FDA Briefing Document

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

November 14, 2019

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 Vascepa (AMR101) 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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Division Director Memorandum/Division Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
M E M O R A N D U M

Date: October 23, 2019

From: John Sharretts, MD
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Office of Drug Evaluation II
Office of New Drugs, CDER, FDA

To: Chair, Members and Invited Guests
Endocrinologic and Metabolic Diseases Advisory Committee (EMDAC)

Subject: Overview of the November 14, 2019 EMDAC meeting

Thank you for agreeing to participate in November 14, 2019 Advisory Committee Meeting.

The purpose of this meeting is to discuss the benefits and risks of Vascepa (icosapent ethyl) for an indication to reduce the risk of cardiovascular (CV) events as an adjunct to statin therapy in adult patients with elevated triglyceride levels (TG ≥135 mg/dL) and other risk factors for cardiovascular disease (CVD). In support of this indication, the Applicant has submitted the results of the Reduction of Cardiovascular Events with EPA—Intervention Trial (REDUCE-IT) trial. This proposed indication has never been approved for any other lipid-altering drug and would have the potential to impact the health of a large portion of the US population at risk for CV events, who would be eligible for therapy as an adjunct to their current medical regimen.

Vascepa, also known as AMR101, is an omega-3 fatty acid drug product containing purified ethyl ester of eicosapentaenoic acid (EPA) derived from fish oil. It was originally approved in the US in 2012 as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia. TG lowering is not considered a surrogate endpoint for cardiovascular risk reduction.

The REDUCE-IT trial was a randomized, double-blind, placebo-controlled trial designed to evaluate the effect of AMR101 on major adverse cardiovascular events (MACE) in adult patients with controlled LDL-C levels on statin therapy, but with elevated triglyceride levels. The trial population consisted of two risk cohorts: patients aged 45 and older with established cardiovascular disease (70%), and patients aged 50 and older with type 2 diabetes mellitus and at least one additional risk factor for CVD (30%). The trial design and methods, including two protocol amendments instituted during the trial, were agreed upon by the FDA.

In over 8,000 patients followed for a median of nearly 5 years, AMR101 reduced the risk of the primary endpoint – a composite of CV death, non-fatal myocardial infarction (MI), non-fatal stroke, unstable angina requiring hospitalization, and coronary revascularization – compared to placebo (HR 0.752; 95% CI: 0.682 to 0.830). Results for each individual component's contribution to the primary endpoint favored AMR101 over placebo. Results of the primary endpoint were consistent across multiple subgroups and across the two CV risk categories. AMR101 reduced the risk of all secondary endpoints except all-cause mortality as a stand-alone endpoint.

Safety findings were generally consistent with the product labeling, but two new signals emerged in the trial as follows.

More patients treated with AMR101 than placebo (3.1% versus 2.1%) experienced an adjudicated event of atrial fibrillation or atrial flutter requiring hospitalization. The absolute incidence of atrial fibrillation or flutter was greater in the subset of patients with a history of either condition at baseline and the relative risk was numerically increased. This signal was not identified in the original development program for AMR101.

More patients in the AMR101 treatment arm (11.8%) experienced a bleeding event, such as gastrointestinal bleeding or contusions, compared to patients in the placebo arm (9.9%). The Vascepa label states that some studies with omega-3 fatty acids have demonstrated prolongation of bleeding time (in vitro), but this finding has not been previously associated with clinical bleeding episodes to our knowledge.

While REDUCE-IT demonstrated a significant benefit on CV outcomes, the pattern of lipid and inflammatory biomarkers measured during the course of the trial raises questions about the internal validity of the study. In the placebo treatment arm, several biomarkers associated with cardiovascular disease, including low-density lipoprotein (LDL-C) and high-sensitivity CRP (hs-CRP), increased from baseline.

Because a similar pattern emerged in in the placebo arm of a previous trial (ANCHOR) conducted by the applicant (Ballantyne 2012), using the same dose of the same placebo product in a similar population of patients (adults at increased risk for CVD on moderate- and high-intensity statin therapy), a hypothesis has arisen that there is a significant drug interaction between statin drugs and mineral oil, the principal component of the placebo, resulting in

reduced absorption of statins.

Notably, this pattern of biomarker trends did not occur in another trial conducted by the applicant using the same mineral oil placebo (MARINE) at the same dose (H. Bays 2011). In MARINE, the proportion of patients taking statin therapy was only 25%. These data reinforce the notion that decreased absorption of statin medications, rather than a direct effect of the mineral oil itself, could explain the elevation of lipid and inflammatory markers.

FDA analyses attempting to differentiate whether increases in LDL-C and other biomarkers were due to the mineral oil placebo are inconclusive. Due to lack of certain key measurements, we could neither rule out the possibility that mineral oil – at least to some extent – interfered with statin absorption nor estimate the magnitude of LDL-C or other biomarker increase that could be attributed to such an interaction. From the scientific perspective, therefore, it remains necessary to consider what impact the increase in LDL-C and other biomarkers had on CV outcomes. The most sensitive approach to assess these possible effects was to consider the worst-case, that the entire difference between treatment arms was due to mineral oil. FDA's exploratory analyses to assess the effect of these markers suggested that the difference in LDL-C between the study groups could not account for the positive CV outcomes.

Finally, although there is less plausibility for an interaction between mineral oil and other background cardiovascular medications with known CV benefits (antihypertensives, antiplatelet agents, and anticoagulant medications), we considered whether trial data indicated any effects on these drugs that might further impact the observed effect of AMR101 on outcomes. We concluded that these analyses showed no evidence of such a signal.

Thank you in advance for your participation in the discussion of these important considerations. We look forward to the discussion and advice as we consider the potential approval of Vascepa for a new cardiovascular risk reduction indication.

Draft Points to Consider

The major topics for the panel to address include the robustness of this single trial to support a new indication for CV risk reduction, identification of the appropriate indicated population, whether it is appropriate to include in the indication in labeling all of the components of the primary endpoint.

1. Provide your interpretation of the efficacy results from the REDUCE-IT trial. Specifically discuss the:
    a. Overall strengths and limitations of the data, including the use of a single trial to support a first-in-class cardiovascular outcomes indication and robustness of the results
    b. Confidence in the trial outcomes when considering the mineral oil placebo.
    c. Magnitude /clinical relevance of the observed treatment effect.
    d. Components of the primary composite endpoint or secondary endpoints, including the robustness of the data to support an indication for CV death

2. Discuss your level of concern about the new safety findings (increased risk of atrial fibrillation/atrial flutter and bleedings events) from the REDUCE-IT trial and whether labeling can reasonably manage these risks.

3. Discuss whether the efficacy and safety data from the REDUCE-IT trial provide substantial evidence to support approval of an indication for Vascepa to reduce the risk of cardiovascular events.

    If yes, discuss the population – beyond patients with established CVD – that should be included in the indication. Options could include, but are not limited to:

    - adult patients with triglyceride levels greater than 135 mg/dL and additional risk factors for CVD, without regard for age, diabetes status, or adequacy of LDL-C control (proposed by applicant).
    - Risk Cohort 2, which represented 30% of the REDUCE-IT trial population and comprised patients aged 50 years and older without established CVD, who had diabetes, one or more additional risk factors for CVD, and hypertriglyceridemia despite optimized statin therapy to achieve LDL-C less than 100 mg/dL.

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1. Executive Summary

1.1. Introduction

Vascepa is a purified ethyl ester of eicosapentaenoic acid (EPA 20:5 n-3) derived from fish oil. It was originally approved in 2012 as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia (TG ≥ 500 mg/dL).

Vascepa, or AMR101, was initially approved for the severe hypertriglyceridemia indication with support from the MARINE trial (Study AMR-01-01-0016), a 12-week, randomized, placebo-controlled, double-blind trial of 151 adult patients with severe hypertriglyceridemia (TG between 500 and 2000 mg/dL), randomized 1:1 to AMR101 or matching placebo. In this trial, AMR101 decreased TG by 33% versus placebo.

The Applicant also conducted Study AMR-01-01-0017 (ANCHOR), a 12-week, randomized, placebo-controlled, double-blind trial of adult patients with persistent high fasting TG levels (≥200 mg/dL and <500 mg/dL), despite statin treatment to LDL-C goal. The REDUCE-IT trial was designed to provide data to inform the potential cardiovascular (CV) benefit of AMR101 in this context.

REDUCE-IT was a CV outcomes trial conducted to evaluate the clinical benefit of AMR101 compared to Placebo. The Applicant submitted the results of the REDUCE-IT trial to support a new indication for Vascepa:

> *to reduce the risk of cardiovascular death, myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization as an adjunct to statin therapy in adult patients with elevated triglyceride levels (TG ≥135 mg/dL) and other risk factors for cardiovascular disease.*

1.2. Evidence of Effectiveness

The REDUCE-IT trial was completed on 31 May 2018. The main objective was to evaluate the clinical benefit of AMR101 when added to optimized background statin therapy in patients at high risk for CVD. The trial was a randomized, double-blind, placebo-controlled, multi-center, multinational trial of 8,179 patients, randomly assigned 1:1 to either 4 grams of AMR101 or matching Placebo (containing mineral oil). The primary endpoint was a composite of cardiovascular death, nonfatal myocardial infarction (including silent MI), nonfatal stroke, coronary revascularization, and unstable angina requiring hospitalization.

Baseline characteristics were balanced between treatment arms. The mean age was 63.4 years,

about 29% of patients were female, 90% were Caucasian, 6% were Asian, and 2% were Black or African American, and 2% were Hispanic or Latino.

The Intention-To-Treat (ITT) population included 4,089 patients in the AMR101 arm and 4,090 patients in the Placebo arm. Approximately 9.9% of patients in the AMR101 group and 11.2% of patients the Placebo group had an early withdrawal (excluding death) from the study, and approximately 22% of patients in the AMR101 group and 26% in the placebo group permanently discontinued study drug prematurely but remained in the trial.

Compared to Placebo, AMR101 reduced the risk of the primary composite endpoint by 25% (HR = 0.752 [95% CI: 0.682 to 0.830]; p<0.001). The absolute risk reduction in the study population was 4.7% and the number needed to treat (NNT) was 21.

AMR101 also reduced the risk of the key secondary endpoint, the time from randomization to the first occurrence of the composite of CV death, nonfatal MI, or nonfatal stroke (HR = 0.735 [95% CI: 0.651 to 0.830; p=0.0000006]). The absolute risk reduction for the key secondary endpoint was 3.6% and NNT was 28.

AMR101 reduced the risk of individual components of the primary endpoint and secondary composite endpoints, such as fatal or nonfatal MI, fatal or nonfatal stroke, and 3-point MACE plus all-cause mortality. All results were statistically significant per the pre-specified testing plan, except for the final endpoint in the hierarchy, all-cause mortality.

Results of the primary endpoint were consistent across multiple subgroups, including demographic characteristics (such as age, sex, race, and region), baseline characteristics (such as diabetes mellitus and baseline statin intensity), biomarkers (such as TG, and hs-CRP levels) and the two CV risk Categories.

Lipid and inflammatory biomarkers predictive of cardiovascular risk increased in the placebo arm of the trial. LDL-C increased about 7-10 mg/dL from baseline (10-13%) to year one, with the range indicating variability in this parameter depending on which assay (Ultracentrifugation, Direct) or calculated value (Friedewald, Hopkins) was used. High-sensitivity CRP (hs-CRP) increased 0.47 mg/L (32%) from baseline to year 2. In light of these changes, a question has arisen whether there is a drug interaction between statins and mineral-oil placebo leading to reduced absorption of statin medications, and what impact a change in LDL-C (or hs-CRP) in the placebo arm might have had on the observed treatment effect.

1.3. **Summary of Safety**

Current Vascepa labeling include the following safety information:

- A contraindication in patients with known hypersensitivity to any of its components
- A Warning recommending monitoring of liver transaminases in patients with hepatic impairment (Patients with active severe liver disease were excluded from REDUCE-IT)

- A Warning regarding the risk of allergic reactions in patients with known hypersensitivity to fish or shellfish (patients with known hypersensitivity were excluded from REDUCE-IT)
- Adverse reactions of Arthralgia and Oropharyngeal pain, occurring more frequently than in placebo
- A statement in Drug interactions that some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time, but not clinically significant bleeding episodes

Overall safety findings in REDUCE-IT were generally consistent with product labeling, with the exception of two new safety signals that emerged in the trial, atrial fibrillation or atrial flutter events and bleeding events.

More patients in the AMR101 group experienced an adjudicated event of atrial fibrillation or atrial flutter event requiring hospitalization 24 hours or greater compared with patients the Placebo group (3.1% versus 2.1%), and more patients experienced any TEAE of atrial fibrillation or atrial flutter in the AMR101 arm versus placebo. The incidence of atrial fibrillation or atrial flutter was greater in the subset of patients with a previous history of atrial fibrillation or flutter, and the relative imbalance was numerically greater between arms in this subgroup compared with the imbalance in those without a previous history.

More patients in the AMR101 group experienced an adverse event of bleeding compared with patients in the placebo group. Excluding hemorrhagic strokes (which were adjudicated efficacy events), 482 patients (11.8%) in the AMR101 treatment arm experienced bleeding events compared to 404 patients (9.9%) in the Placebo treatment arm.

2. Therapeutic Context

2.1. Cardiovascular Risk Reduction with Omega-3 Fatty Acids

Although observational studies have showed associations between consumption of fish- or plant-derived omega-3 fatty acids and reduced rates of CV death in various populations (Kromhout 1985) (Psota 2006), the suitability of observational studies to provide context for findings in the REDUCE-IT trial is limited by both low strength of evidence and limited applicability of the studies to the effects of fish oil products. Multiple systematic reviews of the cardiovascular and other effects of fish oil either excluded observational studies (Siscovick 2017) (Abdelhamid 2018) or found the strength of evidence derived from observational studies to be low (Balk 2017)[1].

As mentioned previously, AMR101 is a fish oil product containing 4 grams of purified EPA, whereas most other fish oil supplements and fish oil-derived drug products contain a mixture of primarily EPA and docosahexaenoic acid (DHA, 22:6 n-3). Importantly, observational studies generally assessed *dietary fish intake* or measured circulating omega-3 polyunsaturated fatty acids (PUFA) (Siscovick 2017) (Del Gobbo 2016) (Djousse 2012), not fish oil products generally or EPA specifically. Additionally, internal validity of observational studies may be complicated by factors such as healthy user bias (Harris, 2016), whereby patients who purchase and ingest fish oil products are more health-conscious, have higher socioeconomic status, and have lower CVD burden compared to non-users.

Randomized, controlled interventional trials to evaluate the effect of omega-3 fatty acids on rates of CV events have generated inconsistent findings and may also not be entirely applicable to the current discussion due to differences in test product and dose. Following favorable results from an early open-label trial (GISSI-Prevenzione Investigators 1999), subsequent trials have shown inconsistent effects. A recent meta-analysis of 10 randomized clinical trials concluded that randomization to trial arms with omega-3 fatty acid supplementation for a mean of 4.4 years had no significant effect on major vascular events (Aung 2018), including no benefit in any high-risk subgroups such as patients with prior vascular disease. As with the observational data, an important caveat is that most of these trials evaluated supplements containing mixture of DHA and EPA, and all evaluated an EPA dose much lower than that studied in REDUCE-IT, ranging from 226 to 1150 mg/day in nine of the trials and 1800 mg/day in the other.

[1] The AHRQ investigators rated the strength of evidence for each potential association as high, moderate, low, or insufficient, based on the number of studies, their limitations, consistency, precision, and other factors. Associations based on observational studies were consistently rated as low strength of evidence.

3. Overview of REDUCE-IT

Trial Administrative Structure and Oversight

Steering Committee

The Steering Committee (SC) was composed of the Applicant and its representative (two positions) and seven additional members. SC members were blinded to treatment assignments until after final database lock and formal unblinding. The Steering Committee had several responsibilities related to trial design and operations. The Steering Committee Chair could communicate with the Data Monitoring Committee (DMC) Chairperson prior to any formal DMC recommendation release. We did not find evidence that the DMC shared unblinded information with the SC, as SC recommendations for protocol amendments appeared reasonable based on blinded data on the overall study population.

Study Operations Committee

The Study Operations Committee (SOC) was as subgroup of the SC and responsible for study execution and management of the trial; specifically, to monitor recruitment, compliance, and the adjudication process and to address day to day issues. The SOC was composed of representatives from the Applicant and the organizations conducting the study (delegated by the Applicant) and at least one investigator participating in the trial.

Clinical Event Committee

The Clinical Event Committee (CEC) was composed of independent medical experts who were responsible for validating in a blinded fashion the primary and secondary efficacy endpoints reported by investigators through a defined adjudication process. The CEC was comprised of one CEC Chairperson, two board-certified cardiologists and one board-certified neurologist. Boston Clinical Research Institute provided event adjudication services and helped with management. An Endpoint Management (EPM) team was responsible for compiling and providing complete event packets electronically via the adjudication database to the CEC. The CEC chairperson was responsible for participating in the adjudication process as a tie-breaker if the two primary adjudicators disagreed and for communicating with the SOC, DMC, and SC as needed.

Data Monitoring Committee (DMC)

The independent DMC was instituted to ensure the ongoing safety and to oversee and review the interim analysis. It performed its duties by monitoring unblinded safety data for all patients in the trial.

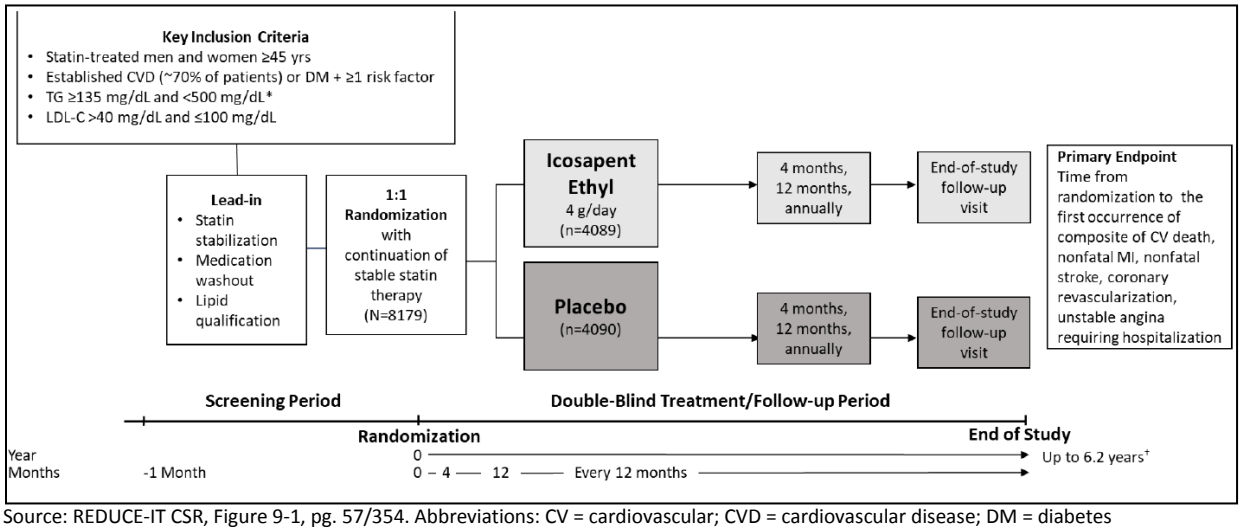
3.1. **Study Design**

Study Title: A Multi-Center, Prospective, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effect of AMR101 on Cardiovascular Health and Mortality in Hypertriglyceridemic Patients with Cardiovascular Disease or at High Risk for Cardiovascular Disease otherwise known as: "REDUCE-IT" (Reduction of Cardiovascular Events with EPA – Intervention Trial)

Methods

REDUCE-IT was a randomized, double-blind, placebo-controlled, event-driven cardiovascular outcomes trial (CVOT) to evaluate 4 grams daily AMR101 (Vascepa) versus placebo. Patients were statin-treated men and women with either established cardiovascular disease (CVD) or diabetes mellitus with one or more risk factors for CVD. Eligible patients had LDL-C between 40 and 100 mg/dL and TG ≥ 200 mg/dL but < 500 mg/dL. There were approximately 473 study sites in 11 countries (United States, the Netherlands, Ukraine, Russian Federation, South Africa, Poland, India, Canada, Romania, Australia, and New Zealand). The trial design and two protocol amendments were agreed to with the Agency under a Special Protocol Assessment. The following figure is a schematic of the trial design.

Figure 1: Schematic of Trial Design



Source: REDUCE-IT CSR, Figure 9-1, pg. 57/354. Abbreviations: CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; icosapent ethyl = AMR101; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; TG = triglycerides; yrs = years.* Due to TG variability, a 10% allowance from the lower qualifying target of > 150 mg/dL existed in the initial protocol, which permitted patients to be enrolled with qualifying TG > 135 mg/dL. This was changed in Protocol Amendment 1 to lower limit of TG to > 200 mg/dL, with no variability allowance.

Randomization was stratified by CV risk category, use of ezetimibe (yes/no), and by geographical region ('Westernized', Eastern European, and Asia Pacific).
The trial enrolled patients in two CV risk categories, CV Risk Category 1 (planned to be

70% of enrolled patients) which included patients with established CVD, and CV Risk Category 2 (planned to be 30% of enrolled patients) which included patients aged 55 years and older with diabetes and at least one additional risk factor, defined below in '*Key Inclusion Criteria*'.

Note that CV Risk Category 2 comprised patients with diabetes and multiple risk factors, including some patients with established CVD, therefore the terms "primary prevention" and "secondary prevention" used by the applicant are imprecise to describe the categories. This review will refer to CV Risk Category 1 as 'Established CVD Cohort' and CV Risk Category 2 as 'Diabetes Cohort' interchangeably with 'CV Risk Category 1' and 'CV Risk Category 2'.

Key Inclusion Criteria

1. The **original protocol** stipulated a lower end of qualifying **fasting TG level of ≥135 mg/dL**, reflecting a 10% allowance due to the variability in TG levels and a target lower end qualifying fasting TG level of ≥150 mg/dL, and an upper TG level limit of <500 mg/dL. **Protocol Amendment 1** (16 May 2013) increased the lower end of fasting TG levels from ≥135 mg/dL to **≥200 mg/dL** to increase enrollment of patients with TG levels at or above 200 mg/dL.
2. **LDL-C >40 mg/dL and ≤100 mg/dL** and on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks prior to the LDL-C and TG baseline qualifying measurements for randomization.
3. Either having **established CVD (in CV Risk Category 1) or at high risk for CVD (in CV Risk Category 2)**. The CV risk categories were **defined as follows**:

CV Risk Category 1 *(a.k.a. Established CVD Cohort)*: defined as men and women ≥45 years of age with **one or more of the following**:

A. Documented coronary artery disease (CAD); **one or more of the following** primary criteria must have been satisfied:
    - Documented multi-vessel CAD
    - Documented prior MI.
    - Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome, with objective evidence of ischemia.
B. Documented cerebrovascular or carotid disease; including at least **one of the following** primary criteria:
    - Documented prior ischemic stroke.
    - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis.
    - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis.

- History of carotid revascularization (catheter-based or surgical).

C. Documented peripheral arterial disease; **one or more of the following** primary criteria must have been satisfied:

- Ankle brachial index (ABI) <0.9 with intermittent claudication.
- History of aorto-iliac or peripheral arterial intervention.

CV Risk Category 2 *(a.k.a. Diabetes Cohort)*: defined as patients with:

- **Diabetes mellitus** (Type 1 or Type 2) requiring treatment with medication.
- Men and women **≥50 years of age**.
- **One or more of the following** at Visit 1 (additional risk factor for CVD):
  - Men ≥ 55 years of age or women ≥ 65 years of age.
  - Cigarette smoker or stopped smoking within 3 months before Visit 1.
  - Hypertension (blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic) or on antihypertensive medication.
  - HDL-C ≤ 40 mg/dL for men or ≤50 mg/dL for women.
  - hs-CRP >3.00 mg/L (0.3 mg/dL).
  - Renal dysfunction: creatinine clearance (CrCL) >30 and <60 mL/min (>0.50 and <1.00 mL/sec).
  - Retinopathy.
  - Micro- or macroalbuminuria.
  - ABI <0.9 without intermittent claudication.

Note: Patients with diabetes and CVD, as defined above, were eligible, based on the CVD requirements and were to be included in CV risk category 1.

Key Exclusion Criteria

1. Known familial lipoprotein lipase deficiency (Fredrickson Type 1), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type 3).
2. Intolerance or hypersensitivity to statin therapy.
3. Non-study drug-related, non-statin, lipid-altering medications, supplements or foods, including the following:
   - Niacin >200 mg/day or fibrates within 28 days of screening (Visit 1); 28-day washout with re-screening permitted (Visit 1.1).
   - Any O3FA medications (prescription EPA and/or DHA) within 28 days of screening (Visit 1); 28-day washout with re-screening permitted (Visit 1.1) except patients in the Netherlands no washout was allowed.

- Dietary supplements containing O3FAs (e.g., flaxseed, fish, krill, or algal oils) > 300 mg/day (combined amount of EPA and DHA) within 28 days of screening (Visit 1); 28-day washout with re-screening permitted (Visit 1.1).
- Bile acid sequestrants within 7 days of screening (Visit 1); 7-day washout with re-screening permitted (Visit 1.1).
- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors within 90 days prior to screening.

4. Other medications: tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids (local, topical, inhalation, or nasal allowed), or human immunodeficiency virus (HIV)-protease inhibitors; up to 28-day stabilization period with re-screening permitted (Visit 1.1).
    - Cyclophosphamide or systemic retinoids within 28 days of screening (Visit 1); 28-day washout with rescreening permitted (Visit 1.1).

3.2. **Statistical Methods**

Primary Endpoint
The primary endpoint was time to first occurrence of 5-point MACE, a 5-component composite endpoint consisting of CV death, nonfatal myocardial infarction, and nonfatal stroke, coronary revascularization, and hospitalization for unstable angina.

Secondary Endpoints
The secondary endpoints are listed as follows:

1. 3-point MACE (composite of CV death, nonfatal myocardial infarction, and nonfatal stroke) (Key secondary)
2. Composite of CV death or nonfatal MI
3. All MI
4. Urgent of emergent revascularization
5. CV death
6. Hospitalization for unstable angina
7. All stroke
8. Composite of total mortality, nonfatal MI, or nonfatal stroke
9. Total mortality

Protocol Specified Primary Analyses
Primary analysis set: The analysis population was the intention-to-treat (ITT) population defined as all randomized patients.

Primary efficacy analysis: The log-rank test stratified by randomization stratification variables was used to compare the time-to-event between treatment groups. REDUCE-IT

was an event driven trial. Two interim analyses were planned for the primary endpoint when adjudication of approximately 60% and 80% of the total target number of primary endpoint events planned (1612) were reached. The 2-sided alpha level for the primary analysis was adjusted to 0.0437 from 0.05 to account for the two interim analyses.

The hazard ratio comparing the two treatment groups along with the 95% CI were calculated from a stratified Cox proportional hazards model.

Times to first MACE were censored in the analysis for non-CV deaths. Patients who died with an adjudicated undetermined cause of death and without a preceding endpoint event were included as events in the primary analysis.

FDA Statistical Reviewer's Analyses of the Primary Endpoint
A multiple imputation analysis was performed to address missing follow-up time using data from retrieved drop-outs. Retrieved drop-out data were defined as the follow-up data between treatment discontinuation and the EOS from patients who did not develop a 5-point MACE prior to treatment discontinuation.

Protocol Specified Control of Type-I Error
The primary and secondary endpoints were tested sequentially as follows:

1. 5-point MACE
2. 3-point MACE
3. Composite of CV death or nonfatal MI
4. All MI
5. Urgent of emergent revascularization
6. CV death
7. Hospitalization for unstable angina
8. All stroke
9. Composite of total mortality, nonfatal MI, or nonfatal stroke
10. Total mortality

Protocol Amendments
Notable changes to the protocol during the trial (after initiation) included:

- Increase of the required fasting TG level at Screening from 135 mg/dL (reflecting a 10% variability allowance from the target of 150 mg/dL) to 200 mg/dL (without a variability allowance).

