Official Title:
Evaluation of the Effect of AMR101 on Cardiovascular Health and Mortality in Hypertriglyceridemic Patients With Cardiovascular Disease or at High Risk for Cardiovascular Disease: REDUCE-IT (Reduction of Cardiovascular Events With EPA - Intervention Trial)

Protocol Number:
AMR-01-01-0019

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This document contains the following items:

CLINICAL STUDY PROTOCOL

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: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

Investigational Product: AMR101 (icosapent ethyl [ethyl-EPA])
Protocol Number: AMR-01-01-0019

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SIGNATURE PAGE

TRIAL 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: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

We, the undersigned, have reviewed and approved this protocol.

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SYNOPSIS

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: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

PROTOCOL NUMBER: AMR-01-01-0019

INVESTIGATIONAL PRODUCT: AMR101 (icosapent ethyl [ethyl-EPA])

PHASE: 3b

INDICATION:

Treatment with AMR101 to reduce the risk of cardiovascular events in patients with clinical cardiovascular disease or with multiple risk factors for cardiovascular disease.

OBJECTIVES:

The primary objective is, in patients at LDL-C goal while on statin therapy, with established cardiovascular disease (CVD) or at high risk for CVD, and hypertriglyceridemia (fasting triglycerides, TG, ≥150 mg/dL and <500 mg/dL), to evaluate the effect of 4 g/day AMR101 for preventing the occurrence of a first major cardiovascular event of the composite endpoint that includes:

- Cardiovascular (CV) death,
- Nonfatal myocardial infarction (MI),
- Nonfatal stroke,
- Coronary revascularization,
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

[Because of the variability in TG levels, the lower TG qualifying limit is 10% lower than the target of 150 mg/dL, i.e., 135 mg/dL.]

The secondary objectives of this study are the following:

The key secondary objective is to evaluate the effect of therapy on the composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina, nonfatal stroke, or peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair.

Other secondary objectives :

- To evaluate the effect of therapy on combinations of each of the key secondary objective clinical events in addition to the following clinical events:
    - Cardiac arrhythmia requiring hospitalization
    - Cardiac arrest

- Peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair
- Total mortality

The tertiary objectives of this study are the following:

- Evaluate the effect of therapy on the occurrence of a second, third, fourth, and fifth major cardiovascular event (same as the primary composite endpoint but for events occurring after the first event);
- To evaluate the effect of therapy on the primary endpoint in subgroups of patients including:
  - Diabetes mellitus
  - Metabolic syndrome as defined by the NCEP ATP III or future criteria as they may evolve;
- To evaluate the effect of therapy on the individual endpoints of new congestive heart failure (CHF), on new CHF as a primary cause of hospitalization, on transient ischemic attack, on amputation for vascular disease and on carotid revascularization;
- Elective coronary revascularization and emergent coronary revascularization;
- To assess the effects regarding lipids, lipoproteins and inflammatory markers including triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high- density lipoprotein cholesterol (HDL-C), non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein B (apo B), high sensitivity C-reactive protein (hs-CRP) and high sensitivity troponin (hsTnT), as follows:
  - Assessment of the effect of AMR101 on each marker (on-treatment change of markers)
  - Assessment of the effect of the baseline value of each marker on treatment effects (baseline effect on outcomes)
  - To evaluate the effect of therapy for preventing clinical events, as defined above, among all patients in the study, and in subgroups such as patients with diabetes mellitus and patients with substantial on-treatment changes of any of the markers (on-treatment effect on outcomes).
- To evaluate the effect of therapy on new onset diabetes (See appendix C);
- To explore the effect of AMR101 on weight and waist circumference.

ENDPOINTS:

Primary endpoint:
Time from randomization to the first occurrence of the composite of the following clinical events:

- CV death,

- Nonfatal MI (including silent MI; ECGs will be performed annually for the detection of silent MIs),
- Nonfatal stroke,
- Coronary revascularization,
- Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing.

The first occurrence of any of these major adverse vascular events during the follow-up period of the study will be included in the incidence.

Secondary endpoints:

The key secondary efficacy endpoint is:

- The composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina, nonfatal stroke, or peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair.

Other secondary efficacy endpoints are as follows (to be tested in said order):

- The composite of total mortality, nonfatal MI, or nonfatal stroke;
- The composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina, peripheral CVD, or cardiac arrhythmia requiring hospitalization;
- The composite of death from CV causes, nonfatal MI, coronary revascularization, or unstable angina;
- The composite of death from CV causes or nonfatal MI;
- Total mortality;
- Fatal and nonfatal MI (including silent MI);
- Coronary Revascularization;
- Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing ;
- Fatal and nonfatal stroke.

For the secondary endpoints that count a single event, the first occurrence of this type of event will be counted in each patient. For secondary endpoints that are composites of two or more types of events, the first occurrence of any of the event types included in the composite will be counted in each patient.

Tertiary endpoints:

- The second, third, fourth, and fifth major CV event of the primary composite endpoint. The type of (nonfatal) events may occur in any order.
- Primary endpoint in subset of patients with diabetes mellitus;
- Primary endpoint in subset of patients with metabolic syndrome;
- Individual endpoints of new CHF, new CHF leading to hospitalization, transient ischemic attack, amputation for CVD and carotid revascularization;

- Elective coronary revascularization and emergent coronary revascularization;
- New onset diabetes;
- Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP, and hsTnT: on treatment change and baseline effect;
- CV mortality;
- Cardiac Arrhythmias requiring hospitalization;
- Cardiac Arrest;
- To explore the effect of AMR101 on weight and waist circumference.

For the tertiary endpoints that count a single event, the first occurrence of this type of event will be counted in each patient. For tertiary endpoints that are composites of two or more types of events, the first occurrence of any of the event types included in the composite will be counted in each patient (except when stated otherwise, for the second, third, fourth, and fifth major CV event).

POPULATION:

Inclusion Criteria:

1. Fasting TG levels of ≥135 mg/dL and <500 mg/dL. The target for the lower end of the fasting TG level is ≥150 mg/dL but because of the variability in TG levels, patients will qualify for enrolment within 10% of this limit (i.e., ≥135 mg/dL).
2. On stable therapy with a statin (with or without ezetimibe), for at least 4 weeks prior to the LDL-C/TG baseline qualifying measurements for randomization, to maintain LDL-C >40 mg/dL and ≤100 mg/dL
   - Stable therapy is defined as the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable, the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C). Patients who have their statin therapy or use of ezetimibe initiated at Visit 1, or have their statin, statin dose and/or ezetimibe dose changed at Visit 1, will need to go through a stabilization period of at least 28 days since initiation/change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).
   - Statins may be administered with or without ezetimibe.

   NOTE: If patients qualify at the first qualification visit (Visit 1) for TG and LDL-C, and meet all other inclusion/exclusion criteria, they may be randomized at Visit 2. If patients do not qualify at the first qualifying visit (Visit 1), a second re-qualifying visit (Visit 1.1) is allowed. For some patients, because they need to stabilize medications and/or need to washout medications, the second re-qualifying visit (Visit 1.1) will be needed after the stabilization/washout period.
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 are defined as follows:

CV Risk Category 1: defined as men and women ≥45 years of age with one or more of the following:

- Documented coronary artery disease (CAD; one or more of the following primary criteria must be satisfied):
  - Documented multivessel CAD (one or more >50% stenosis in two major epicardial coronary arteries – with or without antecedent revascularization);
  - Documented prior MI;
  - Hospitalization for high-risk NSTE ACS (with objective evidence of ischemia: ST-segment deviation or biomarker positivity).
- Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied):
  - Documented prior ischemic stroke;
  - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis;
  - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound;
  - History of carotid revascularization (catheter-based or surgical).
- Documented peripheral arterial disease (PAD; one or more of the following primary criteria must be satisfied):
  - Ankle-brachial index (ABI) <0.9 with symptoms of intermittent claudication;
  - History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical).

OR

CV Risk Category 2: defined as patients with:

1. Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication AND
2. Men and women ≥50 years of age AND
3. One of the following at Visit 1 (additional risk factor for CVD):
   - Men ≥55 years of age and 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 >3.0 mg/L;
   - Renal dysfunction: Creatinine clearance (CrCL) >30 and <60 mL/min;

- Retinopathy, defined as any of the following: non-proliferative retinopathy, preproliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation;
- Micro- or macroalbuminuria. Microalbuminuria is defined as either a positive micral or other strip test, an albumin/creatinine ratio ≥2.5 mg/mmol or an albumin excretion rate on timed collection ≥20 mg/min all on at least two successive occasions; macroalbuminuria, defined as albustix or other dipstick evidence of gross proteinuria, an albumin/creatinine ratio ≥25 mg/mmol or an albumin excretion rate on timed collection ≥200 mg/min all on at least two successive occasions;
- ABI <0.9 without symptoms of intermittent claudication (patients with ABI <0.9 with symptoms of intermittent claudication are counted under CV Risk Category 1).

Note: Patients with diabetes and vascular disease as defined above are eligible based on the vascular disease requirements and will be counted under CV Risk Category 1. Only patients with diabetes and no documented CV disease as defined above need at least one additional risk factor as listed, and will be counted under CV Risk Category 2.

4. Women may be enrolled if all 3 of the following criteria are met:
   - They are not pregnant;
   - They are not breastfeeding;
   - They do not plan on becoming pregnant during the study.
5. Women of child-bearing potential must have a negative urine pregnancy test before randomization.

   Note: Women are not considered to be of childbearing potential if they meet one of the following criteria as documented by the investigator:

   - They have had a hysterectomy, tubal ligation or bilateral oophorectomy prior to signing the informed consent form;
   - They are post-menopausal, defined as ≥1 year since their last menstrual period or have a follicle-stimulating hormone (FSH) level in a menopausal range.
6. Women of childbearing potential must agree to use an effective method of avoiding pregnancy from screening to the end of the study, unless their sexual partner(s) is/are surgically sterile or the women is abstinent. Effective methods of avoiding pregnancy are contraceptive methods used consistently and correctly (including implantable contraceptives, injectable contraceptives, oral contraceptives, transdermal contraceptives, intrauterine devices, diaphragm with spermicide, male or female condoms with spermicide, or cervical cap).
7. Understanding of the study procedures, willing to adhere to the study schedules, and agreement to participate in the study by giving written informed consent prior to screening.

8. Agree to maintain their current dietary regimen, and to not alter their normal activity routines maintain through the duration of the study.

Exclusion Criteria:

1. Severe (class IV) heart failure.
2. Any life-threatening disease expected to result in death within the next 2 years (other than CVD).
3. Active severe liver disease (evaluated at Visit 1): cirrhosis, active hepatitis, ALT or AST >3 x ULN, or biliary obstruction with hyperbilirubinemia (total bilirubin >2 x ULN).
4. Hemoglobin A_{1c} >10.0% at screening (Visit 1). If patients fail this criterion (HbA_{1c} >10.0%) at Visit 1, they may have their antidiabetic therapy optimized and be retested at Visit 1.1.
5. Poorly controlled hypertension: blood pressure ≥200 systolic mmHg OR ≥100 mmHg diastolic (despite antihypertensive therapy).
6. Planned coronary intervention (such as stent placement or heart bypass) or any non-cardiac major surgical procedure. Patients can be (re)evaluated for participation in the trial (starting with Visit 1.1) after their recovery from the intervention/surgery.
7. Known familial lipoprotein lipase deficiency (Fredrickson Type I), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type III)].
8. Participation in another clinical trial involving an investigational agent within 90 days prior to screening (Visit 1). Patients cannot participate in any other investigational medication or medical device trial while participating in this study.
9. Intolerance or hypersensitivity to statin therapy.
10. Known hypersensitivity to fish oil products.
11. History of acute or chronic pancreatitis.
12. Non-study drug related, non-statin, lipid-altering medications, supplements or foods:
    - Patients are excluded if they used niacin >200 mg/day or fibrates during the last 28 days before Visit 1, during the screening period and/or plan to use during the treatment/follow-up period of the study;
    - Patients are excluded if they take any omega-3 fatty acid medications (prescription medicines containing EPA and/or DHA) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking omega-3 fatty acid medications during the last 28 days before Visit 1, need to go through a washout period of at least 28 days after their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);
    - Patients are excluded if they use dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking >300 mg/day omega-3 fatty

acids (combined amount of EPA and DHA) within 28 days before Visit 1, need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);

- Patients are excluded if they use bile acid sequestrants during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking bile acid sequestrants within 7 days before Visit 1, need to go through a washout period of at least 7 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);

13. Other medications (not indicated for lipid alteration):
    - Treatment with tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are allowed), HIV-protease inhibitors that have not been stable for ≥28 days prior to the qualifying lipid measurements (TG and LDL-C) during screening. To be eligible for participation in the study, patients who are not taking a stable dose of these medications within 28 days before Visit 1, need to go through a stabilization period of at least 28 days since their last dose change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);
    - Patients are excluded if they use cyclophosphamide or systemic retinoids during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking bile acid sequestrants within 28 days before Visit 1, need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).
14. Known to have AIDS (patients who are HIV positive without AIDS are allowed).
15. Requirement for peritoneal dialysis or hemodialysis for renal insufficiency or creatinine clearance (CrCL) <30 mL/min.
16. Unexplained creatine kinase concentration >10 × ULN or creatine kinase elevation due to known muscle disease (e.g., polymyositis, mitochondrial dysfunction) at Visit 1.
17. Any condition or therapy which, in the opinion of the investigator, might pose a risk to the patient or make participation in the study not in the patient's best interest.
18. Drug or alcohol abuse within the past 6 months, and unable/unwilling to abstain from drug abuse and excessive alcohol consumption during the study. Excessive alcohol consumption is on average >2 units of alcohol per day. A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.
19. Mental/psychological impairment or any other reason to expect patient difficulty in complying with the requirements of the study or understanding the goal and potential risks of participating in the study (evaluated at Visit 1).

STUDY DESIGN AND DURATION:

This is a multi-center, multi-national, prospective, randomized, double-blind, placebo-controlled, parallel-group study.

This is an event-driven trial: It is expected that a minimum of 1612 primary efficacy endpoint events will be required during the study. Approximately 7990 patients will be randomized at multiple Research Sites worldwide over a planned period of 18 months. After randomization, patients will be treated and followed over 3.25-4.75 years with a planned median follow-up of 4 years. The study end date is determined to be when approximately 1612 primary efficacy events have occurred.

Screening Period:

During the screening period, patients will be evaluated for inclusion/exclusion criteria. Patients will be eligible for randomization if they meet all the inclusion/exclusion criteria. Prospectively, eligible patients with documented CVD or diabetes (with at least one additional risk factor for CVD) will undergo screening to establish suitability for inclusion in the trial. The qualifying lipid determination at Visit 1 requires that eligible patients must have a fasting TG level ≥135 mg/dL and <500 mg/dL in order to enter the treatment/follow-up period of the trial (and they need to meet all other inclusion/exclusion criteria). These patients will be randomized at Visit 2, which will occur soon after Visit 2 (there will be no Visit 1.1 for these patients).

Patients who do not qualify at Visit 1, may return to the Research Site for a second qualifying visit (Visit 1.1) at which time procedures that caused failure of eligibility at Visit 1 will be repeated. In this case, patients will be eligible for randomization after Visit 1.1 if they meet all inclusion criteria and if they no longer fail the exclusion criteria.
For some patients, Visit 1.1 will be mandatory at least 28 days after Visit 1 in order to check eligibility. These are patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications. Any of these changes at Visit 1 may affect the qualifying lipid levels and therefore, patients will need to have Visit 1.1 to determine whether they qualify based on lipid level requirements (TG and LDL-C) determined at Visit 1. Other procedures that caused failure of eligibility at Visit 1 will also be repeated at Visit 1.1. Details are listed in the main section of the protocol.

Treatment/Follow-Up Period:

At Visit 2 (Day 0), eligible patients will be randomly assigned 1:1 to one of the following treatment groups:

- AMR101 4 g daily, or
- Placebo.

Stratification will be by CV risk category (established CVD or the presence of diabetes with ≥1 risk factor for CVD), use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries).

During the treatment/follow-up period, patients will return to the Research Site at regular intervals for efficacy and safety evaluations, and drug supply and compliance checks. The visits after the randomization visit (Visit 2; Day 0) are at approximately after 6 months for Visit 3, and then every year thereafter.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Eligible patients will be randomly assigned at Visit 2 to receive orally AMR101 4 g daily or matching placebo. AMR101 is provided in 1000 mg liquid-filled, oblong, gelatin capsules. The matching placebo capsule is filled with light liquid paraffin and contains 0 mg of AMR101. AMR101 capsules are to be taken with food (i.e. with or at the end of a meal).

During the treatment period, the daily dose of study drug is 4 capsules per day taken as two capsule taken on two occasions per day (2 capsule given twice daily).

STATISTICAL ANALYSES:

- Intent-to-treat analysis.
- Parameters will be summarized using mean, standard deviation, median, minimum, maximum, and interquartile range for continuous data and percentage for categorical data.
- Survival analysis using the log-rank test for the primary efficacy outcome comparing the 2 treatment groups (AMR101 and Placebo) and including the stratification factors CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries).
- All statistical analyses for the efficacy and safety outcomes will be performed at the 5% significance level using 2-sided tests unless otherwise noted.
- One interim analysis is planned when approximately 60% of the planned total number of events has occurred.

The analysis is planned to:

- Describe at baseline: Patient characteristics, including lipids and lipoproteins, stroke history, cardiovascular risk factors, diabetes mellitus, or metabolic syndrome, among others.
- Compare the primary, secondary, and tertiary endpoints between treatment groups at the corresponding follow-up time points.

SAMPLE SIZE DETERMINATION:

Sample size estimation is based on the assumption that the primary composite endpoint (time from randomization to the first occurrence of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina requiring hospitalization) would be relatively reduced by 15%, from an event rate by 4 years of 23.6% in the placebo group to 20.5% in the AMR101 group. It is expected that a minimum of 1612 primary efficacy endpoint events will be required during the study. A total of approximately 6990 patients are needed to be able to detect this difference at 4.76% significance level (decreased from 5.00% because of one interim analysis) and with 90% power, assuming an 18-month enrollment period and a median follow-up of 4 years. The current sample size calculation is based on an estimated placebo yearly event rate of 5.9% (23.6% over 4 years). To protect against the possibility that the actual placebo event rate is lower than estimated, an extra 1000 patients will be enrolled (approximately 7990 patients in total). By adding the extra 1000 patients, the event rate in the placebo group could be 5.2% per year (20.8% over 4 years) without having to modify the other sample size assumptions. Before completing the enrollment phase of the trial, the actual event rate based on pooled, blinded accumulation of primary efficacy endpoint events will be calculated and may be used to increase the sample size. If the sample size is increased, the enrollment phase will be extended to allow enrollment of the additional patients.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AA	Arachidonic acid
ABI	Ankle-brachial index
ACC	American College of Medicine
ACS	Acute coronary syndrome
AHA	American Heart Association
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AP	Angina pectoris
apo B	Apolipoprotein B
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CBC	Complete blood count
CEC	Clinical Event Committee
CI	Confidence interval
CHD	Coronary heart disease
CHF	Congestive heart failure
CK-MB	Creatine kinase-MB fraction
CrCL	Creatinine clearance
CNS	Central nervous system
CRF	Case Report Form
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
%CV	Percent coefficient of variation
DART	Diet and Reinfarction Trial
DCCT	Diabetes Control and Complications Trial
DHA	Docosahexaenoic acid
DSMB	Data and Safety Monitoring Board
EDC	Electronic data capture
ECG	Electrocardiogram
EPA	Eicosapentaenoic acid
Ethyl-EPA	Ethyl icosapentaenoate; icosapent ethyl
FSH	Follicle-stimulating hormone
GC/FID	Gas chromatograph with flame ionization detector
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
Hct	Hematocrit

HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
hs-CRP	High-sensitivity C-reactive protein
hsTnT	High-sensitivity troponin T
HR	Hazard ratio
ICAM-1	Intercellular adhesion molecule-1
ICF	Informed consent form
ICH	International Conference on Harmonization
EC	Independent Ethics Committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IVRS	Interactive voice response system
JELIS	Japan Eicosapentaenoic Acid Lipid Intervention Study
LBBB	Left bundle branch block
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LDL-C	Low-density lipoprotein cholesterol
MACE	Major adverse coronary event
MI	Myocardial infarction
NCEP	National Cholesterol Education Program
NGSP	National Glycohemoglobin Standardization Program
NMR	Nuclear magnetic resonance
NO	Nitric oxide
NSTE-ACS	Non-ST-Segment Elevation Acute Coronary Syndrome
O3FA	Omega-3 fatty acid
OGTT	Oral Glucose Tolerance Test
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PH	Proportional hazard
PI	Principal investigator
PP	Per protocol
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
PTCA	Percutaneous transluminal coronary angioplasty
RBC	Red blood cells
RR	Relative risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCD	Sudden cardiac death
SD	Standard deviation
SOC	Study Operations Committee
SPC	Summary of Product Characteristics
ST	Steering committee
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Half-life

TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TIMI	Thrombolysis In Myocardial Infarction
T_{max}	Time of maximum concentration
ULN	Upper limit of normal
USPI	United States Prescribing Information
VCAM-1	Vascular cell adhesion molecule-1
VF	Ventricular fibrillation
WBC	White cell blood count

1. INTRODUCTION AND BACKGROUND INFORMATION

AMR101 (icosapent ethyl [ethyl-EPA]) is a highly purified ethyl ester of eicosapentaenoic acid (EPA) derived from fish oil, and is being developed by Amarin Pharma Inc. (hereafter referred to as Amarin or the Sponsor) for the treatment of hypertriglyceridemia. The purpose of this study is to evaluate whether the triglyceride-lowering drug AMR101, combined with a statin therapy, will be superior to the statin therapy alone, when used as a prevention in reducing long-term clinical events in patients with mixed dyslipidemia at high risk for cardiovascular (CV) events.

1.1. Background

Since the initial observation of a link between fish oil consumption and the reduced incidence of coronary heart disease in the Eskimos of Greenland (Bang 1972), a large body of evidence has accumulated showing that regular intake of omega-3 fatty acids (O3FAs) exerts cardioprotective effects in both primary and secondary coronary heart disease prevention (Harris 2008, Lee 2008). Several mechanisms have been proposed to account for these beneficial effects, including the reduction of triglycerides (TG), suppression of cardiac arrhythmias, decreased platelet aggregation, improved plaque composition and stabilization, and hemodynamic changes. This mounting body of evidence has led the American Heart Association (AHA) to recommend the consumption of O3FAs in dietary fish or in capsule form at a dose of 1 g/day for secondary prevention of cardiovascular disease (CVD) (Kris-Etherton 2002). This recommendation has now been included in American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the long-term management of patients with stable angina and acute coronary syndromes (Antman 2004, Fraker 2007, Anderson 2007).

A large number of studies have also demonstrated the triglyceride-lowering effects of O3FAs (Harris 1997, Ginsberg 2001). The US FDA has approved a product containing approximately 90% esters of the O3FAs EPA and DHA for use at a dose of 4 g/day as an adjunct to diet for the treatment of patients with very high triglyceride levels (≥500 mg/dL) (Lovaza® USPI 2009). The same medicinal product under the name Omacor® (Omacor SPC 2008) is approved in Europe for the treatment of endogenous hypertriglyceridemia at a dose of up to 4 grams daily as a supplement to diet when dietary measures alone are insufficient to produce an adequate response. Omacor® at a dose of 1 gram daily is also approved in key European and certain Asian markets for the secondary prevention of myocardial infarction (Post-MI).

Epadel® capsules, which contain highly purified (>95%) ethyl-EPA, have been marketed by Mochida in Japan since 1991 for the treatment of arteriosclerosis obliterans and since 1994 for the treatment of hyperlipidemia (Epadel SPC 2007). The recommended dose is 1.8 g/day for arteriosclerosis obliterans and 1.8 to 2.7 g/day for hyperlipidemia. Hypertriglyceridemia is a feature of many dyslipidemias and often occurs in persons who are obese and/or have Type 2 diabetes mellitus in isolation or as a component of the metabolic syndrome (Jacobson 2007, Bays 2008).

Elevation in TG confers dual risks of acute pancreatitis (most marked in patients with severe hypertriglyceridemia [TG >1500 mg/dL]) (Yadav 2003) and accelerated atherosclerosis

leading to CV events, the latter even after correction for other lipid and non-lipid risk factors (Jacobson 2007). With this in mind, Amarin is assessing the potential of AMR101 capsules, which contain highly purified icosapent ethyl (ethyl-EPA), for the treatment of patients, as an adjunct to diet, with very high TG levels (≥500 mg/dL) and those with high TG levels (≥200 and <500 mg/dL) despite optimal statin therapy. Amarin-sponsored studies with AMR101 in patients with very high TGs (Study AMR-01-01-0016, the MARINE study) and in patients with high TGs on statins (Study AMR-01-01-0017, the ANCHOR study) are in progress.

1.2. Summary of Amarin-Sponsored Clinical Studies with AMR101

To date, Amarin has completed 8 double-blind, placebo-controlled clinical trials with AMR101 in patients with CNS disorders including Huntington's disease, depression, schizophrenia and age-associated memory impairment. Males and females were almost equally represented. The majority of patients were Caucasian, but the studies also included, among the patients receiving AMR101, 14 Blacks, 6 Asians and 11 patients of another race.

The patients received 0.5-4 g/day AMR101 or placebo. The duration of the double-blind treatment period ranged from 6 weeks to 1 year. In addition, 24 healthy volunteers have received AMR101 2 g/day for up to 28 days in a pharmacokinetic study (LA01.01.0009). In these studies, AMR101 was administered in the form of 500-mg soft gelatin capsules, orally with meals as a twice-daily regimen with half of the daily dose in the morning and half in the evening.

Across all 9 completed Amarin-sponsored studies (1 in healthy volunteers and 8 in patients), a total of 1243 patients were randomized (24 healthy volunteers and 1219 patients with CNS disorders). From the 1243 patients, 724 (24 healthy patients and 700 patients) were randomized to receive AMR101 and 519 to receive placebo. See the Investigator's Brochure for more information.

In 4 of the Amarin-sponsored studies in patients with CNS disorders, patients who completed the double-blind period were rolled-over into an open-label extension phase and received 1-2 g/day AMR101 (most received 2 g/day). The treatment period in the open-label extensions ranged from 6 months to 1 year. Across all studies, including patients from the double-blind periods receiving AMR101 and also those switched from placebo to AMR101 in the open-label extensions, a total of 1071 patients have been exposed to ethyl-EPA from AMR101 capsules.

In addition, two Phase 3 studies in patients with hypertriglyceridemia have been completed . These trials have investigated the efficacy of AMR101 in lowering triglycerides:

- Study AMR-01-01-0016 (the MARINE study) in 229 patients with very high triglycerides (>500 mg/dL).
- Study AMR-01-01-0017 (the ANCHOR study) in approximately 702 patients with mixed dyslipidemia (high triglycerides: ≥200 to <500 mg/dL) who are taking statins

1.3. Study AMR-01-01-0017 (ANCHOR Study)

The results from the ANCHOR study are particularly relevant for the dose selection of the present study since the ANCHOR study was conducted in the same patient population. The

primary objective in the ANCHOR study was to determine the efficacy of AMR101 2 g daily and 4 g daily, compared to placebo, in lowering fasting TG levels in patients with high risk for cardiovascular disease (CVD) and fasting TG levels ≥200 mg/dL and <500 mg/dL, despite treatment to low density lipoprotein cholesterol (LDL-C) goal (>40 mg/dL and <100 mg/dL) on statin therapy.

After a 6- to 8-week screening period which included diet and lifestyle stabilization, a washout period for excluded non-statin lipid-altering medications (if needed), and a TG qualifying period, patients were randomized to one of 3 treatment groups and received study medication during a 12-week, double-blind treatment period. Patients had to be treated with one of 3 statins (simvastatin, atorvastatin or rosuvastatin) to reach their LDL-C goal of 100 mg/dL (+15% allowed for variability) and had to be on a stable dose for a minimum period of 4 weeks before the TG qualifying measurements. The TG target for enrollment was for patients to have qualifying fasting TG levels of ≥200 mg/dL and <500 mg/dL based on the mean of 2 measurements. During the 12-week double-blind treatment period, patients received orally AMR101 2 g/day, AMR101 4 g/day, or placebo.

In the ITT population (687 patients), the baseline median TG level was 259.0 mg/dL (IQR: 81.00 mg/dL), 264.8 mg/dL (IQR: 93.00 mg/dL) and 254.0 mg/dL (IQR: 92.50 mg/dL) for the patients receiving placebo, AMR101 4 g/day and AMR101 2 g/day, respectively. At the Week 12 endpoint, the median percent change from baseline TG level was +5.9%, -17.5% and-5.6% for the patients receiving placebo, AMR101 4 g/day and AMR101 2 g/day, respectively. The median difference between AMR101 4 g/day and placebo was -21.5% ($p<0.0001$). The median difference between AMR101 2 g/day was -10.1% ($p=0.0005$).

The TG lowering effect of AMR101 was similar in males and females at the 4 g/day dose. Efficacy of AMR101 was similar in diabetics and non-diabetics, and was similar irrespective of the type of statin administered. The higher the potency of the statin regimen, the greater the TG reduction in the AMR101 4 g/day group. The higher the baseline TG tertile, the greater the TG reduction for both AMR101 dose groups.

Key lipoprotein variables were decreased by AMR101 even after patients were on stable doses of statin therapy, with LDL-C levels at goal. Compared to placebo, statistically significant reductions with AMR101 were observed for non-HDL-C, Apo B, Lp-PLA_2, VLDL-C, TC and VLDL-TG for both dose groups. The Apo B placebo-adjusted percent change from baseline was reduced by 9.3% in the AMR101 4 g/day group versus the placebo group ($p<0.0001$).

The non-inferiority criterion for LDL-C was met at both AMR101 doses, because the pre-specified upper boundary of the 97.5% confidence interval (-1.7 and 0.05 for AMR101 4 g/day and AMR101 2 g/day, respectively) did not cross the 6% non-inferiority threshold. For the AMR101 4 g/day group, LDL-C decreased significantly by 6.2% versus placebo, demonstrating superiority over placebo ($p=0.0067$).

TC and VLDL-TG decreased significantly relative to placebo in both AMR101 dose groups, and high sensitivity C-reactive protein (hsCRP) decreased significantly ($p=0.0003$) by 0.5 mg/L relative to placebo in the AMR101 4 g/day group. HDL-C was unchanged in the groups, but relative to placebo, there were small decreases of -4.5% and -2.2% for the AMR101 4 g/day and 2 g/day treatment groups, respectively. The difference was statistically significant for the AMR101 4 g/day group compared to placebo ($p=0.0013$).

1.4. Clinical Safety

Across all completed Amarin-sponsored studies, during the double-blind periods of the trials, a total of 1071 patients have been exposed to ethyl-EPA from AMR101 capsules. AMR101 has been well tolerated (with incidence of adverse events similar to placebo) and there have been no major safety concerns. The most commonly reported side effects for AMR101 were diarrhea, nausea, headache, arthralgia, and skin rash. See the Investigator's Brochure for more information.

In the pivotal Phase 3 trials in patients with hypertriglyceridemia, treatment with AMR101 at doses of 2 and 4 g/day was safe and well tolerated with no safety concerns. The types (by preferred term) of common treatment-emergent adverse events (TEAEs) and their incidence in the MARINE and ANCHOR trials, are listed in Table 1.

Table 1. Incidence of Common TEAEs (>3% in Any Treatment Group) by Preferred Term

	Number (%) of Patients with TEAE		
Preferred Term	Placebo n (%)	AMR101 2 g/day n (%)	AMR101 4 g/day n (%)
	MARINE Study		
	N=76	N=76	N=77
Subjects with any TEAE	28 (36.8)	26 (34.2)	27 (35.1)
Diarrhea	5 (6.6)	4 (5.3)	1 (1.3)
Nausea	4 (5.3)	5 (6.6)	1 (1.3)
Eructation	3 (3.9)	1 (1.3)	0 (0.0)
	ANCHOR Study		
	N= 233	N= 236	N= 233
Subjects with any TEAE	112 (48.1)	106 (44.9)	106 (45.5)
Diarrhea	10 (4.3)	9 (3.8)	8 (3.4)
Arthralgia	1 (0.4)	8 (3.4)	4 (1.7)

TEAE = treatment-emergent adverse event
TEAE are adverse events that start after the first dose of randomized study medication or occur prior to the first dose and worsen in severity during the double-blind period.

In a large study with Japanese patients (Japan EPA Lipid Intervention Study [JELIS]), long-term administration of 1.8 g/day ethyl-EPA (Epadel®) was associated with an excellent safety and tolerability profile (Yokoyama 2007). Most AEs attributable to ethyl-EPA were regarded as mild. The most common adverse events were gastro-intestinal (nausea, diarrhea, epigastric discomfort) or dermatologic (eruption, itching, exanthema, eczema) in nature.

1.5. Rationale

Hypothesis

The hypothesis is that combination anti-dyslipidemic therapy of a LDL-C lowering drug (statin therapy) with the triglyceride-lowering drug AMR101 will be superior to the LDL-C

lowering therapy alone when used as prevention in reducing long-term clinical events in patients with mixed dyslipidemia at high risk for cardiovascular events.

TG-Lowering as a Therapeutic CV Target

Studies have shown that elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are associated with increased risk of coronary heart disease (CHD) (LaRosa 2003), and therapeutic strategies that lead to a statistically significant reduction in LDL-C lower CHD event rates (Baigent 2005). One potential impediment, limiting further reduction in CHD events despite low on-treatment LDL-C, is residual elevation in serum TG levels (Miller 2000). Indeed, even after adjustment for HDL-C, detailed evaluation of population-based prospective studies has disclosed an independent effect of TG on CHD events (Sarwar 2007). Coupled with the knowledge that combined hyperlipidemia (i.e., elevated LDL-C and TG) promotes CHD to a significantly greater extent than either high LDL-C or TG alone (Manninem 1992), the hypothesis is strong that low on-treatment levels of TG when added to low LDL-C would be superior to low LDL-C alone in reducing subsequent CHD events. Supporting evidence for this hypothesis was obtained in a post hoc analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 Trial (PROVE IT-TIMI 22) (Miller 2008) wherein among patients receiving statin therapy after acute coronary syndrome (ACS), on treatment TG <150 mg/dL was associated with a lower risk of recurrent CHD events independently of the level of LDL-C. For each 10% lowering of TG attained during the first 30 days of treatment after an ACS event, the risk for death, myocardial infarction, or recurrent acute coronary syndrome was reduced by 2.3% (p =0.035) after adjustment for high LDL-C (>70 mg/dL) and HDL-C (<40 and 50 mg/dL in men and women, respectively).

Omega-3 Fatty Acids in Fish Oils

There is a growing body of evidence, encompassing molecular, cellular, animal and human studies defining the roles for O3FAs as bioactive agents for reducing the risks of and treating CVD (Torrejon 2007). Many epidemiological studies have demonstrated inverse associations between fish intake and CV mortality, and more specifically between the intake and blood levels of O3FAs and CV mortality. For example, when comparing blood levels of O3FAs among men who had died of sudden cardiac death with controls matched for age and smoking status, it was found that participants with the highest blood levels of EPA and DHA had a 90% risk reduction for sudden cardiac death compared with those with the lowest levels (Albert 2002).

Clinical trials and experimental studies, suggest important antiatherogenic and antithrombotic effects of O3FAs. These result from wide-ranging biological effects, including benefits on lipoprotein metabolism, blood pressure, endothelial function and vascular reactivity, inflammation, platelet and fibrinolytic function, cytokine production, coagulation and oxidative stress (Mori and Woodman 2006). Evidence suggests that increased consumption of O3FAs from fish or fish-oil supplements reduces the rates of all-cause mortality, cardiac and sudden death, and possibly stroke (Wang 2006). The effect was evident in both primary-prevention (general population without a history of CVD) and secondary-prevention (patients with a history of CVD) studies with a stronger effect in secondary prevention.

The Diet and Reinfarction Trial (DART) was one of the first randomized, controlled studies to demonstrate the beneficial effects of O3FAs in secondary prevention of CHD and reported

a 29% reduction in all-cause mortality over a 2-year period in 2033 male MI survivors advised to increase their intake of oily fish (200 to 400 g of fatty fish per week, which provided 500 to 800 mg/day of O3FAs) (Burr 1989). While not statistically significant, there was also a trend toward a reduction in recurrent ischemic heart disease events with increased fatty fish consumption. A post hoc analysis of patients receiving fish oil capsules (900 mg/day of EPA+DHA) in DART suggested that the protective effect was attributable to O3FAs (Burr 1994). The greatest benefit was seen in fatal MIs, and this observation led to the hypothesis that O3FAs might protect the myocardium against the adverse sequela of acute ischemic stress.

A cardioprotective effect for O3FAs derived from fish oil is supported by prospective studies demonstrating inverse associations between fish intake and coronary heart disease mortality, especially amongst high-risk individuals (Mori and Woodman 2006). Early separation of survival curves in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione study (GISSI-Prevenzione Investigators 1999) and the DART trial support a reduction in ventricular fibrillation and a decreased incidence of myocardial infarction (Leaf 1996) as the primary mechanisms through which O3FAs prevent CVD (Mori and Woodman 2006).

Many international bodies including the AHA, American College of Cardiology, and the European Society of Cardiology have found the overall evidence for benefit sufficiently strong to make public recommendations for increased O3FA intake for both primary and secondary prevention (Harris 2007).

Omega-3 Fatty Acid Ethyl Esters

The largest prospective, randomized, controlled trial to test the efficacy of O3FAs for secondary prevention of CHD is the GISSI study (GISSI-Prevenzione Investigators 1999). In this study, 11,324 patients with preexisting CHD (experienced an MI and were receiving conventional cardiac pharmacotherapy) were randomized to either 300 mg of vitamin E, 850 mg of O3FA ethyl esters (as EPA and DHA), both, or neither. After 3.5 years of follow-up, the group given the O3FAs alone experienced a 15% reduction in the primary end point of death, nonfatal MI, and nonfatal stroke ($p < 0.02$). There was a 20% reduction in all-cause mortality ($p = 0.01$) and a 45% reduction in sudden death ($p < 0.001$) compared with the control group; vitamin E provided no additional benefit. Triglycerides decreased by 4% and LDL cholesterol levels increased by 2.5% after six months in the O3FA treatment groups compared with controls. This trial, although very large and carried out in a relatively "usual-care" setting, was not placebo controlled, and dropout rates were high (>25%). A follow-up study (Marchioli 2002) assessed the time-course of the benefit of O3FAs on mortality in subjects in the GISSI-P Study and found that survival curves diverged early after randomization. Total mortality was significantly lowered by 28% after 3 months of treatment (RR =0.59), and by 4 months, the risk of sudden cardiac death was reduced by 45% (RR =0.47).

Ethyl-EPA

In another larger trial, the Japan EPA Lipid Intervention Study (JELIS), 18,645 patients with hypercholesterolemia (70% women; mean age, 61 years) were randomly assigned to either statin alone or statin and pure ethyl-EPA (1.8 g/day). Of all patients, 15,000 patients (80%) were without existing CAD and 3,645 (20%) with existing CAD (Matsuzaki 2009). The

primary endpoint was any major adverse coronary event (MACE including SCD, fatal and nonfatal MI, and other nonfatal events including unstable angina pectoris (determined to be caused by myocardial ischemia by invasive/non-invasive testing), angioplasty, stenting, and coronary artery bypass grafting).

In the overall analysis (Yokoyama 2007), during the 4.6-year follow-up, ethyl-EPA reduced major adverse coronary events by 19% (p =0.011). EPA treatment was also associated with a significant 24% reduction in the incidence of unstable angina and a 19% decrease in nonfatal coronary events. This treatment also produced nonsignificant reductions of 21%, 25%, and 14% in fatal MI, nonfatal MI, and revascularizations, respectively.

In a subgroup analysis of primary prevention cases, compared to patients with normal serum TG and HDL-C levels, those with abnormal levels (TG ≥150 mg/dL; HDL-C <40 mg/dL) had a significantly higher major adverse coronary event (MACE) rate by 71% (p=0.014). In this higher risk group, ethyl-EPA treatment suppressed the MACE risk by 53% (p=0.043) (Saito 2008).

While there was no significant difference in the incidence of first stroke between ethyl-EPA and control groups, the incidence of stroke recurrence was significantly lower in the EPA group at 6.8% versus the control group at 10.5%, a reduction of 20% (p<0.05; Tanaka 2008). Further, while there was no difference in the incidence of recurrent hemorrhagic cerebral events between the two groups, ethyl-EPA was effective in reducing the recurrence of ischemic cerebral vascular events such as cerebral infarction (Harris 2009).

O3FA supplementation lowered CV risk in both the GISSI-Prevenzione study and JELIS, despite aggressive therapy with standard pharmacotherapy (e.g., statins, aspirin, β-blockers and angiotensin-converting enzyme inhibitors). Additionally, the JELIS trial established the safety and efficacy of combination therapy with ethyl-EPA and a statin vs statin therapy alone for improving CV prognosis. The JELIS trial was conducted with Epadel that contains the same active ingredient, ethyl-EPA, as AMR101. Ethyl-EPA was shown in the JELIS study to reduce CAD events even in a Japanese population with very high intakes of O3FAs due to the high fish consumption. The evidence supporting a benefit in primary prevention comes from an observed 18% decrease in CV events in the 80% of patients in the JELIS trial without documented CAD (p =0.13); this effect size was essentially the same as that observed in the secondary prevention cohort (19%, p <0.05) (Lee 2008).

Medical Need

CVD resulting from progressive atherosclerosis remains the most common cause of morbidity and mortality all over the world. Based on 2006 US statistics (American Heart Association 2010), an estimated 81 million American adults (more than one in three) have one or more types of CVD. Of these, 38 million are estimated to be age 60 or older. Total CVD includes coronary heart disease (CHD): 17.6 million, heart failure (HF): 5.8 million and stroke: 6.4 million. CHD further divided includes myocardial infarction (MI): 8.5 million, and angina pectoris (AP): 10.2 million. Final mortality data show that CVD as the underlying cause of death accounted for 34.4% of all deaths (about 830,000 of all 2.4 million deaths in 2006). CHD is the leading cause of death in all Western industrialized countries, despite considerable improvement since the mid-1960s. In developing countries, the incidence of CVD is increasing alarmingly. In addition to death, CVD also causes many serious non-fatal

events and is the major cause of disability. Therefore, additional therapies for prevention of CVD would have a considerable public health benefit.

A large number of studies have demonstrated the TG-lowering effects of O3FAs (Ginsberg 2001; Harris 1997). Hypertriglyceridemia is a common lipid abnormality and often occurs in persons who are obese and have insulin resistance, Type 2 diabetes mellitus, or the metabolic syndrome (Jacobson 2007; Bays 2008). Elevation in TG is positively associated with accelerated atherosclerosis leading to CV events, the latter even after correction for other lipid and non-lipid risk factors (Jacobson 2007). In the US (American Heart Association 2010), the mean TG level for American adults age 18 and older is 144.2 mg/dL (men, 156.5 mg/dL; women, 132.1 mg/dL).

Lifestyle modification is important for the management of patients with hypertriglyceridemia; however, for patients who do not adequately respond to dietary and lifestyle restrictions, relatively few classes of drugs are available to treat hypertriglyceridemia, and each is associated with risks that may limit their use alone or in combination. Currently available pharmacological treatments for hypertriglyceridemia include fibric acid derivatives (such as gemfibrozil and fenofibrate), niacin in various formulations, prescription omega-3-acid ethyl esters (Lovaza/Omacor) and statins (3 hydroxy 3 methylglutaryl coenzyme A reductase inhibitors).

Although the above agents have robust TG-lowering effects in patients with hypertriglyceridemia, the degree of TG-lowering is highly variable; generally greater TG-lowering effects are observed for fibrates and niacin compared with statins. Many patients will be satisfactorily treated with one or more of the above range of drugs (combined with appropriate diet and attention to other CV risk factors and lifestyle).

Lovaza, comprised predominantly of ethyl-EPA and the ethyl ester of docosahexaenoic acid (ethyl-DHA), is indicated only in patients with very high TG levels (>500 mg/dL), raises LDL-C even when combined with statins in patients with high TGs (200-499 mg/dL), and is approved at 4 g/day (equivalent to 4 capsules/day) resulting in poor patient compliance. A non-compliance rate of 35% was reported in one clinical trial (Leaf 2005).

Fibrates are clearly effective at raising HDL-C and lowering TG concentrations. However, their effects on vascular events remain uncertain. Several large-scale trials of fibrate therapy have been completed in the past few years. Although some of these trials have suggested benefit, others have shown no effect, leading to uncertainty about the presence and magnitude of any cardiovascular protective effects and difficulties for clinicians in interpretation of the results (Jun 2010). The ACCORD study (Ginsberg 2010) reported no overall benefit for fenofibrate, raising further questions about the usefulness of these agents.

There are also safety issues with the above agents that limit their clinical use. Statins, particularly at high doses, may cause increases in hepatic transaminases and are also known to cause myopathy and occasionally rhabdomyolysis, which may lead to death from acute renal failure. This risk may be increased when fibrates and statins are co-administered and many clinicians will avoid co-prescribing these 2 medications. Fibrates are also associated with interactions with warfarin and hepatic transaminase elevations. The utility of niacin is limited by the occurrence of severe flushing and associated symptoms which can be difficult to manage even with careful dose titration and pre administration of aspirin or other non-

steroidal anti-inflammatory drugs. Niacin is also associated with impairment of glucose tolerance and precipitation of attacks of gout in susceptible patients.

The DYSlipidemia International Study (DYSIS) assessed the prevalence of dyslipidemia among patients taking statins. This epidemiological observational study included more than 22,000 patients in Europe and Canada aged 45 and older who received statin therapy for at least three months, and had a clinical diagnosis of coronary or other atherosclerotic disease, or were at high risk of developing CVD. The study found 48% of patients had LDL-C not at goal; 26% had low HDL-C levels; and 38% had elevated triglycerides. This study demonstrates that persistent dyslipidemia is highly prevalent in statin-treated patients.

Patients with dyslipidemia, particularly those with established CVD or diabetes, have therapeutic needs that cannot be met by statin monotherapy. It is hypothesized that achieving target values for LDL-C/non-HDL-C in these patients using a therapeutic approach of the combination of AMR101 and a statin will benefit these patients. Such a combination therapy might increase the likelihood of therapeutic success in these patients with regards to future risk of CVD, based on meeting of both LDL-C/non-HDL-C goals and TG goals according to the ACC/AHA guidelines (Anderson 2007). Approximately 40 million Americans have high TG levels (>200 mg/dL), however only a minority (3.6%) are currently treated with prescription medication (Ford 2009). Patients with elevated TGs are currently under-served and would benefit from a new, safe and effective product that can provide the following attributes:

- Robust efficacy to lower TGs
- Safe to use with other lipid-lowering agents, including statins
- Does not increase LDL-C when used in patients on statin therapy (TG = 200-499 mg/dL)
- Has convenient dosing regimen
- Has class-specific positive outcomes data

Pleiotropic Effects

There is ample evidence that O3FAs decrease TGs in patients with hypertriglyceridemia which is a beneficial effect related to the fact that elevated TGs have been identified as an independent risk factor for CVD. Lowering TGs in patients with hypertriglyceridemia would lead to a slowing of the development of atherosclerosis. However O3FAs including EPA have a wide range of additional pharmacological effects that most likely contribute to a beneficial effect in patients with CVD.

