6 (0.4)	(-1.3, 0.2)	0.4192	-0.1 (0.5)	(-1.2, 0.9)	0.8022
AMR101 4g/d	213	6.8 (7.0)	6.9 (6.7)	-0.1 (0.4)	(-0.8, 0.7)	0.2462	0.3 (0.6)	(-0.7, 1.4)	0.5225

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.
LS means, SE, CI, and p-values are from linear contrasts of an ANCOVA model of change from baseline to Week 12 EP with treatment as a factor and baseline value as a covariate
CI = confidence interval; EP = endpoint; SE = standard error, SD = standard deviation
Source: Table 19-21, Post-text table 14.2.25- 29, 35-37 ANCHOR CSR

There were no nominally statistically significant changes in inflammatory biomarkers with the exception of hsCRP. In a post-hoc analysis, the within-group median percent changes from baseline were +17.1% and -2.4% for the placebo and AMR101 4g groups, respectively, resulting in a nominally statistically significant treatment difference (p=0.0005). There were no significant treatment differences between the placebo group and AMR101 2g group.

Reviewer comment: The original statistical analysis of hsCRP was based on the median change from baseline in mg/L. Most hsCRP changes are reported as a percent change in baseline; therefore, a post-hoc analysis was performed and described in the table below. Median values for hsCRP in the American population are 2.5 mg/L for women and 1.5 mg/L for men.[16] *The baseline median values of*

[16] Woloshin S et al. Distribution of C-reactive protein values in the United States. NEJM 2005;352: 1611-13.

the ANCHOR population represent an intermediate risk for CVD (hsCRP 1-3 mg/L).[17] *Measurement of hsCRP demonstrates large within subject variation (estimated standard deviation of 1.2 mg/L) and is influenced by numerous factors such as infections.*[18] *Therefore, most clinical guidelines recommend multiple measurements of hsCRP in medical evaluations. The single measurements at baseline and Week 12 of hsCRP in the ANCHOR trial limit the strength of any association observed. Furthermore, there is no clinical evidence to suggest that an intervention that targets specifically hsCRP corresponds to decrease in adverse cardiovascular events.*

Table 22: Percent Change from Baseline and Difference from Placebo- Inflammatory Biomarkers Exploratory Endpoints – MITT Population

Treatment + Statin	n [1]	Baseline[2] Median (IQR)	Week 12 EP [3] Median (IQR)	Change from Baseline			Difference from placebo		
				Median (IQR)	(Q1, Q3)	p-value	Estimated median	95% CI	p-value
ICAM-1 (ng/mL)									
Placebo	83	269.0 (122.0)	257.0 (131.0)	9.0 (31.0)	(-6.0, 25.0)	0.0085	--	--	--
AMR101 2g/d	74	267.0 (97.0)	268.5 (89.0)	1.5 (37.0)	(-15.0, 22.0)	0.3718	-6.0	(-15.0, 3.0)	0.2086
AMR101 4g/d	78	273.0 (96.0)	270.0 (110.0)	2.5 (40.0)	(-18.0, 22.0)	0.4487	-6.0	(-16.0, 4.0)	0.1910
IL-6 (pg/mL)									
Placebo	83	3.2 (3.2)	2.9 (3.0)	0.1 (1.8)	(-0.8, 0.9)	0.6566	--	--	--
AMR101 2g/d	74	2.4 (2.0)	2.7 (2.3)	0.2 (1.3)	(-0.4, 0.9)	0.1344	0.1	(-0.3, 0.6)	0.5979
AMR101 4g/d	78	2.7 (2.6)	2.6 (2.1)	0.1 (1.8)	(-1.0, 0.8)	0.9920	-0.1	(-0.6,0.4)	0.7608
PAI-1 (ng/mL)									
Placebo	54	72.2 (62.0)	86.4 (60.7)	-1.7 (73.3)	(-29.1, 44.2)	0.8618	--	--	--
AMR101 2g/d	50	28.1 (58.1)	90.3 (67.4)	14.6 (38.8)	(-8.7, 30.1)	0.0551	12.1	(-9.1, 29.4)	0.2631

[17] Pearson TA et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals form the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107:499-511

[18] Ockene IS et al. Variability and classification accuracy of serial high-sensitivity C-reactive protein measurements in healthy adults. Clin Chem 2001; 47:444-450.

Treatment + Statin	n [1]	Baseline[2] Median (IQR)	Week 12 EP [3] Median (IQR)	Change from Baseline			Difference from placebo		
				Median (IQR)	(Q1, Q3)	p-value	Estimated median	95% CI	p-value
AMR101 4g/d	55	84.7 (73.5)	85.6 (86.3)	-3.1 (45.2)	(-24.2, 21.0)	0.9967	0.6	(-16.7, 17.8)	0.9420
hsCRP (mg/L)[4]									
Treatment + Statin	**n [1]**	**Baseline[2] Median (IQR)**	**Week 12 EP [3] Median (IQR)**	**Median % chg from BL**	**(Q1, Q3)**	**p-value**	**Estimated median**	**95% CI**	**p-value**
Placebo	219	2.2 (4.0)	2.6 (4.7)	17.1 (108.0)	(-26.5, 81.5)	<0.0001	--	--	--
AMR101 2g/d	227	1.9 (2.9)	2.5 (3.4)	10.3 (88.6)	(-24.3, 64.3)	<0.0001	-6.8	(-20.0, 6.0)	0.2889
AMR101 4g/d	217	2.2 (2.7)	2.0 (3.0)	-2.4 (62.8)	(-29.4, 33.3)	0.5544	-22.0	(-34.1, -9.4)	0.0005

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. Post-hoc analysis of hsCRP based on median percent change from baseline

p-values are from Wilcoxon rank-sum test. When hsCRP = <0.2, 0.1 was imputed for the analysis
CI = confidence interval; EP = endpoint; IQR = interquartile range; Q1 = first quartile; Q3 = third quartile
Source: Post-text table 14.2.47-54 ANCHOR CSR

EPA concentrations (expressed in µg/mL) were measured in the plasma and red blood cell samples with a validated liquid chromatography with tandem mass spectrometry method (LC-MS/MS). This assay measured total EPA concentrations in plasma, which included unesterified EPA and EPA incorporated (esterified) in circulating phospholipids, triacylglycerols (triglycerides), and cholesteryl esters. In red blood cells, this assay measured EPA in the cell membrane, where EPA is incorporated mainly in the phospholipids. The lower limits of quantification were 10 µg/mL and 5 µg/mL for plasma and red blood cells, respectively.

As expected, increases in EPA and fatty acid concentrations in plasma and red blood cell membranes were greater in the AMR101-treated groups compared to the placebo groups.

Table 23: Changes in EPA Concentration From Baseline to Week 12 Endpoint – MITT Population

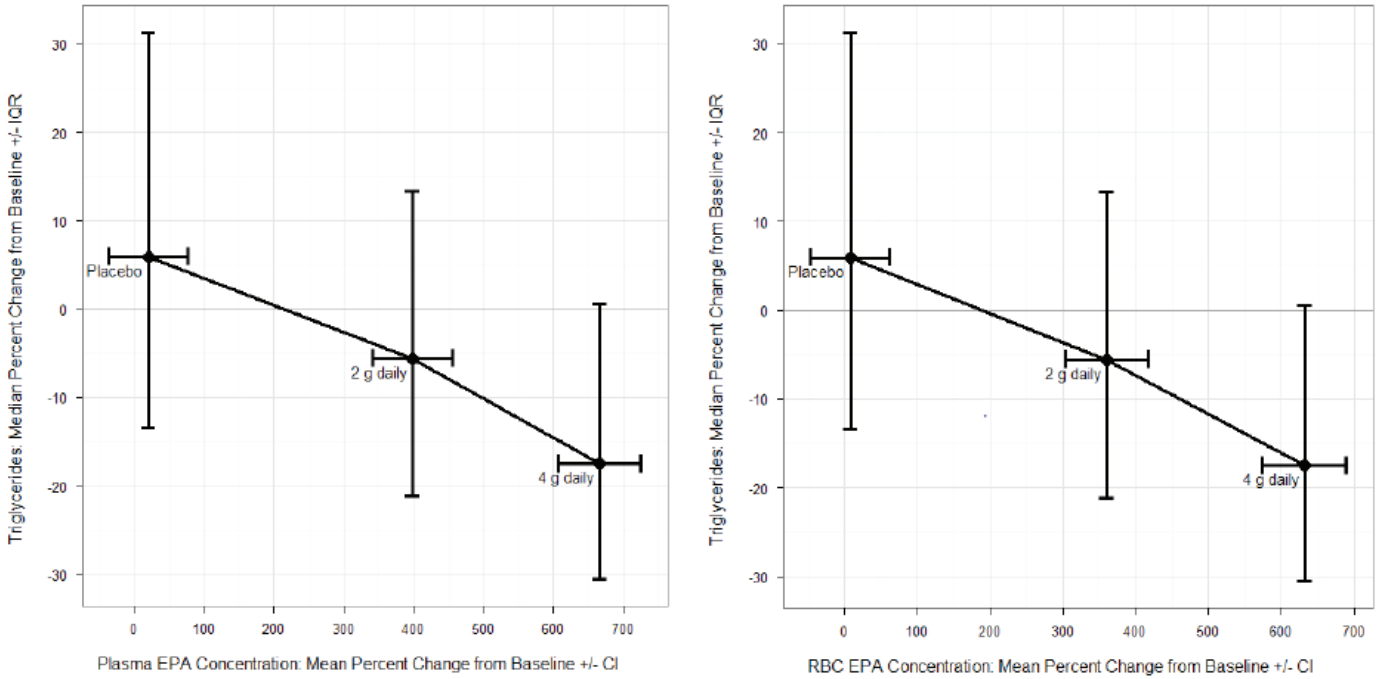
	Placebo				AMR101 2 g				AMR101 4 g			
Parameter	n [1]	Baseline [2] Mean (SD)	Week 12 Endpoint [3] Mean (SD)	LS Mean Change (SE) [4] From Baseline	n [1]	Baseline [3] Mean (SD)	Week 12 Endpoint [4] Mean (SD)	LS Mean Change (SE) [5] From Baseline	n [2]	Baseline [3] Mean (SD)	Week 12 Endpoint [4] Mean (SD)	LS Mean Change (SE) [5] From Baseline
Plasma EPA concentration (µg/mL)	81	28.1 (28.01)	30.6 (27.90)	8.1 (6.59)	73	28.1 (13.71)	123.8 (67.82)	100.5 (6.83)	71	28.1 (18.79)	182.6 (71.73)	159.5 (6.95)
RBC EPA concentration (µg/mL)	79	11.2 (6.64)	9.9 (5.70)	0.4 (2.38)	71	10.9 (5.21)	43.7 (16.84)	34.6 (2.48)	69	11.6 (5.56)	72.7 (31.49)	62.8 (2.55)

Outliers were identified within each treatment group as percent change values <Q1-1.5*IQR or >Q3+1.5*IQR. Patients with outliers were excluded from the analysis.
When LLOQ was <10.0, 5 µg/mL was imputed for analysis. When LLOQ was <5.00, 2.5 µg/mL was imputed for analysis.
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. Week 12 endpoint was defined as the Visit 7 (Week 12) measurement. If missing, the LOCF method was used.
4. Least-squares means and SEs were from linear contrasts of an ANCOVA model of change from baseline to Week 12 endpoint, with treatment, gender, type of statin, and presence of diabetes as factors and baseline value as a covariate.

ANCOVA = analysis of covariance; EPA = eicosapentaenoic acid; IQR = interquartile range; LLOQ = lower limit of quantitation; LOCF = last observation carried forward; LS = least squares; Q1 = first quartile; Q3 = third quartile; RBC = red blood cell; SD = standard deviation; SE = standard error.
Sources: Post-text Tables 14.2.55 and 14.2.57

The figure below displays the relationship between changes in EPA concentration (plasma and RBC) and changes in fasting TG. This supports an exposure-response relationship between EPA and TG.

Figure 5: Percent Change in Fasting TG versus Percent Change in EPA Concentration from Baseline to Week 12 Endpoint – MITT Population



Vertical error bars represent Q1 and Q3; horizontal bars represent 95% CIs.
Concentration of EPA is total concentration measured with LC/MS-MS.
CI = confidence interval; EPA = eicosapentaenoic acid; IQR = interquartile range; LC/MS-MS = liquid chromatography with tandem mass spectrometry; Q1 = first quartile; Q3 = third quartile; RBC = red blood cell.
Sources: Post-text Tables 14.2.1, 14.2.55, and 14.2.57

Source: ANCHOR CSR Figure 5

5.4 Subpopulations

The protocol and SAP pre-specified subgroup analyses of the primary efficacy variable based on age group, race, sex, type of statin use, and the presence or absence of diabetes, baseline TG values, and statin "potency" (herein, intensity). Further details regarding these subgroups are available in the Appendix.

Age: Approximately 40% of the ANCHOR MITT population was 65 years old or greater. The magnitude of the treatment effect of AMR 4g compared to placebo between the two subgroups (<65 years, ≥65 years) was similar for fasting TG (-21.4% and -22.5%, respectively).

Gender: No important differences in the magnitude of the treatment effect of AMR101 4g relative to placebo were observed between gender subgroups.

Race: The randomized population only included 26 subjects (3.7%) who were not white, which precludes any meaningful subgroup analyses by race. Approximately 12% of the study population was Hispanic or Latino.

Statin type: At baseline, the majority of patients (57%) were treated with simvastatin. The effects of AMR101 4g/day on TG and non-HDL-C, compared with placebo, were of the same general magnitude across statin subgroups. For LDL-C, all treatment groups and statin types demonstrated an increase in LDL-C from baseline with the exception of AMR101 4g + rosuvastatin patients. Only the AMR101 4g + rosuvastatin treatment group had a nominally statistically significant estimated median treatment difference of -14.8% from the placebo + rosuvastatin treatment group.

Statin regimen intensity: More patients were on medium-intensity statin regimens at baseline (62.3%) than low (6.6%) and high (31.1%) intensity regimens. In each of these subgroups, fasting triglycerides decreased from baseline to Week 12 in both AMR101-treated groups but increased in the placebo group. Nominally statistically significant treatment differences from placebo were observed in the medium and high-intensity statin regimen subgroups treated with AMR101; the low-intensity regimen only comprised 14-16 subjects per group.

Consistent with the overall population, LDL-C levels increased after baseline except in patients treated with a placebo and low intensity statin regimen (-4.4% decrease) and in patients treated with AMR101 and medium intensity regimen (-2.2%). There were no nominally significant treatment differences between placebo- and AMR101-treated patients on a high-intensity regimen. In patients on a medium-intensity statin regimen, there was a nominally significant treatment difference between AMR101 4g and placebo and AMR101 2g and placebo.

Reviewer comment: Taken together, there do not appear to be meaningful differences in the treatment effect of AMR101, compared with placebo, on TG in patients on either medium- or high-intensity statin regimens. Although the low-intensity subgroup appears

to have less consistent results, it is difficult to draw any conclusions given the very small size of this subgroup.

Baseline TG tertile: The ranges of baseline TG by tertile were <230.5, 230.5 to <289.5, and ≥289.5 mg/dL. The magnitude of the treatment effect of AMR101 4g on reducing fasting TG, compared with placebo, was greater in patients in the highest TG tertile than in patients in middle and lowest baseline TG tertiles. With regard to effects of AMR101 on LDL-C, compared with placebo, patients with the lowest baseline TG exhibited the greatest estimated median reductions in LDL-C. Similar to the overall results, LDL-C increased modestly from baseline to Week 12 within each treatment group (regardless of baseline TG), but the magnitude of the increases in the placebo group exceeded those in the AMR101 groups.

Non-statin washout status: No important differences in the treatment effect of AMR101, compared with placebo, were observed regardless of whether subjects required washout of non-statin lipid-altering therapy prior to randomization.

Diabetes status: Overall, 73% of the MITT population had diabetes at baseline. No important differences in the treatment effect of AMR101, compared with placebo, were observed across diabetes status. There were nominally statistically significant treatment differences in TG between placebo and each dose of AMR101 across diabetes subgroups. Consistent with the overall population, LDL-C levels increased after baseline in all treatment groups and to a similar degree regardless of the presence of diabetes.

5.5 Placebo Group Effects

As previously mentioned, the magnitude of the changes in several lipid and lipoprotein parameters, as well as biomarkers of inflammation, between baseline and Week 12 in the placebo group are rather atypical for lipid-lowering trials. These trials, including ANCHOR, often include a several-week lead-in period to stabilize diet and concomitant lipid-altering medications well before baseline measurements. Although even highly statistically significant within-group changes can certainly result from factors other than the intended experimental intervention, one concerning possibility is that the mineral oil placebo may not be biologically inert. If this were true, the estimated treatment effects may be biased.

Thus, the review team sought evidence that might help explain the changes observed in the mineral oil group. These included considering the plausibility that treatment assignment could have been unmasked due to physical differences in study drug appearance or manufacture; reviewing the literature for mineral oil-specific effects on lipid parameters or absorption of fat-soluble vitamins; evaluating whether the statin-treated subjects in the placebo group from MARINE demonstrated a similar pattern; and considering elements of the ANCHOR study design that may have contributed. Finally, the Division reviewed lipid changes observed in the placebo groups of other lipid-lowering trials.

The Chemistry, Manufacturing, and Controls data do not suggest that blinding would have been compromised. The only difference between the active capsules and the placebo capsules was that the drug substance (icosapent ethyl) was replaced with mineral oil. All other formulation components and composition remained the same and were added in an identical fashion. The submitted certificates of analysis for the AMR101 and placebo lots used in this trial describe identical appearances of the blister packs and capsules. Admittedly, even if study subjects were able to discern their assignment to placebo or AMR101, it is difficult to predict what direction bias would be introduced (e.g., how might treatment assignment influence one's adherence to dietary instruction?).

Three studies using mineral oil as a placebo and reporting baseline and end-of-treatment lipid values were reviewed to determine if similar changes were observed to those that occurred in ANCHOR. [19,20,21] The population of patients studied varied greatly: dyslipidemic women with type 2 diabetes, patients infected with HIV, and healthy volunteers. The exposure to mineral oil placebo ranged from 10 days to 2 months with daily doses of 6 grams or less. Despite these differences, in general, the effect of the

[19] Kabir M et al. Treatment for 2 mo with n-2 polyunsaturated fatty acids reduces adiposity and some atherogenic factors but does not improve insulin sensitivity in women with type 2 diabetes: a randomized controlled study. Am J Clin Nutr 2007;86:1670-9.
[20] De Truchis P et al. Reduction in Triglyceride Level with N-3 Polyunsaturated Fatty Acids in HIV-Infected Patients Taking Potent Antiretroviral Therapy: A Randomized Prospective Study. J Acquir Immune Defic Sydr 2007;44:278-85.
[21] Horrobin DF et al. The Effects of Evening Primrose Oil, Safflower Oil and Paraffin on Plasma Fatty Acid Levels in Humans: Choice of an Appropriate Placebo for Clinical Studies on Primrose Oil. Prostaglandins Leukotrienes and Essential Fatty Acids 1991;42:245-49.

mineral oil placebo on lipid parameters was small. For example, after 8 weeks of mineral oil (6g/day), the median percent change of TG from baseline in HIV-infected patients was +1%. [22]

Studies from the 1940s suggested that mineral oil may block the absorption of fat-soluble vitamins.[23,24] Articles submitted by the applicant and independent review of the available medical literature on this issue were reviewed. Although initial studies suggested possible malabsorption with mineral oil, subsequent studies using large volumes of mineral oil (up to 150 mL/day) over a long period of time called these findings into question.[25,26,27,28] Of course, patients in the ANCHOR trial's placebo group ingested far smaller volumes of mineral oil than this as well (approximately 4 mL/day), which weakens but does not eliminate the possibility of a local intestinal effect of mineral oil on statin absorption.

Whether mineral oil affects statin absorption has not been formally tested to our knowledge. The applicant submitted data regarding patients who were taking concomitant statin therapy in the MARINE trial and who were randomized to the mineral oil group. Only 18 patients in the mineral oil group were taking a statin. The median percent change in LDL-C was -8% in the statin-treated mineral oil group, with large variability (Q1 -36.0%, Q3 +30.8%); the median change was 0% in LDL-C among the 57 patients not taking statins in the mineral oil group. The applicant contends that if mineral oil reduced statin exposure, then LDL-C should have increased after 12 weeks of treatment, not decreased. While the reduction in LDL-C in this group is somewhat reassuring, the small number of statin-treated patients and the large intra-subject variability do not allow definitive conclusions from this subgroup.

Patient compliance (indirect measures): There was no dietary compliance assessment or measurement of physical activity in the ANCHOR trial. However, indirect measurements of diet and physical activity, i.e., weight, waist circumference, and BMI did not demonstrate significant changes between the placebo and AMR101 treatment groups, suggesting that physical and dietary habits between groups were not dramatically different throughout the trial and are unlikely to have contributed to the effects observed in the placebo group.

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[22] De Truchis P et al. Reduction in Triglyceride Level with N-3 Polyunsaturated Fatty Acids in HIV-Infected Patients Taking Potent Antiretroviral Therapy: A Randomized Prospective Study. J Acquir Immune Defic Sydr 2007;44:278-85.
[23] Curtis AC, Ballmer RS. The prevention of carotene absorption by liquid petrolatum. JAMA 1939:1785-8.
[24] Javert CT, Macri C. Prothrombin concentration and mineral oil. Am J Obstet Gynecol 1941:409-14.
[25] Gal-Ezer S et al. The safety of mineral oil in the treatment of constipation – A lesson from prolonged overdose. Clin Pediatr. 2006;45:856-8.
[26] Clark JH et al. Serum beta-carotene, retinol, and alpha-tocopherol levels during mineral oil therapy for constipation. Am j Dis Child. 1987;141:1210-12.
[27] McClung HJ et al. Is combination therapy for encopresis nutritionally safe? Pediatrics 1993;91:591-4.
[28] Ballantine TVM, Zeigler D, Greecher CP, et al: The effect of mineral oil on fat-soluble vitamin levels, abstracted. JPEN 1986;10:18.

Regression to the mean: Subjects enrolled in ANCHOR were selected non-randomly from a broader population of subjects of which 70% failed to be randomized. The applicant contends that the asymmetric selection process may have contributed to a regression-to-the mean phenomenon apparent across the lipoprotein lipids and other biomarkers within the placebo group. If true, this would be a design element expected to affect all treatment groups similarly and the between-group differences should provide unbiased estimates of the treatment effects. Averaging two qualifying values separated by one week, all following a ≥4-week lead-in stabilization period, should have reduced the contribution of regression to the mean, although its possible contribution cannot be ruled out.