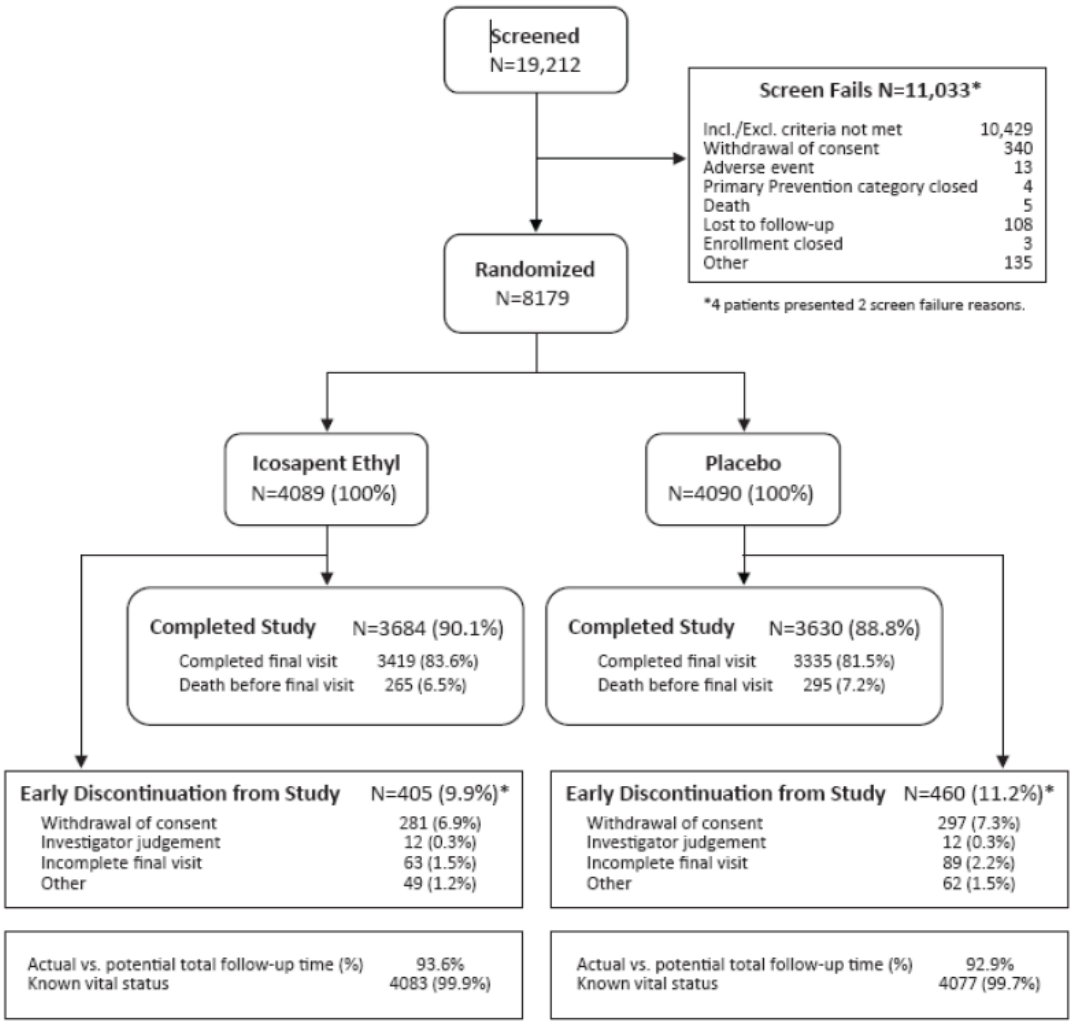
- Addition of direct measurement of LDL-C to fasting lipid profile at Visits 2 and 4 and calculation of Hopkins LDL-C at all visits.

4. Review of Efficacy

4.1. Patient Disposition and Demographics

Figure 2 shows the patient disposition in the REDUCE IT trial. 8,179 patients were randomized, and vital status was available for over 99% of patients. Median follow up time was 4.9 years.

Figure 2: Patient Disposition



*Early discontinuation from study (9.9% icosapent ethyl; 11.2% placebo) includes patients that discontinued after having a primary event (25 [0.6%] icosapent ethyl; 52 [1.3%] placebo) and prior to having an event (380 [9.3%] icosapent ethyl; 408 [10.0%] placebo).

Source: REDUCE IT Complete Study Report, Figure 10-1, pg. 116/354.

Approximately 10% of patients in the AMR101 arm and 11% in the Placebo arm discontinued early from the study (not counting deaths). Table 1 summarizes these data.

Table 1: Summary of Total Early Termination Including and Excluding Patient Death While in Study, ITT population

	AMR101 (N=4089)	Placebo (N=4090)	Total (N=8179)
Total Early Termination including death, n (%)	670 (16.4)	755 (18.5)	1425 (17.4)
Death while in Study, n (%)	274 (6.7%)	310 (7.6%)	584 (7.1%)
Total Early Termination excluding death in Study, n (%)	396 (9.7%)	445 (10.9%)	841 (10.3%)
Source: Reviewer			

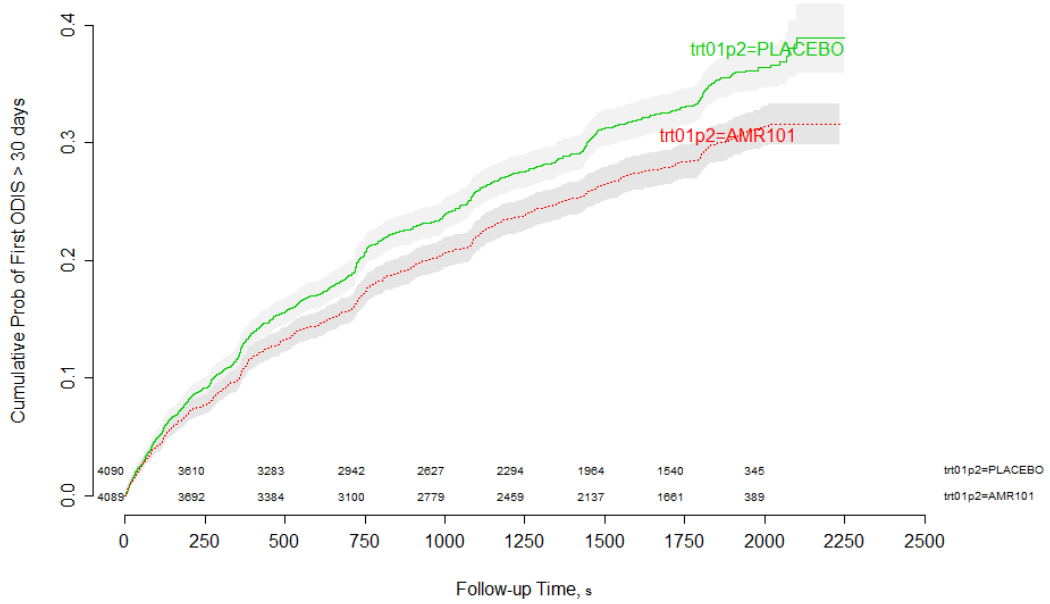
Among patients who discontinued the study early, the most common reasons overall were as follows. (Note that the most comment reason for study *drug* withdrawal was adverse events, discussed in the safety section of this memo).

- Withdrawal of consent: 6.9% in the AMR101 group and 7.3% in the Placebo group
- Incomplete final visit (lost to follow-up): 1.5% in the AMR101 group and 2.2% in the Placebo group
- Investigator judgment: 0.3% in the AMR101 group and 0.3% in the placebo group

Of note, patients who discontinued study *drug* prematurely for reasons other than withdrawal of consent were to stay in study and be monitored until the end of the study. Patients who continued in the study after ≥30 days following cessation of therapy were to be characterized as "off drug in study" (ODIS) and were to be asked to return to the study site for an interim ODIS visit once the patient had been off study drug for ≥30 days. If not contraindicated, ODIS patients had the option to restart study drug at any point. Because some analyses presented later in this document pertain to ODIS patients, we describe this subset in detail here.

The cumulative incidence of ODIS events was greater in the placebo arm than the AMR101 arm, and the proportion of ODIS patients was greater in placebo at all study visits. Figure 3 shows a time to event analysis of the first episode of study drug discontinuation among patients who remained in the study. Approximately 26.8% of patients in the AMR101 group and 31.1% of patients in the Placebo group were identified as being ODIS *at some point* during the study, including patients who discontinued study drug temporarily (≥30 days) and later resumed therapy. At the final visit, 22.4% and 26.2% in the AMR101 and Placebo groups, respectively, were ODIS.

Figure 3: Time to First Ever "Off Drug in Study (ODIS)" Episode, ITT Population



Source: Dr. Changming (Sherman) Xia, FDA Safety Statistician

Overall, 91.9% of patients in the AMR101 group and 91.2% of patients in the placebo group were at least 80% adherent to study drug (i.e., took at least 80% of their prescribed study drug capsules while on treatment during the study). Approximately 3.4% (139/4089) in the AMR group and 3.3% (133/4090) were <80% adherent with background statin use.

Demographic Characteristics

Randomization appeared successful; there were no important differences in demographic characteristics between arms that would have altered the study results. Table 2 and Table 3 summarize demographics and baseline characteristics.

Of the 8179 patients randomized into the study, 71% were men and 90% were white. The mean age was 63.4 years with 46% of patients age ≥ 65 years. Mean BMI was 31.6 kg/m^2. Approximately 22% of patients had eGFR <60 $mL/min/1.73m^2$. Approximately 41% had diabetes mellitus, and over 86% had hypertension. Disease characteristics by Risk Category (such as history of a previous CV event) are discussed later in this memo.

The proportion of male patients in the trial is consistent with the earlier incidence of CV disease in males. The proportion of non-white patients is low compared to the US population, as is the proportion of Hispanic or Latino patients. It is unknown whether underrepresentation of racial and ethnic groups, particularly groups at increased risk of

CVD might impact generalizability of the trial results to the US population (Clark 2019).

Table 2: Demographic Characteristics, ITT Population

Parameter	AMR101 (N=4089) n (%)	Placebo (N= 4090) n (%)	Overall (N=8179) n (%)
Sex			
Male	2927 (71.6)	2895 (70.8)	5822 (71.2)
Female	1162 (28.4)	1195 (29.2)	2357 (28.8)
Age			
Mean years[1] (SD)	63.4 (8.37)	63.4 (8.43)	63.4 (8.40)
Median (years)	64.0	64.0	64.0
Min, max (years)	45.0, 92.0	44.0, 91.0	44.0, 92.0
Age Group			
< 65 years	2232 (54.6)	2184 (53.4)	4416 (54.0)
≥ 65 years	1857 (45.4)	1906 (46.6)	3763 (46.0)
Race			
White	3691 (90.3)	3688 (90.2)	7379 (90.2)
Black or African American	69 (1.7)	89 (2.2)	158 (1.9)
Asian	225 (5.5)	221 (5.4)	446 (5.5)
American Indian or Alaska Native	18 (0.4)	11 (0.3)	29 (0.4)
Native Hawaiian or Pacific Islander	7 (0.2)	3 (0.1)	10 (0.1)
Multiple	49 (1.2)	42 (1.0)	91 (1.1)
Other	30 (0.7)	35 (0.9)	65 (0.8)
Missing	0	1 (0.0)	1 (0.0)
Ethnicity			
Hispanic or Latino	188 (4.6)	157 (3.8)	345 (4.2)
Not Hispanic or Latino	3901 (95.4)	3933 (96.2)	7834 (95.8)
BMI (kg/m^2)			
< 25 kg/m^2	320 (7.8)	295 (7.2)	615 (7.5)
≥ 25 to <30 kg/m^2	1427 (34.9)	1414 (34.6)	2841 (34.7)
≥ 30 kg/m^2	2331 (57.0)	2362 (57.8)	4693 (57.4)
Missing	11 (0.3)	19 (0.5)	30 (0.4)

1 Age (years) was at randomization.
Source: REDUCE-IT CSR, Table 11-1, pg. 123/354.

Table 3: Baseline Characteristics, ITT Population

Parameter	AMR101 N=4089 n (%)	Placebo N=4090 n (%)	Overall N=8179 n (%)
Diabetes			
No diabetes at Baseline	1695 (41.5)	1694 (41.4)	3389 (41.4)
Type 1 Diabetes	27 (0.7)	30 (0.7)	57 (0.7)
Type 2 Diabetes	2366 (57.9)	2363 (57.8)	4729 (57.8)
Both Type 1 and Type 2 Diabetes	1 (0.0)	0	1 (0.0)
Missing	0	3 (0.1)	3
Hypertension[1]			
Yes	3541 (86.6)	3543 (86.6)	7084 (86.6)
No	548 (13.4)	547 (13.4)	1095 (13.4)
Metabolic Syndrome [2]			
Yes	3792 (92.7)	3753 (91.8)	7545 (92.2)
No	297 (7.3)	337 (8.2)	634 (7.8)
Impaired Glucose[3] Metabolism			
Yes	1454 (35.6)	1517 (37.1)	2971 (36.3)
No	2630 (64.3)	2571 (62.9)	5201 (63.6)
Missing	5 (0.1)	2 (0.0)	7 (0.1)
Renal Impairment[4]			
Yes	905 (22.1)	911 (22.3)	1816 (22.2)
No	3180 (77.8)	3177 (77.7)	6357 (77.7)
Missing	4 (0.1)	2 (0.0)	6 (0.1)

1 Hypertension as identified on the CRF "Cardiovascular History."
2 Definition per Alberti KG, et al. Circulation 2009; 120: 1640-5.
3 Impaired glucose metabolism was based on Visit 2 fasting blood glucose of 100 to 125 mg/dL.
4 eGFR <60 mL/min/1.73m^2.
Source: REDUCE-IT CSR Table 11-1 p. 123-125/354

Baseline lipid parameters and C-reactive protein levels were similar between treatment arms. Table 4 summarizes these data. Median LDL-C was approximately 75 mg/dL, and median triglycerides were 216 mg/dL at baseline.

Table 4: Baseline Lipid Parameters and C-Reactive Protein, ITT population

Parameter	AMR101 N=4089	Placebo N=4090
Total cholesterol	**n=4085**	**n=4089**
Baseline mg/dL (median)	158.5	160.0
Q1, Q3	144.0, 174.5	144.5, 176.0
LDL (derived) mg/dL	**n=4086**	**n=4089**
Baseline (median)	74.0	76.0
Q1, Q3	61.5, 88.0	63.0, 89.0
HDL mg/dL	**n=4077**	**n=4080**
Baseline (median)	40.0	40.0
Q1, Q3)	34.5, 46.0	35.0, 46.0
Triglyceride mg/dL	**n=4086**	**4089**
Baseline (median)	216.5	216.0
Q1, Q3	176.5, 272.0	175.5, 274.0
Non-HDL-C mg/dL	**n=4086**	**n=4089**
Baseline (median)	118.0	118.5
Q1, Q3	104.0, 132.0	105.0, 133.0
C Reactive Protein mg/dL	**n=4086**	**n=4089**
Baseline (median)	2.18	2.15
Q1, Q3	1.07, 4.49	1.07, 4.50
Source: Applicant Response to Information Request, 30 September 2019		

4.2. **Results**

Overview

The primary efficacy analysis demonstrated superiority of AMR101 to the study placebo as adjunctive to statin therapy. The hazard ratio and 95% confidence interval (CI) from the protocol specified analysis of the primary endpoint are 0.752 (0.682, 0.830). There was also a statistically significant lower risk in the 3-point MACE (CV death, nonfatal MI, and nonfatal stroke) with AMR101 than with the placebo. The hazard ratio and 95% CI for the 3-point MACE are 0.735 (0.651, 0.830).

The treatment effect for the primary endpoint was assessed across multiple subgroups. The results were generally consistent with findings from the overall population. There was no qualitative treatment-by-subgroup interaction observed.

The percentage of patients who were lost to follow-up before the end-of-study (EOS) was moderate (10%). A multiple imputation analysis based on retrieved drop-outs was performed to evaluate the impact of missing follow-up on the study conclusion. Additionally, a tipping point analysis was performed to stress test the non-informative

censoring assumption for those with missing follow-up. Findings from these analyses were generally supportive of the primary analysis.

Protocol Specified Analysis of the Primary Endpoint

Table 5 shows the analysis results of the primary endpoint. There was a statistically significant reduction in CV risk with AMR101 versus placebo. (The p-value from the log-rank test was less than 0.0437). When comparing AMR101 to placebo, the hazard ratio for time to first occurrence of 5-point MACE is 0.752 with a 95% CI of (0.682, 0.830). The absolute risk reduction was 4.8% and the number needed to treat to prevent one primary event over 4.9 years was 21. Nonfatal MI had the highest percent of event occurrence among the components of the primary endpoint.

Table 5: Time to the First Occurrence of 5-point MACE

	AMR101 (N=4089) n (%)	**Placebo (N=4090) n (%)**	**AMR101 vs. Placebo HR (95% C.I.)**	**P-value**
5-Point MACE	705 (17.2)	901 (22.0)	0.752 (0.682, 0.830)	< 0.0001
Components Contribution to the Primary Endpoint				
CV Death	137 (3.4)	149 (3.6)		
Nonfatal MI	205 (5.0)	280 (6.8)		
Nonfatal Stroke	80 (2.0)	105 (2.6)		
Coronary Revascularization	189 (4.6)	244 (6.0)		
Hospitalization for Unstable Angina	94 (2.3)	123 (3.0)		

[Source: CSR (Page 132) and Statistical Reviewer's Analysis]

Table 6 displays the results for the time to first occurrence of each of the individual components of the primary endpoint. AMR101 is superior to placebo for each component.

Table 6: Time to the First Occurrence of Individual Components of 5-point MACE

Endpoint	AMR101 (N=4089)	Placebo (N=4090)	AMR101 vs. Placebo HR (95% C.I.)	P-value
CV Death	174 (4.3)	213 (5.2)	0.803 (0.657, 0.981)	0.03
Nonfatal MI	237 (5.8)	332 (8.1)	0.697 (0.590, 0.823)	< 0.0001
Nonfatal Stroke	85 (2.1)	118 (2.9)	0.708 (0.536, 0.936)	0.01
Coronary Revascularization	376 (9.2)	544 (13.3)	0.664 (0.583, 0.758)	< 0.0001
Hospitalization for Unstable Angina	108 (2.6)	157 (3.8)	0.679 (0.531, 0.868)	0.002

[Source: CSR (Page 137) and Statistical Reviewer's Analysis]

Table 7 below characterizes the follow-up. The percentage of patients enrolled in the study who experienced a 5-point MACE event is 19.6%, while 69% of patients were followed through the end of study (EOS) without experiencing an event. The percentage of patients who were censored for a non-CV death was 1.4%. About 10% of patients were lost-to-follow up before experiencing an event (i.e., censored before the EOS).

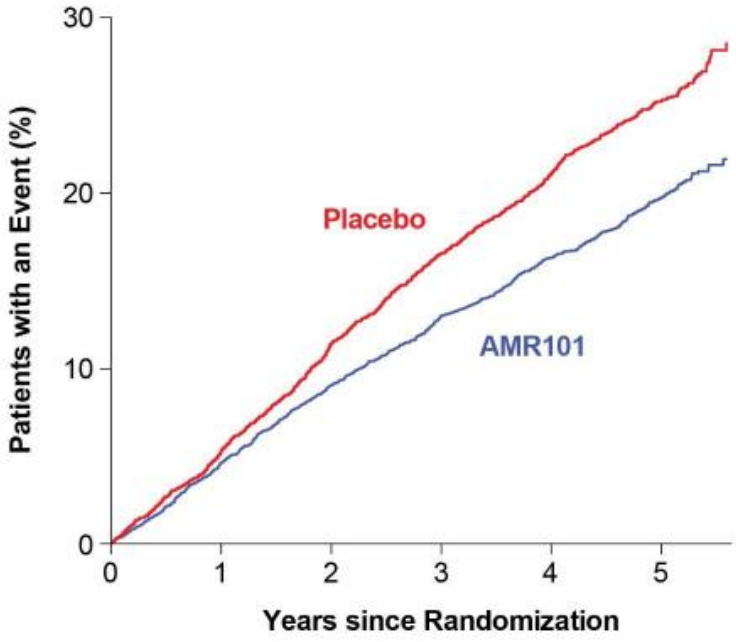
Table 7: Characterization of Follow-Up

Follow-up for 5-point MACE	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Total (N=8179) n (%)
5-point MACE Event	705 (17.2)	901 (22.0)	1606 (19.6)
Censored at EOS Without any 5-point MACE Event	2931 (71.7)	2712 (66.3)	5643 (69.0)
Censored for non-CV Death	57 (1.4)	54 (1.3)	111 (1.4)
Censored Before EOS (Missing Follow-Up)	396 (9.7)	423 (10.3)	819 (10.0)

[Source: Response to FDA Information Request dated 7/2/19 (Page 10) and Statistical Reviewer's Analysis]
Note: Subjects who died due to a non-CV Death cause or with the last contact date during the study close-out (01Mar2018-31May2018) were considered as completers

Figure 4 displays the Kaplan-Meier estimates for time to first occurrence of 5-point MACE by treatment groups.

Figure 4: Kaplan-Meier Estimate of First Occurrence of 5-point MACE



No. at Risk						
Placebo	4090	3743	3327	2807	2347	1358
AMR101	4089	3787	3431	2951	2503	1430

[Source: CSR (Page 133) and Statistical Reviewer's Analysis]

FDA Statistical Reviewer's Analysis of the Primary Endpoint

A multiple imputation analysis was performed to assess the impact of missing follow-up data on the primary analysis using data from retrieved drop-outs. Retrieved drop-outs were defined as patients who discontinued treatment and who did not experience a 5-point MACE prior to treatment discontinuation and remained in study until occurrence of a 5-point MACE event or EOS.

The retrieved drop-out set is comprised of 1455 patients (665 from AMR101 and 790 from placebo), which includes 285 (126 from AMR101 and 159 from placebo) patients who experienced a 5-point MACE occurrence, plus 1170 patients who were followed until EOS without experiencing any 5-point MACE event.

The imputation model was a piece-wise exponential time model which utilized the observed time to 5-point MACE data from the retrieved drop-out population. The assumption is that event rate of patients who were lost to follow-up was like that of retrieved drop-outs. The imputed remaining time to an event was integrated with the observed data to generate 100 datasets. The primary efficacy model for each imputed dataset was run and inference for the hazard ratio and 95% CI was made using Rubin's

rule. Table 8 below displays the results of the analysis. The hazard ratio and 95% CI is 0.776 and (0.707, 0.852), similar to the protocol specified analysis.

Table 8: Multiple Imputation Analysis of 5-point MACE

	AMR101 (N=4089)	**Placebo (N=4090)**	**AMR101 vs. Placebo HR (95% C.I.)**
Without Imputation	705 (17.2)	901 (22.0)	0.752 (0.682, 0.830)
MI Piecewise			0.776 (0.707, 0.852)
Imputed event number: median (min, max)	90 (62, 125)	91 (52, 117)	

[Source: Response to FDA Information Request dated 9/17/19 (Page 3) and Statistical Reviewer's Analysis]

FDA Tipping Point Analysis

A tipping point analysis was performed to address the impact of missing follow-up and to evaluate under which conditions the results tip to a non-significant result. The event rates chosen for the tipping point analysis were based on the following reference groups:

1. Overall placebo group. The estimated hazard rate is 57.44 per 1,000 patient-years.

2. Patients who were ODIS at any time during the study; pooled from both placebo and AMR101 groups. The estimated hazard rate is 61.55 per 1,000 patient-years

3. First year post-randomization data for patients who were ODIS at any time during the study; pooled from both placebo and AMR101 groups. The estimated hazard rate is 56.03 per 1,000 patient-years

4. Patients within the first year of study; pooled from both placebo and AMR101 groups. The estimated hazard rate is 48.45 per 1,000 patient-years

Table 9 displays the results of the tipping point analysis. The event rate in the AMR101 group needs to be between 3.7 to 4.3 times greater than the event rate in the placebo group to tip to a non-significant result (depending on the reference group). Therefore, we conclude the efficacy findings based on the pre-specified analysis remain robust.

Table 9: Tipping Point Analysis of 5-point MACE

Event rate per 1000 patient-years for Placebo arm		Hazard Ratio					
	Statistic	2.80	3.10	3.40	3.70	4.00	4.30
57.44 [1]	HR	0.87	0.88	0.89	0.91	0.92	0.93
	CI	(0.79, 0.95)	(0.80, 0.97)	(0.81, 0.98)	(0.82, 1.00)	(0.83, 1.01)	(0.85, 1.02)
	p-value	0.0037	0.0090	0.0204	0.0403	0.0747	0.1250
61.55 [2]	HR	0.87	0.89	0.90	0.92	0.93	0.94
	CI	(0.79, 0.96)	(0.81, 0.98)	(0.82, 0.99)	(0.83, 1.01)	(0.84, 1.02)	(0.85, 1.03)
	p-value	0.0055	0.0142	0.0321	0.0629	0.1183	0.1941
56.03 [3]	HR	0.87	0.88	0.90	0.91	0.92	0.93
	CI	(0.79, 0.96)	(0.80, 0.97)	(0.81, 0.99)	(0.82, 1.00)	(0.84, 1.01)	(0.85, 1.02)
	p-value	0.0047	0.0116	0.0243	0.0489	0.0856	0.1403
48.45 [4]	HR	0.86	0.87	0.88	0.89	0.90	0.91
	CI	(0.78, 0.94)	(0.79, 0.96)	(0.80, 0.97)	(0.81, 0.98)	(0.82, 0.99)	(0.83, 1.01)
	p-value	0.0016	0.0042	0.0093	0.0191	0.0352	0.0606

[1] Placebo
[2] All treatments ever ODIS
[3] All treatments first year ODIS
[4] All treatments first year
Assumed hazard rates for Placebo missing follow-up are shown in the first column.
Assumed Hazard Ratios for the missing follow-up in AMR101/Placebo are shown in the first row.
Resulting Hazard Ratios, 95% Confidence Intervals, and p-values are based on the observed + imputed datasets.
[Source: Response to FDA Information Request dated 9/17/19 (Page 7-8) and Statistical Reviewer's Analysis]

Primary Endpoint and its Components – Event Rates

Table 10 summarizes the event rates for the primary endpoint and components by arm. In this analysis, the event rates for the individual components of the primary endpoint were analyzed as independent endpoints (e.g. event rate of nonfatal MI, regardless of the rate of any other endpoint).

Table 10: Event Rates for Individual Components of the Primary Endpoint, ITT Population

Endpoint	Number of Participants	Overall Event Rate per 1000 Patient-Years	
		AMR101	Placebo
Primary Composite Endpoint	8179	43.4	57.4
CV Death	8179	9.9	12.2
Nonfatal MI	8179	13.9	19.8
Nonfatal Stroke	8179	4.9	6.9
Coronary Revascularization	8179	22.5	33.7
Hospitalization for Unstable Angina	8179	6.2	9.2
Source: Applicant response to information request 25 June 2019.			

Key Secondary and Other Secondary Endpoints

Table 11 below shows the results of the key secondary endpoint (3-point MACE). When comparing AMR101 to placebo, the hazard ratio for time to first occurrence of 3-point MACE is 0.735 with a 95% CI of (0.651, 0.830); hence, there was a significant reduction in 3-point MACE. As with 5-point MACE, we see that nonfatal MI had the largest contribution of events.

Table 11: Time to the First Occurrence of 3-point MACE

	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	AMR101 vs. Placebo HR (95% C.I.)	P-value
3-Point MACE	459 (11.2)	606 (14.8)	0.735 (0.651, 0.830)	< 0.0001
Components Contribution to 3-point MACE				
CV Death	149 (3.6)	167 (4.1)		
Nonfatal MI	230 (5.6)	325 (7.9)		
Nonfatal Stroke	80 (2.0)	114 (2.8)		

[Source: CSR (Page 134) and Statistical Reviewer's Analysis]

Table 12 shows the results of other secondary endpoints (listed in the order in which they were tested). The only secondary endpoint that was not significant was total mortality.

Table 12: Time to the First Occurrence of Other Secondary Endpoints

Endpoint	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	AMR101 vs. Placebo HR (95% C.I.)	P-value
CV Death or Nonfatal MI	392 (9.6)	507 (12.4)	0.753 (0.660, 0.859)	< 0.0001
All MI	250 (6.1)	355 (8.7)	0.688 (0.585, 0.808)	< 0.0001
Urgent or Emergent Revascularization	216 (5.3)	321 (7.8)	0.653 (0.550, 0.776)	< 0.0001
CV Death	174 (4.3)	213 (5.2)	0.803 (0.657, 0.981)	0.0315
Hospitalization for Unstable Angina	108 (2.6)	157 (3.8)	0.679 (0.531, 0.868)	0.0018
All Stroke	98 (2.4)	134 (3.3)	0.720 (0.555, 0.934)	0.0129
Mortality, Nonfatal MI, or Nonfatal Stroke	594 (13.4)	690 (16.9)	0.772 (0.690, 0.864)	< 0.0001
Mortality	274 (6.7)	310 (7.6)	0.870 (0.739, 1.023)	0.0915

[Source: CSR (Page 139) and Statistical Reviewer's Analysis]

Discussion of Individual Components

Myocardial Infarction (MI)

The proportion of the types of nonfatal MI that contributed to the primary composite endpoint were similar between the two treatment arms. Nearly all MIs were non-procedural (spontaneous or silent MIs).

Table 13: Summary of First Occurrence of Nonfatal MI Contributing to Primary Composite Endpoint by Type

	First Occurrence of Nonfatal MI Contributing to the Primary Composite Endpoint N (%)		
Type of MI	Total (N=485)	AMR101 (N=205)	Placebo (N=280)
Spontaneous MI	436 (89.9%)	183 (89.3%)	253 (90.4%)
PCI-related MI	3 (0.6%)	0 (0.0%)	3 (1.1%)
CABG-related MI	0 (0.0%)	0 (0.0%)	0 (0.0%)
Silent MI	42 (8.7%)	22 (10.7%)	20 (7.1%)
Missing	4 (0.8%)	0 (0.0%)	4 (1.4%)
Overall	485 (100.0%)	205 (100.0%)	280 (100.0%)

MI= Myocardial Infarction; PCI=Percutaneous Coronary Intervention; CABG=Coronary Artery Bypass Grafting.
Source: Applicant response to information request 22 May 2019.