Beneficial effects in clinical trials have been attributed in part to reducing arrhythmias (Lee 2003; Goel 2002; Calo 2005). The case for an antiarrhythmic effect of O3FAs comes from clinical trials and from animal studies. Clinical trials have shown that the risk of sudden death in patients who have survived myocardial infarction is greatly reduced by inclusion of O3FAs in the diet (Siscovick 2000). Thus it seems that fatal ventricular fibrillation is less likely to occur during sufficient intake of O3FAs. Animal studies support this. Coronary ligation studies in a variety of species (rats, dogs and marmosets) have shown that the incidence of ventricular fibrillation is lower in animals fed a diet rich in O3FAs before

ligation (McLennan 1992; Leaf 1996). In isolated cells, the story is similar (Li 1997, Engler 2000; Omura 2001). In neonatal rat cardiac myocytes, EPA prevents the arrhythmogenic action of many interventions, including high external Ca^{2+} and ouabain (Kang 1994). The antiarrhythmic effect is caused by a reduction in electrical excitability caused by partitioning O3FAs into the phospholipid cell membranes of the cardiac myocytes, which modulates membrane ion channels. This is the postulated direct mechanism that refers to the antiarrhythmic effect of O3FAs which inhibits the fast, voltage-dependent sodium current along with the L-type calcium currents. This reduces the action potential of cardiac myocytes, reducing the susceptibility to arrhythmia. These cellular alterations are likely to reduce the severity of ventricular arrhythmias by inhibiting the rapid accumulation of intracellular Ca^{2+} following ischemia. It was also shown in patients with coronary artery disease that long-term treatment with EPA augments both NO-mediated and non-NO-mediated endothelium-dependent forearm vasodilatation (Tagawa 1999).

Another, indirect mechanism refers to the effect of O3FAs on cardiac arrhythmias by modifying the balance of different eicosanoids which are produced as end-products from chain elongation of their parent polyunsaturated fatty acids (Nair 1997). Most investigations of the link between O3FAs and heart disease have demonstrated the competition between AA and O3FAs to become substrates in the production of eicosanoids. O3FAs compete with AA in several ways, but EPA in particular competes with AA as the substrate for the cyclooxygenase enzyme inhibiting the production of thromboxane A_2 (TXA_2) and in endothelial cells, prostaglandin I_3 (PGI_3) is synthesized from EPA (Nair 1997). The net result of these actions is vasodilatation. A reduced ratio of AA/EPA shifts the spectrum of eicosanoid production toward an increase in thromboxane A_3 (TXA_3) and PGI_3 at the expense of TXA_2 and PGI_2, respectively. This shift was found to reduce the risk of ventricular fibrillation (VF) and sudden cardiac death (SCD) (Coker 1982). Excessive production of eicosanoids derived from omega-6 fatty acids have been associated with heart attacks, thrombotic stroke, and arrhythmia, while those from O3FAs are antiarrhythmic.

Probably one of the most important pharmacologic properties of EPA is its anti-inflammatory and immune-modulating activity (Calder 2006; Calder 2010). Because of the inflammatory events underlying plaque rupture, the variety of anti-inflammatory effects of O3FAs may be of relevance to atherosclerosis and its clinical manifestations of myocardial infarction, sudden death, and stroke (Mori 2004; Thies 2003). A randomized controlled study, in patients awaiting surgery to remove atherosclerotic plaques in the carotid artery, has shown that an anti-inflammatory response might be involved, by demonstrating an association between the intake of O3FAs as a supplement (1.4 g/day) and the stability of atherosclerotic plaques (Thies 2003). This improved stability was achieved by incorporation of the O3FAs into the plaque.

The omega-6 fatty acid AA gives rise to eicosanoid mediators that have established roles in inflammation and AA metabolism is a long recognized target for commonly used anti-inflammatory therapies. O3FAs, are incorporated into inflammatory cell phospholipids in a time- and dose-dependent manner. They are incorporated partly at the expense of AA, but also other omega-6 fatty acids. EPA and DHA inhibit AA metabolism. Thus production of AA-derived eicosanoids is decreased by these O3FAs. EPA gives rise to an alternative family of eicosanoids (e.g. PGE_3), which frequently have lower anti-inflammatory potency than those produced from AA, and to resolvins (E- and D-series) which have potent anti-

inflammatory and inflammation resolving properties (Serhan 2006; Dona 2008). The plasma AA/EPA ratio has been used as a marker of the inflammatory status in patients with CVD (Rupp 2004; Holub 2009). In favor of the concept that less pro-inflammatory processes can be observed already at lower AA/EPA ratios is the finding that 1.4 g/day ethyl-EPA reduced the incidence of plaque rupture (Thies 2003). The AA/EPA ratio had a strong relationship with the incidence of CV events such as MACE in patients undergoing elective PCI (Domei 2009).

In addition to modifying the profile of lipid-derived mediators, O3FAs can also influence peptide mediator (i.e. cytokine) production. Pro-inflammatory cytokines, or cytokines reflecting inflammatory processes, e.g. IL-1beta, IL-2, IL-6, TNFalpha, platelet-derived growth factor (PDGF)-A and -B and monocyte chemoattractant protein-1 (MCP-1), are reduced by EPA and DHA in human subjects (von Schacky 2007), and soluble cytokines reflecting interactions between blood cells and the vessel wall, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (Yamada 2008).

EPA and DHA intake also resulted in a decreased expression of genes involved in inflammatory- and atherogenic-related pathways, such as nuclear transcription factor κB signaling, eicosanoid synthesis, scavenger receptor activity, adipogenesis, and hypoxia signaling (Bouwens 2009).

In conclusion, the pleiotropic effects of EPA may contribute to the overall beneficial effects on the risk of CVD, in addition to the TG-lowering effect. Therefore, it is possible that the efficacious dose of EPA that decreases the CV event rate is lower than the dose needed to exert the maximum TG-lowering effect, and/or that a modest decrease of TGs after EPA treatment could still lead to a significant decrease in the risk for CVD.

Dose Selection

This trial will be conducted with a dose of AMR101 of 4 g/day (4 capsules/day).

To date, only one study was published investigating the effects of combination treatment with an O3FA plus statins on clinical cardiovascular events. This is the Japan EPA Lipid Intervention Study (JELIS) (Yokoyama 2007), as previously discussed, wherein ethyl-EPA combined with low-dose pravastatin or simvastatin compared with statin therapy alone reduced major coronary events without altering rates of sudden cardiac death. These effects were achieved without any significant changes in total, LDL- or HDL-C and a statistically significant ($p < 0.0001$) decrease in triglycerides, suggesting that EPA can lower CVD risk by mechanisms other than LDL-C lowering (Yokoyama 2007). In a subanalysis of this study, the addition of ethyl-EPA to pravastatin or simvastatin reduced also the incidence of coronary heart disease events in high-risk patients with metabolic syndrome and atherogenic dyslipidemia characterized by high triglycerides and low HDL-C (Saito 2008). The JELIS study was performed in a large patient population wherein an ethyl-EPA dose of 1.8 g/day translated to significant benefits on CV events.

In the ANCHOR study (Amarin-sponsored), both the 2 and 4 g/day dosing regimens of AMR101 resulted in statistically significant reductions of TGs (see Section 1.3). However, since the 4 g/day dose caused a larger reduction in TG and other lipid, lipoprotein and inflammatory markers, the AMR101 4 g/day dose was selected for the present study.

1.6. Risk/Benefit

Across all completed Amarin-sponsored studies, the proportion of patients (based on the safety population from the randomized, double-blind periods of the studies) experiencing any adverse events was similar for patients on placebo (light paraffin oil) and patients on AMR101 (57.1% and 57.4% for placebo and AMR101, respectively). The proportion of patients experiencing a serious adverse event (SAE) was also similar for both treatment groups (5.2% and 6.0% for placebo and AMR101, respectively). The safety profile in the open-label extensions was similar to that observed in the double-blind treatment periods. There were no SAEs attributed to AMR101 during the open-label extension periods of the studies.

In summary, AMR101 is very well tolerated at daily doses up to 4 g. The side effects reported by the patients taking AMR101 were generally similar to those reported by the patients taking placebo. Ethyl-EPA is a pro-drug, and is rapidly and completely hydrolyzed to EPA. EPA is a natural substance found universally as a component of all cell membranes. It is classified as an essential fatty acid. Because of the nature of EPA, as an essential component of normal tissue and its part in normal metabolism, human studies have demonstrated that it is safe. See the Investigator's Brochure for more information.

2. STUDY OBJECTIVES

The primary objective is, in patients at LDL-C goal while on statin therapy, with established cardiovascular disease (CVD) or at high risk for CVD, and hypertriglyceridemia (fasting triglycerides, TG, ≥150 mg/dL and <500 mg/dL), to evaluate the effect of 4 g/day AMR101 for preventing the occurrence of a first major cardiovascular event of the composite endpoint that includes:

- Cardiovascular (CV) death,
- Nonfatal myocardial infarction (MI),
- Nonfatal stroke,
- Coronary revascularization,
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

[Because of the variability in TG levels, the lower TG qualifying limit is 10% lower than the target of 150 mg/dL, i.e., 135 mg/dL.]

Refer to Appendix B for cardiovascular event definitions

The secondary objectives of this study are the following:

The key secondary objective is to evaluate the effect of therapy on the composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina, nonfatal stroke, or peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair.

Other secondary objectives :

- To evaluate the effect of therapy on combinations of each of the key secondary objective clinical events in addition to the following clinical events:
    - Cardiac arrhythmia requiring hospitalization
    - Cardiac arrest
    - Peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair
    - Total mortality

The tertiary objectives of this study are the following:

- Evaluate the effect of therapy on the occurrence of a second, third, fourth, and fifth major cardiovascular event (same as the primary composite endpoint but for events occurring after the first event);
- To evaluate the effect of therapy on the primary endpoint in subgroups of patients including:
    - Diabetes mellitus
    - Metabolic syndrome as defined by the NCEP ATP III or future criteria as they may evolve;
- To evaluate the effect of therapy on the individual endpoints of new congestive heart failure (CHF), on new CHF as a primary cause of hospitalization, on transient ischemic attack, on amputation for vascular disease and on carotid revascularization;
- Elective coronary revascularization and emergent coronary revascularization;
- To assess the effects regarding lipids, lipoproteins and inflammatory markers including triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high- density lipoprotein cholesterol (HDL-C), non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein B (apo B), high sensitivity C-reactive protein (hs-CRP) and high sensitivity troponin (hsTnT), as follows:
    - Assessment of the effect of AMR101 on each marker (on-treatment change of markers)
    - Assessment of the effect of the baseline value of each marker on treatment effects (baseline effect on outcomes)
    - To evaluate the effect of therapy for preventing clinical events, as defined above, among all patients in the study, and in subgroups such as patients with diabetes mellitus and patients with substantial on-treatment changes of any of the markers (on-treatment effect on outcomes).
- To evaluate the effect of therapy on new onset diabetes (See appendix C);
- To explore the effect of AMR101 on weight and waist circumference.

3. STUDY DESIGN

3.1. Type of Study

Phase 3b, multi-Center, multinational, prospective, randomized, double-blind, placebo-controlled, parallel-group study

3.2. Study Population

The population for this study is men and women ≥45 years of age with established CVD, or men and women ≥50 years of age with diabetes in combination with one additional risk factor for CVD. In addition, all patients will have atherogenic dyslipidemia defined as on treatment for hypercholesterolemia (but at treatment goal for LDL-C, by treatment with a statin) and hypertriglyceridemia. More details are listed in the inclusion criteria.

The patients will need to provide written consent to participate in the study and be willing and able to comply with the protocol and the study procedures.

3.3. Study Periods

This study consists of the following study periods:

- **Screening Period**: During the screening period, patients will be evaluated for inclusion/exclusion criteria.

  At the first visit to the Research Unit (Visit 1), study procedures will be performed for evaluation of patient's eligibility in the study. At this screening visit, patients will sign an informed consent form before any study procedure is performed; the informed consent form will cover the treatment/follow-up period. Based on the evaluation from Visit 1, the following situations may occur:

  - Patients who are eligible for participation based on the study procedures on Visit 1 will return to the Research Unit for Visit 2 (randomization visit) to start the treatment/follow-up period. This case includes, for example, patients at Visit 1who are on a stable dose of a statin, are planning to stay on the same statin and the same dose of the statin, and who not need to wash out any non-statin lipid-altering medications.
  - Patients who are <u>not</u> eligible for participation based on the study procedures on Visit 1 and are <u>unlikely</u> to become eligible in the next 28 days (for example: unlikely to stabilize statin dose, unable to wash out non-statin lipid-altering medications, etc.): these patients will be screen failed after Visit 1.
  - Patients not eligible for participation in the study based on the study procedures on Visit 1 may possibly become eligible in the next 28 days: these patients may return at the discretion of the investigator for a second optional screening visit (Visit 1.1) at which time the procedures needed for re-evaluation of the previously failed inclusion/exclusion criteria will be repeated. This case includes, for example, patients who are started on a statin at Visit 1, whose statin dose is changed at Visit 1, and/or needed to wash out non-statin lipid-altering medications. The following applies for these patients:
    - Patients with a change in the statin or statin dose on Visit 1 will need to be on a stable statin dose for at least 28 days before the lipid qualifying measurements

at Visit 1.1. Other concomitant medications (antidiabetic therapy, for example) can be optimized or stabilized during this period.

- Patients starting a washout at Visit 1 will have a washout period of at least 28 days (only 7 days for bile acid sequestrants) before the lipid qualifying measurements at Visit 1.1.
- Patients at Visit 1 who are on a stable dose of a statin, are planning to stay on the same statin at the same dose, and who do not need any medication washout, but were asked to return for Visit 1.1 to repeat one or more of the other study procedures not related to concomitant medications

- Patients who become eligible for participation based on the additional study procedures at Visit 1.1 will return to the Research Unit for Visit 2 (randomization visit) to start the treatment/follow-up period.

At the end of the screening period, patients will need to meet all inclusion/exclusion criteria before they can be randomized. Patients who are not eligible for participation after the screening period (based on study procedures at Visit 1 and/or Visit 1.1) may return at a later date for rescreening. These patients will need to re-start with all procedures starting with Visit 1. This includes patients who need more time to stabilize one or more conditions or therapies (for example: statin, antidiabetic, antihypertensive, thyroid hormone, HIV-protease inhibitor therapy).

- **Treatment/Follow-Up Period**: Within 42 days after the first screening visit and within 14 days after the second screening visit, if one is conducted, eligible patients will enter the treatment/follow-up period. During this period, the patients will receive study drug during the planned visits at the Research Site and take the study drug while away from the Research Site.

During the visits, study procedures will be performed for evaluation of efficacy and safety. A detailed schedule of procedures is provided in Appendix A.

3.4. Study Duration

The estimated study duration includes a planned 18-month enrollment period followed by a follow-up period of approximately 3.5 years in expected duration (approximately 5 years in total). Patients will be randomized at different times during the enrollment period but will all end the study at the same date (study end date). It is planned that all randomized patients will receive study medication and be followed-up until the study end date. This is an event-driven trial and patients will continue in the trial if the trial runs longer than expected, or will terminate earlier if the trial runs shorter than expected.

The total duration of the trial is based on a median 4-year follow-up period across patients. The first patient randomized would be followed for 4.75 years (the longest individual follow-up duration), and the last patient randomized would be followed for 3.25 year (the shortest individual follow-up duration).

3.5. Study Groups

At Visit 2 (Day 0), eligible study patients will be randomly assigned to the following treatment groups:

- **Group 1**: AMR101 4 g daily (four 1000 mg capsules daily)

- **Group 2**: placebo (four capsules daily)

The four AMR101 or placebo capsules daily will be taken as two capsules in the morning and two capsules in the evening (twice-per-day dosing regimen).

3.6. Number of Patients

This is an event-driven trial: It is expected that a minimum of 1612 primary efficacy endpoint events will be required during the study. A total of approximately 7990 patients will be entered into the study to either receive AMR101 or placebo (approximately 3995 patients per treatment group) in order to observe an estimated 1612 events that make up the primary composite endpoint for efficacy.

3.7. Number of Study Sites

Participants will be enrolled at multiple Research Sites in multiple countries.

3.8. Randomization

On Day 0, eligible patients will be randomized to one of 2 study groups using a computer-generated randomization schema. Randomized treatment assignment to either AMR101 or placebo in a 1:1 ratio will be provided using the internet or a touch-tone telephone via an interactive voice response system (IVRS).

3.9. Blinding

This is a double-blind study. Patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors supporting the study will be unaware of the randomization code (i.e., they will not know which study participants are receiving the experimental drug and which are receiving the placebo drug). The study medication, AMR101 and placebo capsules, will be similar in size and appearance to maintain blinding.

During the double-blind treatment/follow-up period, everyone (patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors managing/supporting the study), with the exception of the laboratory personnel performing the analysis, will be blinded to individual results of the efficacy laboratory measurements (including lipid values). Individual results from the lipid profile may be unblinded in the event of an emergency for a patient.

3.10. Stratification

Participants will be assigned to treatment groups stratified by CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries). There are two CV risk categories:

- CV Risk Category 1: patients with established CVD defined in the inclusion criteria. Patients with diabetes and established CVD are included in this category.
- CV Risk Category 2: patients with diabetes and at least one additional risk factor for CVD, but no established CVD. This is primary prevention group.

Stratification will be recorded in the IVRS at the time of enrollment. Approximately 70% of randomized patients will be in the CV Risk Category 1 and approximately 30% of

randomized patients will be in the CV Risk Category 2. Enrollment with patients of a CV risk category will be stopped when the planned number of patients in that risk category is reached.

4. STUDY POPULATION

4.1. Inclusion Criteria

Patients meeting the following criteria will be eligible to participate in the study:

1. Fasting TG levels of ≥135 mg/dL and <500 mg/dL. The target for the lower end of the fasting TG level is ≥150 mg/dL but because of the variability in TG levels, patients will qualify for enrolment within 10% of this limit (i.e., ≥135 mg/dL).
2. On stable therapy with a statin (with or without ezetimibe), for at least 4 weeks prior to the LDL-C/TG baseline qualifying measurements for randomization, to maintain LDL-C >40 mg/dL and ≤100 mg/dL
   - Stable therapy is defined as the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable, the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C). Patients who have their statin therapy or use of ezetimibe initiated at Visit 1, or have their statin, statin dose and/or ezetimibe dose changed at Visit 1, will need to go through a stabilization period of at least 28 days since initiation/change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).
   - Statins may be administered with or without ezetimibe.

   NOTE: If patients qualify at the first qualification visit (Visit 1) for TG and LDL-C, and meet all other inclusion/exclusion criteria, they may be randomized at Visit 2. If patients don't qualify at the first qualifying visit (Visit 1), a second re-qualifying visit (Visit 1.1) is allowed. For some patients, because they need to stabilize medications and/or need to washout medications, the second re-qualifying visit (Visit 1.1) will be needed after the stabilization/washout period.
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 are defined as follows:

   CV Risk Category 1: defined as men and women ≥45 years of age with one or more of the following:
   - Documented coronary artery disease (CAD; one or more of the following primary criteria must be satisfied):
     - Documented multivessel CAD (one or more >50% stenoses in two major epicardial coronary arteries – with or without antecedent revascularization)
     - Documented prior MI
     - Hospitalization for high-risk NSTE-ACS (with objective evidence of ischemia: ST-segment deviation or biomarker positivity)

- Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied):
  - Documented prior ischemic stroke
  - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis
  - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound
  - History of carotid revascularization (catheter-based or surgical)
- Documented peripheral arterial disease (PAD; one or more of the following primary criteria must be satisfied):
  - ABI <0.9 with symptoms of intermittent claudication
  - History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical)

OR

CV Risk Category 2: defined as patients with:

1. Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication AND
2. Men and women ≥50 years of age AND
3. One 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 >3.0 mg/L;
   - Renal dysfunction: CrCL >30 and <60 mL/min;
   - Retinopathy, defined as any of the following: non-proliferative retinopathy, preproliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation;
   - Micro- or macroalbuminuria. Microalbuminuria is defined as either a positive micral or other strip test, an albumin creatinine ratio ≥2.5 mg/mmol or an albumin excretion rate on timed collection ≥20 mg/min all on at least two successive occasions; macroalbuminuria, defined as albustix or other dipstick evidence of gross proteinuria, an albumin:creatinine ratio ≥25 mg/mmol or an albumin excretion rate on timed collection ≥200 mg/min all on at least two successive occasions;
   - ABI <0.9 without symptoms of intermittent claudication (patients with ABI <0.9 with symptoms of intermittent claudication are counted under CV Risk Category 1).

   Note: Patients with diabetes with CVD as defined above are eligible based on the CVD requirements and will be counted under CV Risk Category 1. Only patients

with diabetes and no documented CVD as defined above need at least one additional risk factor as listed, and will be counted under CV Risk Category 2.

4. Women may be enrolled if all 3 of the following criteria are met:
   - They are not pregnant;
   - They are not breastfeeding;
   - They do not plan on becoming pregnant during the study.
5. Women of child-bearing potential must have a negative urine pregnancy test before randomization.

   Note: Women are not considered to be of childbearing potential if they meet one of the following criteria as documented by the investigator:
   - They have had a hysterectomy, tubal ligation or bilateral oophorectomy prior to signing the informed consent form;
   - They are post-menopausal, defined as ≥1 year since their last menstrual period or have a follicle-stimulating hormone (FSH) level in a menopausal range.
6. Women of childbearing potential must agree to use an effective method of avoiding pregnancy from screening to the end of the study, unless their sexual partner(s) is/are surgically sterile or the women is abstinent. Effective methods of avoiding pregnancy are contraceptive methods used consistently and correctly (including implantable contraceptives, injectable contraceptives, oral contraceptives, transdermal contraceptives, intrauterine devices, diaphragm with spermicide, male or female condoms with spermicide, or cervical cap).
7. Understanding of the study procedures, willing to adhere to the study schedules, and agreement to participate in the study by giving written informed consent prior to screening.
8. Agree to maintain their current dietary regimen, and to not alter their normal activity routines maintain through the duration of the study.

4.2. Exclusion Criteria

Patients are excluded from participation in the study if any of the following criteria apply:

1. Severe (class IV) heart failure.
2. Any life-threatening disease expected to result in death within the next 2 years (other than CVD).
3. Active severe liver disease (evaluated at Visit 1): cirrhosis, active hepatitis, ALT or AST >3 x ULN, or biliary obstruction with hyperbilirubinemia (total bilirubin >2 x ULN).
4. Hemoglobin A_{1c} >10.0% at screening (Visit 1). If patients fail this criterion (HbA_{1c} >10.0%) at Visit 1, they may have their antidiabetic therapy optimized and be retested at Visit 1.1.
5. Poorly controlled hypertension: blood pressure ≥200 systolic mmHg OR ≥100 mmHg diastolic (despite antihypertensive therapy).

6. Planned coronary intervention (such as stent placement or heart bypass) or any non-cardiac major surgical procedure. Patients can be (re)evaluated for participation in the trial (starting with Visit 1.1) after their recovery from the intervention/surgery.
7. Known familial lipoprotein lipase deficiency (Fredrickson Type I), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type III)].
8. Participation in another clinical trial involving an investigational agent within 90 days prior to screening (Visit 1). Patients cannot participate in any other investigational medication or medical device trial while participating in this study.
9. Intolerance or hypersensitivity to statin therapy.
10. History of acute or chronic pancreatitis.
11. Known hypersensitivity to fish oil products.
12. Non-study drug related, non-statin, lipid-altering medications, supplements or foods:
    - Patients are excluded if they used niacin >200 mg/day or fibrates during the last 28 days before Visit 1, during the screening period and/or plan to use during the treatment/follow-up period of the study;
    - Patients are excluded if they take any omega-3 fatty acid medications (prescription medicines containing EPA and/or DHA) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking omega-3 fatty acid medications during the last 28 days before Visit 1 need to go through a washout period of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (at Visit 1.1);
    - Patients are excluded if they use dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking >300 mg/day omega-3 fatty acids (combined amount of EPA and DHA) within 28 days before Visit 1, need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);
    - Patients are excluded if they use bile acid sequestrants during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking bile acid sequestrants within 7 days before Visit 1, need to go through a washout period of at least 7 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);
13. Other medications (not indicated for lipid alteration):
    - Treatment with tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are allowed), HIV-protease inhibitors, and antihypertensive that have not been stable for ≥28 days prior

to the qualifying lipid measurements (TG and LDL-C) during screening. To be eligible for participation in the study, patients who are not taking a stable dose of these medications within 28 days before Visit 1, need to go through a stabilization period of at least 28 days since their last dose change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).

- Patients are excluded if they use cyclophosphamide or systemic retinoids during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking these medications within 28 days before Visit 1, need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).

14. Known to have AIDS (patients who are HIV positive without AIDS are allowed).
15. Requirement for peritoneal dialysis or hemodialysis for renal insufficiency or if creatinine clearance (CrCL) <30 mL/min.
16. Unexplained creatine kinase concentration >10 × ULN or creatine kinase elevation due to known muscle disease (e.g., polymyositis, mitochondrial dysfunction) at Visit 1.
17. Any condition or therapy which, in the opinion of the investigator, might pose a risk to the patient or make participation in the study not in the patient's best interest.
18. Drug or alcohol abuse within the past 6 months, and unable/unwilling to abstain from drug abuse and excessive alcohol consumption during the study. Excessive alcohol consumption is on average >2 units of alcohol per day. A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.
19. Mental/psychological impairment or any other reason to expect patient difficulty in complying with the requirements of the study or understanding the goal and potential risks of participating in the study (evaluated at Visit 1).

5. STUDY COMMITTEES

5.1. Steering Committee

The Steering Committee (SC) will include the chairperson, the Principal Investigator (PI), key representatives from the Sponsor and its designees (for example, from the organization(s) conducting the study as delegated by the Sponsor), and key representatives from each region who are deemed to have clinical and methodological expertise (national coordinators).

The SC has overall responsibility for:

- Scientific and strategic direction for the trial. The SC must address and resolve all scientific issues regarding the conduct of the trial. All sub-studies must be approved by the SC.
- The execution of the study protocol, and the reporting and publication of the study results.

- Logistical coordination of the different study committees.

The SC will meet at least twice per year.

5.2. Study Operations Committee (SOC)

The Study Operations Committee (SOC) is responsible for ensuring that study execution and management is of the highest quality, and will monitor recruitment, compliance, and the adjudication process and address the day to day issues arising from the trial. The SOC will be composed of representatives from the Sponsor and the organization(s) conducting the study (as delegated by the sponsor), and at least two investigators participating in the trial. This committee will meet by telephone and/or in person on a monthly or bimonthly basis, and each meeting will be documented with minutes.

5.3. Clinical Event Committee (CEC)

The CEC is composed of multidisciplinary medical experts. This committee will be responsible for blindly validating all the primary and secondary efficacy outcome events reported by the investigators (event adjudication). The committee will create a charter with details of the adjudication process and methods based on the definitions of the events.

5.4. Data and Safety Monitoring Board (DSMB)

A DSMB will be instituted for this study in order to ensure its ongoing safety and to oversee and review the interim analysis. Recommendation for trial continuation will be guided by monitoring boundaries at an interim analysis at which a formal efficacy analysis is performed as well as safety evaluations at all safety data reviews. Members of the DSMB will not be otherwise participating in the trial. The committee will include at least one cardiologist and one independent statistician. A DSMB Charter will be drafted and approved by the DSMB and the Steering Committee. The Charter will provide details regarding the interim analysis and monitoring plan.

6. STUDY PROCEDURES

6.1. Assessment Schedule

A detailed schedule of procedures is provided in Appendix A.

6.1.1. Screening Period

6.1.1.1. Screening Visit (Visit 1)

Patients will come to the Research Site for Visit 1. They will be instructed to fast for at least 10 hours before their visit.

If patients qualify for randomization based on the procedures at Visit 1, they need to be randomized within 42 days after Visit 1. The following procedures will be performed at the screening visit:

- Obtain signed informed consent
- Assign the patient a patient number
- Obtain medical, surgical and family history

- Record demographics
- Obtain height, weight, and body mass index
- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and oral body temperature)
- Obtain a 12-lead electrocardiogram
- Evaluate inclusion/exclusion criteria
- This includes procedures and (fasting) blood samples (for example, hs-CRP, calculated creatinine clearance) as needed to determine the CV risk category (see inclusion criteria)
- Obtain fasting blood samples for chemistry and hematology testing
- Obtain a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C)
- Perform a urine pregnancy test on women of childbearing potential
- Record concomitant medication(s)
- Instruct patient to fast for ≥10 hours prior to the next visit

6.1.1.2. Screening Visit (Visit 1.1)

Some patients will skip Visit 1.1: Patients who qualify for study participation after Visit 1 because they meet all inclusion criterion and none of the exclusion criteria, may return to the Research Site for Visit 2 to be randomized and to start the treatment/follow-up period of the study. For these patients, Visit 2 will occur soon after Visit 1.

Patients, who do not qualify at Visit 1, may return to the Research Site for a second qualifying visit (Visit 1.1) at the discretion of the investigator. At Visit 1.1, procedures that caused failure of eligibility at Visit 1 will be repeated. Patients will be eligible for randomization after Visit 1.1 if they meet all inclusion criteria and if they no longer fail the exclusion criteria. If patients are evaluated at Visit 1.1 and qualify for randomization based on the repeated procedures at Visit 1.1, they need to be randomized within 14 days after Visit 1.1.

For some patients, Visit 1.1 will be mandatory at least 28 days after Visit 1 in order to check eligibility. These are patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications (see inclusion/exclusion criteria for details). Any of these changes at Visit 1 may affect the qualifying lipid levels and therefore, patients will need to have Visit 1.1 to determine whether they qualify based on lipid level requirements (TG and LDL-C) determined at Visit 1. Other procedures that caused failure of eligibility at Visit 1 will also be repeated at Visit 1.1.

The following procedures will be performed at the screening visit:

- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and oral body temperature)

- Evaluate inclusion/exclusion criteria; only those evaluations will be repeated that deemed the patient not eligible on Visit 1.
- Obtain fasting blood samples for chemistry and hematology testing. Only those samples will be obtained that deemed the patient not eligible on Visit 1.
- Obtain a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C) if the patient was deemed not eligible on Visit 1. This includes patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications (see inclusion/exclusion criteria for details). These patients will have a fasting blood sample collected at Visit 1.1 for the qualifying lipid values (TG and LDL-C), and the TG and LDL-C inclusion criteria will be evaluated.
- Record concomitant medication(s)

6.1.2. Treatment/Follow-Up Period

Every attempt should be made to complete the follow-up visits during the defined window periods.

6.1.2.1. Randomization visit (Visit 2; Day 0)

Qualified patients will return to the Research Site for Visit 2.

The following procedures will be performed at Visit 2:

- Perform physical examination
- Obtain weight
- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and oral body temperature)
- Measure waist circumference (one of the factors to diagnose metabolic syndrome)
- Obtain a 12-lead electrocardiogram
- Evaluate inclusion/exclusion criteria
- Obtain fasting blood samples for:
  - Chemistry and hematology testing
  - Lipid profile (baseline)
  - Biomarker assays (baseline)
  - Genetic testing (optional blood sample)
  - Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)
- Perform a urine pregnancy test on women of childbearing potential (must be negative for randomization)
- Dispense study drug and record randomization number
- Instruct patient on how to take study drug

- Administer study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples
- Assess for and record adverse events
- Record concomitant medication(s)
- Instruct patient:
  - To bring all study supplies with them to the next visit
  - Not to take study drug on the morning of their next visit
  - To fast for ≥10 hours prior to the next visit

6.1.2.2. Visit 3 (Day 120; ~4 Months)

Patients will return to the Research Site for Visit 3 on Day 120 ±10 days.

The following procedures will be performed:

- Perform physical examination
- Obtain weight
- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and oral body temperature)
- Obtain fasting blood samples for:
  - Chemistry and hematology testing
  - Lipid profile
- Review study drug compliance by unused capsule count; discuss with and counsel patients about compliance if needed
- Administer study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples
- Assess and record efficacy events
- Assess for and record adverse events
- Record concomitant medication(s)
- Instruct patient:
  - To bring all study supplies with them to the next visit
  - Not to take study drug on the morning of their next visit
  - To fast for ≥10 hours prior to the next visit

6.1.2.3. Visits 4, 5, 6 and 7

At Visit 4: Day 360 ± 10; Visit 5: Day 720 ± 10; Visit 6: Day 1080 ± 10; and Visit 7: Day 1440 ± 10, the following procedures will be performed:

- Perform physical examination
- Obtain weight

- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and oral body temperature)
- Measure waist circumference (collected at Visit 5 only)
- Obtain a 12-lead electrocardiogram
- Obtain fasting blood samples for:
  - Chemistry and hematology testing
  - Lipid profile
  - Biomarker assays (collected at Visit 5 only)
  - Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)
- Review study drug compliance by unused capsule count; discuss with and counsel patients about compliance if needed
- Administer study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples
- Assess and record efficacy events
- Assess for and record adverse events
- Record concomitant medication(s)
- Instruct patient:
  - To bring all study supplies with them to the next visit
  - Not to take study drug on the morning of their next visit
  - To fast for ≥10 hours prior to the next visit

6.1.2.4. Additional Visits

The end date of the study is expected for Day 1800 but the actual end date will be dependent on the determination of the study end date by the DSMB. The study end date is determined to be when approximately 1612 primary efficacy events have occurred. If the actual study end date is later than the expected end date, additional visits will be planned between Visit 7 and the Last Visit with a maximum of 360 ±10 days between visits. If the actual study end date is sooner than the expected end date, fewer visits will occur, and the last visit (See Section 6.1.2.5) will occur sooner.

On additional visits the same procedures will be performed as listed in Section 6.1.2.3. Irrespective of the number of additional visits, after the DSMB has established the end of the study date, there will be a last visit with procedures as listed in Section 6.1.2.5.

6.1.2.5. Last Visit – End of Study

All patients will complete the study at the same time (within a 30-day window after the study end date), irrespective of the date that they were randomized. The end date of the study is planned for Day 1800 but the actual end date will be dependent on the determination of the study end date by the DSMB when approximately 1612 primary efficacy events have occurred (event-driven trial). For each patient, the last visit may occur within 30 day after the

actual study end date as determined by the DSMB. However, for the efficacy endpoints based on CV events, only events occurring up to and including the scheduled actual study end date will be included in the efficacy analyses.

A final follow-up visit is required for all patients. In the rare cases that a final follow-up visit cannot occur within the 30-day timeframe following the study end date, any attempt to contact the patient must be recorded on a special contact form, until/unless appropriate information is obtained.

At Visit 13, the following procedures will be performed:

- Perform physical examination
- Obtain weight
- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and oral body temperature)
- Measure waist circumference
- Obtain a 12-lead electrocardiogram
- Obtain fasting blood samples for:
  - Chemistry and hematology testing
  - Lipid profile
  - Biomarker assays
  - Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)
- Determine study drug compliance by unused capsule count
- Assess and record efficacy events
- Assess for and record adverse events
- Record concomitant medication(s)

6.2. Telephone Follow-up Contact

Site personnel will contact each patient by telephone on the following study days:

- Day 60 ±3 days
- Day 180 ±5 days
- Day 450 ±5 days
- Day 540±5 days
- Day 630 ±5 days
- Day 810 ±5 days
- Day 900 ±5 days
- Day 990 ±5 days

- Day 1170 ±5 days
- Day 1260 ±5 days
- Day 1350 ±5 days
- Day 1530 ±5 days
- Day 1620 ±5 days
- Day 1710 ±5 days

If the treatment/follow-up period of the study is extended beyond the expected end date (Day 1800), additional follow-up phone calls will be made every 3 months in-between additional visits ±5 days. See Section 6.1.2.4 for the timing of the additional visits. If the treatment/follow period of the study is shorter than the expected end date, less follow-up phone calls will be needed.

Every attempt will be made to talk to each patient within this time frame.

The following information will be collected from the patient:

- Possible efficacy endpoints related to CV events. Patients will be asked to return to the Research Site to assess for any endpoints or events identified.
- Adverse events
- Concomitant medications
- Current address and contact information (update if changed or will be changing)

Patients will be reminded about the following items:

- To take the study medication according to the dosing schedule assigned, with food
- When to return to the Research Center for the next visit
- To bring the unused study medication to the next visit
- To not take study drug on the morning of their next visit
- To fast for at least 10 hours prior to the next visit

6.3. Laboratory Procedures

6.3.1. Clinical Laboratory Procedures

All clinical laboratory determinations for screening and safety will be performed by a certified clinical laboratory under the supervision of the Sponsor or its designee.

Whenever possible and appropriate, samples for the clinical laboratory procedures will be collected after fasting for at least 10 hours. For the purposes of this study, fasting is defined as nothing by mouth except water (and any essential medications).

The investigator must review and sign all laboratory test reports. At screening, patients who have laboratory values that are outside the exclusionary limits specified in the exclusion criteria may not be enrolled in the study (patients can be considered for the study if values are classified as not clinically significant by the investigator). After randomization, the

investigator will be notified if laboratory values are outside of their normal range. In this case, the investigator will be required to conduct clinically appropriate follow-up procedures.

6.3.1.1. Safety Laboratory Tests

The safety laboratory tests include:

- Hematology with complete blood count (CBC), including RBC, hemoglobin (Hgb), hematocrit (Hct), white cell blood count (WBC), white cell differential, and platelet count
- Biochemistry panel including total protein, albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), total bilirubin, glucose, calcium, electrolytes (sodium, potassium, chloride), blood urea nitrogen (BUN), serum creatinine, uric acid, creatinine phosphokinase, HbA_{1c}.

6.3.1.2. Fasting Lipid Profile

The fasting lipid panel includes: TG, TC, LDL-C, HDL-C, non-HDL-C, and VLDL-C.

At all visits, LDL-C will be calculated using the Friedewald equation, or measured by preparative ultracentrifugation (Beta Quant) if at the same visit TG >400 mg/dL . These LDL-C values will be used for the evaluation of the LDL-C inclusion criterion (LDL-C qualifying measurements for randomization) and for the assessment of changes in the statin therapy when LDL-C is not at goal. In addition, irrespective of the TG levels, at Visit 2 (0 Months of Follow-up, baseline) and at Visit 4 (12 Months of Follow-up), LDL-C will be measured by ultracentrifugation (Beta Quant). These direct LDL-C measurements will be used in the statistical analysis including the calculation of the percent change from baseline (1 year versus baseline).

6.3.1.3. Genetic testing

A fasting blood sample will be stored for future genetic testing at the discretion of the sponsor. The specifics of this test will be determined at a later date. This sample is optional as local regulations may prohibit genetic samples to be collected or shipped outside the country, or patients may not consent.

6.3.1.4. Biomarkers Assays

The biomarker assays include: hs-CRP, Apo B and hsTnT.

6.3.1.5. Additional laboratory tests

Additional laboratory tests include:

- A urine pregnancy test will be administered to women of childbearing potential at certain visits as listed in schedule of procedures (Appendix A). The urine pregnancy tests will be performed at the Research Site utilizing marketed test kits, or at a certified clinical laboratory.
- A fasting blood sample (12 mL) for archiving. This sample will be collected only at sites in countries where allowed by local regulations and at sites for which approved by the IRB or IEC. The plasma from the archiving sample will be stored frozen in 2 separate equal aliquots, and will be used at the Sponsor's discretion to perform

repeat analyses described in the protocol or to perform other tests related to cardiovascular health.

6.3.1.6. Blinding of Laboratory Results

All efficacy laboratory results during the double-blind period of the trial will be blinded (values not provided) to patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors managing and/or supporting the study, with the exception of the laboratory personnel conducting the assays.

6.3.1.7. Flagging of Critical Lab Values

Critical lab values are values that may warrant medical intervention to avoid possible harm to a patient. Critical lab values will be defined in the Laboratory Manual for the study, and the Research Site will be notified of the occurrence of a critical lab value (critical high or critical low) by a special annotation (flag) in the laboratory reports provided to the Research Sites. Although laboratory values that are part of the efficacy endpoints during the double-blind period of the study will not be provided to the Research Site (see Section 6.3.1.6), the sites will be notified when the TG value of a patient sample is >1000 mg/dL (critical high TG value) or if the LDL-C values of a patient sample is >130 mg/dL. These critical high values will need to be confirmed by a repeat measurement (new fasting blood sample) within 7 days.

If TG values are confirmed high, patients may be discontinued from study drug with the option to remain on study (see Section 11.1 ODIS).

If LDL-C values are confirmed high the investigator may either increase the dose of the present statin therapy or may add ezetimibe to lower LDL-C. The investigator should use the best clinical judgment for each patient.

6.3.2. Medical Procedures

6.3.2.1. Medical, Surgical and Family History

Medical history, including family history and details regarding all illnesses and allergies, date(s) of onset, status of current condition, and smoking and alcohol use will be collected on all patients.

6.3.2.2. Demographics

Demographic information including day, month, and year of birth, race, and gender will be collected for all patients.

6.3.2.3. Vital Signs

Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and oral body temperature. Blood pressure will be measured using a standardized process:

- Patient should sit for ≥5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level.
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery.

Blood pressure should be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device. A blood pressure reading should be repeated 1 to 2 minutes later, and the second reading should also be recorded to the nearest 2 mmHg mark.

6.3.2.4. Physical Examination

A physical examination must include source documentation of general appearance, skin, and specific head and neck, heart, lung, abdomen, extremities, and neuromuscular assessments.

6.3.2.5. Height, Weight and Body Mass Index

Height and weight will be measured. Measurement of weight should be performed with the patient dressed in indoor clothing, with shoes removed, and bladder empty.

6.3.2.6. Waist Circumference

Waist circumference will be measured with a tape measure, as follows: Start at the top of the hip bone then bring the tape measure all the way around – level with the navel. Make sure the tape measure is snug, but without compressing the skin, and that it is parallel with the floor.

Patients should not hold their breath while measuring waist circumference.

6.3.2.7. Electrocardiogram (ECG)

ECGs (standard 12-lead) will be obtained annually. Site personnel should make every attempt to perform a patient's ECG using the same equipment at each visit. ECGs will be reviewed by the site for the detection of silent MI. Silent MIs will be sent for event adjudication.

7. TREATMENT AND RESTRICTIONS

7.1. Treatment

7.1.1. Treatment Regimen, Dosage, and Duration

Eligible study patients will be randomly assigned on Day 0 to one of the 2 treatment groups. Patients in each group will receive either 4 g/day AMR101 or placebo for up to 4.75 years (4 years planned median treatment duration) according to Table 1.

The daily dose of study drug is 4 capsules per day taken as two capsules taken on two occasions per day (2 capsules given twice daily).

Table 2. Dosing Schedule during the Treatment Period

Treatment Group	Daily Dose	Number of Capsules per Day
1	4 g	4 capsules of 1000 mg AMR101

2	Placebo	4 capsules of matching placebo

Patients will be instructed to take study drug with food (i.e., with or at the end of their morning and evening meals). On days that patients are scheduled for study visits, the daily dose of study drug will be administered by site personnel with food provided by the site following collection of all fasting blood samples. For the purposes of this study, fasting is defined as nothing by mouth except water (and any essential medications) for at least 10 hours.

7.1.2. Treatment Assignment

7.1.2.1. Identification number

A unique patient identification number (patient number) will be established for each patient at each site. The patient number will be used to identify the patient throughout the study and will be entered on all documentation. If a patient is not eligible to receive treatment, or if a patient discontinues from the study, the patient number cannot be reassigned to another patient. The patient number will be used to assign patients to one of the 2 treatment groups according to the randomization schedule.

7.1.2.2. Drug Randomization

Only qualified patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized and will receive study medication starting at Visit 2 (Day 0). Eligible patients will be randomly assigned to one of the 2 treatment groups. Randomization will be stratified by CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries) (See Section 3.10). Approximately 70% of randomized patients will be in the CV Risk Category 1, including patients with established CVD, and approximately 30% of randomized patients will be in the CV Risk Category 2, including patients with diabetes and at least one additional risk factor but no established CVD. Enrollment with patients of a CV risk category will be stopped when the planned number of patients in that risk category is reached.

7.1.2.3. Emergency Unblinding

In an emergency, when knowledge of the patient's treatment assignment is essential for the clinical management or welfare of the patient, the investigator may request the patient's treatment assignment for unblinding. Prior to unblinding the patient's individual treatment assignment, the investigator should assess the relationship of an adverse event to the administration of the study drug (Yes or No). If the blind is broken for any reason, the investigator must record the date and reason for breaking the blind on the appropriate Case Report Form (CRF) and source documents.

7.1.3. Compliance Control

It is recommended that, unless clear contraindications arise, patients be strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any

interruptions of therapy should, if possible, be brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. Discontinuations will be discouraged as much as possible. Any discontinuations should be based on compelling clinical reasons.

For every patient, an assessment of compliance to the study drug treatment regimen must be obtained at each scheduled visit. Study medication will be dispensed in amounts exceeding the amount required for the study. Patients will be instructed to return all unused study medication at the next visit. Compliance to the study drug regimen will be evaluated at each visit by counting unused capsules. Discrepancies will be evaluated and discussed with each patient to assess compliance. If compliance is unsatisfactory, the patient will be counseled about the importance of compliance to the dosing regimen. At the end of the study, the final study medication compliance will be determined by unused capsule count (see Section 12.2.2).

7.2. Study Restrictions

7.2.1. Concomitant Medications during Treatment/Follow-Up Period

Any medications administered during the study period must be documented on the Concomitant Medication CRF. Patients must not have taken any investigational agent within 90 days prior to screening. Patients cannot participate in any other investigational medication trial while participating in this study.

The following non-study drug related, non-statin, lipid-altering medications and supplements, and foods are prohibited during the screening period (after Visit 1 to Visit 2), and are strongly discouraged during the study after Visit 2:

- niacin >200 mg/day;
- fibrates;
- prescription omega-3 fatty acid medications;
- dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils);
- bile acid sequestrants;
- cyclophosphamide;
- systemic retinoids

If any of these products would be used during the treatment/follow-up period of the study, it should be for compelling medical reasons, and it should be documented in the Concomitant Medication CRF.

Foods enriched with omega-3 fatty acids are strongly discouraged after Visit 1 for the duration of the study.

The following products are allowed: statins, ezetimibe, and herbal products & dietary supplements not containing omega-3 fatty acids.