Considering the 609 subjects who were excluded at the end of the screening period because of ineligible lipid values, the majority (65%) had TG levels that were too low. Although one cannot determine with certainty, this suggests that the study might have been more likely to enroll patients who had "random highs" rather than "random lows," and if this were the case, TG levels would be expected to regress downward rather than upward. Regarding LDL-C, most (60%) of the subjects excluded for lipid reasons had LDL-C in range with the remainder more likely to be excluded for low LDL-C than high LDL-C.

Therapeutic changes during Lead-in period: The applicant has put forward the hypothesis that changes in lipid-lowering regimens and wash-out of non-statin therapy during the lead-in period may have increased variability of TG levels after randomization. Although this could occur, it doesn't seem that "larger variability" would explain the highly statistically significant changes observed in the placebo group between baseline and Week 12.

Lipid changes in patients randomized to placebo: The applicant provided a table of studies (see Appendix) listing the lipid changes observed in placebo-treated patients from baseline in studies of patients with high or very high TG levels to compare with ANCHOR. In reviewing the trajectory of lipids in a placebo group, it is important to consider if the placebo group was on background statin therapy and if all lipid-lowering drugs were stopped during a washout period prior to randomization, as this may affect the degree and direction of lipid alterations. For example, if a placebo group was not on any lipid-lowering medications, it may be reasonable to expect a worsening of lipid parameters over time. However, if a placebo group was on statin therapy that required at least 4 weeks of consistency, it might to reasonable to expect lipid parameters to remain stable over time with minor fluctuations. Acknowledging the limitations of cross-comparisons, two studies (COMBOS and FIRST) had patient populations and study designs with lead-in periods of diet and background statin stabilization similar to ANCHOR. The placebo groups in COMBOS and FIRST had small reductions from baseline in TG at the 8 week and 13 week time points (-6.3% and -2.0%, respectively). The placebo-treated patients in COMBOS also had reductions in other measured lipid parameters. These results suggest the changes in ANCHOR are atypical, but the etiology of this remains unclear.

5.6 Conclusions: Efficacy of AMR101

- The principal efficacy finding in the ANCHOR study was a statistically significant estimated median 21.5% reduction in fasting triglycerides with AMR101 4g/day treatment, compared with placebo, when added on to a statin ($p<0.0001$) in patients with persistent high TG at high risk for cardiovascular disease.

- In the study population, which had a median baseline TG level of 259 mg/dL, fewer than 10% of patients achieved a TG <150 mg/dL with the addition of either placebo (5.7%), AMR101 2g /day (3.8%), or AMR101 4g/day (7.1%) to background statin for 12 weeks.

- Treatment with AMR101 4g/day + statin resulted in a smaller median rise in LDL-C from baseline (1.5%) than did placebo + statin (8.8%), resulting in an estimated median reduction in LDL-C of -6.2%. Although the intent was only to exclude an AMR101-induced increase in LDL-C of ≥6%, the data suggest that AMR101 may be superior to placebo with regard to lowering LDL-C. Accepting this conclusion, however, requires one to be confident that whatever factor(s) contributed to the nearly 9% median increase in the placebo group should have influenced the AMR101 groups equally as well.

- The following secondary endpoints were reduced from baseline with AMR101 4g/day + statin treatment and were statistically significant compared with placebo + statin: non-HDL-C (estimated median difference, -13.6%; p=0.0001), VLDL-C (-24.4%; p=0.0001), and Apo B (-9.3%; p=0.0001); the cardiovascular biomarker lipoprotein-associated phospholipase A2 (Lp-PLA2) was significantly lower in the AMR101 4g/day group as well (-19.0%; p=0.0001) compared with placebo.

- HDL-C, an exploratory endpoint, decreased slightly from baseline in the AMR101 4g/day group (median -1.0%). Compared with placebo, HDL-C changed an estimated median of -4.8% with AMR101 4g/day (unadjusted p=0.0013). The absolute change in median HDL-C was small (approximately 1 mg/dL).

- In a post-hoc analysis, hsCRP levels on background statin therapy increased from baseline in the placebo and AMR101 2g/day groups by 17% and 10%, respectively. In contrast, hsCRP fell by a median 2.4% in the AMR101 4g/day group, an estimated median change of -22% compared with placebo (p=0.0005).

- In subgroup analyses, patients in the highest baseline TG tertile had greater reductions in TG with AMR101 treatment compared with the lower two TG tertiles. Otherwise, AMR101 treatment effects were generally consistent across subgroups of age, gender, background statin and regimen, and diabetes status.

- The study population only included 26 subjects who were not white (3.7%), precluding any meaningful subgroup analyses by race.

- The changes in lipid and lipoprotein parameters from baseline to Week 12 in the mineral oil placebo group are rather atypical for a trial that included a stabilization period for diet and lipid-lowering therapy, raising the possibility that mineral oil may not be as inert as assumed. If true, the treatment effects observed with AMR101 may be overestimated.

6. ANCHOR SAFETY RESULTS

6.1. Safety Background

ANCHOR's safety results were incorporated into a larger integrated safety database of hypertriglyceridemic patients, which was analyzed during the initial review and approval of VASCEPA. This information is summarized in VASCEPA labeling. The safety review of ANCHOR is consistent with labeling and post-marketing reports. At this time, no new safety signals are observed. Therefore, a high-level overview of the safety results from the individual ANCHOR study is presented in this review.

6.2. Adverse Events

Categories of treatment emergent AEs (TEAE) are summarized by treatment group for the ANCHOR Safety population in Table 24. Numbers of patients with TEAEs or SAEs were similar between treatment groups. One death occurred in a patient treated with placebo, described in Section 5.3.1. Twenty-five patients discontinued study drug due to an AE. There were slightly more placebo-treated patients who discontinued study drug due to an AE than patients in the AMR101-treated groups.

Table 24. Summary of Adverse Events During the Randomized Treatment Period – Safety Population

Category of adverse event (AE)	Placebo+statin N=233 n(%)	AMR101 2g/day+statin N=236 n(%)	AMR 101 4g/day+statin N=233 n(%)
Deaths	1 (0.4)	0	0
Serious Adverse Events	5 (2.1)	6 (2.5)	7 (3.0)
Discontinuation of study drug due to AE	12 (5.2)	8 (3.4)	5 (2.1)
Treatment emergent AE	112 (48.1)	106 (44.9)	106 (45.5)

TEAE defined as an adverse event that started after the first dose of double-blind study drug or occurred prior the first dose and worsened in severity during the double-blind treatment period
Source: ANCHOR CSR Table 40

6.3. Deaths and Serious Adverse Events

6.3.1. Deaths

One patient in the placebo group died during the randomized treatment period. The patient narrative is described below.

Patient narrative – death

Patient 057-046, a 65-year-old white male with a history of hypertriglyceridemia, type 2 DM, hypertension, obesity, and hypertension was randomized to placebo. On Study Day 84, the patient's death notice was found in the newspaper by the site. It was noted that the patient had passed away on Study Day 80. The death certificate noted myocardial infarction as the immediate cause of death and coronary artery disease, dyslipidemia, and type 2 DM as underlying conditions leading to the cause of death.

6.3.2. Serious Adverse Events

There were a total of 18 patients who experienced a SAE during the randomized treatment period: 5 patients in the placebo group, 6 patients in the AMR101 2 g/day group, and 7 patients in the AMR101 4 g/day group. The preferred terms of these SAEs are listed in the table below. Two patients experienced a myocardial infarction in the placebo-treated group, one of which was fatal; the other led to cardiac catheterization and stent placement. Two patients treated with AMR101 reported a SAE of subarachnoid hemorrhage – one event occurred after a fall/elevated blood alcohol level and the other was a result of a ruptured cerebral aneurysm. One additional cardiac catheterization requiring stent placement occurred in a patient treated with AMR101.

Table 25: Listing of Patients with SAEs (fatal and non-fatal) During Randomized Treatment Period – Safety Population

Treatment Group Patient Number	Adverse Event Preferred Term	Resulted in Discontinuation
Placebo + statin 5 patients (2.1%)		
049-051	Clostridium difficile colitis	No
057-007	Bradycardia	No
	Coronary artery disease	No
	Myocardial infarction	No
057-028	Lumbar radiculopathy	No
	Spondylolisthesis	No
057-046	Myocardial infarction [1]	Yes
102-043	Multiple myeloma [2]	Yes
AMR101 2g + statin 6 patients (2.5%)		
008-002	Angina unstable	No
010-017	Subarachnoid hemorrhage	No
	Subdural hematoma	No
	Syncope	No
047-019	Coronary artery disease	No
053-025	Breast cancer in situ	No
065-017	Non-cardiac chest pain	No
	Abdominal pain upper	No
095-006	Non-cardiac chest pain	No
AMR101 4g + statin 7 patients (3.0%)		
019-016	Subarachnoid hemorrhage	Yes
	Ruptured cerebral aneurysm	Yes
043-003	Non-cardiac chest pain	No
055-001	Chronic obstructive pulmonary disease	No
056-025	Atrioventricular block complete	No
076-008	Non-cardiac chest pain	No
083-009	Presyncope	No
096-008	Herpes zoster	No

[1] Led to patient death
[2] Patient discontinued study drug; however, completed all study visits
Source: ANCHOR CSR Table 44

6.4. Discontinuations Due to Adverse Events

A total of 25 patients discontinued study drug due to an AE (DAE): 12 (5.2%) patients in the placebo group, 8 (3.4%) patients in the AMR101 2g group, and 5 (2.1%) patients in the AMR101 4g group. The majority of these patients (80%) also withdrew their participation in the study as a result of the AE. The most common AEs related to discontinuation were associated with GI disorders, such as diarrhea and nausea.

Table 26: Listing of Patients with DAEs During Randomized Treatment Period – Safety Population

Treatment Group Patient Number	Adverse Event Preferred Term	SAE
	Placebo 12 patients (5.2%)	
003-005	Abdominal pain upper [2]	No
016-037	Diarrhea [2]	No
035-013	Gastritis	No
042-030	Nausea	No
057-046	Myocardial infarction [1]	Yes
082-017	Abdominal pain	No
083-004	Headache	No
088-024	Herpes zoster [2]	No
097-012	Nightmare	No
102-043	Multiple myeloma [2]	Yes
105-006	Throat tightness	No
107-006	Rash	No
	AMR101 2g 8 patients (3.4%)	
006-014	Abdominal distension	No
014-007	Muscle spasms	No
015-005	Bursitis	No
	Rheumatoid arthritis	No
065-006	Diarrhea	No
	Listless	No
	Nausea	No
065-027	Diarrhea	No
086-024	Dizziness	No
	Diarrhea	No
	Nausea	No
096-007	Esophageal edema	No
102-036	Palpitations	No
	AMR101 4g 5 patients (2.1%)	
010-018	Diarrhea	No
019-016	Subarachnoid hemorrhage	Yes
	Ruptured cerebral aneurysm	Yes
	Brain edema	No
039-016	Gastroesophageal reflux disease	No
042-020	Regurgitation	No
092-003	Lip swelling	No

[1] Led to patient death
[2] Patient discontinued study drug but completed all study visits
Source: ANCHOR CSR Table 45

6.5. Conclusions on Safety in the ANCHOR Study

- The 702 patients composing the safety population of ANCHOR experienced relatively few and similar numbers of treatment-emergent adverse events, serious adverse events, and discontinuations due to adverse events. Only one adverse event was fatal (myocardial infarction), and this occurred in a placebo-treated patient.

- The individual safety results from ANCHOR are consistent with current VASCEPA labeling and post-market safety reporting.

- During the mean treatment exposure of approximately 12 weeks, the number of serious cardiovascular- and cerebrovascular-related events was low in all treatment groups and insufficient, as expected, to draw any conclusions regarding cardiovascular benefit from AMR101 treatment.

- Elevations in ALT and/or AST >3x ULN occurred infrequently (overall, three patients). No patients developed laboratory or clinical findings consistent with drug-induced liver injury defined by Hy's Law.

- Evaluation of adverse events by subgroups of the safety population including age, sex, diabetic status, or type of statin did not suggest a treatment interaction with AMR101.

6.6. Post-marketing Safety Experience with VASCEPA

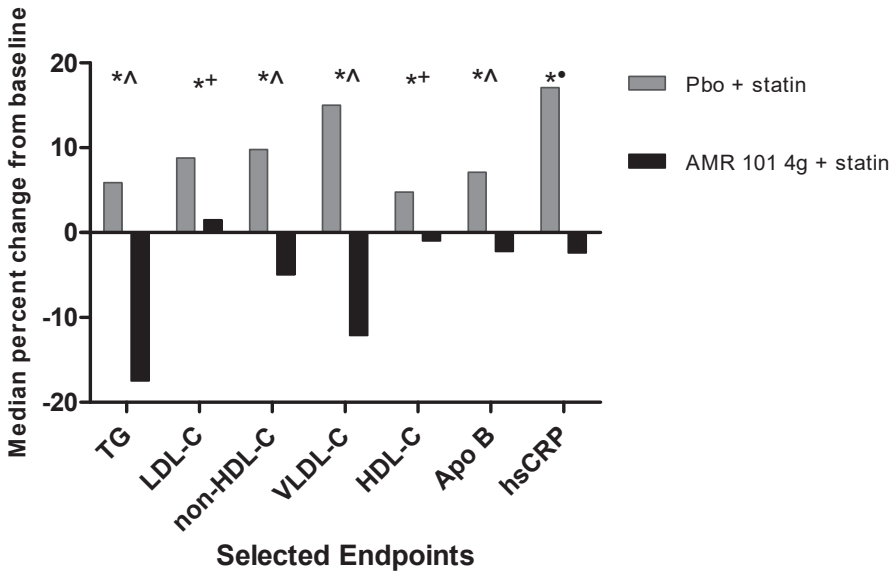
As of June 17, 2013, there have been no reports of post-marketing SAEs with VASCEPA since it was first marketed on January 28, 2013 in the United States. The last Periodic Adverse Drug Experience Report reviewed for AMR101 covered the period of January 23 2013 to April 22, 2013. In this report, no SAEs and 38 non-serious AEs were reported. Gastrointestinal disorders (n=12; primarily nausea and abdominal discomfort) and musculoskeletal disorders (n=12; primarily arthralgia) were the events reported most frequently.

7. BENEFIT/RISK ASSESSMENT

7.1. Summary of Benefits Observed in ANCHOR

The ANCHOR study demonstrated that 12 weeks of treatment with AMR101 4g/day, the recommended dose, led to statistically significant reductions, compared with the mineral oil placebo, in all lipid endpoints and hsCRP among patients with mixed dyslipidemia who were taking a statin. All of these changes, with the exception of the 4.5% reduction in HDL-C compared with placebo, would be considered "improvements" in the lipid profile; whether this AMR101-induced modulation of the lipid profile also leads to a reduction in cardiovascular risk, among patients optimally treated with contemporary statins, is speculative. Furthermore, as shown in the figure below, the effect of AMR101 on the various lipid endpoints may be overestimated if the "adverse" changes in the placebo group were the result of mineral oil itself not being inert.

Figure 6: Change from Baseline in Selected Endpoints



*p<0.001 for within group changes in placebo group
^p<0.0001 between group changes
· p<0.001 between group changes
+p<0.01 between group change
Source: FDA reviewer graph of submitted data

7.2. Summary of Risks Observed in ANCHOR

The ANCHOR trial assessed the tolerability of short-term treatment with AMR101 2 g and 4 g daily in patients on statin therapy. Overall, AMR101 was well tolerated with low occurrences of treatment-emergent and serious adverse events. Consistent with current VASCEPA labeling, arthralgia was the most common musculoskeletal-related adverse event occurring in small proportion (<5%) of AMR101-treated patients. There

were no instances of rhabdomyolysis or drug-induced liver injury defined by Hy's Law associated with AMR101 treatment. No new safety signals were identified.

8. BENEFIT/RISK EVALUATION IN CONTEXT OF CURRENT SCIENTIFIC KNOWLEDGE

The indication sought for VASCEPA as an adjunct to diet and in combination with a statin to reduce TG, non-HDL-C, Apo-B, LDL-C, TC, and VLDL-C in adult patients with mixed dyslipidemia and CHD or a CHD risk equivalent is based on the lipid changes observed in the ANCHOR trial. With rare exception, FDA has historically considered granting approval for lipid-altering drugs based on favorable changes in the lipid profile, with the assumption that these changes would translate into a benefit on clinical outcomes. The experience with statin therapy, where effects on the lipid profile (primarily LDL-C) consistently later translated into proven cardiovascular risk reduction, seems to provide a supportive example. However, as demonstrated in large trials of patients with congestive heart failure or end-stage renal disease on dialysis, even lowering LDL-C with statins does not always appear to decrease cardiovascular risk. More relevant to the current proposed indication, other non-LDL-C lipid surrogates (e.g., TG) have not uniformly conformed to the paradigm that improving lipid values reduces the risk of cardiovascular events, especially among contemporary patients treated with statins. Therefore, in considering the benefits of AMR101 treatment and the implications of granting approval for co-administration with statins, EMDAC members should consider the clinical significance of the observed lipid changes in ANCHOR in the context of the available scientific knowledge, such as clinical trials and meta-analyses that have evaluated the cardiovascular benefit observed with omega-3 FA consumption as well as recent large cardiovascular outcome trials that have failed to demonstrate a reduction in residual cardiovascular risk with non-statin lipid-altering treatment, despite improving parameters such as HDL-C and/or TG, in patients optimally treated with statin therapy.

8.1. Omega-3 Fatty Acids and Cardiovascular Outcomes

In 1999, the open-label Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico-Prevenzione (GISSI-P) trial was one of the first randomized clinical trials to evaluate the effect of omega-3 FA on CV outcomes.[29] GISSI-P randomized 11,324 patients with a recent history (3 months or less) of MI to 1 g/day of EPA/DHA (n=2836), vitamin E (n=2830), both (n=2830), or no treatment (the control group; n=2828). Mean baseline lipid values included TC 211 mg/dL, LDL-C 137 mg/dL, TG 162 mg/dL, and HDL-C 42 mg/dL. Five percent of patients were on cholesterol-lowering drugs (authors did not provide percentage on statin therapy) at baseline. After an average follow-up of 3.5 years, a 20% reduction in the primary endpoint of CV death, nonfatal MI, and nonfatal stroke was observed in the EPA/DHA treated group compared with the no-treatment group (RR 0.80, 95% CI 0.68-0.95). These results were driven by effects on fatal outcomes; no statistically significant effects on non-fatal events were observed.

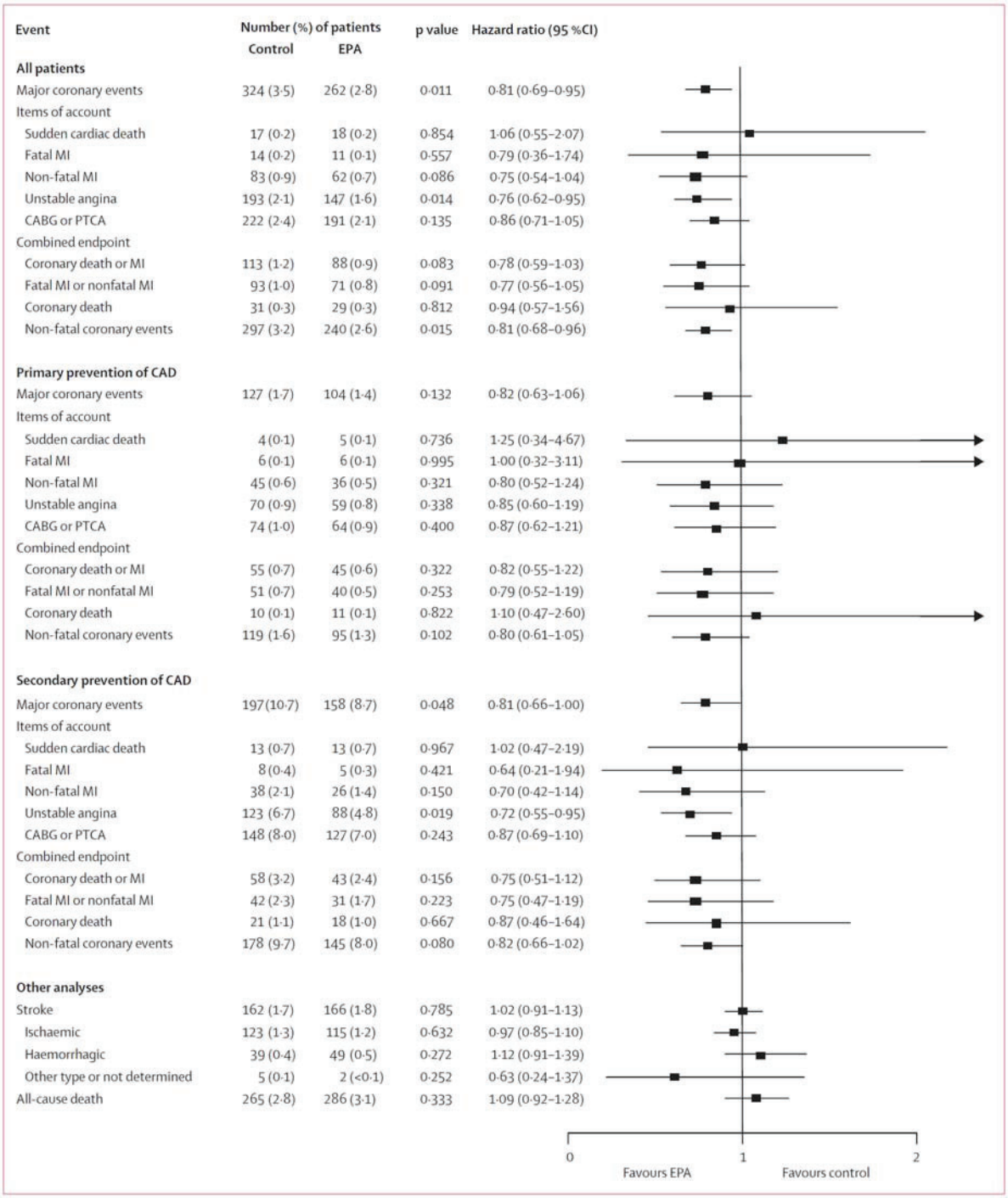
[29] GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Lancet 1999;354:447-55

Compared with the control group, no clinically significant differences in lipids were observed at 6 months. There was a small, statistically significant decrease of 3.4% in triglyceride concentrations in patients receiving EPA/DHA (without vitamin E) compared with a 1.4% increase in controls; changes in LDL-C were +9.9% and +7.4% for EPA/DHA and controls, respectively.