Stroke

As noted above, there was a reduced risk of ischemic stroke in the AMR101 arm compared with the placebo arm. There was no significant difference in the incidence of hemorrhagic strokes between arms, but the small number of events limits interpretation of the analysis. The imbalance in events favored placebo (more hemorrhagic stroke events in the AMR101 arm). Bleeding was a safety signal that emerged from REDUCE-IT and is discussed in the safety section of this document. Table 14 summarizes strokes by category.

Table 14: Stratified Analysis of Time to Stroke Endpoints from Date of Randomization, ITT Population

				Rate/1000 patient-years	
Endpoint	**AMR101 (N=4089)**	**Placebo (N=4090)**	**HR (95% CI)**	**AMR101**	**Placebo**
Any Stroke	98 (2.4%)	134 (3.3%)	0.720 (0.555, 0.934)	5.6	7.8
Nonfatal Stroke	85 (2.1%)	118 (2.9%)	0.708 (0.536, 0.936)	4.9	6.9
Fatal Stroke	14 (0.3%)	18 (0.4%)	0.767 (0.382, 1.543)	0.8	1.0
Ischemic Stroke	80 (2.0%)	122 (3.0%)	0.644 (0.486, 0.854)	4.6	7.1
Hemorrhagic Stroke	13 (0.3%)	10 (0.2%)	1.284 (0.563, 2.929)	0.7	0.6
Source: Adapted from REDUCE-IT CSR, Section 14, Table 14.2.1.6.1, p. 689/2510					

Coronary Revascularization

There were 189 coronary revascularizations in the AMR101 treatment arm and 244 coronary revascularizations in the placebo arm that contributed to the primary composite endpoint. Most of these revascularizations (approximately 78%) were elective. Approximately 81% of all revascularization procedures were percutaneous coronary interventions (PCI). Table 15 summarizes the number and percent of the types of coronary revascularizations that contributed to the primary composite endpoint by treatment arm.

Table 15: Summary of First Occurrence of Coronary Revascularization Contributing to Primary Composite Endpoint by Type and Percent

		First Occurrence of Coronary Revascularizations Contributing to the Primary Composite Endpoint N (%)		
Type of Coronary Revascularization	Status of Coronary Revascularization	Total (N=433)	AMR101 (N=189)	Placebo (N=244)
CABG	Emergent	2 (0.5%)	1 (0.5%)	1 (0.4%)
	Urgent	13 (3.0%)	6 (3.2%)	7 (2.9%)
	Elective	68 (15.7%)	30 (15.9%)	38 (15.6%)
	Salvage	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Total	83 (19.2%)	37 (19.6%)	46 (18.9%)
PCI	Emergent	13 (3.0%)	4 (2.1%)	9 (3.7%)
	Urgent	65 (15.0%)	28 (14.8%)	37 (15.2%)
	Elective	271 (62.6%)	120 (63.5%)	151 (61.9%)
	Salvage	1 (0.2%)	0 (0.0%)	1 (0.4%)
	Total	350 (80.8%)	152 (80.4%)	198 (81.1%)
Overall	Emergent	15 (3.5%)	5 (2.6%)	10 (4.1%)
	Urgent	78 (18.0%)	34 (18.0%)	44 (18.0%)
	Elective	339 (78.3%)	150 (79.4%)	189 (77.5%)
	Salvage	1 (0.2%)	0 (0.0%)	1 (0.4%)
	Total	433 (100.0%)	189 (100.0%)	244 (100.0%)

Note: If multiple revascularizations occured on the same day for a subject, then the hierarchy of revascularizations for determination of firstness is (Salvage -> Emergent -> Urgent -> Elective)
Note: One subject ((b) (6) with Elective (PCI) and Emergent (PCI) revascularizations is included in the Emergent (PCI) count.
PCI=Percutaneous Coronary Intervention; CABG=Coronary Artery Bypass Grafting

Source: Applicant submission in response to information request on 22 May 2019.

Total Mortality

Table 16 below characterizes the follow-up and missing follow-up with respect to mortality. In total, 7.9% patients died from any cause in the study; 7.1% while enrolled in the study and 0.7% were confirmed through a public's records search.

Table 16: Characterization of Follow-Up Mortality

Follow-up for Mortality	AMR101 (N=4089)	Placebo (N=4090)	Total (N=8179)
Mortality [n(%)]	302 (7.4)	341 (8.3)	643 (7.9)
Death While in Study [n(%)]	274 (6.7)	310 (7.6)	584 (7.1)
Death Confirmed Through Public Record Search [n(%)]	28 (0.7)	31 (0.8)	59 (0.7)
Alive [n(%)]	3781 (92.5)	3736 (91.3)	7517 (91.9)
Alive While in Study [n(%)]	3628 (88.7)	3531 (86.3)	7159 (87.5)
Alive Confirmed Through Public Record Search [n(%)]	153 (3.7)	205 (5.0)	358 (4.4)
Unknown [n(%)]	6 (0.1)	13 (0.2%)	19 (0.2)

[Source: Response to FDA Information Request dated 7/2/19 (Page 12) and Statistical Reviewer's Analysis]

Of the 8179 patients in the ITT population, 584 died during the study, and the CEC classified 197 of these as non-CV deaths. There were no meaningful imbalances between arms in non-CV deaths overall, with 100 (2.5%) in the AMR101 arm and 97 (2.4%) in the Placebo arm.

The most common individual causes of non-cardiovascular death were consistent with the patient population. The majority consisted of cancer deaths (lung, pancreas, colon and rectal) followed by serious infections (pneumonia and sepsis) and all other causes. Table 17 summarizes PTs under the SOC – Neoplasms benign, malignant and unspecified (including cysts and polyps) occurring in more than one patient in either arm, and Table 18 summarizes PTs (excluding Neoplasms) occurring in more than one patient in either treatment arm.

The imbalance in death due to renal cancer (encompassing two PTs: Renal cancer and Renal cancer metastatic) is most likely a chance finding. To investigate this category further, we reviewed TEAEs under the MedDRA High Level Term (HLT) Renal malignant neoplasms (encompassing 5 PTs) and found them to be more balanced, with 11 (0.3%) patients with TEAEs under this category in the AMR101 arm versus 10 (0.2%) in placebo.

Table 17: CEC Adjudicated Non-Cardiovascular Causes of Death Occurring in More Than One Patient by MedDRA Preferred Terms and Treatment Arm within the MedDRA SOC – Neoplasms benign, malignant, and unspecified, Safety Population

System Organ Class, n (%) Preferred Term, n (%)	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)
Neoplasms, benign malignant and unspecified	**58 (1.4)**	**53 (1.3)**	**111 (1.4)**
Lung cancer cell type unspecified*	12 (0.29)	12 (0.29)	24 (0.29)
Non-small cell lung cancer*	7 (0.17)	7 (0.17)	14 (0.17)
Pancreatic carcinoma*	7 (0.17)	6 (0.15)	13 (0.16)
Colon and rectal cancers*	4 (0.10)	6 (0.15)	10 (0.12)
Gastric cancer*	4 (0.10)	2 (0.05)	6 (0.07)
Prostate cancer*	3 (0.07)	3 (0.07)	6 (0.07)
Acute myeloid leukemia	2 (0.05)	3 (0.07)	5 (0.06)
Renal cancer*	4 (0.10)	0 (0.00)	4 (0.05)
Metastases to liver	2 (0.05)	2 (0.05)	4 (0.05)
Hepatic cancers*	1 (0.02)	2 (0.02)	3 (0.04)
Breast cancer metastatic	2 (0.05)	0 (0.00)	2 (0.02)
Bladder carcinomas*	2 (0.05)	0 (0.00)	2 (0.02)
Esophageal carcinoma*	1 (0.02)	1 (0.02)	2 (0.02)
Neoplasm malignant	0 (0.00)	2 (0.05)	2 (0.02)

Source: Applicant Response to Information Request 29 Aug 2019
[*} More than one individual PTs were combined (e.g. Lung cancer metastatic, Lung neoplasm malignant, and Lung cancer cell type unspecified)
Abbreviations: CV = Cardiovascular; CEC = Clinical Endpoint Committee; SOC = System Organ Class; PT = Preferred Term; CSR = Clinical Study Report.

Table 18: CEC Adjudicated Non-Cardiovascular Cause of Death Occurring in More than One Patient by MedDRA Preferred Terms and Treatment Arm – Excluding Neoplasms, Safety Population

Preferred Term, n (%) [1]	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)
Death	6 (0.15)	8 (0.20)	14 (0.17)
Pneumonia	9 (0.22)	4 (0.10)	13 (0.16)
Sepsis*	5 (0.12)	4 (0.10)	9 (0.11)
Acute respiratory failure	1 (0.02)	3 (0.07)	4 (0.05)
Chronic obstructive pulmonary disease	1 (0.02)	2 (0.05)	3 (0.04)
Respiratory failure	1 (0.02)	2 (0.05)	3 (0.04)
Cardio-respiratory arrest	1 (0.02)	3 (0.07)	4 (0.05)
Urosepsis	1 (0.02)	2 (0.05)	3 (0.04)
Completed suicide	1 (0.02)	2 (0.05)	3 (0.04)
Cardiac arrest	0 (0.00)	3 (0.07)	3 (0.04)
Drowning	2 (0.05)	0 (0.00)	2 (0.02)
Gastrointestinal haemorrhage	2 (0.05)	0 (0.00)	2 (0.02)
Pneumonia aspiration	1 (0.02)	1 (0.02)	2 (0.02)

Source: Applicant Response to Information Request 29 Aug 2019
[1] All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
If multiple events were associated with a patient's non-CV death, the patient is counted only once in each distinct PT.
[*] Indicates more than one individual PTs were combined (e.g. Sepsis and Septic Shock)
Abbreviations: CV = Cardiovascular; CEC = Clinical Endpoint Committee; SOC = System Organ Class; PT = Preferred Term; CSR = Clinical Study Report.

Alignment Between Investigators and CEC

The Agency requested the Applicant provide data regarding the concordance between investigator-reported events and CEC-confirmed events. Table 19 summarizes the concordance between investigator-reported cases and the CEC by treatment arm as well as ascertainment by investigators of potential endpoints (as opposed to other triggering methods, such as programmatic review of AEs/SAEs/hospitalizations). The relatively low concordance among MI, and Unstable angina most likely reflects good ascertainment of cases overall with discrepancies due to data available to adjudicators (ECG, laboratory) subsequent to the initial referral by the investigator. No systematic bias (AMR101 vs. placebo) is apparent from these data.

Table 19: Investigator-Reported vs. CEC-Confirmed Events

	AMR101		Placebo	
Event	Percent of Investigator-Reported Events Confirmed by CEC	Percent of Total Confirmed Events Initially Reported by Investigator	Percent of Investigator Reported Events Confirmed by CEC	Percent of Total Confirmed Events Initially Reported by Investigator
Death	278/279 (99.6%)	278/279 (99.6%)	309/313 (98.7%)	309/313 (98.7%)
Non-fatal MI	218/ 332 (65.7%)	218/308 (70.8%)	332/483 (68.7%)	332/450 (73.8%)
Non-fatal Stroke	97/130 (74.6%)	97/108 (89.8%)	135/175 (77.1%)	135/154 (87.7%)
Coronary Revascularization	469/479 (97.9%)	469/473 (99.2%)	720/733 (98.2%)	720/731 (98.5%)
Unstable Angina Requiring Hospitalization	118/377 (31.3%)	118/122 (96.7%)	167/491 (34.0%)	167/177 (94.4%)
Total MACE	1207/1570 (76.9%)	1207/1290 (93.6%)	1705/2153 (79.2%)	1705/1825 (93.4%)

Source: Derived from 22 May 2019 response to information request. Note: Investigators were not specifically required to denote whether an event was CV or non-CV death. The above table shows concordance/discordance for all deaths (irrespective of CV cause or not). Note: Percentages are based on total number of events identified by the investigator (regardless of CEC adjudication decision) and positively adjudicated events identified by the CEC.

Findings in Special/Subgroup Populations

This section summarizes results from the analysis of the primary endpoint within subgroup levels. The subgroup levels explored are:

- Risk category (Risk Cohort 1; Risk Cohort 2)
- Sex (Male; Female)
- Age (<65; ≥ 65)
- Race (White; Non-White)

Subgroup Analyses Results

Table 20 below display the results of the subgroup analysis for risk category, sex, age and race. There is no significant interaction in risk category, sex, and race. There is a significant interaction for age. However, this interaction is not qualitative.

Table 20: Subgroup Analysis of Time to First Occurrence of 5-point MACE

Group	Category	AMR101 n/N (%)	Placebo n/N (%)	HR (95% C.I.)	Interaction P-value
Risk Category	Risk Cohort 1	559/2892 (19.3)	738/2893 (25.5)	0.726 (0.650, 0.810)	0.1388
	Risk Cohort 2	146/1197 (12.2)	163/1197 (13.6)	0.876 (0.700, 1.095)	
Sex	Male	551/2927 (18.8)	715/2895 (24.7)	0.732 (0.655, 0.818)	0.3264
	Female	154/1162 (13.3)	186/1195 (15.6)	0.818 (0.661, 1.013)	
Age	< 65 Years	322/2232 (14.4)	460/2184 (21.1)	0.650 (0.564, 0.750)	0.0037
	≥ 65 Years	383/1857 (20.6)	441/1906 (23.1)	0.873 (0.761, 1.001)	
Race	White	646/3691 (17.5)	812/3688 (22.0)	0.768 (0.693, 0.852)	0.1797
	Non-White	59/398 (14.8)	89/401 (22.2)	0.598 (0.429, 0.832)	

[Source: CSR (Page 180, 182) and Statistical Reviewer's Analysis]

Cardiovascular Risk Stratum – Characteristics and Discussion

REDUCE-IT enrolled patients in two different risk categories:

- CV Risk Category 1: patients with **established CVD** as defined by the inclusion criteria
- CV Risk Category 2: patients with **diabetes and at least one additional risk factor** for CVD, but no established CVD

CV Risk category was a stratification variable used in hazard ratio comparisons between treatment arms, but evaluation of outcomes in the Risk Categories was not prespecified. The effect size for the primary endpoint was numerically lower for Risk Cohort 2 versus Risk Cohort 1, but the confidence intervals overlap: 12% estimated risk reduction vs. 27%, respectively. The 95% CI for the HR for Risk Cohort 2 included 1.0.

The estimates of the effect sizes for the key secondary endpoint were numerically more similar between risk cohorts (19% versus 28% relative risk reduction), although the confidence interval again crossed 1.0 for Cohort 2 (HR 0.81; 95% CI 0.62, 1.06). In Risk Cohort 1, the HR was 0.72 (95% CI: 0.63, 0.82), similar to the values for the overall population (HR 0.74; 95% CI: 0.65, 0.83).

Approximately 5,785 patients were in the Risk Category 1 (Established CVD) and 2,384 patients were in Risk Category 2 (DM plus Risk Factors). Table 21 summarizes the baseline characteristics by Risk Category.

Table 21: Baseline Characteristics by Risk Category

	Risk Category 1 Established CVD	Risk Category 2 DM plus Risk Factors
	N=5875	**N=2394**
Demographics		
Age (years)	63.2	63.7
Male	78.4%	53.7%
Race		
White	92.5%	84.7%
Black or African American	1.3%	3.6%
Asian	4.2%	8.4%
Region		
Westernized	68.8%	76.4%
Eastern Europe	28.8%	18.3%
Asia Pacific	2.4%	5.2%
Medical History		
Current Smoker	16.5%	11.9%
Hypertension	97.8%	95.7%
CHF	21.0%	9.6%
Diabetes	41.2%	99.2%
Duration (years) - Mean	8.55	9.44
Retinopathy	3.2%	5.9%
Nephropathy	1.2%	2.6%
Neuropathy	6.4%	14.7%
Myocardial Infarction	63.8%	5.3%
Unstable Angina	32.5%	6.3%
Coronary Revascularization		
PCI	55.8%	7.6%
CABG	30.5%	3.1%
Stroke	13.7%	4.9%
Carotid Revascularization	3.5%	0.4%
Peripheral Revascularization	6.0%	0.8%
ABI <0.9 Without Intermittent Claudication	2.7%	0.8%
ABI <0.9 With Intermittent Claudication	5.0%	0.2%

Table 21 Continued

	Risk Category 1 Established CVD	Risk Category 2 DM plus Risk Factors
	N=5875	**N=2394**
Medications		
Insulin	9.3%	24.4%
Sulfonylurea	15.1%	41.4%
Metformin	28.0%	81.5%
Statin Intensity		
Moderate	60.3%	67.6%
High	35.2%	20.0%
Ezetimibe	7.5%	3.9%
Anti-thrombotic	94.9%	62.8%
RAAS Inhibitor	76.8%	79.4%
Beta blocker	80.0%	48.1%
Diuretics	37.3%	48.4%
Calcium channel blocker	28.2%	29.3%
Vital Signs		
Median BMI (kg/m2)	30.3	32.4
Systolic BP (mmHg) - Mean	132.6	132.7
Diastolic BP (mmHg) - Mean	78.4	77.3
Laboratory		
HbA1C (%) – Mean	6.35%	7.17%
eGFR (ml/min/1.73m2) - Mean	74.1	75.3
Total Cholesterol (mg/dL) - Median	159.5	158.5
Triglycerides (mg/dL) - Median	219.0	210.0
HDL-C (mg/dL) - Median	39.5	41.0
LDL-C (mg/dL) – Median	76.0	74.0
hs-CRP (mg/L) – Median	2.04	2.55
Source: Applicant response to Information Request 25 June 2019 and 16 October 2019		

Risk Cohort 1 (Established CVD) had more males, fewer non-white patients, and more patients form Eastern Europe than Risk Cohort 2 (Diabetes). Mean age was similar in both cohorts. A higher proportion of patients in Risk Cohort 1 were smokers.

Nearly all (99.2%) of patients in Risk Cohort 2 had diabetes mellitus versus 41.2% in Risk Cohort 1. The mean duration of diabetes was longer in Risk Cohort 2, a greater proportion of patients were on diabetes medications, and a greater proportion had microvascular complications, such as retinopathy, nephropathy, and neuropathy. Baseline HbA1C was higher in Risk Cohort 2.

Baseline lipid parameters were similar in both arms, although median plasma triglycerides were slightly lower in Risk Cohort 2 (Diabetes plus Risk Factors). Median C-reactive protein and mean eGFR was similar in both arms.

The Applicant uses the terms "Primary Prevention Cohort" to describe Risk Cohort 2, but this term is a misnomer. Review of the dataset revealed that some patients in the cohort had established CVD by history, although the precise number is unclear as the categories (including MI 5%, Stroke 5%, PCI 7.6%, CABG 3%) are not mutually exclusive.

Rate of events in Risk Cohorts

Overall, Risk Cohort 1 (Established CVD) had higher event rates for both the composite endpoints and their components compared with Risk Cohort 2 (Diabetes plus Risk Factors). Table 22 summarizes the event rates in the two cohorts.

Table 22: Rates of Events by Risk Cohort, ITT Population

	Event rate (95% CI) per 1000 patient-years	
Endpoint	**Risk Cohort 1 (Established CVD) (N=5785)**	**Risk Cohort 2 (DM + Risk Factors) (N=2394)**
Primary Composite Endpoint	59.5 (45.8, 77.2)	30.5 (21.1, 44.0)
Key Secondary Endpoint	36.9 (26.1, 51.0)	20.7 (13.0, 32.1)
CV Death	12.3 (6.2, 21.0)	8.2 (3.5, 15.8)
Nonfatal MI	20.4 (12.2, 30.9)	8.8 (4.1, 17.1)
Nonfatal Stroke	6.3 (2.2, 13.1)	4.9 (1.6, 11.7)
Coronary Revascularization	34.2 (23.5, 47.5)	14.5 (8.4, 24.7)
Hospitalization for Unstable Angina	10.0 (4.8, 18.4)	2.7 (0.6, 8.8)
Total Mortality	18.7 (11.4, 29.7)	12.1 (6.2, 21.0)
Source: Applicant Response to information request 25 June 2019. CV=Cardiovascular; MI=Myocardial Infarction		

Other Subgroup Analyses of the Primary Endpoint

The primary composite endpoint was analyzed by various subgroups, including baseline lipid medications, and laboratory parameters. There were no significant interactions for most parameters. Sample size limits interpretation of a trend suggesting absence of a favorable effect in patients on low intensity or no statin. Statin intensity categories at Baseline were as defined in the American College of Cardiology/ American Heart Association Cholesterol Guidelines summarized in Table 23. Figure 5 on the following pages summarizes analyses of subgroups.

Table 23: 2013 ACC/AHA Guideline for Statin Intensity Classification

	Intensity		
Statin	**High**	**Moderate**	**Low**
Atorvastatin	≥40 mg	10 to <40 mg	<10 mg
Rosuvastatin	≥20 mg	5 to <20 mg	<5 mg
Simvastatin	80 mg	20 to <80 mg	<20 mg
Pravastatin		≥40 mg	<40 mg
Lovastatin		≥40 mg	<40 mg
Fluvastatin		80 mg	<80 mg
Pitavastatin		≥2 mg	<2 mg

Total daily doses

Source: Stone SJ, et al. Circulation. 2014;129[suppl 2]:S1-S45

Figure 5: Forest Plots of Analyses of the Primary Composite Endpoint by Subgroups, ITT Population

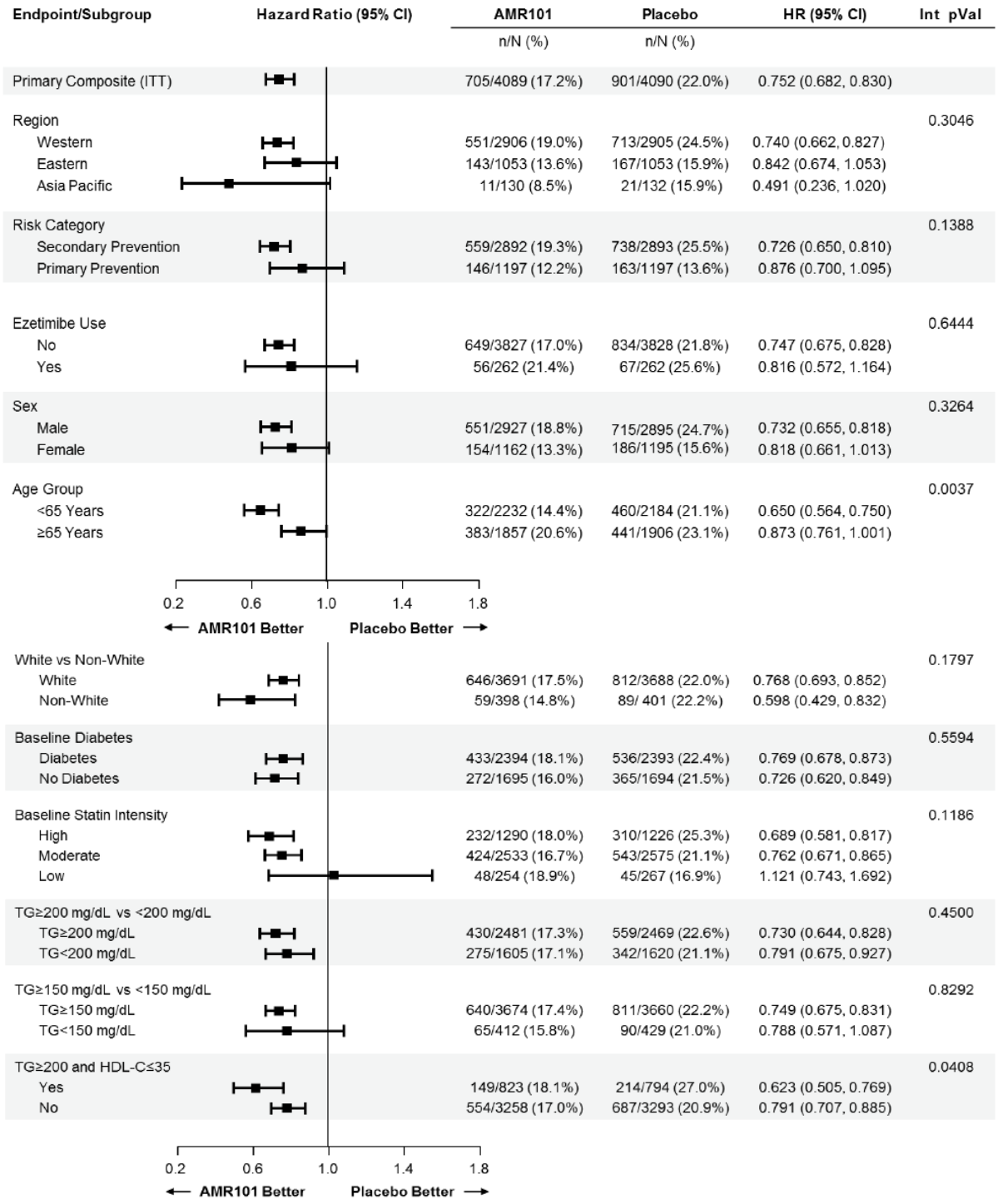
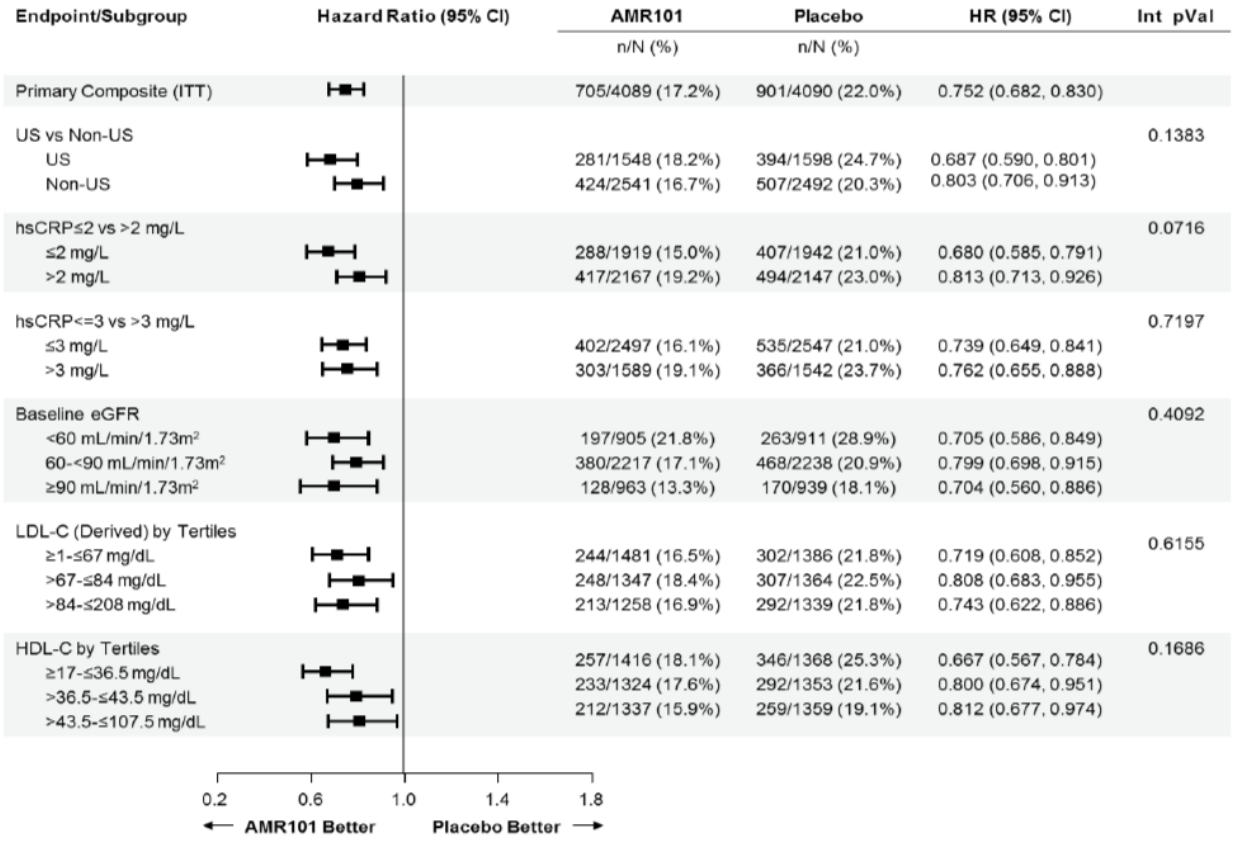


Figure 5 (continued): Forest Plots of Analyses of the Primary Composite Endpoint by Subgroups, ITT Population



Abbreviations: CI = confidence interval; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; hsCRP = high-sensitivity C-reaction protein; Int = interaction; ITT = Intent-to-Treat; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; pVal = p-value; US = United States; vs = versus.
Source: REDUCE-IT CSR, Table 11-16 to 11-18, p. 180-184/354

4.3. **Patient population and proposed indication**

The applicant is seeking an indication for Vascepa as an adjunct to statin therapy in adult patients with elevated triglyceride levels (TG $\geq$135 mg/dL) and other risk factors for CVD, but the trial inclusion criteria and data do not appear to support such a broad population.