Statins:

- The same statin at the same dose should be continued until the end of the study, unless deemed medically necessary to change because of an adverse event or lack of efficacy (LOE). It is preferred that if LOE is the determining factor that ezetimibe be added to the present dose.
- Switching between a brand name statin and the generic version of the same statin is allowed at any time during the study.
- Statins may be administered with or without ezetimibe.
- Based on the FDA recommendation, simvastatin 80 mg be used only in patients who have been taking this dose for 12 months or more and have not experienced any muscle toxicity. (See reference: FDA Drug Safety Communication: Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury. (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204882.htm)
- Changing of the type of statin or the statin dose during the treatment/follow-up period of the study should only be done for compelling medical reasons and must be documented in the CRF.

LDL-C Rescue:

- If the level of LDL-C exceeds 130 mg/dL during the study (initial measurement and confirmed by a second determination at least 1 week later), the investigator may either increase the dose of the present statin therapy or may add ezetimibe to lower LDL-C. The investigator should use the best clinical judgment for each patient.

No data are available with regard to potential interactions between ethyl-EPA and oral contraceptives. There are no reports suggesting that omega-3 fatty acids, including ethyl-EPA, would decrease the efficacy of oral contraceptives.

7.2.2. Patient Restrictions

Beginning at the screening visit, all patients should be instructed to refrain from excessive alcohol consumption, to maintain their current dietary regimen, and to not alter their normal activity routines. Excessive alcohol consumption is on average >2 units of alcohol per day. A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.

8. INVESTIGATIONAL PRODUCT

8.1. Clinical Trial Material

The following will be supplied by the Sponsor:

- AMR101 1000 mg capsules
- Placebo capsules

The Sponsor will supply sufficient quantities of AMR101 1000 mg capsules and placebo capsules to allow for completion of the study. The lot numbers of the drugs supplied will be recorded in the final study report.

Records will be maintained indicating the receipt and dispensation of all drug supplies. At the conclusion of the study, any unused study drug will be destroyed.

8.2. Pharmaceutical Formulations

AMR101 1000 mg and placebo capsules are provided in liquid-filled, oblong, gelatin capsules. Each capsule is filled with a clear liquid (colorless to pale yellow in color). The capsules are approximately 25.5 mm in length with a diameter of approximately 9.5 mm.

Table 2 summarizes the components of each capsule.

Table 3. Components of AMR101 Capsules

Component	AMR101 1000 mg capsules Quantity (mg/capsule)	Placebo capsules Quantity (mg/capsule)	Function
Capsule fill			
Icosapent ethyl	998	-	Active
Paraffin, light liquid	-	932	
All-rac-α-tocopherol	2	1.86	Antioxidant
Capsule shell			
Gelatin	279	279	Capsule shell material
Sorbitol, liquid (non-crystallizing)	78	78	Plasticizer
Glycerol	44	44	Plasticizer
Purified water	37	37	Solvent
Maltitol, liquid	28	28	Plasticizer

8.3. Labeling and Packaging

Study medication will be packaged in high-density polyethylene bottles. Labeling and packaging will be performed according to GMP guidelines and all applicable country-specific requirements. The bottles will be numbered for each patient based on the randomization schedule. The patient randomization number assigned by IVRS or a designee of the Sponsor for the study (if no IVRS system is used), will correspond to the number on the bottles. The bottle number for each patient will be recorded in the Electronic Data Capture (EDC) system for the study.

8.4. Dispensing Procedures and Storage Conditions

8.4.1. Dispensing Procedures

At Visit 2 (Day 0), patients will be assigned study drug according to their treatment group determined by the randomization schedule. Once assigned to a treatment group, patients will receive study drug supplies. At each visit, patients will bring unused drug supplies dispensed to them earlier. From the drug supplies assigned to each patient, site personnel will administer drug while the patients are at the Research Site.

The investigator or designee must contact the IVRS system or a designee of the Sponsor for the study (if no IVRS system is used) when any unscheduled replacements of study medication are needed.

During the last visit during the treatment period, patients will bring the unused drug supplies for site personnel to calculate the final study medication compliance by unused capsule count (see Section 12.2.2).

8.4.2. Storage Conditions

At the Research Sites, study drugs must be stored at room temperature, 68°F to 77°F (20°C to 25°C). Do not allow storage temperature to go below 59°F (15°C) or above 86°F (30°C). Store in the original package.

Study drugs must be stored in a pharmacy or locked and secure storage facility, accessible only to those individuals authorized by the investigator to dispense the drug. The investigator or designee will keep accurate dispensing records. At the conclusion of the study, study site personnel will account for all used and unused study drug. Any unused study drug will be destroyed. The investigator agrees not to distribute study drug to any patient, except those patients participating in the study.

9. EFFICACY ASSESSMENTS

9.1. Specification of Variables and Procedures

The primary endpoint and the majority of the secondary and tertiary endpoints are based on clinical events related to CVD and mortality. All events occurring between randomization and the study end date (inclusive) must be recorded. Only adjudicated events will be included in the final analyses. Further details on the assessment of clinical events and their definitions will be found in the CEC charter. Important definitions are listed in Appendix B of this protocol.

9.2. Efficacy Endpoints

9.2.1. Primary Efficacy Endpoint

Time from randomization to the first occurrence of the composite of the following clinical events:

- CV death,
- Nonfatal MI (including silent MI; ECGs will be performed annually for the detection of silent MIs),
- Nonfatal stroke,
- Coronary revascularization
- Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing .

The first occurrence of any of these major adverse vascular events during the follow-up period of the study will be included in the incidence.

9.2.2. Secondary Efficacy Endpoints

The key secondary efficacy endpoint is:

- The composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina, nonfatal stroke, or peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair.

Other secondary efficacy endpoints are as follows (to be tested in said order):

- The composite of total mortality, nonfatal MI, or nonfatal stroke;
- The composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina, peripheral CVD, or cardiac arrhythmia requiring hospitalization;
- The composite of death from CV causes, nonfatal MI, coronary revascularization, or unstable angina;
- The composite of death from CV causes or nonfatal MI;
- Total mortality;
- Fatal and nonfatal MI (including silent MI);
- Coronary Revascularization;
- Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing ;
- Fatal and nonfatal stroke.

For the secondary endpoints that count a single event, the first occurrence of this type of event will be counted in each patient. For secondary endpoints that are composites of two or more types of events, the first occurrence of any of the event types included in the composite will be counted in each patient.

9.2.3. Tertiary Efficacy Endpoints:

- The second, third, fourth, and fifth major CV event of the primary composite endpoint. The type of (nonfatal) events may occur in any order.
- Primary endpoint in subset of patients with diabetes mellitus;
- Primary endpoint in subset of patients with metabolic syndrome;
- New CHF, new CHF leading to hospitalization, transient ischemic attack, amputation for CVD and carotid revascularization;
- Elective coronary revascularization and emergent coronary revascularization;
- New onset diabetes;
- Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP, and hsTnT: on treatment change and baseline effect;
- CV mortality;
- Cardiac Arrhythmias requiring hospitalization;
- Cardiac Arrest;
- To explore the effect of AMR101 on weight and waist circumference.

For the tertiary endpoints that count a single event, the first occurrence of this type of event will be counted in each patient. For tertiary endpoints that are composites of two or more types of events, the first occurrence of any of the event types included in the composite will be counted in each patient (except when stated otherwise, for the second, third, fourth, and fifth major CV event).

10. SAFETY ASSESSMENTS

10.1. Specification of Variables and Procedures

Safety assessments will include adverse events, clinical laboratory measurements (chemistry, hematology), 12-lead ECGs, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and oral body temperature), and physical examinations as per Study Procedures/Appendix A.

A complete medical, surgical and family history will be completed at Visit 1.

A list of the analytes to be measured for the safety evaluation is found in Section 6.3.1.1. All laboratory test results must be evaluated by the investigator as to their clinical significance. Any observations at physical examinations or laboratory values considered by the investigator to be clinically significant should be considered an adverse event.

10.2. Adverse Events

An adverse event is defined as any untoward medical occurrence, which does not necessarily have a causal relationship with the medication under investigation. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medication product, whether or not related to the investigational medication product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate CRF. Each adverse event is to be evaluated for duration, intensity, and causal relationship with the study medication or other factors.

Adverse events, which include clinical laboratory test variables, will be monitored from the time of informed consent until study participation is complete. Patients should be instructed to report any adverse event that they experience to the investigator. Beginning with Visit 2, investigators should assess for adverse events at each visit and record the event on the appropriate adverse event CRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate adverse event on the CRF.

Any medical condition that is present when a patient is screened or present at baseline that does not deteriorate should not be reported as an adverse event. However, medical conditions or signs or symptoms present at baseline and that change in severity or seriousness at any time during the study should be reported as an adverse event.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen will be reported as adverse events or SAEs. The investigator will exercise his or her medical and scientific

judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

The investigator will rate the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of Yes or No.

Severity:

- Mild – An event that is usually transient in nature and generally not interfering with normal activities.
- Moderate – An event that is sufficiently discomforting to interfere with normal activities.
- Severe – An event that is incapacitating with inability to work or do usual activity or inability to work or perform normal daily activity.

Causality Assessment:

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

- No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.
- Yes – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

- The temporal sequence from study medication administration
- The event should occur after the study medication is given. The length of time from study medication exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases
- Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication
- The other medications the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study medication
- Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses
- The exposure to stress might induce adverse changes in the patient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study medication

- The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study medication should be considered.

Unexpected Adverse Events – An unexpected adverse event is an adverse event either not previously reported or where the nature, seriousness, severity, or outcome is not consistent with the current Investigator's Brochure.

10.2.1. Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets **any** of the following criteria:

- Results in death
- Is life-threatening- Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization- Note: In general, hospitalization for treatment of a pre-existing condition(s) that did not worsen from baseline is not considered adverse events and should not be reported as SAEs.
- Results in disability/incapacity
- Is a congenital anomaly/birth defect;
- Is an important medical event- Note: Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

For the purposes of this study SAEs that are primary endpoint events will only be recorded for the endpoint determination and not captured as SAEs. Following adjudication if the event is determined to not meet the criteria for a primary event, the event will be evaluated as an SAE beginning with that day as Day 0.

10.3. Serious Adverse Event Reporting – Procedure for Investigators

10.3.1. Initial Reports

All SAEs occurring from the time of informed consent until 30 days following the last administration of study medication must be reported to the Sponsor or designee **within 24 hours** of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). SAEs that the investigator considers related to study medication occurring after the 30-day follow-up period will also be reported to the Sponsor or designee.

The investigator is required to submit SAE reports to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local requirements. All investigators involved in studies using the same investigational medicinal product (IMP) will receive any Suspected Unexpected Serious Adverse Reaction (SUSAR) reports for onward submission to their local IRB as required. All reports sent to investigators will be blinded.

10.3.2. Follow-Up Reports

The investigator must continue to follow the patient until the SAE has subsided, or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., laboratory test reports, patient discharge summary, or autopsy reports) to the Sponsor or designee via fax or email.

10.3.3. Reporting by the Sponsor

IRBs and IECs will be informed of SUSARs according to local requirements. Cases will be unblinded for reporting purposes as required.

10.4. Exposure *In Utero* During Clinical Trials

If a patient becomes pregnant during the study, the investigator should report the pregnancy to the Sponsor or designee within 24 hours of being notified. The Sponsor or designee will then forward the Exposure *In Utero* form to the investigator for completion.

The patient should be followed by the investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the Sponsor or designee. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

11. TREATMENT DISCONTINUATION/PATIENT WITHDRAWAL

Patients may withdraw from the study at any time and for any reason. Study drug administration may also be discontinued at any time, at the discretion of the investigator. In any case, follow-up for efficacy and safety should be continued.

11.1. Reasons for Early Study Drug Discontinuation

Study drug discontinuation should be avoided as much as possible, but may be done for any of the following reasons:

- Patient withdraws consent or requests early discontinuation from the study for any reason. Patients should be encouraged to continue to participate in the study for the entire duration of the study even if they choose not to take study medication any longer.
- Occurrence of a clinical or laboratory adverse event, either serious or non-serious, at the discretion of the investigator. The Sponsor or designee should be notified if a patient is discontinued because of an adverse event or laboratory abnormality. It is recommended that, unless clear contraindications arise, patients be strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy should, if possible, be brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. The following should be considered reason for discontinuation:
    - ALT > 3x ULN and bilirubin > 1.5x ULN

  - ALT >5x ULN
  - ALT >3x ULN and appearance or worsening of hepatitis
  - ALT > 3x ULN persisting for >4weeks
  - ALT > 3x ULN and cannot be monitored weekly for 4 weeks
- Any medical condition or personal circumstance that, in the opinion of the investigator, exposes the patient to risk by continuing in the study or precludes adherence to the protocol.
- Sponsor discontinues the study.
- A TG value that is flagged as critically high, i.e., > 1000 mg/dL, and confirmed as critically high by a repeat measurement (new fasting blood sample) within 7 days. In this case, a patient may be discontinued from study drug and other lipid-altering medications may be (re)initiated.

Occurrence of an outcome event according to the judgment of the investigator is not considered a valid reason for study drug discontinuation.

Patients whose treatment with study medication is discontinued early, and have not withdrawn consent, may stay in study and will be monitored until the end of the study. Patients that continue in the study after indefinite cessation of therapy will be characterized as Off Drug In Study (ODIS). If not contraindicated, patients will also have the option to restart study medication at any point once characterized as ODIS.

The reason for study drug discontinuation or interruption will be recorded on the CRF.

11.2. Follow-Up after Early Study Drug Discontinuation/Lost to Follow-Up

- Patients who prematurely discontinue study drug are not to be replaced.
- All randomized patients must be followed up according to the study flowchart until the study end date or death, regardless of whether they discontinue study drug prematurely or not. Any event occurring after early study drug discontinuation will be recorded up through the study end date.
- In order to follow the medical status of the patients, especially when they withdraw after having experienced an adverse event, investigators are encouraged to obtain information from the patient's primary care practitioner (physician or any other medical care provider). Investigators are also requested to try as much as possible to re-contact those patients at the end of the trial to obtain at least their vital status as well as their status with respect to the primary endpoint, and thus avoid lost to follow-up for the efficacy assessment.
- If patients are lost to follow-up, the CRF must be completed up to the last visit or contact. Patients who didn't have a study visit for 1 year or longer are considered lost to follow-up.

12. STATISTICS

12.1. Analysis Populations

12.1.1. Randomized Population

The randomized population will include all patients who sign the informed consent form and are assigned a randomization number at Visit 2 (Day 0).

12.1.2. Intent-to-Treat Population

The Intent-to-Treat (ITT) population will consist of all randomized patients who take at least one dose of study drug. The ITT population is the primary analysis population. All efficacy analyses will be performed on the ITT population.

12.1.3. Per-Protocol Population

The per-protocol (PP) population will include all ITT patients without any major protocol deviations, and who had ≥80% compliance with study drug while on treatment (up to discontinuation for patients whose treatment is terminated early). The per-protocol efficacy analysis for CV events will be restricted to each patient's time on study drug plus 30 days thereafter.

12.1.4. Safety Population

All safety analyses will be conducted based on the safety population, which is defined as all randomized patients who receive at least one dose of study drug. This is the same as the ITT population.

12.2. Statistical Methods

Safety and efficacy variables will be analyzed using appropriate statistical methods to be described in detail in a separate Statistical Analysis Plan (SAP). The SAP will be finalized before study unblinding.

12.2.1. Patient Disposition and Demographic/Baseline Characteristics

The numbers of patients screened, the number of patients randomized per treatment group (randomized population), and the number of patients in the ITT and PP populations by treatment group will be listed.

For randomized patients who discontinued treatment with study drug, the primary reason for discontinuation will be listed and summarized by treatment group.

Summary statistics (mean, standard deviation, median, minimum and maximum) will be provided by treatment group for demographic characteristics (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., body weight, height, and body mass index) in the ITT and PP populations.

Demographic data and baseline characteristics will be compared among treatment groups for the ITT and PP population. Differences in demographic and baseline characteristics will be tested using a chi-square test (for categorical variables) or a 1-way analysis of variance model with treatment as a factor (for continuous variables). The p-values will be used as descriptive statistics, primarily as an assessment of the adequacy of randomization.

12.2.2. Study Medication Exposure and Compliance

The final compliance to study drug will be calculated as the percent of doses taken relative to doses scheduled to be taken. Overall percent compliance will be calculated per patient in the ITT and PP populations and summarized by treatment group using summary statistics (n, mean, standard deviation, median, minimum, and maximum).

12.2.3. Concomitant Therapies

Concomitant medication/therapy verbatim terms will be coded using the latest version of the World Health Organization Drug Dictionary. The numbers and percentages of patients in each treatment group taking concomitant medications will be summarized by anatomic and therapeutic chemical classification and preferred term.

12.2.4. Analysis of Efficacy

For efficacy endpoints including CV events, only adjudicated events will be included in the final statistical analyses.

12.2.4.1. Summary Statistics

Summary statistics (n, mean, standard deviation, median, minimum, and maximum) for the baseline and post-baseline measurements, the percent changes, or changes from baseline will be presented by treatment group and by visit for all efficacy variables to be analyzed. The summary statistics will include changes in body weight and body mass index from baseline by treatment group and by visit.

12.2.4.2. Primary Endpoint

The primary efficacy endpoint is the time from randomization to the first occurrence of any component of the composite of the following clinical events:

- CV death,
- Nonfatal MI (including silent MI),
- Nonfatal stroke,
- Coronary revascularization,
- Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing.

The analysis of the primary efficacy endpoint will be performed using the log-rank test comparing the 2 treatment groups (AMR101 and placebo) and including the stratification factor "CV risk category", use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries) as recorded in the IVRS at the time of enrollment. Treatment difference will be tested at alpha level of 0.0476 accounting for one interim efficacy analysis. The hazard ratio for treatment group (AMR101 vs. placebo) from a Cox proportional hazard model that includes the stratification factor will also be reported, along with the associated 95% confidence interval. Kaplan-Meier estimates from the time to the primary efficacy endpoint will be plotted.

12.2.4.3. Secondary Endpoints

The statistical analyses of the secondary endpoints will be analyzed by the same log-rank test specified above for the primary efficacy endpoint. Treatment differences will be tested at alpha level of 0.05 using a sequential procedure for controlling type 1 error starting with the key secondary variable. The remaining secondary variables will be tested in the order specified in Section 9.2.2. Estimates of the hazard ratios from the Cox proportional hazard and the associated 95% confidence intervals will also be provided. Kaplan-Meier estimates from the time to the secondary efficacy endpoints will be plotted.

12.2.4.4. Tertiary Endpoints

For event rates, the statistical analyses of the tertiary endpoints will be similar to the analysis of the secondary efficacy endpoints.

For measurements of lipids, lipoproteins and inflammatory markers the change from baseline will be analyzed in the units of each marker, and the percent change from baseline.

New onset diabetes is defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period (i.e. patients with no history of diabetes at randomization, with the test as listed in Appendix C).

12.2.4.5. Subgroup Analyses

The following subgroups will be explored. Log-rank tests, treatment effects and the associated 95% confidence intervals for the primary and secondary efficacy endpoints within each subgroup will be provided using the Cox proportional hazard model with treatment (AMR101 or placebo), and stratification as a factor (with the exception of the subgroup analyses of those subgroup variables related to the stratification factors, i.e., CV risk category that will not have stratification as a factor):

- Gender,
- age (<65 yr and ≥65 yr),
- race (white and nonwhite, or any other subset with at least 10% of the total number of patients),
- CV risk category (previous CV disease or not),
- the presence/absence of diabetes at baseline,
- baseline LDL-C (by tertile),
- baseline HDL-C (by tertile),
- baseline TG (by tertile),
- hs-CRP (≤3 mg/L and >3 mg/L),
- Apo B (by tertile)

The consistency of the treatment effects in subgroups will be assessed for the primary and secondary efficacy endpoints. For each subgroup variable, a Cox proportional hazard model with terms for treatment, stratification factors (with the exception of those subgroup variables related to the stratification factors, i.e., CV risk category), subgroup, and treatment-by-subgroup interaction will be performed. The main treatment effect will not be tested with this model. P-values for testing the interaction terms will be provided.

12.2.4.6. Interim Efficacy Analysis

One interim analysis will be performed for the primary efficacy endpoint using best available data (adjudicated events and site reported endpoints) based on data when approximately 60% of the total number of primary endpoint events is reached. The interim analysis will be based on a group sequential design that includes early stopping rules for benefit while preserving the overall Type I error rate (O'Brien-Fleming). This allows for interim analysis and preserves the overall Type I error probability of α=0.05 for the primary endpoint.

Approximately 1612 events are planned to be observed during the trial, based on sample size calculation assumptions. Therefore, the interim analysis will occur after at least 967 events have been observed. According to this boundary, the critical p-value at the interim analysis has to be p<=0.0076, resulting in the final evaluation p-value of 0.0476.

The interim results of the study will be monitored by an independent DSMB. The analyses will be performed by the independent statistical group unblinded to the treatment assignment. The results will be reported only to the DSMB. The unblinded information will not be released to sponsor under any circumstance before the completion of the study. Specific statistical guidelines for data monitoring will be discussed and formalized in a separate Interim Statistical Analysis Plan and DSMB Charter.

12.2.5. Analysis of Safety

All analyses of safety will be conducted on the safety population, which is defined as all randomized patients who receive at least one dose of study drug. The safety assessment will be based on the frequency of adverse events, physical exams, vital signs and safety laboratory tests.

Adverse events with new onset during the study between the initiation of study drug and 30 days after the last dose of study drug for each patient will be considered treatment-emergent (TEAEs). This will include any AE with onset prior to initiation of study drug and increased severity after the treatment initiation.

Treatment-emergent adverse events will be summarized by system organ class and preferred term, and by treatment. This will include overall incidence rates (regardless of severity and relationship to study drug), and incidence rates for moderate or severe adverse events. A summary of SAEs, and adverse events leading to early discontinuation from the study will be presented through data listings.

Safety laboratory tests and vital signs will be summarized by post-treatment change from baseline for each of the parameters using descriptive statistics by treatment group. Those patients with significant laboratory abnormalities will be identified in data listings. Additional safety parameters will be summarized in data listings.

12.3. Sample Size Determination

Sample size estimation is based on the assumption that the primary composite endpoint (time from randomization to the first occurrence of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina requiring hospitalization) event rate by 4 years would be relatively reduced by 15%, from an event rate by 4 years of 23.6% in the placebo group to 20.5% in the AMR101 group. It is expected that a minimum of 1612 primary efficacy endpoint events will be required during the study. A total of approximately 6990 patients are needed to be able to detect this difference at 4.76% significance level (because of the interim analysis described in Section 12.2.4.6) and with 90% power, assuming an 18-month enrollment period and a median follow-up of 4 years. The current sample size calculation is based on an estimated placebo yearly event rate of 5.9% (23.6% over 4 years). To protect against the possibility that the actual placebo event rate is lower than estimated, an extra 1000 patients will be enrolled (approximately 7990 patients in total). By adding the extra 1000 patients, the event rate in the placebo group could be 5.2% per year (20.8% over 4 years) without having to modify the other sample size assumptions.

Before completing the enrollment phase of the trial, the actual event rate based on pooled, blinded accumulation of primary efficacy endpoint events will be calculated and may be used to increase the sample size. If the sample size is increased, the enrollment phase will be extended to allow enrollment of the additional patients.

13. MONITORING, DATA MANAGEMENT, AND RECORD KEEPING

13.1. Data Management

13.1.1. Data Handling

Data will be recorded at the site on CRFs. All entries on a CRF are ultimately the responsibility of the Investigator, who is expected to review each form for completeness, accuracy and legibility before signing. All forms must be filled out by using ink. Errors should be lined out but not obliterated and the correction inserted, initialed and dated. A CRF must be completed for each randomized patient. The CRFs and source documents must be made available to the Sponsor and/or its designee.

13.2. Record Keeping

The Investigator must maintain all documents and records, originals or certified copies of original records, relating to the conduct of this trial, and necessary for the evaluation and reconstruction of the clinical trial. This documentation includes, but is not limited to protocol, CRFs, AE reports, patient source data (including records of patients, patient visit logs, clinical observations and findings), correspondence with health authorities and IRB, consent forms, inventory of study product, Investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures, and laboratory director curriculum vitae.

The Investigator and affiliated institution should maintain the trial documents as required by the applicable regulations. The Investigator and affiliated institution should take measures to prevent accidental or premature destruction of documents. Clinical trial documents must be kept in the clinical site's archives indefinitely, unless written authorization is obtained from the Sponsor.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator and research institution agree that the Sponsor, their representatives and designees, the IRB or IEC, and representatives from worldwide regulatory agencies will have the right, both during and after the clinical trial, to review and inspect pertinent medical records related to the clinical trial.

15. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and/or its designee(s), will perform quality control and quality assurance checks of all clinical trials that it sponsors. Before the enrollment of any patient in this study, the Sponsor or its designee will review with the investigator and site personnel the following documents: protocol, Investigator's Brochure, CRFs and procedures for their completion, the informed consent process, and the procedure for reporting SAEs. Site visits will be

performed by the Sponsor and/or its designees. During these visits, information recorded on the CRFs will be verified against source documents and requests for clarification or correction may be made. After the CRF data is entered by the site, the Sponsor or designee will review for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical trial. If necessary, requests for clarification or correction will be sent to investigators.

By signing the protocol, the Sponsor agrees directly or through its designee(s) to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice (GCP), International Conference on Harmonization (ICH) and other applicable regulations.

16. ETHICS AND GOOD CLINICAL PRACTICE COMPLIANCE

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well being of trial patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. In this study, the 2008 version of the Declaration of Helsinki will be adhered to. It can be found on the website of The World Medical Association:

http://www.wma.net/en/30publications/10policies/b3/17c.pdf

17. INFORMED CONSENT

Prior to participation in a study, the participant, or participant's legal representative must sign an IRB/IEC-approved written informed consent form (ICF). The approved written informed consent must abide to all applicable laws in regards to the safety and confidentiality of the patients. To obtain and document informed consent, the Investigator should comply with applicable regulations; adhere to GCP standards and the ethical principles in the Declaration of Helsinki (see Section 16).

The language in the oral and written information about the trial, including the written informed consent form should be as non-technical as practical and should be understandable to the participant or participant's legal representative and the impartial witness, where applicable. Before informed consent is obtained, the Investigator should provide the participant, or participant's legal representative ample time and opportunity to inquire about the trial and to decide whether or not to participate.

All questions about the trial should be answered to the satisfaction of the participant, or the participant's legal representative. The written ICF should be signed and personally dated by the participant or participant's legal representative, and by the person who conducted the informed consent discussion. Participants will be informed that participation is voluntary and that he/she can withdraw from the study at any time. A signed copy of the consent form must be given to the participant, and this fact will be documented in the CRF.

Of special concern regarding informed consent is the collection of blood samples for genetic analysis. Local regulations may not allow the collection of blood samples for genetic testing or the shipment of blood samples for genetic testing outside the region. In these cases, blood samples for genetic testing will not be collected, and the portion of the ICF describing the genetic component of the study will not be included. If blood samples for genetic testing will be collected, the ICF will clearly indicate that a sample will be drawn for this purpose, but that the participant has the right to refuse this procedure.

18. PUBLICATION POLICY

The Steering Committee (SC) is responsible for the reporting and publication of the study results. All decisions regarding the use of study data for public presentation, and publication including issues of authorship must be approved by the Sponsor. The results of the study will be published irrespective of whether the endpoints are met, or whether the results are regarded positive or negative.

Confidentiality, publication, and patent applications related to unpublished study-related information and unpublished information given to the investigator by the Sponsor and/or its designee(s) shall be handled as set forth in the Clinical Trial Agreement.

19. FINANCING AND INSURANCE

19.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a Clinical Trial Agreement with the Sponsor and/or its designee(s). This agreement will include the financial information agreed upon by the parties.

19.2. Insurance Compensation

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the investigator and the other collaborators from maintaining their own liability insurance policy. An insurance certificate will be provided to the IRB/IEC and Competent Authority according to country specific regulatory requirements.

20. COMPLETION OF STUDY

The end of the study will be at the time of the last patient-last visit of the follow-up period of the study. The IRB and IEC will be notified about the end of the study according to country-specific regulatory requirements.

21. STUDY ADMINISTRATIVE INFORMATION

21.1. Protocol Amendments

Any amendments to the study protocol considered to be a substantial amendment will be communicated to the investigator by the Sponsor or its designee. All substantial protocol amendments will undergo the same review and approval process as the original protocol and

may be implemented after it has been approved by the IRB/IEC and Competent Authority , unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC and Competent Authority according to all relevant country-specific regulatory requirements.

A protocol amendment is considered to be a substantial amendment if it is likely to affect the safety, physical, or mental integrity of patients in the study; the scientific value of the study; the conduct or management of the study; or the quality or safety of any IMP used in the study.

Any other minor changes to the protocol not considered to be substantial amendments will not need prior approval of the IRB/IEC and Competent Authority and will be communicated to the investigator by the Sponsor or its designee.

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23. INVESTIGATOR'S AGREEMENT

This document is a confidential communication of Amarin. The authorized investigators agree to personally conduct or supervise the conduct of this investigational study in compliance with the current protocol, good clinical practices, and all applicable laws, regulations, and guidelines. No changes will be made to the protocol without prior notification to Amarin, except to protect the safety, rights, and welfare of the study patients, and always in compliance with all applicable laws, regulations, and guidelines. Acceptance of this document constitutes the agreement by the Investigator that no unpublished information contained herein or related to the study will be published or disclosed without prior written approval from Amarin.

I have read this protocol in its entirety and agree to conduct the study accordingly.

_____ _____

Signature Date
Principal Investigator

_____

Printed Name

APPENDIX A: SCHEDULE OF PROCEDURES

	Screening		Follow-Up (FU) [13]						
Study Day	**Up to 42 days before Day 0**	**Up to 14 days before Day 0[2]**	**0**	**120 ± 10**	**360 ± 10**	**720 ± 10**	**1080 ± 10**	**1440 ± 10**	**1800 + 30**
Months of FU			**0**	**4**	**12**	**24**	**36**	**48**	**60**
Years of FU			**0**	**0.33**	**1**	**2**	**3**	**4**	**5**
Visit #	**1**	**1.1**	**2**	**3**	**4**	**5**	**6**	**7**	**LV [14]**
Study Procedures:									
Informed Consent	X								
Medical, Surgical & Family History	X								
Demographics	X								
Evaluate inclusion / exclusion criteria	X [1]	X [3]	X						
Physical Examination			X	X	X X		X	X	X
Weight, Height [4]	X		X	X	X X		X	X	X
Vital Signs [5]	X	X	X	X	X X		X	X	X
Waist Circumference			X			X			X
12-Lead ECG	X		X		X	X	X	X	X
Urine pregnancy test [6]	X		X						
Concomitant Meds	X	X	X	X	X X		X	X	X
Randomization			X						
Dosing at the Research Site [7]			X	X	X X		X	X	
Efficacy events				X	X X		X	X	X
AE Evaluations			X	X	X X		X	X	X
Compliance Check [8]				X	X X		X	X	X
Chemistry and hematology [9]	X	X [3]	X	X	X X		X	X	X
Fasting lipid profile [10]	X	X [3]	X	X	X X		X	X	X
Genetic testing [11]			X						
Biomarkers: hs-CRP, apo B, hsTNT			X			X			X
Fasting blood sample for archiving [12]			X		X	X	X	X	X

1. Includes procedures and (fasting) blood samples (for example, hs-CRP, calculated creatinine clearance) as needed to determine the CV risk category (see inclusion criteria).
2. Screening visit to re-evaluate inclusion/exclusion criteria for patients who are not eligible for participation based on data from Visit 1.

3. Inclusion/exclusion criteria will be re-evaluated for selected study procedures that are performed on Visit 1.1 because patients failed to meet them at Visit 1.
4. Height at first screening visit only.
5. Vital signs, including systolic and diastolic blood pressure (mmHg), heart rate, respiratory rate and oral body temperature. Participants must be seated for at least 5 minutes before assessments of vital signs.
6. For women of childbearing potential.
7. The patients will fast of at least 10 hours before arriving at the Research Site, when all fasting blood samples will be obtained. After blood samples are obtained, patients will be given drug with food.
8. Review study drug compliance by unused capsule count, discuss with and counsel patients about compliance if needed; final study compliance at last visit.
9. Safety Laboratories — Complete Blood Count: Includes RBC, Hgb, Hct, WBC and differential, and platelet count. Biochemistry includes total protein, albumin, alkaline phosphatase, ALT, AST, total bilirubin, glucose, calcium, electrolytes (sodium, potassium, chloride), blood urea nitrogen (BUN), serum creatinine, uric acid, creatinine phosphokinase, HbA1c. Safety labs may be repeated as deemed necessary by the Investigator.
10. TG, TC, HDL-C, LDL-C, non-HDL-C, and VLDL-C.
11. Fasting blood sample that will be stored for future genetic testing at the discretion of the sponsor. This sample is optional as local regulations may prohibit genetic samples to be collected or shipped outside the country, or patients may not consent.
12. Used at the sponsor's discretion to perform repeat analyses described in the protocol or to perform other tests related to cardiovascular health.
13. Site personnel will contact each patient by telephone in-between Visit 2 and Visit 3 and between Visit 3 and Visit 4. After Visit 4 contact will be made every 3 months. The purpose of the contact is to collect information about efficacy events, adverse events, concomitant medications, confirm patient's current address and contact information and remind patients about taking their study medication and logistics for the next visit.
14. The last visit (LV) may occur within 30 day after the study end date as determined by the DSMB; the study end date is tentatively schedule for Day 1800 but the actual date as determined by the DSMB may be different.

APPENDIX B: STANDARDIZED DEFINITIONS FOR END POINT EVENTS IN CARDIOVASCULAR TRIALS

Reference:
http://www.cdisc.org/stuff/contentmgr/files/0/2356ae38ac190ab8ca4ae0b222392b37/misc/cdisc_november_16__2010.pdf

DEFINITION OF CARDIOVASCULAR DEATH

Cardiovascular death includes death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

1. **Death due to Acute Myocardial Infarction** refers to a death by any mechanism (arrhythmia, heart failure, low output) within 30 days after a myocardial infarction (MI) related to the immediate consequences of the myocardial infarction, such as progressive congestive heart failure (CHF), inadequate cardiac output, or recalcitrant arrhythmia. If these events occur after a "break" (e.g., a CHF and arrhythmia free period of at least a week), they should be designated by the immediate cause, even though the MI may have increased the risk of that event (e.g., late arrhythmic death becomes more likely after an acute myocardial infarction (AMI)). The acute myocardial infarction should be verified to the extent possible by the diagnostic criteria outlined for acute myocardial infarction or by autopsy findings showing recent myocardial infarction or recent coronary thrombus. Sudden cardiac death, if accompanied by symptoms suggestive of myocardial ischemia, new ST elevation, new LBBB, or evidence of fresh thrombus by coronary angiography and/or at autopsy should be considered death resulting from an acute myocardial infarction, even if death occurs before blood samples or 12-lead electrocardiogram (ECG) could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.

   Death resulting from a procedure to treat a myocardial infarction (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), or to treat a complication resulting from myocardial infarction, should also be considered death due to acute MI.

   Death resulting from a procedure to treat myocardial ischemia (angina) or death due to a myocardial infarction that occurs as a direct consequence of a cardiovascular investigation/procedure/operation should be considered as a death due to other cardiovascular causes.

2. **Sudden Cardiac Death** refers to a death that occurs unexpectedly, not following an acute AMI, and includes the following deaths:

   a. Death witnessed and instantaneous without new or worsening symptoms

   b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest AMI

   c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an

electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)

d. Death after unsuccessful resuscitation from cardiac arrest

e. Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology (Post-Cardiac Arrest Syndrome)

f. Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations

- A subject seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death." Typical scenarios include
  - Subject well the previous day but found dead in bed the next day
  - Subject found dead at home on the couch with the television on

- Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes" or in some trials, "undetermined cause of death." Please see Definition of Undetermined Cause of Death, for full details.

3. **Death due to Heart Failure or Cardiogenic Shock** refers to a death occurring in the context of clinically worsening symptoms and/or signs of heart failure (see Definition of Heart Failure Requiring Hospitalization) without evidence of another cause of death and not following an AMI. Note that deaths due to heart failure can have various etiologies, including one or more AMIs (late effect), ischemic or non-ischemic cardiomyopathy, or valve disease.

   Death due to Heart Failure or Cardiogenic shock should include sudden death occurring during an admission for worsening heart failure as well as death from progressive heart failure or cardiogenic shock following implantation of a mechanical assist device.

   New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

   a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure

   b. Heart failure symptoms or signs requiring continuous intravenous therapy or chronic oxygen administration for hypoxia due to pulmonary edema

   c. Confinement to bed predominantly due to heart failure symptoms

   d. Pulmonary edema sufficient to cause tachypnea and distress not occurring in the context of an acute myocardial infarction, worsening renal function, or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

   e. Cardiogenic shock not occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

   Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than

1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypoperfusion:

- Cool, clammy skin ***or***
- Oliguria (urine output < 30 mL/hour) ***or***
- Altered sensorium ***or***
- Cardiac index < 2.2 L/min/m^2

Cardiogenic shock can also be defined if SBP < 90 mm Hg and increases to ≥ 90 mm Hg in less than 1 hour with positive inotropic or vasopressor agents alone and/or with mechanical support.

General Considerations

Heart failure may have a number of underlying causes, including acute or chronic ischemia, structural heart disease (e.g. hypertrophic cardiomyopathy), and valvular heart disease. Where treatments are likely to have specific effects, and it is likely to be possible to distinguish between the various causes, then it may be reasonable to separate out the relevant treatment effects. For example, obesity drugs such as fenfluramine (pondimin) and dexfenfluramine (redux) were found to be associated with the development of valvular heart disease and pulmonary hypertension. In other cases, the aggregation implied by the definition above may be more appropriate.

4. **Death due to Stroke** refers to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.

5. **Death due to Other Cardiovascular Causes** refers to a cardiovascular death not included in the above categories (e.g. dysrhythmia unrelated to sudden cardiac death, pulmonary embolism, cardiovascular intervention (other than one related to an AMI), aortic aneurysm rupture, or peripheral arterial disease). Mortal complications of cardiac surgery or non-surgical revascularization should be classified as cardiovascular deaths.

DEFINITION OF NON-CARDIOVASCULAR DEATH

Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. Detailed recommendations on the classification of non-cardiovascular causes of death are beyond the scope of this document. The level of detail required and the optimum classification will depend on the nature of the study population and the anticipated number and type of non-cardiovascular deaths. Any specific anticipated safety concern should be included as a separate cause of death. The following is a suggested list of non-cardiovascular* causes of death:

Non-Malignant Causes

- Pulmonary

- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Hemorrhage, not intracranial
- Non-cardiovascular system organ failure (e.g., hepatic failure)
- Non-cardiovascular surgery
- Other non-cardiovascular
- Accidental/Trauma
- Suicide
- Drug Overdose

*Death due to a gastrointestinal bleed should **not** be considered a cardiovascular death.

Malignant Causes
Malignancy should be coded as the cause of death if:

- Death results directly from the cancer; or
- Death results from a complication of the cancer (e.g. infection, complication of surgery / chemotherapy / radiotherapy); or
- Death results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer

Cancer deaths may arise from cancers that were present prior to randomization or which developed subsequently. It may be helpful to distinguish these two scenarios (i.e. worsening of prior malignancy; new malignancy).

Suggested categorization includes common organ systems, hematologic, or unknown.

DEFINITION OF UNDETERMINED CAUSE OF DEATH

Undetermined Cause of Death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, the use of this category of death should be discouraged and should apply to a minimal number of patients in well-run clinical trials.

A common analytic approach for cause of death analyses is to assume that all undetermined cases are included in the cardiovascular category (e.g., presumed cardiovascular death, specifically "death due to other cardiovascular causes"). Nevertheless, the appropriate classification and analysis of undetermined causes of death depends on the population, the intervention under investigation, and the disease process. The approach should be prespecified and described in the protocol and other trial documentation such as the end point adjudication procedures and/or the

statistical analysis plan.

DEFINITION OF MYOCARDIAL INFARCTION

1. General Considerations

The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.

In general, the diagnosis of MI requires the combination of:

- Evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and
- Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

2. Criteria for Myocardial Infarction

a. Clinical Presentation

The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be taken into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, congestive heart failure, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.

b. Biomarker Elevations

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. CK-MB and troponin are preferred, but CK may be used in

the absence of CK-MB and troponin.

For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin will be required. The specific criteria will be referenced to the URL.

In many studies, particularly those in which patients present acutely to hospitals which are not participating sites, it is not practical to stipulate the use of a single biomarker or assay, and the locally available results are to be used as the basis for adjudication. However, if possible, using the same cardiac biomarker assay and preferably, a core laboratory, for all measurements reduces inter-assay variability.

Since the prognostic significance of different types of myocardial infarctions (e.g., periprocedural myocardial infarction versus spontaneous myocardial infarction) may be different, consider evaluating outcomes for these subsets of patients separately.

c. Electrocardiogram (ECG) Changes

Electrocardiographic changes can be used to support or confirm a MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

- **Criteria for acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)):**

  - ST elevation

    New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

  - ST depression and T-wave changes

    New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

- **Criteria for pathological Q-wave**

  - Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
  - Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)[a]

  [a]The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

- **Criteria for Prior Myocardial Infarction**

- Pathological Q-waves, as defined above
- R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

3. Myocardial Infarction Subtypes

Several MI subtypes are commonly reported in clinical investigations and each are defined below:

a. Spontaneous MI

1. Detection of rise and/or fall of cardiac biomarkers with at least one value above the URL with at least one of the following:
   - Clinical presentation consistent with ischemia
   - ECG evidence of acute myocardial ischemia
   - New pathological Q waves
   - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
   - Autopsy evidence of acute MI

2. If biomarkers are elevated from a prior infarction, then a spontaneous myocardial infarction is defined as:

   a. One of the following:

   - Clinical presentation consistent with ischemia
   - ECG evidence of acute myocardial ischemia
   - New pathological Q waves
   - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
   - Autopsy evidence of acute MI

   AND

   b. Both of the following:

   - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI*
   - ≥ 20% increase (and > URL) in troponin or CK-MB between a measurement made at the time of the initial presentation and a further sample taken 3-6 hours later

   *If biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent MI is generally not possible.

b. Percutaneous Coronary Intervention-Related Myocardial Infarction

Peri-PCI MI is defined by any of the following criteria. Symptoms of cardiac ischemia are not required.

1. Biomarker elevations within 48 hours of PCI:
   - Troponin or CK-MB (preferred) > 3 x URL ***and***
   - No evidence that cardiac biomarkers were elevated prior to the procedure;

     OR
   - Both of the following must be true:
     - ≥ 50%[1] increase in the cardiac biomarker result
     - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI
2. New pathological Q waves
3. Autopsy evidence of acute MI

c. Coronary Artery Bypass Grafting-Related Myocardial Infarction

Peri-coronary artery bypass graft surgery (CABG) MI is defined by the following criteria. Symptoms of cardiac ischemia are not required.

1. Biomarker elevations within 72 hours of CABG:
   - Troponin or CK-MB (preferred) > 5 x URL and
   - No evidence that cardiac biomarkers were elevated prior to the procedure;

     OR
   - Both of the following must be true:
     - ≥ 50%[2] increase in the cardiac biomarker result
     - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI.

   AND

2. One of the following:
   - New pathological Q-waves persistent through 30 days
   - New persistent non-rate-related LBBB
   - Angiographically documented new graft or native coronary artery occlusion
   - Other complication in the operating room resulting in loss of myocardium
   - Imaging evidence of new loss of viable myocardium

[1, 2] Data should be collected in such a way that analyses using ≥ 20% or ≥ 50% could both be performed.

OR

3. Autopsy evidence of acute MI

d. Silent Myocardial Infarction

Silent MI is defined by the following:

1. No evidence of acute myocardial infarction

AND

2. Any one of the following criteria:
   - New pathological Q-waves. A confirmatory ECG is recommended if there have been no clinical symptoms or history of myocardial infarction.
   - Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
   - Autopsy evidence of a healed or healing MI

COMMON CLASSIFICATION SCHEMES FOR MYOCARDIAL INFARCTION CATEGORIES

For some trials, categorization of MI end points may be helpful or necessary using one or more of the classification schemes below:

1. **By the Universal MI Definition:**

a. Clinical Classification of Different Types of Myocardial Infarction

- **Type 1**

  Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

- **Type 2**

  Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

- **Type 3**

  Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

- **Type 4a**

Myocardial infarction associated with PCI

- **Type 4b**

  Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

- **Type 5**

  Myocardial infarction associated with CABG

b. Sample Clinical Trial Tabulation of Randomized Patients by Types of Myocardial Infarction

Types of MI	Treatment A Number of patients (N =)	Treatment B Number of patients (N =)
MI Type 1	n, %	n, %
MI Type 2	n, %	n, %
MI Type 3	n, %	n, %
MI Type 4	n, %	n, %
MI Type 5	n, %	n, %
Total number	n, %	n, %
N = total number of patients; n = number of patients with a particular MI.		

2. **By Electrocardiographic Features:**

- **ST-Elevation MI (STEMI)**
  - Additional subcategories may include:
    - Q-wave
    - Non-Q-wave
    - Unknown (no ECG or ECG not interpretable)
- **Non-ST-Elevation MI (NSTEMI)**
  - Additional subcategories may include:
    - Q-wave
    - Non-Q-wave
    - Unknown (no ECG or ECG not interpretable)
- **Unknown (no ECG or ECG not interpretable)**

3. By Biomarker Elevation (per Universal MI Definition):

The magnitude of cardiac biomarker elevation can be calculated as a ratio of the peak biomarker value divided by the 99th percentile URL.

The biomarker elevation can be provided for various MI subtypes, as shown in the example below.

Classification of the Different Types of Myocardial Infarction According to Multiples of the 99th percentile URL of the Applied Cardiac Biomarker

Multiples X 99%	M1 Type (spontaneous)	MI Type 2 (secondary)	M1 Type 3 (sudden death)	**M1 Type 4** (PCI)**	**M1 Type 5** (CABG)**	**Total Number**
1-2X						
>2-3X						
>3-5X						
>5-10X						
Total Number						

*Biomarkers are not available for this type of myocardial infarction since the patients expired before biomarker determination could be performed.

** For the sake of completeness, the total distribution of biomarker values should be reported. The hatched areas represent biomarker elevations below the decision limit used for these types of myocardial infarction.

DEFINITION OF HOSPITALIZATION FOR UNSTABLE ANGINA

Unstable angina requiring hospitalization is defined as

1. Symptoms of myocardial ischemia at rest (chest pain or equivalent) or an accelerating pattern of angina with frequent episodes associated with progressively decreased exercise capacity

   AND

2. Prompting an unscheduled visit to a healthcare facility and hospitalization (including chest pain observation units) **within 24 hours** of the most recent symptoms

   AND

3. At least one of the following:

   a. New or worsening ST or T wave changes on resting ECG
   - ST elevation
     New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.