The JELIS trial, reported in 2007, suggested that treatment with 1.8 g/day of EPA reduced cardiovascular adverse outcomes in Japanese hypercholesterolemic patients on low-dose statins.[30] In this open-label trial, 18,645 Japanese men and postmenopausal women with or without a history of coronary artery disease, with total cholesterol levels ≥6.5 mmol/L (>250 mg/dL), were randomized to either statin (pravastatin 10 mg or simvastatin 5 mg) + 1.8 g/day EPA or statin alone with a planned 5-year follow-up. The primary endpoint was a cardiovascular composite, which included sudden cardiac death, fatal and non-fatal myocardial infarction, unstable angina pectoris including hospitalization, angioplasty, stenting, or coronary bypass grafting. Mean baseline lipid values after a 4-8-week washout of any lipid-lowering drugs, included TC 7.1 mmol/L (~275 mg/dL), LDL-C 4.7 mmol/L (~182 mg/dL), TG 1.7 mmol/L (~150 mg/dL), and HDL-C 1.5 mmol/L (~58 mg/dL). During a mean follow-up of 4.6 years, a 19% relative reduction in the primary CV composite endpoint was observed (p=0.011). Among the components of the primary composite, only unstable angina including hospitalization for documented ischemic episodes, achieved nominal statistical significance (p=0.014). Lipid changes in the EPA + statin and statin alone group were similar, with the exception of triglycerides. As expected with the introduction of statin therapy, both groups exhibited decreases in LDL-C and small increases in HDL-C. Triglycerides decreased 9% in the EPA + statin group and decreased 4% in the statin-alone group (p<0.0001 between groups). Although underpowered to evaluate subgroups, there were no apparent differences in the treatment effect on the primary endpoint across various subgroups defined using baseline characteristics, including whether baseline TG was below or above 1.7 mmol/L (150 mg/dL). A post-hoc analysis of the primary prevention cohort of JELIS suggested that EPA reduced the incidence of major coronary events by 53% (95% CI, 2% to 77%, p=0.043) in 957 patients with high TG (≥150 mg/dL) and low HDL-C (<40 mg/dL).[31] Overall, 32 (3.3%) of the patients in this subpopulation experienced a major cardiovascular event. With the exception of a 5% difference in on-treatment TG between the EPA + statin group compared with the statin-alone group, no other differences in blood pressure or lipid parameters were detected between groups.

[30] Yokoyama M et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolemic patients (JELIS): a randomized open-label, blinded endpoint analysis. Lancet 2007;369:1090-98.
[31] Saito Y et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: Sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis 2008;200:135-140.

Figure 7: JELIS: Estimated Hazard Ratios of Clinical Endpoints



Source: Figure 3 from Yokoyama et al. *Lancet* 2007; 369:1090-98.

Since 2007, multiple interventional cardiovascular outcome trials in patients receiving omega-3 FA have been published with varying effect on the primary cardiovascular endpoint. In recent years, the majority have reported negligible impacts on cardiovascular events. One possible reason for the difference between the older trials (GISSI-P and JELIS) and the more recent trials is the open-label study designs of GISSI-P and JELIS, which may have introduced bias in patient/physician behavior that could have confounded the treatment effect, particularly in physician-directed outcomes such as hospitalization and interventional procedures. Another factor is the notable differences in background therapy: only ~5% of patients were on statins at baseline in the GISSI-P trial compared with >40-50% in the two most recent trials, ORIGIN and Risk & Prevention trial; in the JELIS trial, patients were treated with low doses of pravastatin or simvastatin despite a baseline mean LDL-C of 185 mg/dL. It is unknown, of course, whether the favorable treatment effects with EPA in JELIS would have been observed in the setting of higher-intensity statin therapy. Last, baseline consumption of dietary omega-3 FA has been postulated to modulate the treatment effect of supplemental omega-3 FA.

Further details on recent trials, most published after the ANCHOR study was initiated, are summarized in the table below. Note that all have used lower doses of EPA/DHA (or EPA) than the 4 g/day recommended in VASCEPA labeling and being studied in the ongoing REDUCE-IT trial. The rationales for the doses used in these other trials included observational data regarding quantities of fish intake and associations with CV risk, the dose used in GISSI-P, or the findings of the Diet and Reinfarction Trial, a randomized controlled trial in the 1980s in which dietary advice to increase fish intake reduced all-cause mortality by nearly 30% among non-diabetic men who had been hospitalized for acute MI.

Table 27: Recent Omega-3 FA Cardiovascular Outcomes Trials

	JELIS[32]	GISSI-HF[33]	SU.FOL.OM3[34]	Alpha Omega[35]	Omega[36]	DOIT[37]	ORIGIN[38]	R&P Study[39]	REDUCE IT
Date published	2007	2008	2010	2010	2010	2010	2012	2013	Ongoing
Formulation and Dosage	EPA 1.8 g/day	EPA/DHA 1 g/day	EPA/DHA 0.6 g/day	EPA/DHA 0.4 g/day	EPA/DHA 1g/day	EPA/DHA 2.4 g/day	EPA/DHA 1 g/day	EPA/DHA 1g/day	EPA 4g/day
Placebo	None	Yes not specified	Yes not specified	Margarine ± ALA	Olive oil	Corn oil	Olive oil	Olive oil	Mineral oil
Population	Japan	Italy	France	Netherlands	Germany	Norway	Int'l	Italy	Int'l
N (ITT pop)	18,645	6975	2501	4837	3804	563	12,536	12,505	8000
Gender	31% M	78% M	79% M	78% M	74% M	100% M	65% M	61.5% M	
Risk Profile	With or without CAD (previous MI, coronary intervention, angina pectoris	Clinical evidence of heart failure	Acute coronary or cerebral ischemic event within the 12 months	Previous MI	Hospitalized for acute STEMI or non-STEMI	Survivors from population of healthy men with hypercholesterolemia from OSLO Diet & Antismoking study	High risk CV events and IFG, IGT, or type 2 diabetes	Multiple CV risk factors (diabetes included), evidence of atherosclerotic vascular disease (h/o of revasc) excluded previous history of MI	TG≥200 mg/dL and CHD or CHD risk factor
Follow-up	4.6 years (mean)	3.9 years (median)	4.7 years (median)	3.4 years (mean)	1 year (mean)	3 years (mean)	6.2 years (median)	5 years (median)	4 years

[32] Yokoyama M et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolemic patients (JELIS): a randomized open-label, blinded endpoint analysis. Lancet 2007;369:1090-98

[33] GISSI-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomized, double-blind, placebo-controlled trial. Lancet 2008;372:1223-30.

[34] Galan P et al. Effects of B vitamins and omega 3 fatty acids on cardiovascular disease: a randomized placebo controlled trial. BMJ 2010;341:c6273

[35] Kromhout D et al. n-3 fatty acids and cardiovascular events after myocardial infarction. NEJM 2010;363:2015-26

[36] Rauch B et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction clinical perspective. Circulation 2010;122:2152-59.

[37] Einvik G et al. A randomized clinical trial on n-3 polyunsaturated fatty acids supplementation and all-cause mortality in elderly men at high cardiovascular risk. Eur J Cardiovasc Prev Rehabil 2010;17:588-92.

[38] The ORIGIN Trial Investigators. n-3 Fatty acids and cardiovascular outcomes in patients with dysglycemia. NEJM 2012;367:309-18

[39] The Risk and Prevention Study Collaborative Group. n-3 Fatty acids in patients with multiple cardiovascular risk factors. NEJM 2013;368:1800-8.

	JELIS[32]	GISSI-HF[33]	SU.FOL.OM3[34]	Alpha Omega[35]	Omega[36]	DOIT[37]	ORIGIN[38]	R&P Study[39]	REDUCE IT
Statin use	By study design all on low-dose statin (prava 10 mg or simva 5 mg)	Baseline OM3 22.3% Pbo 23.0%	Not specifically reported 85% on lipid lowering medications	Not specifically reported 85% on lipid lowering medications	Baseline OM3 94.6% Pbo 93.8%	Not specifically reported 20% with "treated hyperlipidemia"	Baseline OM3 53.0% Pbo 54.5%	Baseline OM3 40.8% Pbo 41.4% (p=0.48) End of trial OM3 61.8% Pbo 62.1%	100% to LDL-C goal
Primary EP	Major coronary event: SCD, fatal and nonfatal MI, unstable angina, coronary revasc	1)All cause mortality 2)All cause mortality or hospitalization for CV cause	Non fatal MI, ischemic stroke, CV death	Fatal and NF CV events and CABG, PCI	SCD	Not primary EP 1)All-cause mortality 2) CV events: fatal/nonfatal sudden cardiac arrest, MI, PTCA, CABG, stroke, abdominal aortic aneurysm surgery, peripheral revasc	CV death	MACE plus	MACE plus
Result	HR=0.81 (0.69-0.95) p=0.011	1) HR= 0.91 (0.83-0.99) p=0.04 2) HR=0.92 (0.85-0.99) p=0.009	HR=1.08 (0.79 – 1.47) p=0.64	HR=1.01 (0.87–1.17) p=0.93	OR=0.95 (0.56-1.60) p=0.84	1) HR=0.53 (0.27-1.04) p=0.063 2) HR=0.89 (0.55-1.44) p=0.624	HR=0.98 (0.87 – 1.10) p=0.72	HR=0.97 (0.88 – 1.08) p=0.58	Powered for 15% RRR
LDL-C	Mean % Δ from BL EPA + statin -25% Statin -25%	No difference between groups (data not provided by authors)	NR	Mean Δ from BL (mg/dL) OM3 -15.9 Pbo -15.1	No difference between groups	NR	Mean Δ from BL (mg/dL) OM3 -11.8 Pbo -12.4 p=0.44	LS Mean Δ mg/dL from BL OM3 -21.8 Pbo -21.5 p=0.63	-
TG	Mean % Δ from BL EPA +statin -9% Statin -4% p<0.0001	Median Δ from BL (mg/dL) OM3: -5.3 at 1 yr –7.1 at 3 yr Pbo no change	NR	Mean Δ from BL (mg/dL) OM3 -7.1 Pbo -4.4	End of study value (mg/dL) OM3: 121 Pbo: 127 p<0.01	NR	Mean Δ from BL (mg/dL) OM3 -23.5 Pbo -9.0 p<0.001	LS Mean Δ from BL (mg/dL) OM3 -28.2 Pbo -20.1 p <0.0001	--

BL: baseline; Δ: change; SCD: sudden cardiac death; NR: not reported; OM3: omega-3 FA
MACE definition: Cardiovascular death, non-fatal MI, non-fatal stroke
MACE plus definition: REDUCE IT: MACE plus coronary revascularization, hospitalization for unstable angina R&P Study: cardiovascular death or hospitalization for cardiovascular reasons(includes non-fatal MI, non-fatal stroke)

Within the last two years, two large, randomized, placebo-controlled cardiovascular outcome trials have failed to demonstrate an effect of supplementation with omega-3 FA on the risk for cardiovascular events. The ORIGIN trial, which included patients with (or at risk for) diabetes, and the Italian R&P trial, which included patients with multiple cardiovascular risk factors, are described below.

The Outcome Reduction with an Initial Glargine Intervention (**ORIGIN**) trial tested the hypothesis that long-term supplementation with a 1 g/day capsule containing at least 900 mg of ethyl esters of omega-3 FA (465 mg EPA and 375 mg DHA), compared with an olive oil placebo, would reduce the rate of cardiovascular events in patients with diabetes or pre-diabetes.[40] During a median follow-up of 6.2 years, a total of 12,536 adults (mean age 64 years, 65% men) were followed for the primary endpoint of death from cardiovascular causes. At baseline, almost 80% had hypertension and 59% had a history of MI, stroke, or revascularization procedure. Baseline lipid levels included median TG 141 mg/dL, mean TC 189 mg/dL, mean LDL-C 112 mg/dL, and mean HDL-C 46 mg/dL; overall, 54% of patients were on statin therapy at baseline. At the end of the trial, no statistically significant effect of supplementing omega-3 FA was detected on the risk for the primary outcome (HR 0.98; 95% CI 0.87 – 1.10; p=0.72) or on either secondary outcomes, which included a cardiovascular composite of cardiovascular death, non-fatal MI, or non-fatal stroke (Figure 8), or on several nonfatal outcomes. By the end of the trial, the mean reduction in TG was 14.5 mg/dL lower among patients assigned to EPA/DHA than among those assigned to placebo ($p<0.001$). There were no statistically significant differences in the change in other lipid parameters between the EPA/DHA group and placebo (LDL-C -11.8 mg/dL vs. -12.4 mg/dL, respectively, p=0.44; HDL-C -0.1 mg/dL vs. -0.2 mg/dL, p=0.78; TC -15.7 mg/dL vs. -14.6 mg/dL, p=0.17). Pre-specified subgroup analyses of baseline glycemic status, omega-3 FA consumption, and triglyceride level did not suggest any particular subgroups that may benefit, although even if positive, such analyses would have to be interpreted with caution, especially since the trial failed to detect a treatment effect on its primary outcome.

[40] ORIGIN Trial Investigators. N-3 Fatty Acids and Cardiovascular Outcomes in Patients with dysglycemia. NEJM 2012;367:309-18.

Figure 8: Primary and Secondary Outcomes – ORIGIN trial

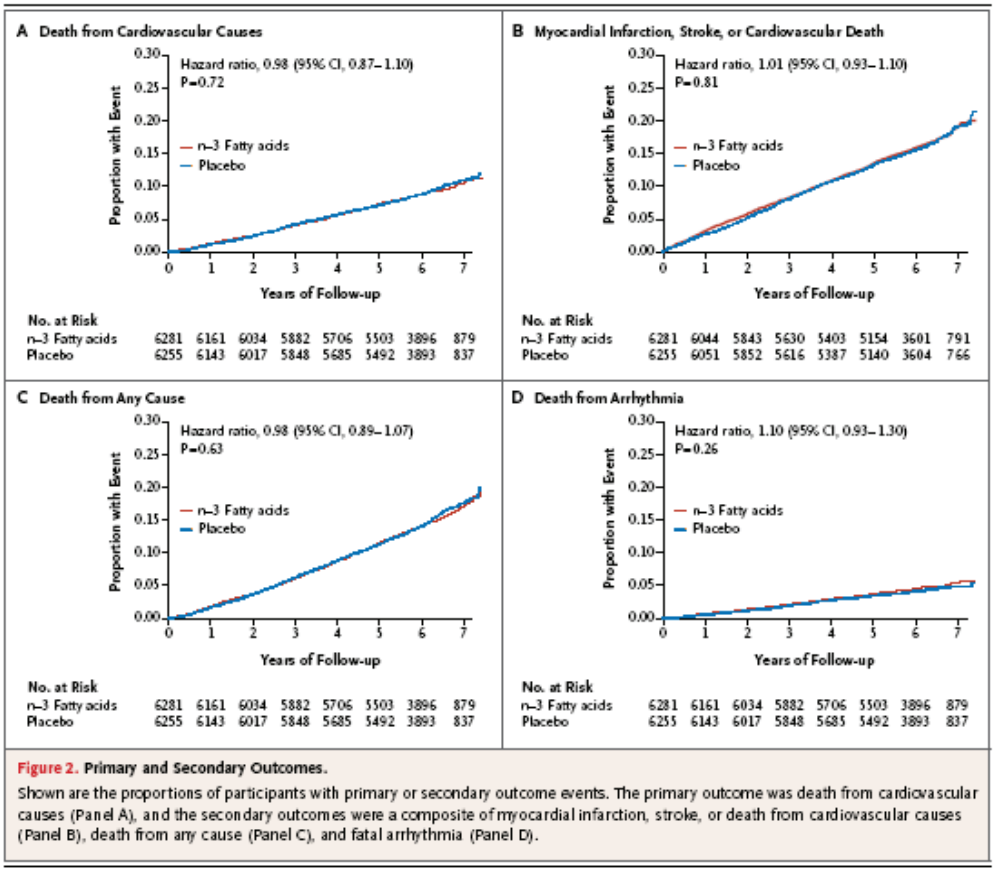
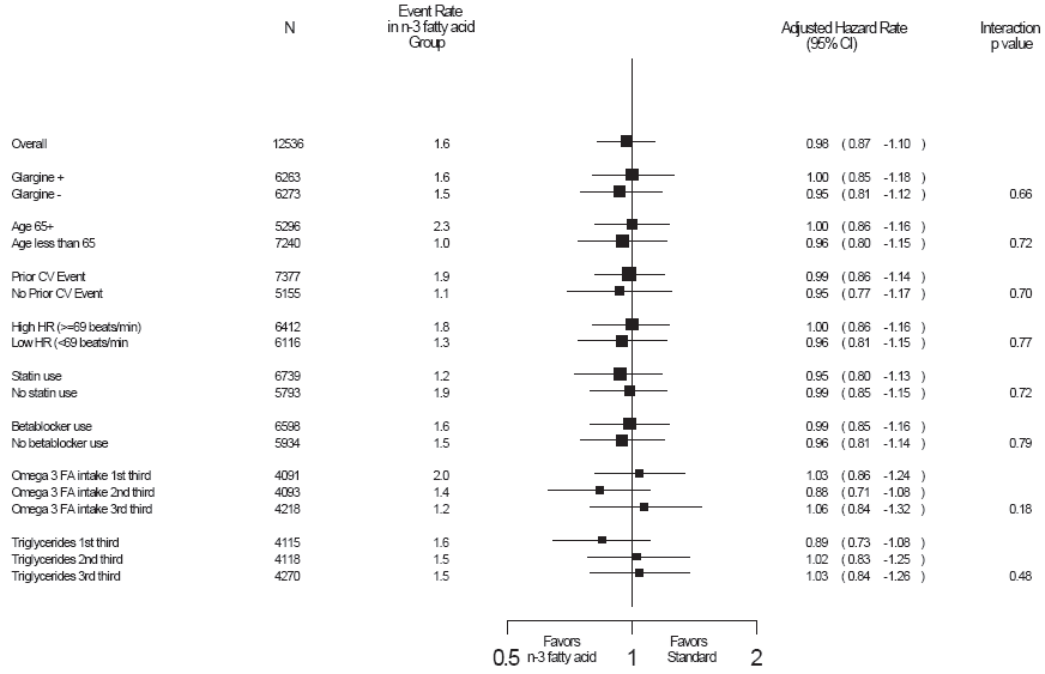


Figure 2. Primary and Secondary Outcomes.

Shown are the proportions of participants with primary or secondary outcome events. The primary outcome was death from cardiovascular causes (Panel A), and the secondary outcomes were a composite of myocardial infarction, stroke, or death from cardiovascular causes (Panel B), death from any cause (Panel C), and fatal arrhythmia (Panel D).

Figure 9: Primary outcome in subgroups – ORIGIN trial



Omega-3 FA intake tertiles (mg/day): 1st third 0-73, 2nd third 74-378, 3rd third ≥379

Triglyceride tertiles (mmol/L): 1st third: 0-1.28, 2nd third 1.29-1.92, 3rd third ≥1.93 mmol/L.

In May 2013, the completed Italian **Risk and Prevention Study** (R&P study) reported that treatment with one capsule daily containing 1 g of omega-3 FA (EPA/DHA content ≥85%, in a ratio that could range from 0.9:1 to 1.5:1) did not reduce the risk for cardiovascular death or hospitalization for cardiovascular causes, compared with an olive oil placebo, among 12,505 adults with multiple CV risk factors followed for an average of 5 years (HR 0.97; 95% CI 0.88 – 1.08; p=0.58).[41] At baseline, the mean age was 64 years, the majority (61.5%) were men, 84% had hypertension, 60% were diabetic, and almost half (48.6%) were obese. Concomitant statin therapy was reported in approximately 41% of patients at baseline. Baseline lipid levels included median TG 150 mg/dL, mean TC 216 mg/dL, mean LDL-C 132 mg/dL, and mean HDL-C 51 mg/dL. At the end of the study, similar proportions of patients had discontinued treatment prematurely (17.9% omega-3 FA, 19.4% placebo), and the per-protocol analysis was consistent with the primary ITT analysis (HR 1.01; 95% CI 0.89 - 1.14; p=0.89). According to the manuscript (data not shown), post hoc analyses of the interaction of baseline statin use with omega-3 FA treatment showed no evidence of interaction (p=0.28).

Table 28: Primary and Secondary Endpoints – Risk and Prevention study

Table 2. Primary and Secondary Outcomes.

Outcome	n–3 Fatty Acids (N=6239)	Placebo (N=6266)	Unadjusted Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary end point	733 (11.7)	745 (11.9)	0.98 (0.88–1.08)	0.64
Components of primary end point				
Death from cardiovascular cause	142 (2.3)	137 (2.2)	1.03 (0.82–1.30)	0.80
Hospitalization for cardiovascular cause	620 (9.9)	630 (10.1)	0.98 (0.87–1.09)	0.68
Death or nonfatal myocardial infarction or stroke	484 (7.8)	467 (7.5)	1.03 (0.91–1.17)	0.64
Death from cardiovascular cause or nonfatal myocardial infarction or stroke	290 (4.6)	276 (4.4)	1.05 (0.89–1.23)	0.59
Fatal or nonfatal coronary event	310 (5.0)	324 (5.2)	0.95 (0.81–1.11)	0.51
Death from coronary cause	82 (1.3)	76 (1.2)	1.07 (0.78–1.46)	0.66
Sudden death from cardiac cause or major ventricular arrhythmia	60 (1.0)	47 (0.8)	1.27 (0.87–1.86)	0.22
Sudden death from cardiac cause	49 (0.8)	40 (0.6)	1.22 (0.80–1.85)	0.36

Changes in cardiovascular risk factors in the R&P trial are listed in the table below. Most improvements in lipid parameters in the omega-3 FA group could not be distinguished from those that occurred in the placebo group. Lipid changes that achieved nominal statistical significance in the omega-3 FA group, compared with placebo, included TG (p<0.0001) and HDL-C (p=0.04).