The trial provides strong evidence that AMR101 is beneficial in patients with established CVD and persistently elevated triglycerides despite optimized statin therapy, as these patients accounted for about 70% of the patients in the trial. While it appears that AMR101 is also beneficial in a subset of patients aged 50 or greater with diabetes, additional CV risk factors, and hypertriglyceridemia (despite optimized statin therapy), it is arguable how broadly this second population should be drawn.

The applicant's proposed indicated population is notably silent on several issues including appropriate patient age, presence of established CVD, presence of diabetes in patients without established CVD, statin intensity, and resulting LDL-C levels on therapy.

The planned population in REDUCE-IT was considerably narrower than the proposed indicated population. To this point, the trial had three key inclusion criteria:

- Fasting triglyceride >200 mg/dL (following the first protocol amendment in 2013)
- LDL-C >40 mg/dL but $\leq$100 mg/dL on stable statin therapy
- Established CVD or high risk for CVD recruited in 2 risk cohorts

Cohort 1 was planned to account for 70% of patients in the trial, and included patients aged 45 and older with established CVD (diagnosed due to prior CV event, revascularization procedure, or imaging study). Cohort 2 was planned to account for 30% of the trial population, and included men and women aged 50 and older with diabetes mellitus and one or more additional risk factors (such as age, smoking, hypertension, retinopathy, and albuminuria).

Baseline characteristics suggest that the actual trial population was narrower than defined. For example, although as planned, 30% of the total population met enrollment criteria per the Cohort 2 definition, baseline characteristic data reveal that:

- 99% of patients had diabetes
- 95% had hypertension or were taking antihypertensive medication
- 68% met age criteria for an additional risk factor

Therefore, most patients in Cohort 2 had diabetes plus at least two additional risk factors, as defined. Additionally, the rate of established CVD in the diabetes cohort was not insignificant, including patients with prior MI, stroke, and revascularization.

Furthermore, not only did most patients had baseline triglycerides 200 mg/dL or greater but approximately 72% were 175 mg/dL or greater, significantly higher than the proposed threshold of 135 mg/dL. More importantly, these triglyceride levels were achieved in a population in which 88% of patients were on either moderate- or high-intensity statin therapy with adequate control of LDL-C.

In summary, the trial population represents a higher risk group than the proposed indicated population, encompassing patients with diabetes and additional risk factors, and hypertriglyceridemia despite optimized statin therapy. There is no evidence in REDUCE-IT that AMR101 is the appropriate therapy in lower-risk patients who may have elevated LDL-C in addition to mild hypertriglyceridemia and who would benefit from optimization of statin therapy first.

4.4. **Effects on biomarkers – PK and PD endpoints**

Overview

EPA: Although PK samples for measuring EPA serum concentrations were collected in the REDUCE-IT trial, the concentration results were considered unreliable because the stability of collected PK samples was not covered by the long-term stability established in the validated bioanalytical assay.

Icosapent ethyl is de-esterified during the absorption process, and the active metabolite EPA is absorbed in the small intestine and enters the systemic circulation mainly via the thoracic duct lymphatic system. EPA is mainly metabolized by the liver via beta-oxidation similar to dietary fatty acids. Conversion of EPA to docosahexaenoic acid [DHA, 22:6 (n-3)] in the human body is negligible. The plasma elimination half-life of EPA is approximately 89 hours. EPA does not undergo renal excretion.

PK was not listed as an endpoint in the protocol of the REDUCE-IT trial. Nevertheless, blood samples for measuring pre-dose EPA serum concentration were collected at baseline, Year 1, and the last visit. Almost all the PK samples were stored at -20°C or -70°C for at least 30 days before the measurement of EPA concentration. However, since the long-term stability of the validated bioanalytical assay for measuring EPA serum concentrations was only established up to 30 days, we did not review the PK results from REDUCE-IT.

LDL: An increase of LDL-C from baseline (10-13%) was observed in the placebo (mineral oil) group, which raised the question if mineral oil interfered with statin absorption and if an increase of LDL-C in placebo group contributed to the overall AMR101 treatment effect size compared to placebo. In the absence of a dedicated drug-interaction study, indirect evidence suggests the presence of a potential inhibitory effect on statin absorption by mineral oil. However, an exploratory analysis indicates that the effect of LDL-C values on the time to the primary endpoint is numerically small and unlikely to change the overall conclusion of treatment benefit.

Hs-CRP: Among all the biomarkers recorded in REDUCE-IT trial, hs-CRP demonstrated the greatest percentage increase from baseline (32%) in placebo group (Table 24). An exploratory analysis indicates that despite this remarkable percentage increase from baseline for hs-CRP, the change in hs-CRP had only a negligible effect on the time to the primary endpoint. Of note, hs-CRP concentrations were scheduled to be measured at only two time points (baseline and 720 days) in the REDUCE-IT trial. Due to the high temporal variability of hs-CRP, the clinical meaning of these observations and exploratory analysis is unclear.

Highlights of Pharmacodynamics (PD)

In the REDUCE-IT trial, major components of the fasting lipid panel were tested at the Screening Visit, the Randomization Visit (Day 0), Days 120, 360, 720, 1080, 1440, 1800, 2160, and the Last Visit. Other biomarkers such as hs-CRP, apo-B, and high-sensitivity troponin T (hs-TNT) were tested at Day 0, Day 720, and the last Visit. The descriptive summary of fasting lipid panel and other PD biomarkers at baseline and follow up (1 or 2 years) is listed in Table 24.

Table 24: Comparison of Fasting Lipid Panel and Plasma Biomarkers from Baseline to Years 1 or 2 (ITT Population[1])

Parameter	Treatment	Baseline[2]	Year 1 or 2[2, 3]	Change from Baseline[4]	% Change from Baseline[5]
TG (mg/dL)	AMR101	216.5 (N=4086)	175 (N=3689)	-39.0	-18.3%
	Placebo	216.0 (N=4089)	221 (N=3633)	4.5	2.2%
Non-HDL-C (mg/dL)	AMR101	118.0 (N=4086)	113 (N=3674)	-4	-3.6%
	Placebo	118.5 (N=4089)	130 (N=3619)	12	10.4%
LDL-C (Derived)[6] (mg/dL)	AMR101	74 (N=4086)	77 (N=3685)	2	3.1%
	Placebo	76 (N=4089)	84 (N=3623)	7	10.2%
LDL-C (Hopkins) (mg/dL)	AMR101	86 (N=4086)	85 (N=3672)	-1.1	-1.2%
	Placebo	87 (N=4089)	96 (N=3618)	9.3	10.9%
LDL-C (Friedewald) (mg/dL)	AMR101	73 (N=4040)	76 (N=3504)	2.5	3.5%
	Placebo	75 (N=4042)	84 (N=3271)	9.5	12.9%
LDL-C (UC) (mg/dL)	AMR101	74 (N=3726)	77 (N=3542)	2	2.8%
	Placebo	75 (N=3700)	83 (N=3487)	7	10.0%
HDL-C (mg/dL)	AMR101	40 (N=4077)	39 (N=3676)	-1.0	-2.6%
	Placebo	40 (N=4080)	42 (N=3619)	1.5	3.8%
RLP-C (mg/L)	AMR101	30.9 (N=4077)	27.0 (N=3672)	-3.7	-12.2%
	Placebo	40.0 (N=4080)	32.8 (N=3618)	1.5	5.1%
Apo-B (mg/dL)	AMR101	82 (N=4060)	80 (N=3317)	-2	-2.5%
	Placebo	83 (N=4047)	89 (N=3227)	6	7.8%
hs-CRP (mg/L)	AMR101	2.2 (N=4086)	1.8 (N=3322)	-0.18	-13.9%
	Placebo	2.1 (N=4089)	2.8 (N=3229)	0.47	32.3%

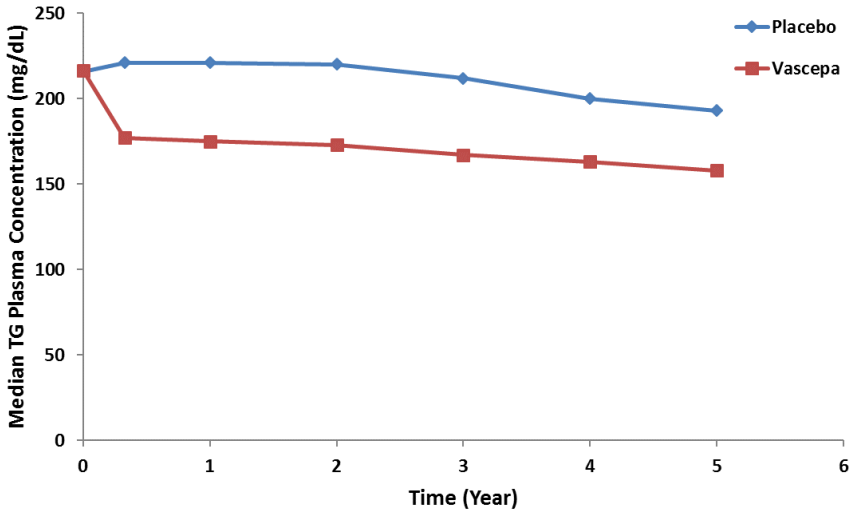
[1] At Randomization Visit, there were 4089 and 4090 subjects in AMR101 group and placebo group, respectively.
[2] median (N)
[3] Apo B and hsCRP were measured at Year 2; all other biomarkers presented were measured at Year 1.
[4] median change from baseline
[5] median percentage change from baseline
[6] The derived LDL-C values are obtained from following priority, based on the availability of the results:

- Preparative ultracentrifugation (UC) values (only available at Baseline and Day 360 for most patients)
- Direct LDL-C measurement
- Friedewald calculation (only for patients with TG <400 mg/dL)
- Johns Hopkins University calculation

Change from baseline values were obtained by matching the same LDL-C method based on their availability
Source: Reviewer's summary

The time profile of median TG plasma concentration change from baseline is depicted in Figure 6.

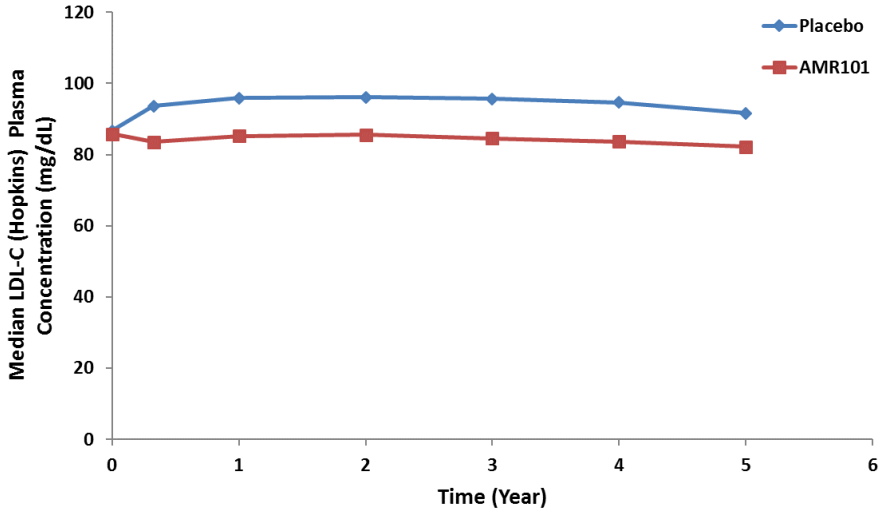
Figure 6: Median TG plasma concentration change over time by treatment (ITT Population)



(Source: Reviewer's analysis)

The time profile of median LDL-C (Hopkins) plasma concentration change from baseline is depicted in Figure 7. Consistently, a greater proportion of patients in the placebo group (70%) experienced increase of LDL-C (Hopkins) from baseline at Year 1 compared to patients in AMR101 group (47%). A similar trend in the time profile of the placebo group (i.e., increase from baseline since Day 120) was observed when using LDL-C Friedewald values.

Figure 7: Median LDL-C (Hopkins) plasma concentration change over time by treatment (ITT Population)



(Source: FDA Reviewer's analysis)

Highlights of PD Exploratory Analyses

Exploratory analyses of some PD-clinical endpoints were listed as tertiary objectives of the REDUCE-IT trial. These analyses are exploratory in nature and are not used for final adjustment for the primary analysis of the primary and secondary clinical endpoints. The FDA reviewer conducted similar relevant analyses and the results of these analyses are summarized below.

- *Effect of TG on the time to the primary composite endpoint*

TG was chosen as a relevant covariate for exploratory analysis because TG reduction is the approved indication of Vascepa, and some published literature has identified TG as an independent risk factor for adverse cardiovascular outcomes.

TG baseline values, Year 1 values, and change from baseline values at Year 1 were used as continuous covariates for the primary composite endpoint (Table 25). Neither TG absolute value nor change from baseline was identified as a clinically meaningful covariate for the primary composite endpoint. The estimated hazard ratio per unit TG value suggests that the approximately 40 mg/dL (20%) difference in TG between the AMR101 and placebo arms from baseline (Table 24) would reduce the risk of cardiovascular outcomes by only 1.3% in the AMR101 arm of the REDUCE-IT trial. Compared with the result from the primary analysis, the hazard ratio for the time to the primary endpoint changed only slightly in these exploratory analyses using available TG results from patients at Year 1.

Table 25: Stratified Analysis of Time to the Primary Endpoint by Adjusting for Varying TG Covariates (ITT Population)

TG Covariate	Treatment (AMR101/Placebo) HR[1]	HR[1] for TG Covariate[4]
Baseline (mg/dL) (N=8175)	0.752 (0.681, 0.829)	1.001 (1.001, 1.002)
Year 1 (mg/dL) (N=7319[2])	0.756 (0.680, 0.841)	1.001 (1.000, 1.001)
Year 1 Change from Baseline (mg/dL) (N=7319[2])	0.746 (0.670, 0.830)	1.000 (1.000, 1.001)[3]
Year 1 Change from Baseline (%) (N=7319[2])	0.744 (0.668, 0.828)	1.001 (1.000, 1.002)[3]

[1] Hazard ratio and 95% CI are reported from a Cox proportional hazards model with treatment as a factor, and stratified by geographic region, CV risk category, use of ezetimibe, and TG as continuous covariate.
[2] Three (3) subjects without baseline values were excluded from the analysis.
[3] After baseline adjustment
[4] Hazard ratio as per unit (1 mg/dL or 1%) absolute value or change from baseline
Source: Reviewer's analysis

- *Effect of LDL-C on the time to primary composite endpoint*

Since LDL-C is accepted as a major risk factor of cardiovascular outcomes, and there was an imbalance of LDL-C change from baseline between the AMR101 group and the placebo group, FDA conducted exploratory analyses using LDL-C (Hopkins) baseline values, Year 1 values, and change from baseline values at Year 1, respectively, as continuous covariates for the time to the primary composite endpoint (Table 26). The reasons for selection of Hopkins method are 1) it was calculated for every patient at all timepoints when lipid data was available; and 2) it represents the greatest post-baseline difference between treatment groups (median Year 1 change from baseline was -1.1 mg/dL and 9.3 mg/dL for AMR101 group and placebo group, respectively) among the various methods to estimate LDL-C.

Both LDL-C (Hopkins) absolute value and change from baseline had only a marginal effect on the time to the primary endpoint. The estimated hazard ratio per unit LDL-C value suggests that the approximately 10 mg/dL (12%) difference in LDL-C (Hopkins) between the Placebo and AMR101 arms from baseline (Table 24) would increase the risk of cardiovascular outcomes by only 3.1% in the placebo arm of the REDUCE-IT trial.

Table 26: Stratified Analysis of Time to the Primary Endpoint by Adjusting for Varying LDL-C (Hopkins) Covariates (ITT Population)

LDL-C (Hopkins) Covariate	Treatment (AMR101/Placebo) HR[1]	HR[1] for LDL-C Covariate[4]
Baseline (mg/dL) (N=8175)	0.754 (0.683, 0.832)	1.002 (0.999, 1.005)
Year 1 (mg/dL) (N=7287[2])	0.756 (0.680, 0.842)	1.003 (1.001, 1.005)
Year 1 Change from Baseline (mg/dL) (N=7287[2])	0.757 (0.680, 0.842)	1.003 (1.000, 1.005)[3]
Year 1 Change from Baseline (%) (N=7287[2])	0.757 (0.680, 0.843)	1.003 (1.001, 1.005)[3]

[1] Hazard ratio and 95% CI are reported from a Cox proportional hazards model with treatment as a factor, and stratified by geographic region, CV risk category, use of ezetimibe, and LDL-C (Hopkins) as continuous covariate.
[2] Three (3) subjects without baseline values were excluded from the analysis.
[3] After baseline adjustment
[4] Hazard ratio as per unit (1 mg/dL or 1%) absolute value or change from baseline
Source: Reviewer's analysis

- *Effect of hs-CRP on the time to the primary composite endpoint*

Most patients in the REDUCE-IT trial had hs-CRP measured only at Baseline and on Day 720 (Year 2). The proportion of patients having hs-CRP measured at other timepoints was less than 3% of the total patient population. Since hs-CRP levels vary considerably temporally, especially at the lower range (Bogaty 2013) (Koc 2010), it is unclear if the exploratory analysis of results obtained from single post-baseline (Year 2) will provide critical meaningful information. However, we looked at hs-CRP baseline values, Year 2 values, and change from baseline values at Year 2 as continuous covariates for the exploratory analyses for the time to the primary endpoint (Table 27).

These data show that hs-CRP absolute values, but not percentage change from baseline, are statistically significant co-variates for the hazard ratio on the time to the primary endpoint. The risk of cardiovascular outcome increases by 1.4% and 0.5% for every 1.0 mg/L increase of hs-CRP absolute value at baseline and at Year 2, respectively. The estimated hazard ratio per unit hs-CRP value suggests that the approximately 0.65 mg/L (50%) difference in hs-CRP between arms from baseline would increase the risk of cardiovascular outcomes by less than 0.3% in the placebo arm of the REDUCE-IT trial.

Table 27: Stratified Analysis of Time to the Primary Endpoint by Adjusting for Varying hs-CRP Covariates (ITT Population)

Hs-CRP Covariate	Treatment (AMR101/Placebo) HR[1]	HR[1] for hs-CRP Covariate[3]
Baseline (mg/L) (N=8175)	0.751 (0.681, 0.829)	1.014 (1.009, 1.019)
Year 2 (mg/L) (N=6551)	0.711 (0.636, 0.795)	1.005 (1.001, 1.009)
Year 2 Change from Baseline (mg/L) (N=6551)	0.709 (0.634, 0.793)	1.005 (1.000, 1.009)[2]
Year 2 Change from Baseline (%) (N=6551)	0.706 (0.632, 0.790)	1.000 (1.000, 1.000)[2]

[1] Hazard ratio and 95% CI are reported from a Cox proportional hazards model with treatment as a factor, and stratified by geographic region, CV risk category, use of ezetimibe, and hs-CRP as continuous covariate.
[2] After baseline adjustment
[3] Hazard ratio as per unit (1 mg/L or 1%) absolute value or change from baseline
Source: Reviewer's analysis

Highlights of Analyses of Mineral Oil as Placebo

Patients were required to have relatively low LDL-C (LDL-C between 40 and 100 mg/dL) upon stabilized statin treatment (for at least 4 weeks prior to randomization) to be enrolled in the REDUCE-IT trial. Among all the statins, atorvastatin, simvastatin, rosuvastatin, and pravastatin were being used in approximately 99% of the study population at randomization. Table 28 summarizes concomitant statin use by treatment arm.

In terms of strength of statin, 6% of patients were on low intensity (atorvastatin <10 mg, rosuvastatin <5 mg, simvastatin <20 mg, pravastatin <40 mg, lovastatin <40 mg, fluvastatin <80 mg, and pitavastatin <2 mg), 62% of patients were on moderate intensity (atorvastatin 10 to <40 mg, rosuvastatin 5 to <20 mg, simvastatin 20 to <80 mg, pravastatin 40 mg, lovastatin 40 mg, fluvastatin 80 mg, pitavastatin 2 mg), and 31% of patients were on high intensity (atorvastatin 40 mg, rosuvastatin 20 mg, and simvastatin 80 mg) statin treatment. Switching between different statins and/or intensity was generally uncommon (<10%) during the study.

Table 28: Summary of Concomitant Statins by Type at Randomization (ITT Population)

Statin	AMR101 (N=4089[1])	Placebo (N=4090[2])	Total (N=8179)
Atorvastatin	1624 (39.7%)	1641 (40.1%)	3265 (39.9%)
Simvastatin	1238 (30.3%)	1223 (29.9%)	2461 (30.1%)
Rosuvastatin	888 (21.7%)	867 (21.2%)	1755 (21.5%)
Pravastatin	314 (7.7%)	303 (7.4%)	617 (7.5%)
Lovastatin	62 (1.5%)	67 (1.6%)	129 (1.6%)
Fluvastatin	9 (0.2%)	14 (0.3%)	23 (0.3%)
Pitavastatin	8 (0.2%)	13 (0.3%)	21 (0.3%)
N/A[3]	12 (0.3%)	22 (0.5%)	44 (0.5%)

[1] 65 subjects (1.6%) have multiple records of different statins use at randomization
[2] 59 subjects (1.4%) have multiple records of different statins use at randomization
[3] No information available
Source: Adapted from sponsor's Table 14.1.25.1

From the clinical pharmacology perspective, the change of LDL-C may be related to change in the PK of statins (i.e., change in statin systemic exposure). Therefore, the potential interference with statin absorption by mineral oil is discussed below.

- *Potential drug-absorption interference mechanism by mineral oil*

A significant interaction between mineral oil and statins (leading to decreased absorption of statin in the GI tract) cannot be excluded when the mineral oil and statin are co-administered. Although the magnitude of the interaction is uncertain, such an interaction is plausible based on exploratory analyses of trial data. As noted above, however, this would not likely have changed the direction of the treatment difference between AMR101 and placebo in REDUCE-IT.

Mineral oil, or liquid paraffin, is a light mixture of higher alkanes from a mineral source which is only minimally absorbed in human gastrointestinal (GI) tract and thus is used as a lubricant laxative. Due to its chemical property, mineral oil can be a good solvent for many lipophilic compounds, and thus conceivably can function as a vector to reduce the absorption and facilitate the excretion of mineral oil-dissolved lipophilic compounds from the GI tract.

The proposed dosing regimen of AMR101 or mineral oil in the REDUCE-IT trial was 2 grams (two 1-gram capsules, or about 2.5 mL) twice daily. Patients were instructed to take the treatments with food (i.e., with or at the end of their morning and evening meals).

A dedicated drug-interaction study was not conducted to assess the effect of mineral oil on statin absorption, and neither were statin plasma concentrations collected in the REDUCE-IT trial. While searching for mineral oil-drug interaction related clinical studies in literature, the FDA clinical pharmacology reviewer found only well-documented literature on interference with absorption of vitamin A/beta-carotene (the precursor of vitamin A) by mineral oil. A well-controlled study (Steigmann 1952) investigated the effect of a 4-week ingestion of mineral oil on absorption of beta-carotene from a controlled diet in adults. It appears that interference with beta-carotene absorption by mineral oil is dose-dependent (2.5 mL, 5 mL, and 10 mL per meal reduced mean plasma carotene by 16%, 33%, and 42%, respectively) and meal-dependent (30 mL mineral oil at bed time had little effect whereas 30 mL at the noon-time meal reduced mean plasma carotene concentration by 28%).

When taken separately, any interaction between the mineral oil placebo used in REDUCE-IT and statins is predicted to be minimal. As noted in the previous paragraph, the interaction between mineral oil and beta carotene was minimal when taken separately, and (as shown in Table 29) all statins are less lipophilic than beta-carotene (Note that logP increases with increasing lipophilicity, and the beta-carotene logP is 17.6 per the US EPA). Therefore, it is expected that the effect of mineral oil on statin absorption would be minimal if the two were taken separately.

Table 29: Experimental LogP[1] Value and Approved Dosing Regimen of Statins

Statin	logP	Approved Regimen	Taken with Food	Results from Food Effect Study
Atorvastatin	1.61	once daily, any time	with or without food	food ↓ AUC by 9%
Simvastatin	2.06	once daily in the evening	no specification	food ↑ AUC by 49%
Rosuvastatin	0.13	once daily, any time	with or without food	no effect
Pravastatin	-0.23	once daily, any time	with or without food	food ↓ AUC by 31%
Lovastatin	1.7	once daily in the evening at bedtime	no specification	food ↓ AUC by ~50%
Fluvastatin	1.67	once daily in the evening	with or without food	food ↓ AUC by 11% (IR)

[1] lipophilicity increases with increase of logP value. Different sources provide different logP values for beta-carotene, but all are higher than statins' logP values.
Source FDA approved drug labels, (Rageh 2017), (Alakhali 2013), (Pan 1993)

The situation could be more complex if mineral oil is co-administered with statins:

1) In the absence of food, the volume of mineral oil may be comparable to or even exceed the volume of statin tablets. This could result in more dissolution of statin in mineral oil without buffering/dilution by a much bigger food volume if statin and

mineral oil were co-administered in the fasting state, and thus a greater interaction (decreased absorption of statin) would be predicted;

2) In the presence of food, the food alone reduces absorption of most statins (Table 29), although dissolution of statin in the mineral oil may be diluted by relatively large volume of food, thus reducing the predicted interaction between mineral oil and statin. Therefore, the net effect of co-administering mineral oil and statins with a meal is unclear. It could be greater than, less than, or similar to the effect of co-administration of mineral oil and placebo in the fasting state.

Therefore, by mechanism, the potential interference with statin absorption by mineral oil cannot be excluded when they are co-administered.

- *Indirect evidence for interference with statin absorption by mineral oil*

Although direct evidence of an interaction between mineral oil and statins (such as statin PK or a dedicated drug-drug interaction study) is not available, indirect evidence from both REDUCE-IT and previous trials conducted by Amarin using the same mineral oil placebo could point to an interaction between mineral oil and statins that resulted in decreased statin absorption among placebo patients in the REDUCE-IT trial.

LDL-C increased significantly from baseline in the placebo arm of the two Amarin trials of patients on optimized statin therapy, but not in the one trial in which most patients were not on statin. The same trend of increased LDL-C (ultracentrifugation) from baseline in the mineral oil placebo group occurred in both the ANCHOR trial (8.8% increase from baseline) and the REDUCE-IT trial (10% increase from baseline), but not in the MARINE trial (-3% change from baseline). Nearly all the patients in both REDUCE-IT and ANCHOR were on background statin treatment, but only about 25% of patients in MARINE trial were taking any dose of statin.

Additionally, LDL-C had much less fluctuation from baseline in the AMR101 arms of these three clinical trials (-4.5%, 1.5%, and 2.8% change from baseline in MARINE, ANCHOR, and REDUCE-IT, respectively). This phenomenon suggests that the LDL-C increase from baseline observed in the mineral oil groups of REDUCE-IT and ANCHOR could perhaps be statin-dependent, an indicator of potential drug-drug interaction between mineral oil and statin.

Another interesting observation in the REDUCE-IT trial is that in the mineral oil placebo group, patients on low-intensity statin experienced greater LDL-C increase from baseline than patients on high-intensity statin (Table 30).