   - ST depression and T-wave changes
     New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads;

and/or new T inversion ≥ 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. It is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

b. Definite evidence of myocardial ischemia on myocardial scintigraphy (clear reversible perfusion defect), stress echocardiography (reversible wall motion abnormality), or MRI (myocardial perfusion deficit under pharmacologic stress) that is believed to be responsible for the myocardial ischemic symptoms/signs

c. Angiographic evidence of ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs

d. Need for coronary revascularization procedure (PCI or CABG) during the same hospital stay. This criterion would be fulfilled if the admission for myocardial ischemia led to transfer to another institution for the revascularization procedure without interceding home discharge

AND

4. No evidence of acute myocardial infarction

General Considerations

1. Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β-blockers, should be considered supportive of the diagnosis of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3, would be insufficient alone to support classification as hospitalization for unstable angina.

2. If subjects are admitted with suspected unstable angina, and subsequent testing reveals a non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for myocardial infarction should not be adjudicated as unstable angina.

3. Planned rehospitalization for performance of an elective revascularization in the absence of symptoms at rest prompting admission should not be considered a hospitalization for unstable angina. For example, a patient with stable exertional angina whose admission for coronary angiography and PCI is prompted by a positive outpatient stress test should not be considered a hospitalization for unstable angina.

4. A patient who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina end point.

DEFINITION OF TRANSIENT ISCHEMIC ATTACK AND STROKE

Transient Ischemic Attack

Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, *without* acute infarction.

Stroke

Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

Classification:

A. Ischemic Stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.

Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

B. Hemorrhagic Stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

C. Undetermined Stroke

Undetermined stroke is defined as a stroke with insufficient information to allow categorization as A or B.

2. **Stroke Disability**

Stroke disability should be measured by a reliable and valid scale in all cases. For example, the modified Rankin Scale may be used to address this requirement:

Scale	Disability
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; requiring some help, but able to walk without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6	Dead

Additional Considerations

In trials involving patients with stroke, evidence of vascular central nervous system injury without recognized neurological dysfunction may be observed. Examples include microhemorrhage, silent infarction, and silent hemorrhage. When encountered, the clinical relevance of these findings may be unclear. If appropriate for a given clinical trial, however, they should be precisely defined and categorized.

The distinction between a Transient Ischemic Attack and an Ischemic Stroke is the presence of infarction, not the transience of the symptoms. In addition to laboratory documentation of infarction, persistence of symptoms is an acceptable indicator of infarction. Thus, symptom transience should be defined for any clinical trial in which it will be used to distinguish between transient ischemia and infarction.

DEFINITION OF HEART FAILURE REQUIRING HOSPITALIZATION

Heart failure (HF) requiring hospitalization is defined as an event that meets the following criteria:

a. Requires hospitalization defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24* hour stay (or a date change if the time of admission/discharge is not available).

*For this end point in any given clinical trial, there should be some flexibility in the required duration of stay, depending on the population and the adverse event profile of the drug to be studied. For example, a clinical trial studying patients with NYHA Class III/IV heart failure may not wish to capture hospitalizations less than 24 hours in duration, because this population may have frequent hospital visits requiring short-term therapy. On the contrary, clinical trials in patients with NYHA Class I/II heart failure may wish to capture shorter hospitalizations that may be predictive of subsequent decompensation.

AND

b. Clinical symptoms of heart failure, including at least one of the following:

New or worsening

- dyspnea
- orthopnea
- paroxysmal nocturnal dyspnea
- increasing fatigue/worsening exercise tolerance

AND

c. Physical signs of heart failure, including at least two of the following:

1. edema (greater than 2+ lower extremity)
2. pulmonary crackles greater than basilar (pulmonary edema must be sufficient to cause tachypnea and distress **not** occurring in the context of an acute myocardial infarction or as the consequence of an arrhythmia occurring in the absence of worsening heart failure)
3. jugular venous distension
4. tachypnea (respiratory rate > 20 breaths/minute)
5. rapid weight gain
6. S3 gallop
7. increasing abdominal distension or ascites
8. hepatojugular reflux
9. radiological evidence of worsening heart failure
10. A right heart catheterization within 24 hours of admission showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mm Hg or a cardiac output < 2.2 L/min/m^2

NOTE: Biomarker results (e.g., brain natriuretic peptide (BNP)) consistent with congestive heart failure will be supportive of this diagnosis, but the elevation in BNP cannot be due to other conditions such as cor pulmonale, pulmonary embolus, primary pulmonary hypertension, or congenital heart disease. Increasing levels of BNP, although not exceeding the ULN, may also be supportive of the diagnosis of congestive heart failure in selected cases (e.g. morbid obesity).

AND

d. Need for additional/increased therapy

1. Initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure and including at least one of the following:
   - Initiation of or a significant augmentation in oral therapy for the treatment of congestive heart failure
   - Initiation of intravenous diuretic, inotrope, or vasodilator therapy
   - Uptitration of intravenous therapy, if already on therapy
   - Initiation of mechanical or surgical intervention (mechanical circulatory support, heart transplantation or ventricular pacing to improve cardiac function), or the use of ultrafiltration, hemofiltration, or dialysis that is specifically directed at treatment of heart failure.

AND

e. No other non-cardiac etiology (such as chronic obstructive pulmonary disease, hepatic cirrhosis, acute renal failure, or venous insufficiency) and no other cardiac etiology (such as pulmonary embolus, cor pulmonale, primary pulmonary hypertension, or congenital heart disease) for signs or symptoms is identified.

NOTE: It is recognized that some patients may have multiple simultaneous disease processes. Nevertheless, for the end point event of heart failure requiring hospitalization, the diagnosis of congestive heart failure would need to be the primary disease process accounting for the above signs and symptoms.

INTERVENTIONAL CARDIOLOGY DEFINITIONS

1. **Coronary Revascularization Procedure:** A coronary revascularization procedure is a catheter-based or open surgical procedure designed to improve myocardial blood flow. Catheter-based tools (e.g., balloon catheters, cutting balloons, atherectomy devices, lasers, bare metal stents, and drug-eluting stents) improve myocardial blood flow by increasing the luminal area at a site of an obstructive coronary lesion. Bypass grafts (arterial, venous, or synthetic) improve myocardial blood flow by providing a conduit for blood flow distal to an obstructive coronary lesion. Insertion of a guidewire through a coronary guide catheter into a coronary vessel or bypass graft for the purpose of percutaneous coronary intervention (PCI) is considered intention for PCI. However, in the assessment of the severity of intermediate lesions with the use of intravascular ultrasound, Doppler flow velocity, or fractional flow reserve, insertion of a guidewire will NOT be considered PCI.

2. **Procedural Success:** Achievement of <30 % residual diameter stenosis of the target lesion assessed by visual inspection or quantitative coronary angiography (QCA) and no in-hospital major adverse cardiac events (MACE, a composite of death, MI, or repeat coronary revascularization of the target lesion). Ideally, the assessment of the residual stenosis at the end of the procedure should be performed by an angiographic core laboratory.

   Comment: *For some devices or clinical settings (e.g., plain old balloon angioplasty (POBA) for patients undergoing non-cardiac surgery), achievement of < 50% diameter stenosis by visual inspection is an acceptable definition for procedural success.*

3. **Elective and Non-elective Procedures:**

   Elective: An elective procedure is one performed on a patient with stable cardiac function in the days or weeks prior to the procedure. Elective cases are usually scheduled at least 1 day prior to the procedure.

   Non-Elective: A non-elective procedure is one performed on a patient who has been stabilized following initial treatment of acute coronary ischemia, and there is clinical consensus that the procedure should occur within the next 24 hours.

   OR

A procedure that is performed without delay on a patient with evidence of ongoing refractory ischemia with or without hemodynamic instability.

4. **Target Lesion:** A target lesion is any lesion treated or attempted to be treated during the trial procedure with the study device. The target lesion is the treated segment starting 5 mm proximal and ending 5 mm distal to the study device (stent, in most cases).

5. **Target Vessel:** A target vessel is any native coronary vessel (e.g., left main coronary artery (LMCA), left anterior descending coronary artery (LAD), left circumflex coronary artery (LCX), or right coronary artery (RCA)) or bypass graft to the LAD, LCX, or RCA containing the target lesion. The target vessel includes the target lesion as well as segments of the vessel that are upstream and downstream to the target lesion, including side branches (native vessel).

6. **Non-Target Lesion**: A non-target lesion is one for which revascularization is not attempted or one in which revascularization is performed using a non-study device.

7. **Non-Target Vessel**: A non-target vessel is one for which revascularization is not attempted or one in which revascularization is performed using a non-study device.

8. **Target Vessel, Non-Target Lesion**: Any lesion or revascularization of a lesion in the target vessel other than the target lesion.

9. **Target Lesion Revascularization (TLR)**: Target lesion revascularization is any repeat percutaneous intervention of the target lesion (including 5 mm proximal and distal to the target lesion) or surgical bypass of the target vessel performed for restenosis or other complication involving the target lesion. In the assessment of TLR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the Clinical End Points Committee (CEC) for review.

10. **Target Vessel Revascularization (TVR)**: Target vessel revascularization is any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. In the assessment of TVR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the CEC for review.

11. **Clinically-Driven Target Lesion Revascularization**: Revascularization is clinically-driven if the subject has a target lesion diameter stenosis ≥ 50% by QCA and clinical or functional ischemia which cannot be explained by another native coronary or bypass graft lesion. Clinical or functional ischemia includes any of the following:

    a. A history of angina pectoris, presumably related to the target vessel
    b. Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel
    c. Abnormal results of any invasive functional diagnostic test (e.g., Doppler flow velocity reserve or fractional flow reserve (FFR))
    d. A diameter stenosis ≥70% by QCA even in the absence of the above signs or symptoms.

Comment: *In the absence of QCA data or if a <50% stenosis is present, TLR may be considered clinically-driven by the CEC if severe ischemic signs and symptoms attributed to the target lesion are present.*

DEFINITION OF PERIPHERAL ARTERIAL REVASCULARIZATION PROCEDURE

1. **Peripheral Arterial Revascularization Procedure**: A peripheral arterial revascularization procedure is a catheter-based or open surgical procedure designed to improve peripheral arterial blood flow. This procedure may include thrombectomy, embolectomy, atherectomy, dissection repair, angioplasty, and stent placement.

   The intention to perform percutaneous peripheral arterial intervention is denoted by the insertion of a guidewire through a guide catheter into a peripheral artery.

   The target vessel(s) should be specified (e.g., aorta, renal, mesenteric, iliac, femoral, tibial) and recorded as well as the type of revascularization procedure (e.g., surgical, angioplasty, stent placement, thromboembolectomy). For simplicity, this definition applies to non-cardiac and non-cerebrovascular vessels, including the aorta, but does not address aortic aneurysm repair.

2. **Procedural Success**: In the case of percutaneous intervention for obstructive lesions, procedural success is defined as the achievement of a final residual diameter stenosis < 30% by angiography at the end of the procedure (and without flow limiting arterial dissection and hemodynamically significant translesional pressure gradient) without any in-hospital major adverse events (death, acute onset of limb ischemia, need for urgent/emergent vascular surgery). The balloon inflation and/or stent placement may be preceded by use of adjunctive devices (e.g., percutaneous mechanical thrombectomy, directional or rotational atherectomy, laser, chronic total occlusion crossing device).

3. **Elective and Non-Elective Procedures:**

   Elective: An elective procedure is one that is scheduled and is performed on a patient with stable peripheral arterial disease.

   Non-Elective: A non-elective procedure is one performed on a patient who has been stabilized following initial treatment of acute peripheral limb ischemia, and there is clinical consensus that the procedure should occur within the next 24 hours.

   OR

   A procedure that is performed without delay because of urgency of the medical condition (e.g., acute limb ischemia, acute aortic dissection).

4. **Target Lesion**: A target lesion is any lesion treated or attempted to be treated during the trial procedure with the index device. The target lesion is the treated segment starting 5 mm proximal and ending 5 mm distal to the index device (stent, in most cases).

5. **Target Vessel**: A target vessel is any vessel (e.g., non-cardiac or non-cerebrovascular vessel) that contains the target lesion treated with the study device. The target vessel includes the target lesion as well as the entire vessel upstream and downstream to the target lesion, including side branches (native vessel).

6. **Non-Target Lesion**: A non-target lesion is one for which revascularization is not attempted or one in which revascularization is performed using a non-study device.

7. **Non-Target Vessel**: A non-target vessel is one for which revascularization is not attempted or one in which revascularization is performed using a non-study device.

8. **Target Vessel, Non-Target Lesion**: Any lesion or revascularization of a lesion in the target vessel other than the target lesion.

9. **Target Lesion Revascularization (TLR)**: Target lesion revascularization is any repeat percutaneous intervention of the target lesions (including 5 mm proximal and distal to the index device) or surgical bypass of the target vessel performed for restenosis or other complication involving the target lesion. In the assessment of TLR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the Clinical End Points Committee (CEC) for review.

10. **Target Vessel Revascularization (TVR)**: Target vessel revascularization is any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. In the assessment of TVR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the CEC for review.

11. **Clinically-Driven Target Lesion Revascularization**: Clinically-driven target lesion revascularization is a target lesion revascularization prompted by recurrent ipsilateral limb symptoms (intermittent claudication, critical limb ischemia) or objective imaging evidence of target lesion restenosis (i.e., most commonly with duplex ultrasonography). In the assessment of clinically driven TLR based on duplex ultrasonography, ultrasonographic images should be assessed by a duplex ultrasound core laboratory (if designated) and made available to the CEC for review.

APPENDIX C: CRITERIA FOR THE DIAGNOSIS OF DIABETES

Reference:
American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010; 33 Suppl 1:S62.

1. HbA_{1c} ≥6.5%. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.*

OR

2. Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hr.*

OR

3. 2-hr plasma glucose ≥200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

* In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

CLINICAL STUDY PROTOCOL

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: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

Investigational Product: AMR101 (icosapent ethyl [ethyl-EPA])
Protocol Number: AMR-01-01-0019

Sponsor:
Amarin Pharma Inc.
1430 Route 206
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Amendment #1: Final 16 May 2013
Amendment #1 Protocol Version Number: Final v 2.0
Original Protocol: 2 August 2011

SIGNATURE PAGE

TRIAL 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: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

We, the undersigned, have reviewed and approved this protocol.

Signature	Date
[Name / signature redacted] Vice President, Clinical Development Amarin Pharma Inc.	[Signed (16 May 2013)]
[Name / signature redacted] Senior Director, Clinical Development Amarin Pharma Inc.	[Signed (16 May 2013)]
[Name / signature redacted] Vice President & Head of Regulatory Affairs Amarin Pharma Inc.	[Signed (16 May 2013)]
[Name / signature redacted] Principal Investigator	[Signed (16 May 2013)]

SYNOPSIS

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: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

PROTOCOL NUMBER: AMR-01-01-0019

INVESTIGATIONAL PRODUCT: AMR101 (icosapent ethyl [ethyl-EPA])

PHASE: 3b

INDICATION:

Treatment with AMR101 to reduce the risk of cardiovascular events in patients with clinical cardiovascular disease or with multiple risk factors for cardiovascular disease.

OBJECTIVES:

The primary objective is, in patients at LDL-C goal while on statin therapy, with established cardiovascular disease (CVD) or at high risk for CVD, and hypertriglyceridemia (fasting triglycerides, TG, ≥200 mg/dL and <500 mg/dL [≥2.26 mmol/L and <5.64 mmol/L]), to evaluate the effect of 4 g/day AMR101 for preventing the occurrence of a first major cardiovascular event of the composite endpoint that includes:

- Cardiovascular (CV) death,
- Nonfatal myocardial infarction (MI),
- Nonfatal stroke,
- Coronary revascularization,
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

The secondary objectives of this study are the following:

The key secondary objective is to evaluate the effect of therapy on the composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair.

Other secondary objectives:

- To evaluate the effect of therapy on combinations of each of the key secondary objective clinical events in addition to the following clinical events:
    - Cardiac arrhythmia requiring hospitalization
    - Cardiac arrest

- Peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair
- Total mortality

The tertiary objectives of this study are the following:

- Evaluate the effect of therapy on the occurrence of a second, third, fourth, and fifth major cardiovascular event (same as the primary composite endpoint but for events occurring after the first event);
- To evaluate the effect of therapy on the primary endpoint in subgroups of patients including:
  - Diabetes mellitus
  - Metabolic syndrome as defined by the NCEP ATP III or future criteria as they may evolve;
- To evaluate the effect of therapy on the individual endpoints of new congestive heart failure (CHF), on new CHF as a primary cause of hospitalization, on transient ischemic attack, on amputation for vascular disease and on carotid revascularization;
- Elective coronary revascularization and emergent coronary revascularization;
- To assess the effects regarding lipids, lipoproteins and inflammatory markers including triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein B (apo B), high sensitivity C-reactive protein (hs-CRP) and high sensitivity troponin (hsTnT), as follows:
  - Assessment of the effect of AMR101 on each marker (on-treatment change of markers)
  - Assessment of the effect of the baseline value of each marker on treatment effects (baseline effect on outcomes)
  - To evaluate the effect of therapy for preventing clinical events, as defined above, among all patients in the study, and in subgroups such as patients with diabetes mellitus and patients with substantial on-treatment changes of any of the markers (on-treatment effect on outcomes).
- To evaluate the effect of therapy on new onset diabetes (See appendix C);
- To explore the effect of AMR101 on weight and waist circumference.

ENDPOINTS:

Primary endpoint:
Time from randomization to the first occurrence of the composite of the following clinical events:

- CV death,

- Nonfatal MI (including silent MI; ECGs will be performed annually for the detection of silent MIs),
- Nonfatal stroke,
- Coronary revascularization,
- Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing.

The first occurrence of any of these major adverse vascular events during the follow-up period of the study will be included in the incidence.

Secondary endpoints:

The key secondary efficacy endpoint is:

- The composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair.

Other secondary efficacy endpoints are as follows (to be tested in said order):

- The composite of total mortality, nonfatal MI, or nonfatal stroke;
- The composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, peripheral CVD requiring intervention, or cardiac arrhythmia requiring hospitalization;
- The composite of death from CV causes, nonfatal MI, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- The composite of death from CV causes or nonfatal MI;
- Total mortality;
- Fatal and nonfatal MI (including silent MI);
- Coronary Revascularization;
- Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing ;
- Fatal and nonfatal stroke.

For the secondary endpoints that count a single event, the first occurrence of this type of event will be counted in each patient. For secondary endpoints that are composites of two or more types of events, the first occurrence of any of the event types included in the composite will be counted in each patient.

Tertiary endpoints:

- The second, third, fourth, and fifth major CV event of the primary composite endpoint. The type of (nonfatal) events may occur in any order.
- Primary endpoint in subset of patients with diabetes mellitus;

- Primary endpoint in subset of patients with metabolic syndrome;
- Individual endpoints of new CHF, new CHF leading to hospitalization, transient ischemic attack, amputation for CVD and carotid revascularization;
- Elective coronary revascularization and emergent coronary revascularization;
- New onset diabetes;
- Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP, and hsTnT: effect of baseline and on-treatment change of biomarkers on primary and key secondary endpoints;
- CV mortality;
- Cardiac Arrhythmias requiring hospitalization;
- Cardiac Arrest;
- To explore the effect of AMR101 on weight and waist circumference.

For the tertiary endpoints that count a single event, the first occurrence of this type of event will be counted in each patient. For tertiary endpoints that are composites of two or more types of events, the first occurrence of any of the event types included in the composite will be counted in each patient (except when stated otherwise, for the second, third, fourth, and fifth major CV event).

POPULATION:

Inclusion Criteria:

1. Fasting TG levels of ≥200 mg/dL (2.26 mmol/L) and <500 mg/dL (5.64 mmol/L).
2. LDL-C >40 mg/dL (1.04 mmol/L) and ≤100 mg/dL (2.60 mmol/L) and on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks prior to the LDL-C/TG baseline qualifying measurements for randomization

    - Stable therapy is defined as the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable, the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C). Patients who have their statin therapy or use of ezetimibe initiated at Visit 1, or have their statin, statin dose and/or ezetimibe dose changed at Visit 1, will need to go through a stabilization period of at least 28 days since initiation/change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).
    - Statins may be administered with or without ezetimibe.

    NOTE: If patients qualify at the first qualification visit (Visit 1) for TG and LDL-C, and meet all other inclusion/exclusion criteria, they may be randomized at Visit 2. If patients do not qualify at the first qualifying visit (Visit 1), a second re-qualifying visit (Visit 1.1) is allowed. For some patients, because they need to stabilize medications and/or need to washout medications, the second re-qualifying visit (Visit 1.1) will be needed after the stabilization/washout period.

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 are defined as follows:

   CV Risk Category 1: defined as men and women ≥45 years of age with one or more of the following:

   - Documented coronary artery disease (CAD; one or more of the following primary criteria must be satisfied):
     - Documented multi vessel CAD (≥50% stenosis in at least two major epicardial coronary arteries – with or without antecedent revascularization);
     - Documented prior MI;
     - Hospitalization for high-risk NSTE ACS (with objective evidence of ischemia: ST-segment deviation or biomarker positivity).
   - Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied):
     - Documented prior ischemic stroke;
     - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis;
     - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound;
     - History of carotid revascularization (catheter-based or surgical).
   - Documented peripheral arterial disease (PAD; one or more of the following primary criteria must be satisfied):
     - Ankle-brachial index (ABI) <0.9 with symptoms of intermittent claudication;
     - History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical).

   OR

   CV Risk Category 2: defined as patients with:

   1. Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication AND
   2. Men and women ≥50 years of age AND
   3. One of the following at Visit 1 (additional risk factor for CVD):
      - Men ≥55 years of age and 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, defined as any of the following: non-proliferative retinopathy, preproliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation;
- Micro- or macroalbuminuria. Microalbuminuria is defined as either a positive micral or other strip test (may be obtained from medical records), an albumin/creatinine ratio ≥2.5 mg/mmol or an albumin excretion rate on timed collection ≥20 mg/min all on at least two successive occasions; macroalbuminuria, defined as albustix or other dipstick evidence of gross proteinuria, an albumin/creatinine ratio ≥25 mg/mmol or an albumin excretion rate on timed collection ≥200 mg/min all on at least two successive occasions;
- ABI <0.9 without symptoms of intermittent claudication (patients with ABI <0.9 with symptoms of intermittent claudication are counted under CV Risk Category 1).

Note: Patients with diabetes and vascular disease as defined above are eligible based on the vascular disease requirements and will be counted under CV Risk Category 1. Only patients with diabetes and no documented CV disease as defined above need at least one additional risk factor as listed, and will be counted under CV Risk Category 2.

4. Women may be enrolled if all 3 of the following criteria are met:
   - They are not pregnant;
   - They are not breastfeeding;
   - They do not plan on becoming pregnant during the study.
5. Women of child-bearing potential must have a negative urine pregnancy test before randomization.

   Note: Women are not considered to be of childbearing potential if they meet one of the following criteria as documented by the investigator:

   - They have had a hysterectomy, tubal ligation or bilateral oophorectomy prior to signing the informed consent form;
   - They are post-menopausal, defined as ≥1 year since their last menstrual period or have a follicle-stimulating hormone (FSH) level in a menopausal range.
6. Women of childbearing potential must agree to use an acceptable method of avoiding pregnancy from screening to the end of the study, unless their sexual partner(s) is/are surgically sterile or the woman is abstinent.
7. Understanding of the study procedures, willing to adhere to the study schedules, and agreement to participate in the study by giving informed consent prior to screening.
8. Agree to follow a physician recommended diet, and to maintain it through the duration of the study.

Exclusion Criteria:

1. Severe (class IV) heart failure.
2. Any life-threatening disease expected to result in death within the next 2 years (other than CVD).
3. Active severe liver disease (evaluated at Visit 1): cirrhosis, active hepatitis, ALT or AST >3 x ULN, or biliary obstruction with hyperbilirubinemia (total bilirubin >2 x ULN).
4. Hemoglobin A_{1c} >10.0% (or 86 mmol/mol IFCC units) at screening (Visit 1). If patients fail this criterion (HbA_{1c} >10.0% or 86 mmol/mol IFCC units) at Visit 1, they may have their antidiabetic therapy optimized and be retested at Visit 1.1.
5. Poorly controlled hypertension: blood pressure ≥200 systolic mmHg OR ≥100 mmHg diastolic (despite antihypertensive therapy).
6. Planned coronary intervention (such as stent placement or heart bypass) or any non-cardiac major surgical procedure. Patients can be (re)evaluated for participation in the trial (starting with Visit 1.1) after their recovery from the intervention/surgery.
7. Known familial lipoprotein lipase deficiency (Fredrickson Type I), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type III)].
8. Participation in another clinical trial involving an investigational agent within 90 days prior to screening (Visit 1). Patients cannot participate in any other investigational medication or medical device trial while participating in this study (participation in a registry or observational study without additional therapeutic intervention is allowed).
9. Intolerance or hypersensitivity to statin therapy.
10. Known hypersensitivity to any ingredients of the study product or placebo (refer to Table 3); known hypersensitivity to fish and or shellfish.
11. History of acute or chronic pancreatitis.
12. Malabsorption syndrome and/or chronic diarrhea. (Note: patients who have undergone gastric/intestinal bypass surgery are considered to have malabsorption, hence are excluded; patients who have undergone gastric banding are allowed to enter the trial).
13. Non-study drug related, non-statin, lipid-altering medications, supplements or foods:
    - Patients are excluded if they used niacin >200 mg/day or fibrates during the screening period (after Visit 1) and/or plan to use during the study; patients who are taking niacin >200 mg/day or fibrates during the last 28 days before Visit 1 need to go through washout of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (Visit 1.1);
    - Patients are excluded if they take any omega-3 fatty acid medications (prescription medicines containing EPA and/or DHA) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking omega-3 fatty acid medications during the last 28 days before Visit 1 (except patients in The Netherlands), need to go through a washout period of at least 28 days after their last use and have their

qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);

- For patients in The Netherlands only: patients being treated with omega-3 fatty acid medications containing EPA and /or DHA are excluded; no washout is allowed.

- Patients are excluded if they use dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking >300 mg/day omega-3 fatty acids (combined amount of EPA and DHA) within 28 days before Visit 1 (except patients in The Netherlands), need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);
    - For patients in The Netherlands only: patients being treated with dietary supplements containing omega-3 fatty acids of >300 mg/day EPA and/or DHA are excluded; no washout is allowed.
- Patients are excluded if they use bile acid sequestrants during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking bile acid sequestrants within 7 days before Visit 1, need to go through a washout period of at least 7 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);

14. Other medications (not indicated for lipid alteration):
    - Treatment with tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are allowed), HIV-protease inhibitors that have not been stable for ≥28 days prior to the qualifying lipid measurements (TG and LDL-C) during screening. To be eligible for participation in the study, patients who are not taking a stable dose of these medications within 28 days before Visit 1, need to go through a stabilization period of at least 28 days since their last dose change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);
    - Patients are excluded if they use cyclophosphamide or systemic retinoids during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking these medications within 28 days before Visit 1, need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).
15. Known to have AIDS (patients who are HIV positive without AIDS are allowed).
16. Requirement for peritoneal dialysis or hemodialysis for renal insufficiency or creatinine clearance (CrCL) <30 mL/min (0.50 mL/sec).
17. Unexplained creatine kinase concentration >5 × ULN or creatine kinase elevation due to known muscle disease (e.g., polymyositis, mitochondrial dysfunction) at Visit 1.

18. Any condition or therapy which, in the opinion of the investigator, might pose a risk to the patient or make participation in the study not in the patient's best interest.
19. Drug or alcohol abuse within the past 6 months, and unable/unwilling to abstain from drug abuse and excessive alcohol consumption during the study or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking). Excessive alcohol consumption is on average >2 units of alcohol per day. A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.
20. Mental/psychological impairment or any other reason to expect patient difficulty in complying with the requirements of the study or understanding the goal and potential risks of participating in the study (evaluated at Visit 1).

STUDY DESIGN AND DURATION:

This is a multi-center, multi-national, prospective, randomized, double-blind, placebo-controlled, parallel-group study.

This is an event-driven trial: It is expected that a minimum of 1612 primary efficacy endpoint events will be required during the study. Approximately 7990 patients will be randomized at multiple Research Sites worldwide over a planned period of 18 months. After randomization, patients will be treated and followed over 3.25-4.75 years with a planned median follow-up of 4 years. The study end date is determined to be when approximately 1612 primary efficacy events have occurred.

Screening Period:

During the screening period, patients will be evaluated for inclusion/exclusion criteria. Patients will be eligible for randomization if they meet all the inclusion/exclusion criteria. Prospectively, eligible patients with documented CVD or diabetes (with at least one additional risk factor for CVD) will undergo screening to establish suitability for inclusion in the trial. The qualifying lipid determination at Visit 1 requires that eligible patients must have a fasting TG level ≥200 mg/dL (2.26 mmol/L) and <500 mg/dL (5.64 mmol/L) in order to enter the treatment/follow-up period of the trial (and they need to meet all other inclusion/exclusion criteria). These patients will be randomized at Visit 2, which will occur soon after Visit 1 (there will be no Visit 1.1 for these patients).

Patients who do not qualify at Visit 1, may return to the Research Site for a second qualifying visit (Visit 1.1) at which time procedures that caused failure of eligibility at Visit 1 will be repeated. In this case, patients will be eligible for randomization after Visit 1.1 if they meet all inclusion criteria and if they no longer fail the exclusion criteria.

For some patients, Visit 1.1 will be mandatory at least 28 days after Visit 1 in order to check eligibility. These are patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications. Any of these changes at Visit 1 may affect the qualifying lipid levels and therefore, patients will need to have Visit 1.1 to determine whether they qualify based on lipid level requirements (TG and LDL-C)

determined at Visit 1. Other procedures that caused failure of eligibility at Visit 1 will also be repeated at Visit 1.1. Details are listed in the main section of the protocol.

Treatment/Follow-Up Period:

At Visit 2 (Day 0), eligible patients will be randomly assigned 1:1 to one of the following treatment groups:

- AMR101 4 g daily, or
- Placebo.

Stratification will be by CV risk category (established CVD or the presence of diabetes with ≥1 risk factor for CVD), use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries).

During the treatment/follow-up period, patients will return to the Research Site at regular intervals for efficacy and safety evaluations, and drug supply and compliance checks. The visits after the randomization visit (Visit 2; Day 0) are scheduled for 4 months after Visit 2 (for Visit 3); 8 months after Visit 3 (for Visit 4); and then every year thereafter.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Eligible patients will be randomly assigned at Visit 2 to receive orally AMR101 4 g daily or matching placebo. AMR101 is provided in 1000 mg liquid-filled, oblong, gelatin capsules. The matching placebo capsule is filled with light liquid paraffin and contains 0 mg of AMR101. AMR101 or matching placebo capsules are to be taken with food (i.e. with or at the end of a meal).

During the treatment period, the daily dose of study drug is 4 capsules per day taken as two capsules taken on two occasions per day (2 capsules given twice daily).

STATISTICAL ANALYSES:

- Intent-to-treat analysis.
- Parameters will be summarized using mean, standard deviation, median, minimum, maximum, and interquartile range for continuous data and percentage for categorical data.
- Survival analysis using the log-rank test for the primary efficacy outcome comparing the 2 treatment groups (AMR101 and Placebo) and including the stratification factors CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries).
- All statistical analyses for the efficacy and safety outcomes will be performed at the 5% significance level using 2-sided tests unless otherwise noted.
- One interim analysis is planned when approximately 60% of the planned total number of events has occurred.

The analysis is planned to:

- Describe at baseline: Patient characteristics, including lipids and lipoproteins, stroke history, cardiovascular risk factors, diabetes mellitus, or metabolic syndrome, among others.
- Compare the primary, secondary, and tertiary endpoints between treatment groups at the corresponding follow-up time points.

SAMPLE SIZE DETERMINATION:

Sample size estimation is based on the assumption that the primary composite endpoint (time from randomization to the first occurrence of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina requiring hospitalization) would be relatively reduced by 15%, from an event rate by 4 years of 23.6% in the placebo group to 20.5% in the AMR101 group. It is expected that a minimum of 1612 primary efficacy endpoint events will be required during the study. A total of approximately 6990 patients are needed to be able to detect this difference at 4.76% significance level (decreased from 5.00% because of one interim analysis) and with 90% power, assuming an 18-month enrollment period and a median follow-up of 4 years. The current sample size calculation is based on an estimated placebo yearly event rate of 5.9% (23.6% over 4 years). To protect against the possibility that the actual placebo event rate is lower than estimated, an extra 1000 patients will be enrolled (approximately 7990 patients in total). By adding the extra 1000 patients, the event rate in the placebo group could be 5.2% per year (20.8% over 4 years) without having to modify the other sample size assumptions.

Since this is an events-driven trial, the 'sample size' is the number of events rather than the number of patients. The number of events that occur depends primarily on three factors: how many patients are enrolled, the combined group event rate, and how long the patients are followed. Because of the difficulty in predicting the combined event rate, the sponsor will monitor that event rate as the trial progresses. If the combined event rate is less than anticipated, either increasing the number of patients, extending the length of follow-up, or a balance of adjusting both factors may be necessary to achieve the sample size of 1612 events.

Before completing the enrollment phase of the trial, *i.e.* approximately 3- to 6-months prior to the projected enrollment of the 7990th patient, the actual event rate based on pooled, blinded accumulation of primary efficacy endpoint events will be calculated and plotted. If those analyses suggest the number of patients with at least 1 adjudicated, primary event (and appropriately accounting for patients with potential primary events for which the adjudication process is then incomplete) is consistent with projections, then the study could continue toward the protocol-specified target enrollment of 7990 patients. However, if the number of such events appears less than, and inconsistent with projections, the Sponsor will consider (under blinded conditions) re-calculating the number of patients needed to achieve the target number of events within the desired timeline or extend the follow-up period. If the projected increase in number of patients is ≤ 25% of the original 7990 target population, the Sponsor may, with documented approval of both the REDUCE-IT Steering Committee and the Data Monitoring Committee, extend enrollment to the revised target number without

need for an additional protocol amendment. Under those conditions, all principal investigators, ethics committees, and regulatory authorities associated with the protocol will be promptly notified of the action. Should the projected increase in number of patients be more than 25% above the original 7990 target (*i.e.* more than 1998 additional patients) a formal protocol amendment will be initiated.

If the number of patients to be studied is increased, the enrollment phase will be extended to allow enrollment of the additional patients.

At completion of study enrollment, the actual number of patients randomized may vary from the target number (either original or revised) as a result of the inherent lag between the date the last patient started screening and the date the last patient was randomized.

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AA	Arachidonic acid
ABI	Ankle-brachial index
ACC	American College of Cardiology
ACS	Acute coronary syndrome
AHA	American Heart Association
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AP	Angina pectoris
apo B	Apolipoprotein B
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CABG	Coronary Artery Bypass Graft
CAD	Coronary artery disease
CBC	Complete blood count
CEC	Clinical Event Committee
CI	Confidence interval
CHD	Coronary heart disease
CHF	Congestive heart failure
CK-MB	Creatine kinase-MB fraction
CrCL	Creatinine clearance
CNS	Central nervous system
CRF	Case Report Form
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
%CV	Percent coefficient of variation
DART	Diet and Reinfarction Trial
DCCT	Diabetes Control and Complications Trial
DHA	Docosahexaenoic acid
DMC	Data Monitoring Committee
EDC	Electronic data capture
ECG	Electrocardiogram
EPA	Eicosapentaenoic acid
Ethyl-EPA	Ethyl icosapentaenoate; icosapent ethyl
FSH	Follicle-stimulating hormone
GC/FID	Gas chromatograph with flame ionization detector
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
Hct	Hematocrit

HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
hs-CRP	High-sensitivity C-reactive protein
hsTnT	High-sensitivity troponin T
HR	Hazard ratio
ICAM-1	Intercellular adhesion molecule-1
ICF	Informed consent form
ICH	International Conference on Harmonization
EC	Independent Ethics Committee
IFCC	International Federation of Clinical Chemistry
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWR	Interactive Web Response
JELIS	Japan Eicosapentaenoic Acid Lipid Intervention Study
LBBB	Left bundle branch block
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LDL-C	Low-density lipoprotein cholesterol
MACE	Major adverse coronary event
MI	Myocardial infarction
NCEP	National Cholesterol Education Program
NGSP	National Glycohemoglobin Standardization Program
NMR	Nuclear magnetic resonance
NO	Nitric oxide
NSTE-ACS	Non-ST-Segment Elevation Acute Coronary Syndrome
O3FA	Omega-3 fatty acid
OGTT	Oral Glucose Tolerance Test
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PH	Proportional hazard
PI	Principal Investigator
PP	Per protocol
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
PTCA	Percutaneous transluminal coronary angioplasty
RBC	Red blood cells
RR	Relative risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCD	Sudden cardiac death
SD	Standard deviation
SOC	Study Operations Committee
SPC	Summary of Product Characteristics
ST	Steering committee
SUSAR	Suspected Unexpected Serious Adverse Reaction

$T_{1/2}$	Half-life
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TIMI	Thrombolysis In Myocardial Infarction
T_{max}	Time of maximum concentration
ULN	Upper limit of normal
USPI	United States Prescribing Information
VCAM-1	Vascular cell adhesion molecule-1
VF	Ventricular fibrillation
WBC	White cell blood count

1. INTRODUCTION AND BACKGROUND INFORMATION

AMR101 (icosapent ethyl [ethyl-EPA]) is a highly purified ethyl ester of eicosapentaenoic acid (EPA) derived from fish oil, and is being developed by Amarin Pharma Inc. (hereafter referred to as Amarin or the Sponsor) for the treatment of hypertriglyceridemia. The purpose of this study is to evaluate whether the triglyceride-lowering drug AMR101, combined with a statin therapy, will be superior to the statin therapy alone, when used as a prevention in reducing long-term clinical events in patients with mixed dyslipidemia at high risk for cardiovascular (CV) events.

1.1. Background

Since the initial observation of a link between fish oil consumption and the reduced incidence of coronary heart disease in the Eskimos of Greenland (Bang 1972), a large body of evidence has accumulated showing that regular intake of omega-3 fatty acids (O3FAs) exerts cardioprotective effects in both primary and secondary coronary heart disease prevention (Harris 2008, Lee 2008). Several mechanisms have been proposed to account for these beneficial effects, including the reduction of triglycerides (TG), suppression of cardiac arrhythmias, decreased platelet aggregation, improved plaque composition and stabilization, and hemodynamic changes. This mounting body of evidence has led the American Heart Association (AHA) to recommend the consumption of O3FAs in dietary fish or in capsule form at a dose of 1 g/day for secondary prevention of cardiovascular disease (CVD) (Kris-Etherton 2002). This recommendation has now been included in American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the long-term management of patients with stable angina and acute coronary syndromes (Antman 2004, Fraker 2007, Anderson 2007).

A large number of studies have also demonstrated the triglyceride-lowering effects of O3FAs (Harris 1997, Ginsberg 2001). The US FDA has approved a product containing approximately 90% esters of the O3FAs EPA and DHA for use at a dose of 4 g/day as an adjunct to diet for the treatment of patients with very high triglyceride levels (≥500 mg/dL) (Lovaza® USPI 2009). The same medicinal product under the name Omacor® (Omacor SPC 2008) is approved in Europe for the treatment of endogenous hypertriglyceridemia at a dose of up to 4 grams daily as a supplement to diet when dietary measures alone are insufficient to produce an adequate response. Omacor® at a dose of 1 gram daily is also approved in key European and certain Asian markets for the secondary prevention of myocardial infarction (Post-MI).

Epadel® capsules, which contain highly purified (>95%) ethyl-EPA, have been marketed by Mochida in Japan since 1991 for the treatment of arteriosclerosis obliterans and since 1994 for the treatment of hyperlipidemia (Epadel SPC 2007). The recommended dose is 1.8 g/day for arteriosclerosis obliterans and 1.8 to 2.7 g/day for hyperlipidemia. Hypertriglyceridemia is a feature of many dyslipidemias and often occurs in persons who are obese and/or have Type 2 diabetes mellitus in isolation or as a component of the metabolic syndrome (Jacobson 2007, Bays 2008).

Elevation in TG confers dual risks of acute pancreatitis (most marked in patients with severe hypertriglyceridemia [TG >1500 mg/dL]) (Yadav 2003) and accelerated atherosclerosis leading to CV events, the latter even after correction for other lipid and non-lipid risk factors

(Jacobson 2007). With this in mind, Amarin is assessing the potential of AMR101 capsules, which contain highly purified icosapent ethyl (ethyl-EPA), for the treatment of patients, as an adjunct to diet, with very high TG levels (≥500 mg/dL) and those with high TG levels (≥200 and <500 mg/dL) despite optimal statin therapy. Amarin-sponsored studies with AMR101 in patients with very high TGs (Study AMR-01-01-0016, the MARINE study) and in patients with high TGs on statins (Study AMR-01-01-0017, the ANCHOR study) are in progress.

1.2. Summary of Amarin-Sponsored Clinical Studies with AMR101

To date, Amarin has completed 8 double-blind, placebo-controlled clinical trials with AMR101 in patients with CNS disorders including Huntington's disease, depression, schizophrenia and age-associated memory impairment. Males and females were almost equally represented. The majority of patients were Caucasian, but the studies also included, among the patients receiving AMR101, 14 Blacks, 6 Asians and 11 patients of another race.

The patients received 0.5-4 g/day AMR101 or placebo. The duration of the double-blind treatment period ranged from 6 weeks to 1 year. In addition, 24 healthy volunteers have received AMR101 2 g/day for up to 28 days in a pharmacokinetic study (LA01.01.0009). In these studies, AMR101 was administered in the form of 500-mg soft gelatin capsules, orally with meals as a twice-daily regimen with half of the daily dose in the morning and half in the evening.

Across all 9 completed Amarin-sponsored studies (1 in healthy volunteers and 8 in patients), a total of 1243 patients were randomized (24 healthy volunteers and 1219 patients with CNS disorders). From the 1243 patients, 724 (24 healthy patients and 700 patients) were randomized to receive AMR101 and 519 to receive placebo. See the Investigator's Brochure for more information.

In 4 of the Amarin-sponsored studies in patients with CNS disorders, patients who completed the double-blind period were rolled-over into an open-label extension phase and received 1-2 g/day AMR101 (most received 2 g/day). The treatment period in the open-label extensions ranged from 6 months to 1 year. Across all studies, including patients from the double-blind periods receiving AMR101 and also those switched from placebo to AMR101 in the open-label extensions, a total of 1071 patients have been exposed to ethyl-EPA from AMR101 capsules.

In addition, two Phase 3 studies in patients with hypertriglyceridemia have been completed. These trials have investigated the efficacy of AMR101 in lowering triglycerides:

- Study AMR-01-01-0016 (the MARINE study) in 229 patients with very high triglycerides (>500 mg/dL).
- Study AMR-01-01-0017 (the ANCHOR study) in approximately 702 patients with mixed dyslipidemia (high triglycerides: ≥200 to <500 mg/dL) who are taking statins

1.3. Study AMR-01-01-0017 (ANCHOR Study)

The results from the ANCHOR study are particularly relevant for the dose selection of the present study since the ANCHOR study was conducted in a very similar patient population. The primary objective in the ANCHOR study was to determine the efficacy of AMR101 2 g

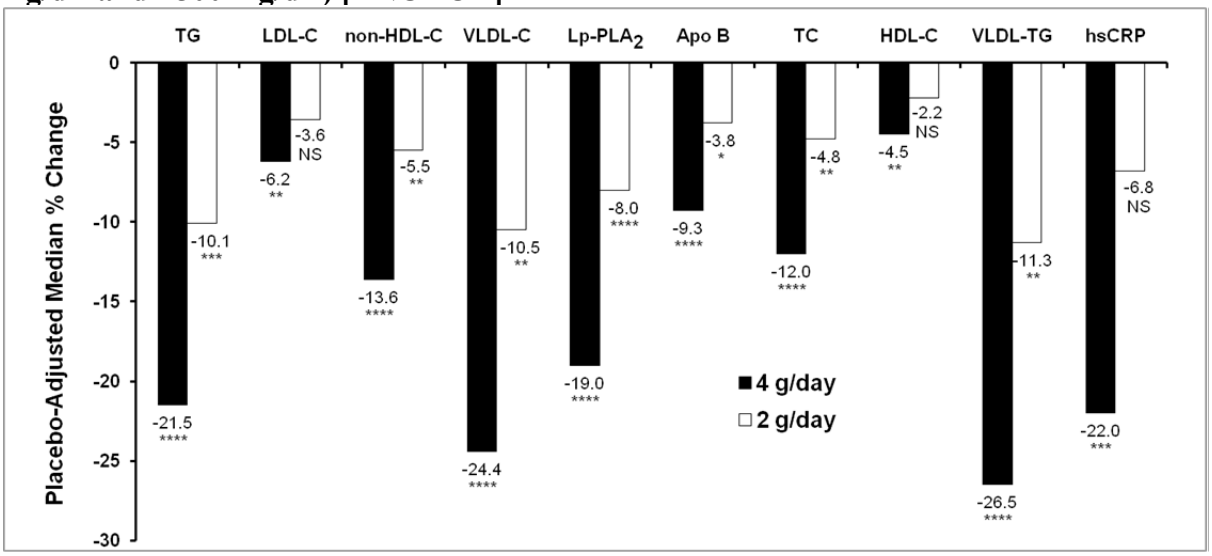
daily and 4 g daily, compared to placebo, in lowering fasting TG levels in patients with high risk for cardiovascular disease (CVD) and fasting TG levels ≥200 mg/dL and <500 mg/dL, despite treatment to low density lipoprotein cholesterol (LDL-C) goal (>40 mg/dL and <100 mg/dL) on statin therapy.

After a 6- to 8-week screening period which included diet and lifestyle stabilization, a washout period for excluded non-statin lipid-altering medications (if needed), and a TG qualifying period, patients were randomized to one of 3 treatment groups and received study medication during a 12-week, double-blind treatment period. Patients had to be treated with one of 3 statins (simvastatin, atorvastatin or rosuvastatin) to reach their LDL-C goal of 100 mg/dL (+15% allowed for variability) and had to be on a stable dose for a minimum period of 4 weeks before the TG qualifying measurements. The TG target for enrollment was for patients to have qualifying fasting TG levels of ≥200 mg/dL and <500 mg/dL based on the mean of 2 measurements. During the 12-week double-blind treatment period, patients received orally AMR101 2 g/day, AMR101 4 g/day, or placebo.

Patients were randomized to either 2 or 4 g/day of AMR101 or placebo for 12 weeks. The primary endpoint was the reduction in triglyceride levels compared to placebo. Secondary endpoints were percent change in LDL-C compared to placebo, non-HDL-C, apoB, $LpPLA_2$, and VLDL-C.

The median placebo-adjusted changes in the major lipid parameters for the groups receiving statin plus AMR101 are shown in Figure 1.