[41] The Risk and Prevention Study Collaborative Group. n-3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors. NEJM 2013;368:1800-8.

Table 29: Change in CV Risk Factors – Risk and Prevention study

	n-3 Fatty Acids (LSM±SE)	Placebo (LSM±SE)	p-value
Systolic blood pressure (mmHg)	-5.221±0.204	-5.389±0.205	0.57
Diastolic blood pressure (mmHg)	-3.653±9.013	-3.396±8.972	0.77
Heart rate (beats/min)	-1.045±0.130	-0.796±0.130	0.18
Total cholesterol (mg/dL)	-27.346±0.585	-26.817±0.589	0.52
LDL cholesterol (mg/dL)	-21.871±0.518	-21.521±0.524	0.63
HDL cholesterol (mg/dL)	+0.237±0.187	-0.311±0.189	0.04
Triglycerides (mg/dL)	-28.215±1.278	-20.131±1.286	<.0001
Blood glucose (mg/dL)	-3.963±0.570	-5.441±0.573	0.07
Glycated hemoglobin* (%)	-0.024±0.031	-0.047±0.031	0.59

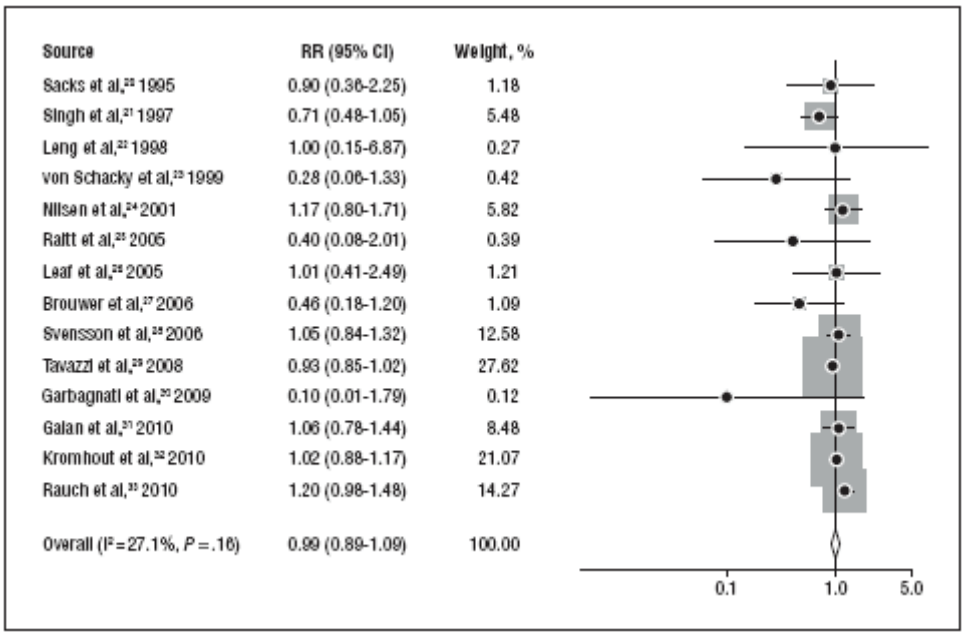
LSM, least square means; SE, standard error; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
* measured only in diabetic patients

In addition to these trials, several meta-analyses of clinical trials of omega-3 FA and cardiovascular events have been published recently. The majority have failed to confirm cardiovascular benefit from EPA and DHA supplementation, [42,43,44] but despite large overlap in the studies reviewed, one meta-analysis did suggest possible cardiovascular benefit.[45]

A meta-analysis published by Kwak and colleagues in May 2012 included 14 randomized, double-blind, placebo-controlled trials of supplementation with omega-3 FA involving 20,485 patients with a history of CVD. The primary endpoint was overall cardiovascular events and included angina, sudden cardiac death, cardiovascular death, congestive heart failure, peripheral vascular disease, transient ischemic attack and stroke, fatal and non-fatal MI, and nonscheduled cardiovascular interventions (CABG, angioplasty). The results of the primary outcome are depicted in the figure below, which did not show a treatment benefit of omega-3 FA supplementation on the risk of overall cardiovascular events (RR 0.99, 95% CI 0.89 – 1.09). JELIS and GISSI-P, two large positive trials, were not included in this analysis because of their open-label study design; however, when they were included as a sensitivity analysis, the primary results did not differ greatly (RR 0.95 95% CI 0.87 – 1.03).

[42] Kwak SM et al. Efficacy of Omega-3 Fatty Acid Supplements (Eicosapentaenoic Acid and Docosahexaenoic Acid) in the Secondary Prevention of Cardiovascular Disease. Arch Intern Med 2012; 172:686-94.
[43] Kotwal S et al. Omega 3 Fatty Acids and Cardiovascular Outcomes: Systematic review and Meta-analysis. Circ Cardiovasc Qual Outcomes 2012;5:808-18.
[44] Rizos EC et al. Association between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events. JAMA 2012;308 (10):1024-33.
[45] Delgado-Lista J et al. Long chain omega-3 fatty acids and cardiovascular disease: a systematic review. British Journal of Nutrition 2012:107:S201-S213

Figure 10: Efficacy of Omega-3 FA Supplements in the Secondary Prevention of Overall Cardiovascular Events – Kwak et al.



In subgroup analyses, no significant preventive effect was found regardless of the type of placebo used in the trials, including olive oil, sunflower oil, corn oil, or nonoil (inert or ill-defined substances).

Table 30: Subgroup Analyses of the Efficacy of Omega-3 FA Supplements and Overall CV Events

Variable	No. of Trials	RR(95% CI)	I^2 Value,%
Type of placebo material in the trial			
Oil	11 Trials[20-29,32,33]	1.05 (0.95-1.16)	2.3
Olive oil	5 Trials[20,25,26,28,33]	1.11 (0.96-1.29)	0.0
Sunflower oil	2 Trials[22,27]	0.54 (0.23-1.26)	0.0
Corn oil	1 Trial[24]	1.17 (0.80-1.71)	0.0
Nonoil	4 Trials[21,29-31]	0.91 (0.75-1.10)	37.9

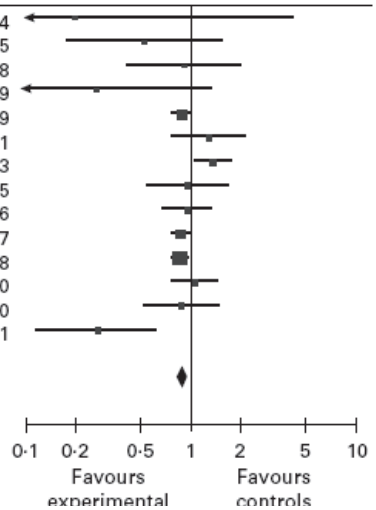
Published one month later, in the June 2012 issue of British Journal of Nutrition, a review of 14 trials involving 45,285 participants, which included GISSI-P and JELIS, suggested a 10% reduction in the odds of overall cardiovascular events, defined as stroke, coronary events, myocardial infarction or angina, peripheral limb disease event, or death from cardiovascular causes (OR 0.90; 95% CI 0.85-0.96, p=0.001, I^2 53%).

Figure 11: Efficacy of Omega-3 FA Supplements and Cardiovascular Events – Delgado-Lista et al.

Study or subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds ratio M-H, fixed, 95% CI	Year
Leaf 1994	0	275	2	276	0·1%	0·20 [0·01, 4·17]	1994
Sacks 1995	7	41	11	39	0·4%	0·52 [0·18, 1·53]	1995
Leng 1998	17	60	18	60	0·6%	0·92 [0·42, 2·03]	1998
Von Schacky 1999	2	112	7	111	0·3%	0·27 [0·05, 1·33]	1999
GISSI-prevenzione 1999	547	5666	608	5668	24·8%	0·89 [0·79, 1·00]	1999
Nilsen 2001	48	150	40	150	1·2%	1·29 [0·79, 2·13]	2001
Burr 2003	180	1571	135	1543	5·4%	1·35 [1·07, 1·71]	2003
Raitt 2005	48	100	49	100	1·1%	0·96 [0·55, 1·67]	2005
Brouwer 2006	153	273	156	273	3·1%	0·96 [0·68, 1·34]	2006
Yokoyama 2007	430	9326	486	9319	20·9%	0·88 [0·77, 1·00]	2007
GISSI-HF 2008	2347	3494	2452	3481	36·4%	0·86 [0·78, 0·95]	2008
Galan 2010	81	1253	76	1248	3·2%	1·07 [0·77, 1·47]	2010
Einvik 2010	32	281	36	282	1·4%	0·88 [0·53, 1·46]	2010
Nodari 2011	10	67	26	66	1·0%	0·27 [0·12, 0·62]	2011
Total (95% CI)		22669		22616	100·10%	0·90 [0·85, 0·96]	
Total events	3902		4102				

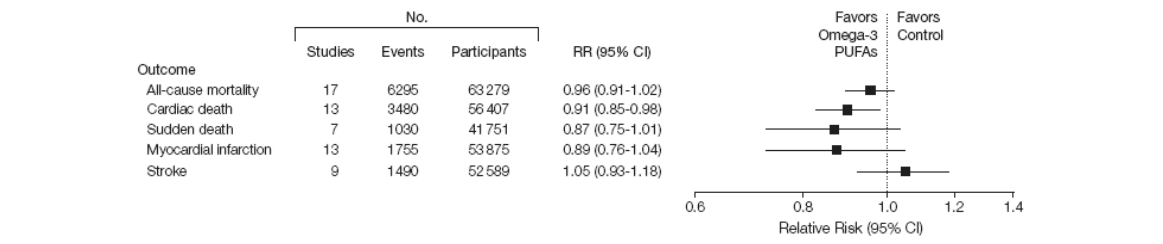
Heterogeneity: $Chi^2 = 27·77$, df = 13 ($P = 0·010$); $I^2 = 53\%$

Test for overall effect: Z = 3·28 ($P = 0·001$)



A systematic review and meta-analysis published in JAMA in September 2012 by Rizos and colleagues also assessed the efficacy of omega-3 FA on cardiovascular events. The majority of patients had a history of CVD, the median age was 68 years, most patients were of European ancestry, the mean omega-3 FA dose was 1.51 g per day, and 10 studies used a dose greater than 1 g/day. Among the included trials were GISSI-P, JELIS, GISSI-HF, and ORIGIN. Using studies where the intervention was an omega-3 FA supplement instead of dietary counseling, there was no statistically significant reduction observed with all-cause mortality, cardiac deaths (after correction for multiple comparisons), sudden deaths, MI, and stroke (Figure 12). Without considering multiple comparisons, there was a nominally statistically significant risk reduction for cardiac death (RR 0.91; 95% CI 0.85 – 0.98; p=0.01; I^2=6%), but the absolute risk reduction was not statistically significant (risk difference -0.01; 95% CI -0.02 – 0.00; p=0.09; I^2=78%).

Figure 12: Efficacy of Omega-3 FA Supplements on Mortality and CV Outcomes



Error bars indicate 95% CIs; PUFAs, polyunsaturated fatty acids; RR, relative risk.

In addition, in the pre-specified subgroup analyses, there was no evidence of an association between treatment effect, prevention setting, blinding, or omega-3 FA dose (Figure 13).

Figure 13: Subgroup Analyses for the Omega-3 FA Supplements Effect

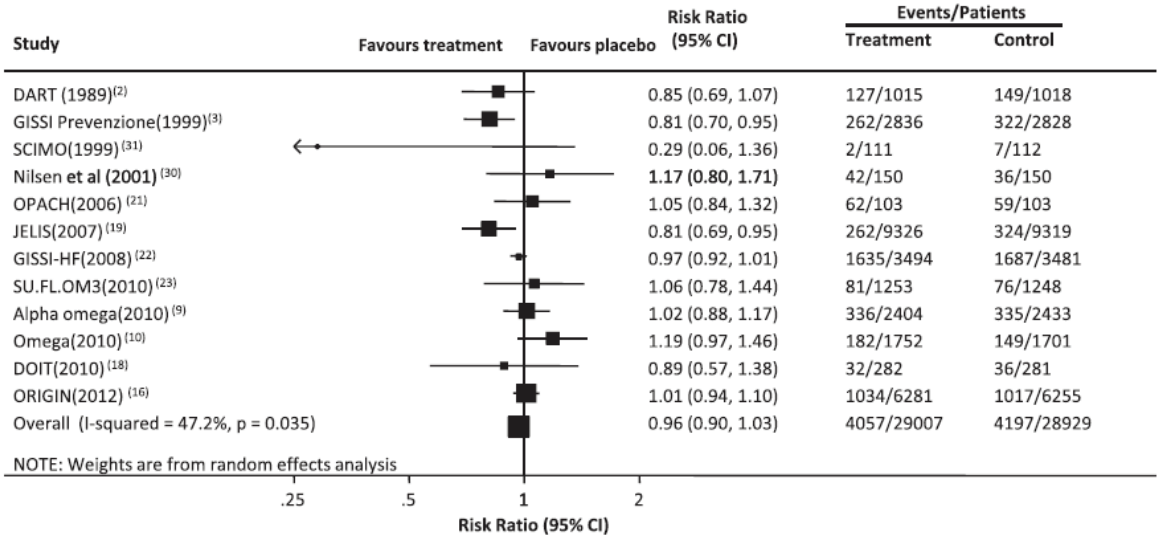
Outcome	Subgroup	No. of Studies	RR (95% CI)	*P* Value	I^2 Value, %
All-cause mortality					
Prevention	Secondary	10	0.95 (0.86-1.04)	.51	2
	ICD	3	0.69 (0.39-1.23)		20
	Mixed	4	0.97 (0.90-0.05)		39
Blinding	Open-label	2	0.96 (0.78-1.19)	.69	78
	Blinding	15	0.97 (0.92-1.02)		0
Omega-3 dose		17		.75[a]	
Cardiac death					
Prevention[b]	Secondary	8	0.81 (0.70-0.93)	.07	0
	ICD	3	0.65 (0.35-1.18)		0
	Mixed	3	0.95 (0.89-1.02)		0
Blinding	Open-label	2	0.80 (0.68-0.93)	.08	0
	Blinding	11	0.94 (0.88-1.00)		0
Omega-3 dose		13		.54[a]	
Sudden death					
Prevention[b]	Secondary	4	0.78 (0.61-1.01)	.22	12
	ICD	1	5.00 (0.2-102.9)		
	Mixed	3	0.94 (0.81-1.09)		0
Blinding	Open-label	2	0.77 (0.62-0.96)	.21	0
	Blinding	5	0.91 (0.70-1.17)		29
Omega-3 dose		7		.78[a]	
Myocardial infarction					
Prevention[b]	Secondary	9	0.82 (0.63-1.08)	.40	42
	ICD	2	0.33 (0.07-1.64)		0
	Mixed	3	0.95 (0.77-1.17)		47
Blinding	Open-label	2	0.91 (0.76-1.10)	.97	15
	Blinding	11	0.86 (0.67-1.01)		43
Omega-3 dose		13		.84[a]	
Stroke					
Prevention	Secondary	6	1.17 (0.90-1.53)	.33	7
	Mixed	3	1.01 (0.89-1.14)		20
Blinding	Open-label	2	1.09 (0.92-1.30)	.64	0
	Blinding	7	1.04 (0.86-1.26)		23
Omega-3 dose		9		.79[a]	

Abbreviations: ICD, implantable cardioverter-defibrillator; PUFA, polyunsaturated fatty acid; RR, relative risk.
[a] *P* value for the meta-regression.
[b] Primary and secondary prevention populations reported separately for the JELIS study.[3]

Kotwal and colleagues assessed the effect of omega-3 FA in randomized controlled trials on cardiovascular outcomes overall and in major patient subgroups. Their meta-analysis, published in November 2012, included 20 trials involving 62,851 patients (31,456 assigned to active treatment). The median age of the participants was 61 years and 50% were men. Fourteen of the 20 trials used supplements comprising a combination of EPA and DHA; daily doses of EPA ranged from 464 to 1860 mg and daily doses of DHA from 335 to 1500 mg. The placebo composition varied: 4 studies used corn oil, 4 used olive oil, and the controls for the remaining studies were not specified.

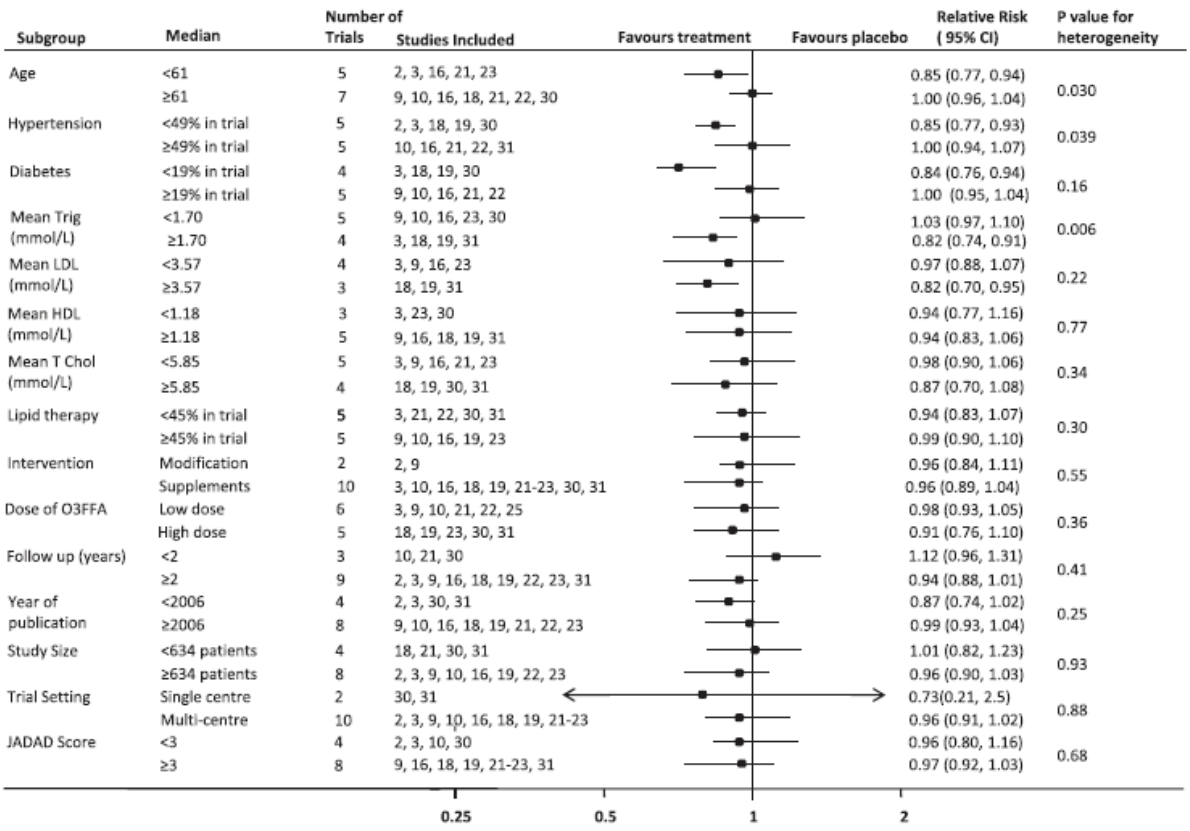
The primary outcome was a composite of cardiovascular events (MI, stroke, and CV death). In this analysis, 12 studies involving 57,936 participants recorded 8254 events. Among the included trials were GISSI-P, GISSI-HF, JELIS, and ORIGIN. The results did not demonstrate a significant reduction in the CV composite of MI, stroke, and CV death with omega-3 FA supplementation; RR 0.96; 95% CI 0.90 – 1.03; p=0.24 (Figure 14). Significant heterogeneity was noted, but sensitivity analyses did not identify a single trial driving the results.

Figure 14: Effect of Omega-3 FA on Composite Cardiovascular Outcomes



In this meta-analysis, the treatment effect did not appear to differ by omega-3 FA dose, the proportion of patients on lipid-altering therapies, or mean LDL-C levels. Interestingly, however, there did appear to be a greater treatment benefit among trials with higher mean baseline TG levels (Figure 15).

Figure 15: Subgroup Analyses for the Effect of Omega-3 FA on the Primary CV Outcome



8.2. Lipid Modification beyond LDL-C and Cardiovascular Outcomes

Three cardiovascular outcome trials, ACCORD-Lipid,[46] AIM-HIGH,[47] and HPS2-THRIVE, designed to address residual cardiovascular risk by improving HDL-C and/or TG in patients treated with statin therapy, have failed to demonstrate additional benefit of adding non-statin lipid-altering therapy on cardiovascular outcomes despite improvements in lipid profiles.

ACCORD-Lipid

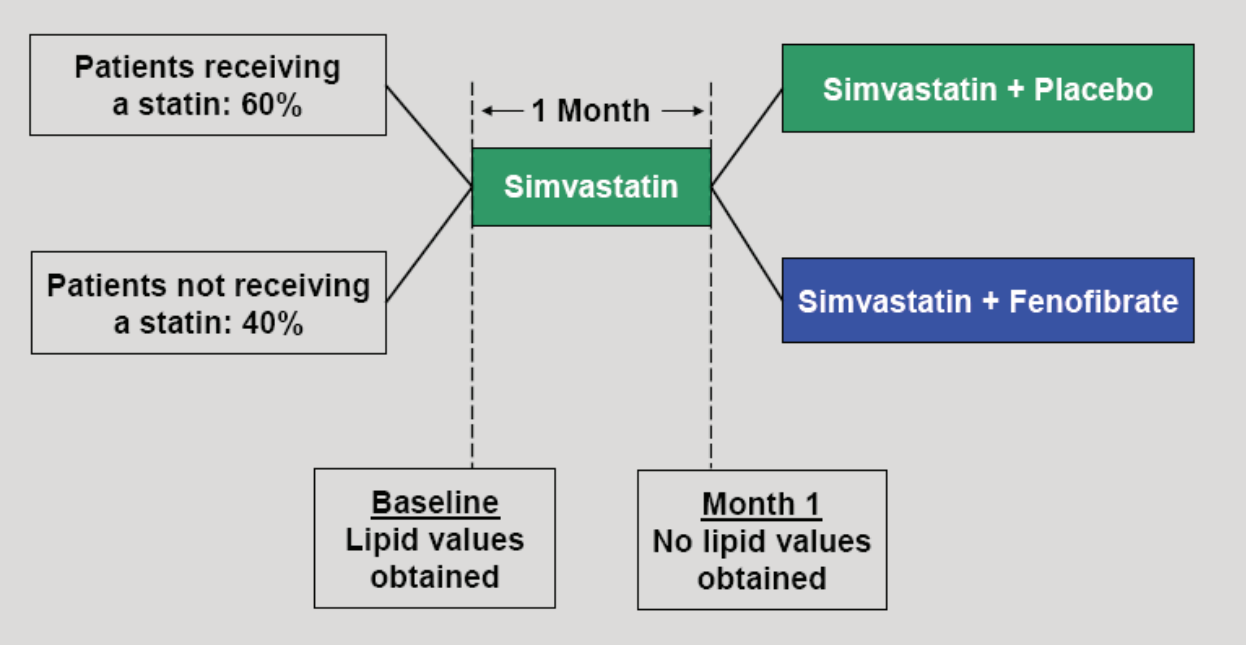
A lipid substudy of the Action to Control Cardiovascular Risk in Diabetes trial (ACCORD-Lipid) was designed to answer the following question: In middle-aged or older people with type 2 diabetes who are at high risk for having a cardiovascular disease event, does a therapeutic strategy that uses a fibrate to raise HDL-C/lower TG levels and uses a statin for treatment of LDL-C reduce the rate of CVD events compared to a strategy that only uses a statin for treatment of LDL-C? The primary efficacy outcome was MACE: nonfatal MI, nonfatal stroke, and CHD death.