Table 30: Increase of LDL-C (Hopkins) from Baseline in Placebo Group by Statin Intensity[1] (ITT Population)

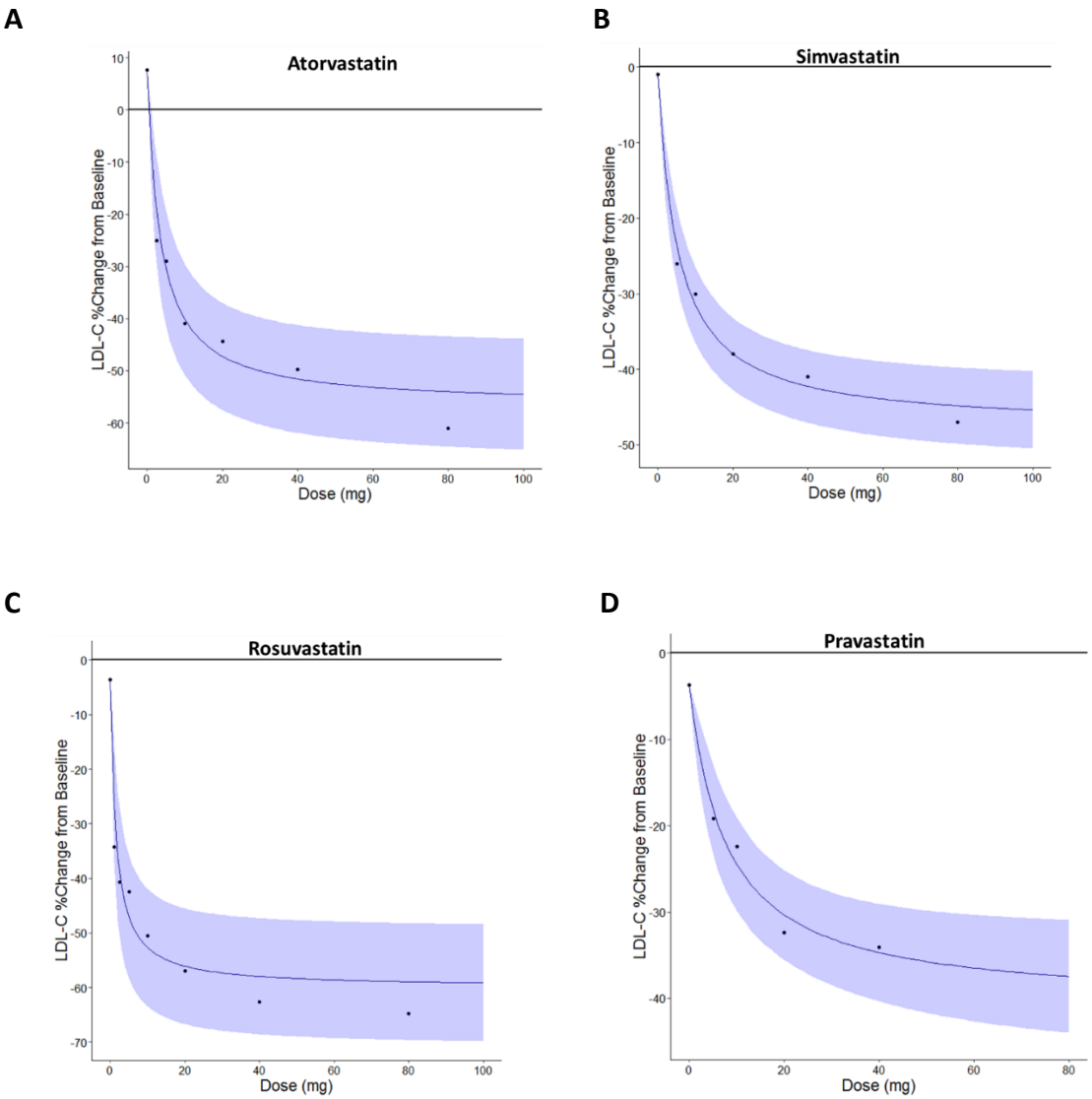
Parameter	Baseline (mg/dL)[2]	Year 1 (mg/dL)[2]	Change from Baseline (mg/dL)[2]	% Change from Baseline[2]
Low Intensity	89.1 (N=254)	98.6 (N=218)	11.0	12.2%
Moderate Intensity	87.3 (N=2531)	97.0 (N=2251)	9.6	11.3%
High Intensity	84.8 (N=1289)	93.7 (N=1131)	8.0	10.0%

[1] as recorded at Year 1; [2] median
Source: FDA reviewer's analysis

Consistently, a larger proportion of patients experienced LDL-C increase from baseline in the low-intensity group (78%) than in the moderate-intensity group (71%) and high-intensity group (68%), and notably, the same trend was not observed in the AMR101 group. This pattern could be explained by the established dose-response characteristics of statins if there is a potential interference with statin absorption by mineral oil.

The dose-response relationship of atorvastatin, simvastatin, rosuvastatin, and pravastatin (used in approximately 99% of the study population) on LDL-C reduction follows a typical E_{max} pharmacological trend (Figure 8). The trend is that the reduction rate of LDL-C from baseline is steeper at lower dose range than higher dose range.

Figure 8: E_{max} dose-response trend of statins



E_{max} dose-response trend of atorvastatin(A), simvastatin (B), rosuvastatin (C), and pravastatin (D) on reduction of LDL-C (percentage change from baseline). The solid blue line represent estimated E_{max} dose-response curve and blue shade represent the 95% CI of the curve. *(Source: reviewer's analysis)*

Atorvastatin, simvastatin, rosuvastatin, and pravastatin systemic exposure (AUC) generally follows a reasonably linear PK within the range of therapeutic doses. This indicates that if there is any interference of absorption by mineral oil, then the interference should also be linear (consistent percentage decrease of statin AUC by mineral oil across the therapeutic dose range). In this context, a similar percentage reduction of statin AUC would result in steeper increase of LDL-C from baseline at lower doses than at higher doses. This trend was observed in the placebo group of REDUCE-IT trial (Table 30).

- *Effect of LDL-C increase in placebo group on the time to the primary endpoint*

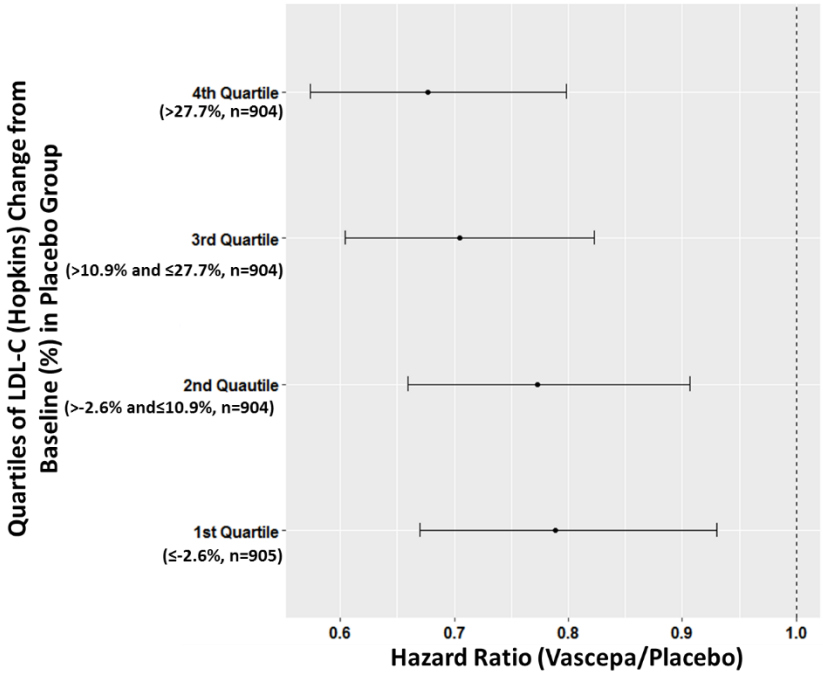
Although some indirect evidence suggests that interference with statin absorption by mineral oil may exist, the ultimate clinical question that needs to be addressed is whether the median 10-13% increase of LDL-C from baseline in the mineral oil group contributed to the overall effect size between the two treatment groups.

As stated above, LDL-C increase from baseline was identified as a marginal covariate for the time to the primary endpoint (HR about 1.002 to 1.003) in the exploratory analyses summarized in Table 26. By this estimate, the median increase of 10-13% LDL-C from baseline observed in the trial would increase cardiovascular risk by approximately 3%. This small increase of risk appears numerically small and is unlikely to change the overall treatment effect direction.

To support this contention, an exploratory subgroup analysis was further conducted to evaluate hazard ratios (AMR101/Placebo) in the placebo group patients by their LDL-C (Hopkins) categories. In brief, patients in placebo group were categorized by quartiles with their LDL-C (Hopkins) Year 1 value percentage change from baseline. This categorization was introduced as a factor (against the AMR101 group) in the same Cox proportional hazards model with baseline adjustment. The model is stratified by geographic region, CV risk category, and use of ezetimibe.

The result demonstrates a clear trend of increase of hazard ratio (AMR101/placebo), or reduction of effect size of AMR101 treatment effect, over placebo subgroups with lower LDL-C values (Figure 9). The result is consistent with the knowledge that further reduction of LDL-C is associated with improvement of cardiovascular risk. The upper boundaries of the hazard ratios of AMR101 versus placebo across all placebo subgroups are less than 1.

Figure 9: Hazard ratios of AMR101 versus placebo subgroups categorized by LDL-C change from baseline values



Hazard ratios and 95% CI (AMR101/Placebo) on the time to the primary endpoint between placebo subgroups [by quartiles of percentage change from baseline on LDL-C (Hopkins) at Year 1]. Patients with unavailable LDL-C values were excluded from both groups.
(Source: FDA reviewer's analysis)

5. Review of Safety

5.1. Review of Safety

5.1.1. Overall Exposure

A summary of study drug exposure is presented below, overall and by treatment group. Exposure was higher in the AMR101 arm compared to the placebo arm, and a greater proportion of patients in the placebo arm discontinued study drug prematurely. The median duration of AMR101 and placebo treatment was 1614 days (4.5 years) and 1512 days (4.2 years), respectively. In the placebo arm, 11.2% of patients discontinued study drug prematurely compared with 9.9% in the AMR101 arm. Approximately 12% of patients in either arm received study drug for less than one year (< 360 days per the applicant's analysis) and 0.5% (37/8179) of patients received study drug for ≥6 years (≥2160 days).

Table 31: Overall Study Drug Exposure, Safety Population

Overall Treatment Duration	**AMR101 N=4089**	**Placebo N= 4090**	**Overall N=8179**
	n=4083	n=4077	n=8160
Mean (SD)	1355.4 (637.73)	1300.6 (650.07)	1328.0 (644.47)
Median	1614.0	1512.0	1583.0
Q1, Q3	856.0, 1877.0	748.0, 1861.0	799.0, 1870.0
Patients exposed for n (%)			
≥ 12 months	3589 (87.8%)	3519 (86.0%)	7108 (86.9%)
≥ 24 months	3225 (78.9%)	3090 (75.6%)	6315 (77.2%)
≥36 months	2723 (66.6%)	2563 (62.7%)	5286 (64.6%)
≥ 48 months	2271 (55.5%)	2113 (51.7%)	4384 (53.6%)
≥ 60 months	1251 (30.6%)	1159 (28.3%)	2410 (29.5%)
Overall treatment duration was derived as (last dose date - first dose date + 1) - the cumulative time off drug in study. Source: REDUCE-IT Complete Study Report, Section 14, Table 14.1.18.1, pg. 276/2510.			

5.2. Safety Results

Current Vascepa labeling included the following safety information. Results of REDUCE-IT were consistent with the known safety profile of Vascepa with the exception of two newly identified safety signals: an increased risk of bleeding events and an increased risk of cardiac (atrial) arrhythmias. These issues are discussed in the sections below.

- A contraindication in patients with known hypersensitivity to any of its components

- A Warning regarding the risk of allergic reactions in patients with known hypersensitivity to fish or shellfish
- Adverse reactions of Arthralgia and Oropharyngeal pain

5.2.1. **Serious Adverse Events**

The most frequent serious adverse events (SAEs) were generally balanced between treatment groups and consistent with expected events for the patient population. Table 32 summarizes the most common SAEs by MedDRA Preferred Term (PT). The most common SAEs overall were Pneumonia and Osteoarthritis. Notable imbalances in Gastrointestinal hemorrhages and Cardiac arrhythmias are discussed later in this section, under the heading of Significant Adverse Events.

Table 33 summarizes SAEs by SOC and HLT, providing a broader view of the most common categories of SAEs. The most frequent events were serious infections (pneumonia, sepsis), malignancies (prostate, colorectal), and gastrointestinal hemorrhages. More patients experienced events of Pulmonary embolism, 22 (0.5%), in the Placebo arm than in the AMR101 arm, 14 (0.3%).

Table 32: Serious Adverse Events by Preferred Term, Safety Population

Preferred Term, n (%)	**AMR101 N=4089**	**Placebo N=4090**
Pneumonia	105 (2.6%)	118 (2.9%)
Osteoarthritis	81 (2.0%)	73 (1.9%)
Chest pain	66 (1.6%)	66 (1.6%)
Non-cardiac chest pain	49 (1.2%)	52 (1.3%)
Angina pectoris	48 (1.2%)	48 (1.2%)
Acute kidney injury	47 (1.1%)	34 (0.8%)
Angina unstable	41 (1.0%)	53 (1.3%)
Cellulitis	36 (0.9%)	28 (0.7%)
Chronic obstructive pulmonary disease	33 (0.8%)	34 (0.8%)
Syncope	28 (0.7%)	31 (0.8%)
Prostate cancer	26 (0.6%)	26 (0.6%)
Gastrointestinal hemorrhage	26 (0.6%)	20 (0.5%)
Sepsis	25 (0.6%)	31 (0.8%)
Urinary tract infection	25 (0.6%)	22 (0.5%)
Anemia	22 (0.5%)	20 (0.5%)
Atrial fibrillation	21 (0.5%)	17 (0.4%)

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term. Adverse Events were coded using MedDRA, Version 20.1
Source: Reviewer

Table 33: Serious Adverse Events by SOC and HLT Occurring at an Incidence of > 0.5% (by HLT) in the AMR101 arm, with Preferred Terms Under Certain Categories, Safety Population

System Organ Class, n (%) High Level Term, n *Preferred Term*, n	AMR101 N=4089	Placebo N=4090
Patients with at least 1 serious TEAE	1252 (30.6)	1254 (30.7)
Infections and infestations	*332 (8.1)*	*309 (7.6)*
Lower respiratory tract and lung infections	119	133
Pneumonia	*105*	*118*
Bronchitis	*11*	*10*
Bacterial infections NEC	52	33
Cellulitis	*36*	*28*
Sepsis, bacteremia, viremia and fungemia NEC	49	46
Abdominal and gastrointestinal infections	45	41
Urinary tract infections	35	32
Infections NEC	25	17
Neoplasms benign, malignant and unspecified	222 (5.4)	208 (5.1)
Prostatic neoplasms malignant	33	33
Colorectal neoplasms malignant	25	26
Breast and nipple neoplasms malignant	21	12
Breast cancer	*14*	*8*
Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	16	23
Lung cancer metastatic	*8*	*9*
Lung neoplasm malignant	*8*	*14*
Cardiac disorders	192 (4.7)	224 (5.5)
Ischemic coronary artery disorders	98	126
Heart failures NEC	32	24
Supraventricular arrhythmias	25	20
Gastrointestinal disorders	191 (4.7)	176 (4.3)
Non-site-specific gastrointestinal hemorrhages	40	31
Gastrointestinal hemorrhage	*26*	*20*
Duodenal and small intestinal stenosis and obstruction	16	12
Gastrointestinal and abdominal pains (excl oral and throat)	13	11
Musculoskeletal and connective tissue disorders	188 (4.6)	165 (4.0)
Osteoarthropathies	84	76
Osteoarthritis	*81*	*73*
Musculoskeletal and connective tissue pain and discomfort	33	18
Back pain	*17*	*11*

Spine and neck deformities	23	20
Intervertebral disc disorders NEC	19	11
Respiratory, thoracic and mediastinal disorders	143 (3.5)	141 (3.4)
Bronchospasm and obstruction	43	41
Respiratory failures (excl neonatal)	33	30
Breathing abnormalities	23	20
Injury, poisoning and procedural complications	142 (3.5)	125 (3.1)
Limb fractures and dislocations	30	34
Non-site specific injuries NEC	25	21
Non-site specific procedural complications	23	15
General disorders and administration site conditions	139 (3.4)	153 (3.7)
Pain and discomfort NEC	106	118
Chest pain	*66*	*66*
Non-cardiac chest pain	49	52
Renal and urinary disorders	120 (2.9)	100 (2.4)
Renal failure and impairment	69	47
Acute kidney injury	*47*	*34*
Nephrolithiasis	*13*	*12*
Renal failure	*11*	*6*
Renal lithiasis	13	13
Nervous system disorders	104 (2.5)	100 (2.4)
Disturbances in consciousness NEC	28	35
Metabolism and nutrition disorders	86 (2.1)	69 (1.7)
Diabetes mellitus (incl subtypes)	17	15
Total fluid volume decreased	17	12
Vascular disorders	73 (1.8)	81 (2.0)
Accelerated and malignant hypertension	17	12
Hepatobiliary disorders	50 (1.2)	45 (1.1)
Cholecystitis and cholelithiasis	39	32
Blood and lymphatic system disorders	39 (1.0)	35 (0.9)
Anemias NEC	26	22
Reproductive system and breast disorders	33 (0.8)	25 (0.6)
Prostatic neoplasms and hypertrophy	29	18
Benign prostatic hyperplasia	*18*	*11*
Psychiatric disorders	21 (0.5)	18 (0.4)

For each subject, multiple serious TEAEs of the same High-Level Term will be counted only once within each High-Level Term. Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included. [1] All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
Source: Reviewer analysis

5.2.2. Dropouts and/or Discontinuations Due to Adverse Effects

There were no meaningful differences in study drug discontinuations due to adverse events (AEs) between arms. Table 34 summarizes study drug discontinuations overall, categorized by clinical AEs and laboratory AEs. Clinical AEs accounted for the majority of

discontinuations. Nine placebo patients discontinued due to elevated triglyceride levels versus none in the AMR101 arm. Otherwise, the incidence of laboratory-related AEs was low, and there were no meaningful imbalances between arms.

Table 34: Summary of Treatment Emergent Adverse Events Leading to Permanent Study Drug Discontinuation

Treatment Arm	Randomized (N)	Discontinuation Total N, (%)	Discontinuation due to Clinical AE N, (%)	Discontinuation due to Laboratory AE N,(%)
AMR101	4089	321 (7.9%)	302 (7.4%)	19 (0.5%)
Placebo	4090	335 (8.2%)	309 (7.6%)	26 (0.6%)

Source: Applicant response to information request, 07 June 2019.

Most AEs leading to discontinuation were in the SOC – Gastrointestinal disorders. The most frequent AEs leading to discontinuation were Diarrhea and Constipation (Table 35). Diarrhea was more frequent in the placebo arm relative to AMR101, and alone led to discontinuations than all PTs within any SOC other than Gastrointestinal disorders. Constipation was more frequent in the AMR101 arm relative to placebo, but the significance of this imbalance is unclear given the small number of events and apparent effect of Placebo on GI motility.

Table 35: Adverse Events Leading to Permanent Study Drug Discontinuation by Preferred Term, Safety Population

Preferred Term, n (%)	**AMR101 N=4089**	**Placebo N=4090**
Diarrhea	47 (1.1)	76 (1.9)
Nausea	23 (0.6)	18 (0.4)
Constipation	9 (0.2)	3 (0.1)
Source: Adapted from REDUCE-IT CSR Section 14, Table 14.3.2.2.1 p. 2034/2510		

5.2.3. **Significant Adverse Events**

Bleeding Events

A higher proportion of patients in the AMR101 arm experienced a bleeding event compared to patients in the placebo arm. Excluding hemorrhagic strokes, which were adjudicated events, approximately 12% of patients in AMR101 treatment arm and 10% of patients in the Placebo arm reported a bleeding event.

Table 36 summarizes bleeding events by category. The most frequent preferred terms under the category of “Other Bleeding” were Contusion (2.3% overall), Hematuria

(1.7%), and Epistaxis (1.4%). From review of individual PTs, no single type of bleeding event accounted for the majority of events.

Table 36: Summary of All Bleeding Related Adverse Events

	AMR101 N=4089	**Placebo N=4090**
All bleeding related disorders	482 (11.8%)	404 (9.9%)
Serious bleeding TEAEs	111 (2.7%)	85 (2.1%)
Gastrointestinal bleeding	127 (3.1%)	116 (2.8%)
Central nervous system bleeding	20 (0.5%)	12 (0.3%)
Other bleeding	376 (9.2%)	312 (7.6%)
Contusion	102 (2.5%)	85 (2.1%)
Hematuria	77 (1.9%)	60 (1.5%)
Epistaxis	61 (1.5%)	48 (1.2%)
Bleeding-related disorders are identified by the SMQs of "Gastrointestinal hemorrhage," "Central Nervous System hemorrhages and cerebrovascular conditions," and "Hemorrhage terms (excl laboratory terms)." Source: Applicant response to information request, 07 June 2019.		

Fatal Bleeding Events

Bleeding events leading to death were rare and balanced between treatment groups. Bleeding-related clinical events that occurred proximal to death occurred in 23 (0.6%) patients in the AMR101 group and 34 (0.8%) patients in the Placebo group. The applicant's medical assessment classified 20 (0.5%) patients in the AMR101 group and 23 (0.6%) patients in the placebo group as having a bleeding event that likely contributed to death. The FDA clinical reviewer agrees with the applicant's assessments. Examples of these events include deaths following hemorrhagic stroke in a patient with supratherapeutic INR, ischemic stroke in a patient with atrial fibrillation who temporarily discontinued warfarin for a diagnostic procedure, and hemorrhagic stroke in a patient over one year after discontinuation of study drug.

CNS Bleeding

Twenty patients in AMR101 had a CNS bleeding event (excluding hemorrhagic strokes) compared to 12 patients in the Placebo treatment arm. Table 37 summarizes CNS bleeding events by Preferred Term, excluding hemorrhagic stroke. As noted previously, 13 patients in the AMR101 arm and 10 patients in the placebo arm experienced an adjudicated hemorrhagic stroke event.

Table 37: CNS Bleeding Events, Excluding Hemorrhagic Strokes, by Preferred Term, Safety Population

Category/Preferred Term	AMR101 N=4089	Placebo N=4090	Overall N=8179
Subjects with CNS bleeding	20 (0.5%)	12 (0.3%)	32 (0.4%)
Subdural hematoma	11 (0.3%)	6 (0.1%)	17 (0.2%)
Subarachnoid hemorrhage	4 (0.1%)	1 (0.0%)	5 (0.1%)
Cerebral hemorrhage	2 (0.0%)	2 (0.0%)	4 (0.0%)
Extradural hematoma	2 (0.0%)	0 (0.0%)	2 (0.0%)
Subdural hemorrhage	2 (0.0%)	1 (0.0%)	3 (0.0%)
Hemorrhagic transformation stroke	1 (0.0%)	0 (0.0%)	1 (0.0%)
Hemorrhage intracranial	0 (0.0%)	2 (0.0%)	2 (0.0%)

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each subject, multiple TEAEs of the same Preferred Term will be counted only once within each Preferred Term. TEAEs are listed in descending order of AMR101 frequency. Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
Source: Applicant response to information request, 07 June 2019.

GI Bleeding

Table 38 summarizes the most frequent causes (5 or more patients in the AMR101 arm) of gastrointestinal bleeding by Preferred term.

Table 38: Gastrointestinal Bleeding Events by Preferred Term, Safety Population

Category/Preferred Term	AMR101 N=4089	Placebo N=4090	Overall N=8179
Subjects with GI bleeding	127 (3.1%)	116 (2.8%)	243 (3.0%)
Gastrointestinal hemorrhage	34 (0.8%)	23 (0.6%)	57 (0.7%)
Rectal hemorrhage	29 (0.7%)	26 (0.6%)	55 (0.7%)
Melaena	18 (0.4%)	9 (0.2%)	27 (0.3%)
Hematochezia	14 (0.3%)	21 (0.5%)	35 (0.4%)
Hematemesis	8 (0.2%)	3 (0.1%)	11 (0.1%)
Upper gastrointestinal hemorrhage	8 (0.2%)	4 (0.1%)	12 (0.1%)
Hemorrhoidal hemorrhage	7 (0.2%)	10 (0.2%)	17 (0.2%)
Lower gastrointestinal hemorrhage	5 (0.1%)	7 (0.2%)	12 (0.1%)
Occult blood positive	5 (0.1%)	9 (0.2%)	14 (0.2%)

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each subject, multiple
TEAEs of the same Preferred Term will be counted only once within each Preferred Term. TEAEs are listed in descending order of AMR101 frequency. Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
Source: Applicant response to information request, 07 June 2019.

Bleeding risk and Omega-3 Fatty Acids

The mechanism of action of omega-3 fatty acid products appears to be poorly understood overall. Theoretically, the omega-3 fatty acids are incorporated into the platelet cell membrane, altering the ratio of DHA/EPA to arachidonic acid (AA), which has a shorter fatty acid chain, and leading to inhibition of platelet aggregation. (Goodnight 1981) While some publications that indicate that omega-3 fatty acids may have an adverse effect on platelet aggregation and bleeding time (Knapp 1997) (Lorenz 1983), others showed no effect (Bagge 2018). Neither parameter was evaluated in REDUCE-IT.

Data regarding the clinical risk of bleeding with omega-3 fatty acid products are limited. Published summary reviews (Begtrup 2017), (Wachira 2014), (Harris, 2007), (H. Bays 2007) and a recent clinical trial report (Akintoye 2018) appear to show no increased risk of bleeding in clinical studies, although trial-level analyses may not be sufficient to detect small or modest increased risks of bleeding without patient-level data. Studies specifically evaluating the interaction between fish oil and warfarin appear to refute the idea of interaction affecting PK and INR parameters (Braeckman 2014), (Bender 1998).

Anti-thrombotic medication Use and Bleeding Events

Not unexpectedly, the number of bleeding events was greater in the subset of patients taking anti-thrombotic medications (including both anti-platelet medications and anti-coagulant medications) versus those who were not taking such medications. Table 39 summarizes bleeding events by use of anti-thrombotic medications (at baseline and on treatment). The small number of events, and relatively smaller number of patients, in the subgroup of patients not taking antithrombotic medications at baseline limits interpretation of these analyses.

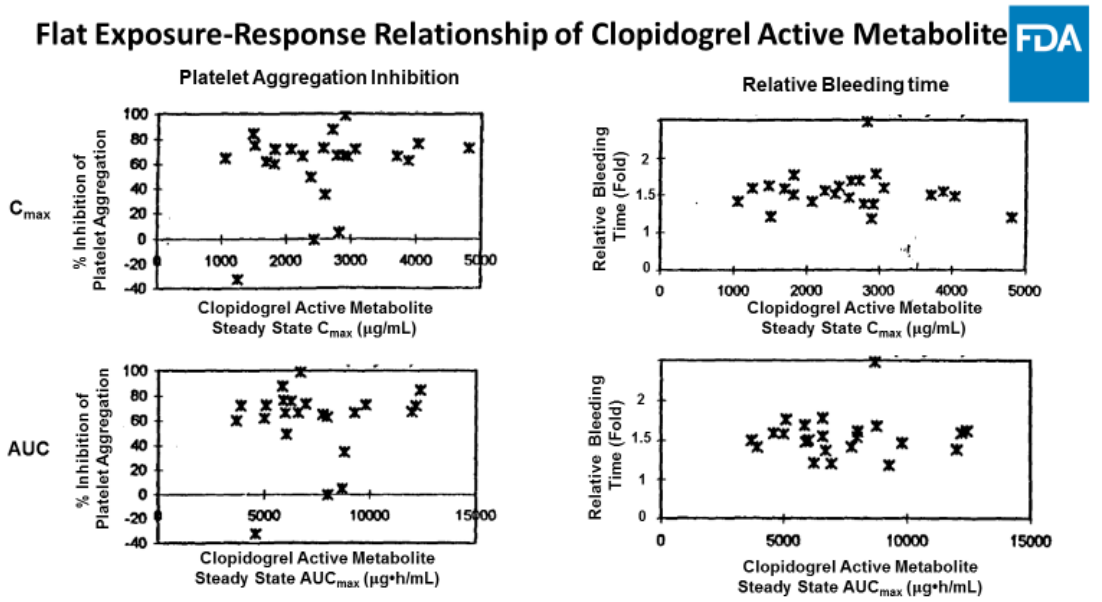
The imbalance appears more prominent in the subset of patients taking antithrombotic medications. This finding could be due to multiple factors including, but not limited to, a direct effect of AMR101 on bleeding in patients who are already at higher risk, interaction between AMR101 and antithrombotic agents leading to increased risk, inhibitory interaction between placebo and antithrombotic agents leading to decreased bleeding in the placebo arm, or a chance finding in a large clinical study.

Table 39: Summary of Bleeding Events, Including Hemorrhagic Stroke by Anti-thrombotic Medication Use and Treatment Arm, ITT Population

	AMR101 n/N (%)	Placebo n/N (%)	Total n/N (%)
At Baseline			
Yes	449/3505 (12.8%)	370/3489 (10.6%)	819/6994 (11.7%)
No	45/ 584 (7.7%)	42/ 601 (7.0%)	87/1185 (7.3%)
On Treatment			
Yes	472/3640 (13.0%)	390/3635 (10.7%)	862/7275 (11.8%)
No	22/ 449 (4.9%)	22/ 455 (4.8%)	44/904 (4.8%)
Source: Applicant Response to Information Request 25 June 2019			

Because of the pharmacologic profile of the two most frequently used antiplatelet agents (aspiring and clopidogrel), we would not expect an interaction (i.e. reduced absorption) between mineral oil and either of these products to account for a difference in bleeding events between arms. Aspirin has a flat dose-response curve for its antiplatelet effects over a range of daily doses from 50 mg to 1500 (Johnson 1999). Clopidogrel has a wide, flat exposure-response (stable over a 4- to 5-fold range of exposures). Even a substantial interaction between aspirin and mineral oil or between aspirin and mineral oil would have negligible effects on clinical antiplatelet activity of either drug. Figure 10 demonstrates the exposure-response profile of clopidogrel's active metabolite in two assays used to assess antiplatelet activity.