Figure 1. Median Placebo-Adjusted Baseline and Percent Change from Baseline in Lipid Parameters in 687 Patients (ITT population) with High Triglyceride Levels (≥200 mg/dL and <500 mg/dL) [ANCHOR]



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

Median Baseline TG: 259 (placebo, N=227), 265 (4 g/day, N=226), 254 (2 g/day, N=234) mg/dL
Median Baseline LDL-C: 84 (placebo, N=226), 82 (4 g/day, N=225), 82 (2 g/day, N=233) mg/dL
Median Baseline non-HDL-C: 128 mg/dL for all treatment groups.
Median Baseline apoB: 91 (placebo, n=219), 93 (4 g/day, n=217), 91 (2 g/day, n=227) mg/dL
Medians are Hodges-Lehmann medians; p-values are from the Wilcoxon rank-sum test.

Apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein; ITT=intent to treat; LDL-C = low-density lipoprotein cholesterol; Lp-PLA_2 = lipoprotein-associated phospholipase A_2; non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; VLDL-C = very low density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides.

AMR101 4g/day reduced median placebo-adjusted triglyceride levels by 13.1% (p=0.5467) in the lowest statin potency regimen (simvastatin 5-10 mg/day); by 20.1% (p<0.0001) in the medium potency statin regimen (rosuvastatin 5-10 mg, atorvastatin 10-20 mg, simvastatin 20-40 mg, simvastatin 10-20 mg + ezetimibe 5-10 mg); and by 26% (p<0.0001) in the highest statin potency regimen (rosuvastatin 20-40 mg, atorvastatin 40-80 mg, simvastatin 80 mg or simvastatin with ezetimibe 5-10 mg). The statin potency regimens were pre-defined.

Of the 702 patients with high triglycerides enrolled in this study, 514 had diabetes mellitus. Efficacy results in patients with diabetes were similar to those of the non-diabetics, and no significant changes in fasting plasma glucose or HbA_{1c} with AMR101 *vs*. placebo were observed.

The reduction in triglycerides observed with AMR101 was also associated with a placebo-adjusted decrease in median LDL-C levels at both doses. Median baseline LDL-C levels were 82.0 mg/dL (4 g/day), 82.0 mg/dL (2 g/day), and 84.0 mg/dL (placebo). AMR101 4 g/day decreased median placebo-adjusted LDL-C by 6.2% (p=0.0067) which was superior to placebo, based on a pre-specified +6% margin.

1.4. Clinical Safety

In the MARINE and ANCHOR trials, a total of 622 patients have been exposed to ethyl-EPA from AMR101 capsules. AMR101 has been well tolerated (with incidence of adverse events similar to placebo) and there have been no major safety concerns. See the Investigator's Brochure for more information.

The types (by preferred term) of common treatment-emergent adverse events (TEAEs) and their incidence in the MARINE and ANCHOR trials are listed in Table 1.

Table 1. Adverse Reactions Occurring at Incidence >2% and Greater than Placebo in Double-Blind, Placebo-Controlled Trials*

Adverse Reaction	Placebo (N=309)		AMR101 (N=622)	
	N	%	N	%
Arthralgia	3	1.0	14	2.3

*Studies included patients with triglycerides values of 200 to 2000 mg/dL.

An additional adverse reaction from clinical studies was oropharyngeal pain.

Source: Vascepa PI, Table 1

In a large study with Japanese patients (Japan EPA Lipid Intervention Study [JELIS]), long-term administration of 1.8 g/day ethyl-EPA (Epadel®) was associated with an excellent safety and tolerability profile (Yokoyama 2007). Most AEs attributable to ethyl-EPA were regarded as mild. The most common adverse events were gastro-intestinal (nausea, diarrhea, epigastric discomfort) or dermatologic (eruption, itching, exanthema, eczema) in nature.

1.5. Rationale

Hypothesis

The hypothesis is that combination anti-dyslipidemic therapy of a LDL-C lowering drug (statin therapy) with the triglyceride-lowering drug AMR101 will be superior to the LDL-C lowering therapy alone when used as prevention in reducing long-term clinical events in patients with mixed dyslipidemia at high risk for cardiovascular events.

TG-Lowering as a Therapeutic CV Target

Studies have shown that elevated levels of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are associated with increased risk of coronary heart disease (CHD) (LaRosa 2003), and therapeutic strategies that lead to a statistically significant reduction in LDL-C lower CHD event rates (Baigent 2005). One potential impediment, limiting further reduction in CHD events despite low on-treatment LDL-C, is residual elevation in serum TG levels (Miller 2000). Indeed, even after adjustment for HDL-C, detailed evaluation of population-based prospective studies has disclosed an independent effect of TG on CHD events (Sarwar 2007). Coupled with the knowledge that combined hyperlipidemia (i.e., elevated LDL-C and TG) promotes CHD to a significantly greater extent than either high LDL-C or TG alone (Manninen 1992), the hypothesis is strong that low on-treatment levels of TG when added to low LDL-C would be superior to low LDL-C alone in reducing subsequent CHD events. Supporting evidence for this hypothesis was obtained in a post hoc analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In

Myocardial Infarction 22 Trial (PROVE IT-TIMI 22) (Miller 2008) wherein among patients receiving statin therapy after acute coronary syndrome (ACS), on treatment TG <150 mg/dL was associated with a lower risk of recurrent CHD events independently of the level of LDL-C. For each 10% lowering of TG attained during the first 30 days of treatment after an ACS event, the risk for death, myocardial infarction, or recurrent acute coronary syndrome was reduced by 2.3% (p =0.035) after adjustment for high LDL-C (>70 mg/dL) and HDL-C (<40 and 50 mg/dL in men and women, respectively).

Omega-3 Fatty Acids in Fish Oils

There is a growing body of evidence, encompassing molecular, cellular, animal and human studies defining the roles for O3FAs as bioactive agents for reducing the risks of and treating CVD (Torrejon 2007). Many epidemiological studies have demonstrated inverse associations between fish intake and CV mortality, and more specifically between the intake and blood levels of O3FAs and CV mortality. For example, when comparing blood levels of O3FAs among men who had died of sudden cardiac death with controls matched for age and smoking status, it was found that participants with the highest blood levels of EPA and DHA had a 90% risk reduction for sudden cardiac death compared with those with the lowest levels (Albert 2002).

Clinical trials and experimental studies, suggest important antiatherogenic and antithrombotic effects of O3FAs. These result from wide-ranging biological effects, including benefits on lipoprotein metabolism, blood pressure, endothelial function and vascular reactivity, inflammation, platelet and fibrinolytic function, cytokine production, coagulation and oxidative stress (Mori and Woodman 2006). Evidence suggests that increased consumption of O3FAs from fish or fish-oil supplements reduces the rates of all-cause mortality, cardiac and sudden death, and possibly stroke (Wang 2006). The effect was evident in both primary-prevention (general population without a history of CVD) and secondary-prevention (patients with a history of CVD) studies with a stronger effect in secondary prevention.

The Diet and Reinfarction Trial (DART) was one of the first randomized, controlled studies to demonstrate the beneficial effects of O3FAs in secondary prevention of CHD and reported a 29% reduction in all-cause mortality over a 2-year period in 2033 male MI survivors advised to increase their intake of oily fish (200 to 400 g of fatty fish per week, which provided 500 to 800 mg/day of O3FAs) (Burr 1989). While not statistically significant, there was also a trend toward a reduction in recurrent ischemic heart disease events with increased fatty fish consumption. A post hoc analysis of patients receiving fish oil capsules (900 mg/day of EPA+DHA) in DART suggested that the protective effect was attributable to O3FAs (Burr 1994). The greatest benefit was seen in fatal MIs, and this observation led to the hypothesis that O3FAs might protect the myocardium against the adverse sequela of acute ischemic stress.

A cardioprotective effect for O3FAs derived from fish oil is supported by prospective studies demonstrating inverse associations between fish intake and coronary heart disease mortality, especially amongst high-risk individuals (Mori and Woodman 2006). Early separation of survival curves in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione study (GISSI-Prevenzione Investigators 1999) and the DART trial support a reduction in ventricular fibrillation and a decreased incidence of

myocardial infarction (Leaf 1996) as the primary mechanisms through which O3FAs prevent CVD (Mori and Woodman 2006).

Many international bodies including the AHA, American College of Cardiology, and the European Society of Cardiology have found the overall evidence for benefit sufficiently strong to make public recommendations for increased O3FA intake for both primary and secondary prevention (Harris 2007).

Omega-3 Fatty Acid Ethyl Esters

The largest prospective, randomized, controlled trial to test the efficacy of O3FAs for secondary prevention of CHD is the GISSI study (GISSI-Prevenzione Investigators 1999). In this study, 11,324 patients with preexisting CHD (experienced an MI and were receiving conventional cardiac pharmacotherapy) were randomized to either 300 mg of vitamin E, 850 mg of O3FA ethyl esters (as EPA and DHA), both, or neither. After 3.5 years of follow-up, the group given the O3FAs alone experienced a 15% reduction in the primary end point of death, nonfatal MI, and nonfatal stroke ($p < 0.02$). There was a 20% reduction in all-cause mortality ($p = 0.01$) and a 45% reduction in sudden death ($p < 0.001$) compared with the control group; vitamin E provided no additional benefit. Triglycerides decreased by 4% and LDL cholesterol levels increased by 2.5% after six months in the O3FA treatment groups compared with controls. This trial, although very large and carried out in a relatively "usual-care" setting, was not placebo controlled, and dropout rates were high (>25%). A follow-up study (Marchioli 2002) assessed the time-course of the benefit of O3FAs on mortality in subjects in the GISSI-P Study and found that survival curves diverged early after randomization. Total mortality was significantly lowered by 28% after 3 months of treatment (RR =0.59), and by 4 months, the risk of sudden cardiac death was reduced by 45% (RR =0.47).

Ethyl-EPA

In another larger trial, the Japan EPA Lipid Intervention Study (JELIS), 18,645 patients with hypercholesterolemia (70% women; mean age, 61 years) were randomly assigned to either statin alone or statin and pure ethyl-EPA (1.8 g/day). Of all patients, 15,000 patients (80%) were without existing CAD and 3,645 (20%) with existing CAD (Matsuzaki 2009). The primary endpoint was any major adverse coronary event (MACE including SCD, fatal and nonfatal MI, and other nonfatal events including unstable angina pectoris (determined to be caused by myocardial ischemia by invasive/non-invasive testing), angioplasty, stenting, and coronary artery bypass grafting).

In the overall analysis (Yokoyama 2007), during the 4.6-year follow-up, ethyl-EPA reduced major adverse coronary events by 19% ($p = 0.011$). EPA treatment was also associated with a significant 24% reduction in the incidence of unstable angina and a 19% decrease in nonfatal coronary events. This treatment also produced nonsignificant reductions of 21%, 25%, and 14% in fatal MI, nonfatal MI, and revascularizations, respectively.

In a subgroup analysis of primary prevention cases, compared to patients with normal serum TG and HDL-C levels, those with abnormal levels (TG ≥150 mg/dL; HDL-C <40 mg/dL) had a significantly higher major adverse coronary event (MACE) rate by 71% ($p=0.014$). In this higher risk group, ethyl-EPA treatment suppressed the MACE risk by 53% ($p=0.043$) (Saito 2008).

While there was no significant difference in the incidence of first stroke between ethyl-EPA and control groups, the incidence of stroke recurrence was significantly lower in the EPA group at 6.8% versus the control group at 10.5%, a reduction of 20% ($p<0.05$; Tanaka 2008). Further, while there was no difference in the incidence of recurrent hemorrhagic cerebral events between the two groups, ethyl-EPA was effective in reducing the recurrence of ischemic cerebral vascular events such as cerebral infarction (Harris 2009).

O3FA supplementation lowered CV risk in both the GISSI-Prevenzione study and JELIS, despite aggressive therapy with standard pharmacotherapy (e.g., statins, aspirin, β-blockers and angiotensin-converting enzyme inhibitors). Additionally, the JELIS trial established the safety and efficacy of combination therapy with ethyl-EPA and a statin vs statin therapy alone for improving CV prognosis. The JELIS trial was conducted with Epadel that contains the same active ingredient, ethyl-EPA, as AMR101. Ethyl-EPA was shown in the JELIS study to reduce CAD events even in a Japanese population with very high intakes of O3FAs due to the high fish consumption. The evidence supporting a benefit in primary prevention comes from an observed 18% decrease in CV events in the 80% of patients in the JELIS trial without documented CAD ($p =0.13$); this effect size was essentially the same as that observed in the secondary prevention cohort (19%, $p <0.05$) (Lee 2008).

Medical Need

CVD resulting from progressive atherosclerosis remains the most common cause of morbidity and mortality all over the world. Based on 2006 US statistics (American Heart Association 2010), an estimated 81 million American adults (more than one in three) have one or more types of CVD. Of these, 38 million are estimated to be age 60 or older. Total CVD includes coronary heart disease (CHD): 17.6 million, heart failure (HF): 5.8 million and stroke: 6.4 million. CHD further divided includes myocardial infarction (MI): 8.5 million, and angina pectoris (AP): 10.2 million. Final mortality data show that CVD as the underlying cause of death accounted for 34.4% of all deaths (about 830,000 of all 2.4 million deaths in 2006). CHD is the leading cause of death in all Western industrialized countries, despite considerable improvement since the mid-1960s. In developing countries, the incidence of CVD is increasing alarmingly. In addition to death, CVD also causes many serious non-fatal events and is the major cause of disability. Therefore, additional therapies for prevention of CVD would have a considerable public health benefit.

A large number of studies have demonstrated the TG-lowering effects of O3FAs (Ginsberg 2001; Harris 1997). Hypertriglyceridemia is a common lipid abnormality and often occurs in persons who are obese and have insulin resistance, Type 2 diabetes mellitus, or the metabolic syndrome (Jacobson 2007; Bays 2008). Elevation in TG is positively associated with accelerated atherosclerosis leading to CV events, the latter even after correction for other lipid and non-lipid risk factors (Jacobson 2007). In the US (American Heart Association 2010), the mean TG level for American adults age 18 and older is 144.2 mg/dL (men, 156.5 mg/dL; women, 132.1 mg/dL).

Lifestyle modification is important for the management of patients with hypertriglyceridemia; however, for patients who do not adequately respond to dietary and lifestyle restrictions, relatively few classes of drugs are available to treat hypertriglyceridemia, and each is associated with risks that may limit their use alone or in combination. Currently available pharmacological treatments for hypertriglyceridemia

include fibric acid derivatives (such as gemfibrozil and fenofibrate), niacin in various formulations, prescription omega-3-acid ethyl esters (Lovaza/Omacor) and statins (3 hydroxy 3 methylglutaryl coenzyme A reductase inhibitors).

Although the above agents have robust TG-lowering effects in patients with hypertriglyceridemia, the degree of TG-lowering is highly variable; generally greater TG-lowering effects are observed for fibrates and niacin compared with statins. Many patients will be satisfactorily treated with one or more of the above range of drugs (combined with appropriate diet and attention to other CV risk factors and lifestyle).

Lovaza, comprised predominantly of ethyl-EPA and the ethyl ester of docosahexaenoic acid (ethyl-DHA), is indicated only in patients with very high TG levels (>500 mg/dL), raises LDL-C even when combined with statins in patients with high TGs (200-499 mg/dL), and is approved at 4 g/day (equivalent to 4 capsules/day) resulting in poor patient compliance. A non-compliance rate of 35% was reported in one clinical trial (Leaf 2005).

Fibrates are clearly effective at raising HDL-C and lowering TG concentrations. However, their effects on vascular events remain uncertain. Several large-scale trials of fibrate therapy have been completed in the past few years. Although some of these trials have suggested benefit, others have shown no effect, leading to uncertainty about the presence and magnitude of any cardiovascular protective effects and difficulties for clinicians in interpretation of the results (Jun 2010). The ACCORD study (Ginsberg 2010) reported no overall benefit for fenofibrate, raising further questions about the usefulness of these agents.

There are also safety issues with the above agents that limit their clinical use. Statins, particularly at high doses, may cause increases in hepatic transaminases and are also known to cause myopathy and occasionally rhabdomyolysis, which may lead to death from acute renal failure. This risk may be increased when fibrates and statins are co-administered and many clinicians will avoid co-prescribing these 2 medications. Fibrates are also associated with interactions with warfarin and hepatic transaminase elevations. The utility of niacin is limited by the occurrence of severe flushing and associated symptoms which can be difficult to manage even with careful dose titration and pre administration of aspirin or other non-steroidal anti-inflammatory drugs. Niacin is also associated with impairment of glucose tolerance and precipitation of attacks of gout in susceptible patients.

The DYSlipidemia International Study (DYSIS) assessed the prevalence of dyslipidemia among patients taking statins. This epidemiological observational study included more than 22,000 patients in Europe and Canada aged 45 and older who received statin therapy for at least three months, and had a clinical diagnosis of coronary or other atherosclerotic disease, or were at high risk of developing CVD. The study found 48% of patients had LDL-C not at goal; 26% had low HDL-C levels; and 38% had elevated triglycerides. This study demonstrates that persistent dyslipidemia is highly prevalent in statin-treated patients.

Patients with dyslipidemia, particularly those with established CVD or diabetes, have therapeutic needs that cannot be met by statin monotherapy. It is hypothesized that achieving target values for LDL-C/non-HDL-C in these patients using a therapeutic approach of the combination of AMR101 and a statin will benefit these patients. Such a combination therapy might increase the likelihood of therapeutic success in these patients with regards to future risk of CVD, based on meeting of both LDL-C/non-HDL-C goals and TG goals according to the ACC/AHA guidelines (Anderson 2007). Approximately 40 million Americans have high

TG levels (>200 mg/dL), however only a minority (3.6%) are currently treated with prescription medication (Ford 2009). Patients with elevated TGs are currently under-served and would benefit from a new, safe and effective product that can provide the following attributes:

- Robust efficacy to lower TGs
- Safe to use with other lipid-lowering agents, including statins
- Does not increase LDL-C when used in patients on statin therapy (TG = 200-499 mg/dL)
- Has convenient dosing regimen
- Has class-specific positive outcomes data

Pleiotropic Effects

There is ample evidence that O3FAs decrease TGs in patients with hypertriglyceridemia which is a beneficial effect related to the fact that elevated TGs have been identified as an independent risk factor for CVD. Lowering TGs in patients with hypertriglyceridemia would lead to a slowing of the development of atherosclerosis. However O3FAs including EPA have a wide range of additional pharmacological effects that most likely contribute to a beneficial effect in patients with CVD.

Beneficial effects in clinical trials have been attributed in part to reducing arrhythmias (Lee 2003; Goel 2002; Calo 2005). The case for an antiarrhythmic effect of O3FAs comes from clinical trials and from animal studies. Clinical trials have shown that the risk of sudden death in patients who have survived myocardial infarction is greatly reduced by inclusion of O3FAs in the diet (Siscovick 2000). Thus it seems that fatal ventricular fibrillation is less likely to occur during sufficient intake of O3FAs. Animal studies support this. Coronary ligation studies in a variety of species (rats, dogs and marmosets) have shown that the incidence of ventricular fibrillation is lower in animals fed a diet rich in O3FAs before ligation (McLennan 1992; Leaf 1996). In isolated cells, the story is similar (Li 1997, Engler 2000; Omura 2001). In neonatal rat cardiac myocytes, EPA prevents the arrhythmogenic action of many interventions, including high external Ca^{2+} and ouabain (Kang 1994). The antiarrhythmic effect is caused by a reduction in electrical excitability caused by partitioning O3FAs into the phospholipid cell membranes of the cardiac myocytes, which modulates membrane ion channels. This is the postulated direct mechanism that refers to the antiarrhythmic effect of O3FAs which inhibits the fast, voltage-dependent sodium current along with the L-type calcium currents. This reduces the action potential of cardiac myocytes, reducing the susceptibility to arrhythmia. These cellular alterations are likely to reduce the severity of ventricular arrhythmias by inhibiting the rapid accumulation of intracellular Ca^{2+} following ischemia. It was also shown in patients with coronary artery disease that long-term treatment with EPA augments both NO-mediated and non-NO-mediated endothelium-dependent forearm vasodilatation (Tagawa 1999).

Another, indirect mechanism refers to the effect of O3FAs on cardiac arrhythmias by modifying the balance of different eicosanoids which are produced as end-products from chain elongation of their parent polyunsaturated fatty acids (Nair 1997). Most investigations of the link between O3FAs and heart disease have demonstrated the competition between AA

and O3FAs to become substrates in the production of eicosanoids. O3FAs compete with AA in several ways, but EPA in particular competes with AA as the substrate for the cyclooxygenase enzyme inhibiting the production of thromboxane A_2 (TXA_2) and in endothelial cells, prostaglandin I_3 (PGI_3) is synthesized from EPA (Nair 1997). The net result of these actions is vasodilatation. A reduced ratio of AA/EPA shifts the spectrum of eicosanoid production toward an increase in thromboxane A_3 (TXA_3) and PGI_3 at the expense of TXA_2 and PGI_2, respectively. This shift was found to reduce the risk of ventricular fibrillation (VF) and sudden cardiac death (SCD) (Coker 1982). Excessive production of eicosanoids derived from omega-6 fatty acids have been associated with heart attacks, thrombotic stroke, and arrhythmia, while those from O3FAs are antiarrhythmic.

Probably one of the most important pharmacologic properties of EPA is its anti-inflammatory and immune-modulating activity (Calder 2006; Calder 2010). Because of the inflammatory events underlying plaque rupture, the variety of anti-inflammatory effects of O3FAs may be of relevance to atherosclerosis and its clinical manifestations of myocardial infarction, sudden death, and stroke (Mori 2004; Thies 2003). A randomized controlled study, in patients awaiting surgery to remove atherosclerotic plaques in the carotid artery, has shown that an anti-inflammatory response might be involved, by demonstrating an association between the intake of O3FAs as a supplement (1.4 g/day) and the stability of atherosclerotic plaques (Thies 2003). This improved stability was achieved by incorporation of the O3FAs into the plaque.

The omega-6 fatty acid AA gives rise to eicosanoid mediators that have established roles in inflammation and AA metabolism is a long recognized target for commonly used anti-inflammatory therapies. O3FAs are incorporated into inflammatory cell phospholipids in a time- and dose-dependent manner. They are incorporated partly at the expense of AA, but also other omega-6 fatty acids. EPA and DHA inhibit AA metabolism. Thus production of AA-derived eicosanoids is decreased by these O3FAs. EPA gives rise to an alternative family of eicosanoids (e.g. PGE_3), which frequently have lower anti-inflammatory potency than those produced from AA, and to resolvins (E- and D-series) which have potent anti-inflammatory and inflammation resolving properties (Serhan 2006; Dona 2008). The plasma AA/EPA ratio has been used as a marker of the inflammatory status in patients with CVD (Rupp 2004; Holub 2009). In favor of the concept that less pro-inflammatory processes can be observed already at lower AA/EPA ratios is the finding that 1.4 g/day ethyl-EPA reduced the incidence of plaque rupture (Thies 2003). The AA/EPA ratio had a strong relationship with the incidence of CV events such as MACE in patients undergoing elective PCI (Domei 2009).

In addition to modifying the profile of lipid-derived mediators, O3FAs can also influence peptide mediator (i.e. cytokine) production. Pro-inflammatory cytokines, or cytokines reflecting inflammatory processes, e.g. IL-1beta, IL-2, IL-6, TNFalpha, platelet-derived growth factor (PDGF)-A and -B and monocyte chemoattractant protein-1 (MCP-1), are reduced by EPA and DHA in human subjects (von Schacky 2007), and soluble cytokines reflecting interactions between blood cells and the vessel wall, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) (Yamada 2008).

EPA and DHA intake also resulted in a decreased expression of genes involved in inflammatory- and atherogenic-related pathways, such as nuclear transcription factor κB

signaling, eicosanoid synthesis, scavenger receptor activity, adipogenesis, and hypoxia signaling (Bouwens 2009).

In conclusion, the pleiotropic effects of EPA may contribute to the overall beneficial effects on the risk of CVD, in addition to the TG-lowering effect. Therefore, it is possible that the efficacious dose of EPA that decreases the CV event rate is lower than the dose needed to exert the maximum TG-lowering effect, and/or that a modest decrease of TGs after EPA treatment could still lead to a significant decrease in the risk for CVD.

Dose Selection

This trial will be conducted with a dose of AMR101 of 4 g/day (4 capsules/day).

To date, only one study was published investigating the effects of combination treatment with an O3FA plus statins on clinical cardiovascular events. This is the Japan EPA Lipid Intervention Study (JELIS) (Yokoyama 2007), as previously discussed, wherein ethyl-EPA combined with low-dose pravastatin or simvastatin compared with statin therapy alone reduced major coronary events without altering rates of sudden cardiac death. These effects were achieved without any significant changes in total, LDL- or HDL-C and a statistically significant ($p < 0.0001$) decrease in triglycerides, suggesting that EPA can lower CVD risk by mechanisms other than LDL-C lowering (Yokoyama 2007). In a subanalysis of this study, the addition of ethyl-EPA to pravastatin or simvastatin reduced also the incidence of coronary heart disease events in high-risk patients with metabolic syndrome and atherogenic dyslipidemia characterized by high triglycerides and low HDL-C (Saito 2008). The JELIS study was performed in a large patient population wherein an ethyl-EPA dose of 1.8 g/day translated to significant benefits on CV events.

In the ANCHOR study (Amarin-sponsored), both the 2 and 4 g/day dosing regimens of AMR101 resulted in statistically significant reductions of TGs (see Section 1.3). However, since the 4 g/day dose caused a larger reduction in TG and other lipid, lipoprotein and inflammatory markers, the AMR101 4 g/day dose was selected for the present study.

1.6. Risk/Benefit

Across all completed Amarin-sponsored studies, the proportion of patients (based on the safety population from the randomized, double-blind periods of the studies) experiencing any adverse events was similar for patients on placebo (light paraffin oil) and patients on AMR101 (57.1% and 57.4% for placebo and AMR101, respectively). The proportion of patients experiencing a serious adverse event (SAE) was also similar for both treatment groups (5.2% and 6.0% for placebo and AMR101, respectively). The safety profile in the open-label extensions was similar to that observed in the double-blind treatment periods. There were no SAEs attributed to AMR101 during the open-label extension periods of the studies.

In summary, AMR101 is very well tolerated at daily doses up to 4 g. The side effects reported by the patients taking AMR101 were generally similar to those reported by the patients taking placebo. Ethyl-EPA is a pro-drug, and is rapidly and completely hydrolyzed to EPA. EPA is a natural substance found universally as a component of all cell membranes. It is classified as an essential fatty acid. Because of the nature of EPA, as an essential component of normal tissue and its part in normal metabolism, human studies have demonstrated that it is safe. See the Investigator's Brochure for more information.

2. STUDY OBJECTIVES

The primary objective is, in patients at LDL-C goal while on statin therapy, with established cardiovascular disease (CVD) or at high risk for CVD, and hypertriglyceridemia (fasting triglycerides, TG, ≥200 mg/dL and <500 mg/dL [≥2.26 mmol/L and <5.64 mmol/L]), to evaluate the effect of 4 g/day AMR101 for preventing the occurrence of a first major cardiovascular event of the composite endpoint that includes:

- Cardiovascular (CV) death,
- Nonfatal myocardial infarction (MI),
- Nonfatal stroke,
- Coronary revascularization,
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

Refer to Appendix B for cardiovascular event definitions.

The secondary objectives of this study are the following:

The key secondary objective is to evaluate the effect of therapy on the composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair.

Other secondary objectives:

- To evaluate the effect of therapy on combinations of each of the key secondary objective clinical events in addition to the following clinical events:
    - Cardiac arrhythmia requiring hospitalization
    - Cardiac arrest
    - Peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair
    - Total mortality

The tertiary objectives of this study are the following:

- Evaluate the effect of therapy on the occurrence of a second, third, fourth, and fifth major cardiovascular event (same as the primary composite endpoint but for events occurring after the first event);
- To evaluate the effect of therapy on the primary endpoint in subgroups of patients including:
    - Diabetes mellitus
    - Metabolic syndrome as defined by the NCEP ATP III or future criteria as they may evolve;

- To evaluate the effect of therapy on the individual endpoints of new congestive heart failure (CHF), on new CHF as a primary cause of hospitalization, on transient ischemic attack, on amputation for vascular disease and on carotid revascularization;
- Elective coronary revascularization and emergent coronary revascularization;
- To assess the effects regarding lipids, lipoproteins and inflammatory markers including triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein B (apo B), high sensitivity C-reactive protein (hs-CRP) and high sensitivity troponin (hsTnT), as follows:
    - Assessment of the effect of AMR101 on each marker (on-treatment change of markers)
    - Assessment of the effect of the baseline value of each marker on treatment effects (baseline effect on outcomes)
    - To evaluate the effect of therapy for preventing clinical events, as defined above, among all patients in the study, and in subgroups such as patients with diabetes mellitus and patients with substantial on-treatment changes of any of the markers (on-treatment effect on outcomes).
- To evaluate the effect of therapy on new onset diabetes (See appendix C);
- To explore the effect of AMR101 on weight and waist circumference.

3. STUDY DESIGN

3.1. Type of Study

Phase 3b, multi-Center, multinational, prospective, randomized, double-blind, placebo-controlled, parallel-group study

3.2. Study Population

The population for this study is men and women ≥45 years of age with established CVD, or men and women ≥50 years of age with diabetes in combination with one additional risk factor for CVD. In addition, all patients will have atherogenic dyslipidemia defined as on treatment for hypercholesterolemia (but at treatment goal for LDL-C, by treatment with a statin) and hypertriglyceridemia. More details are listed in the inclusion criteria.

The patients will need to provide consent to participate in the study and be willing and able to comply with the protocol and the study procedures.

3.3. Study Periods

This study consists of the following study periods:

- **Screening Period**: During the screening period, patients will be evaluated for inclusion/exclusion criteria.

  At the first visit to the Research Unit (Visit 1), study procedures will be performed for evaluation of patient's eligibility in the study. At this screening visit, patients will sign an

informed consent form before any study procedure is performed; the informed consent form will cover the treatment/follow-up period. Based on the evaluation from Visit 1, the following situations may occur:

- Patients who are eligible for participation based on the study procedures on Visit 1 will return to the Research Unit for Visit 2 (randomization visit) to start the treatment/follow-up period. This case includes, for example, patients at Visit 1who are on a stable dose of a statin, are planning to stay on the same statin and the same dose of the statin, and who not need to wash out any non-statin lipid-altering medications.
- Patients who are not eligible for participation based on the study procedures on Visit 1 and are unlikely to become eligible in the next 28 days (for example: unlikely to stabilize statin dose, unable to wash out non-statin lipid-altering medications, etc.): these patients will be screen failed after Visit 1.
- Patients not eligible for participation in the study based on the study procedures on Visit 1 may possibly become eligible in the next 28 days: these patients may return at the discretion of the investigator for a second optional screening visit (Visit 1.1) at which time the procedures needed for re-evaluation of the previously failed inclusion/exclusion criteria will be repeated. This case includes, for example, patients who are started on a statin at Visit 1, whose statin dose is changed at Visit 1, and/or needed to wash out non-statin lipid-altering medications. The following applies for these patients:
  - Patients with a change in the statin or statin dose on Visit 1 will need to be on a stable statin dose for at least 28 days before the lipid qualifying measurements at Visit 1.1. Other concomitant medications (antidiabetic therapy, for example) can be optimized or stabilized during this period.
  - Patients starting a washout at Visit 1 will have a washout period of at least 28 days (only 7 days for bile acid sequestrants) before the lipid qualifying measurements at Visit 1.1.
  - Patients at Visit 1 who are on a stable dose of a statin, are planning to stay on the same statin at the same dose, and who do not need any medication washout, but were asked to return for Visit 1.1 to repeat one or more of the other study procedures not related to concomitant medications
- Patients who become eligible for participation based on the additional study procedures at Visit 1.1 will return to the Research Unit for Visit 2 (randomization visit) to start the treatment/follow-up period.

At the end of the screening period, patients will need to meet all inclusion/exclusion criteria before they can be randomized. Patients who are not eligible for participation after the screening period (based on study procedures at Visit 1 and/or Visit 1.1) may return at a later date for rescreening. These patients will need to re-start with all procedures starting with Visit 1. This includes patients who need more time to stabilize one or more conditions or therapies (for example: statin, antidiabetic, antihypertensive, thyroid hormone, HIV-protease inhibitor therapy).

- **Treatment/Follow-Up Period**: Within 42 days after the first screening visit (Visit 1) or within 60 days after the first screening visit (Visit 1) for those patients that have a second

screening visit (Visit 1.1), eligible patients will enter the treatment/follow-up period. During this period, the patients will receive study drug during the planned visits at the Research Site and take the study drug while away from the Research Site.

During the visits, study procedures will be performed for evaluation of efficacy and safety. A detailed schedule of procedures is provided in Appendix A.

3.4. Study Duration

The estimated study duration includes a planned 18-month enrollment period followed by a follow-up period of approximately 3.5 years in expected duration (approximately 5 years in total). Patients will be randomized at different times during the enrollment period but will all end the study at the same date (study end date). It is planned that all randomized patients will receive study medication and be followed-up until the study end date. This is an event-driven trial and patients will continue in the trial if the trial runs longer than expected, or will terminate earlier if the trial runs shorter than expected.

The total duration of the trial is based on a median 4-year follow-up period across patients. The first patient randomized would be followed for 4.75 years (the longest individual follow-up duration), and the last patient randomized would be followed for 3.25 year (the shortest individual follow-up duration).

3.5. Study Groups

At Visit 2 (Day 0), eligible study patients will be randomly assigned to the following treatment groups:

- **Group 1**: AMR101 4 g daily (four 1000 mg capsules daily)
- **Group 2**: placebo (four capsules daily)

The four AMR101 or placebo capsules daily will be taken as two capsules in the morning and two capsules in the evening (twice-per-day dosing regimen).

3.6. Number of Patients

This is an event-driven trial: It is expected that a minimum of 1612 primary efficacy endpoint events will be required during the study. A total of approximately 7990 patients will be entered into the study to either receive AMR101 or placebo (approximately 3995 patients per treatment group) in order to observe an estimated 1612 events that make up the primary composite endpoint for efficacy.

3.7. Number of Study Sites

Participants will be enrolled at multiple Research Sites in multiple countries.

3.8. Randomization

On Day 0, eligible patients will be randomized to one of 2 study groups using a computer-generated randomization schema. Randomized treatment assignment to either AMR101 or placebo in a 1:1 ratio will be provided using the internet (IWR).

3.9. Blinding

This is a double-blind study. Patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and

personnel at the organization(s) and vendors supporting the study will be unaware of the randomization code (i.e., they will not know which study participants are receiving the experimental drug and which are receiving the placebo drug). The study medication AMR101 and placebo capsules will be similar in size and appearance to maintain blinding.

During the double-blind treatment/follow-up period, everyone (patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors managing/supporting the study), with the exception of the laboratory personnel performing the analysis, will be blinded to individual results of the efficacy laboratory measurements (including lipid values). Individual results from the lipid profile may be unblinded in the event of an emergency for a patient.

3.10. Stratification

Participants will be assigned to treatment groups stratified by CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries). There are two CV risk categories:

- CV Risk Category 1: patients with established CVD defined in the inclusion criteria. Patients with diabetes and established CVD are included in this category.
- CV Risk Category 2: patients with diabetes and at least one additional risk factor for CVD, but no established CVD.

Stratification will be recorded in the IWR at the time of enrollment. Approximately 70% of randomized patients will be in the CV Risk Category 1 and approximately 30% of randomized patients will be in the CV Risk Category 2. Enrollment with patients of a CV risk category will be stopped when the planned number of patients in that risk category is reached.

4. STUDY POPULATION

4.1. Inclusion Criteria

Patients meeting the following criteria will be eligible to participate in the study:

1. Fasting TG levels of ≥200 mg/dL (2.26 mmol/L) and <500 mg/dL (5.64 mmol/L).
2. LDL-C >40 mg/dL (1.04 mmol/L) and ≤100 mg/dL (2.60 mmol/L) and on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks prior to the LDL-C/TG baseline qualifying measurements for randomization
    - Stable therapy is defined as the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable, the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C). Patients who have their statin therapy or use of ezetimibe initiated at Visit 1, or have their statin, statin dose and/or ezetimibe dose changed at Visit 1, will need to go through a stabilization period of at least 28 days since initiation/change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).
    - Statins may be administered with or without ezetimibe.

NOTE: If patients qualify at the first qualification visit (Visit 1) for TG and LDL-C, and meet all other inclusion/exclusion criteria, they may be randomized at Visit 2. If patients don't qualify at the first qualifying visit (Visit 1), a second re-qualifying visit (Visit 1.1) is allowed. For some patients, because they need to stabilize medications and/or need to washout medications, the second re-qualifying visit (Visit 1.1) will be needed after the stabilization/washout period.

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 are defined as follows:

   CV Risk Category 1: defined as men and women ≥45 years of age with one or more of the following:

   - Documented coronary artery disease (CAD; one or more of the following primary criteria must be satisfied):
     - Documented multivessel CAD (≥50% stenosis in at least two major epicardial coronary arteries – with or without antecedent revascularization)
     - Documented prior MI
     - Hospitalization for high-risk NSTE-ACS (with objective evidence of ischemia: ST-segment deviation or biomarker positivity)
   - Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied):
     - Documented prior ischemic stroke
     - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis
     - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound
     - History of carotid revascularization (catheter-based or surgical)
   - Documented peripheral arterial disease (PAD; one or more of the following primary criteria must be satisfied):
     - ABI <0.9 with symptoms of intermittent claudication
     - History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical)

OR

CV Risk Category 2: defined as patients with:

1. Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication AND
2. Men and women ≥50 years of age AND
3. One 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: CrCL >30 and <60 mL/min (>0.50 and <1.00 mL/sec);
- Retinopathy, defined as any of the following: non-proliferative retinopathy, preproliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation;
- Micro- or macroalbuminuria. Microalbuminuria is defined as either a positive micral or other strip test (may be obtained from medical records), an albumin creatinine ratio ≥2.5 mg/mmol or an albumin excretion rate on timed collection ≥20 mg/min all on at least two successive occasions; macroalbuminuria, defined as albustix or other dipstick evidence of gross proteinuria, an albumin:creatinine ratio ≥25 mg/mmol or an albumin excretion rate on timed collection ≥200 mg/min all on at least two successive occasions;
- ABI <0.9 without symptoms of intermittent claudication (patients with ABI <0.9 with symptoms of intermittent claudication are counted under CV Risk Category 1).

Note: Patients with diabetes with CVD as defined above are eligible based on the CVD requirements and will be counted under CV Risk Category 1. Only patients with diabetes and no documented CVD as defined above need at least one additional risk factor as listed, and will be counted under CV Risk Category 2.

4. Women may be enrolled if all 3 of the following criteria are met:
   - They are not pregnant;
   - They are not breastfeeding;
   - They do not plan on becoming pregnant during the study.
5. Women of child-bearing potential must have a negative urine pregnancy test before randomization.

   Note: Women are not considered to be of childbearing potential if they meet one of the following criteria as documented by the investigator:

   - They have had a hysterectomy, tubal ligation or bilateral oophorectomy prior to signing the informed consent form;
   - They are post-menopausal, defined as ≥1 year since their last menstrual period or have a follicle-stimulating hormone (FSH) level in a menopausal range.
6. Women of childbearing potential must agree to use an acceptable method of avoiding pregnancy from screening to the end of the study, unless their sexual partner(s) is/are surgically sterile or the woman is abstinent.
7. Understanding of the study procedures, willing to adhere to the study schedules, and agreement to participate in the study by giving informed consent prior to screening.
8. Agree to follow a physician recommended diet and to maintain it through the duration of the study.

4.2. Exclusion Criteria

Patients are excluded from participation in the study if any of the following criteria apply:

1. Severe (class IV) heart failure.
2. Any life-threatening disease expected to result in death within the next 2 years (other than CVD).
3. Active severe liver disease (evaluated at Visit 1): cirrhosis, active hepatitis, ALT or AST >3 x ULN, or biliary obstruction with hyperbilirubinemia (total bilirubin >2 x ULN).
4. Hemoglobin A_{1c} >10.0% (or 86 mmol/mol IFCC units) at screening (Visit 1). If patients fail this criterion (HbA_{1c} >10.0% or 86 mmol/mol IFCC units) at Visit 1, they may have their antidiabetic therapy optimized and be retested at Visit 1.1.
5. Poorly controlled hypertension: blood pressure ≥200 systolic mmHg OR ≥100 mmHg diastolic (despite antihypertensive therapy).
6. Planned coronary intervention (such as stent placement or heart bypass) or any non-cardiac major surgical procedure. Patients can be (re)evaluated for participation in the trial (starting with Visit 1.1) after their recovery from the intervention/surgery.
7. Known familial lipoprotein lipase deficiency (Fredrickson Type I), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type III)].
8. Participation in another clinical trial involving an investigational agent within 90 days prior to screening (Visit 1). Patients cannot participate in any other investigational medication or medical device trial while participating in this study (participation in a registry or observational study without an additional therapeutic intervention is allowed).
9. Intolerance or hypersensitivity to statin therapy.
10. Known hypersensitivity to any ingredients of the study product or placebo (refer to Table 3); known hypersensitivity to fish and or shellfish.
11. History of acute or chronic pancreatitis.
12. Malabsorption syndrome and/or chronic diarrhea (Note: patients who have undergone gastric/intestinal bypass surgery are considered to have malabsorption, hence are excluded; patients who have undergone gastric banding are allowed to enter the trial).
13. Non-study drug related, non-statin, lipid-altering medications, supplements or foods:
    - Patients are excluded if they used niacin >200 mg/day or fibrates during the during the screening period (after Visit 1) and/or plan to use during the study; patients who are taking niacin >200 mg/day or fibrates during the last 28 days before Visit 1 need to go through washout of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (Visit 1.1);
    - Patients are excluded if they take any omega-3 fatty acid medications (prescription medicines containing EPA and/or DHA) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking omega-3 fatty acid medications

during the last 28 days before Visit 1 (except patients in The Netherlands), need to go through a washout period of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (at Visit 1.1);

  - For patients in The Netherlands only: patients being treated with omega-3 fatty acid medications containing EPA and/or DHA are excluded; no washout is allowed.

- Patients are excluded if they use dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking >300 mg/day omega-3 fatty acids (combined amount of EPA and DHA) within 28 days before Visit 1 (except patients in The Netherlands), need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);
  - For patients in The Netherlands only: patients being treated with dietary supplements containing omega-3 fatty acids of >300 mg/day EPA and/or DHA are excluded; no washout is allowed.
- Patients are excluded if they use bile acid sequestrants during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking bile acid sequestrants within 7 days before Visit 1, need to go through a washout period of at least 7 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);

14. Other medications (not indicated for lipid alteration):
    - Treatment with tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are allowed), HIV-protease inhibitors that have not been stable for ≥28 days prior to the qualifying lipid measurements (TG and LDL-C) during screening. To be eligible for participation in the study, patients who are not taking a stable dose of these medications within 28 days before Visit 1, need to go through a stabilization period of at least 28 days since their last dose change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).
    - Patients are excluded if they use cyclophosphamide or systemic retinoids during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking these medications within 28 days before Visit 1, need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).
15. Known to have AIDS (patients who are HIV positive without AIDS are allowed).
16. Requirement for peritoneal dialysis or hemodialysis for renal insufficiency or if creatinine clearance (CrCL) <30 mL/min (0.50 mL/sec).

17. Unexplained creatine kinase concentration >5 × ULN or creatine kinase elevation due to known muscle disease (e.g., polymyositis, mitochondrial dysfunction) at Visit 1.
18. Any condition or therapy which, in the opinion of the investigator, might pose a risk to the patient or make participation in the study not in the patient's best interest.
19. Drug or alcohol abuse within the past 6 months, and unable/unwilling to abstain from drug abuse and excessive alcohol consumption during the study or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking). Excessive alcohol consumption is on average >2 units of alcohol per day. A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.
20. Mental/psychological impairment or any other reason to expect patient difficulty in complying with the requirements of the study or understanding the goal and potential risks of participating in the study (evaluated at Visit 1).

5. STUDY COMMITTEES

5.1. Steering Committee

The Steering Committee (SC) will include the chairperson, the Principal Investigator (PI), key representatives from the Sponsor and its designees (for example, from the organization(s) conducting the study as delegated by the Sponsor), and key representatives from each region who are deemed to have clinical and methodological expertise (national coordinators).

The SC has overall responsibility for:

- Scientific and strategic direction for the trial. The SC must address and resolve all scientific issues regarding the conduct of the trial. All sub-studies must be approved by the SC.
- The execution of the study protocol, and the reporting and publication of the study results.
- Logistical coordination of the different study committees.

The SC will meet at least twice per year.

5.2. Study Operations Committee (SOC)

The Study Operations Committee (SOC) is responsible for ensuring that study execution and management is of the highest quality, and will monitor recruitment, compliance, and the adjudication process and address the day to day issues arising from the trial. The SOC will be composed of representatives from the Sponsor and the organization(s) conducting the study (as delegated by the sponsor). This committee will meet by telephone and/or in person on a monthly or bimonthly basis, and each meeting will be documented with minutes.

5.3. Clinical Event Committee (CEC)

The CEC is composed of multidisciplinary medical experts. This committee will be responsible for blindly validating all the primary and secondary efficacy outcome events

reported by the investigators (event adjudication). The committee will create a charter with details of the adjudication process and methods based on the definitions of the events.

5.4. Data Monitoring Committee (DMC)

A DMC will be instituted for this study in order to ensure its ongoing safety and to oversee and review the interim analysis. Recommendation for trial continuation will be guided by monitoring boundaries at an interim analysis at which a formal efficacy analysis is performed as well as safety evaluations at all safety data reviews. Members of the DMC will not otherwise be participating in the trial. The committee will include at least one cardiologist and one independent statistician. A DMC Charter will be drafted and approved by the DMC and the Steering Committee. The Charter will provide details regarding the interim analysis and monitoring plan.

6. STUDY PROCEDURES

6.1. Assessment Schedule

A detailed schedule of procedures is provided in Appendix A.

6.1.1. Screening Period

6.1.1.1. Screening Visit (Visit 1)

Patients will come to the Research Site for Visit 1. They will be instructed to fast for at least 10 hours before their visit.

If patients qualify for randomization based on the procedures at Visit 1, they need to be randomized within 42 days after Visit 1. The following procedures will be performed at the screening visit:

- Obtain signed informed consent
- Assign the patient a patient number
- Obtain medical, surgical and family history
- Record demographics
- Obtain height, weight, and body mass index
- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)
- Obtain a 12-lead electrocardiogram
- Evaluate inclusion/exclusion criteria
- This includes procedures and (fasting) blood samples (for example, hs-CRP, calculated creatinine clearance) as needed to determine the CV risk category (see inclusion criteria)
- Obtain fasting blood samples for chemistry and hematology testing
- Obtain a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C)

- Perform a urine pregnancy test on women of childbearing potential
- Record concomitant medication(s)
- Instruct patient to fast for ≥10 hours prior to the next visit

6.1.1.2. Screening Visit (Visit 1.1)

Some patients will skip Visit 1.1: Patients who qualify for study participation after Visit 1 because they meet all inclusion criterion and none of the exclusion criteria, may return to the Research Site for Visit 2 to be randomized and to start the treatment/follow-up period of the study. For these patients, Visit 2 will occur soon after Visit 1.