[46] The ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. NEJM 2010;362:1563-74.
[47] The AIM-HIGH Investigators. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. NEJM 2011;365:2255-67.

Patients were eligible if they had stable type 2 diabetes for more than 3 months, HbA1c 7.5 to 11%, were at high risk for cardiovascular events, and were 55 years or older. Lipid requirements included LDL-C between 60 and 180 mg/dL, inclusive, HDL-C less than 50 mg/dL (<55 mg/dL for women or African Americans), and TG < 750 mg/dL if not on therapy, or <400 mg/dL otherwise. There was no minimum requirement for TG.

A total of 2,765 diabetics were randomized to simvastatin plus fenofibrate and 2,753 diabetics were randomized to simvastatin plus placebo. All study participants started open-label simvastatin (20-40 mg) for 4 weeks prior to initiation of blinded therapy with fenofibrate or placebo. The treatment groups were well-matched for baseline demographic characteristics. The mean age was 62 years, approximately 70% of the subjects were male and Caucasian, and approximately 37% had a history of a previous CVD event. The study subjects were obese, with an average baseline BMI of 32 kg/m^2. The mean baseline HbA1c was 8.3%. Nearly 65% of the subjects were taking a lipid-altering drug at entry into the study, with 60% receiving statin therapy. The mean baseline LDL-C was 101 mg/dL, mean HDL-C was 38 mg/dL, and median TG was 162 mg/dL. It is important to note that the baseline lipid levels reflect measurements taken prior to the start of open-label simvastatin. Lipid levels following open-label simvastatin and immediately prior to starting blinded treatment with fenofibrate or placebo were not measured (Figure 16).

Figure 16: ACCORD-Lipid Study Design



Source: Abbott AC presentation ACCORD AC May 2011

By the end of the study LDL-C changes from baseline were -19.0 % for the fenofibrate plus simvastatin group and -21% from baseline for the simvastatin plus placebo group. HDL-C increased by 8.4% to 41.2 mg/dL in the fenofibrate plus simvastatin group and by 6.0% to 40.5 mg/dL in the simvastatin plus placebo group. Median TG levels decreased from 164 mg/dL to 122 mg/dL in the fenofibrate plus simvastatin group and from 160 mg/dL to 144 mg/dL in the simvastatin plus placebo group.

After an average follow-up of 4.7 years, the results of ACCORD-Lipid demonstrated no statistically significant differences in MACE between treatment groups. The incidence rates of MACE in the simvastatin plus placebo group and the simvastatin plus fenofibrate group were 11.3% and 10.5%, respectively (HR 0.92; 95% CI 0.79 – 1.08; p=0.32) (Figure 17).

Study group effects on the primary outcome by the pre-specified baseline tertiles of TG did not show evidence of heterogeneity in the treatment effect.

Figure 17: Hazard ratios for the primary outcome in prespecified subgroups – ACCORD-Lipid

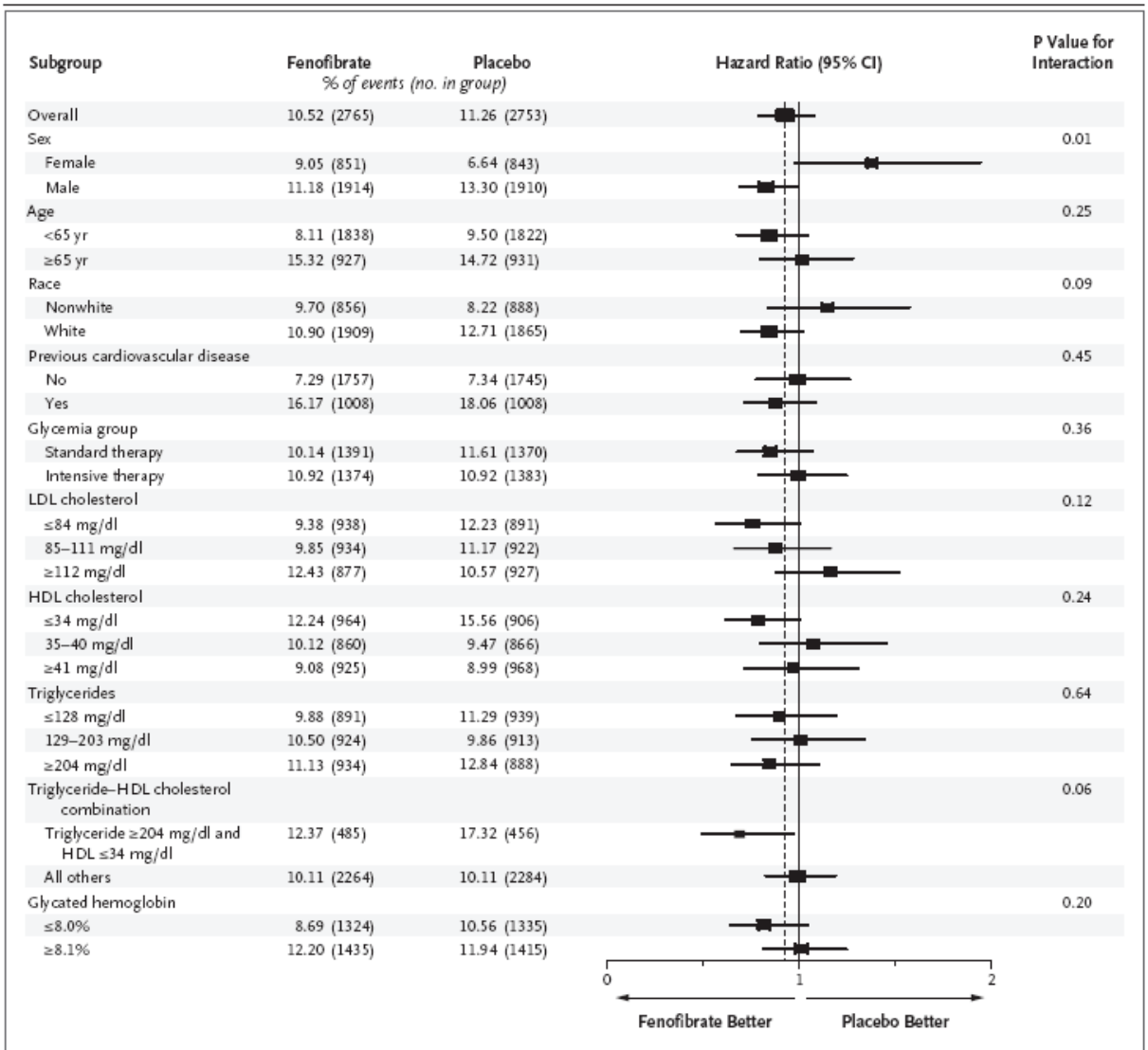


Figure 3. Hazard Ratios for the Primary Outcome in Prespecified Subgroups.
The horizontal bars represent 95% confidence intervals, and the vertical dashed line indicates the overall hazard ratio. The size of each square is proportional to the number of patients. P values are for tests for interaction. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

The pre-specified subgroup analysis of subjects with baseline (i.e., before beginning open-label simvastatin) TG levels ≥ 204 mg/dL (upper tertile) and HDL-C ≤ 34 mg/dL (lower tertile) suggested favorable risk reduction for MACE with fenofibrate therapy compared with baseline TG and HDL-C levels classified as "all others" (HR 0.69; 95%CI 0.49 – 0.97; p=0.032 within subgroup, p=0.06 for interaction). This subgroup of 941 patients composed approximately 17% of the total population, had a larger proportion of white men, and had slightly less use of statin therapy at baseline compared to the overall population (Table 31).

Table 31: Demographic and Baseline Characteristics of Subgroup with Dyslipidemia: ACCORD-Lipid

		Subgroup with Dyslipidemia	
Characteristic	**Overall Population (N = 5518)**	**Fenofibrate-Simvastatin (N = 485)**	**Simvastatin Monotherapy (N = 456)**
Categorical Variable		**n (%)**	
Gender			
Female	1694 (30.7)	97 (20.0)	92 (20.2)
Male	3824 (69.3)	388 (80.0)	364 (79.8)
Race			
White	3774 (68.4)	375 (77.3)	372 (81.6)
Black	834 (15.1)	36 (7.4)	22 (4.8)
Hispanic	407 (7.4)	24 (4.9)	27 (5.9)
Had previous CVD event	2016 (36.5)	195 (40.2)	186 (40.8)
Statin use at baseline	3299 (59.8)	247 (50.9)	230 (50.4)
Numeric Variable		**Mean (SD)**	
Age, years	62.3 (6.8)	60.8 (6.3)	61.6 (6.9)
Duration of diabetes, years (median)	9	8	8
Baseline lipid values, mg/dL			
LDL-C	100.6 (30.7)	96.3 (32.0)	98.3 (32.8)
HDL-C	38.1 (7.8)	29.5 (3.8)	29.4 (3.7)
TG, median (Q1, Q3)	162 (113, 229)	291 (238, 375)	276 (232, 357)
Total-C	175.2 (37.3)	187.0 (38.5)	188.9 (42.1)

Source: Abbott Briefing Document. ACCORD AC May 2011 Table 12

The lipid changes within this subgroup showed that the high TG/low HDL-C subgroup had a greater response to therapy compared to those without these lipid cutoffs ("others"), and there was a numerically larger treatment difference between the high TG/low HDL-C fenofibrate + statin group and statin alone group compared to the "others."

Table 32: Lipid Changes by Baseline Dyslipidemic Status – ACCORD-Lipid

Lipid Response (baseline to 48 mos) to Fenofibrate/Placebo by Dyslipidemic Status

Lipid Measurement (mg/dl)	Dyslipidemic (F 316/P 287)	Others (F 1465/P 1495)
Triglyceride	-127/-84	-26/-3
HDL-C	+4.5/+3.3	1.6/1.5
LDL-C	-11/-20	-20/-21
Means		

Data are means

ACCORD

Source: H. Ginsberg presentation ACCORD AC May 2011

Reviewer comment: Following the release of ACCORD-Lipid results in 2010, the FDA held an advisory committee meeting to discuss the findings of the ACCORD-Lipid trial as they related to the indication granted to fenofibric acid (Trilipix) for coadministration with a statin. Since 2008, Trilipix is FDA-approved for use in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal.

EMDAC members were asked to comment on their interpretation of the two subgroup analyses with significant interaction terms suggesting a treatment effect according to gender and baseline lipid subgroups (TG≥204 mg/dL, HDL-C≤34 mg/dL), in the context of the negative ACCORD-Lipid MACE primary outcome. In response, members cautioned against the over or under interpretation of subgroups from clinical trials in general, but particularly with negative trials. Suggestions of benefit or harm from subgroup analyses were defined as hypothesis generating that should not alter clinical practice or regulatory decisions until properly validated, especially in the context of an overall null result.

Members voted unanimously to require the conduct of a clinical trial designed to test the hypothesis that, in high-risk men and women at LDL-C goal on a statin with residually high TG

and low HDL-C, add-on therapy with Trilipix versus placebo significantly lowers the risk for MACE. Furthermore, members commented that numerical benefits in lipid surrogate endpoints such as TG and HDL-C when added to statin therapy should not trump clinical outcome data.

Finally EMDAC made recommendations to the FDA regarding what further actions to take regarding Trilipix's current indication for coadministration with a statin including (a) continued marketing with or without revision to labeling or (b) withdraw approval of Trilipix's indication for coadminstration with a statin. The majority of members voted to allow the indication to stand pending the results from a dedicated CVOT. Some members felt there was not enough evidence from the ACCORD-Lipid trial relevant to the specific Trilipix coadministration indication to warrant withdrawal of the indication. Others felt that with no additional relevant clinical evidence provided by ACCORD-Lipid, and because the indication had already been granted based on numerical improvements and supported by regulatory standards of the time, this should be honored until further information on clinical outcomes were available. However, several members recommended that the FDA consider requiring a different level of evidence for future lipid altering drugs, transitioning away from surrogate endpoints to relevant clinical cardiovascular outcomes especially for indications for add-on therapy to statins.

AIM-HIGH

The Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) was a randomized, placebo-controlled, multicenter study designed to prospectively evaluate the safety and efficacy of niacin + simvastatin combination therapy versus simvastatin monotherapy in a high CV risk population with on-treatment LDL-C values of 40 to 80 mg/dL. The primary endpoint was the first event of the composite of CHD death, nonfatal MI, ischemic stroke, hospitalization for an acute coronary syndrome, or symptom-driven coronary or cerebral revascularization.

The study consisted of a 4-week washout period during which all lipid-modifying medications except statins and ezetimibe were required to be withdrawn. A 4- to 8-week open-label run-in period followed, during which all subjects were to receive simvastatin 40 mg daily plus niacin extended release (ER) titrated from 500 mg to 2,000 mg over 4 weeks. Subjects who tolerated niacin ER at 1,500 mg or above were randomly assigned (1:1) to one of the 2 treatment arms: simvastatin + niacin ER 1,500 to 2,000 mg or simvastatin + matching placebo, which included 50 mg niacin immediate-release (IR) per tablet, for a cumulative daily dose of 100 to 200 mg, to maintain the study blind by provoking a flushing effect. In order to achieve and/or maintain pre-specified on-treatment LDL-C criteria between 40 and 80 mg/dL, the dosage of simvastatin was to be adjusted throughout the treatment period. Additional therapy with 10 mg ezetimibe was allowed throughout the treatment period to assist in maintaining LDL-C levels at target.

The patients were all at least 45 years or older and had established cardiovascular disease, defined as documented stable coronary heart disease, cerebrovascular or carotid disease, or peripheral arterial disease. All eligible patients had low baseline levels of HDL-C (<40 mg/dL for men; <50 mg/dL for women), elevated triglyceride levels (150 to 400 mg/dL), and LDL-C <180 mg/dL if not taking a statin at entry. At baseline, 93.6% of patients were taking a statin. In these patients the baseline median LDL-C was 71 mg/dL, HDL-C 35 mg/dL, TG 161 mg/dL, and

non-HDL-C 106 mg/dL. Only ~33% of randomized subjects had baseline TG levels ≥198 mg/dL.

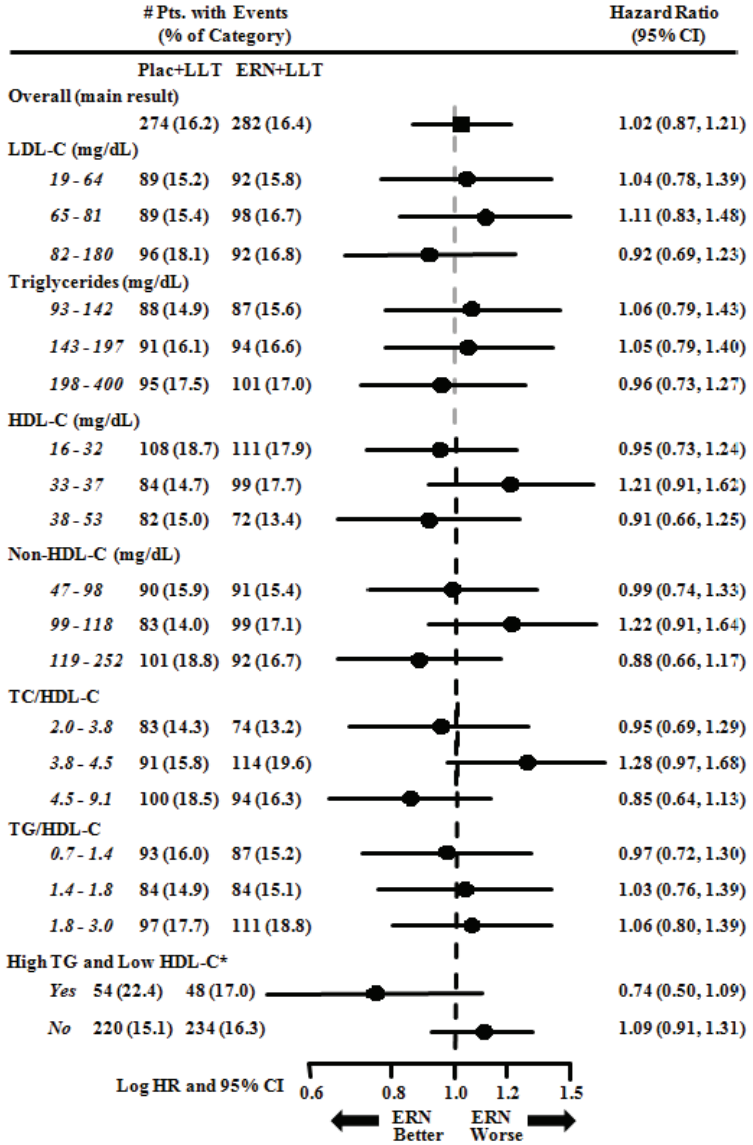
On-treatment lipid changes at two years for LDL-C were -12.0% for the simvastatin plus niacin ER group and -5.5% for the simvastatin plus placebo group. HDL-C increased by 25.0% to 42 mg/dL in the simvastatin plus niacin ER group and by 9.8% to 38 mg/dL in the simvastatin plus placebo group ($p<0.001$). Triglyceride levels decreased by 28.6% in the simvastatin plus niacin ER group and by 8.1% in the simvastatin plus placebo group.

The trial was stopped after a mean follow-up period of 3 years due to a lack of efficacy. The primary outcome occurred in 282 patients in the simvastatin plus niacin ER group (16.4%) and in 274 patients in the simvastatin plus placebo group (16.2%) (HR 1.02; 95% CI,0.87 – 1.21; P=0.79).

A recently published post-hoc analysis examined the treatment effect on cardiovascular events in subgroups defined by baseline lipid values (Figure 18). In a small subgroup of patients (n=522; 15.3% of trial population) in the highest TG tertile (≥ 198 mg/dL) and lowest HDL-C tertile (<33 mg/dL), there was suggestion of a 26% reduction in risk with niacin ER, compared with placebo, added on to statin treatment, but this did not reach nominal statistical significance (HR 0.74; 95% CI 0.50 – 1.09; p=0.07).[48] In an even smaller group of patients (n=439 12.9% of population) that met a modestly narrower definition of mixed dyslipidemia (TG > 200 mg/dl and HDL-C < 32 mg/dl), the treatment effect in the niacin group was larger (HR 0.64, p = 0.032). Although treatment effects of non-statin lipid-altering therapy have been suggested in several trials in variably defined high TG/low HDL-C subgroups, the hypothesis has not yet been tested that a patient population can be prospectively identified who will benefit from such therapy.

[48] Guyton JR et al. Relationship of lipoproteins to cardiovascular events in the Atherothrombosis Intervention in Metabolic syndrome with low HDL/High TG and Impact on Global Health outcomes (AIMH-HIGH) trial. JACC 2013

Figure 18: Effect of Treatment on Cardiovascular Events by Baseline Lipoprotein/lipid Tertiles – AIM-HIGH



*TG≥198 mg/dL and HDL-C <33 mg/dL
LLT: LDL-C lowering therapy

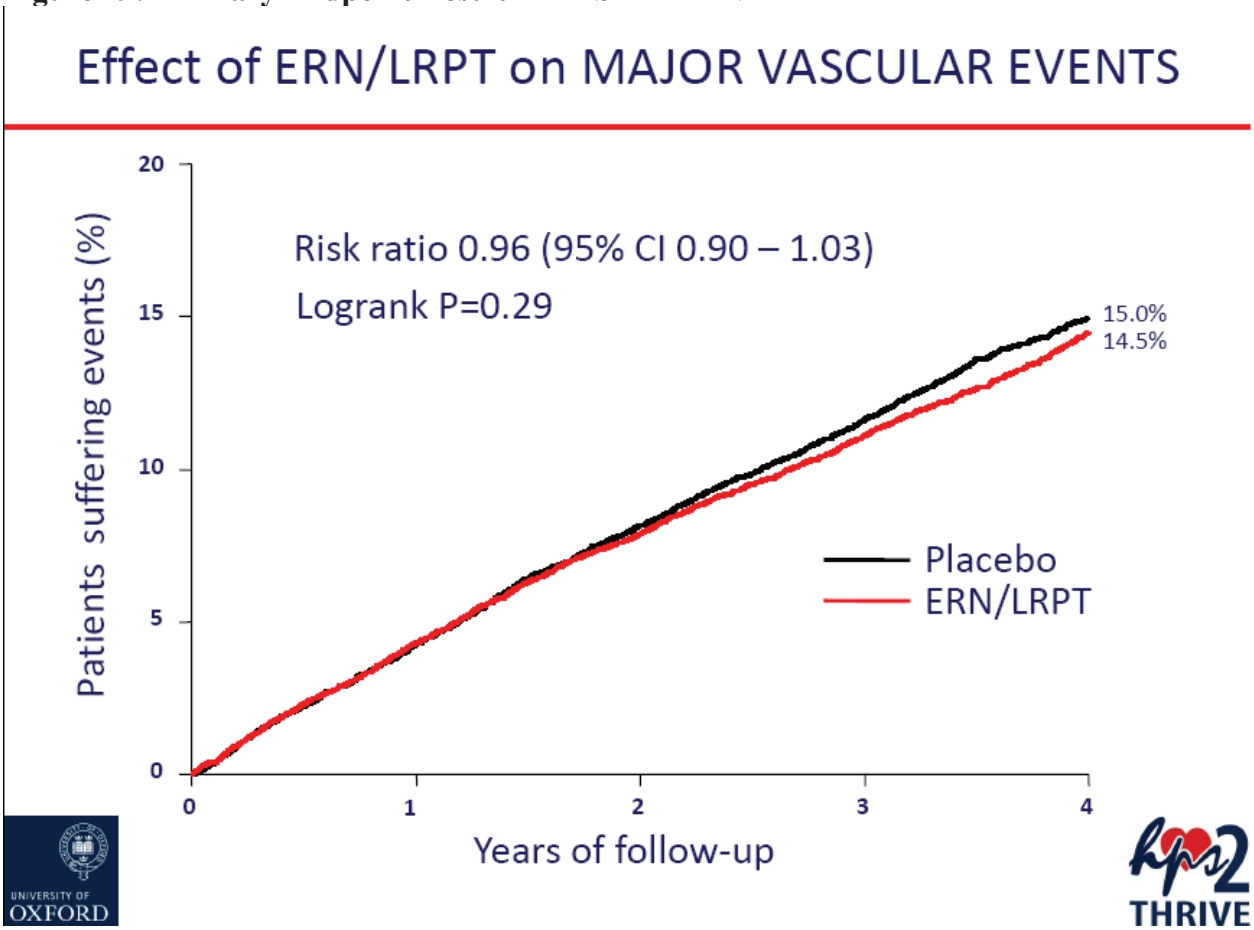
HPS2-THRIVE

Note: At the time that this review is being written, HPS2-THRIVE has not yet been published; therefore, the discussion below is limited to material that the investigators have made publicly available to date.