Figure 10: Exposure-Response Relationship of Clopidogrel



Source: Yunzhao Ren, FDA Clinical Pharmacology Reviewer from FDA Review available on: Drugs@FDA at https://www.accessdata.fda.gov/drugsatfda_docs/nda/pre96/020839_s000.pdf pp. 223-224/289

In addition, because warfarin is monitored and adjusted to achieve International Normalize Ratio (INR) within a target range, we would expect that any interactions with mineral oil would be addressed with dose-adjustment to achieve the appropriate effect.

Nonetheless, to investigate whether the imbalance in bleeding events could have been related to an interaction between mineral oil placebo and a specific antithrombotic agent, we analyzed bleeding events by specific background therapy. Table 40 summarizes bleeding events by baseline antithrombotic therapy, regardless of concomitant antithrombotic therapy (i.e. patients could be on more than one antithrombotic, such as aspirin and warfarin). Small differences in the denominator of patients on no antithrombotics versus the applicant's analysis (Table 39) are due to our exclusion of patients taking salicylates intermittently, e.g. as needed for pain or fever.

There were more bleeding events in the AMR101 arm compared to placebo for the three most commonly used antithrombotics: aspirin, clopidogrel, and warfarin, and the relative increase in bleeding events between AMR101 and placebo was similar, regardless of background therapy. The consistent trend of increased bleeding with AMR101 suggests that there was no interaction between mineral oil and any one of the three most commonly used antithrombotics.

Although individual trends for other antithrombotics (ticagrelor, prasugrel, dipyridamole, and non-vitamin K antagonist oral anticoagulants) were variable (some favored placebo and some favored AMR101), low event rates and a low proportion of

patients taking any single agent limits interpretation of these data.

Table 40: Patients with Bleeding events by Concomitant Baseline Oral Antithrombotic Therapy, Regardless of Background Therapy, Safety Population

Item	Antithrombotic therapy (at baseline)	Patients with bleeding / at risk (%)	
		AMR N (%)	Placebo N(%)
	All randomized patients	482/4089 (11.8)	404/4090 (9.9)
A	No antithrombotic	45/582 (7.7)	42/596 (7.0)
B	Aspirin	369/3095 (11.9)	301/3082 (9.8)
C	Clopidogrel	122/847 (14.4)	80/817 (9.8)
D	Warfarin	69/327 (21.1)	57/332 (17.1)
E	Ticagrelor	3/59 (5.1)	7/57 (12.2)
F	Prasugrel	8/50 (16.0)	12/62 (19.3)
G	Dipyridamole	7/43 (16.2)	6/42 (14.2)
H	Dabigatran	7/27 (25.9)	4/26 (15.4)
I	Rivaroxaban	5/20 (25.0)	1/21 (4.5)
J	Apixaban	0/6	2/7 (28.5)
K	Ticlopidine	1/2 (50.0)	0/0 (0.0)
L	Phenindione	0/2	0/1

B includes: ACETYLSALICYLIC ACID, ACETYLSALICYLATE CALCIUM, CARBASALATE, CARBASALATE CALCIUM, ASCAL BRISPER CARDIO-NEURO, PAYNOCIL, ASPIMAG (Aspirin/Magnesium), MAGNYL (Aspirin/Magnesium), AXANUM (Aspirin and Esomeprazole), ASASANTIN (Aspirin and Dipyridamole), CLOGNIL PLUS (Aspirin and Clopidogrel), NEFAZAN COMPUESTO (Aspirin and Clopidogrel)
C includes CLOPIDOGREL BISULFATE, CLOPIDOGREL, CLOPIDOGREL BESYLATE, NEFAZAN COMPUESTO, CLOGNIL PLUS
D includes: WARFARIN, ACENOCOUMAROL, PHENPROCOUMON
F includes: PRASUGREL, PRASUGREL HYDROCHLORIDE
G includes DIPYRIDAMOLE, ASASANTIN
H includes DABIGATRAN ETEXILATE MESILATE, DABIGATRAN ETEXILATE, DABIGATRAN
Source: Changming (Sherman) Xia, PhD, FDA Safety Statistical Reviewer

We also requested that the applicant conduct the same analysis stratifying patients by antithrombotic use at the time of the event, that is, an on-treatment analysis. Such an exploratory analysis, which introduces a post-randomization variable (change in antithrombotic therapy from baseline) has limitations and should be interpreted with caution. Nonetheless, the results were similar to the results of the baseline analysis, with an increased number of patients with bleeding events in the AMR101 arm, among patients taking aspirin, clopidogrel, or warfarin. Table 41 summarizes the on-treatment analysis.

Table 41: Patients with Bleeding events by Concomitant On-Treatment Oral Antithrombotic Therapy, Regardless of Background Therapy, Safety Population

Item	Antithrombotic therapy (on treatment) [1]	Patients with bleeding / at risk (%)	
		AMR N (%)	Placebo N(%)
	All randomized patients	482/4089 (11.8)	404/4090 (9.9)
A	No antithrombotic [2]	22/449 (4.9)	22/455 (4.8)
B	Aspirin	290/2832 (10.2)	219/2800 (7.8)
C	Clopidogrel	124/951 (13.0)	91/971 (9.4)
D	Warfarin	70/345 (20.3)	50/339 (14.7)
E	Ticagrelor	10/90 (11.1)	21/125 (16.8)
F	Prasugrel	10/59 (16.9)	13/73 (17.8)
G	Dipyridamole	8/46 (17.4)	6/44 (13.6)
H	Dabigatran	13/52 (25.0)	7/60 (11.7)
I	Rivaroxaban	16/82 (19.5)	17/87 (19.5)
J	Apixaban	26/100 (26.0)	10/70 (14.3)
K	Ticlopidine	1/2 (50.0)	0/0 (0.0)
L	Phenindione	0/2	0/1

B includes: ACETYLSALICYLIC ACID, ACETYLSALICYLATE CALCIUM, CARBASALATE, CARBASALATE CALCIUM, ASCAL BRISPER CARDIO-NEURO, PAYNOCIL, ASPIMAG (Aspirin/Magnesium), MAGNYL (Aspirin/Magnesium), AXANUM (Aspirin and Esomeprazole), ASASANTIN (Aspirin and Dipyridamole), CLOGNIL PLUS (Aspirin and Clopidogrel), NEFAZAN COMPUESTO (Aspirin and Clopidogrel), ACETYLSALICYLIC ACID W/CITRIC ACID, ASPIRIN W/BUTALBITAL/CAFFEINE, ANACIN, ASCRIPTIN, ACETYLSALICYLATE LYSINE, ALKA SELTZER PLUS, ASPIRIN PLUS C, TABCIN
C includes CLOPIDOGREL, CLOPIDOGREL BESYLATE, CLOPIDOGREL BISULFATE, CLOGNIL PLUS NEFAZAN COMPUESTO
D includes: WARFARIN, ACENOCOUMAROL, PHENPROCOUMON
F includes: PRASUGREL, PRASUGREL HYDROCHLORIDE
G includes DIPYRIDAMOLE, ASASANTIN
H includes DABIGATRAN ETEXILATE MESILATE, DABIGATRAN ETEXILATE, DABIGATRAN
[1] Excludes patients on parenteral antithrombotic drugs (HEPARIN, ENOXAPARIN, NADROPARIN CALCIUM, FONDAPARINUX, DALTEPARIN, BIVALIRUDIN, EPTIFIBATIDE, HEPARIN PORCINE, HEPARIN SODIUM, HEPARIN SODIUM W/SODIUM CHLORIDE, ENOXAPARIN SODIUM, NADROPARIN, FONDAPARINUX SODIUM, DALTEPARIN SODIUM, LOWER MOLECULAR WEIGHT HEPARIN, GLUCOSE W/HEPARIN) from medication categories presented on the table
[2] Excludes patients with ANY antithrombotic medications on-treatment
Source: Applicant response to Information Request 16 October 2019

Because concomitant antithrombotic therapy (for example, concomitant warfarin in the subgroup of patients taking aspirin) could partly mask an interaction between mineral oil and the antithrombotic of interest in these analyses, we asked the applicant to conduct an on-treatment analysis of bleeding by type of antithrombotic (aspirin, clopidogrel, or warfarin) as monotherapy (i.e. with no other concomitant antithrombotic). The number of patients on other antithrombotics as monotherapy was too small analyze.

Table 42 summarizes the on-treatment analysis of bleeding events in patients taking the

three most commonly used antithrombotics (aspirin/acetylsalicylic acid, clopidogrel, and warfarin) as monotherapy. Again, the imbalance in bleeding events between arms was consistent, regardless of specific antithrombotic therapy for the three most widely used antithrombotic drugs, and regardless of whether patients were on low-dose (<100 mg daily) or higher daily doses of aspirin. The consistency of the effect across categories, including consistency among patients on low dose aspirin, suggests that there did not appear to be a drug interaction between placebo and any individual antithrombotic (attenuating the antiplatelet or anticoagulant effect) or between AMR101 and any individual antithrombotic (increasing the antiplatelet or antithrombotic effect) that might have impacted the trial results.

Table 42: Bleeding events by concomitant antithrombotic therapy as monotherapy (no concomitant background antithrombotics) on-treatment, Safety Population

Antithrombotic therapy (on treatment) [1]	**Patients with bleeding / at risk (%)**	
	AMR N (%)	**Placebo N(%)**
Aspirin Only (Aspirin as monotherapy) [2]	125/1699 (7.4)	93/1631 (5.7)
< 100 mg daily	83/1092 (7.6)	59/1021 (5.8)
≥ 100 mg daily	42/570 (7.4)	32/569 (5.6)
Unknown [3]	0/37 (0.0)	2/41 (4.9)
Warfarin Only (Warfarin monotherapy)	26/143 (18.2)	16/140 (11.4)
Clopidogrel Only (Clopidogrel monotherapy)	7/ 103 (6.8)	6/ 91 (6.6)

[1] Patients on parenteral antithrombotic drugs (HEPARIN, ENOXAPARIN, NADROPARIN CALCIUM, FONDAPARINUX, DALTEPARIN, BIVALIRUDIN, EPTIFIBATIDE, HEPARIN PORCINE, HEPARIN SODIUM, HEPARIN SODIUM W/SODIUM CHLORIDE, ENOXAPARIN SODIUM, NADROPARIN, FONDAPARINUX SODIUM, DALTEPARIN SODIUM, LOWER MOLECULAR WEIGHT HEPARIN, GLUCOSE W/HEPARIN) excluded.
[2] Aspirin dose categories based on the average daily dose.
[3] Includes patients with missing dose information or dose reported in units other than mg.
Note: n is the number of patients with treatment emergent adverse events of bleeding; N is the total number subjects within each medication category.
Aspirin Only INCLUDES patients in Item B and EXCLUDES patients in Items C, D, E, F, G, H, I, J, K, L Note: This category excludes: ASASANTIN,also in Item G, and CLOGNIL PLUS and NEFAZAN COMPUESTO, also in Item C.
Warfarin Only INCLUDES patients in Item D and EXCLUDES patients in Items B, C, E, F, G, H, I, J, K, L.
Clopidogrel Only INCLUDES patients in Item C and EXCLUDES patients in Items B, D, E, F, G, H, I, J, K, L.
Source: Applicant Response to Information Request 16 October 2019

Atrial Fibrillation, Atrial Flutter and Other Cardiac Arrythmias

There was an increased risk of adjudicated events of atrial fibrillation or atrial flutter events resulting in hospitalization, or prolongation of hospitalization ≥24 hours in the AMR101 arm compared to the placebo arm. The incidence of atrial fibrillation/flutter was greater among patients with a self-reported history of atrial fibrillation or atrial flutter. The observed increase in atrial fibrillation or atrial flutter had minimal apparent effect on stroke, as adjudicated stroke events (a component of the primary efficacy endpoint) favored AMR101 (fewer events in AMR101 despite increased incidence of

atrial fibrillation or flutter).

Atrial fibrillation and atrial flutter were adjudicated by the CEC and analyzed as a tertiary endpoint, added as a potential safety signal by the DMC (and confirmed by the SC) during real-time review of the safety data. Table 43 summarizes time to event analyses of adjudicated cardiac arrhythmias. Note that the subcategories are not mutually exclusive. Three patients in the category "Other Tachycardias" were also included in the category "Atrial Fibrillation or Flutter."

The pre-specified endpoint for cardiac arrythmias per the CEC charter included 3 types of arrythmias:

Definition of Cardiac Arrhythmia Requiring Hospitalization
An arrhythmia that either results in hospitalization (≥24 hours) during or within 24 hours of the termination of the last episode for treatment or requires continued hospitalization for treatment, including any one of the following:

1. Atrial arrhythmia – atrial fibrillation, atrial flutter, supraventricular tachycardia that requires cardio-version, drug therapy, or is sustained for greater than 1 minute)
2. Ventricular arrhythmia - Ventricular tachycardia or ventricular fibrillation requiring cardioversion and/or intravenous antiarrhythmics
3. Brady arrhythmia - High-level AV block (defined as third-degree AV block or second-degree AV block), junctional or ventricular escape rhythm, or severe sinus bradycardia (typically with heart rate (HR) < 30 bpm). The bradycardia must require temporary or permanent pacing

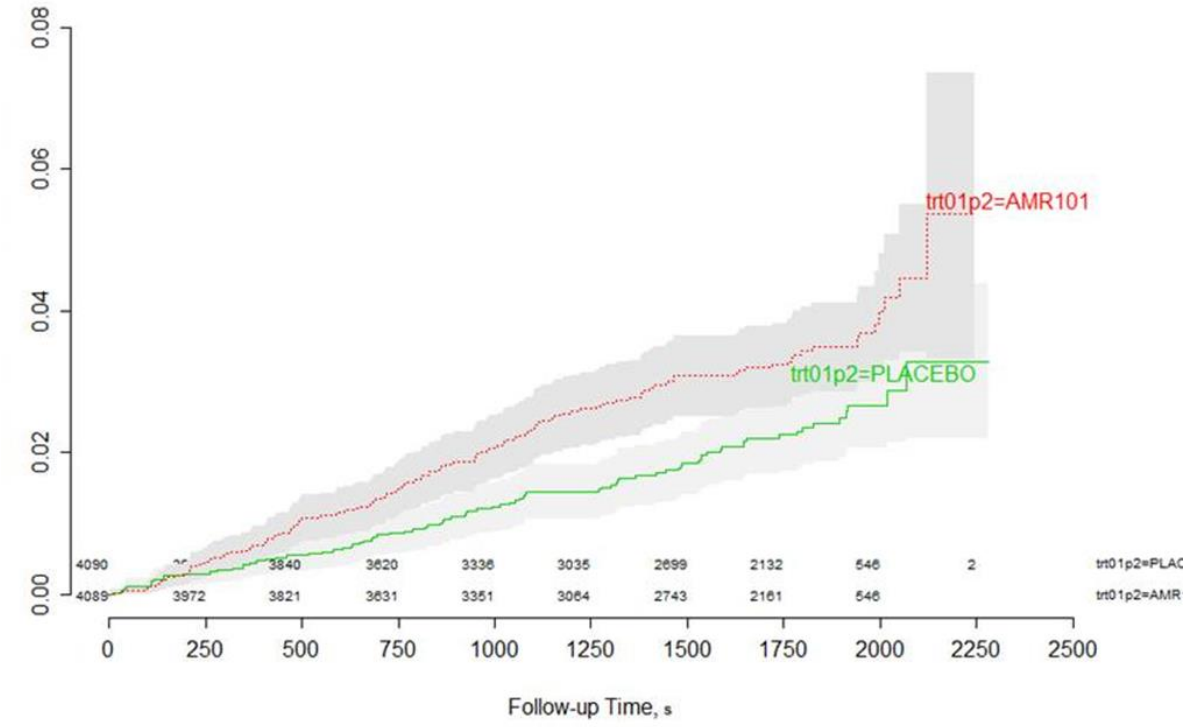
Table 43: Stratified Analysis of Time to Cardiac Arrythmia Endpoint Events from Date of Randomization, ITT Population

Endpoint Event, n (%)[2]	AMR101 (N=4089)	Placebo (N=4090)	Treatment Comparison[1] P-value from Log-Rank Test	Treatment Comparison[1] HR (95% CI) AMR101/Placebo
Cardiac Arrhythmia Requiring Hospitalization of ≥24 Hours	188 (4.6)	154 (3.8)	0.0856	1.21 (0.97 – 1.49)
Atrial Fibrillation or Flutter Requiring Hospitalization of ≥24 Hours	127 (3.1)	84 (2.1)	0.0037	1.50 (1.14 – 1.98)
Bradycardia/Heart Block Requiring Hospitalization of ≥24 Hours	28 (0.7)	40 (1.0)	0.1248	0.69 (0.42 – 1.11)
Ventricular Tachycardia or Ventricular Fibrillation Requiring Hospitalization of ≥24 Hours	35 (0.9)	37 (0.9)	0.7564	0.93 (0.59 – 1.48)
Other Tachycardia Requiring Hospitalization of ≥24 Hours	7 (0.2)	7 (0.2)	0.9819	0.99 (0.35 – 2.82)

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = Intent-to-Treat.
Note: The number of patients with event (n) is the number of patients with the event in the ITT population within each treatment
group (N).
1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.
2 Based on a patient's first post-randomization occurrence of the endpoint event.
Source: REDUCE-IT CSR, Table 11-12, p. 151/354.

The following figure shows the Kaplan-Meier estimate of time to atrial fibrillation/flutter requiring hospitalization of ≥24 hours.

Figure 11: Kaplan-Meier Curve for Time to Event Atrial Fibrillation/Flutter Requiring Hospitalization of ≥24 Hours by Treatment Arm, Safety Population



Source: Dr. Changming (Sherman) Xia, Safety Statistical Reviewer.

Previous Atrial fibrillation/ flutter history

According to the Applicant, previous atrial fibrillation and/or atrial flutter medical history were not pre-populated terms on the CV history Case Report Form, but rather captured as self-reported history. Table 44 summarizes medical history in the MedDRA SOC – Cardiac Disorders.

Table 44: Selected Medical History by System Organ Class and Preferred Term in Cardiac Disorders (Safety Population)

System Organ Class, n (%) Preferred Term [1]	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)
Cardiac disorders	1576 (38.5%)	1604 (39.2%)	3180 (38.9%)
Coronary artery disease	518 (12.7%)	527 (12.9%)	1045 (12.8%)
Angina pectoris	473 (11.6%)	474 (11.6%)	947 (11.6%)
Atrial fibrillation	351 (8.6%)	362 (8.9%)	713 (8.7%)
Myocardial ischaemia	162 (4.0%)	129 (3.2%)	291 (3.6%)
Mitral valve incompetence	93 (2.3%)	103 (2.5%)	196 (2.4%)
Ventricular extrasystoles	97 (2.4%)	82 (2.0%)	179 (2.2%)
Left ventricular hypertrophy	79 (1.9%)	80 (2.0%)	159 (1.9%)
Sinus bradycardia	75 (1.8%)	76 (1.9%)	151 (1.8%)
Tricuspid valve incompetence	63 (1.5%)	66 (1.6%)	129 (1.6%)
Bundle branch block right	69 (1.7%)	59 (1.4%)	128 (1.6%)
Arteriosclerosis coronary artery	56 (1.4%)	54 (1.3%)	110 (1.3%)
Bundle branch block left	55 (1.3%)	49 (1.2%)	104 (1.3%)
Palpitations	43 (1.1%)	45 (1.1%)	88 (1.1%)
Atrioventricular block first degree	33 (0.8%)	38 (0.9%)	71 (0.9%)
Supraventricular extrasystoles	37 (0.9%)	28 (0.7%)	65 (0.8%)
Cardiac failure chronic	27 (0.7%)	35 (0.9%)	62 (0.8%)
Aortic valve incompetence	24 (0.6%)	34 (0.8%)	58 (0.7%)
Bradycardia	21 (0.5%)	34 (0.8%)	55 (0.7%)
Cardiac failure	25 (0.6%)	29 (0.7%)	54 (0.7%)
Atrial flutter	25 (0.6%)	26 (0.6%)	51 (0.6%)
Cardiac failure congestive	24 (0.6%)	22 (0.5%)	46 (0.6%)

Note: For each subject, multiple events of the same system organ class and/or preferred term will be counted only once within each system organ class and preferred term. Medical history is listed in descending order of overall frequency within system organ class and preferred term. Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N) or subgroup of interest. [1] Medical history is coded using the Medical Dictionary for Regulatory Activities 20.1.
Source: REDUCE-IT CSR, Section 14, Table 14.1.15.1, pg. 111-112/2510.

The applicant conducted a stratified analysis of time to first onset of atrial fibrillation and atrial flutter requiring hospitalization of ≥ 24 hours by baseline history of atrial fibrillation or flutter. Table 45 summarizes the analysis of adjudicate atrial fibrillation or flutter by self-reported history. The incidence of atrial fibrillation was higher in the subset of patients with self-reported previous history. There was not a significant interaction between previous history of atrial fibrillation or atrial flutter and the incidence of subsequent event, but the small number of events limits interpretation of the analysis. The trend (higher estimate of the hazard ratio) in the subgroup of patients with a prior history suggests that the risk may be greater in patients with a history of atrial fibrillation or flutter, but the results are not conclusive.

Table 45: Stratified Analysis of Time to First Onset of Atrial Fibrillation or Flutter from Date of Randomization by Subjects With/Without Atrial Fibrillation or Flutter History, ITT Population

AMR101 N=4089	Placebo N=4090	Treatment Comparison		
Event (%)		HR (95% CI) [1]	NNH	Interaction P-value [2]
Adverse Event / Yes – Atrial fibrillation or flutter history				
46/368 (12.5%)	24/383 (6.3%)	1.96 (1.20, 3.22)	16	0.21
Adverse Event / No – Atrial fibrillation or flutter history				
81/3721 (2.2%)	60 /3707 (1.6%)	1.3 (0.95, 1.86)	179	

Source: Adapted from Table 14.2.6.40.1 and FDA Statistical Reviewer Changming (Sherman) Xia
[1] Hazard ratio and 95% CI for each subgroup are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.
[2] P-value for treatment by the subgroup interaction is reported from a Cox proportional hazard model with treatment, afib or aflutter history, and treatment by afib or aflutter history interaction as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

Atrial Fibrillation and Flutter - Treatment Emergent Adverse Events

Consistent with the adjudicated events, the incidence of atrial fibrillation/flutter TEAEs reported in the AE dataset within the clinical database (i.e., not positively adjudicated as endpoints) was numerically higher in the AMR101 group than in the placebo. The incidence of atrial fibrillation/flutter SAEs reported in the safety database (i.e., not positively adjudicated as endpoints and meeting seriousness criteria) were similar between arms. Table 46 summarizes these data.

Table 46 : Summary of Atrial Fibrillation/Flutter not adjudicated as endpoints

	AMR101 N=4089	Placebo N=4090
Treatment Emergent Adverse Events - Atrial fib/flutter	236 (5.8%)	183 (4.5%)
Serious Treatment Emergent Adverse Events - Atrial fib/flutter	22 (0.5%)	20 (0.5%)
Source: Reviewer		

6. Appendices

6.1. General Safety Analyses

Treatment Emergent Adverse Events

As noted previously, labeled safety issues include hypersensitivity reactions, arthralgia and oropharyngeal pain.

The AE term Drug hypersensitivity occurred in 17 patients (0.4%) in the AMR101 arm compared with 10 patients (0.02%) in Placebo, and no events in this category were assessed as serious adverse events (SAEs). The AE term Hypersensitivity (not specified as drug hypersensitivity) occurred in 19 patients (0.5%) in the AMR101 arm versus 8 patients (0.2%) in the Placebo arm. One event in each arm (0.02%) was assessed as serious (SAE). These imbalances in predominantly non-serious events, are consistent with current labeling.

There were no observed imbalances between arm in events of Arthralgia or Oropharyngeal Pain. Arthralgia occurred in 313 patients in the AMR101 arm versus 310 in the Placebo arm, while Oropharyngeal pain occurred in 58 patients in each arm (no difference).

Table 47 summarizes the number of subjects experiencing treatment emergent adverse events by System Organ Class. The most frequently reported class of TEAEs were Infections and infestations, Musculoskeletal and connective tissue disorders, and Gastrointestinal disorders. There were no notable imbalances.

Table 47: Number (%) of Subjects with Treatment Emergent Adverse Events by System Organ Class, Safety Population

System Organ Class, n (%)	AMR101 N=4089	Placebo N=4090
Subjects with at least one TEAE	3343 (82)	3326 (81)
Infections and infestations	1822 (45)	1774 (43)
Musculoskeletal and connective tissue disorders	1466 (36)	1406 (34)
Gastrointestinal disorders	1350 (33)	1437 (35)
General disorders and administration site conditions	1030 (25)	979 (24)
Nervous system disorders	1004 (25)	972 (24)
Respiratory, thoracic and mediastinal disorders	989 (24)	946 (23)
Metabolism and nutrition disorders	953 (23)	877 (21)

Cardiac disorders	910 (22)	855 (21)
Investigations	869 (21)	931 (23)
Injury, poisoning and procedural complications	748 (18)	697 (17)
Vascular disorders	709 (17)	717 (18)
Skin and subcutaneous tissue disorders	619 (15)	557 (14)
Renal and urinary disorders	607 (15)	561 (14)
Neoplasms benign, malignant and unspecified	510 (13)	513 (13)
Eye disorders	478 (12)	429 (11)
Psychiatric disorders	372 (9)	362 (9)
Blood and lymphatic system disorders	321 (8)	372 (9)
Reproductive system and breast disorders	275 (7)	268 (7)
Ear and labyrinth disorders	227 (6)	208 (5)
Surgical and medical procedures	217 (5)	186 (5)
Hepatobiliary disorders	181 (4)	176 (4)
Endocrine disorders	122 (3)	139 (3)
Immune system disorders	100 (2)	74 (2)
Congenital, familial and genetic disorders	31 (1)	25 (1)
Product issues	13 (0.3)	16 (0.4)
Social circumstances	4 (0.1)	13 (0.3)

A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each subject, multiple TEAEs of the same system organ class will be counted only once within each system organ class. TEAEs are listed in descending order of AMR101 frequency. Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included. All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
Source: Reviewer and REDUCE-IT CSR

The most common TEAEs (preferred terms) that occurred in ≥3% in the AMR101 group and were ≥ 1% greater than Placebo were:

- Musculoskeletal pain
- Constipation
- Edema peripheral
- Gout
- Atrial fibrillation

Events of Diarrhea and Anemia occurred more frequently in placebo than in the AMR101 group.

Adverse events related to eructation, taste perversion, pruritus, and rash have been previously reported by patients taking other omega-3 fatty acid products. None of these events was reported frequently overall in the REDUCE-IT trial and there were no notable imbalances in these categories of events between arms.

Table 48 summarizes the applicant's analysis of TEAEs occurring at ≥ 3% in either treatment group.