Patients, who do not qualify at Visit 1, may return to the Research Site for a second qualifying visit (Visit 1.1) at the discretion of the investigator. At Visit 1.1, procedures that caused failure of eligibility at Visit 1 will be repeated. Patients will be eligible for randomization after Visit 1.1 if they meet all inclusion criteria and if they no longer fail the exclusion criteria. If patients are evaluated at Visit 1.1 and qualify for randomization based on the repeated procedures at Visit 1.1, they need to be randomized within 60 days after Visit 1.

For some patients, Visit 1.1 will be mandatory at least 28 days after Visit 1 in order to check eligibility. These are patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications (see inclusion/exclusion criteria for details). Any of these changes at Visit 1 may affect the qualifying lipid levels and therefore, patients will need to have Visit 1.1 to determine whether they qualify based on lipid level requirements (TG and LDL-C) determined at Visit 1. Other procedures that caused failure of eligibility at Visit 1 will also be repeated at Visit 1.1.

The following procedures will be performed at the screening visit:

- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)
- Evaluate inclusion/exclusion criteria; only those evaluations will be repeated that deemed the patient not eligible on Visit 1.
- Obtain fasting blood samples for chemistry and hematology testing. Only those samples will be obtained that deemed the patient not eligible on Visit 1.
- Obtain a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C) if the patient was deemed not eligible on Visit 1. This includes patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications (see inclusion/exclusion criteria for details). These patients will have a fasting blood sample collected at Visit 1.1 for the qualifying lipid values (TG and LDL-C), and the TG and LDL-C inclusion criteria will be evaluated.
- Record concomitant medication(s)

6.1.2. Treatment/Follow-Up Period

Every attempt should be made to complete the follow-up visits during the defined window periods.

6.1.2.1. Randomization visit (Visit 2; Day 0)

Qualified patients will return to the Research Site for Visit 2.

The following procedures will be performed at Visit 2:

- Perform physical examination
- Obtain weight
- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)
- Measure waist circumference (one of the factors to diagnose metabolic syndrome)
- Obtain a 12-lead electrocardiogram
- Evaluate inclusion/exclusion criteria
- Obtain fasting blood samples for:
    - Chemistry and hematology testing
    - Lipid profile (baseline)
    - Biomarker assays (baseline)
    - Genetic testing (optional blood sample)
    - Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)
- Perform a urine pregnancy test on women of childbearing potential (must be negative for randomization)
- Dispense study drug and record randomization number
- Instruct patient on how to take study drug
- Administer study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples
- Assess for and record adverse events
- Record concomitant medication(s)
- Instruct patient:
    - To bring all study supplies with them to the next visit
    - Not to take study drug on the morning of their next visit
    - To fast for ≥10 hours prior to the next visit

6.1.2.2. Visit 3 (Day 120; ~4 Months)

Patients will return to the Research Site for Visit 3 on Day 120 ±10 days.

The following procedures will be performed:

- Perform physical examination
- Obtain weight
- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)
- Obtain fasting blood samples for:
  - Chemistry and hematology testing
  - Lipid profile
- Review study drug compliance by unused capsule count; discuss with and counsel patients about compliance if needed
- Administer study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples
- Assess and record efficacy events
- Assess for and record adverse events
- Record concomitant medication(s)
- Instruct patient:
  - To bring all study supplies with them to the next visit
  - Not to take study drug on the morning of their next visit
  - To fast for ≥10 hours prior to the next visit

6.1.2.3. Visits 4, 5, 6 and 7

At Visit 4: Day 360 ± 10; Visit 5: Day 720 ± 10; Visit 6: Day 1080 ± 10; and Visit 7: Day 1440 ± 10, the following procedures will be performed:

- Perform physical examination
- Obtain weight
- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)
- Measure waist circumference (collected at Visit 5 only)
- Obtain a 12-lead electrocardiogram
- Obtain fasting blood samples for:
  - Chemistry and hematology testing
  - Lipid profile
  - Biomarker assays (collected at Visit 5 only)
  - Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)

- Review study drug compliance by unused capsule count; discuss with and counsel patients about compliance if needed
- Administer study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples
- Assess and record efficacy events
- Assess for and record adverse events
- Record concomitant medication(s)
- Instruct patient:
  - To bring all study supplies with them to the next visit
  - Not to take study drug on the morning of their next visit
  - To fast for ≥10 hours prior to the next visit

6.1.2.4. Additional Visits

The end date of the study is expected for Day 1800 but the actual end date will be dependent on the determination of the study end date by the DMC. The study end date is determined to be when approximately 1612 primary efficacy events have occurred. If the actual study end date is later than the expected end date, additional visits will be planned between Visit 7 and the Last Visit with a maximum of 360 ±10 days between visits. If the actual study end date is sooner than the expected end date, fewer visits will occur, and the last visit (See Section 6.1.2.5) will occur sooner.

On additional visits the same procedures will be performed as listed in Section 6.1.2.3. Irrespective of the number of additional visits, after the DMC has established the end of the study date, there will be a last visit with procedures as listed in Section 6.1.2.5.

6.1.2.5. Last Visit – End of Study

All patients will complete the study at the same time (within a 30-day window after the study end date), irrespective of the date that they were randomized. The end date of the study is planned for Day 1800 but the actual end date will be dependent on the determination of the study end date by the DMC when approximately 1612 primary efficacy events have occurred (event-driven trial). For each patient, the last visit may occur within 30 day after the actual study end date as determined by the DMC. However, for the efficacy endpoints based on CV events, only events occurring up to and including the scheduled actual study end date will be included in the efficacy analyses.

A final follow-up visit is required for all patients. In the rare cases that a final follow-up visit cannot occur within the 30-day timeframe following the study end date, any attempt to contact the patient must be recorded on a special contact form, until/unless appropriate information is obtained.

At the Last Visit, the following procedures will be performed:

- Perform physical examination
- Obtain weight

- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)
- Measure waist circumference
- Obtain a 12-lead electrocardiogram
- Obtain fasting blood samples for:
  - Chemistry and hematology testing
  - Lipid profile
  - Biomarker assays
  - Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)
- Determine study drug compliance by unused capsule count
- Assess and record efficacy events
- Assess for and record adverse events
- Record concomitant medication(s)

6.2. Telephone Follow-up Contact

Site personnel will contact each patient by telephone on the following study days:

- Day 60 ±3 days
- Day 180 ±5 days
- Day 270 ±5 days
- Day 450 ±5 days
- Day 540±5 days
- Day 630 ±5 days
- Day 810 ±5 days
- Day 900 ±5 days
- Day 990 ±5 days
- Day 1170 ±5 days
- Day 1260 ±5 days
- Day 1350 ±5 days
- Day 1530 ±5 days
- Day 1620 ±5 days
- Day 1710 ±5 days

If the treatment/follow-up period of the study is extended beyond the expected end date (Day 1800), additional follow-up phone calls will be made every 3 months in-between

additional visits ±5 days. See Section 6.1.2.4 for the timing of the additional visits. If the treatment/follow period of the study is shorter than the expected end date, less follow-up phone calls will be needed.

Every attempt will be made to talk to each patient within this time frame.

The following information will be collected from the patient:

- Possible efficacy endpoints related to CV events. Patients will be asked to return to the Research Site to assess for any endpoints or events identified.
- Adverse events
- Concomitant medications
- Current address and contact information (update if changed or will be changing)

Patients will be reminded about the following items:

- To take the study medication according to the dosing schedule assigned, with food
- When to return to the Research Center for the next visit
- To bring the unused study medication to the next visit
- To not take study drug on the morning of their next visit
- To fast for at least 10 hours prior to the next visit

6.3. Laboratory Procedures

6.3.1. Clinical Laboratory Procedures

All clinical laboratory determinations for screening and safety will be performed by a certified clinical laboratory under the supervision of the Sponsor or its designee.

Whenever possible and appropriate, samples for the clinical laboratory procedures will be collected after fasting for at least 10 hours. For the purposes of this study, fasting is defined as nothing by mouth except water (and any essential medications).

The investigator must review and sign all laboratory test reports. At screening, patients who have laboratory values that are outside the exclusionary limits specified in the exclusion criteria may not be enrolled in the study (patients can be considered for the study if values are classified as not clinically significant by the investigator). After randomization, the investigator will be notified if laboratory values are outside of their normal range. In this case, the investigator will be required to conduct clinically appropriate follow-up procedures.

6.3.1.1. Safety Laboratory Tests

The safety laboratory tests include:

- Hematology with complete blood count (CBC), including RBC, hemoglobin (Hgb), hematocrit (Hct), white cell blood count (WBC), white cell differential, and platelet count
- Biochemistry panel including total protein, albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), total

bilirubin, glucose, calcium, electrolytes (sodium, potassium, chloride), blood urea nitrogen (BUN), serum creatinine, uric acid, creatine kinase, and HbA_{1c}.

6.3.1.2. Fasting Lipid Profile

The fasting lipid panel includes: TG, TC, LDL-C, HDL-C, non-HDL-C, and VLDL-C.

At all visits, LDL-C will be calculated using the Friedewald equation. At Visit 1 and Visit 1.1 Direct LDL-C will be used if at the same visit TG >400 mg/dL (4.52 mmol/L). These LDL-C values will be used for the evaluation of the LDL-C inclusion criterion (LDL-C qualifying measurements for randomization) and for the assessment of changes in the statin therapy when LDL-C is not at goal. At all remaining visits (except Visit 2 and Visit 4) LDL-C will be measured by Direct LDL Cholesterol or by Preparative Ultracentrifugation if at the same visit TG >400 mg/dL (4.52 mmol/L). In addition, irrespective of the TG levels, at Visit 2 (0 Months of Follow-up, baseline) and at Visit 4 (12 Months of Follow-up), LDL-C will be measured by Preparative Ultracentrifugation. These Preparative Ultracentrifugation LDL-C measurements will be used in the statistical analysis including the calculation of the percent change from baseline (1 year versus baseline).

6.3.1.3. Genetic testing

A fasting blood sample will be stored for future genetic testing at the discretion of the sponsor. The specifics of this test will be determined at a later date. This sample is optional as local regulations may prohibit genetic samples to be collected or shipped outside the country, or patients may not consent.

Research on genetic testing will look for links between genes and certain diseases, including their treatment(s) such as medicines and medical care. The blood samples will be collected in the study center with the regular protocol-required labs. Each patient tube with sample for genetic testing will be labeled with patient number only. The site will maintain a Subject Code Identification List for cross-reference. The patient number does not contain any identifiable information (i.e. Patient initials, date of birth, etc). Un-analyzed samples will be stored frozen by the sponsor for a period of up to 2 years following the end of the study, at which time they will be destroyed. If samples are tested, results will not be reported to the patient, parents, relatives, or attending physician and will not be recorded in the patient's medical records. There will be no follow-up contact with the sites or patients regarding this sample. The subject can withdraw their consent for genetic testing at any time up to analysis, even after the sample has been obtained. The subject can notify the site in writing that they withdraw their consent for the genetic testing portion of the study, and it will be documented by the site in the subject chart, as well as captured in the CRF. The lab will be notified to pull the sample and destroy it.

6.3.1.4. Biomarkers Assays

The biomarker assays include: hs-CRP, Apo B and hsTnT.

6.3.1.5. Additional laboratory tests

Additional laboratory tests include:

- A urine pregnancy test will be administered to women of childbearing potential at certain visits as listed in schedule of procedures (Appendix A). The urine pregnancy

tests will be performed at the Research Site utilizing marketed test kits, or at a certified clinical laboratory.

- A fasting blood sample (12 mL) for archiving. This sample will be collected only at sites in countries where allowed by local regulations and at sites for which approved by the IRB or IEC. The plasma from the archiving sample will be stored frozen in 2 separate equal aliquots, and will be used at the Sponsor's discretion to perform repeat analyses described in the protocol or to perform other tests related to cardiovascular health.

6.3.1.6. Blinding of Laboratory Results

All efficacy laboratory results during the double-blind period of the trial will be blinded (values not provided) to patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors managing and/or supporting the study, with the exception of the laboratory personnel conducting the assays. To ensure patient safety, hsTnT values will be reported to the site.

6.3.1.7. Flagging of Critical Lab Values

Critical lab values are values that may warrant medical intervention to avoid possible harm to a patient. Critical lab values will be defined in the Laboratory Manual for the study, and the Research Site will be notified of the occurrence of a critical lab value (critical high or critical low) by a special annotation (flag) in the laboratory reports provided to the Research Sites. Although laboratory values that are part of the efficacy endpoints during the double-blind period of the study will not be provided to the Research Site (see Section 6.3.1.6), the sites will be notified when the TG value of a patient sample is >1000 mg/dL (11.29 mmol/L) (critical high TG value) or if the LDL-C values of a patient sample is >130 mg/dL (3.37 mmol/L) (critical high LDL-C value). These critical high values will need to be confirmed by a repeat measurement (new fasting blood sample) within 7 days. TG value of >2000 mg/dL (22.58 mmol/L) will also be flagged, so that appropriate medical action can be taken by the investigator as soon as possible.

If TG values are confirmed critically high, patients may be discontinued from study drug with the option to remain on study (see Section 11.1 ODIS). The investigator should use the best clinical judgment for each patient which could include the use of approved TG-lowering medications after patients have been discontinued from study drug.

If LDL-C values are confirmed critically high, the investigator may need to take appropriate medical action which could include: reinforce/intensify therapeutic lifestyle changes (including diet and physical activity), increase the dose of the present statin therapy, add ezetimibe, or prescribe a more potent statin to lower LDL-C. The investigator should use the best clinical judgment for each patient.

6.3.2. Medical Procedures

6.3.2.1. Medical, Surgical and Family History

Medical history, including family history and details regarding all illnesses and allergies, date(s) of onset, status of current condition, and smoking and alcohol use will be collected on all patients.

6.3.2.2. Demographics

Demographic information including day, month, and year of birth, race, and gender will be collected for all patients.

6.3.2.3. Vital Signs

Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Blood pressure will be measured using a standardized process:

- Patient should sit for ≥5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level.
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery.

Blood pressure should be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device. A blood pressure reading should be repeated 1 to 2 minutes later, and the second reading should also be recorded to the nearest 2 mmHg mark.

6.3.2.4. Physical Examination

A physical examination must include source documentation of general appearance, skin, and specific head and neck, heart, lung, abdomen, extremities, and neuromuscular assessments.

6.3.2.5. Height, Weight and Body Mass Index

Height and weight will be measured. Measurement of weight should be performed with the patient dressed in indoor clothing, with shoes removed, and bladder empty.

6.3.2.6. Waist Circumference

Waist circumference will be measured with a tape measure, as follows: Start at the top of the hip bone then bring the tape measure all the way around – level with the navel. Make sure the tape measure is snug, but without compressing the skin, and that it is parallel with the floor.

Patients should not hold their breath while measuring waist circumference.

6.3.2.7. Electrocardiogram (ECG)

ECGs (standard 12-lead) will be obtained annually. Site personnel should make every attempt to perform a patient's ECG using the same equipment at each visit. ECGs will be reviewed by the site for the detection of silent MI. Silent MIs will be sent for event adjudication.

7. TREATMENT AND RESTRICTIONS

7.1. Treatment

7.1.1. Treatment Regimen, Dosage, and Duration

Eligible study patients will be randomly assigned on Day 0 to one of the 2 treatment groups. Patients in each group will receive either 4 g/day AMR101 or placebo for up to 4.75 years (4 years planned median treatment duration) according to Table 2.

The daily dose of study drug is 4 capsules per day taken as two capsules taken on two occasions per day (2 capsules given twice daily).

Table 2. Dosing Schedule during the Treatment Period

Treatment Group	Daily Dose	Number of Capsules per Day
1	4 g	4 capsules of 1000 mg AMR101
2	Placebo	4 capsules of matching placebo

Patients will be instructed to take study drug with food (i.e., with or at the end of their morning and evening meals). On days that patients are scheduled for study visits, the daily dose of study drug will be administered by site personnel with food provided by the site following collection of all fasting blood samples. For the purposes of this study, fasting is defined as nothing by mouth except water (and any essential medications) for at least 10 hours.

7.1.2. Treatment Assignment

7.1.2.1. Identification number

A unique patient identification number (patient number) will be established for each patient at each site. The patient number will be used to identify the patient throughout the study and will be entered on all documentation. If a patient is not eligible to receive treatment, or if a patient discontinues from the study, the patient number cannot be reassigned to another patient. The patient number will be used to assign patients to one of the 2 treatment groups according to the randomization schedule.

7.1.2.2. Drug Randomization

Only qualified patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized and will receive study medication starting at Visit 2 (Day 0). Eligible patients will be randomly assigned to one of the 2 treatment groups. Randomization will be stratified by CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries) (See Section 3.10). Approximately 70% of randomized patients will be in the CV Risk Category 1, including patients with established CVD, and approximately 30% of randomized patients will be in the CV Risk Category 2, including patients with diabetes and at least one additional risk factor but no established CVD. Enrollment with patients of a CV risk category will be stopped when the planned number of patients in that risk category is reached.

7.1.2.3. Emergency Unblinding

In an emergency, when knowledge of the patient's treatment assignment is essential for the clinical management or welfare of the patient, the investigator may request the patient's treatment assignment for unblinding. Prior to unblinding the patient's individual treatment assignment, the investigator should assess the relationship of an adverse event to the administration of the study drug (Yes or No). If the blind is broken for any reason, the investigator must record the date and reason for breaking the blind on the appropriate Case Report Form (CRF) and source documents.

7.1.3. Compliance Control

It is recommended that, unless clear contraindications arise, patients be strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy should, if possible, be brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. Discontinuations will be discouraged as much as possible. Any discontinuations should be based on compelling clinical reasons.

For every patient, an assessment of compliance to the study drug treatment regimen must be obtained at each scheduled visit. Study medication will be dispensed in amounts exceeding the amount required for the study. Patients will be instructed to return all unused study medication at the next visit. Compliance to the study drug regimen will be evaluated at each visit by counting unused capsules. Discrepancies will be evaluated and discussed with each patient to assess compliance. If compliance is unsatisfactory, the patient will be counseled about the importance of compliance to the dosing regimen. At the end of the study, the final study medication compliance will be determined by unused capsule count (see Section 12.2.2).

7.2. Study Restrictions

7.2.1. Concomitant Medications during Treatment/Follow-Up Period

Any medications administered during the study period must be documented on the Concomitant Medication CRF. Patients must not have taken any investigational agent within 90 days prior to screening. Patients cannot participate in any other investigational medication trial while participating in this study.

The following non-study drug related, non-statin, lipid-altering medications and supplements, and foods are prohibited during the study (from Visit 1 until after the Last Visit-End of Study), except for compelling medical reasons in ODIS patients (see description of ODIS in section 11.1):

- niacin >200 mg/day;
- fibrates;
- prescription omega-3 fatty acid medications;
- dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils);
- bile acid sequestrants;
- cyclophosphamide;
- systemic retinoids

If any of these products would be used during the treatment/follow-up period of the study, it should be for compelling medical reasons in ODIS patients, and it should be documented in the Concomitant Medication CRF. If the ODIS patient agrees to restart study medication, the use of excluded medication must be discontinued.

Foods enriched with omega-3 fatty acids are strongly discouraged after Visit 1 for the duration of the study (does not apply to The Netherlands or Canada only. Therefore, all centers in The Netherlands and Canada must ignore this request).

The following products are allowed: statins, ezetimibe, and herbal products & dietary supplements not containing omega-3 fatty acids.

Statins:

- The same statin at the same dose should be continued until the end of the study, unless deemed medically necessary to change because of an adverse event or lack of efficacy (LOE). It is preferred that if LOE is the determining factor that ezetimibe be added to the present dose.
- Switching between a brand name statin and the generic version of the same statin is allowed at any time during the study.
- Statins may be administered with or without ezetimibe.
- Based on the FDA recommendation, simvastatin 80 mg be used only in patients who have been taking this dose for 12 months or more and have not experienced any muscle toxicity. (See reference: FDA Drug Safety Communication: Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury. (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204882.htm)
- Changing of the type of statin or the statin dose during the treatment/follow-up period of the study should only be done for compelling medical reasons and must be documented in the CRF.

LDL-C Rescue:

- If the level of LDL-C exceeds 130 mg/dL (3.37 mmol/L) during the study (initial measurement and confirmed by a second determination at least 1 week later), the investigator may either increase the dose of the present statin therapy or may add ezetimibe to lower LDL-C. The investigator should use the best clinical judgment for each patient.

No data are available with regard to potential interactions between ethyl-EPA and oral contraceptives. There are no reports suggesting that omega-3 fatty acids, including ethyl-EPA, would decrease the efficacy of oral contraceptives.

7.2.2. Patient Restrictions

Beginning at the screening visit, all patients should be instructed to refrain from excessive alcohol consumption, to follow a physician recommended diet and to maintain it through the duration of the study. Excessive alcohol consumption is on average >2 units of alcohol per day or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking). A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.

8. INVESTIGATIONAL PRODUCT

8.1. Clinical Trial Material

The following will be supplied by the Sponsor:

- AMR101 1000 mg capsules

- Placebo capsules

The Sponsor will supply sufficient quantities of AMR101 1000 mg capsules and placebo capsules to allow for completion of the study. The lot numbers of the drugs supplied will be recorded in the final study report.

Records will be maintained indicating the receipt and dispensation of all drug supplies. At the conclusion of the study, any unused study drug will be destroyed.

8.2. Pharmaceutical Formulations

AMR101 1000 mg and placebo capsules are provided in liquid-filled, oblong, gelatin capsules. Each capsule is filled with a clear liquid (colorless to pale yellow in color). The capsules are approximately 25.5 mm in length with a diameter of approximately 9.5 mm.

Table 3 summarizes the components of each capsule.

Table 3. Components of AMR101 Capsules

Component	AMR101 1000 mg capsules Quantity (mg/capsule)	Placebo capsules Quantity (mg/capsule)	Function
Capsule fill			
Icosapent ethyl	998	-	Active
Paraffin, light liquid	-	932	
All-rac-α-tocopherol	2	1.86	Antioxidant
Capsule shell			
Gelatin	279	279	Capsule shell material
Sorbitol, liquid (non-crystallizing)	78	78	Plasticizer
Glycerol	44	44	Plasticizer
Purified water	37	37	Solvent
Maltitol, liquid	28	28	Plasticizer

8.3. Labeling and Packaging

Study medication will be packaged in high-density polyethylene bottles. Labeling and packaging will be performed according to GMP guidelines and all applicable country-specific requirements. The bottles will be numbered for each patient based on the randomization schedule. The patient randomization number assigned by IWR or a designee of the Sponsor for the study (if no IWR system is used), will correspond to the number on the bottles. The bottle number for each patient will be recorded in the Electronic Data Capture (EDC) system for the study.

8.4. Dispensing Procedures and Storage Conditions

8.4.1. Dispensing Procedures

At Visit 2 (Day 0), patients will be assigned study drug according to their treatment group determined by the randomization schedule. Once assigned to a treatment group, patients will receive study drug supplies. At each visit, patients will bring unused drug supplies dispensed

to them earlier. From the drug supplies assigned to each patient, site personnel will administer drug while the patients are at the Research Site.

The investigator or designee must contact the IWR system or a designee of the Sponsor for the study (if no IWR system is used) when any unscheduled replacements of study medication are needed.

During the last visit during the treatment period, patients will bring the unused drug supplies for site personnel to calculate the final study medication compliance by unused capsule count (see Section 12.2.2).

8.4.2. Storage Conditions

At the Research Sites, study drugs must be stored at room temperature, 68°F to 77°F (20°C to 25°C). Do not allow storage temperature to go below 59°F (15°C) or above 86°F (30°C). Store in the original package.

Study drugs must be stored in a pharmacy or locked and secure storage facility, accessible only to those individuals authorized by the investigator to dispense the drug. The investigator or designee will keep accurate dispensing records. At the conclusion of the study, study site personnel will account for all used and unused study drug. Any unused study drug will be destroyed. The investigator agrees not to distribute study drug to any patient, except those patients participating in the study.

9. EFFICACY ASSESSMENTS

9.1. Specification of Variables and Procedures

The primary endpoint and the majority of the secondary and tertiary endpoints are based on clinical events related to CVD and mortality. All events occurring between randomization and the study end date (inclusive) must be recorded. Only adjudicated events will be included in the final analyses. Further details on the assessment of clinical events and their definitions will be found in the CEC charter. Important definitions are listed in Appendix B of this protocol.

9.2. Efficacy Endpoints

9.2.1. Primary Efficacy Endpoint

Time from randomization to the first occurrence of the composite of the following clinical events:

- CV death,
- Nonfatal MI (including silent MI; ECGs will be performed annually for the detection of silent MIs),
- Nonfatal stroke,
- Coronary revascularization
- Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing.

The first occurrence of any of these major adverse vascular events during the follow-up period of the study will be included in the incidence.

9.2.2. Secondary Efficacy Endpoints

The key secondary efficacy endpoint is:

- The composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair.

Other secondary efficacy endpoints are as follows (to be tested in said order):

- The composite of total mortality, nonfatal MI, or nonfatal stroke;
- The composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, peripheral CVD requiring intervention, or cardiac arrhythmia requiring hospitalization;
- The composite of death from CV causes, nonfatal MI, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- The composite of death from CV causes or nonfatal MI;
- Total mortality;
- Fatal and nonfatal MI (including silent MI);
- Coronary Revascularization;
- Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing ;
- Fatal and nonfatal stroke.

For the secondary endpoints that count a single event, the first occurrence of this type of event will be counted in each patient. For secondary endpoints that are composites of two or more types of events, the first occurrence of any of the event types included in the composite will be counted in each patient.

9.2.3. Tertiary Efficacy Endpoints:

- The second, third, fourth, and fifth major CV event of the primary composite endpoint. The type of (nonfatal) events may occur in any order.
- Primary endpoint in subset of patients with diabetes mellitus;
- Primary endpoint in subset of patients with metabolic syndrome;
- New CHF, new CHF leading to hospitalization, transient ischemic attack, amputation for CVD and carotid revascularization;
- Elective coronary revascularization and emergent coronary revascularization;
- New onset diabetes;
- Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP, and hsTnT: effect of baseline and on-treatment change of biomarkers on primary and key secondary endpoints;

- CV mortality;
- Cardiac Arrhythmias requiring hospitalization;
- Cardiac Arrest;
- To explore the effect of AMR101 on weight and waist circumference.

For the tertiary endpoints that count a single event, the first occurrence of this type of event will be counted in each patient. For tertiary endpoints that are composites of two or more types of events, the first occurrence of any of the event types included in the composite will be counted in each patient (except when stated otherwise, for the second, third, fourth, and fifth major CV event).

10. SAFETY ASSESSMENTS

10.1. Specification of Variables and Procedures

Safety assessments will include adverse events, clinical laboratory measurements (chemistry, hematology), 12-lead ECGs, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), and physical examinations as per Study Procedures/Appendix A.

A complete medical, surgical and family history will be completed at Visit 1.

A list of the analytes to be measured for the safety evaluation is found in Section 6.3.1.1. All laboratory test results must be evaluated by the investigator as to their clinical significance. Any observations at physical examinations or laboratory values considered by the investigator to be clinically significant should be considered an adverse event.

10.2. Adverse Events

An adverse event is defined as any untoward medical occurrence, which does not necessarily have a causal relationship with the medication under investigation. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medication product, whether or not related to the investigational medication product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate CRF. Each adverse event is to be evaluated for duration, intensity, and causal relationship with the study medication or other factors.

Adverse events, which include clinical laboratory test variables, will be monitored from the time of informed consent until study participation is complete. Patients should be instructed to report any adverse event that they experience to the investigator. Beginning with Visit 2, investigators should assess for adverse events at each visit and record the event on the appropriate adverse event CRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate adverse event on the CRF.

Any medical condition that is present when a patient is screened or present at baseline that does not deteriorate should not be reported as an adverse event. However, medical conditions

or signs or symptoms present at baseline and that change in severity or seriousness at any time during the study should be reported as an adverse event.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen will be reported as adverse events or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

The investigator will rate the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of Yes or No.

Severity:

- Mild – An event that is usually transient in nature and generally not interfering with normal activities.
- Moderate – An event that is sufficiently discomforting to interfere with normal activities.
- Severe – An event that is incapacitating with inability to work or do usual activity or inability to work or perform normal daily activity.

Causality Assessment:

The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

- No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.
- Yes – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

- The temporal sequence from study medication administration
- The event should occur after the study medication is given. The length of time from study medication exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases
- Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication
- The other medications the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study medication
- Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses
- The exposure to stress might induce adverse changes in the patient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study medication
- The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study medication should be considered.

Unexpected Adverse Events – An unexpected adverse event is an adverse event either not previously reported or where the nature, seriousness, severity, or outcome is not consistent with the current Investigator's Brochure.

10.2.1. Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that meets **any** of the following criteria:

- Results in death
- Is life-threatening- Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization- Note: In general, hospitalization for treatment of a pre-existing condition(s) that did not worsen from baseline is not considered adverse events and should not be reported as SAEs.
- Results in disability/incapacity
- Is a congenital anomaly/birth defect;
- Is an important medical event- Note: Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

By design of this study SAEs that are endpoint events will only be recorded for the endpoint determination and not captured as SAEs. The intention is that the endpoint events are not reported to IRBs as SAEs, unless the IRB requires that these are reported. Investigators should specifically inform their institution/IRB of this plan and confirm whether or not they want the endpoint events reported. By agreement with the US FDA, these endpoints will also not be reported to the US FDA as SAEs; rather they will be reported as endpoint events. Following adjudication if the event is determined to not meet the criteria for an event, the event will be evaluated as an SAE beginning with that day as Day 0.

10.3. Serious Adverse Event Reporting – Procedure for Investigators

10.3.1. Initial Reports

All SAEs occurring from the time of informed consent until 28 days following the last administration of study medication must be reported to the Sponsor or designee **within 24 hours** of the knowledge of the occurrence (this refers to any adverse event that meets any of

the aforementioned serious criteria). SAEs that the investigator considers related to study medication occurring after the 28-day follow-up period will also be reported to the Sponsor or designee.

The investigator is required to submit SAE reports to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local requirements. All investigators involved in studies using the same investigational medicinal product (IMP) will receive any Suspected Unexpected Serious Adverse Reaction (SUSAR) reports for onward submission to their local IRB as required. All reports sent to investigators will be blinded.

In addition, regulatory agencies will be notified of SAEs per the requirements of the specific regulatory jurisdiction regulations and laws.

10.3.2. Follow-Up Reports

The investigator must continue to follow the patient until the SAE has subsided, or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., laboratory test reports, patient discharge summary, or autopsy reports) to the Sponsor or designee via fax or email.

10.3.3. Reporting by the Sponsor

IRBs and IECs will be informed of SUSARs according to local requirements. Cases will be unblinded for reporting purposes as required.

10.4. Exposure *In Utero* During Clinical Trials

If a patient becomes pregnant during the study, the investigator should report the pregnancy to the Sponsor or designee within 24 hours of being notified. The Sponsor or designee will then forward the Exposure *In Utero* form to the investigator for completion.

The patient should be followed by the investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the Sponsor or designee. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

11. TREATMENT DISCONTINUATION/PATIENT WITHDRAWAL

Patients may withdraw from the study at any time and for any reason. Study drug administration may also be discontinued at any time, at the discretion of the investigator. In any case, follow-up for efficacy and safety should be continued.

11.1. Reasons for Early Study Drug Discontinuation

Study drug discontinuation should be avoided as much as possible, but may be done for any of the following reasons:

- Patient withdraws consent or requests early discontinuation from the study for any reason. Patients should be encouraged to continue to participate in the study for the entire duration of the study even if they choose not to take study medication any longer.
- Occurrence of a clinical or laboratory adverse event, either serious or non-serious, at the discretion of the investigator. The Sponsor or designee should be notified if a patient is discontinued because of an adverse event or laboratory abnormality. It is recommended that, unless clear contraindications arise, patients be strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy should, if possible, be brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. The following should be considered reason for discontinuation:
    - ALT > 3x ULN and bilirubin > 1.5x ULN
    - ALT >5x ULN
    - ALT >3x ULN and appearance or worsening of hepatitis
    - ALT > 3x ULN persisting for >4weeks
    - ALT > 3x ULN and cannot be monitored weekly for 4 weeks
- Any medical condition or personal circumstance that, in the opinion of the investigator, exposes the patient to risk by continuing in the study or precludes adherence to the protocol.
- Sponsor discontinues the study.
- A TG value that is flagged as critically high, i.e., >1000 mg/dL (11.29 mmol/L), and confirmed as critically high by a repeat measurement (new fasting blood sample) within 7 days. In this case, a patient may be discontinued from study drug (with the option to remain ODIS) and other lipid-altering medications may be (re)initiated. If the TG value is flagged as >2000 mg/dL (22.58 mmol/L) then appropriate medical action can be taken by the investigator as soon as possible.

Occurrence of an outcome event according to the judgment of the investigator is not considered a valid reason for study drug discontinuation.

Patients whose treatment with study medication is discontinued early, and have not withdrawn consent, will stay in study and will be monitored until the end of the study. Patients that continue in the study after indefinite cessation of therapy will be characterized as Off Drug In Study (ODIS). ODIS patients should be asked to return to the study site for an interim visit once the patient has been off study drug for >30 days. Procedures at this visit are consistent with those at Visit 5. If not contraindicated, patients will also have the option to restart study medication at any point once characterized as ODIS.

The reason for study drug discontinuation or interruption will be recorded on the CRF.

11.2. Follow-Up after Early Study Drug Discontinuation/Lost to Follow-Up

- Patients who prematurely discontinue study drug are not to be replaced.
- All randomized patients must be followed up according to the study flowchart until the study end date or death, regardless of whether they discontinue study drug prematurely or not. Any event occurring after early study drug discontinuation will be recorded up through the study end date.

- In order to follow the medical status of the patients, especially when they discontinued the study, investigators are encouraged to obtain information from the patient's primary care practitioner (physician or any other medical care provider). Investigators are also requested to try as much as possible to re-contact those patients at the end of the trial to obtain at least their vital status as well as their status with respect to the primary endpoint, and thus avoid lost to follow-up for the efficacy assessment.
- If patients are lost to follow-up, the CRF must be completed up to the last visit or contact.

12. STATISTICS

12.1. Analysis Populations

12.1.1. Randomized Population

The randomized population will include all patients who sign the informed consent form and are assigned a randomization number at Visit 2 (Day 0).

12.1.2. Intent-to-Treat Population

The Intent-to-Treat (ITT) population will consist of all randomized patients who take at least one dose of study drug. The ITT population is the primary analysis population. All efficacy analyses will be performed on the ITT population.

12.1.3. Per-Protocol Population

The per-protocol (PP) population will include all ITT patients without any major protocol deviations, and who had ≥80% compliance with study drug while on treatment (up to discontinuation for patients whose treatment is terminated early). The per-protocol efficacy analysis for CV events will be restricted to each patient's time on study drug plus 30 days thereafter.

12.1.4. Safety Population

All safety analyses will be conducted based on the safety population, which is defined as all randomized patients who receive at least one dose of study drug. This is the same as the ITT population.

12.2. Statistical Methods

Safety and efficacy variables will be analyzed using appropriate statistical methods to be described in detail in a separate Statistical Analysis Plan (SAP). The SAP will be finalized before study unblinding.

12.2.1. Patient Disposition and Demographic/Baseline Characteristics

The numbers of patients screened, the number of patients randomized per treatment group (randomized population), and the number of patients in the ITT and PP populations by treatment group will be listed.

For randomized patients who discontinued treatment with study drug, the primary reason for discontinuation will be listed and summarized by treatment group.

Summary statistics (mean, standard deviation, median, minimum and maximum) will be provided by treatment group for demographic characteristics (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., body weight, height, and body mass index) in the ITT and PP populations.

Demographic data and baseline characteristics will be compared among treatment groups for the ITT and PP population. Differences in demographic and baseline characteristics will be tested using a chi-square test (for categorical variables) or a 1-way analysis of variance model with treatment as a factor (for continuous variables). The p-values will be used as descriptive statistics, primarily as an assessment of the adequacy of randomization.

12.2.2. Study Medication Exposure and Compliance

The final compliance to study drug will be calculated as the percent of doses taken relative to doses scheduled to be taken. Overall percent compliance will be calculated per patient in the ITT and PP populations and summarized by treatment group using summary statistics (n, mean, standard deviation, median, minimum, and maximum).

12.2.3. Concomitant Therapies

Concomitant medication/therapy verbatim terms will be coded using the latest version of the World Health Organization Drug Dictionary. The numbers and percentages of patients in each treatment group taking concomitant medications will be summarized by anatomic and therapeutic chemical classification and preferred term.

12.2.4. Analysis of Efficacy

For efficacy endpoints including CV events, only adjudicated events will be included in the final statistical analyses.

12.2.4.1. Summary Statistics

Summary statistics (n, mean, standard deviation, median, minimum, and maximum) for the baseline and post-baseline measurements, the percent changes, or changes from baseline will be presented by treatment group and by visit for all efficacy variables to be analyzed. The summary statistics will include changes in body weight and body mass index from baseline by treatment group and by visit.

12.2.4.2. Primary Endpoint

The primary efficacy endpoint is the time from randomization to the first occurrence of any component of the composite of the following clinical events:

- CV death,
- Nonfatal MI (including silent MI),
- Nonfatal stroke,
- Coronary revascularization,
- Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing.

The analysis of the primary efficacy endpoint will be performed using the log-rank test comparing the 2 treatment groups (AMR101 and placebo) and including the stratification factor “CV risk category”, use of ezetimibe and geographical region (Westernized, Eastern European, and Asia Pacific countries) (each as recorded in the IWR at the time of

enrollment) as covariates. Treatment difference will be tested at alpha level of 0.0476 accounting for one interim efficacy analysis. The hazard ratio for treatment group (AMR101 vs. placebo) from a Cox proportional hazard model that includes the stratification factor will also be reported, along with the associated 95% confidence interval. Kaplan-Meier estimates from randomization to the time to the primary efficacy endpoint will be plotted.

The size and direction of the treatment effects of the individual components of the composite endpoint and their relative contribution to the composite endpoint will be determined as well.

12.2.4.3. Secondary Endpoints

The statistical analyses of the secondary endpoints will be analyzed by the same log-rank test specified above for the primary efficacy endpoint. Treatment differences will be tested at alpha level of 0.05 using a sequential procedure for controlling type 1 error starting with the key secondary variable. The remaining secondary variables will be tested in the order specified in Section 9.2.2. Estimates of the hazard ratios from the Cox proportional hazard model and the associated 95% confidence intervals will also be provided. Kaplan-Meier estimates from randomization the time to the secondary efficacy endpoints will be plotted.

12.2.4.4. Tertiary Endpoints

For event rates, the statistical analyses of the tertiary endpoints (see section 9.2.3) will be similar to the analysis of the secondary efficacy endpoints. All tertiary analyses will be conducted for the ITT population. No adjustments for multiple testing will be made.

For measurements of lipids, lipoproteins and inflammatory markers the change from baseline will be analyzed in the units of each marker, and the percent change from baseline. Since these biomarkers are typically not normally distributed, the Wilcoxon rank-sum test will be used for treatment comparisons of the percent change from baseline, and medians and quartiles will be provided for each treatment group. The medians of the differences between the treatment groups and 95% confidence intervals will be estimated with the Hodges-Lehmann method.

New onset diabetes is defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period (i.e. patients with no history of diabetes at randomization, with the test as listed in Appendix C).

12.2.4.5. Exploratory Subgroup Analyses

Subgroup analyses of the primary and key secondary endpoints (as defined in the Statistical Analysis Plan) will be performed. All subgroup analyses will be conducted for the ITT population. No adjustments for multiple testing will be made.

Log-rank tests, treatment effects and the associated 95% confidence intervals for the primary and key secondary efficacy endpoints within each subgroup will be provided using the Cox proportional hazard model with treatment (AMR101 or placebo), and stratification as a factor (with the exception of the subgroup analyses of those subgroup variables related to the stratification factors, i.e., CV risk category that will not have stratification as a factor).

Subgroups including, but not limited to the following, will be explored. A complete list will be prospectively defined in the Statistical Analysis Plan.

Demographics:

- Gender,
- age (<65 yr and ≥65 yr),
- race (white and nonwhite, or any other subset with at least 10% of the total number of patients),
- geography (western vs. non-western)

Disease Parameters:

- CV risk category,
- the presence/absence of diabetes at baseline,
- renal impairment

Treatment Parameters:

- by statin intensity (statin type and regimen),
- relevant concomitant medications,

Baseline Lipid and Lipoprotein Parameters:

- LDL-C (by tertile),
- HDL-C (by tertile),
- TG (by tertile),
- TG ≥150 mg/dL,
- TG ≥200 mg/dL and TG <200 mg/dL,
- combined highest tertile for TG and lowest tertile for HDL-C,
- hs-CRP (≤3 mg/L and >3 mg/L),
- Apo B (by tertile),
- non-HDL-C (by tertile)

The consistency of the treatment effects in subgroups will be assessed for the primary and key secondary efficacy endpoints. For each subgroup variable, a Cox proportional hazard model with terms for treatment, stratification factors (with the exception of those subgroup variables related to the stratification factors, i.e., CV risk category), subgroup, and treatment-by-subgroup interaction will be performed. The main treatment effect will not be tested with this model. P-values for testing the interaction terms will be provided.

12.2.4.6. Interim Efficacy Analysis

One interim analysis will be performed for the primary efficacy endpoint using best available data (adjudicated events and site reported endpoints) based on data when approximately 60% of the total number of primary endpoint events is reached. The interim analysis will be based on a group sequential design that includes early stopping rules for benefit while preserving the overall Type I error rate (O'Brien-Fleming). This allows for interim analysis and preserves the overall Type I error probability of $\alpha=0.05$ for the primary endpoint.

Approximately 1612 primary efficacy endpoint events are planned to be observed during the trial, based on sample size calculation assumptions. Therefore, the interim analysis will occur after at least 967 primary efficacy endpoint events have been observed. According to this

boundary, the critical p-value at the interim analysis has to be p<=0.0076, resulting in the final evaluation p-value of 0.0476.

The interim results of the study will be monitored by an independent DMC. The analyses will be performed by the independent statistical group unblinded to the treatment assignment. The results will be reported only to the DMC. The unblinded information will not be released to sponsor under any circumstance before the completion of the study. Specific statistical guidelines for data monitoring will be discussed and formalized in a separate Interim Statistical Analysis Plan and DMC Charter.

12.2.5. Analysis of Safety

All analyses of safety will be conducted on the safety population, which is defined as all randomized patients who receive at least one dose of study drug. The safety assessment will be based on the frequency of adverse events, physical exams, vital signs and safety laboratory tests.

Adverse events with new onset during the study between the initiation of study drug and 30 days after the last dose of study drug for each patient will be considered treatment-emergent (TEAEs). This will include any AE with onset prior to initiation of study drug and increased severity after the treatment initiation.

Treatment-emergent adverse events will be summarized by system organ class and preferred term, and by treatment. This will include overall incidence rates (regardless of severity and relationship to study drug), and incidence rates for moderate or severe adverse events. A summary of SAEs and adverse events leading to early discontinuation from the study will be presented through data listings.

Safety laboratory tests and vital signs will be summarized by post-treatment change from baseline for each of the parameters using descriptive statistics by treatment group. Those patients with significant laboratory abnormalities will be identified in data listings. Additional safety parameters will be summarized in data listings.

12.3. Sample Size Determination

Sample size estimation is based on the assumption that the primary composite endpoint (time from randomization to the first occurrence of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina requiring hospitalization) would be relatively reduced by 15%, from an event rate by 4 years of 23.6% in the placebo group to 20.5% in the AMR101 group. It is expected that a minimum of 1612 primary efficacy endpoint events will be required during the study. A total of approximately 6990 patients are needed to be able to detect this difference at 4.76% significance level (because of the interim analysis described in Section 12.2.4.6) and with 90% power, assuming an 18-month enrollment period and a median follow-up of 4 years. The current sample size calculation is based on an estimated placebo yearly event rate of 5.9% (23.6% over 4 years). To protect against the possibility that the actual placebo event rate is lower than estimated, an extra 1000 patients will be enrolled (approximately 7990 patients in total). By adding the extra 1000 patients, the event rate in the placebo group could be 5.2% per year (20.8% over 4 years) without having to modify the other sample size assumptions.

Since this is an events-driven trial, the 'sample size' is the number of events rather than the number of patients. The number of events that occur depends primarily on three factors: how many patients are enrolled, the combined group event rate, and how long the patients are followed. Because of the difficulty in predicting the combined event rate, the sponsor will monitor that event rate as the trial progresses. If the combined event rate is less than anticipated, either increasing the number of patients, extending the length of follow-up, or a balance of adjusting both factors may be necessary to achieve the sample size of 1612 events.

Before completing the enrollment phase of the trial, *i.e.* approximately 3- to 6-months prior to the projected enrollment of the 7990th patient, the actual event rate based on pooled, blinded accumulation of primary efficacy endpoint events will be calculated and plotted. If those analyses suggest the number of patients with at least 1 adjudicated, primary event (and appropriately accounting for patients with potential primary events for which the adjudication process is then incomplete) is consistent with projections, then the study could continue toward the protocol-specified target enrollment of 7990 patients. However, if the number of such events appears less than, and inconsistent with projections, the Sponsor will consider (under blinded conditions) re-calculating the number of patients needed to achieve the target number of events within the desired timeline or extend the follow-up period. If the projected increase in number of patients is ≤ 25% of the original 7990 target population, the Sponsor may, with documented approval of both the REDUCE-IT Steering Committee and the Data Monitoring Committee, extend enrollment to the revised target number without need for an additional protocol amendment. Under those conditions, all principal investigators, ethics committees, and regulatory authorities associated with the protocol will be promptly notified of the action. Should the projected increase in number of patients be more than 25% above the original 7990 target (*i.e.* more than 1998 additional patients) a formal protocol amendment will be initiated.

If the number of patients to be studied is increased, the enrollment phase will be extended to allow enrollment of the additional patients.

At completion of study enrollment, the actual number of patients randomized may vary from the target number (either original or revised) as a result of the inherent lag between the date the last patient started screening and the date the last patient was randomized.

13. MONITORING, DATA MANAGEMENT, AND RECORD KEEPING

13.1. Data Management

13.1.1. Data Handling

Data will be recorded at the site on CRFs. All entries on a CRF are ultimately the responsibility of the Investigator, who is expected to review each form for completeness and accuracy before signing. A CRF must be completed for each randomized patient. The CRFs and source documents must be made available to the Sponsor and/or its designee.