HPS2-THRIVE randomized a total of 25,673 patients with prior cardiovascular disease to receive either a specially formulated extended-release niacin combined with the anti-flushing agent laropiprant or placebo on background simvastatin therapy (with or without ezetimibe). All patients went through an active pre-randomization run-in phase during which background LDL-

C lowering therapy was standardized with simvastatin 40 mg, with or without ezetimibe, to achieve a total cholesterol target of 135 mg/dL. For the randomized population, the baseline mean LDL-C was 63 mg/dL, TG 125 mg/dL, TC 128 mg/dL, and HDL-C 44 mg/dL. The investigators have reported that the primary composite endpoint of major vascular events defined as coronary death, nonfatal MI, fatal or nonfatal stroke, or coronary or peripheral revascularization was not significantly reduced by niacin/laropiprant (risk ratio 0.96; 95% CI 0.90 – 1.03; p=0.29) (Figure 19).

Figure 19: Primary Endpoint Result in HPS-2 THRIVE

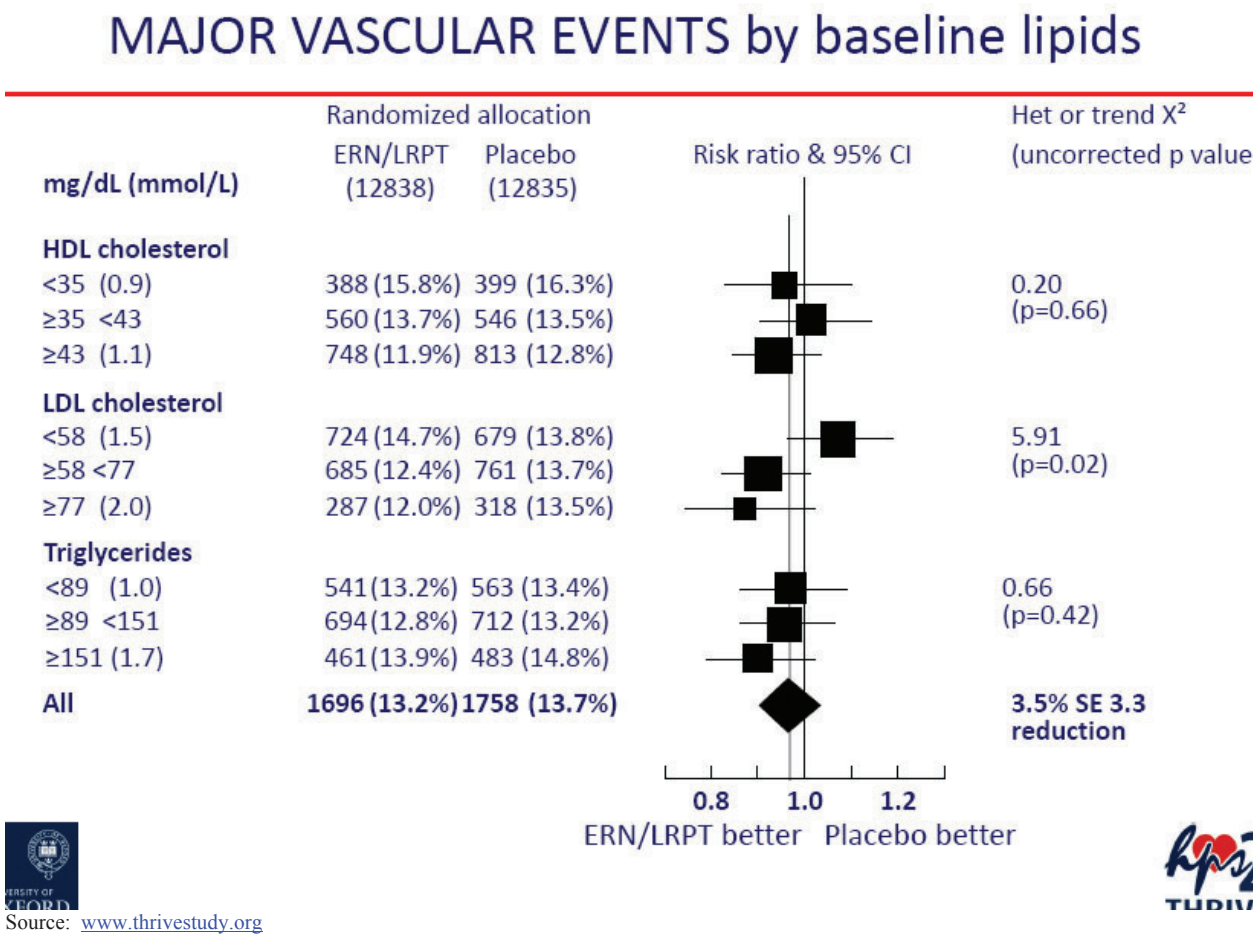


Source: www.thrivestudy.org

The preliminary results of this trial also did not demonstrate any differences in treatment effect across baseline tertiles of HDL or TG (Figure 20). At the National Lipid Association 2013 conference, the HPS2-THRIVE results were presented along with a subgroup analysis of patients with elevated TG and low HDL-C at baseline; this subgroup did not appear distinct from the overall result (interaction p=0.95). The threshold values for TG and HDL-C were not defined.

During the trial, treatment with extended-release niacin/laropiprant resulted in an additional 10 mg/dL reduction in LDL-C, a 6 mg/dL increase in HDL-C, and a 33 mg/dL reduction in TG compared to the placebo group.

Figure 20: Effect of Treatment on Cardiovascular Events by Baseline Lipid– HPS2-THRIVE



Source: www.thrivestudy.org

Table 33: Between Group Lipid Treatment Differences – HPS2 THRIVE

Effects of ER niacin/laropiprant on lipids

Year of FU	LDL-C (mg/dL)	HDL-C (mg/dL)	Triglycerides (mg/dL)
1	-12	6	-35
4	-7	6	-31
STUDY AVERAGE	-10	6	-33
(mmol/L)	(-0.25)	(0.16)	(-0.37)

"Based on previous observational studies and randomized trials, it was anticipated such lipid differences might translate into a 10-15% reduction in vascular events"
Eur Heart Journal 2013

Reviewer comment: In the overall population, only JELIS, an open-label trial utilizing 1.8 g EPA daily, demonstrated a positive treatment outcome when added to a low-dose statin regimen. All four trials, including JELIS, did not demonstrate a cardiovascular treatment benefit across baseline TG levels, which may be due to the fact that study populations did not exhibit very high levels of TG at baseline (mean TG 150 mg/dL in JELIS, median TG 162 mg/dL in ACCORD-Lipid, median TG 161 mg/dL in AIM-HIGH, median TG 125 mg/dL in HPS2-THRIVE). Subgroup analyses from JELIS, ACCORD-Lipid, and AIM-HIGH suggested that patients with elevated TG and low HDL-C might experience a greater potential treatment benefit with additional lipid modifiers to a statin regimen; however, the available HPS2-THRIVE subgroup analyses do not seem to support this hypothesis. Unfortunately, none of these trials were specifically designed to recruit and investigate patients with moderate hypertriglyceridemia with or without low HDL-C; therefore, these results are hypothesis-generating and require validation.

In considering the ANCHOR results, the relative improvements in triglycerides and other lipid parameters with AMR101 4g/day, compared with placebo, reflect changes hoped to translate into cardiovascular benefit. However, as described previously, putatively beneficial changes in lipid/lipoprotein biomarkers other than LDL-C have not consistently confirmed a clinical benefit among patients treated with statin therapy (Table 34). The applicant-sponsored cardiovascular outcomes trial, REDUCE-IT, which is studying patients at high-risk for cardiovascular disease at LDL-C goal on statin therapy with residually high triglycerides (TG ≥200 mg/dL to <500 mg/dL), intends to confirm this implied benefit.

Table 34: Summary of Lipid Changes in Selected Clinical Trials

	ANCHOR[1]		JELIS[2]		ACCORD-Lipid[3]		AIM-HIGH[4]		HPS2-THRIVE[5]
	EPA + statin	Pbo + statin	EPA + statin	Pbo+ statin	Feno + statin	Pbo + statin	Niacin ER + statin	Pbo+ statin	Niacin ER/ LRPT + statin versus Pbo + statin
LDL-C	+1.5%	+8.8%	-25%	-25%	-18.9%	-20.9%	-12.0%	-5.5%	-10 mg/dL
TG	-17.5%	+5.9%	-9.0%	-4%	-22.2%	-8.7%	-28.6%	-8.1%	-33 mg/dL
HDL-C	-1.0%	+4.8%	+3.0%*	+4.0%*	+8.4%	+6.0%	+25.0%	+9.8%	+6 mg/dL

1. Median percent change from BL to Week 12 Endpoint
2. Percent change from BL to last clinic visit (average follow-up 4.6 years/lipids measured annually)
   *Change estimated from Figure 4 in JELIS original publication
3. Mean percent change from BL to Exit Visit (average follow-up years 4.7 years/lipids measured annually)
4. Median percent change from BL to Year 2 visit
5. Absolute difference between groups averaged over study

EMDAC members should consider what implications these recent non-statin CV outcome trials may have when opining whether to recommend expanding the treatment indication for VASCEPA prior to confirming its cardiovascular benefit.

Appendix

Table 35: Change in lipid parameters –by statin type – MITT Population

		Pbo + statin					AMR 101 2g + statin							AMR 101 4g + statin						
Parameter	Statin	n [1]	BL [2] Median (IQR)	EOT [3] Median (IQR)	Median % chg from BL	p from BL	n [1]	BL [2]	EOT [3]	Median % chg from BL	p from BL	Diff from pbo	p value from pbo[4]	n [1]	BL [2]	EOT[3]	Median %chg from BL	p from BL	Diff from pbo	p value from pbo [4]
TG	Atorva	45	247 (71.0)	266.0 (142.5)	7.8	0.1729	43	235.0 (89.0)	245.0 (125.0)	-0.5	0.5764	-2.4	0.6642	41	281.5 (59.0)	216.0 (82.5)	-23.9	<0.0001	-28.4	<0.0001
	Simva	128	262.0 (97.8)	274.5 (148.3)	6.0	0.0016	134	256.5 (102.0)	241.3 (133.0)	-8.8	0.0176	-14.3	0.0004	131	262.0 (106.0)	228.0 (114.5)	-14.7	<0.0001	-18.8	<0.001
	Rosuva	54	258.8 (69.0)	268.3 (147.0)	-0.6	0.1437	57	258.0 (93.5)	252.5 (99.0)	-5.8	0.9656	-5.7	0.2512	54	250.8 (85.5)	204.0 (77.0)	-20.5	0.0001	-23.4	<0.0001
LDL-C	Atorva	45	85.0 (24.0)	88.0 (32.0)	6.8	0.1239	43	82.0 (21.0)	88.0 (29.0)	4.9	0.0264	1.1	0.8477	40	78.5 (24.5)	82.5 (29.5)	9.0	0.0358	2.5	0.6188
	Simva	127	83.0 (30.0)	88.0 (31.0)	8.6	0.0003	133	85.0 (25.0)	88.0 (25.0)	1.8	0.0954	-4.8	0.0844	131	82.0 (24.0)	83.0 (27.0)	1.5	0.2468	-5.4	0.0539
	Rosuva	54	81.0 (28.0)	89.5 (30.0)	10.5	0.0016	57	78.0 (25.)	87.0 (34.0)	4.3	0.0365	-4.2	0.3482	54	85.0 (33.0)	82.5 (40.0)	-3.8	0.3532	-14.8	0.0033
Non-HDL-C	Atorva	45	132.0 (30.0)	141.0 (39.0)	4.2	0.0139	42	128.0 (37.0)	135.0 (46.0)	10.5	<0.0001	2.0	0.7259	41	131.0 (30.0)	122.0 (32.0)	-6.3	0.0936	-13.5	0.0071
	Simva	128	128.0 (37.5)	135.0 (45.00	9.2	<0.0001	134	128.0 (34.0)	133.5 (41.0)	0.0	0.0862	-6.8	0.0067	131	128.0 (35.0)	125.0 (38.0)	-4.3	0.3514	-11.1	<0.0001
	Rosuva	54	126.0 (25.0)	145 (40.0)	12.8	<0.0001	57	125.0 (30.0)	133.0 (44.0)	2.7	0.0659	-9.0	0.0481	54	128.5 (28.0)	118.0 (42.0)	-5.5	0.0240	-20.0	<0.0001

The median differences between the treatment groups were estimated with the Hodges-Lehmann method.
1. Only patients with both baseline and Week 12 endpoint values are included.
2. Baseline for TG was defined as the average of the measurements at 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 measurement 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. Baseline for other parameters were defined as the Visit 4 (Week 0) measurement. If missing, the last valid measurement prior to dosing with study drug was used.
3. For TG: the Week 12 endpoint was defined as the average of measurements at Visit 6 (Week 11) and Visit 7 (Week 12). If the measurement at 1 visit was missing, the other visit measurement 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. For other lipid parameters, the Week 12 endpoint was defined as the Visit 7 (Week 12) measurement. If missing, the LOCF method was used.
4. P-value is from the Wilcoxon rank-sum test.
BL= Baseline pbo = placebo EOT= end of treatment (Week 12 endpoint) IQR = interquartile range; LOCF = last observation carried forward; Q1 = first quartile; Q3 = third quartile.
Source: ANCHOR CSR Table 28-29. Post-text table 14.2.86

Table 36: Change in lipid parameters – by statin regimen intensity – MITT Population

		Pbo + statin					AMR 101 2g + statin							AMR 101 4g + statin						
Parameter	Statin Potency	n [1]	BL [2] Median (IQR)	EOT [3] Median (IQR)	Median %chg from BL	p from BL	n [1]	BL [2]	EOT [3]	Median %chg from BL	p from BL	Diff from pbo	p value from pbo[4]	n [1]	BL [2]	EOT[3]	Median %chg from BL	p from BL	Diff from pbo	p value from pbo [4]
TG	Low	14	315.0 (148.5)	304.5 (158.5)	19.4	0.9515	15	256.0 (64.0)	208.5 (162.0)	-18.8	0.6387	-13.8	0.6784	16	267.8 (87.0)	256.8 (131.5)	0.5	0.6387	-13.1	0.5467
	Medium	140	257.3 (83.5)	268.3 (131.3)	4.6	0.0047	148	253.8 (83.0)	248.0 (116.0)	-5.3	0.3500	-8.7	0.0139	141	269.0 (96.5)	221.0 (91.0)	-15.8	<0.0001	-20.1	<0.0001
	High	73	257.5 (76.5)	266.0 (160.0)	6.5	0.0210	71	256.5 (103.5)	239.5 (115.0)	-5.8	0.2668	-11.7	0.0200	69	254.5 (92.5)	214.5 (87.0)	-20.2	<0.0001	-26.0	<0.0001
LDL-C	Low	14	101.5 (35.0)	98.0 (41.0)	-4.4	0.2661	15	91.0 (30.0)	95.0 (20.0)	0.9	0.6788	7.1	0.4450	16	78.5 (14.5)	84.5 (20.0)	7.8	0.0934	12.4	0.0483
	Medium	140	83.0 (26.0)	91.5 (34.0)	9.9	<0.0001	147	82.0 (23.0)	85.0 (25.0)	2.4	0.0168	-5.9	0.0231	140	85.0 (28.0)	84.0 (35.0)	-2.2	0.9545	-10.0	0.0006
	High	72	83.0 (27.0)	84.0 (26.0)	8.3	0.0133	71	83.0 (26.0)	91.0 (35.0)	3.1	0.0205	-1.7	0.6410	69	79.0 (22.0)	82.0 (29.0)	5.4	0.1139	-2.9	0.4910
Non-HDL-C	Low	14	150 (50.0)	152 (45.0)	1.5	0.7609	15	139 (20.0)	135 (28.0)	-2.2	0.5614	3.3	0.7107	16	128 (24.0)	131 (37.0)	-1.4	0.5282	2.4	0.6326
	Medium	140	128 (35.0)	140 (43.0)	10.5	<0.0001	148	127 (36.0)	133 (40.0)	1.7	0.0094	-7.1	0.0031	141	129 (35.0)	124 (40.0)	-4.3	0.0618	-13.9	<0.0001
	High	73	126 (27.0)	134 (41.0)	12.3	<0.0001	71	128 (31.0)	142 (47.0)	5.4	0.0030	-3.5	0.3266	69	128 (31.0)	118 (38.0)	-6.3	0.0212	-15.8	<0.0001

The median differences between the treatment groups were estimated with the Hodges-Lehmann method.
Low intensity was defined as simvastatin 5-10 mg; medium intensity was defined as rosuvastatin 5-10 mg, atorvastatin 10-20 mg, simvastatin 20-40 mg, or simvastatin 10-20 mg + ezetimibe 5-10 mg; High intensity was defined as rosuvastatin 20-40 mg, atorvastatin 40-80 mg, simvastatin 80 mg, or simvastatin 40-80 mg + ezetimibe 5-10 mg
1. Only patients with both baseline and Week 12 endpoint values are included.
2. Baseline for TG was defined as the average of the measurements at 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 measurement 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. Baseline for other parameters were defined as the Visit 4 (Week 0) measurement. If missing, the last valid measurement prior to dosing with study drug was used.
3. For TG: the Week 12 endpoint was defined as the average of measurements at Visit 6 (Week 11) and Visit 7 (Week 12). If the measurement at 1 visit was missing, the other visit measurement 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. For other lipid parameters, the Week 12 endpoint was defined as the Visit 7 (Week 12) measurement. If missing, the LOCF method was used.
4. P-value is from the Wilcoxon rank-sum test.
BL= Baseline pbo = placebo EOT= end of treatment (Week 12 endpoint) IQR = interquartile range; LOCF = last observation carried forward; Q1 = first quartile; Q3 = third quartile.
Source: ANCHOR CSR Tables 30-31

Table 37: Change in lipid parameters – by TG tertile – MITT Population

		Pbo + statin					AMR 101 2g + statin							AMR 101 4g + statin						
Parameter	Baseline TG tertile	n [1]	BL [2] Median (IQR)	EOT [3] Median (IQR)	Median %chg from BL	p from BL	n [1]	BL [2]	EOT [3]	Median %chg BL from BL	p from BL	Diff from pbo	p value from pbo[4]	n [1]	BL [2]	EOT[3]	Median %chg from BL	p from BL	Diff from pbo	p value from pbo [4]
TG	Lowest	72	203.8 (31.5)	214.5 (71.5)	7.9	0.0055	84	205.8 (33.0)	207.8 (74.5)	0.7	0.1560	-4.1	0.3694	68	207.8 (28.0)	183.5 (67.5)	-10.9	0.1127	-14.4	0.0020
	Middle	80	257.8 (30.3)	263.5 (112.3)	3.3	0.3629	76	257.0 (30.5)	228.3 (83.5)	-13.0	0.0092	-9.9	0.0324	81	261.5 (26.0)	205.0 (74.5)	-19.3	<0.0001	-17.9	<0.0001
	Highest	75	340.5 (94.0)	380.5 (165.5)	5.2	0.0039	74	348.5 (75.0)	320.3 (119.0)	-8.7	0.0914	-16.9	0.0043	77	346.5 (75.5)	260.0 (110.5)	-21.8	<0.0001	-31.1	<0.0001
LDL-C	Lowest	72	85.5 (23.5)	95.0 (28.0)	9.2	0.0002	84	84.5 (28.0)	92.0 (32.0)	3.1	0.0656	-5.7	0.0889	68	82.5 (25.0)	83.0 (30.5)	-3.9	0.3336	-12.2	0.0007
	Middle	80	86.5 (27.0)	90.0 (26.5)	7.3	0.0012	76	82.0 (25.)	86.5 (23.5)	3.1	0.0161	-2.6	0.4097	80	81.5 (29.5)	82.5 (34.0)	2.1	0.3260	-5.8	0.1345
	Highest	74	80.0 (33.0)	80.0 (37.0)	9.2	0.0821	73	81.0 (24.0)	85.0 (26.0)	1.7	0.1876	-2.0	0.6672	77	82.0 (25.0)	83.0 (24.0)	4.8	0.0289	0	0.9970
Non-HDL-C	Lowest	72	117 (23.0)	134 (32.0)	12.1	<0.0001	84	121 (32.0)	129 (38.0)	6.9	0.0001	-4.2	0.1926	68	116 (26.0)	118 (31.0)	-2.0	0.4390	-13.8	<0.0001
	Middle	80	132 (26.0)	138 (36.0)	6.0	0.0004	76	129 (30.0)	132 (35.0)	-1.2	0.7214	-7.0	0.0169	81	127 (31.0)	124 (42.0)	-4.0	0.5345	-9.5	0.0039
	Highest	75	140 (48.0)	149 (60.0)	12.2	<0.0001	74	140 (44.0)	150 (51.0)	3.0	0.0183	-5.0	0.2151	77	142 (36.0)	130 (48.0)	-6.9	0.0030	-17.6	<0.0001