Table 48: Treatment-Emergent Adverse Events Occurring at an Incidence of ≥ 3% in Either Treatment Group by Treatment Arm, Safety Population

System Organ Class Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Infections and infestations	1822 (44.6)	1774 (43.4)	3596 (44.0)
Nasopharyngitis	314 (7.7)	300 (7.3)	614 (7.5)
Upper respiratory tract infection	312 (7.6)	320 (7.8)	632 (7.7)
Bronchitis	306 (7.5)	300 (7.3)	606 (7.4)
Pneumonia	263 (6.4)	277 (6.8)	540 (6.6)
Influenza	263 (6.4)	271 (6.6)	534 (6.5)
Urinary tract infection	253 (6.2)	261 (6.4)	514 (6.3)
Sinusitis	169 (4.1)	166 (4.1)	335 (4.1)
Musculoskeletal and connective tissue disorders	1466 (35.9)	1406 (34.4)	2872 (35.1)
Back pain	335 (8.2)	309 (7.6)	644 (7.9)
Arthralgia	313 (7.7)	310 (7.6)	623 (7.6)
Osteoarthritis	241 (5.9)	218 (5.3)	459 (5.6)
Pain in extremity	235 (5.7)	241 (5.9)	476 (5.8)
Musculoskeletal pain	176 (4.3)	130 (3.2)	306 (3.7)
Myalgia	135 (3.3)	147 (3.6)	282 (3.4)
Muscle spasms	101 (2.5)	136 (3.3)	237 (2.9)
Gastrointestinal disorders	1350 (33.0)	1437 (35.1)	2787 (34.1)
Diarrhea	367 (9.0)	453 (11.1)	820 (10.0)
Constipation	221 (5.4)	149 (3.6)	370 (4.5)
Nausea	190 (4.6)	197 (4.8)	387 (4.7)
Gastroesophageal reflux disease	124 (3.0)	118 (2.9)	242 (3.0)
General disorders and administration site conditions	1030 (25.2)	979 (23.9)	2009 (24.6)
Chest pain	273 (6.7)	290 (7.1)	563 (6.9)
Edema peripheral	267 (6.5)	203 (5.0)	470 (5.7)
Fatigue	228 (5.6)	196 (4.8)	424 (5.2)
Non-cardiac chest pain	161 (3.9)	173 (4.2)	334 (4.1)
Nervous system disorders	1004 (24.6)	972 (23.8)	1976 (24.2)
Dizziness	235 (5.7)	246 (6.0)	481 (5.9)
Headache	171 (4.2)	180 (4.4)	351 (4.3)
Respiratory, thoracic, and mediastinal disorders	989 (24.2)	946 (23.1)	1935 (23.7)
Dyspnea	254 (6.2)	240 (5.9)	494 (6.0)
Cough	241 (5.9)	241 (5.9)	482 (5.9)

System Organ Class Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Metabolism and nutrition disorders	953 (23.3)	877 (21.4)	1830 (22.4)
Gout	171 (4.2)	127 (3.1)	298 (3.6)
Diabetes mellitus	169 (4.1)	173 (4.2)	342 (4.2)
Type 2 diabetes mellitus	147 (3.6)	133 (3.3)	280 (3.4)
Cardiac disorders	910 (22.3)	855 (20.9)	1765 (21.6)
Atrial fibrillation	215 (5.3)	159 (3.9)	374 (4.6)
Angina pectoris	200 (4.9)	205 (5.0)	405 (5.0)
Injury, poisoning, and procedural complications	748 (18.3)	697 (17.0)	1445 (17.7)
Fall	149 (3.6)	138 (3.4)	287 (3.5)
Vascular disorders	709 (17.3)	717 (17.5)	1426 (17.4)
Hypertension	320 (7.8)	344 (8.4)	664 (8.1)
Eye disorders	478 (11.7)	429 (10.5)	907 (11.1)
Cataract	233 (5.7)	208 (5.1)	441 (5.4)
Psychiatric disorders	372 (9.1)	362 (8.9)	734 (9.0)
Insomnia	124 (3.0)	111 (2.7)	235 (2.9)
Blood and lymphatic system disorders	321 (7.9)	372 (9.1)	693 (8.5)
Anemia	191 (4.7)	236 (5.8)	427 (5.2)
Metabolism and nutrition disorders	953 (23.3)	877 (21.4)	1830 (22.4)
Gout	171 (4.2)	127 (3.1)	298 (3.6)
Diabetes mellitus	169 (4.1)	173 (4.2)	342 (4.2)
Type 2 diabetes mellitus	147 (3.6)	133 (3.3)	280 (3.4)
Cardiac disorders	910 (22.3)	855 (20.9)	1765 (21.6)
Atrial fibrillation	215 (5.3)	159 (3.9)	374 (4.6)
Angina pectoris	200 (4.9)	205 (5.0)	405 (5.0)
Injury, poisoning, and procedural complications	748 (18.3)	697 (17.0)	1445 (17.7)
Fall	149 (3.6)	138 (3.4)	287 (3.5)
Vascular disorders	709 (17.3)	717 (17.5)	1426 (17.4)
Hypertension	320 (7.8)	344 (8.4)	664 (8.1)
Eye disorders	478 (11.7)	429 (10.5)	907 (11.1)
Cataract	233 (5.7)	208 (5.1)	441 (5.4)
Psychiatric disorders	372 (9.1)	362 (8.9)	734 (9.0)
Insomnia	124 (3.0)	111 (2.7)	235 (2.9)
Blood and lymphatic system disorders	321 (7.9)	372 (9.1)	693 (8.5)
Anemia	191 (4.7)	236 (5.8)	427 (5.2)

Source: REDUCE-IT CSR. Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term. TEAEs are listed in descending order of AMR101 frequency. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

1 All adverse events were coded using the MedDRA, Version 20.1.

We also considered TEAEs by other levels of the MedDRA hierarchy. Table 49 summarizes the most frequent events by high-level term (HLT). The most frequent TEAEs by HLT were Upper and lower respiratory tract infections, and Musculoskeletal and unspecified pain. Notable imbalances are consistent with the findings by PT,

including increased incidence of musculoskeletal and other pain in the AMR101 arm, and increased incidence of diarrhea in the placebo arm.

Table 49: Treatment Emergent Adverse Events by MedDRA High Level Term, Safety Population

High Level Term, n (%)	AMR101 N=4089	Placebo N=4090
Upper respiratory tract infections	767	783
Musculoskeletal and connective tissue pain and discomfort	689	659
Lower respiratory tract and lung infections	578	570
Pain and discomfort NEC	464	494
Breathing abnormalities	413	399
Diabetes mellitus (incl subtypes)	369	334
Diarrhoea (excl infective)	367	454
Joint related signs and symptoms	348	340
Gastrointestinal atonic and hypomotility disorders NEC	338	265
Urinary tract infections	333	341
Vascular hypertensive disorders NEC	322	347
Oedema NEC	308	225
Supraventricular arrhythmias	300	236
Ischaemic coronary artery disorders	291	313
Asthenic conditions	287	256
Osteoarthropathies	287	258
Neurological signs and symptoms NEC	277	280
Influenza viral infections	265	273
Coughing and associated symptoms	262	254
Cataract conditions	245	219
Non-site specific injuries NEC	241	224
Gastrointestinal and abdominal pains (excl oral and throat)	238	237
Nausea and vomiting symptoms	233	246
Renal failure and impairment	231	212
Anaemias NEC	219	257
Disorders of purine metabolism	203	145
Source: Reviewer's analysis		

<u>Musculoskeletal and Connective Tissue Disorders</u>

Overall no meaningful imbalance was seen in the musculoskeletal and connective tissue disorder system organ class (SOC), 35.9% AMR101 vs. 34.4% Placebo, with the exception of the preferred term "musculoskeletal pain" which occurred in ≥ 3% of patients in the AMR101 group and was 1.1% greater than Placebo).

There were no differences in patients experiencing the PT Rhabdomyolysis, 3 (0.1%) patients in the AMR101 group and 6 (0.1%) in the Placebo group. The PT Blood creatine phosphokinase increased occurred in 54 (1.3%) patients in the AMR101 group and 79 (1.9%) in the Placebo group.

Table 50 summarizes creatine phosphokinase elevations in the study arms. Creatinine kinase elevations > 5XULN to 10XULN, and >10XULN were similar between the two arms, but more patients on AMR101 experienced elevations in creatine kinase between 1X ULN and 5XULN.

Table 50: Number and Percent of Patients with Increases in Creatine Kinase

	AMR101 N=4089	**Placebo N=4090**
Creatine kinase	n= 3977	n= 3978
>10X ULN	3 (0.1%)	5 (0.1%)
5X ULN to 10X ULN	6 (0.2%)	12 (0.3%)
> 1XULN to 5X ULN	920 (23.1%)	733 (18.4%)

Source: REDUCE IT Section 14, Table 14.3.4.3.4

Gastrointestinal Disorders

In post-marketing safety surveillance, the most commonly reported experiences associated with AMR101 were gastrointestinal disorders (abdominal discomfort and diarrhea). In REDUCE-IT, adverse events related to the SOC Gastrointestinal Disorders occurred in 33% of the AMR101 group and 35.1% in Placebo. Diarrhea occurred in 9% of patients in AMR101 vs. 11.1% in Placebo, a difference of 2.1% between arms (worse in placebo). The difference in diarrhea between treatment arms may be due to the mineral oil content of Placebo, but this is an unconfirmed hypothesis.

Peripheral Edema

Under the General disorders and administration site conditions, more patients in the AMR101 group reported the preferred term Edema peripheral than in Placebo (6.5% vs. 5.0%, respectively, a difference of 1.5% from Placebo. A variety of clinical conditions are associated with the development of edema, including heart failure, cirrhosis, and the nephrotic syndrome, as well as local conditions such as venous and lymphatic disease.

No significant differences were observed between the AMR101 and placebo groups for the tertiary endpoints of newly emergent CHF events (HR of 0.95 [95% CI: 0.77 to 1.17]) or newly emergent CHF events requiring hospitalization (HR of 0.97 [95% CI: 0.77 to 1.22]). Patients with cirrhosis were excluded from the trial.

A literature search of “peripheral edema” and “omega-3 fatty acids” was conducted, and the data available were limited. There were no published reports of omega-3 fatty acids causing peripheral edema. One article concluded that EPA supplementation lead to decreased pulmonary edema in a rat model (Sane 2000).

Gout

Under the Metabolism and General Disorders SOC, The PT Gout occurred in 171 patients (4.2%) of the AMR101 group and 127 patients (3.1%) in the Placebo group, at a difference of 1.1% more in the AMR101 arm than in the Placebo arm. Hyperuricemia was reported in 33 (0.8%) in the AMR101 group and 19 (0.5%) in the Placebo group.

A literature search of “gout” and “omega-3 fatty acids” was conducted, and the data available do not suggest an association with gout and omega-3 fatty acids. Some articles found a lower rate of recurrent gout flares when dietary omega-3 rich fish consumption was adjusted for total purine intake (Zhang 2019). Another article suggested the potential use of omega-3 fatty acids in gout for their anti-inflammation mechanism (Yan 2013).

6.1.1. **Laboratory Findings**

Potentially Clinically Significant Laboratory Results

The Applicant defined potentially clinically significant chemistry values at the outset of the trial. A treatment-emergent potentially clinically significant (PCS) high value at any time was defined as a change from a value less than or equal to the upper reference limit at baseline to a PCS high value at any post-baseline measurement. A treatment-emergent PCS low value at any time was defined as a change from a value greater than or equal to the lower reference limit at baseline to a PCS low value at any post-baseline measurement. The criteria for PCS chemistry and hematology values are provided below.

Table 51: Potentially Clinically Significant Chemistry Values

Parameter	PCS Low	PCS High
Albumin	≤3.3 g/dL	≥5.8 g/dL
Alkaline Phosphatase	NA	>1 × ULN to 2 × ULN >2 × ULN to 3 × ULN >3 × ULN
ALT	NA	>1 × ULN to 2 × ULN >2 × ULN to 3 × ULN >3 × ULN
AST	NA	>1 × ULN to 2 × ULN >2 × ULN to 3 × ULN >3 × ULN
Bilirubin	NA	>1 × ULN to 2 × ULN >2 × ULN to 3 × ULN >3 × ULN
ALT + Bilirubin	NA	>3 × ULN (ALT) + 2 × ULN (Bilirubin)
AST + Bilirubin	NA	>3 × ULN (AST) + 2 × ULN (Bilirubin)
Calcium	≤7 mg/dL	≥11 mg/dL; ≥12 mg/dL
Chloride	<70 mmol/L	>120 mmol/L
Creatinine	<0.5 mg/dL (female) <0.65 mg/dL (male)	>1.6 mg/dL (female) >2.0 mg/dL (male); ≥50% increase from baseline
Creatine Kinase	<30 U/L (female) <0.55 U/L (male)	>1 × ULN to 5 × ULN >5 × ULN to 10 × ULN >10 × ULN
Glucose (fasting)	≤36 mg/dL; ≤70 mg/dL	≥126 mg/dL; ≥130 mg/dL
Potassium	≤3.0 mEq/L	≥5.5 mEq/L
Sodium	≤130 mEq/L	≥150 mEq/L
Total Protein	<5.0 g/dL	≥9.5 g/dL
Urea Nitrogen (BUN)	NA	≥31 mg/dL
Uric Acid	<1.9 mg/dL (female) <2.5 mg/dL (male)	>7.5 mg/dL (female) >8 mg/dL (male)

Source: REDUCE IT CSR, pg. 107/354. Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; NA = not applicable; PCS = potentially clinically significant; ULN = upper limit of normal.

Table 52: Potentially Clinically Significant Hematology Values

Parameter	PCS Low	PCS High
Red Blood Cells	<3.5 × 10^6/uL (female) <3.8 × 10^6/uL (male)	>5.5 × 10^6/uL (female) >6.0 × 10^6/uL (male)
Hemoglobin	<10.0 g/dL (female) <10.0 g/dL (male)	>16.5 g/dL (female) >18.0 g/dL (male)
Hematocrit	<37% (female) <42% (male)	>42% (female) >50% (male)
White Blood Cells	<1.5 × 10^3/uL	NA
White Cell Differential	Segmented neutrophils <50% Lymphocytes <30% Monocytes NA Basophils NA Eosinophils NA	Segmented neutrophils >70% Lymphocytes >45% Monocytes >6% Basophils >1% Eosinophils >3%
Platelet Count	<100 × 10^3/uL	>500 × 10^3/uL

Source: REDUCE-IT CSR, pg. 108/354. Abbreviations: NA = not applicable; PCS = potentially clinically significant.

Hemoglobin and Platelet Counts

Bleeding and anemia have been previously reported by patients taking omega-3 fatty acids. However, bleeding time and PT/PTT were not collected in this study.

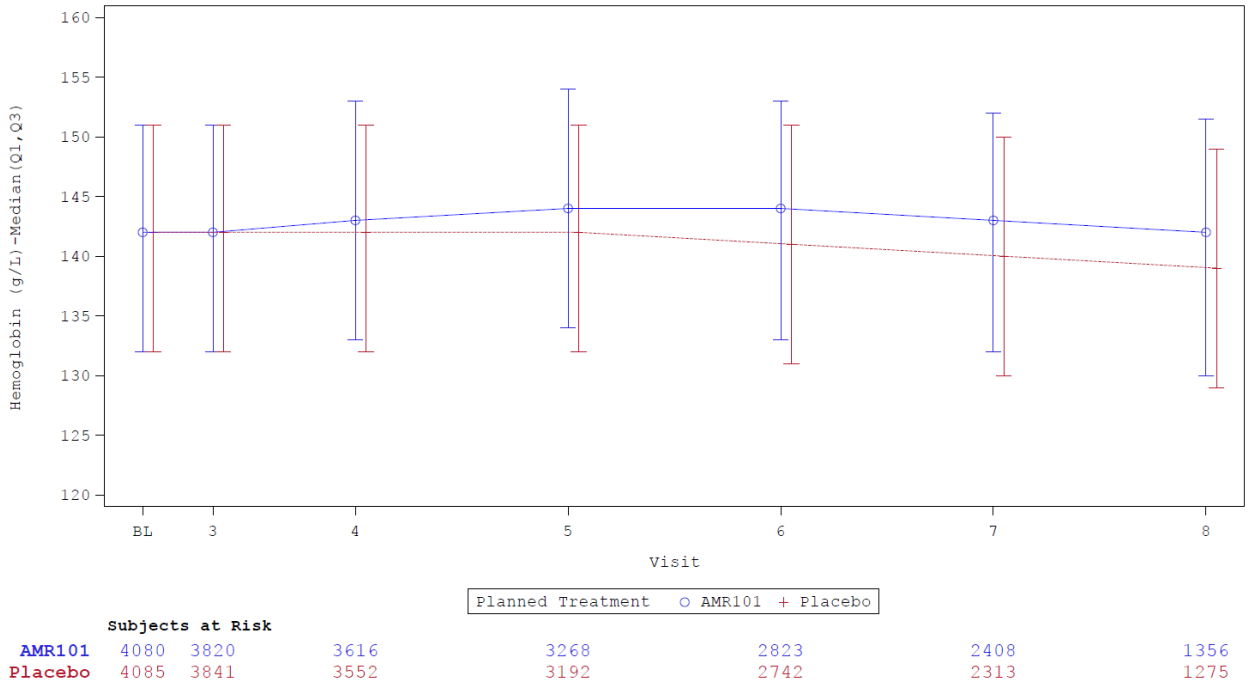
Table 53 summarizes mean baseline values and changes from baseline over time in hemoglobin and platelet count, by treatment group, and Figure 12 depicts hemoglobin over time. Changes from baseline in hemoglobin and platelets were relatively small and less than changes observed in placebo.

Table 53: Mean (SD) Baseline Values and Change in Baseline in Hemoglobin and Platelet Count from Baseline to Last Visit, by Treatment Arm (Safety Population)

Parameter Time point	AMR101 (N=4089)		Placebo (N=4090)	
	n	Mean (SD)	n	Mean (SD)
Hemoglobin (g/L)				
Baseline (Visit 2)	4080	141.16 (14.270)	4085	141.73 (14.219)
Change from BL to Last Visit	3960	-1.12 (12.326)	3963	-3.88 (12.727)
Platelet Count (×10^9/L)				
Baseline (Visit 2)	4075	243.01 (66.094)	4075	241.51 (64.636)
Change from BL to Last Visit	3951	-5.52 (51.553)	3952	-10.84 (52.235)

Source: Adapted from REDUCE-IT CSR Table 12-15, p. 236/354
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; SD = standard deviation.

Figure 12: Median (Q1, Q3) Hemoglobin Over Time



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Liver Enzymes and Related Adverse Events

Patients with active severe liver disease: cirrhosis, active hepatitis, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3X upper limit of normal (ULN), or with biliary obstruction with hyperbilirubinemia (total bilirubin > 2 XULN) were excluded from the study. During the trial, ALT and AST, total bilirubin, and alkaline phosphatase testing were collected at Screening, Day 0/Randomization, and Days 120, 360, 720, 1080, 1440, 1800, 2160, and at Last Visit.

The following reasons were considered for study drug discontinuation:
- ALT >3 × ULN and bilirubin >1.5 × ULN
- ALT >5 × ULN
- ALT >3 × ULN and appearance or worsening of hepatitis
- ALT >3 × ULN persisting for >4 weeks
- ALT >3 × ULN and could not be monitored weekly for 4 weeks

Median AST and ALT decreased slightly from baseline in both arms. Table 54 summarizes ALT and AST at baseline and the final visit.

Table 54: Mean (SD) Baseline and Change from Baseline in AST and ALT to Last Visit, By Treatment Group (Safety Population)

Parameter Time point	AMR101 (N=4089)		Placebo (N=4090)	
	n	Mean (SD)	n	Mean (SD)
ALT (U/L)				
Baseline (Visit 2)	4085	27.72 (13.730)	4088	28.64 (21.080)
Change from BL to Last Visit	3968	-2.33 (17.416)	3970	-3.47 (24.834)
AST (U/L)				
Baseline (Visit 2)	4084	24.47 (9.564)	4086	24.76 (11.641)
Chang from BL to Last Visit	3965	-1.25 (12.925)	3965	-1.01 (22.231)

Source: Adapted from REDUCE-IT CSR Table 12-16, p. 238/354
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; SD = standard deviation.
Upper limit of normal: ALT 32-43; AST 34-46

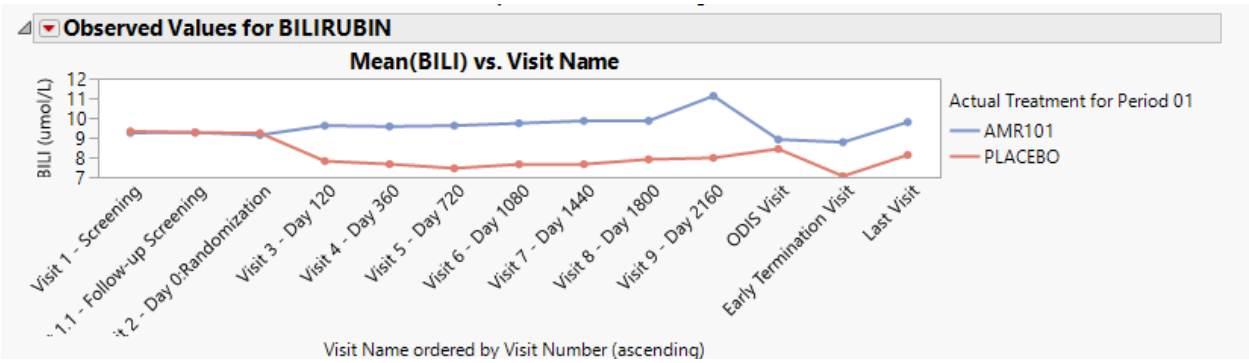
Total bilirubin increased in the AMR101 arm relative to placebo, largely due to a decrease in bilirubin in the placebo arm. The significance of the difference between arms is unclear. Table 55 and Figure 13 summarize total bilirubin over time.

Table 55: Summary of Serum Total Bilirubin Change from Baseline, Safety Population

Bilirubin (umol/L) [Ref: 3.42 – 20.52]			AMR101 (N=4089)	Placebo (N=4090)
Baseline	Observed Result	n	4086	4088
		Mean (SD)	9.14 (4.569)	9.24 (4.532)
Visit 3 – Day 120	Change from Baseline	n	3860	3862
		Mean (SD)	0.46 (3.442)	-1.43 (3.349)
Visit 4 - Day 360	Change from Baseline	n	3661	3606
		Mean (SD)	0.42 (3.550)	-1.60 (3.454)
Visit 5 - Day 720	Change from Baseline	n	3328	3239
		Mean (SD)	0.36 (3.819)	-1.86 (3.568)
Visit 6 - Day 1080	Change from Baseline	n	2870	2775
		Mean (SD)	0.44 (3.817)	-1.75 (4.164)
Visit 7 - Day 1440	Change from Baseline	n	2444	2343
		Mean (SD)	0.51 (3.757)	-1.75 (3.755)
Visit 8 - Day 1800	Change from Baseline	n	1371	1292
		Mean (SD)	0.50 (3.871)	-1.54 (4.062)
Analysis Last Visit	Change from Baseline	n	3969	3970
		Mean (SD)	0.53 (4.151)	-1.22 (4.884)

Source: Adapted from REDUCE-IT CSR Section 14, Table 14.3.4.3.1 pp. 2306-2310/2510

Figure 13: Total Bilirubin by Visit, Safety Population



Source: Reviewer Analysis

Table 56 summarizes potentially clinically significant changes in ALT, AST, total bilirubin, and alkaline phosphatase. Increases in ALT >3X ULN, AST >3X ULN, and ALP >2XULN were lower in the AMR101 arm versus Placebo. ALT or AST >ULN occurred in slightly more patients in the AMR101 arm. The higher rate of AST and ALT elevations above the normal range are of unclear significance.

Bilirubin elevations >ULN and >2x ULN were more frequent in the AMR101 arm, whereas ALP elevations above normal and >2x ULN were more frequent in placebo patients.

Table 56: Treatment Emergent Liver Function Test Elevations, by Treatment Group, Safety Population

Statistic at Any Post-Baseline Visit, n (%)	AMR101 (N=4089)	Placebo (N=4090)
ALT	3977	3978
>3 × ULN	44 (1.1)	57 (1.4)
>ULN	1308 (32.9)	1206 (30.3)
AST	3975	3975
>3 × ULN	36 (0.9)	40 (1.0)
>ULN	932 (23.4)	894 (22.5)
Total Bilirubin	3977	3978
>2 × ULN	21 (0.5)	7 (0.2)
>ULN	297 (7.5)	106 (2.7)
ALP	3977	3978
>2 × ULN	18 (0.5)	30 (0.8)
>ULN	308 (7.7)	494 (12.4)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; PCS = potentially clinically significant; ULN = upper limit of normal.
Note: Potential drug-induced liver injuries were investigated through the above analysis of liver toxicity. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N) at any post-baseline visit (or last visit) for the referenced laboratory tests (n). Categories are not mutually exclusive.
Source: REDUCE-IT CSR, Table 12-17, p. 241/354.

Cholestatic Jaundice

Three patients experienced an TEAE of jaundice, cholestatic, all on AMR101. We reviewed the narrative summaries of these patients. Two cases were confounded by diagnoses of pancreatic cancer, and the jaundice appeared to be unrelated to study drug. In the third case, an association with AMR101 could not be excluded, but the case was confounded by other factors, including concomitant medications.

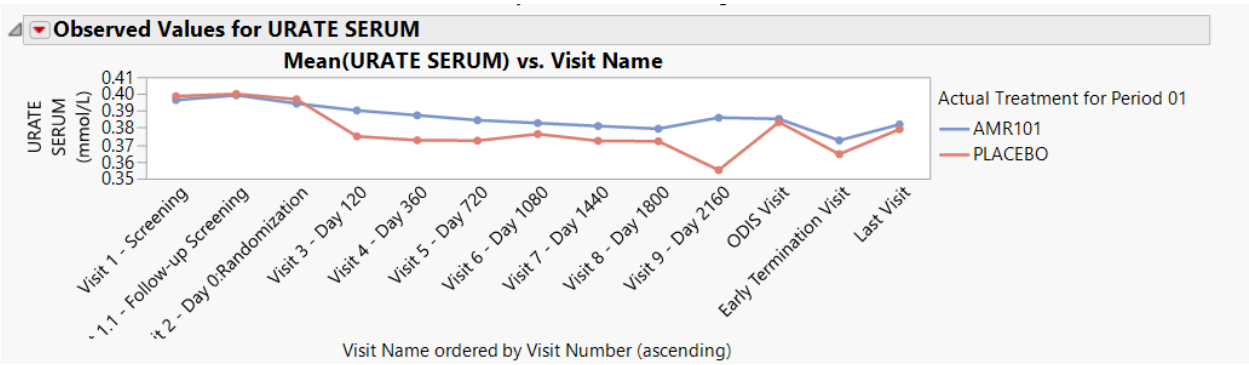
Potential Hy's Law Cases

One patient in the AMR101 arm and one patient in the placebo arm met laboratory criteria for potential Hy's law, with an ALT or AST >3X ULN, total bilirubin >2XnULN, and Alkaline phosphatase <2X ULN (Patient (b) (6)). Although an association with AMR101 could not be completely ruled out, the AMR101 case was confounded by multiple concomitant medications, including simvastatin, colchicine, and allopurinol. The placebo case was confounded by a diagnosis of pancreatic cancer.

<u>Other Clinical Chemistries</u>

There were no clinically significant changes from baseline in other laboratory parameters, including leukocytes, serum electrolytes, plasma glucose, HbA1C, blood urea nitrogen, or creatinine. In the ITT population, mean HbA1C increased from 6.59% at baseline to 6.66% at Year 1 and 6.78% at the final study visit, with no meaningful difference between arms at any timepoint. In the placebo arm, mean serum urate decreased slightly from baseline and relative to the AMR101 arm (Figure 14). The significance of this difference is unclear.

Figure 14: Serum Urate by Visit, Safety Population



Source: Reviewer analysis

6.1.2. **Vital Signs and Electrocardiogram**

Blood Pressure

Mean blood pressure changed minimally over time, and the between-arm difference was small. From baseline to Visit 3 (Day 120), systolic BP decreased by 0.5 mmHg in the AMR101 versus a 0.9 mmHg increase in the Placebo arm, while diastolic blood pressure increased slightly in both arms (0.1 mmHg placebo versus 0.7 mmHg AMR101). At the Last Visit, systolic BP increased in both the AMR101 and Placebo arms (0.9 versus 1.5 mmHg, respectively), while diastolic BP decreased in both arms (0.7 versus 0.4).

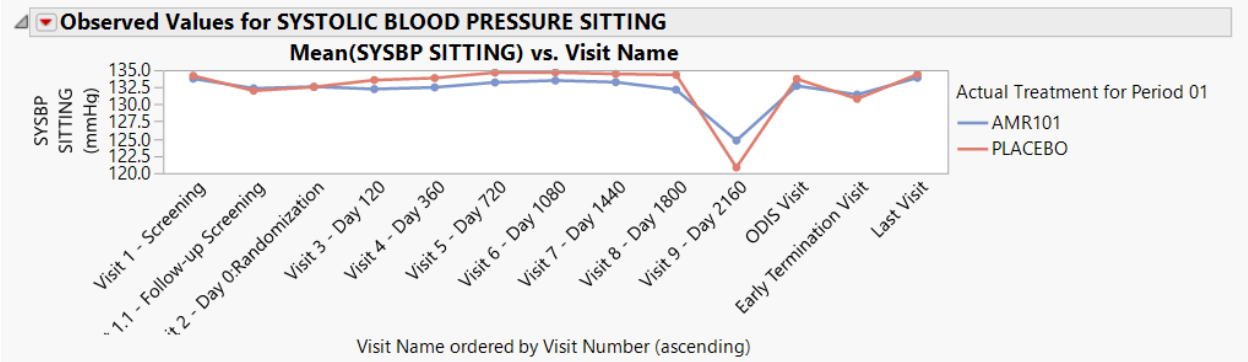
Table 57 and Figure 15 summarize the mean (SD) change from Baseline in systolic and diastolic blood pressure to different visits.