13.2. Record Keeping

The Investigator must maintain all documents and records, originals or certified copies of original records, relating to the conduct of this trial, and necessary for the evaluation and reconstruction of the clinical trial. This documentation includes, but is not limited to protocol, CRFs, AE reports, patient source data (including records of patients, patient visit

logs, clinical observations and findings), correspondence with health authorities and IRB, consent forms, inventory of study product, Investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures, and laboratory director curriculum vitae.

The Investigator and affiliated institution should maintain the trial documents as required by the applicable regulations. The Investigator and affiliated institution should take measures to prevent accidental or premature destruction of documents. Clinical trial documents must be kept in the clinical site's archives indefinitely, unless written authorization is obtained from the Sponsor.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator and research institution agree that the Sponsor, their representatives and designees, the IRB or IEC, and representatives from worldwide regulatory agencies will have the right, both during and after the clinical trial, to review and inspect pertinent medical records related to the clinical trial.

15. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and/or its designee(s) will perform quality control and quality assurance checks of all clinical trials that it sponsors. Before the enrollment of any patient in this study, the Sponsor or its designee will review with the investigator and site personnel the following documents: protocol, Investigator's Brochure, CRFs and procedures for their completion, the informed consent process, and the procedure for reporting SAEs. Site visits will be performed by the Sponsor and/or its designees. During these visits, information recorded on the CRFs will be verified against source documents and requests for clarification or correction may be made. After the CRF data is entered by the site, the Sponsor or designee will review for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical trial. If necessary, requests for clarification or correction will be sent to investigators.

By signing the protocol, the Sponsor agrees directly or through its designee(s) to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice (GCP), International Conference on Harmonization (ICH) and other applicable regulations.

16. ETHICS AND GOOD CLINICAL PRACTICE COMPLIANCE

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well being of trial patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. In this study,

the 2008 version of the Declaration of Helsinki will be adhered to. It can be found on the website of The World Medical Association:

http://www.wma.net/en/30publications/10policies/b3/17c.pdf

17. INFORMED CONSENT

Prior to participation in a study, the participant, or participant's legal representative/impartial witness must sign an IRB/IEC-approved written informed consent form (ICF). The approved written informed consent must abide to all applicable laws in regards to the safety and confidentiality of the patients. To obtain and document informed consent, the Investigator should comply with applicable regulations; adhere to GCP standards and the ethical principles in the Declaration of Helsinki (see Section 16).

The language in the oral and written information about the trial, including the written informed consent form should be as non-technical as practical and should be understandable to the participant or participant's legal representative/impartial witness, where applicable. Before informed consent is obtained, the Investigator should provide the participant, or participant's legal representative/impartial witness ample time and opportunity to inquire about the trial and to decide whether or not to participate.

All questions about the trial should be answered to the satisfaction of the participant, or the participant's legal representative/impartial witness. The written ICF should be signed and personally dated by the participant or participant's legal representative/impartial witness, and by the person who conducted the informed consent discussion. Participants will be informed that participation is voluntary and that he/she can withdraw from the study at any time. A signed copy of the consent form must be given to the participant, and this fact will be documented in the CRF.

Of special concern regarding informed consent is the collection of blood samples for genetic analysis. Local regulations may not allow the collection of blood samples for genetic testing or the shipment of blood samples for genetic testing outside the region. In these cases, blood samples for genetic testing will not be collected, and the portion of the ICF describing the genetic component of the study will not be included. If blood samples for genetic testing will be collected, the ICF will clearly indicate that a sample will be drawn for this purpose, but that the participant has the right to refuse this procedure.

18. PUBLICATION POLICY

The Steering Committee (SC) is responsible for the reporting and publication of the study results. The Sponsor will be provided a reasonable opportunity to review such manuscripts prior to journal submission. The results of the study will be published irrespective of whether the endpoints are met, or whether the results are regarded positive or negative.

Confidentiality, publication, and patent applications related to unpublished study-related information and unpublished information given to the site investigators by the Sponsor and/or its designee(s) shall be handled as set forth in the Clinical Trial Agreement.

19. FINANCING AND INSURANCE

19.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a Clinical Trial Agreement with the Sponsor and/or its designee(s). This agreement will include the financial information agreed upon by the parties.

19.2. Insurance Compensation

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the investigator and the other collaborators from maintaining their own liability insurance policy. An insurance certificate will be provided to the IRB/IEC and Competent Authority according to country specific regulatory requirements.

20. COMPLETION OF STUDY

The end of the study will be at the time of the last patient-last visit of the follow-up period of the study. The IRB and IEC will be notified about the end of the study according to country-specific regulatory requirements.

21. STUDY ADMINISTRATIVE INFORMATION

21.1. Protocol Amendments

Any amendments to the study protocol considered to be a substantial amendment will be communicated to the investigator by the Sponsor or its designee. All substantial protocol amendments will undergo the same review and approval process as the original protocol and may be implemented after it has been approved by the IRB/IEC and Competent Authority, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC and Competent Authority according to all relevant country-specific regulatory requirements.

A protocol amendment is considered to be a substantial amendment if it is likely to affect the safety, physical, or mental integrity of patients in the study; the scientific value of the study; the conduct or management of the study; or the quality or safety of any IMP used in the study.

Any other minor changes to the protocol not considered to be substantial amendments will not need prior approval of the IRB/IEC and Competent Authority and will be communicated to the investigator by the Sponsor or its designee.

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23. INVESTIGATOR'S AGREEMENT

This document is a confidential communication of Amarin. The authorized investigators agree to personally conduct or supervise the conduct of this investigational study in compliance with the current protocol, good clinical practices, and all applicable laws, regulations, and guidelines. No changes will be made to the protocol without prior notification to Amarin, except to protect the safety, rights, and welfare of the study patients, and always in compliance with all applicable laws, regulations, and guidelines. Acceptance of this document constitutes the agreement by the Investigator that no unpublished information contained herein or related to the study will be published or disclosed without prior written approval from Amarin.

I have read this protocol in its entirety and agree to conduct the study accordingly.

_____ _____

Signature Date
Principal Investigator

_____

Printed Name

APPENDIX A: SCHEDULE OF PROCEDURES

	Screening		Follow-Up (FU) [13]						
Study Day	**Up to 42 days before Day 0**	**If a Visit 1.1 takes place, Visit 1 may occur up to 60 days before Day 0[2]**	**0**	**120 ± 10**	**360 ± 10**	**720 ± 10**	**1080 ± 10**	**1440 ± 10**	**1800 + 30**
Months of FU			**0**	**4**	**12**	**24**	**36**	**48**	**60**
Years of FU			**0**	**0.33**	**1**	**2**	**3**	**4**	**5**
Visit #	**1**	**1.1**	**2**	**3**	**4**	**5**	**6**	**7**	**LV [14]**
Study Procedures:									
Informed Consent	X								
Medical, Surgical & Family History	X								
Demographics	X								
Evaluate inclusion / exclusion criteria	X [1]	X [3]	X						
Physical Examination			X	X	X	X	X	X	X
Weight, Height [4]	X		X	X	X	X	X	X	X
Vital Signs [5]	X	X	X	X	X	X	X	X	X
Waist Circumference			X			X			X
12-Lead ECG	X		X		X	X	X	X	X
Urine pregnancy test [6]	X		X						
Concomitant Meds	X	X	X	X	X	X	X	X	X
Randomization			X						
Dosing at the Research Site [7]			X	X	X	X	X	X	
Efficacy events				X	X	X	X	X	X
AE Evaluations			X	X	X	X	X	X	X
Compliance Check [8]				X	X	X	X	X	X
Chemistry and hematology [9]	X	X [3]	X	X	X	X	X	X	X
Fasting lipid profile [10]	X	X [3]	X	X	X	X	X	X	X
Genetic testing [11]			X						
Biomarkers: hs-CRP, apo B, hsTNT			X			X			X
Fasting blood sample for archiving [12]			X		X	X	X	X	X

1. Includes procedures and (fasting) blood samples (for example, hs-CRP, calculated creatinine clearance) as needed to determine the CV risk category (see inclusion criteria).
2. Screening visit to re-evaluate inclusion/exclusion criteria for patients who are not eligible for participation based on data from Visit 1.
3. Inclusion/exclusion criteria will be re-evaluated for selected study procedures that are performed on Visit 1.1 because patients failed to meet them at Visit 1.
4. Height at first screening visit only.
5. Vital signs, including systolic and diastolic blood pressure (mmHg), heart rate, respiratory rate and body temperature. Participants must be seated for at least 5 minutes before assessments of vital signs.
6. For women of childbearing potential.
7. The patients will fast of at least 10 hours before arriving at the Research Site, when all fasting blood samples will be obtained. After blood samples are obtained, patients will be given drug with food.
8. Review study drug compliance by unused capsule count, discuss with and counsel patients about compliance if needed; final study compliance at last visit.
9. Safety Laboratories — Complete Blood Count: Includes RBC, Hgb, Hct, WBC and differential, and platelet count. Biochemistry includes total protein, albumin, alkaline phosphatase, ALT, AST, total bilirubin, glucose, calcium, electrolytes (sodium, potassium, chloride), blood urea nitrogen (BUN), serum creatinine, uric acid, creatine kinase, HbA1c. Safety labs may be repeated as deemed necessary by the Investigator.
10. TG, TC, HDL-C, LDL-C, non-HDL-C, and VLDL-C.
11. Fasting blood sample that will be stored for future genetic testing at the discretion of the sponsor. This sample is optional as local regulations may prohibit genetic samples to be collected or shipped outside the country, or patients may not consent.
12. Used at the sponsor's discretion to perform repeat analyses described in the protocol or to perform other tests related to cardiovascular health.
13. Site personnel will contact each patient by telephone in-between Visit 2 and Visit 3 and between Visit 3 and Visit 4. After Visit 4 contact will be made every 3 months. The purpose of the contact is to collect information about efficacy events, adverse events, concomitant medications, confirm patient's current address and contact information and remind patients about taking their study medication and logistics for the next visit.
14. The last visit (LV) may occur within 30 day after the study end date as determined by the DMC; the study end date is tentatively schedule for Day 1800 but the actual date as determined by the DMC may be different.

APPENDIX B: STANDARDIZED DEFINITIONS FOR END POINT EVENTS IN CARDIOVASCULAR TRIALS

References:
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23.1. Definition of Cardiovascular Death

Cardiovascular death includes death resulting from an acute myocardial infarction, sudden cardiac death, death due to congestive heart failure (CHF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other cardiovascular causes.

Classifying CV mortality more specifically (MI, sudden death etc.) is usually not needed for outcome trials. In general, such classification is difficult because the classifications refer both to underlying cause (e.g., acute MI) and to mode of death (sudden/arrhythmic, progression of CHF). The following definitions can, however, be used if desired.

1. **Death due to Acute Myocardial Infarction** refers to a death by any mechanism (arrhythmia, CHF) within 30 days after a MI related to the immediate consequences of the MI, such as progressive CHF or recalcitrant arrhythmia.

   Mortal events that occur after a "break" (e.g., a CHF and arrhythmia-free period of at least a week) should be classified as CV or non-CV death, and if classified as a CV death, should be attributed to the immediate cause, even though the MI may have increased the risk of that event (e.g., the risk of arrhythmic death is increased for many months after an acute MI).

Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI (see Chapter 4, Universal Definition of MI) or by autopsy findings showing recent MI or recent coronary thrombosis.

Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)), or to treat a complication resulting from MI, should also be considered death due to acute MI.

Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

2. **Sudden Cardiac Death** refers to a death that occurs unexpectedly, not following an acute acute MI, and includes the following deaths:
    a. Death witnessed and instantaneous without new or worsening symptoms
    b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest an acute MI
    c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
    d. Death after unsuccessful resuscitation from cardiac arrest
    e. Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology
    f. Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

    General Considerations
    A subject seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death."

Deaths for which there is no information beyond "Patient found dead at home" may be classified as "death due to other cardiovascular causes" or in some trials, "undetermined cause of death." Please see Definition of Undetermined Cause of Death, for full details.

3. **Death due to Congestive Heart Failure** refers to a death in association with clinically worsening symptoms and/or signs of heart failure (see Definition of Heart Failure Event). Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

4. **Death due to Stroke** refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke (see Definition of Transient Ischemic Attack and Stroke).

5. **Death due to Cardiovascular Procedures** refers to death caused by the immediate complications of a cardiac procedure.

6. **Death due to Cardiovascular Hemorrhage** refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage (see Definition of Transient Ischemic Attack and Stroke), non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

7. **Death due to Other Cardiovascular Causes** refers to a CV death not included in the above categories (e.g., pulmonary embolism or peripheral arterial disease).

23.2. Definition of Non-Cardiovascular Death

Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. Detailed recommendations on the classification of non-cardiovascular causes of death are beyond the scope of this document. The level of detail required and the optimal classification will depend on the nature of the study population and the anticipated

number and type of non-cardiovascular deaths. Any specific anticipated safety concern should be included as a separate cause of death. The following is a suggested list of non-cardiovascular* causes of death:

- Pulmonary
- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Hemorrhage that is neither cardiovascular bleeding nor a stroke
- Accidental (e.g., physical accidents or drug overdoses) or trauma
- Suicide
- Prescription Drug Error (e.g., prescribed drug overdose, use of inappropriate drug, or drug-drug interaction)
- Neurological process that is not a stroke or hemorrhage
- Other non-CV
- Malignancy

  Malignancy should be coded as the cause of death if:
  - Death results directly from the cancer; or
  - Death results from a concurrent illness that could be a consequence of a cancer or
  - Death results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer
  - Death results from an illness that is not a consequence of a cancer

Cancer deaths may arise from cancers that were present prior to randomization or which developed subsequently. It may be helpful to distinguish these two scenarios (i.e. worsening of prior malignancy; new malignancy).

- Suggested categorization includes common organ systems, hematologic, or unknown.

23.3. Definition of Undetermined Cause of Death

Undetermined Cause of Death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause. Inability to classify the cause of death may be due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In general, the use of this category of death should be discouraged and should apply to a minimal number of patients in well-run clinical trials.

A common analytic approach for cause of death analyses is to assume that all undetermined cases are included in the cardiovascular category (e.g., presumed cardiovascular death, specifically "death due to other cardiovascular causes"). Nevertheless, the appropriate classification and analysis of undetermined causes of death depends on the population, the intervention under investigation, and the disease process. The approach should be prespecified and described in the protocol and other trial documentation such as the end point adjudication procedures and/or the statistical analysis plan.

23.4. Definition of Myocardial Infarction

1. **General Considerations**

   The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. In general, the diagnosis of MI requires the combination of:

   - Evidence of myocardial necrosis (either changes in cardiac biomarkers or postmortem pathological findings); and
   - Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

   The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs.

MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

2. **Criteria for Myocardial Infarction**

a. Clinical Presentation

The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be take into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, congestive heart failure, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.

b. Biomarker Elevation

For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. CK-MB and troponin are preferred, but CK may be used in the absence of CK-MB and troponin.

For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin will be required. The specific criteria will be referenced to the URL.

In many studies, particularly those in which patients present acutely to hospitals which are not participating sites, it is not practical to stipulate the use of a single biomarker or assay, and the locally available results are to be used as the basis for adjudication. However, if possible, using the same cardiac biomarker assay and preferably, a core laboratory, for all measurements reduces inter-assay variability.

Since the prognostic significance of different types of myocardial infarctions (e.g., periprocedural myocardial infarction versus spontaneous myocardial infarction) may be different, consider evaluating outcomes for these subsets of patients separately.

c. Electrocardiogram (ECG) Changes

Electrocardiographic changes can be used to support or confirm a MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

- **Criteria for acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB))**:

  - ST elevation

    New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.
  - ST depression and T-wave changes New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser

ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

- **Criteria for pathological Q-wave**
  - Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
  - Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)
  - R-wave 0.04 s in V1–V2 and R/S ratio >1 with a concordant positive T-wave in the absence of a conduction defect

The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

- **Criteria for Prior Myocardial Infarction**
  - Pathological Q-waves, as defined above
  - R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive Twave in the absence of a conduction defect

3. **Myocardial Infarction Subtypes**

Several MI subtypes are commonly reported in clinical investigations and each is defined below:

a. Spontaneous MI

i. Detection of rise and/or fall of cardiac biomarkers with at least one value above the URL with at least one of the following:

- Clinical presentation consistent with ischemia
- ECG evidence of acute myocardial ischemia
- New pathological Q waves

- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Autopsy evidence of acute MI

ii. If biomarkers are elevated from a prior infarction, then a spontaneous myocardial infarction is defined as:

1. One of the following:

- Clinical presentation consistent with ischemia
- ECG evidence of acute myocardial ischemia
- New pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Autopsy evidence of acute MI

AND

2. Both of the following:

- Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI*
- ≥ 20% increase (and > URL) in troponin or CK-MB between a measurement made at the time of the initial presentation and a further sample taken 3-6 hours later

*If biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent MI is generally not possible.

b. Percutaneous Coronary Intervention-Related Myocardial Infarction

Peri-PCI MI is defined by any of the following criteria. Symptoms of cardiac ischemia are not required.

i. Biomarker elevations within 48 hours of PCI:

- Troponin or CK-MB (preferred) > 3 x URL *and*
- No evidence that cardiac biomarkers were elevated prior to the procedure;

OR

- Both of the following must be true:
  - ≥ 50%1 increase in the cardiac biomarker result
  - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI

ii. New pathological Q waves

iii. Autopsy evidence of acute MI

c. Coronary Artery Bypass Grafting-Related Myocardial Infarction

Peri-coronary artery bypass graft surgery (CABG) MI is defined by the following criteria. Symptoms of cardiac ischemia are not required.

i. Biomarker elevations within 72 hours of CABG:

- Troponin or CK-MB (preferred) > 5 x URL and
- No evidence that cardiac biomarkers were elevated prior to the procedure;

OR

- Both of the following must be true:
  - ≥ 50%[2] increase in the cardiac biomarker result
  - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI.

AND

ii. One of the following:

- New pathological Q-waves persistent through 30 days
- New persistent non-rate-related LBBB

- Angiographically documented new graft or native coronary artery occlusion Other complication in the operating room resulting in loss of myocardium
- Imaging evidence of new loss of viable myocardium

Data should be collected in such a way that analyses using ≥ 20% or ≥ 50% could both be performed.

OR

iii. Autopsy evidence of acute MI

d. Silent Myocardial Infarction

Silent MI is defined by the following:

i. No evidence of acute myocardial infarction

AND

ii. Any one of the following criteria:

- New pathological Q-waves. A confirmatory ECG is recommended if there have been no clinical symptoms or history of myocardial infarction.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause
- Autopsy evidence of a healed or healing MI

(NOTE: In the case of evanescent Q waves, the last ECG will determine whether a silent infarction has occurred.)

23.5. Common Classification Schemes for Myocardial Infarction Categories

For some trials, categorization of MI end points may be helpful or necessary using one or more of the classification schemes below:

1. **By the Universal MI Definition:**

a. Clinical Classification of Different Types of Myocardial Infarction

- Type 1

Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection

- Type 2

  Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension

- Type 3

  Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood

- Type 4a

  Myocardial infarction associated with PCI

- Type 4b

  Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy

- Type 5

  Myocardial infarction associated with CABG

b. Sample Clinical Trial Tabulation of Randomized Patients by Types of Myocardial Infarction

Types of MI	Treatment A Number of patients (N =)	Treatment B Number of patients (N =)
MI Type 1	n, %	n, %
MI Type 2	n, %	n, %
MI Type 3	n, %	n, %
MI Type 4	n, %	n, %
MI Type 5	n, %	n, %
Total number	n, %	n, %
N = total number of patients; n = number of patients with a particular MI.		

2. **By Electrocardiographic Features:**

    - **ST-Elevation MI (STEMI)**
        - Additional subcategories may include:
            - Q-wave
            - Non-Q-wave
            - Unknown (no ECG or ECG not interpretable)
    - **Non-ST-Elevation MI (NSTEMI)**
        - Additional subcategories may include:
            - Q-wave
            - Non-Q-wave
            - Unknown (no ECG or ECG not interpretable)
    - **Unknown (no ECG or ECG not interpretable)**

      **All events adjudicated as MI will be classified as STEMI, NSTEMI, or Unknown; however, it is acknowledged that a significant proportion of peri-procedural (PCI or CABG) events may have missing, inadequate or uninterpretable ECG documentation.*

3. **By Biomarker Elevation (per Universal MI Definition):**

   The magnitude of cardiac biomarker elevation can be calculated as a ratio of the peak biomarker value divided by the 99th percentile URL.

   The biomarker elevation can be provided for various MI subtypes, as shown in the example below.

Multiples X 99%	M1 Type (spontaneous)	MI Type 2 (secondary)	M1 Type 3 (sudden death)	MI Type 4** (PCI)	MI Type 5** (CABG)	Total Number
1-2X						
>2-3X						
>3-5X						
>5-10X						
Total Number						

*Biomarkers are not available for this type of myocardial infarction since the patients expired before biomarker determination could be performed.

** For the sake of completeness, the total distribution of biomarker values should be reported. The hatched areas represent biomarker elevations below the decision limit used for these types of myocardial infarction.

23.6. Definition of Hospitalization for Unstable Angina

Unstable angina requiring hospitalization is defined as

1. Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥ 10 minutes in duration occurring
   - at rest, or
   - in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity.

   AND
2. Prompting an unscheduled hospitalization **within 24 hours** of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24* hour stay (or a date change if the time of admission/discharge is not available).

   AND
3. At least one of the following:
   a. New or worsening ST or T wave changes on resting ECG **(**in the absence of confounders, such as LBBB or LVH)
      - Transient ST elevation (duration < 20 minutes)
        New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40

years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads

- ST depression and T-wave changes

  New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

b. Definite evidence of inducible myocardial ischemia as demonstrated by:

- an early positive exercise stress test, defined as ST elevation or ≥ 2 mm ST depression prior to 5 mets

OR

- stress echocardiography (reversible wall motion abnormality) **OR**
- myocardial scintigraphy (reversible perfusion defect), **OR**
- MRI (myocardial perfusion deficit under pharmacologic stress).

c. Angiographic evidence of new or worse ≥ 70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.

d. Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge.

AND

4. Negative cardiac biomarkers and no evidence of acute MI

General Considerations

1. Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β-blockers, should be considered supportive of the diagnosis of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under

category 3, would be insufficient alone to support classification as hospitalization for unstable angina.

2. If subjects are admitted with suspected unstable angina, and subsequent testing reveals a noncardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for myocardial infarction should not be adjudicated as unstable angina.
3. Planned hospitalization or rehospitalization for performance of an elective revascularization in patients who do not fulfill the criteria for unstable angina should not be considered a hospitalization for unstable angina. For example,

    - Hospitalization of a patient with stable exertional angina for coronary angiography and PCI that is prompted by a positive outpatient stress test should not be considered hospitalization for unstable angina.

    - Rehospitalization of a patient meeting the criteria for unstable angina who was stabilized, discharged, and subsequently readmitted for revascularization, does not constitute a second hospitalization for unstable angina

4. A patient who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina end point.

23.7. Definition of Transient Ischemic Attack and Stroke

Transient Ischemic Attack
Transient ischemic attack (TIA) is defined as a transient episode (< 24 hours) of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

Stroke
Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

Classification:

1. **Ischemic Stroke**

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.

Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

2. **Hemorrhagic Stroke**

   Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

   NOTE: Microhemorrhages seen on T2-weighted MRI imaging, subdural and epidural hemorrhages are not considered hemorrhagic strokes.

3. **Undetermined Stroke**

   Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as ischemic or hemorrhagic.

Stroke Disability

Stroke disability should be measured by a reliable and valid scale in all cases, typically at each visit and 90 days after the event. For example, the modified Rankin Scale may be used to address this requirement:

Scale	Disability
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; requiring some help, but able to walk without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderate severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention

Additional Considerations

In trials involving patients with stroke, evidence of vascular central nervous system injury without recognized neurological dysfunction may be observed. Examples include

micro-hemorrhage, silent infarction, and silent hemorrhage. When encountered, the clinical relevance of these findings may be unclear. If appropriate for a given clinical trial, however, they should be precisely defined and categorized.

Subdural hematomas are intracranial hemorrhagic events and not strokes.

The distinction between a Transient Ischemic Attack and an Ischemic Stroke is the presence of Infarction. Persistence of symptoms is an acceptable indicator of acute infarction. Thus, duration of symptom persistence that will be used to distinguish between transient ischemia and acute infarction should be defined for any clinical trial in which it is used.

23.8. Definition of Heart Failure Event

A Heart Failure Event may consist of a hospitalization (a required component of this end point and defined below), as well as urgent outpatient visits (optional component). Depending on the trial, there may be interest in capturing all heart failure (HF) events; however, HF hospitalizations should remain delineated from urgent visits. If urgent visits are included in the HF event endpoint, the number of urgent visits needs to be explicitly presented separately from the hospitalizations.

A Heart Failure Hospitalization is defined as an event that meets **ALL** of the following criteria:

1) The patient is admitted to the hospital with a primary diagnosis of HF

2) The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)

3) The patient exhibits documented new or worsening symptoms due to HF on presentation, including **at least ONE** of the following:

    a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)

b. Decreased exercise tolerance

c. Fatigue

d. Other symptoms of worsened end-organ perfusion or volume overload (must be specified and described by the protocol)

4) The patient has objective evidence of new or worsening HF, consisting of **at least TWO** physical examination findings **OR** one physical examination finding and **at least ONE** laboratory criterion), including:

a. Physical examination findings considered to be due to heart failure, including new or worsened:

i. Peripheral edema

ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)

iii. Pulmonary rales/crackles/crepitations

iv. Increased jugular venous pressure and/or hepatojugular reflux

v. S_3 gallop

vi. Clinically significant or rapid weight gain thought to be related to fluid retention

b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:

i. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline.

ii. Radiological evidence of pulmonary congestion

iii. Non-invasive or invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac

output. For example, echocardiographic criteria could include: E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral (TVI)) **OR** right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m^2

Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

5) The patient receives initiation or intensification of treatment specifically for HF, including **at least ONE** of the following:
    a. Significant augmentation in oral diuretic therapy
    b. Intravenous diuretic, inotrope, or vasodilator therapy
    c. Mechanical or surgical intervention, including:
        i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device)
        ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

New Heart Failure/Heart Failure Not Requiring Hospitalization:

An **Urgent Heart Failure Visit** is defined as an event that meets all of the following:

1) The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization.
2) All signs and symptoms for HF hospitalization must be met as defined in A Heart Failure Hospitalization above.
3) The patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

23.9. Interventional Cardiology Definitions

A. **Clinical Definitions**

1. **Clinically-Driven Target Lesion Revascularization**: Revascularization is clinically-driven if the target lesion diameter stenosis is > 50% by quantitative coronary angiography (QCA) and the subject has clinical or functional ischemia which cannot be explained by another native coronary or bypass graft lesion. Clinical or functional ischemia includes any of the following:
   a. A history of angina pectoris, presumably related to the target vessel
   b. Objective signs of ischemia at rest (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel
   c. Abnormal results of any invasive functional diagnostic test [e.g., coronary flow reserve (CFR) or fractional flow reserve (FFR)]

   Comment: *Target lesion revascularization of a > 70% diameter stenosis by QCA in the absence of the above signs or symptoms may be considered clinically-driven.*

   Comment: *In the absence of QCA data or if a ≤ 50% stenosis is present, TLR may be considered clinically-driven by the Clinical Events Committee (CEC) if severe ischemic signs and symptoms attributed to the target lesion are present.*

2. **Non-Target Lesion and Non-Target Lesion Revascularization**: A lesion for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.

3. **Non-Target Vessel and Non-Target Vessel Revascularization**: A vessel for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.

4. **Percutaneous Coronary Intervention (PCI) Status**:

   a. Elective: The procedure can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of myocardial infarction (MI) or death. For stable in-patients, the procedure is being performed during this hospitalization for convenience and ease of scheduling and NOT because the patient's clinical situation demands the procedure prior to discharge.

b. Urgent: The procedure should be performed on an inpatient basis and prior to discharge because of significant concerns that there is risk of myocardial ischemia, MI, and/or death. Patients who are outpatients or in the emergency department at the time that the cardiac catheterization is requested would warrant hospital admission based on their clinical presentation.

c. Emergency: The procedure should be performed as soon as possible because of substantial concerns that ongoing myocardial ischemia and/or MI could lead to death. "As soon as possible" refers to a patient who is of sufficient acuity that one would cancel a scheduled case to perform this procedure immediately in the next available room during business hours, or one would activate the on-call team were this to occur during off-hours.

d. Salvage: The procedure is a last resort. The patient is in cardiogenic shock when the PCI begins (i.e., the time at which the first guide wire or intracoronary device is introduced into a coronary artery or bypass graft for the purpose of mechanical revascularization) OR within the last ten minutes prior to the start of the case or during the diagnostic portion of the case, the patient has also received chest compressions or has been on unanticipated circulatory support (e.g., intra-aortic balloon pump, extracorporeal mechanical oxygenation, or cardiopulmonary support).

5. **Percutaneous Coronary Intervention (PCI):** Placement of an angioplasty guide wire, balloon, or other device (e.g., stent, atherectomy catheter, brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or coronary artery bypass graft for the purpose of mechanical coronary revascularization. In the assessment of the severity of coronary lesions with the use of intravascular ultrasound, CFR, or FFR, insertion of a guide wire will NOT be considered PCI.

6. **Procedural Success**: Achievement of < 30 % residual diameter stenosis of the target lesion assessed by visual inspection or QCA and no in-hospital major adverse cardiac events (MACE, a composite of death, MI, or repeat coronary revascularization of the

target lesion). Ideally, the assessment of the residual stenosis at the end of the procedure should be performed by an angiographic core laboratory.

Comment: *For some device interventions (e.g., balloon angioplasty), achievement of < 50% diameter stenosis by visual inspection or QCA is an acceptable definition for procedural success.*

7. **Target Lesion**: Any lesion treated or attempted to be treated during the PCI with the study device. The target lesion includes the arterial segment treated with the study device (stent, in most cases) plus 5 mm proximal and 5 mm distal to the treatment site.

8. **Target Lesion Failure (TLF):** The composite of ischemia-driven revascularization of the target lesion, MI related to the target vessel, or cardiac death related to the target vessel. If it cannot be determined with certainty whether the MI or death was related to the target vessel, it is considered a TLF.

9. **Target Lesion Revascularization (TLR):** Any repeat percutaneous intervention of the target lesion (including 5 mm proximal and 5 mm distal to the target lesion) or surgical bypass of the target vessel performed for restenosis or other complication involving the target lesion. In the assessment of TLR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the CEC for review upon request.

10. **Target Vessel**: A major native coronary artery (e.g., left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, or right coronary artery) or bypass graft containing the target lesion. A native coronary artery target vessel includes the arterial segments upstream and downstream to the target lesion plus major side branches.

11. **Target Vessel Failure (TVF):** The composite of ischemia-driven revascularization of the target vessel, MI related to the target vessel, or cardiac death related to the

target vessel. If it cannot be determined with certainty whether the MI or death was related to the target vessel, it is considered a TVF.

12. **Target Vessel, Non-Target Lesion, and Target Vessel, Non-Target Lesion Revascularization:** Any lesion or revascularization of a lesion in the target vessel other than the target lesion, respectively.

13. **Target Vessel Revascularization (TVR):** Any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. In the assessment of TVR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the CEC for review upon request.

14. **Vascular Complications**:
    - Access site hematoma
    - Arteriovenous fistula
    - Peripheral ischemia
    - Peripheral nerve injury
    - Pseudoaneurysm
    - Retroperitoneal hemorrhage

23.10. Definition of Peripheral Vascular Intervention

1. **Peripheral Vascular Intervention (PVI):** Peripheral vascular intervention is a catheter-based or open surgical procedure designed to improve peripheral arterial or venous blood flow or otherwise modify or revise vascular conduits. Procedures may include, but are not limited to, balloon angioplasty, stent placement, thrombectomy, embolectomy, atherectomy, dissection repair, aneurysm exclusion, treatment of dialysis conduits, placement of various devices, intravascular thrombolysis or other pharmacotherapies, and open surgical bypass or revision.

   In general, the intention to perform *percutaneous* peripheral vascular intervention is denoted by the insertion of a guide wire into a peripheral artery or vein.

The target vessel(s) and the type of revascularization procedure (e.g., surgical bypass, thrombectomy, endarterectomy, percutaneous angioplasty, stent placement, thromboembolectomy, and thrombolysis) should be specified and recorded. For the sake of simplicity, this definition applies to the extracranial carotid artery and other non-cardiac arteries and veins and excludes the intracranial vessels and lymphatics.

2. **Procedural Success**: In the case of percutaneous intervention for obstructive lesions, procedural success is defined as the achievement of a satisfactory final residual diameter stenosis by angiography at the end of the procedure (and without flow limiting dissection or hemodynamically significant translesional pressure gradient). The specific parameter for final percent residual stenosis is typically between < 30% and < 50%; selection of the appropriate percentage may vary depending upon the specific intervention applied, the vascular territory, and anticipated or desired therapeutic response. Procedural success also implies absence of in-hospital major adverse events (e.g., death, stroke, myocardial infarction, acute onset of limb ischemia, need for urgent/emergent vascular surgery, and other procedure-specific major adverse events). The balloon inflation, stent placement, or other therapeutic intervention may be preceded by use of adjunctive devices (e.g., percutaneous mechanical thrombectomy, directional or rotational atherectomy, laser, and chronic total occlusion crossing device), as predefined in the protocol.

3. **Procedural Status: Non-Elective and Elective:**

   a. Non-Elective: Non-elective procedures include emergent and urgent procedures. A non-elective procedure is a procedure that is performed without delay, because there is clinical consensus that the procedure should occur imminently. Non-elective procedures imply a degree of instability of the patient, urgency of the medical condition, or instability of the threatening lesion.

   - **Emergent:** A procedure that is performed immediately because of the acute nature of the medical condition (e.g., acute limb ischemia, acute aortic dissection), and the increased morbidity or mortality associated with a temporal delay in treatment.

- **Urgent**: An urgent procedure is one that is not emergent but required to be performed on a timely basis (≤ 24 hrs) (e.g., a patient who has been stabilized following initial treatment of acute limb ischemia, and there is clinical consensus that a definitive procedure should occur within the next 24 hours).

b. Elective: An elective procedure is one that is scheduled and is performed on a patient with stable disease, or in whom there is no urgency and/or increased morbidity or mortality associated with a planned procedure.

1. **Target Lesion**: A target lesion is any lesion treated or attempted to be treated during the trial procedure with the index device. The target lesion is the treated segment starting 5 mm proximal and ending 5 mm distal to the index device (stent, in most cases).
2. **Target Vessel:** A target vessel is any vessel (e.g., non-cardiac or non-cerebrovascular vessel) that contains the target lesion treated with the study device. The target vessel includes the target lesion as well as the entire vessel upstream and downstream to the target lesion, including side branches (native vessel).
3. **Non-Target Lesion:** A non-target lesion is one for which revascularization is not attempted or one in which revascularization is performed using a non-study device.
4. **Non-Target Vessel**: A non-target vessel is one for which revascularization is not attempted or one in which revascularization is performed using a non-study device.
5. **Target Vessel, Non-Target Lesion**: Any lesion or revascularization of a lesion in the target vessel other than the target lesion.
6. **Target Lesion Revascularization (TLR):** Target lesion revascularization is any repeat percutaneous intervention of the target lesions (including 5 mm proximal and distal to the index device) or surgical bypass of the target vessel performed for restenosis or other complication involving the target lesion. In the assessment of TLR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the Clinical End Points Committee (CEC) for review.

7. **Target Vessel Revascularization (TVR)**: Target vessel revascularization is any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. In the assessment of TVR, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the CEC for review.
8. **Clinically-Driven Target Lesion Revascularization**: Clinically-driven target lesion revascularization is a target lesion revascularization prompted by recurrent ipsilateral limb symptoms (intermittent claudication, critical limb ischemia) or objective imaging evidence of target lesion restenosis (i.e., most commonly with duplex ultrasonography). In the assessment of clinically driven TLR based on duplex ultrasonography, ultrasonographic images should be assessed by a duplex ultrasound core laboratory (if designated) and made available to the CEC for review.

23.11. Definition of Any Revascularization Procedure

Any revascularization includes any arterial vascular intervention done to treat ischemia or prevent major ischemic events, including percutaneous or surgical intervention of the coronary, peripheral, or carotid arteries. Aneurysm repairs, dissection repairs, arterial-venous fistula or graft placement or repairs, or renal arterial intervention for hypertension or renal dysfunction are not included.

23.12. Definition of Cardiac Arrhythmia Requiring Hospitalization

An arrhythmia that either results in hospitalization 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 cardio-version and/or intravenous anti-arrhythmics

3. Bradyarrhythmia - 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 HR < 30 bpm). The bradycardia must require temporary or permanent pacing,

23.13. Definition of Cardiac Arrest (Sudden Cardiac Death)

A sudden, unexpected death due to the cessation of cardiac mechanical activity, confirmed by the absence of a detectable pulse, unresponsiveness, and apnea (or agonal, gasping respirations) of presumed cardiac etiology. An arrest is presumed to be cardiac (i.e., related to heart disease) if this is likely, based on the available information, including hospital records and autopsy data. The cardiac arrest will be further sub-classified into either:

a) witnessed, occurring within 60 min from the onset of new symptoms, in the absence of a clear cause other than cardiovascular; or

b) unwitnessed, within 24 hours of being observed alive, in the absence of pre-existing other non-cardiovascular causes of death;

Note: Non-cardiac causes of cardiac arrest, such as drug overdose, suicide, drowning, hypoxia, exsanguination, cerebrovascular accident, subarachnoid hemorrhage, or trauma must not be present.

23.14. Definition of Resuscitated Cardiac Arrest [1]

Resuscitated Cardiac Arrest is present when there is restoration of both:

1. Organized electrical activity, and

2. Organized mechanical activity resulting in restoration of spontaneous circulation (defined as the documented presence of a measurable pulse and blood pressure at any time after initiation of resuscitative efforts).

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[1] Becker LB, Aufderheide TP, Geocadin RG, Callaway CW, Lazar RM, Donnino MW, Nadkarni VM, Abella BS, Adrie C, Berg RA, Merchant RM, O'Connor RE, Meltzer DO, Holm MB, Longstreth WT, Halperin HR. AHA Consensus Statement: Primary Outcomes for Resuscitation Science Sturdies: A Consensus Statement From the American Heart Association. *Circulation* 2011; CIR.0b013e3182340239published online before print October 3 2011, doi:10.1161/CIR.0b013e3182340239

APPENDIX C: CRITERIA FOR THE DIAGNOSIS OF DIABETES

Reference:
American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2010; 33 Suppl 1:S62.

1. HbA_{1c} ≥6.5%. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.*

OR

2. Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hr.*

OR

3. 2-hr plasma glucose ≥200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

* In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

CLINICAL STUDY PROTOCOL

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:
REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

Investigational Product: AMR101 (icosapent ethyl [ethyl-EPA])
Protocol Number: AMR-01-01-0019

Sponsor:
Amarin Pharma Inc.
1430 Route 206
Bedminster, New Jersey 07921, USA
Telephone: +1-908-719-1315
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Amendment #2: Final 8 July 2016
Amendment #2 Protocol Version Number: Final v 3.0
Amendment #1: Final 16 May 2013
Amendment #1 Protocol Version Number: Final v 2.0
Original Protocol: 2 August 2011

SIGNATURE PAGE

TRIAL 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: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

We, the undersigned, have reviewed and approved this protocol.

Signature Date

[Name / signature redacted] [Signed (11 July 2016)]
Executive Director, Clinical Development
Amarin Pharma Inc.

[Name / signature redacted] [Signed (11 July 2016)]
Executive Director, Clinical Development
Amarin Pharma Inc.

[Name / signature redacted] [Signed (11 July 2016)]
Chief Medical Officer, SVP
Amarin Pharma Inc.

[Name / signature redacted] [Signed (15 July 2016)]
President of R&D and Chief Scientific Officer, SVP
Amarin Pharma Inc.

[Name / signature redacted] [Signed (19 July 2016)]
Principal Investigator

SYNOPSIS

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: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

PROTOCOL NUMBER: AMR-01-01-0019

INVESTIGATIONAL PRODUCT: AMR101 (icosapent ethyl [ethyl-eicosapentaenoic acid (EPA)]) 1 g soft gel capsules for oral administration

PHASE: 3b

INDICATION:

The intended expanded indication is treatment with AMR101 as an add-on to statin therapy to reduce the risk of cardiovascular events in patients with clinical cardiovascular disease or with multiple risk factors for cardiovascular disease.

OBJECTIVES:

The primary objective is, in patients at low-density lipoprotein cholesterol (LDL-C) goal while on statin therapy, with established cardiovascular disease (CVD) or at high risk for CVD, and hypertriglyceridemia (fasting triglycerides [TG] ≥200 mg/dL and <500 mg/dL [≥2.26 mmol/L and <5.64 mmol/L]), to evaluate the effect of 4 g/day AMR101 on the time from randomization to first occurrence of any component of the composite of the following major cardiovascular (CV) events:

- CV death;
- Nonfatal myocardial infarction (MI), (including silent MI; electrocardiograms [ECGs] will be performed annually for the detection of silent MIs);
- Nonfatal stroke;
- Coronary revascularization; or
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

The secondary objectives of this study are the following:

The key secondary objective is to evaluate the effect of therapy on the time from randomization to the first occurrence of the composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke.

Other secondary objectives for this study are to evaluate the effect of therapy on time from randomization to the first occurrence of:

- Composite of CV death or nonfatal MI (including silent MI);
- Fatal or nonfatal MI (including silent MI);
- Non-elective coronary revascularization represented as the composite of emergent or urgent classifications;
- CV death;
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Fatal or nonfatal stroke;
- Composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke;
- Total mortality.

The tertiary objectives for this study are to evaluate the effect of therapy on the following. Where applicable and unless specified otherwise, endpoints represent time from randomization to the first occurrence of the individual or composite endpoints.

- Total CV events analysis defined as the time from randomization to occurrence of the first and all recurrent major CV events defined as CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Primary composite endpoint in the subset of patients with diabetes mellitus at baseline;
- Primary composite endpoint in the subset of patients with metabolic syndrome at baseline as defined in *A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity* (Alberti 2009); with cut points of parameters as defined in Table 1 of Alberti *et al.* and waist circumference cut points further guided by Table 2 of Alberti *et al.* and specifically set at ≥35 inches (88 cm) for all women and Asian, Hispanic, or Latino men, and ≥40 inches (102 cm) for all other men (see Appendix D);
- Primary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG of 100-125 mg/dL);
- Key secondary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG 100-125 mg/dL);
- Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalization of ≥24 hours, or cardiac arrest;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina

determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;

- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or PVD requiring intervention, such as angioplasty, bypass surgery, or aneurism repair;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, PVD requiring intervention, or cardiac arrhythmia requiring hospitalization of ≥24 hours;
- New CHF;
- New CHF as the primary cause of hospitalization;
- Transient ischemic attack (TIA);
- Amputation for PVD;
- Carotid revascularization;
- All coronary revascularizations defined as the composite of emergent, urgent, elective, or salvage;
- Emergent coronary revascularizations;
- Urgent coronary revascularizations;
- Elective coronary revascularizations;
- Salvage coronary revascularizations;
- Cardiac arrhythmias requiring hospitalization of ≥24 hours;
- Cardiac arrest;
- Ischemic stroke;
- Hemorrhagic stroke;
- Fatal or nonfatal stroke in the subset of patients with a history of stroke prior to baseline;
- New onset diabetes, defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period;
- New onset hypertension, defined as blood pressure ≥140 mmHg systolic OR ≥90 mmHg diastolic newly diagnosed during the treatment/follow-up period;
- Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP (hsCRP and log[hsCRP]), hsTnT, and RLP-C (to be estimated from standard lipid panel, RLP-C = TC – HDL-C – LDL-C [Varbo 2014]), (based on ITT estimands):

  - Assessment of the relationship between baseline biomarker values and treatment effects within the primary and key secondary endpoints,
  - Assessment of the effect of AMR101 on each marker,
  - Assessment of the relationship between post-baseline biomarker values and treatment effects within the primary and key secondary composite endpoints by including post-baseline biomarker values (for example, at 4 months, or at 1 year) as a covariate;
- Change in body weight;
- Change in waist circumference.

ENDPOINTS:

Primary Endpoint:

The primary efficacy endpoint is the time from randomization to the first occurrence of any component of the composite of the following clinical events:

- CV death;
- Nonfatal MI (including silent MI; ECGs will be performed annually for the detection of silent MIs);
- Nonfatal stroke;
- Coronary revascularization;
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

The first occurrence of any of these major adverse cardiovascular events during the follow-up period of the study will be included in the incidence.

Secondary Endpoints:

The key secondary efficacy endpoint is the time from randomization to the first occurrence of the composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke.

Other secondary efficacy endpoints are time from randomization to the first occurrence of the individual or composite endpoints as follows (to be tested in the order listed):

- Composite of CV death or nonfatal MI (including silent MI);
- Fatal or nonfatal MI (including silent MI);
- Non-elective coronary revascularization represented as the composite of emergent or urgent classifications;
- CV death;
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Fatal or nonfatal stroke;
- Composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke;
- Total mortality.

For the secondary efficacy endpoints that count a single event, the time from randomization to the first occurrence of this type of event will be counted for each patient. For secondary efficacy endpoints that are composites of two or more types of events, the time from randomization to the first occurrence of any of the event types included in the composite will be counted for each patient.

Tertiary Endpoints:

The following tertiary endpoints will be evaluated as supporting efficacy and safety analyses. Where applicable and unless specified otherwise, endpoint analyses will be conducted as time from randomization to the first occurrence of the individual or composite endpoints.