The median differences between the treatment groups were estimated with the Hodges-Lehmann method.
Baseline TG tertiles were <230.5 mg/dL, 230.5 to <289.5 mg/dL, and ≥289.5 mg/dL.
1. Only patients with both baseline and Week 12 endpoint values are included.
2. Baseline for TG was defined as the average of the measurements at 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 measurement 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. Baseline for other parameters were defined as the Visit 4 (Week 0) measurement. If missing, the last valid measurement prior to dosing with study drug was used.
3. For TG: the Week 12 endpoint was defined as the average of measurements at Visit 6 (Week 11) and Visit 7 (Week 12). If the measurement at 1 visit was missing, the other visit measurement 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. For other lipid parameters, the Week 12 endpoint was defined as the Visit 7 (Week 12) measurement. If missing, the LOCF method was used.
4. P-value is from the Wilcoxon rank-sum test.
BL= Baseline pbo = placebo EOT= end of treatment (Week 12 endpoint) IQR = interquartile range; LOCF = last observation carried forward; Q1 = first quartile; Q3 = third quartile.
Source: ANCHOR CSR Tables 36-37; Response to FDA IR submitted 24 June 2013 DARRTS SD#105

Table 38: Changes in Lipid Parameters - by Non-Statin Washout Status – MITT Population

		Pbo + statin					AMR 101 2g + statin							AMR 101 4g + statin						
Parameter	Non-statin washout (Yes/No)	n [1]	BL [2] Median (IQR)	EOT [3] Median (IQR)	Median % chg from BL	p from BL	n [1]	BL [2]	EOT [3]	Median %chg from BL	p from BL	Diff from pbo	p value from pbo[4]	n [1]	BL [2]	EOT[3]	Median % chg from BL	p from BL	Diff from pbo	p value from pbo [4]
TG (mg/dL)	Yes	100	258.3 (81.8)	267.5 (175.5)	3.9	0.0075	109	262.5 (95.5)	249.5 (120.5)	-4.2	0.4771	-9.5	0.0292	92	269.3 (92.8)	220.8 (80.8)	-17.7	<0.0001	-22.4	<0.0001
	No	127	259.0 (85.5)	272.0 (131.5)	6.2	0.0105	125	247.5 (87.0)	229.0 (114.5)	-7.9	0.1416	-10.7	0.0060	134	263.0 (90.5)	220.0 (100.0)	-16.7	<0.0001	-20.8	<0.0001
LDL-C (mg/dL)	Yes	100	82.0 (27.5)	84.5 (27.5)	9.5	0.0002	109	82.0 (24.0)	85.0 (23.0)	2 2	0.1289	-6.3	0.0423	91	82.0 (28.0)	80.0 (33.0)	-1.4	0.4932	-7.5	0.0428
	No	126	85.0 (25.0)	90.0 (35.0)	7.3	0.0007	124	84.0 (26.0)	91.5 (32.5)	3.5	0.0024	-1.2	0.6549	134	82.0 (25.0)	83.5 (30.0)	2.5	0.2283	-5.1	0.0692
Non-HDL-C (mg/dL)	Yes	100	124 (31.0)	136 (40.0)	10.7	<0.0001	109	127 (30.0)	133 (38.0)	0.0	0.0239	-6.9	0.0345	92	129 (35.0)	124 (36.0)	-5.4	0.0900	-14.4	<0.0001
	No	127	129 (35.0)	140 (44.0)	9.6	<0.0001	125	129 (35.0)	135 (44.0)	3.8	0.0020	-4.6	0.0847	134	128 (32.0)	122 (42.0)	-4.9	0.0522	-4.8	<0.0001

The median differences between the treatment groups were estimated with the Hodges-Lehmann method.
1. Only patients with both baseline and Week 12 endpoint values are included.
2. Baseline for TG was defined as the average of the measurements at 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 measurement 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. Baseline for other parameters were defined as the Visit 4 (Week 0) measurement. If missing, the last valid measurement prior to dosing with study drug was used.
3. For TG: the Week 12 endpoint was defined as the average of measurements at Visit 6 (Week 11) and Visit 7 (Week 12). If the measurement at 1 visit was missing, the other visit measurement 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. For other lipid parameters, the Week 12 endpoint was defined as the Visit 7 (Week 12) measurement. If missing, the LOCF method was used.
4. P-value is from the Wilcoxon rank-sum test.
BL= Baseline pbo = placebo EOT= end of treatment (Week 12 endpoint) IQR = interquartile range; LOCF = last observation carried forward; Q1 = first quartile; Q3 = third quartile.
Source: ANCHOR CSR Table 38-39; Response to FDA IR submitted 24 June 2013 DARRTS SD#105

Table 39: Changes in Lipid Parameters – by Diabetes Status – MITT Population

		Pbo + statin					AMR 101 2g + statin							AMR 101 4g + statin						
Parameter	Diabetes (Yes/No)	n [1]	BL [2] Median (IQR)	EOT [3] Median (IQR)	Median %chg from BL	p from BL	n [1]	BL [2]	EOT [3]	Median %chg from BL	p from BL	Diff from pbo	p value from pbo[4]	n [1]	BL [2]	EOT[3]	Median %chg from BL	p from BL	Diff from pbo	p value from pbo [4]
TG (mg/dL)	Yes	165	259.0 (78.0)	275.5 (153.5)	6.2	0.0002	171	253.5 (87.0)	244.0 (116.5)	-1.5	0.7846	-9.8	0.0074	165	262.0 (92.0)	216.5 (88.0)	-18.7	<0.0001	-23.2	<0.0001
	No	62	258.8 (123.5)	258.5 (138.0)	4.3	0.3134	63	256.5 (96.0)	245.0 (121.5)	-12.1	0.0075	-10.8	0.0261	61	271.5 (114.5)	234.5 (90.0)	-15.0	<0.0001	-16.8	0.0005
LDL-C (mg/dL)	Yes	164	84.0 (25.5)	87.5 (31.0)	8.8	<0.0001	170	82.0 (24.0)	87.0 (26.0)	2.2	0.0063	-3.8	0.1482	165	81.0 (26.0)	83.0 (29.0)	2.0	0.2403	-6.3	0.0227
	No	62	85.5 (33.0)	90.0 (31.0)	8.5	0.0060	63	83.0 (29.0)	88.0 (35.0)	2.6	0.0674	-3.1	0.3161	60	83.0 (23.0)	83.5 (37.0)	1.4	0.4317	-5.3	0.1402
Non-HDL-C (mg/dL)	Yes	165	128 (34.0)	136 (44.0)	10.7	<0.0001	171	125 (33.0)	135 (41.0)	5.1	<0.0001	-4.4	0.0723	165	128 (35.0)	121 (40.0)	-5.5	0.0317	-14.4	<0.0001
	No	62	129 (33.0)	143 (36.0)	8.3	0.0001	63	135 (31.0)	133 (42.0)	-0.7	0.7421	-8.6	0.0108	61	131 (38.0)	126 (38.0)	-0.9	0.3032	-11.3	0.0003

The median differences between the treatment groups were estimated with the Hodges-Lehmann method.
1. Only patients with both baseline and Week 12 endpoint values are included.
2. Baseline for TG was defined as the average of the measurements at 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 measurement 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. Baseline for other parameters were defined as the Visit 4 (Week 0) measurement. If missing, the last valid measurement prior to dosing with study drug was used.
3. For TG: the Week 12 endpoint was defined as the average of measurements at Visit 6 (Week 11) and Visit 7 (Week 12). If the measurement at 1 visit was missing, the other visit measurement 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. For other lipid parameters, the Week 12 endpoint was defined as the Visit 7 (Week 12) measurement. If missing, the LOCF method was used.
4. P-value is from the Wilcoxon rank-sum test.
BL= Baseline pbo = placebo EOT= end of treatment (Week 12 endpoint) IQR = interquartile range; LOCF = last observation carried forward; Q1 = first quartile; Q3 = third quartile.
Source: ANCHOR CSR Table 32-33; Response to FDA IR submitted 24 June 2013 DARRTS SD#105

Table 40: Lipid Changes in Placebo-treated Patients – Selected Trials

Study/Active drug	Population	Placebo	Background statin therapy	Lead-in period	Central tendency measure	Duration of PBO	n	TG	LDLc	nHDLc	TC	HDLc	VLDLc	apo B
Very high TG population (≥500 mg/dL)														
MARINE Icosapent Ethyl[49]	**TG 500-2000 mg/dL**	**Mineral oil**	**25% on statin**	**4 to 6 wks**	**Median% CFB**	**12 wks**	**75**	**+9.7**	**-3.0**	**+7.8**	**+7.7**	**0.0**	**+13.7**	**+4.3**
Harris Pownall pooled analysis/Omega 3 acid Ethyl Esters[50,51]	TG 500-2000 mg/dL	Corn oil	No	6 wks	Median% CFB	6-16 wks	42	+6.7	-4.8	-3.6	-1.7	0.0	-0.9	NR
Goldberg[52]/ Fenofibrate	TG 500-1500 mg/dL	Yes	No	6 to 12 weeks	Mean %CFB	8 wks	44	+7.2	-4.2	NR	+0.4	+5.0	+11.0	NR
High TG population (200-500 mg/dL)														
ANCHOR Icosapent Ethyl[53]	**TG 200-499 mg/dL**	**Mineral oil**	**Simva Atorva Rosuva ± Eze**	**6 to 8 wks Stopped all lipid meds except statin**	**Median% CFB**	**12 wks**	**227**	**+5.9**	**+8.8**	**+9.8**	**+9.1**	**+4.8**	**+15.0**	**+7.1**
COMBOS/Omega 3 Ethyl Esters[54]	TG 200-499 mg/dL	Corn oil	Simva 40 mg	8 wks Stopped all lipid meds start simva 40	Median% CFB	8 wks	132	-6.3	-2.8	-2.2	-1.7	-1.2	-7.2	-1.9

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Study/Active drug	Population	Placebo	Background statin therapy	Lead-in period	Central tendency measure	Duration of PBO	n	TG	LDLc	nHDLc	TC	HDLc	VLDLc	apo B
Goldberg[55]/	TG 350-499 mg/dL	Yes	No	6 to 12 weeks	Mean %CFB	8 wks	28	-0.5	+12.0	NR	+2.8	+4.0	+5.8	NR
Simvastatin[56]	Type IV LDL-C<160 TG>200	Yes	No	4 weeks	Median%CFB	6 weeks	74	-9	+1	+1	+2	+3	-7	NR
Atorvastatin[57]	Type IV	Yes	No	Yes duration not specified	Median%CFB	NR	12	-12.4	+3.6	-2.8	-2.3	+3.8	-1.0	NR
Rosuvastatin[58]	primary htg	Yes	No	6 week	Median%CFB	6 wks	26	+0.8	+4.5	+1.7	+1.2	-2.9	+2.1	-0.2
Niacin ER[59]	Primary hyperlipidemia and mixed dyslipidemia	Yes	No	Not specified	Mean %CFB	16 wks	73	+12	+1	NR	+2	+2	NR	+1
FIRST/Fenofibric acid [60]	mixed dyslipidemia TG≥150 HDL-C≤45 M or ≤55 F LDL-C≤100	Yes	Atorva up to 40 mg	2 to 10 week	Mean %CFB	24 mos	329	-2 * Median %CFB	+2*	*0	NR	+3*	NR	NR

NR: Not reported; % CFB: Percent change from baseline; * Results at 13 week timepoint

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

VASCEPA (Icosapent Ethyl)
NDA 202057

Efficacy: Statistical Review
Endocrinologic and Metabolic Drugs Advisory Committee Meeting
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1. INTRODUCTION

VASCEPA® (icosapent ethyl) Capsules was approved on 07/26/2012 under NDA 202057 for treatment as an adjunct to diet to reduce TG (triglyceride) levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia. The efficacy data to support the indication were obtained from Study AMR01-01-0016 and are presented in the current approved label. The sponsor, Amarin Pharma Inc., is now submitting a supplemental NDA to seek approval of a new indication for VASCEPA® which is as an adjunct to diet and in combination with a statin to reduce TG, non-HDL-C (non-high-density lipoprotein cholesterol), Apo B (Apolipoprotein B), LDL-C (low-density lipoprotein cholesterol), TC (total cholesterol), and VLDL-C (very low-density lipoprotein cholesterol) in adult patients with mixed dyslipidemia and CHD (coronary heart disease) or a CHD risk equivalent.

The efficacy of VASCEPA® for this new indication would be determined primarily based on the results from Study AMR01-01-0017 entitled, "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 (ANCHOR)."

The placebos in these two trials were both mineral oil. This briefing document focuses on the efficacy evaluation of the ANCHOR trial.

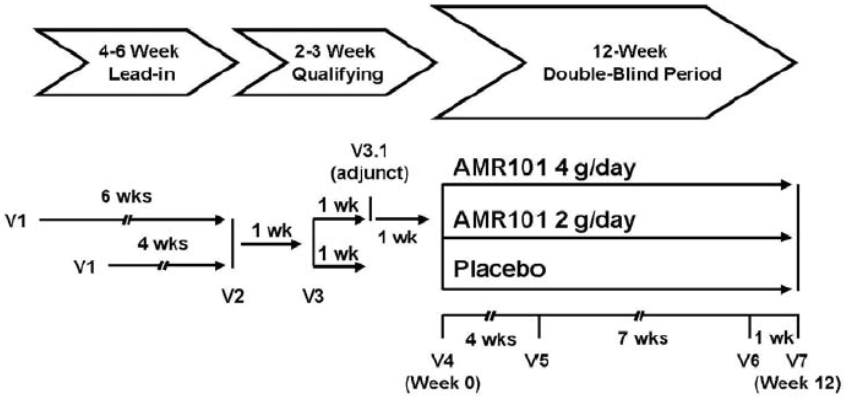
2. STUDY DESIGN AND ENDPOINTS

Study AMR01-01-0017 was a Phase 3, 12-week, randomized, double-blind, placebo-controlled, multicenter (92 site, all in the US) trial conducted in adult patients at high risk for CVD (cardiovascular disease) with high fasting TG level (≥ 200 mg/dL and < 500 mg/dL) despite stable/optimal statin therapy at background. In order to be eligible for randomization at Visit 4 (Week 0), subjects must have met the following criteria based on the LDL-C and TG values collected at Visit 2 (Week -2) and Visit 3 (Week -1) during the qualifying period.

- Mean fasting LDL-C ≥ 40 mg/dL and ≤ 115 mg/dL
- Mean fasting TG ≥ 185 mg/dL with at least one TG ≥ 200 mg/dL
- Mean fasting TG < 500 mg/dL

At Visit 4 (Week 0), subjects were randomized in a 1:1:1 ratio to receive AMR101 2 g, AMR101 4 g, or placebo (see study design schema below). The randomization was stratified by type of statin (atorvastatin, rosuvastatin, or simvastatin), the presence or absence of diabetes, and gender.

The primary efficacy variable was percent change in fasting TG from baseline to Week 12 endpoint. The secondary efficacy variables included percent changes in LDL-C, non-HDL-C, VLDL-C, Lp-PLA$_2$ (lipoprotein-associated phospholipase A$_2$), and Apo B from baseline to Week 12 endpoint. The exploratory efficacy variables included, but were not limited to, percent changes in TC, HDL-C, Apo A-I (Apolipoprotein A-I) from baseline to Week 12.



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 was collected directly by ultracentrifugation (Beta Quant) as well as calculated using the Friedewald equation. TG, calculated LDL-C, non-HDL-C, TC, and HDL-C were measured at all visits. The others were measured at Week 0, Week 4 (for direct LDL-C and VLDL-C only), and Week 12 or early termination.

3. STATISTICAL EVALUATION

3.1 Statistical Methods

According to the sponsor's Statistical Analysis Plan, since there were significant departures from normality (Shapiro-Wilk test $p < 0.01$) in the majority of data of % change from baseline examined, non-parametric analysis methods were employed. Specifically, the Wilcoxon rank-sum test was performed to compare treatment groups using a step-down testing procedure (i.e., AMR101 4 g vs. placebo first and if significant, then AMR101 2 g vs. placebo) to control the Type 1 error rate at $\alpha = 0.05$. The pre-specified multiplicity adjustment was done for the primary efficacy endpoint and each of the secondary efficacy endpoints. Hommel's procedure was used to control the Type 1 error rate across the secondary efficacy endpoints (excluding LDL-C). The multiple comparisons for the exploratory efficacy endpoints were considered descriptive only according to the sponsor. The medians of the treatment differences and 2-sided 95% CIs were estimated by the Hodges-Lehmann method.

The sponsor performed non-inferiority tests for percent change from baseline in LDL-C between each of the AMR101 doses and placebo using a non-inferiority (NI) margin of 6% and a 1-sided significance level of 0.025. This reviewer thinks that the non-inferiority test was not suitable in this setting because the study was a placebo-controlled trial.

Baseline TG was defined as the average of Visit 4 (Week 0) and Visit 3 (Week -1, or Visit 3.1 if it occurred) measurements. Baselines of the other efficacy variables were the Visit 4 measurements. Week 12 endpoint for TG was defined as the average of Visit 6 (Week 11) and Visit 7 (Week 12) measurements. Week 12 endpoints for the other efficacy variables were the Visit 7 measurements. For TG, if the value at 1 visit was missing, the other visit was used. If the values at both visits were missing, the last valid measurement prior to dosing with study drug and the last valid post-baseline measurement during the double-blind treatment period were used as the baseline and endpoint measurements, respectively.

Efficacy evaluations were performed on the ITT population consisting of all randomized subjects who took at least 1 dose of study drug, had a baseline efficacy measurement, and had at least 1 post-randomization efficacy measurement of any type (i.e., the so-called modified ITT population). The LOCF technique was used for missing data imputation. The sponsor also performed the following supportive analyses for the primary efficacy parameter to examine the robustness of the primary analysis results and the impact due to early dropouts.

- Using per-protocol population
- Using completers with valid Week 11 and/or Week 12 fasting TG values
- Using modified definition for baseline TG (average of the 3 latest visits from Visit 2 or later and before the 1st dose of study drug)

In addition, the Van Elteren test (a stratified Wilcoxon rank-sum test) was performed as a sensitivity analysis to take the stratifying factors (gender, type of statin, and presence of diabetes) into consideration. Because there was a concern regarding if placebo was an inert, as requested by the medical reviewers, percent change from baseline data in each study group were analyzed using the Wilcoxon signed-rank test for exploratory purpose; therefore, no multiplicity adjustment was made for these analyses.

3.2 Subject Disposition

A total of 702 subjects were randomized to receive AMR101 4 g (n = 233), AMR101 2 g (n = 236), and placebo (n = 233). The overall dropout rate during the double-blind treatment period was 5.6%. As shown in Table 1, the most recorded reasons for withdrawal were

adverse event (2.8%) and withdrawal of consent (1.7%). The dropout rates and reasons for withdrawal among the 3 study groups were comparable by visual examination. Approximately 98% of the randomized subjects were included in the ITT population.

Table 1 – Patient Disposition (sponsor's table)

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)

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.

3.3 Demographic and Baseline Characteristics

As shown in Table 2, the demographic and baseline characteristics such as age, gender, race, BMI, presence of diabetes, type of statin, potency of statin, TG, LDL-C, non-HDL-C, VLDL-C, Lp-PLA_2, and Apo B values in the randomized population were similar among the 3 treatment groups. Specifically, of the 702 subjects randomized, approximately 61% were < 65 years old and 61% were males. The overall mean age at entry was 61 years, ranging from 31 to 88 years. The majority of subjects were White (96%). The overall mean BMI was about 33 kg/m^2. Approximately 73% of the patients in each group reported having diabetes at entry. Simvastatin was used by 57% of the randomized subjects, then rosuvastatin (24%) and atorvastatin (19%). Slightly more than 93% of the randomized population received at least medium potency of statin drugs (see footnotes under Table 2 for definition).

Table 2 – Demographic and Baseline Characteristics – Randomized Population (sponsor's table)

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.

Table 2 – Demographic and Baseline Characteristics – Randomized Population (sponsor's table) - continued

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.

3.4 Efficacy Results and Discussion

Summary statistics of median, interquartile range (Q3 – Q1), minimum, and maximum of the efficacy endpoints of interest are presented in Table 3 below. Note that the Wilcoxon signed-rank test was performed to analyze % change from baseline within each treatment group as exploratory analyses (see Section 3.1 Statistical Methods above). Statistical results of treatment comparisons analyzed by the Wilcoxon rank-sum test are summarized in Table 4.