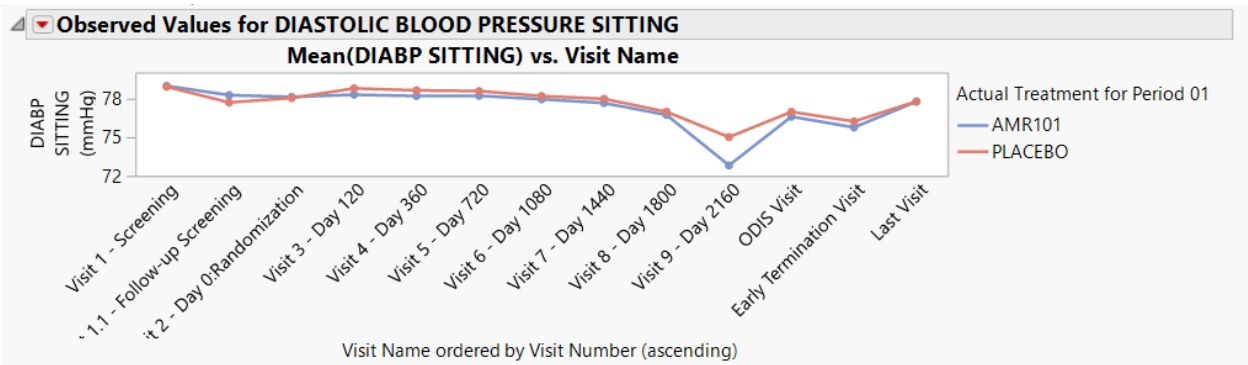
Table 57: Mean Change in Blood Pressure by Treatment Group, Safety Population

Parameter	AMR101 (N=4089)		Placebo (N=4090)	
Time point	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Systolic Blood Pressure (mmHg)				
Baseline (Visit 2)	4082	132.6 (15.64)	4076	132.5 (15.49)
Change from Baseline to:				
Visit 3	3913	-0.5 (13.99)	3904	0.9 (13.93)
Visit 4	3716	-0.2 (14.82)	3660	1.3 (14.81)
Visit 5	3377	0.5 (15.51)	3283	1.8 (15.87)
Visit 6	2920	0.9 (16.17)	2811	2.0 (16.67)
Visit 7	2485	0.8 (16.79)	2378	1.7 (16.89)
Visit 8	1394	0.4 (16.77)	1320	1.8 (17.97)
Visit 9	8	-5.4 (15.57)	3	-1.2 (12.89)
Last Visit	3980	0.9 (17.11)	3981	1.5 (17.13)
Diastolic Blood Pressure (mmHg)				
Baseline (Visit 2)	4082	78.1 (9.13)	4076	78.0 (9.04)
Change from Baseline to:				
Visit 3	3913	0.1 (8.46)	3904	0.7 (8.38)
Visit 4	3716	-0.1 (8.91)	3660	0.5 (8.98)
Visit 5	3377	-0.1 (9.27)	3283	0.3 (9.50)
Visit 6	2920	-0.4 (9.63)	2811	0.0 (9.73)
Visit 7	2485	-0.5 (9.89)	2378	-0.2 (10.26)
Visit 8	1394	-1.0 (10.29)	1320	-1.0 (10.39)
Visit 9	8	-2.7 (10.00)	3	2.0 (15.06)
Last Visit	3980	-0.7 (10.11)	3981	-0.4 (10.11)

Source: REDUCE-IT CSR, Table 12-21, pg. 247/354.

Figure 15: Mean systolic and diastolic pressure by treatment arm and Visit.





There was no clear difference between treatment arms in the proportion of individual patients experiencing potentially clinically significant changes in blood pressure.

A greater proportion of patients in the AMR101 treatment arm met criteria for a potentially clinically significant *decrease* in blood pressure at any time during the study. About 25% of patients in the AMR101 arm experienced an SBP *decrease* of $\geq$ 20 mmHg from baseline versus about 22% of patients in placebo. About 38% of AMR101 patients experienced a DBP *decrease* of $\geq$ 10 mmHg versus about 35% in placebo. Fewer than 1% of patients in either arm met criteria based on absolute SBP $\leq$ 90 mmHg or DBP $\leq$ 50 mmHg.

A slightly greater proportion of Placebo patients (19% v. 17% AMR101) met criteria for a potentially clinically significant increase in SBP $\geq$ 160 mmHg at any time between the treatment arms, while a slightly greater proportion of AMR101 patients (5.5% v. 4.9% placebo) met criteria based on an absolute increase in DBP $\geq$ 100 mmHg. The proportion of patients who met criteria based on relative increase in SBP $\geq$ 20 mmHg or DBP $\geq$ 10 mmHg was similar in both arms. Table 58 summarizes potentially clinically significant blood pressure values.

Table 58: Summary of Potentially Clinically Significant Blood Pressure Values

PCS Category	AMR101 (N=4089)	Placebo (N=4090)
Any Postbaseline SBP PCS Low <= 90 mmHg	40/4089 (1.0%)	22/4090 (0.5%)
Any Postbaseline DBP PCS Low <= 50 mmHg	42/4089 (1.0%)	37/4090 (0.9%)
Any Postbaseline SBP Decrease of >= 20 mmHg	1009/4089 (24.7%)	904/4090 (22.1%)
Any Postbaseline DBP Decrease of >=10 mmHg	1569/4089 (38.4%)	1444/4090 (35.3%)
Any Postbaseline SBP PCS High >= 160 mmHg	715/4089 (17.5%)	784/4090 (19.2%)
Any Postbaseline DBP PCS High >= 100 mmHg	223/4089 (5.5%)	199/4090 (4.9%)
Any Postbaseline SBP Increase of >= 20 mmHg	1163/4089 (28.4%)	1192/4090 (29.1%)
Any Postbaseline DBP Increase of >= 10 mmHg	1442/4089 (35.3%)	1468/4090 (35.9%)

Source: Applicant Response to Information Request 09 03 2019
PCS=Potentially Clinically Significant; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure

Greater than 95% of patients experiencing potentially clinically significant blood pressure changes were on antihypertensive medications at baseline, about the same as the overall population. Imbalances in potentially clinically significant events between arms were similar, regardless of specific background therapy. Table 59 summarizes the results for increase in SBP $\geq$ 160 by baseline antihypertensive medication. Results for other categories (not shown) were similar.

Table 59: Summary of Potentially Clinically Significant Increase in Systolic Blood Pressure > 160 mmHg, by Baseline Antihypertensive Medications, Safety Population

PCS Category Drug Class	AMR101 (N=4089)	Placebo (N=4090)
Any Postbaseline SBP PCS High >= 160 mmHg	715/4089 (17.5%)	784/4090 (19.2%)
Subjects with Any Anti-Hypertensive Medication	692/ 715 (96.8%)	764/ 784 (97.4%)
ACE	365/ 715 (51.0%)	414/ 784 (52.8%)
ARB	243/ 715 (34.0%)	250/ 784 (31.9%)
Beta Blockers	534/ 715 (74.7%)	565/ 784 (72.1%)
Calcium Channel Blockers	278/ 715 (38.9%)	292/ 784 (37.2%)
Diuretics	342/ 715 (47.8%)	367/ 784 (46.8%)
RAAS Inhibitor	594/ 715 (83.1%)	649/ 784 (82.8%)
Other	56/ 715 (7.8%)	53/ 784 (6.8%)

Source: Applicant Response to Information Request 09 03 2019
Note: Percentages for drug classes within each group are based on the number of subjects within each PCS category;
PCS=Potentially Clinically Significant; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure;
ACE=Angiotensin-Converting Enzyme; ARB=Angiotensin-Receptor Blockers; RAAS=Renin-Angiotensin-Aldosterone System

In summary, the magnitude of change in blood pressure (systolic or diastolic) from baseline in each arm was small, as was the difference between-arm. Small differences in

the proportion of patients in the AMR101 arm and the Placebo arm experiencing clinically significant increases or decreases in individual blood pressure parameters, demonstrated no consistent trends favoring either arm. Overall, there was no evidence of a clinically meaningful adverse effect on blood pressure in either arm.

Other findings such as heart rate or physical examination parameters (body weight and waist circumference) were generally consistent across treatment groups.

Electrocardiograms (ECGs)

There were no meaningful differences between arms in patients meeting criteria for clinically significant ECG findings, such as PR Prolongation, QRS prolongation, or QTc prolongation. Overall, there were very few patients with ECG findings reported as treatment-emergent adverse events, 55 (1.3%) patients in the AMR101 arm and 46 (1.1%) in the placebo arm. The most frequently reported MedDRA preferred terms were Electrocardiogram QT prolonged, Electrocardiogram abnormal and Electrocardiogram T wave abnormal.

FDA CARDIOLOGY CONSULT REVIEW

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are very-long-chain polyunsaturated omega-3 fatty acids (OFAs). The human body does not produce OFAs, nor can it synthesize OFAs from dietary omega-6 fatty acids.[2] Dietary sources of EPA and DHA include fish, fish oils, dietary supplements, and fortified food products. FDA approved formulations of OFAs are Lovaza, Vascepa, and Epanova. Table 1 summarizes the composition, and indication of the approved OFAs, and any arrhythmia related warning(s)/precaution(s).

Table 1. FDA Approved Omega 3 Fatty Acid Formulations (Source: Clinical Reviewer)

Drug Product, Sponsor	Formulation	EPA / DHA (g per capsule)	Dose	Warning and Precautions related to arrhythmia	Indication
Lovaza® (GlaxoSmithKline)	Ethyl Esters of EPA and DHA	EPA 0.465 g DHA0.375 g	4 grams per day with food	Recurrent AF	Adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia
Vascepa® (Amarin Pharmaceuticals)	Ethyl Esters of EPA only	EPA 1 g	4 grams per day with food	None	
Epanova® (AstraZeneca)	Free Fatty Carboxylic Acids of EPA and DHA	EPA 0.550 g DHA 0.200 g	2 to 4 grams per day without regard to food	None	
EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, TG: Triglyceride					

Omega-3 Fatty Acids and Cardiovascular Disease

Observational and randomized trial data support the role of OFAs in reducing the incidence of cardiovascular disease (CVD), including ventricular tachycardia (VT) associated sudden cardiac death (SCD).[3] The 2017 American Heart Association (AHA) Science Advisory[4] recommends the consumption of either one to two servings of oily fish per week or daily fish oil supplements (around 1 g of omega-3 polyunsaturated fatty acids per day) in adults. Additionally, AHA recommends that treatment with OFA supplementation is reasonable for

- secondary prevention of coronary heart disease (CHD) and SCD among patients with prevalent CHD (Class IIa Recommendation)
- patients with heart failure with reduced ejection fraction (Class IIa Recommendation)

[2] Chenchen Wang, William S Harris, Mei Chung, Alice H Lichtenstein, Ethan M Balk, Bruce Kupelnick, Harmon S Jordan, Joseph Lau. n−3 Fatty acids from fish or fish-oil supplements, but not α-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. The American Journal of Clinical Nutrition, Volume 84, Issue 1, July 2006, Pages 5–17, https://doi.org/10.1093/ajcn/84.1.5

[3] Christine M. Albert. Omega-3 Fatty Acids, Ventricular Arrhythmias, and Sudden Cardiac Death Antiarrhythmic, Proarrhythmic, or Neither. Circulation: Arrhythmia and Electrophysiology. 5(3):456–459, JUNE 2012
DOI: 10.1161/CIRCEP.112.971416, PMID: 22715236

[4] David S. Siscovick et al, Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease: A Science Advisory From the American Heart Association. *Circulation.* 2017;135:e867–e884. DOI: 10.1161/CIR.0000000000000482

Treatment with OFA is not recommended for general population without prior CHD; and for patients with or at risk for diabetes mellitus (DM) to prevent CVD.

In 2019, following REDUCE-IT trial, the American Diabetic Association medical treatment guideline[5], the American Heart Association advisory,[6] the European Society of Cardiology (ESC), and the European Atherosclerosis Society (EAS) recommend (class IIa, level of evidence B) the use of 4 g/day of Vascepa in high-risk patients with TG levels between 135-499 mg/dL despite statin treatment.

Omega-3 Fatty Acids and Mechanism of Anti-Arrhythmic Effect

The proposed mechanisms of action of OFAs in suppression of ventricular arrhythmias include prolongation of refractory period of the cardiomyocyte via inhibition of voltage-gated sodium channels, decrease in cytosolic free calcium, and increase in vagal tone.[2,7] However, data supporting these and other mechanisms of action of OFAs such as lower triacylglycerol concentrations, lower blood pressure, and decreased platelet aggregation are inconsistent. No major effect of OFAs on atherosclerotic progression, plaque stability, plaque rupture, or thrombosis has been demonstrated.[8]

While most data indicate that OFAs are protective against cardiac arrhythmias, there are some studies that suggest they might be proarrhythmic. Coronel and co-workers[9] demonstrated that dietary n-3 and n-9 fatty acids reduce excitability and cause arrhythmias during regional ischemia in the isolated porcine heart preparation. In patients with structural heart disease and an implantable cardioverter defibrillator (ICD), fish oil supplementation showed no effect or even a proarrhythmic response[10]. There is a paucity of nonclinical data examining the mechanism of action of effect of OFAs on atrial fibrillation/flutter (AF). Some clinical studies, described in the following section, have evaluated the effect of OFAs on AF.

Fish Oil and Atrial Fibrillation/Flutter

Clinical data do not support a benefit of OFA supplementation in primary or secondary prevention of atrial fibrillation/flutter (AF). There are no large randomized, placebo-controlled trials evaluating the role of OFA supplementation in primary prevention of AF. For secondary prevention, randomized controlled trial (RCT) data do not support the use of OFAs to prevent recurrent AF or postoperative AF after cardiac surgery (Class III: No Benefit).[3]

[5] American Diabetes Association. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2019. http://care.diabetesjournals.org/content/42/Supplement_1/S103.

[6] Skulas-Ray AC, Wilson PWF, Harris WS, Brinton EA, Kris-Etherton PM, Richter CK, Jacobson TA, Engler MB, Miller M, Robinson JG, Blum CB, Rodriguez-Leyva D, de Ferranti SD, Welty FK; on behalf of the American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Omega-3 fatty acids for the management of hypertriglyceridemia: a science advisory from the American Heart Association. Circulation. 2019; https://www.ahajournals.org/doi/10.1161/CIR.0000000000000709.

[7] Goel, A.; Pothineni, N.V.; Singhal, M.; Paydak, H.; Saldeen, T.; Mehta, J.L. Fish, Fish Oils and Cardioprotection: Promise or Fish Tale? Int. J. Mol. Sci. 2018, 19, 3703.

[8] Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J Am Coll Cardiol*. 2011;58:2047–2067. doi: 10.1016/j. jacc.2011.06.063.

[9] Coronel R, Wilms-Schopman FJG, Den Ruijter HM, Belterman CN, Schumacher CA, Opthof T, Hovenier R, Lemmens AG, Terpstra AHM, Katan MB, Zock P: Dietary n-3 fatty acids promote arrhythmias during acute regional myocardial ischemia in isolated pig hearts. Cardiovascular Research 73 (2007) 386-394.

[10] Raitt MH, Conner WE, Morris C, Kron J, Halperin B, Chugh SS, McClelland J, Cook J, MacMurdy K, Swenson R, Conner SL, Gerhard G, Kraemer DF, Oseran D, Marchant C, Calhoun D, Shnider R, McAnulty J: Fish oil supplementation and risk of ventricular tachycardia and ventricular fibrillation in patients with implantable defibrillators. JAMA 293 (2005) 2884-2890.

To evaluate the effect of OFAs on recurrent AF, Kowey[11] randomized 663 subjects with symptomatic paroxysmal AF (n = 542) or persistent AF (n = 121) without underlying structural heart disease to 4 grams of Lovaza versus placebo. The median baseline TG level was 127 mg per dL. At 24 weeks, the overall hazard ratio (HR) for incident symptomatic AF (primary endpoint) with Lovaza was 1.25; 95% CI: 1.00, 1.40. While Lovaza did not reduce the incidence of recurrent symptomatic AF, potential pro-arrhythmic effect could not be excluded and led to the AF warning/precaution statement in the Lovaza label. An RCT by Macchia[11] also did not demonstrate a benefit with 1 gram of OFA on recurrent AF. Table 2 summarizes the two RCTs (Kowey and Macchia) of OFA supplementation in patients with AF.[8,12]

Table 2. Randomized Controlled Trials of Secondary Prevention of Atrial Fibrillation with Omega-3 Fatty Acids (Source: AHA Advisory)[3]

Study, Author, Year	Trial Design, No. of Subjects, Duration	Patient Population	Intervention and Control	End Point Results (Primary End Point)	Strengths and Limitations
Kowey et al[8] 2010	RCT n=663 6 mo	Inclusion criteria: age ≥18 y, symptomatic paroxysmal or persistent AF, in normal sinus rhythm at baseline	Intervention: 6.7 g/d EPA+DHA for 7 d, then 3.4 g/d for the duration of the study	Primary end point: symptomatic recurrence of AF (including flutter)	Strengths: double blinding, tested higher dose of omega-3 PUFA relative to prior smaller trials, low dropout rate
		Exclusion criteria: permanent AF, secondary AF (e.g., caused by hypothyroidism), current use of antiarrhythmic therapy, use of amiodarone within past 6 mo, prior ablation therapy for AF, specific structural cardiac disorders	Comparator: placebo (corn oil)	Combined AF recurrence; 314 events; RR, 1.22 (95% CI, 0.98–1.52)	Limitations: lack of information on dietary (background) omega-3 PUFA intake, lower-than-expected AF recurrence rate, may have underestimated AF recurrence because of ascertainment method (trans telephonic monitoring)
				In participants with paroxysmal AF: 264 events; RR, 1.15 (95% CI, 0.90–1.46)	
				In participants with persistent AF: 50 events; RR, 1.64 (95% CI, 0.92–2.92)	
FORWARD Macchia et al[9] 2013	RCT n=586 12 mo	Inclusion criteria: age ≥21 y, previous symptomatic AF that recovered to normal sinus rhythm	Intervention: 0.85 g/d EPA+DHA	Primary end point: time to first recurrence of an AF episode (symptomatic or asymptomatic); 125 events; RR, 1.28 (95% CI, 0.90–1.83)	Strengths: double blinding, low dropout rate
		Exclusion criteria: contraindications for use of omega-3 PUFA; heart failure in NYHA class IV; acute coronary syndromes, coronary artery bypass surgery, or valve replacement within the past 3 mo; clinically significant valvular disease; known diagnosis of Wolff-Parkinson-White; planned or recent implantation of pacemaker or implantable cardioverter-defibrillator; planned or recent ablative treatment for AF; any arrhythmia associated with an acute reversible condition; advanced chronic lung disease; and pregnancy	Comparator: placebo (olive oil)		Limitations: early stoppage of trial reduced statistical power, did not assess dietary (background) omega-3 PUFA intake

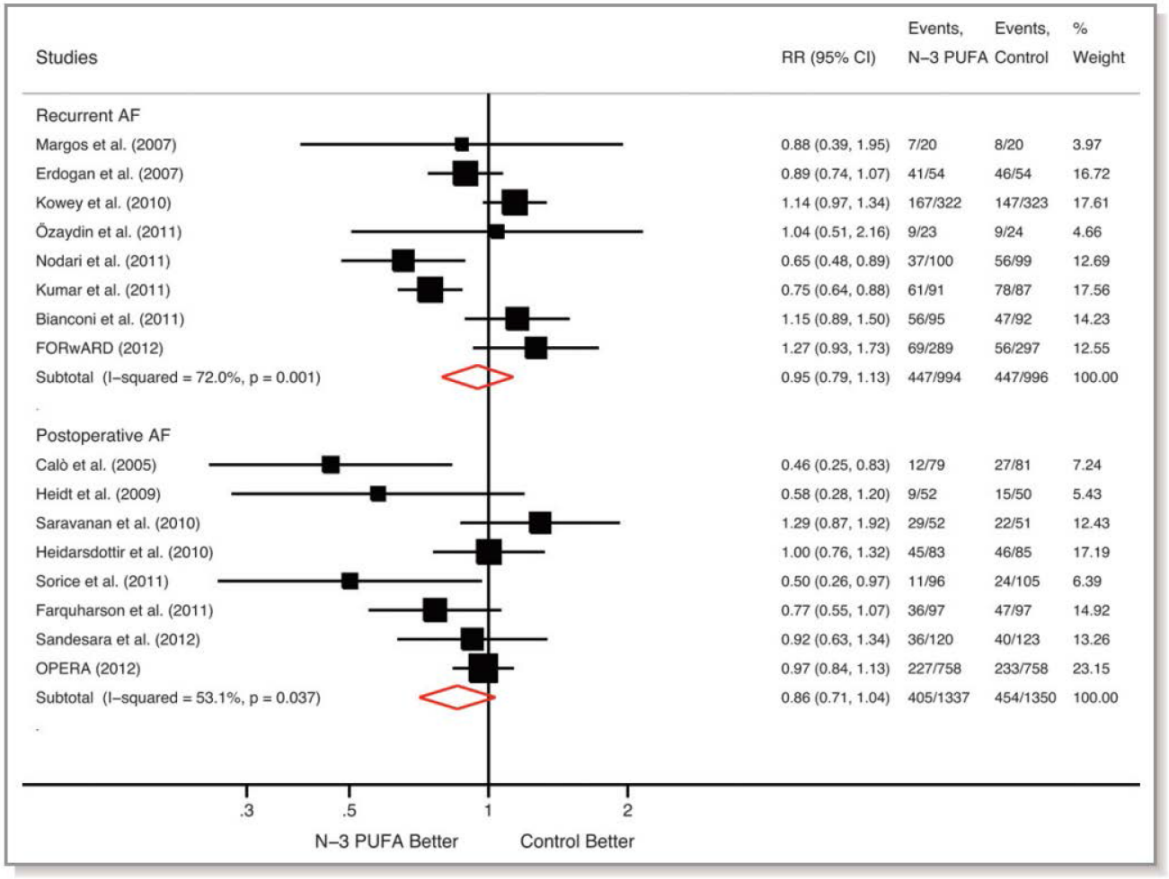
[11] Kowey PR, Reiffel JA, Ellenbogen KA, Naccarelli GV, Pratt CM. Efficacy and safety of prescription omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: a randomized controlled trial. JAMA. 2010;304:2363–2372. doi: 10.1001/jama.2010.1735.

[12] Macchia A, Grancelli H, Varini S, Nul D, Laffaye N, Mariani J, Ferrante D, Badra R, Figal J, Ramos S, Tognoni G, Doval HC; GESICA Investigators. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of SinusRhythm in Persistent atrial Fibrillation) trial. J Am Coll Cardiol.2013;61:463–468. doi: 10.1016/j.jacc.2012.11.021.

A meta-analysis by Mariani[13] showed no effect of OFAs on recurrent or postoperative AF. In this meta-analysis, there were > 4500 patients with 1753 total events, the dose of OFAs used was 0.6 to 4.5 g/day, and the follow up period for AF recurrence was 6 to 12 months. Meta-regression did not show a dose-response relationship. Figure 1 displays a forest plot of the studies analyzed by Mariani.

According to the Micromedex® database, safety concerns regarding the risk of recurrent AF[14] with prescription OFAs remain. REDUCE-IT, discussed in the next section, also demonstrated an increased incidence of AF with OFA supplementation.

Figure 1. Forest plot of the studies analyzed in meta-analysis by Mariani[12]



REDUCE-IT

Trial Safety Finding of AF: A significantly higher incidence of AF was noted in the icosapent ethyl group than in the placebo group. Although not pre-specified as a treatment emergent

[13] Javier Mariani, MD; Hernan C. Doval, MD; Daniel Nul, MD; Sergio Varini, MD; Hugo Grancelli, MD; Daniel Ferrante, MD; Gianni Tognoni, MD; Alejandro Macchia, MD. N-3 Polyunsaturated Fatty Acids to Prevent atrial Fibrillation: Updated Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc. 2013;2:e005033 doi: 10.1161/JAHA.112 005033.

[14] Cheng-Ho Chang, Ping-Tao Tseng, Nai-Yu Chen, Pei-Chin Lin, Pao-Yen Lin, Jane Pei- Chen Chang, Feng-Yu Kuo, Jenshinn Lin, Ming-Chang Wu, Kuan-Pin Su. Safety and tolerability of prescription omega-3 fatty acids: A systematic review and meta-analysis of randomized controlled trials Prostaglandins, Leukotrienes and Essential Fatty Acids, Volume 129, 2018, pp. 1-12

adverse event (TEAE) of special interest, AF was explored post hoc as a potential safety signal. According to the Clinical Events Committee (CEC) charter, the adjudication definition of AF endpoint was AF leading to hospital admission or contributing to prolongation of hospitalization for ≥ 24 hours. The occurrences of AF not meeting the endpoint adjudication definition were counted as TEAEs or serious adverse events (SAEs), per the investigator assessed seriousness criteria.

The Intent-to-Treat (ITT) population consisted of all randomized patients who took at least one dose of the study drug. In the ITT population, the incidence of positively adjudicated AF endpoint events and TEAEs of AF were significantly higher in the icosapent ethyl group than in the placebo group (3.1% versus 2.1%, p=0.0037; and 7.7% versus 5.9%, p=0.0016, respectively). The SAEs of AF reported in the safety database were similar between the icosapent ethyl and placebo groups (0.6% versus 0.5%, respectively; p=0.8827). The number of subjects reported to experience drug-related TEAEs of AF were 2 (out of total n=4089) and 1 (out of total n=4090) in AMR101 and placebo arms, respectively. By geographic region, the incidence of AF in AMR101 versus placebo arm was 6.2% versus 4.4% and 3.2% versus 3.0% in Western region and Eastern Europe, respectively. By strata, the incidence of AF in AMR101 versus placebo arm was 5.4% versus 4.3% and 5.0% versus 3.0% in strata 1 and strata 2, respectively. Table 3 summarizes the incidence of AF in ITT population in REDUCE-IT. The increased incidence of AF was observed regardless of the baseline history of AF. Other baseline risk factors for AF were balanced between the two groups.

Table 3. Incidence of Atrial Fibrillation and Flutter in Intention to Treat Population in REDUCE-IT (Source: Sponsor Table)

	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	P-value
Atrial fibrillation/flutter AEs[1]	315 (7.7)	243 (5.9)	0.0016
Serious atrial fibrillation/flutter AEs[2]	23 (0.6)	22 (0.5)	0.8827
Positively adjudicated atrial fibrillation/flutter requiring ≥24 hours hospitalization[3]	127 (3.1)	84 (2.1)	0.0037

Abbreviations: AE = adverse event; ITT = Intent-to-Treat; MedDRA = Medical Dictionary for Regulatory Activities.
Note: Percentages were based on the number of patients in the ITT population within each treatment group (N). All AEs were coded using the MedDRA, Version 20.1. Counts of atrial fibrillation/flutter AEs and counts of positively adjudicated atrial fibrillation/flutter events are mutually exclusive.

1 Includes atrial fibrillation/flutter AEs. The p-value was based on Fisher's exact test.

2 Includes a subset of atrial fibrillation/flutter AEs meeting seriousness criteria. The p-value was based on Fisher's exact test.

3 Includes positively adjudicated atrial fibrillation/flutter requiring ≥24 hours hospitalization clinical events by the Clinical Endpoint Committee. The p-value was based on stratified log-rank test.

Source: Table 14.3.2.2.6.

A review of the first 12 (out of 211) narratives of positively adjudicated AF events showed that 9 of the 12 events of AF were preceded by clinical events such as percutaneous coronary intervention, endocarditis, decompensated congestive heart failure, uncontrolled hypertension, acute pulmonary embolism, hemicolectomy, and acute abdomen with sepsis during

hospitalization. In these cases, AF was not the primary diagnosis for hospitalization. While, a detailed review of the adjudicated AF events is beyond the scope of this review, the sponsor can consider re-examining the adjudicated AF events. This may provide additional insight in to the potential association of OFA - icosapent ethyl and AF.

FDA Adverse Events Reporting System (FAERS) Public Dashboard search by the reviewer showed that only 4 out of a total of 874 adverse events reported with Vascepa, between 2013 and 2019, were AF cases. Hence, no conclusions can be drawn from FAERS database.

Conclusions:

Observational and randomized trial data support the role of fish oil products in reducing the incidence of ventricular tachycardia (VT) associated sudden cardiac death (SCD).[15] The American Heart Association (AHA)[16] recommends treatment with fish oil supplementation for secondary prevention of coronary heart disease death (Class IIa Recommendation). A potential mechanism for anti-arrhythmic effect of fish oil products on VT is increase in the refractory period of the cardiomyocyte. There are insufficient data to distinguish the anti-arrhythmic effects of different types of fish oil.

With regard to AF, randomized clinical trial data do not support an anti-arrhythmic effect of fish oil products. Instead, in two RCTs – Kowey 2010 and REDUCE-IT, an increased incidence of AF was observed in the fish oil supplement group compared to placebo. The mechanism of pro-arrhythmic effect of fish oil products with regard to AF is not well understood.

The increased incidence of AF in REDUCE-IT is a concerning safety signal, especially in the intended population with elevated baseline risk for AF. A similar signal was observed in the Kowey 2010 trial with Lovaza, albeit in a different population. Given the strength and consistency of the finding of reduction of major adverse cardiovascular events in REDUCE-IT, the benefit-risk assessment favors the use of Vascepa for CVD risk reduction in the intended population with caution regarding a potential increase in risk of AF.

[15] Christine M. Albert. Omega-3 Fatty Acids, Ventricular Arrhythmias, and Sudden Cardiac Death Antiarrhythmic, Proarrhythmic, or Neither. Circulation: Arrhythmia and Electrophysiology. 5(3):456–459, JUNE 2012
DOI: 10.1161/CIRCEP.112.971416, PMID: 22715236

[16] David S. Siscovick et al, Omega-3 Polyunsaturated Fatty Acid (Fish Oil) Supplementation and the Prevention of Clinical Cardiovascular Disease: A Science Advisory From the American Heart Association. *Circulation.* 2017;135:e867–e884. DOI: 10.1161/CIR.0000000000000482

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