Table 3 – Summary Statistics for Efficacy Endpoints of Interest (ITT Population with LOCF)

Variable	Treatment Group	N	Baseline Median (IQR)	Week 12 Endpoint Median (IQR)	% Change From Baseline		
					Median (IQR)	Min, Max	Signed-rank test p-value
Primary Efficacy Endpoint							
TG (mg/dL)	Placebo	227	259.0 (81.0)	269.5 (149.5)	5.9 (44.8)	-65.1, 225.5	0.0002
	AMR101 2 g	234	254.0 (92.5)	244.3 (117.0)	-5.6 (34.5)	-56.3, 245.3	0.1111
	AMR101 4 g	226	264.8 (93.0)	220.8 (92.0)	-17.5 (31.0)	-61.8, 564.3	< 0.0001
Secondary Efficacy Endpoints							
Calculated LDL-C (mg/dL)	Placebo	227	77.0 (31.0)	83.0 (39.0)	11.7 (35.2)	-88.1, 163.6	< 0.0001
	AMR101 2 g	234	76.0 (29.0)	83.5 (31.0)	7.1 (31.8)	-77.3, 134.1	< 0.0001
	AMR101 4 g	226	72.0 (29.0)	77.0 (34.0)	5.1 (33.9)	-98.9, 522.2	0.0053
Direct LDL-C (mg/dL)	Placebo	226	84.0 (27.0)	88.5 (31.0)	8.8 (31.0)	-51.9, 98.2	< 0.0001
	AMR101 2 g	233	82.0 (24.0)	87.0 (27.0)	2.4 (26.1)	-52.5, 122.7	0.0010
	AMR101 4 g	225	82.0 (25.0)	83.0 (31.0)	1.5 (26.6)	-59.1, 134.8	0.1733
Non-HDL-C (mg/dL)	Placebo	227	128.0 (34.0)	138.0 (43.0)	9.8 (27.6)	-40.4, 123.4	< 0.0001
	AMR101 2 g	234	128.0 (33.0)	134.0 (41.0)	2.4 (26.0)	-50.3, 145.7	0.0001
	AMR101 4 g	226	128.0 (32.0)	122.0 (39.0)	-5.0 (21.3)	-51.8, 203.2	0.0106
VLDL-C (mg/dL)	Placebo	226	42.0 (21.0)	49.0 (28.0)	15.0 (58.8)	-68.4, 270.7	< 0.0001
	AMR101 2 g	233	43.0 (21.0)	44.0 (25.0)	1.6 (54.5)	-66.7, 533.3	0.0287
	AMR101 4 g	225	44.0 (21.0)	38.0 (22.0)	-12.1 (47.9)	-76.6, 603.3	0.0043
Lp-PLA_2 (ng/mL)	Placebo	213	185.0 (58.0)	200.0 (71.0)	6.7 (24.0)	-37.6, 95.7	< 0.0001
	AMR101 2 g	224	190.0 (55.5)	183.5 (57.5)	-1.8 (23.1)	-49.3, 114.8	0.2686
	AMR101 4 g	217	180.0 (56.0)	160.0 (57.0)	-12.8 (18.5)	-63.2, 120.0	< 0.0001

Apo B (mg/dL)	Placebo	219	91.0 (24.0)	98.0 (25.0)	7.1 (23.2)	-44.0, 83.0	< 0.0001
	AMR101 2 g	227	91.0 (22.0)	95.0 (24.0)	1.6 (20.7)	-46.1, 60.3	0.0001
	AMR101 4 g	217	93.0 (23.0)	90.0 (25.0)	-2.2 (16.4)	-45.3, 69.7	0.0759
Exploratory Efficacy Endpoints							
TC (mg/dL)	Placebo	227	168.0 (38.0)	181.0 (46.0)	9.1 (20.8)	-34.4, 91.9	< 0.0001
	AMR101 2 g	234	169.0 (34.0)	175.0 (44.0)	2.1 (19.6)	-38.6, 124.5	< 0.0001
	AMR101 4 g	226	167.0 (38.0)	162.0 (38.0)	-3.2 (16.8)	-44.2, 157.4	0.0023
HDL-C (mg/dL)	Placebo	227	39.0 (12.0)	40.0 (14.0)	4.8 (22.0)	-36.2, 70.0	< 0.0001
	AMR101 2 g	234	38.0 (13.0)	38.0 (11.0)	0.0 (19.5)	-40.0, 110.0	0.0164
	AMR101 4 g	226	37.0 (12.0)	37.0 (13.0)	-1.0 (18.2)	-46.2, 44.4	0.8474
Apo A-I (mg/dL)	Placebo	219	140.0 (35.0)	145.0 (34.0)	3.6 (14.9)	-23.5, 50.0	< 0.0001
	AMR101 2 g	227	140.0 (26.0)	141.0 (26.0)	2.0 (13.0)	-24.0, 40.7	0.0007
	AMR101 4 g	217	141.0 (31.0)	137.0 (29.0)	-2.9 (12.6)	-29.2, 39.4	< 0.0001

Table 4 – Statistical Results for % Change From Baseline in Efficacy Endpoints of Interest

ITT Population with LOCF	AMR101 2 g vs. Placebo			AMR101 4 g vs. Placebo		
	Median	95% CI	p-value	Median	95% CI	p-value
TG	-10.1	(-15.7, -4.5)	0.0005	-21.5	(-26.7, -16.2)	< 0.0001
Calculated LDL-C	-2.3	(-7.4, 2.8)	---	-6.8	(-12.0, -1.5)	---
Direct LDL-C	-3.6	(-7.9, 0.5)	---	-6.2	(-10.5, -1.7)	---
Non-HDL-C	-5.5	(-9.4, -1.7)	0.0140	-13.6	(-17.2, -9.9)	0.0001
VLDL-C	-10.5	(-18.3, -2.5)	0.0170	-24.4	(-31.9, -17.0)	0.0001
Lp-PLA_2	-8.0	(-11.6, -4.5)	0.0004	-19.0	(-22.2, -15.7)	0.0001
Apo B	-3.8	(-6.9, -0.7)	0.0170	-9.3	(-12.3, -6.1)	0.0001
TC	-4.8	(-7.8, -1.8)	---	-12.0	(-14.9, -9.2)	---
HDL-C	-2.2	(-4.9, 0.5)	---	-4.5	(-7.4, -1.8)	---
Apo A-I	-1.7	(-3.7, 0.3)	---	-6.9	(-8.9, -4.9)	---

P-values for TG were obtained using the Wilcoxon rank-sum test. P-values for non-HDL-C, VLDL-C, Lp-PLA_2, and Apo B were obtained using the Wilcoxon rank-sum test with Hommel's procedure for multiplicity adjustment. No p-values are reported for the exploratory efficacy variables here as well as LDL-C which was tested by the sponsor for non-inferiority of AMR101 to placebo.

3.4.1 Primary Efficacy Endpoint

After 12 weeks of double-blind treatment period, both the AMR101 dose groups showed a median % decrease in TG from baseline (-5.6% and -17.5% for the 2 g and 4 g, respectively),

while the placebo group showed an increase (+5.9%). As Figure 1 depicts, there was a clear separation in the observed response curves of the 3 treatment groups, favoring AMR101 starting as early as Week 4. The placebo-adjusted treatment effects on median % change from baseline in TG at Week 12 endpoint in the AMR101 dose groups were both statistically significant (-10.1% and -21.5% for the 2 g and 4 g, respectively; both Wilcoxon $p < 0.001$) using the ITT/LOCF population. Results based on the per-protocol population, completers cohort, modified baseline TG, and the Van Elteren test all showed similar findings to the ones from the primary analysis.

From Figure 2 below, one can easily obtain the % of subjects achieving a given level of response for any definition of responders. Approximately 43%, 59%, and 74% of the placebo, AMR101 2 g, and AMR101 4 g treated patients, respectively, showed an improved TG level at the end of the 12-week treatment. One AMR101 4 g treated patient had a +564.3% change from baseline. Excluding this patient from the primary analysis did not change the results at all.

Figure 1

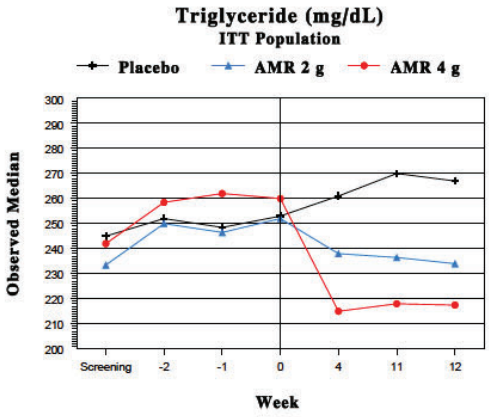
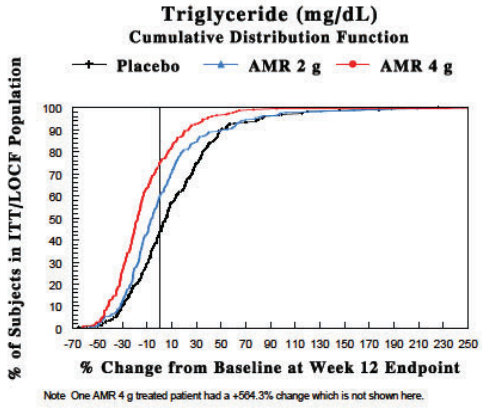


Figure 2



3.4.2 Key Secondary Efficacy Endpoints

The AMR101 4 g dose group consistently showed a median % decrease from baseline in non-HDL-C, VLDL-C, Lp-PLA_2, and Apo B at Week 12 endpoint (-5.0%, -12.1%, -12.8%, and -2.2%, respectively), while the placebo group consistently showed a marked increase in these parameters (+9.8%, +15.0%, +6.7%, and +7.1%, respectively). The % changes from baseline in the AMR101 2 g dose group in these cases were all small and in an increase direction (not in favor of the test dose) except for Lp-PLA_2.

As Figure 3 depicts, there was a clear separation in the observed response curves of the 3 treatment groups for non-HDL-C, favoring AMR101 4 g starting as early as Week 4. The

placebo-adjusted treatment effects on median % change from baseline in non-HDL-C, VLDL-C, Lp-PLA$_2$, and Apo B at Week 12 endpoint in the AMR101 4 g dose group were all highly statistically significant (-13.6%, -24.4%, -19.0%, and -9.3%, respectively; Wilcoxon test with Hommel's multiplicity adjustment p = 0.0001) based on the ITT/LOCF population. The AMR101 2 g dose group also exhibited such significant placebo-adjusted treatment effects, but much less evident.

As seen in Figure 4 below, approximately 29%, 46%, and 62% of the placebo, AMR101 2 g, and AMR101 4 g treated patients, respectively, showed an improved non-HDL-C level at the end of the 12-week treatment.

Figure 3

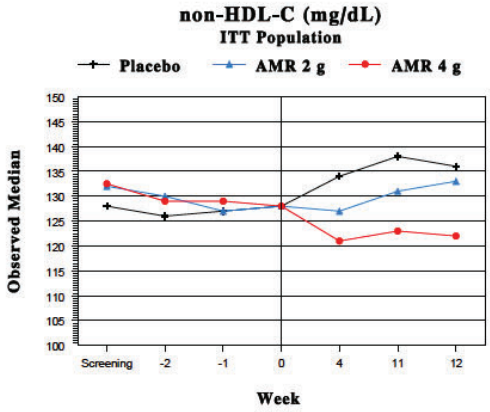
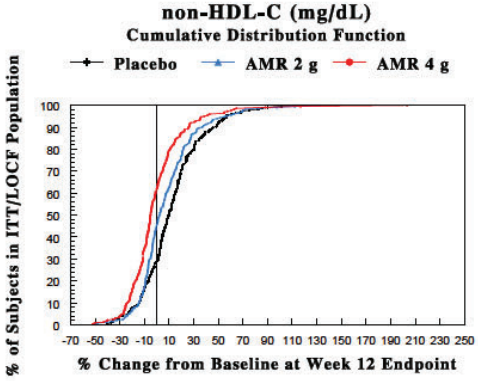


Figure 4



As tables 3 and 4 show, the results from the calculated LDL-C and direct LDL-C were similar. All the 3 treatment groups had a median % increase from baseline in LDL-C at Week 12 endpoint, with placebo exhibiting the largest increase and AMR101 4 g the least. In fact, as Figure 5 depicts, the increases in the 3 treatment groups were seen as early as Week 4 and were continuous throughout the course of the study. In addition, the response levels in the ARM101 2 g dose group were close to those in the placebo group.

The placebo-adjusted treatment effects on median % change from baseline in calculated LDL-C and direct LDL-C at Week 12 endpoint in the AMR101 4 g dose group were -6.8% and -6.2%, respectively, based on the ITT/LOCF population. The placebo-adjusted treatment effects in these cases in the AMR101 2 g dose group were -2.3% and -3.6%, respectively.

As seen in Figure 6 below, approximately 34%, 36%, and 44% (all less than 50%) of the placebo, AMR101 2 g, and AMR101 4 g treated patients, respectively, showed an improved calculated LDL-C level at the end of the 12-week treatment. There were two AMR101 4 g

treated patients with ≥ 400% change from baseline. Excluding these patients from the analysis did not change the results at all.

Figure 5

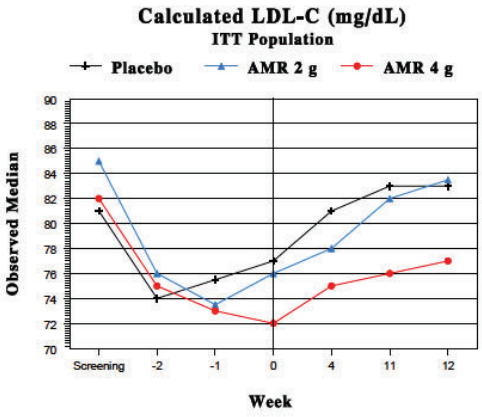
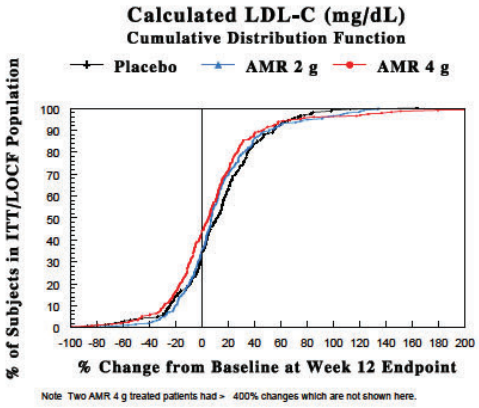


Figure 6



3.4.3 Other Efficacy Endpoints

As in the cases of non-HDL-C, VLDL-C, and Apo B, the AMR101 4 g dose group also exhibited a median % decrease from baseline in TC at Week 12 endpoint (-3.2%), while the AMR101 2 g dose and placebo groups showed an increase (+2.1% and +9.1%, respectively). As Figure 7 depicts, there was a clear separation in the observed response curves of the 3 treatment groups for TC, favoring AMR101 4 g starting as early as Week 4. The estimated placebo-adjusted treatment effect on median % change from baseline in TC at Week 12 endpoint was -12.0% for the AMR101 4 g dose group and -4.8% for the AMR101 2 g dose group based on the ITT/LOCF population.

As seen in Figure 8 below, approximately 27%, 44%, and 63% of the placebo, AMR101 2 g, and AMR101 4 g treated patients, respectively, showed an improved TC level at the end of the 12-week treatment.

Figure 7

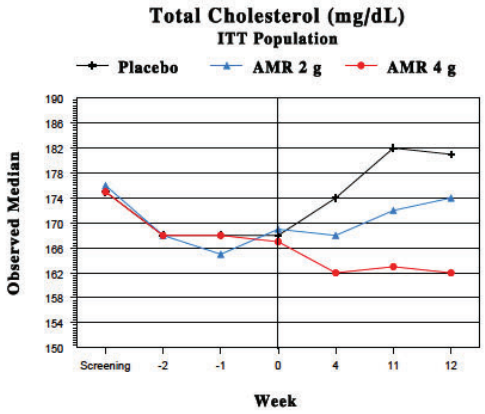
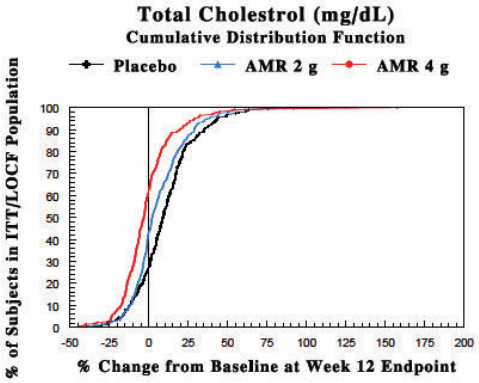


Figure 8



Median % decreases from baseline in HDL-C (-1.0%) and Apo A-I (-2.9%) at Week 12 endpoint were observed in the AMR101 4 g dose group (not in favor of the test dose), while median % increases were seen in the AMR101 2 g dose and placebo groups. As Figure 9 depicts, the response levels in HDL-C in the ARM101 2 g dose group were close to those in the placebo group. As seen in Figure 10 below, approximately 59%, 50%, and 43% of the placebo, AMR101 2 g, and AMR101 4 g treated patients, respectively, showed an improved HDL-C level at the end of the 12-week treatment.

Figure 9

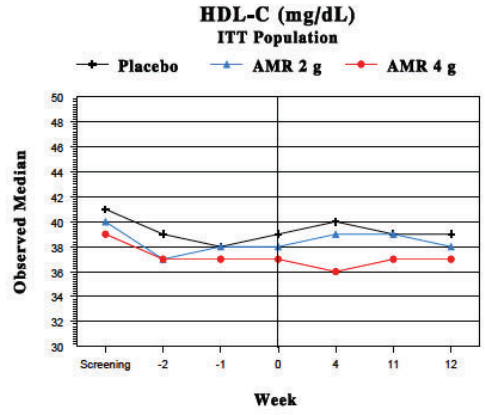
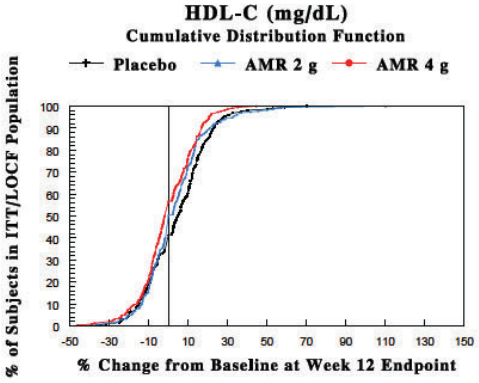


Figure 10



3.4.4 Findings in Special/Subgroup Populations

The placebo-adjusted treatment effects on median % change from baseline in TG at Week 12 endpoint (primary efficacy variable) in the AMR101 4 g dose group were similar between patients aged < 65 years and aged ≥ 65 years (-21.4% vs. -21.7%), between males and females (-21.4% vs. -21.5%), and between some special subgroups such as type of statin, potency of statin, presence of diabetes, baseline TG, and non-statin washout status, as listed

in Table 5 below. The similar treatment effects across the subgroups of interest were not always observed for the AMR101 2 g dose group. The placebo-adjusted treatment effects on median % change from baseline in direct LDL-C at Week 12 endpoint were also not always consistent across the special subgroups evaluated for either AMR101 dose group.

Table 5 – Statistical Results for Subgroups Analyses

	N	Placebo	AMR 2 g	AMR 4 g	AMR 2 g vs. Placebo	AMR 4 g vs. Placebo
% change in TG						
Age < 65 years	422	8.9	-3.4	-14.9	-10.6	-21.4
Age ≥ 65 years	265	0.2	-8.6	-22.5	-9.8	-21.7
% change in TG						
White	661	5.5	-5.3	-17.0	-10.1	-21.2
Non-White	26	8.9	-11.7	-22.7	-17.6	-31.6
% change in TG						
Male	423	6.3	-8.9	-16.0	-14.3	-21.4
Female	264	4.5	0.4	-19.8	-3.3	-21.5
% change in TG						
Atorvastatin	129	7.8	-0.5	-23.9	-2.4	-28.4
Simvastatin	393	6.0	-8.8	-14.7	-14.3	-18.8
Rosuvastatin	165	-0.6	-5.8	-20.5	-5.7	-23.4
% change in Direct LDL-C						
Atorvastatin	128	6.8	4.9	9.0	1.1	2.5
Simvastatin	391	8.6	1.8	1.5	-4.8	-5.4
Rosuvastatin	165	10.5	4.3	-3.8	-4.2	-14.8
% change in TG						
Lower statin potency	45	19.4	-18.8	0.5	-13.8	-13.1
Medium statin potency	429	4.6	-5.3	-15.8	-8.7	-20.1
Higher statin potency	213	6.5	-5.8	-20.2	-11.7	-26.0
% change in Direct LDL-C						
Lower statin potency	45	-4.4	0.9	7.8	7.1	12.4
Medium statin potency	427	9.9	2.4	-2.2	-5.9	-10.0
Higher statin potency	212	8.3	3.1	5.4	-1.7	-2.9
% change in TG						
Patients with diabetes	501	6.2	-1.5	-18.7	-9.8	-23.2
Patients w/o diabetes	186	4.3	-12.1	-15.0	-10.8	-16.8

% change in Direct LDL-C						
Patients with diabetes	499	8.8	2.2	2.0	-3.8	-6.3
Patients w/o diabetes	185	8.5	2.6	1.4	-3.1	-5.3
% change in TG						
< median baseline TG	344	7.2	-1.5	-12.8	-8.0	-17.3
≥ median baseline TG	343	2.4	-9.3	-21.8	-12.8	-24.5
% change in Direct LDL-C						
< median baseline TG	344	9.2	2.6	-2.8	-5.6	-11.3
≥ median baseline TG	340	6.9	2.2	4.1	-1.4	-0.8
% change in TG						
With nonstatin washout	301	3.9	-4.2	-17.7	-9.5	-22.4
W/O nonstatin washout	386	6.2	-7.9	-16.7	-10.7	-20.8
% change in Direct LDL-C						
With nonstatin washout	300	9.5	2.2	-1.4	-6.3	-7.5
W/O nonstatin washout	384	7.3	3.5	2.5	-1.2	-5.1

4. CONCLUSIONS

Data from the ANCHOR trial have demonstrated that VASCEPA (AMR101), either 2 g or 4 g dose, was effective in reducing TG when compared with placebo (mineral oil) in adult patients at high risk for CVD with high fasting TG level (≥ 200 mg/dL and < 500 mg/dL) despite stable/optimal statin therapy at background. In fact, a median % increase in TG from baseline after 12 weeks of treatment was observed in the placebo group (+5.9%).

For the other efficacy variables such as LDL-C, non-HDL-C, VLDL-C, Lp-PLA_2, Apo B, and TC, both doses of VASCEPA also consistently exhibited better median % changes from baseline to Week 12 endpoint favoring VASCEPA when compared with placebo.

For HDL-C and Apo A-I, VASCEPA, especially 4 g dose, however, showed negative efficacy when compared with placebo.

Note that the study was conducted in adult patients with stable and optimal statin therapy (atorvastatin, rosuvastatin, or simvastatin) at background, so lipids and lipoproteins were expected to be under controlled at some degree, particularly for the placebo-treated patients. However, as depicted in Figure 11 below, there were marked median % increases from baseline in the placebo group across all the lipids and lipoproteins evaluated here, resulting in larger treatment differences between the VASCEPA and placebo groups. This reviewer could not find any statistical reasoning to explain this perplexing phenomenon of placebo. Information was not provided on the compliance of the background statin therapy during the

double-blind treatment period. It is also not known whether mineral oil interferes with absorption of statins.

In conclusion, there were positive dose responses in % of subjects with an improved TG, LDL-C, non-HDL-C, and TC level, and a negative dose response in % of subjects with an improved HDL-C level at the end of the 12-week treatment. The median % changes in the VASCEPA 2 g dose group were generally small and in an increase direction that was not in favor of the test drug/dose. The observed beneficial treatment effects of VASCEPA relative to placebo may be over-estimated.

Figure 11