- Total CV events analysis defined as the time from randomization to occurrence of the first and all recurrent major CV events defined as CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Primary composite endpoint in subset of patients with diabetes mellitus at baseline;
- Primary composite endpoint in the subset of patients with metabolic syndrome at baseline as defined in *A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity* (Alberti 2009); with cut points of parameters as defined in Table 1 of Alberti *et al.* and waist circumference cut points further guided by Table 2 Alberti *et al.* and specifically set at ≥35 inches (88 cm) for all women and Asian, Hispanic, or Latino men, and ≥40 inches (102 cm) for all other men (see Appendix D);
- Primary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG of 100-125 mg/dL);
- Key secondary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG 100-125 mg/dL);
- Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalization of ≥24 hours, or cardiac arrest;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or PVD requiring intervention, such as angioplasty, bypass surgery, or aneurism repair;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and

requiring emergent hospitalization, PVD requiring intervention, or cardiac arrhythmia requiring hospitalization of ≥24 hours;

- New CHF;
- New CHF as the primary cause of hospitalization;
- Transient ischemic attack (TIA);
- Amputation for PVD;
- Carotid revascularization;
- All coronary revascularizations defined as the composite of emergent, urgent, elective, or salvage;
- Emergent coronary revascularizations;
- Urgent coronary revascularizations;
- Elective coronary revascularizations;
- Salvage coronary revascularizations;
- Cardiac arrhythmias requiring hospitalization of ≥24 hours;
- Cardiac arrest;
- Ischemic stroke;
- Hemorrhagic stroke;
- Fatal or nonfatal stroke in the subset of patients with a history of stroke prior to baseline;
- New onset diabetes, defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period;
- New onset hypertension, defined as blood pressure ≥140 mmHg systolic OR ≥90 mmHg diastolic newly diagnosed during the treatment/follow-up period;
- Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP (hsCRP and log[hsCRP]), hsTnT, and RLP-C (to be estimated from standard lipid panel, RLP-C = TC – HDL-C – LDL-C [Varbo 2014]), (based on ITT estimands):
    - Assessment of the relationship between baseline biomarker values and treatment effects within the primary and key secondary composite endpoints,
    - Assessment of the effect of AMR101 on each marker,
    - Assessment of the relationship between post-baseline biomarker values and treatment effects within the primary and key secondary composite endpoints by including post-baseline biomarker values (for example, at 4 months, or at 1 year) as a covariate;
- Change in body weight;
- Change in waist circumference.

Where applicable and unless specified otherwise, for the tertiary endpoints that count a single event, the time from randomization to the first occurrence of this type of event will be counted in each patient. Similarly, where applicable and unless specified otherwise, for tertiary endpoints that are composites of two or more types of events, the time from

randomization to the first occurrence of any of the event types included in the composite will be counted in each patient.

POPULATION:

Inclusion Criteria:

1. Fasting TG levels of ≥200 mg/dL (2.26 mmol/L) and <500 mg/dL (5.64 mmol/L).
2. LDL-C >40 mg/dL (1.04 mmol/L) and ≤100 mg/dL (2.60 mmol/L) and on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks prior to the LDL-C/TG baseline qualifying measurements for randomization
   - Stable therapy is defined as the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable, the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C). Patients who have their statin therapy or use of ezetimibe initiated at Visit 1, or have their statin, statin dose and/or ezetimibe dose changed at Visit 1, will need to go through a stabilization period of at least 28 days since initiation/change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).
   - Statins may be administered with or without ezetimibe.

   NOTE: If patients qualify at the first qualification visit (Visit 1) for TG and LDL-C, and meet all other inclusion/exclusion criteria, they may be randomized at Visit 2. If patients do not qualify at the first qualifying visit (Visit 1), a second re-qualifying visit (Visit 1.1) is allowed. For some patients, because they need to stabilize medications and/or need to washout medications, the second re-qualifying visit (Visit 1.1) will be needed after the stabilization/washout period.
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 are defined as follows:

   CV Risk Category 1: defined as men and women ≥45 years of age with one or more of the following:

   - Documented coronary artery disease (CAD; one or more of the following primary criteria must be satisfied):
     - Documented multi vessel CAD (≥50% stenosis in at least two major epicardial coronary arteries – with or without antecedent revascularization);
     - Documented prior MI;
     - Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome (NSTE-ACS) (with objective evidence of ischemia: ST-segment deviation or biomarker positivity).
   - Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied):
     - Documented prior ischemic stroke;
     - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis;
     - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound;

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

- Documented peripheral arterial disease (PAD; one or more of the following primary criteria must be satisfied):
  - Ankle-brachial index (ABI) <0.9 with symptoms of intermittent claudication;
  - History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical).

OR

CV Risk Category 2: defined as patients with:

1. Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication AND
2. Men and women ≥50 years of age AND
3. One of the following at Visit 1 (additional risk factor for CVD):
   - Men ≥55 years of age and 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, defined as any of the following: non-proliferative retinopathy, pre-proliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation;
   - Micro- or macroalbuminuria. Microalbuminuria is defined as either a positive micral or other strip test (may be obtained from medical records), an albumin/creatinine ratio ≥2.5 mg/mmol or an albumin excretion rate on timed collection ≥20 mg/min all on at least two successive occasions; macroalbuminuria, defined as Albustix or other dipstick evidence of gross proteinuria, an albumin/creatinine ratio ≥25 mg/mmol or an albumin excretion rate on timed collection ≥200 mg/min all on at least two successive occasions;
   - ABI <0.9 without symptoms of intermittent claudication (patients with ABI <0.9 with symptoms of intermittent claudication are counted under CV Risk Category 1).

   Note: Patients with diabetes and CVD as defined above are eligible based on the CVD requirements and will be counted under CV Risk Category 1. Only patients with diabetes and no documented CVD as defined above need at least one additional risk factor as listed, and will be counted under CV Risk Category 2.

4. Women may be enrolled if all 3 of the following criteria are met:
   - They are not pregnant;
   - They are not breastfeeding;

- They do not plan on becoming pregnant during the study.

5. Women of child-bearing potential must have a negative urine pregnancy test before randomization.

   Note: Women are not considered to be of childbearing potential if they meet one of the following criteria as documented by the investigator:

   - They have had a hysterectomy, tubal ligation or bilateral oophorectomy prior to signing the informed consent form;
   - They are post-menopausal, defined as ≥1 year since their last menstrual period or have a follicle-stimulating hormone (FSH) level in a menopausal range.

6. Women of childbearing potential must agree to use an acceptable method of avoiding pregnancy from screening to the end of the study, unless their sexual partner(s) is/are surgically sterile or the woman is abstinent.
7. Understanding of the study procedures, willing to adhere to the study schedules, and agreement to participate in the study by giving informed consent prior to screening.
8. Agree to follow a physician recommended diet, and to maintain it through the duration of the study.

Exclusion Criteria:

1. Severe (New York Heart Association [NYHA] class IV) heart failure.
2. Any life-threatening disease expected to result in death within the next 2 years (other than CVD).
3. Active severe liver disease (evaluated at Visit 1): cirrhosis, active hepatitis, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × the upper limit of normal (ULN), or biliary obstruction with hyperbilirubinemia (total bilirubin >2 × ULN).
4. Hemoglobin A_{1c} (HbA_{1c}) >10.0% (or >86 mmol/mol International Federation of Clinical Chemistry [IFCC] units) at screening (Visit 1). If patients fail this criterion (HbA_{1c} >10.0% or >86 mmol/mol IFCC units) at Visit 1, they may have their antidiabetic therapy optimized and be retested at Visit 1.1.
5. Poorly controlled hypertension: blood pressure ≥200 systolic mmHg OR ≥100 mmHg diastolic (despite antihypertensive therapy).
6. Planned coronary intervention (such as stent placement or heart bypass) or any non-cardiac major surgical procedure. Patients can be (re)evaluated for participation in the trial (starting with Visit 1.1) after their recovery from the intervention/surgery.
7. Known familial lipoprotein lipase deficiency (Fredrickson Type I), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type III).
8. Participation in another clinical trial involving an investigational agent within 90 days prior to screening (Visit 1). Patients cannot participate in any other investigational medication or medical device trial while participating in this study (participation in a registry or observational study without additional therapeutic intervention is allowed).
9. Intolerance or hypersensitivity to statin therapy.

10. Known hypersensitivity to any ingredients of the study product or placebo (refer to Table 5); known hypersensitivity to fish and or shellfish.
11. History of acute or chronic pancreatitis.
12. Malabsorption syndrome and/or chronic diarrhea. (Note: patients who have undergone gastric/intestinal bypass surgery are considered to have malabsorption, hence are excluded; patients who have undergone gastric banding are allowed to enter the trial).
13. Non-study drug related, non-statin, lipid-altering medications, supplements or foods:

- Patients are excluded if they used niacin >200 mg/day or fibrates during the screening period (after Visit 1) and/or plan to use during the study; patients who are taking niacin >200 mg/day or fibrates during the last 28 days before Visit 1 need to go through washout of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (Visit 1.1);
- Patients are excluded if they take any omega-3 fatty acid medications (prescription medicines containing EPA and/or docosahexaenoic acid [DHA]) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking omega-3 fatty acid medications during the last 28 days before Visit 1 (except patients in the Netherlands), need to go through a washout period of at least 28 days after their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);
    - For patients in the Netherlands only: patients being treated with omega-3 fatty acid medications containing EPA and /or DHA are excluded; no washout is allowed.
- Patients are excluded if they use dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking >300 mg/day omega-3 fatty acids (combined amount of EPA and DHA) within 28 days before Visit 1 (except patients in the Netherlands), need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);
    - For patients in the Netherlands only: patients being treated with dietary supplements containing omega-3 fatty acids of >300 mg/day EPA and/or DHA are excluded; no washout is allowed.
- Patients are excluded if they use bile acid sequestrants during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking bile acid sequestrants within 7 days before Visit 1, need to go through a washout period of at least 7 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);
- Patients are excluded if they use proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study,

patients cannot have taken a PCSK9 inhibitor within 90 days prior to their screening visit.

14. Other medications (not indicated for lipid alteration):
    - Treatment with tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are allowed), HIV-protease inhibitors that have not been stable for ≥28 days prior to the qualifying lipid measurements (TG and LDL-C) during screening. To be eligible for participation in the study, patients who are not taking a stable dose of these medications within 28 days before Visit 1, need to go through a stabilization period of at least 28 days since their last dose change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);
    - Patients are excluded if they use cyclophosphamide or systemic retinoids during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking these medications within 28 days before Visit 1, need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).
15. Known to have acquired immune deficiency syndrome (AIDS) (patients who are human immunodeficiency virus (HIV) positive without AIDS are allowed).
16. Requirement for peritoneal dialysis or hemodialysis for renal insufficiency or creatinine clearance (CrCL) <30 mL/min (0.50 mL/sec).
17. Unexplained creatine kinase concentration >5 × ULN or creatine kinase elevation due to known muscle disease (e.g., polymyositis, mitochondrial dysfunction) at Visit 1.
18. Any condition or therapy which, in the opinion of the investigator, might pose a risk to the patient or make participation in the study not in the patient's best interest.
19. Drug or alcohol abuse within the past 6 months, and unable/unwilling to abstain from drug abuse and excessive alcohol consumption during the study or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking). Excessive alcohol consumption is on average >2 units of alcohol per day. A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.
20. Mental/psychological impairment or any other reason to expect patient difficulty in complying with the requirements of the study or understanding the goal and potential risks of participating in the study (evaluated at Visit 1).

STUDY DESIGN AND DURATION:

This is a multi-center, multi-national, prospective, randomized, double-blind, placebo-controlled, parallel-group study.

This is an event-driven trial: It is expected that a minimum of approximately 1612 primary endpoint events will be required during the study. Approximately 7990 patients will be randomized at multiple Research Sites worldwide over an estimated period of approximately 4.2 years. After randomization, patients will be treated and followed up to an estimated

maximum of 6.5 years. The study end date is determined to be when approximately 1612 primary efficacy events have been adjudicated.

Screening Period:

During the screening period, patients will be evaluated for inclusion/exclusion criteria. Patients will be eligible for randomization if they meet all the inclusion/exclusion criteria. Prospectively, eligible patients with documented CVD or diabetes (with at least one additional risk factor for CVD) will undergo screening to establish suitability for inclusion in the trial. The qualifying lipid determination at Visit 1 requires that eligible patients must have a fasting TG level ≥200 mg/dL (2.26 mmol/L) and <500 mg/dL (5.64 mmol/L) in order to enter the treatment/follow-up period of the trial (and they need to meet all other inclusion/exclusion criteria). These patients will be randomized at Visit 2, which will occur soon after Visit 1 (there will be no Visit 1.1 for these patients).

Patients who do not qualify at Visit 1, may return to the Research Site for a second qualifying visit (Visit 1.1) at which time procedures that caused failure of eligibility at Visit 1 will be repeated. In this case, patients will be eligible for randomization after Visit 1.1 if they meet all inclusion criteria and if they no longer fail the exclusion criteria.

For some patients, Visit 1.1 will be mandatory at least 28 days after Visit 1 in order to check eligibility. These are patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications. Any of these changes at Visit 1 may affect the qualifying lipid levels and therefore, patients will need to have Visit 1.1 to determine whether they qualify based on lipid level requirements (TG and LDL-C) determined at Visit 1. Other procedures that caused failure of eligibility at Visit 1 will also be repeated at Visit 1.1. Details are listed in the main section of the protocol.

Treatment/Follow-Up Period:

At Visit 2 (Day 0), eligible patients will be randomly assigned 1:1 to one of the following treatment groups:

- AMR101 4 g daily, or
- Placebo.

Stratification will be by CV risk category (established CVD or the presence of diabetes with ≥1 risk factor for CVD), use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries).

During the treatment/follow-up period, patients will return to the Research Site at regular intervals for efficacy and safety evaluations, and drug supply and compliance checks. The visits after the randomization visit (Visit 2; Day 0) are scheduled for 4 months after Visit 2 (for Visit 3); 8 months after Visit 3 (for Visit 4); and then every year thereafter.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Eligible patients will be randomly assigned at Visit 2 to receive orally AMR101 4 g daily or matching placebo. AMR101 is provided in 1 g liquid-filled, oblong, gelatin capsules. The matching placebo capsule is filled with light liquid paraffin and contains 0 mg of AMR101.

AMR101 or matching placebo capsules are to be taken with food (i.e. with or at the end of a meal).

During the treatment period, the daily dose of study drug is 4 capsules per day taken as two capsules taken on two occasions per day (2 capsules given twice daily).

STATISTICAL ANALYSES:

- Intent-to-treat (ITT), Modified ITT (mITT), Per Protocol (PP), and Safety analyses
- Parameters will be summarized using mean, standard deviation, median, minimum, maximum, and interquartile range for continuous data and percentage for categorical data.
- Survival analysis using the log-rank test for the primary efficacy outcome comparing the 2 treatment groups (AMR101 and Placebo) and including the stratification factors CV risk category, use of ezetimibe and geographical region (Westernized, Eastern European, and Asia Pacific countries).
- Exploratory subgroup analyses will be performed for the primary and key secondary endpoints for the ITT, mITT and PP populations, based on demographics, disease parameters, treatment parameters, and baseline characteristics including lipid and lipoprotein parameters.

Two interim analyses are planned, to occur when approximately 60% and 80% of the planned total number of events have been adjudicated.

The analyses are planned to:

- Describe at baseline: Patient characteristics, including lipids and lipoproteins, stroke history, CV risk factors, diabetes mellitus, or metabolic syndrome, among others.
- Compare the primary, secondary, and tertiary endpoints between treatment groups at the corresponding follow-up time points.

SAMPLE SIZE DETERMINATION:

Sample size calculation was based on assumptions of constant hazard, asymmetric recruitment rate over time and without factoring for dropouts. A risk reduction corresponding to a hazard ratio of 0.85 (AMR101 vs. control) was assumed. A total of 1612 events would be required to detect this hazard ratio with approximately 90% power with one-sided alpha-level at 2.5% and with two interim analyses. The operating characteristics of this design are identical to those of a corresponding group sequential design with a two-sided alpha level of 0.05.

The recruitment period was assumed to be approximately 4.2 years with 20% recruitment in the first year, 40% in the second year, 20% in the third year, 19% in the fourth year and the remaining 1% in the last 0.2 years. The expected maximum study duration is estimated at 6.5 years unless the trial is terminated early for efficacy or safety issues. A one-year event rate of 5.2% (hazard = 0.053) in the control arm is also assumed. Under these assumptions the number of patients to be enrolled is N = 7990.

Since this is an events-driven trial, the ‘sample size’ is the number of events rather than the number of patients. The number of events that occur depends primarily on three factors: how

many patients are enrolled, the combined group event rate, and how long the patients are followed. Because of the difficulty in predicting the combined event rate, the sponsor will monitor that event rate as the trial progresses. If the combined event rate is less than anticipated, either increasing the number of patients, extending the length of follow-up, or a balance of adjusting both factors may be necessary to achieve the sample size of 1612 events.

Before completing the enrollment phase of the trial, *i.e.* approximately 3 to 6 months prior to the projected enrollment of the 7990th patient, the actual event rate based on pooled, blinded accumulation of primary efficacy endpoint events would be calculated and plotted. If those analyses suggested the number of patients with at least 1 adjudicated, primary event (and appropriately accounting for patients with potential primary events for which the adjudication process is then incomplete) was consistent with projections, then the study could continue toward the protocol-specified target enrollment of 7990 patients. However, if the number of such events appeared less than, and inconsistent with projections, the Sponsor would consider (under blinded conditions) re-calculating the number of patients needed to achieve the target number of events within the desired timeline or extending the follow-up period. If the projected increase in number of patients was ≤25% of the original 7990 target population, the Sponsor could, with documented approval of both the REDUCE-IT Steering Committee and the Data Monitoring Committee, extend enrollment to the revised target number without need for an additional protocol amendment. Under those conditions, all principal investigators, ethics committees, and regulatory authorities associated with the protocol will be promptly notified of the action. If the projected increase in number of patients was more than 25% above the original 7990 target (*i.e.* more than 1998 additional patients) a formal protocol amendment would be initiated.

Consistent with the plan stated above, an analysis and modeling of pooled, blinded primary efficacy endpoint events across the remainder of the trial was performed prior to the projected enrollment of the 7990th patient. Based on this analysis, the sample size of 7990 randomized patients is with 95% confidence likely to result in the target 1,612 adjudicated primary efficacy events within 2018. The results of this analysis were shared with and approved by the REDUCE-IT Steering Committee and Data Monitoring Committee.

As of the completion of study enrollment, the actual number of patients randomized will vary from the target number as a result of the inherent lag between the date the last patient started screening and the date the last patient was randomized.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABI	Ankle-brachial index
ACC	American College of Cardiology
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACS	Acute coronary syndrome
AE	Adverse event
AHA	American Heart Association
AIDS	Acquired immune deficiency syndrome
AIM-HIGH	Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes
ALT	Alanine aminotransferase
AMR101	Ethyl-EPA; ethyl eicosapentaenoic acid; icosapent ethyl
ANCHOR	Effect of AMR101 (Ethyl Icosapentate) on Triglyceride (Tg) Levels in Patients on Statins with High TG Levels (≥ 200 and < 500 mg/dL)
AP	Angina pectoris
apo B	Apolipoprotein B
APOC3	Apolipoprotein C3
AST	Aspartate aminotransferase
ATP	Adult Treatment Panel
BMI	Body mass index
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CBC	Complete blood count
CEC	Clinical Endpoint Committee
CHD	Coronary heart disease
CHF	Congestive heart failure
CI	Confidence interval
CK-MB	Creatine kinase-MB fraction
CrCL	Creatinine clearance
CRF	Case report form
CV	Cardiovascular
CVD	Cardiovascular disease
DART	Diet and Reinfarction Trial
DCCT	Diabetes Control and Complications Trial
DHA	Docosahexaenoic acid
DMC	Data Monitoring Committee
DYSIS	The DYSlipidemia International Study
EC	Independent Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
eGRF	Estimated glomerular filtration rate

EPA	Eicosapentaenoic acid
Ethyl-EPA	AMR101; ethyl eicosapentaenoic acid; icosapent ethyl
EU	European Union
FBG	Fasting blood glucose
FDA	United States Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GISSI	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico
GMP	Good Manufacturing Practice
GWAS	Genome-wide association study
HbA_{1c}	Hemoglobin A_{1c}
Hct	Hematocrit
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HPS2-THRIVE	Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events
HR	Hazard ratio
hs-CRP	High-sensitivity C-reactive protein
hsTnT	High-sensitivity troponin T
HTG	Hypertriglyceridemia
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFCC	International Federation of Clinical Chemistry
IMP	Investigational medicinal product
IMPROVE-IT	Examining Outcomes in Subjects with Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs Simvastatin
IQR	Interquartile range
IRB	Institutional Review Board
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
JAS	Japanese Atherosclerosis Society
JELIS	Japan Eicosapentaenoic Acid Lipid Intervention Study
LBBB	Left bundle branch block
LDL-C	Low-density lipoprotein cholesterol
LOE	Lack of efficacy
$LpPLA_2$	Lipoprotein-associated phospholipase A2
LVH	Left ventricle hypertrophy
MACE	Major adverse coronary event
MARINE	Efficacy and Safety of AMR101 (Ethyl Icosapentate) in Patients With Fasting Triglyceride (TG) Levels ≥ 500 and ≤ 2000 mg/dL
MI	Myocardial infarction

mITT	Modified Intent-to-Treat
NCEP	National Cholesterol Education Program
NGSP	National Glycohemoglobin Standardization Program
NMR	Nuclear magnetic resonance
NSTE-ACS	Non-ST-segment elevation acute coronary syndrome
O3FA	Omega-3 fatty acid
ODIS	Off drug in study
OGTT	Oral glucose tolerance test
OR	Odds ratio
PAD	Peripheral arterial disease
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin kexin 9
PH	Proportional hazard
PI	Principal Investigator
PP	Per protocol
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy
PVD	Peripheral vascular disease
RBC	Red blood cells
REDUCE-IT	Reduction of Cardiovascular Events with EPA – Intervention Trial
RLP-C	Remnant lipoprotein cholesterol
RR	Relative risk
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SC	Steering Committee
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TIA	Transient Ischemic Attack
TIMI	Thrombolysis In Myocardial Infarction
ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information
VLDL-C	Very low density lipoprotein cholesterol
WBC	White cell blood count

1. INTRODUCTION AND BACKGROUND INFORMATION

AMR101 (marketed as Vascepa® in the United States [US]) is an ethyl ester of eicosapentaenoic acid (EPA) indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia (HTG), which received initial US regulatory approval in 2012. AMR101, derived from fish oil, is being developed by Amarin Pharma Inc. (hereafter referred to as Amarin or the Sponsor) for the treatment of HTG. The purpose of this study is to evaluate whether AMR101, combined with a statin therapy, will be superior to the statin therapy alone, when used as a prevention in reducing long-term clinical events in patients with mixed dyslipidemia at high risk for cardiovascular (CV) events.

1.1. Background

Since the initial observation of a link between fish oil consumption and the reduced incidence of coronary heart disease in the Eskimos of Greenland (Bang 1972), a large body of evidence has accumulated suggesting that regular intake of omega-3 fatty acids (O3FAs) exerts cardioprotective effects in both primary and secondary coronary heart disease prevention (Harris 2008, Lee 2008). Several mechanisms have been proposed to account for these beneficial effects, including the reduction of TG, suppression of cardiac arrhythmias, decreased platelet aggregation, improved plaque composition and stabilization, and hemodynamic changes. This mounting body of evidence has led the American Heart Association (AHA) to recommend the consumption of O3FAs in dietary fish or in capsule form at a dose of 1 g/day for secondary prevention of cardiovascular disease (CVD) (Kris-Etherton 2002). This recommendation has now been included in American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the long-term management of patients with stable angina and acute coronary syndromes (Antman 2004, Fraker 2007, Anderson 2007).

A large number of studies have also demonstrated the TG-lowering effects of O3FAs (Harris 1997, Ginsberg 2001). Multiple products have been approved in the US and European Union (EU) consisting of approximately 85-90% of the O3FAs EPA and docosahexaenoic acid (DHA). These products have generally been approved as prescription products (up to 4 g/day) to lower TG in patients with TG ≥500 mg/dL when diet alone is insufficient (Omacor Summary of Product Characteristics [SPC], 03/2015; Lovaza® United States Prescribing Information [USPI], 05/2014). Omacor® at a dose of 1 g/day is also approved in certain European and Asian markets for the secondary prevention of myocardial infarction (MI), post-MI.

Epadel capsules, which contain highly purified (>95%) ethyl-EPA, have been marketed by Mochida in Japan since 1990 for the treatment of arteriosclerosis obliterans and since 1994 for the treatment of hyperlipidemia (Epadel SPC 10/2013). The recommended dose is 1.8 g/day for arteriosclerosis obliterans and 1.8 to 2.7 g/day for hyperlipidemia.

Hypertriglyceridemia is a feature of many dyslipidemias and often occurs in persons who are obese and/or have Type 2 diabetes mellitus in isolation or as a component of the metabolic syndrome (Jacobson 2007, Bays 2008).

Elevation in TG confers dual risks of acute pancreatitis (most marked in patients with severe HTG [TG >1500 mg/dL]) (Yadav 2003) and accelerated atherosclerosis leading to CV events, the latter even after correction for other lipid and non-lipid risk factors (Jacobson 2007). With this in mind, Amarin is assessing the potential of AMR101 capsules, which contain highly purified ethyl-EPA, as an adjunct to diet, for the treatment of patients with very high TG levels (≥500 mg/dL) and those at high risk for CVD with high TG levels (≥200 and <500 mg/dL) despite optimal statin therapy. Amarin-sponsored studies with AMR101 in patients with very high TGs (Study AMR-01-01-0016, the MARINE study) and in patients at high risk for CVD with high TGs despite statin therapy (Study AMR-01-01-0017, the ANCHOR study) have been completed (Bays 2011, Ballantyne 2012).

In July 2012, Vascepa (AMR101; ethyl-EPA; icosapent ethyl) received initial US regulatory approval as an adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) HTG.

1.2. Summary of Completed Amarin-Sponsored Clinical Studies of AMR101 in Patients with Hypertriglyceridemia

As of Amendment 2 to this protocol, two Phase 3 studies in patients with HTG have been completed. These trials have investigated the efficacy of AMR101 in lowering TG:

- Study AMR-01-01-0016 (the MARINE study) in 229 patients with very high TG (≥500 and ≤2000 mg/dL).
- Study AMR-01-01-0017 (the ANCHOR study) in 702 patients at high risk for CVD with mixed dyslipidemia (high TG: ≥200 to <500 mg/dL) on statin therapy.

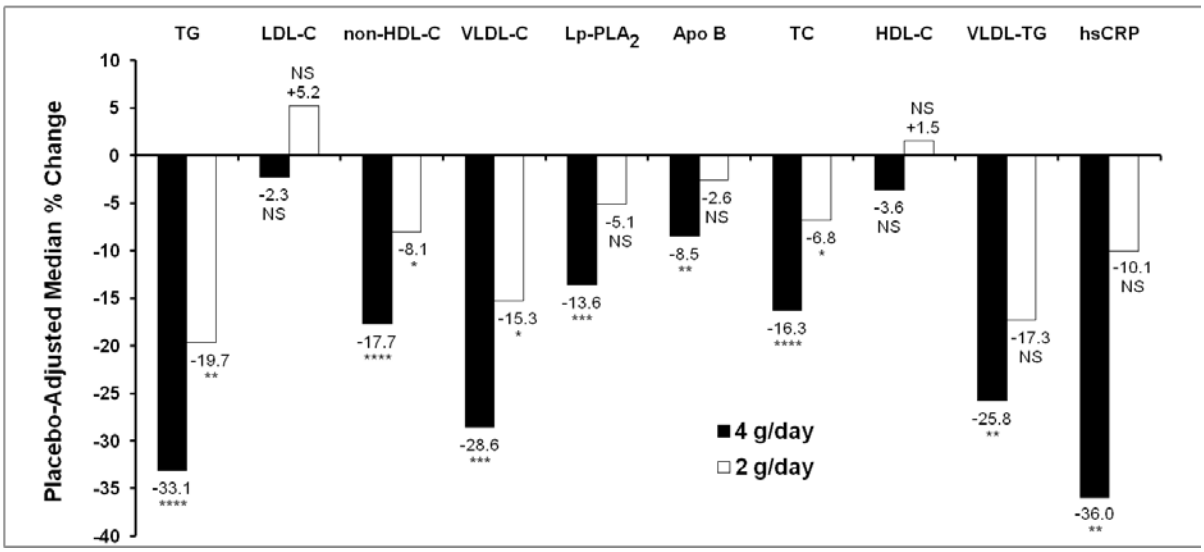
1.2.1. Study AMR-01-01-0016 (MARINE)

The primary objective of the MARINE Study was to determine the efficacy of AMR101 compared to placebo in lowering fasting TG levels in patients with very high fasting TG levels (≥500 and ≤2000 mg/dL).

A total of 229 patients were randomized (1:1:1) to 12-weeks of double-blind treatment with AMR101 2 g/day, AMR101 4 g/day, or placebo. Prior to randomization, there was a 4- to 6-week diet and lifestyle stabilization period and a 2-week TG qualifying period. Baseline characteristics were well balanced between treatment arms. Overall, the mean age was 52.9 years, mean body mass index (BMI) was 30.8 kg/m^2 and approximately 25% of patients were using a statin at baseline. In the evaluation of the primary endpoint, the MARINE results demonstrated significant placebo-adjusted reductions in median fasting TG levels with AMR101 2 g/day (-19.7%; p=0.0051) and 4 g/day (-33.1%; p<0.0001) after 12 weeks of treatment. Placebo-adjusted changes in key lipid and inflammatory endpoints are shown in Figure 1. The magnitudes of reductions in TG levels observed in MARINE are expectedly higher than those seen in ANCHOR, as the patients had very high baseline TG levels. Safety and tolerability results for the AMR101 groups were consistent with those seen in previous clinical studies in other populations and not notably different from the results in the placebo group.

See Section 1.3 for safety.

Figure 1. Placebo-Adjusted Median Percent Change from Baseline to Week 12 in Key Lipid and Inflammatory Endpoints – Intent-to-Treat Population (MARINE)



****** p<0.0001; *** p<0.001; ** p<0.01; * p<0.05; NS = Not Significant (p≥0.05)**
Median Baseline TG: 703 (placebo, N=75), 680 (4 g/day, N=76), 657 (2 g/day, N=73) mg/dL
Median Baseline LDL-C: 86 (placebo, N=75), 91 (4 g/day, N=76), 84 (2 g/day, N=73) mg/dL
Medians are Hodges-Lehmann medians; p-values are from the Wilcoxon rank-sum test.
Apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp-PLA_2 = lipoprotein-associated phospholipase A2; non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; VLDL-C = very low density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides.

1.2.2. Study AMR-01-01-0017 (ANCHOR)

The primary objective in the ANCHOR study was to determine the efficacy of AMR101 2 g daily and 4 g daily, compared to placebo, in lowering fasting TG levels in patients with high risk for CVD and fasting TG levels ≥200 mg/dL and <500 mg/dL, despite statin treatment to low density lipoprotein cholesterol (LDL-C) goal (>40 mg/dL and <100 mg/dL).

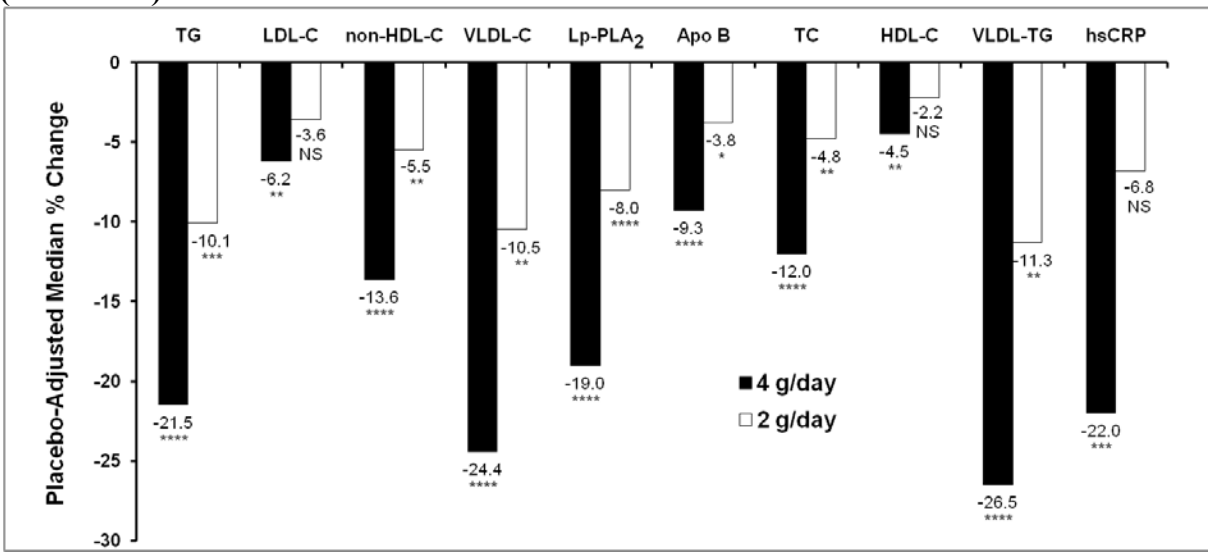
After a 6 - to 8-week screening period which included diet and lifestyle stabilization, a washout period for excluded non-statin lipid-altering medications (if needed), and a TG qualifying period, patients were randomized to one of 3 treatment groups and received study medication during a 12-week, double-blind treatment period. Patients had to be treated with one of 3 statins (simvastatin, atorvastatin or rosuvastatin) to reach their LDL-C goal of <100 mg/dL (+15% allowed for variability) and had to be on a stable dose for a minimum period of 4 weeks before the TG qualifying measurements. The TG target for enrollment was for patients to have qualifying fasting TG levels of ≥200 mg/dL and <500 mg/dL based on the mean of 2 measurements. During the 12-week double-blind treatment period, patients received orally AMR101 2 g/day, AMR101 4 g/day, or placebo.

Patients were randomized to either 2 or 4 g/day of AMR101 or placebo for 12 weeks. The primary endpoint was the reduction in TG levels compared to placebo. Secondary endpoints were percent change in LDL-C compared to placebo, non-high density lipoprotein

cholesterol (non-HDL-C), apoB, $LpPLA_2$, and very low density lipoprotein cholesterol (VLDL-C).

The median placebo-adjusted changes in the major lipid parameters for the groups receiving statin plus AMR101 are shown in Figure 2.

Figure 2. Placebo-Adjusted Median Percent Change from Baseline to Week 12 in Key Lipid Endpoints and Inflammatory Endpoints – Intent-to-Treat Population (ANCHOR)



****** p<0.0001; *** p<0.001; ** p<0.01; * p<0.05; NS = Not Significant (p≥0.05)**
Median Baseline TG: 259 (placebo, N=227), 265 (4 g/day, N=226), 254 (2 g/day, N=234) mg/dL
Median Baseline LDL-C: 84 (placebo, N=226), 82 (4 g/day, N=225), 82 (2 g/day, N=233) mg/dL
Median Baseline non-HDL-C: 128 mg/dL for all treatment groups.
Median Baseline apoB: 91 (placebo, n=219), 93 (4 g/day, n=217), 91 (2 g/day, n=227) mg/dL
Medians are Hodges-Lehmann medians; p-values are from the Wilcoxon rank-sum test.
Apo B = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; hsCRP = high sensitivity C-reactive protein; ITT=intent to treat; LDL-C = low-density lipoprotein cholesterol; Lp-PLA_2 = lipoprotein-associated phospholipase A_2; non-HDL-C = non-high-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; VLDL-C = very low density lipoprotein cholesterol; VLDL-TG = very low-density lipoprotein triglycerides.

AMR101 4g/day reduced median placebo-adjusted TG levels nonsignificantly by 13.1% (n=45, p=0.5467) in the lowest statin potency regimen (simvastatin 5-10 mg/day); significantly by 20.1% (n=429; p<0.0001) in the medium potency statin regimen (rosuvastatin 5-10 mg, atorvastatin 10-20 mg, simvastatin 20-40 mg, simvastatin 10-20 mg + ezetimibe 5-10 mg); and significantly by 26% (n=213, p<0.0001) in the highest statin potency regimen (rosuvastatin 20-40 mg, atorvastatin 40-80 mg, simvastatin 80 mg or simvastatin with ezetimibe 5-10 mg). The statin potency regimens were predefined.

Of the 702 patients with HTG enrolled in this study, 514 h ad diabetes mellitus. Efficacy results in patients with diabetes were similar to those of patients without diabetes, and no significant changes in fasting plasma glucose or HbA_{1c} with AMR101 vs placebo were observed.

The reduction in TG observed with AMR101 was also associated with a placebo-adjusted decrease in median LDL-C levels at both doses. Median baseline LDL-C levels were 82.0 mg/dL (4 g/day), 82.0 mg/dL (2 g/day), and 84.0 m g/dL (placebo). AMR1014 g/day

decreased median placebo-adjusted LDL-C by 6.2% (p=0.0067) which was superior to placebo, based on a prespecified +6% margin.

1.3. Clinical Safety

In the MARINE and ANCHOR trials, a total of 622 patients have been exposed to ethyl-EPA from AMR101 capsules. AMR101 has been well tolerated (with incidence of adverse events [AEs] similar to placebo) and there have been no major safety concerns. See the Investigator's Brochure for more information.

The types (by preferred term) of common treatment-emergent adverse events (TEAEs) and their incidence in the MARINE and ANCHOR trials are listed in Table 1.

Table 1: Adverse Reactions Occurring at Incidence >2% and Greater than Placebo in Double-Blind, Placebo-Controlled Trials*

Adverse Reaction	Placebo (N=309)		AMR101 (N=622)	
	N	%	N	%
Arthralgia	3	1.0	14	2.3

*Studies included patients with triglycerides values of 200 to 2000 mg/dL.An additional adverse reaction from clinical studies was oropharyngeal pain.
Source: Vascepa PI, Table 1

In a large study with Japanese patients (Japan EPA Lipid Intervention Study [JELIS]), long-term administration of 1.8 g/day ethyl-EPA (Epadel®) was associated with an excellent safety and tolerability profile (Yokoyama 2007). Most AEs attributable to ethyl-EPA were regarded as mild. The most common adverse events were gastro-intestinal (nausea, diarrhea, epigastric discomfort) or dermatologic (eruption, itching, exanthema, eczema) in nature.

1.4. Rationale

Hypothesis

The hypothesis is that combination anti-dyslipidemic therapy of an LDL-C lowering drug (statin therapy) with the TG-lowering drug AMR101 will be superior to the LDL-C lowering therapy alone when used as prevention in reducing long-term clinical events in patients with mixed dyslipidemia at high risk for CV events.

Medical Need

CVD resulting from progressive atherosclerosis remains the most common cause of morbidity and mortality all over the world. Based on 2009-2012 US statistics (AHA 2016), an estimated 85.6 million American adults (more than one in three) have one or more types of CVD. Of these, 43.7 million are estimated to be age 60 or older. Total CVD includes 80 million with high blood pressure (HBP), 15.5 million with coronary heart disease (CHD), which includes 7.6 million with myocardial infarction and 8.2 million with angina pectoris, 5.7 million with heart failure (HF) and 6.6 million with stroke (all types). Mortality data show that CVD as the underlying cause of death accounted for 30.8% of all deaths (about 800,937 of all 2.6 million deaths in 2013). CVD is the leading global cause of death, accounting for >17.3 million deaths per year in 2013, a number that is expected to grow to >23 million by 2030. In 2013, CVD deaths represented 31% of all global deaths. In addition

to death, CVD also causes many serious non-fatal events and is the major cause of disability. Therefore, additional therapies for prevention of CVD would have a considerable public health benefit.

Hypertriglyceridemia is a common lipid abnormality and often occurs in persons who are obese and have insulin resistance, Type 2 diabetes mellitus, or the metabolic syndrome (Jacobson 2007; Bays 2008). Elevation in TG is positively associated with accelerated atherosclerosis leading to CV events, the latter even after correction for other lipid and non-lipid risk factors (Jacobson 2007). In the US (AHA 2016), the mean TG level for American adults age 20 and older is 108.8 mg/dL (men, 117.2 mg/dL; women, 101.4 mg/dL). Approximately 25.1% of adults had high triglyceride (TG) levels (>150 mg/dL) during 2009-2012.

Lifestyle modification is important for the management of patients with HTG; however, for patients who do not adequately respond to dietary and lifestyle restrictions, relatively few classes of drugs are available to treat HTG, and each is associated with risks that may limit their use alone or in combination. In addition to Vascepa, currently available pharmacological treatments for high and/or very TG include fibric acid derivatives (such as gemfibrozil and fenofibrate), niacin in various formulations, prescription omega-3-acid ethyl esters (Lovaza/Omacor) and statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors).

Although the above agents have robust TG-lowering effects in patients with HTG, the degree of TG-lowering is highly variable; generally greater TG-lowering effects are observed for each TG-lowering agent compared with statins, particularly compared to the efficacy of statin doubling in patients with dyslipidemia. Many patients will be satisfactorily treated with one or more of the above range of drugs (combined with appropriate diet and attention to other CV risk factors and lifestyle).

A large number of studies have demonstrated the TG-lowering effects of O3FAs (Ballantyne 2012; Ginsberg 2001; Harris 1997). Lovaza, comprised predominantly of ethyl-EPA and the ethyl ester of DHA (ethyl-DHA) and approved at 4 g/day (equivalent to 4 capsules/day), is indicated only in patients with very high TG levels (≥500 mg/dL), and raises LDL-C even when combined with statins in patients with high (200-499 mg/dL) and very high (≥500 mg/dL) TGs. Of the seven CVOTs utilizing mixtures of EPA and DHA (see Table 3), two demonstrated significant primary endpoint risk reduction, one demonstrated CV risk reduction only in the post hoc analysis of diabetic patients, and four did not demonstrate benefit.

Fibrates and niacin are clearly effective at raising HDL-C and lowering TG concentrations; fibrates also raise LDL-C in patients with very high TGs (≥500 mg/dL). However, their effects on vascular events remain uncertain. Several large-scale trials of fibrate therapy have been completed in the past few years. Although some of these trials have suggested benefit, others have shown no effect, leading to uncertainty about the presence and magnitude of any CV protective effects and difficulties for clinicians in interpretation of the results (Jun 2010). The ACCORD-Lipid study (Ginsberg 2010) reported no overall benefit for fenofibrate plus statin therapy over statin monotherapy, although a suggestion of benefit was observed in subjects with dyslipidemia defined by high TG and low HDL-C. Similarly, studies of niacin as add-on therapy to statin have not demonstrated a benefit with regard to CV outcomes in

their full study populations (see AIM-HIGH and HPS2-THRIVE_), although benefit was observed in a subset of AIM-HIGH patients with high TG and low HDL-C. While such subgroup analyses are suggestive of benefit in certain patients with dyslipidemia, the lack of benefit in the primary study populations nonetheless raises further questions about the usefulness of these agents.

There are also safety issues with the above agents that limit th eir clinical use. Statins, particularly at high doses, may cause increases in hepatic transaminases and are also known to cause myopathy and occasionally rhabdomyolysis, which may lead to death from acute renal failure. This risk may be increased when fibrates and statins are co-administered and many clinicians will avoid co-prescribing these 2 medications. Fibrates are also associated with interactions with warfarin and hepatic transaminase elevations. The utility of niacin is limited by the occurrence of severe flushing and associated symptoms which can be difficult to manage even with careful dose titration and pre administration of aspirin or other non-steroidal anti-inflammatory drugs. Niacin is also associated with impairment of glucose tolerance and precipitation of attacks of gout in susceptible patients.

The DYSlipidemia International Study (DYSIS) assessed the prevalence of dyslipidemia among patients taking statins. This epidemiological observational study included more than 22,000 patients in Europe and Canada aged 45 and older who received statin therapy for at least three months, and had a clinical diagnosis of coronary or other atherosclerotic disease, or were at high risk of developing CVD. The study found 48% of patients had LDL-C not at goal; 26% had low HDL-C levels; and 38% had elevated TG. This study demonstrates that persistent dyslipidemia is highly prevalent in statin-treated patients.

Patients with dyslipidemia, particularly those with established CVD or diabetes, have therapeutic needs that cannot be met by statin monotherapy. It is hypothesized that achieving target values for LDL-C/non-HDL-C in these patients using a therapeutic approach of the combination of AMR101 and a statin will benefit these patients. Such a combination therapy might increase the likelihood of therapeutic success in these patients with regards to future risk of CVD, based on meeting of both LDL-C/non-HDL-C goals and TG goals according to the ACC/AHA guidelines (Anderson 2007). Approximately 40 million Americans have high TG levels (≥200 mg/dL), however only a minority (3.6%) are currently treated with prescription medication (Ford 2009). Patients with elevated TGs are currently under-served and would benefit from a new, safe and effective product that can provide the following attributes:

- Robust efficacy to lower TGs
- Safe to use with other lipid-lowering agents, including statins
- Does not increase LDL-C when used in patients on s tatin therapy (TG=200-499 mg/dL)
- Has convenient dosing regimen
- Has class-specific positive outcomes data

TG-Lowering as a Therapeutic CV Target

Epidemiological, clinical, and recent genetic studies contribute to evidence that increased TG levels causatively increase the risk for CVD and that treating elevated TG levels results in CV benefit. Multiple studies of mutations within genes encoding various proteins associated

with TG and the metabolism of TG-rich lipoproteins have independently suggested a link between TG levels and CV risk. For example, in one genetic study mutations of gene loci that lower TG levels were associated with decreased risk of CVD and other studies have further implicated loci associated with TG levels as contributing independently to coronary artery disease (CAD) risk (Pollin 2008, Schunkert 2011, Jørgensen 2014, Do 2013, Do 2015, Dewey 2016, Stitziel 2016). In addition, loss-of-function mutations of the gene encoding apolipoprotein C3 (*APOC3*), associated with low non-fasting levels of TG, resulted in risk reduction of 41% for ischemic vascular disease for heterozygotes compared with non-carriers (hazard ratio [HR] 0.59, 95% confidence interval [CI]: 0.41-0.86; p=0.007) and a risk reduction of 36% for ischemic heart disease (HR 0.64, 95 % CI: 0.41-0.99; p=0.04) (Jørgensen 2014). Similarly, in another study, deleterious mutations to *APOC3* resulted in reductions of risk of 40% (OR 0.60; 95% CI: 0.47-0.75; $P=4\times10^{-6}$) (The TG and HDL Working Group 2014) compared with non-carriers. In yet another study of genes strongly associated with TG levels (but not HDL-C), the direction of the association and its magnitude were both consistent with a contribution of risk for CAD (Do 2013). Moreover, studies centering on the metabolism of TG-rich lipoproteins have also put these TG-rich lipoproteins within the causative pathway of CVD, similar to LDL-C (Wittrup 1999, Do 2015). Of note, the same genetic correlation between HDL-C and CVD was not found.

Epidemiological and clinical studies have shown that elevated levels of total cholesterol (TC) and LDL-C are associated with increased risk of CHD (LaRosa 2003), and therapeutic strategies that lead to a statistically significant reduction in LDL-C lower CHD event rates (Baigent 2005). One potential impediment to optimal reduction in CHD events despite low on-treatment LDL-C is residual elevation in serum TG levels (Miller 2000). Indeed, even after adjustment for HDL-C, detailed evaluation of population-based prospective studies has disclosed an independent effect of TG on CHD events (Sarwar 2007). Coupled with the knowledge that combined hyperlipidemia (i.e., elevated LDL-C and TG) promotes CHD to a significantly greater extent than either high LDL-C or TG alone (Manninen 1992), the hypothesis is strong that low on-treatment levels of TG when added to low LDL-C would be superior to low LDL-C alone in reducing subsequent CHD events. Supporting evidence for this hypothesis was obtained in a post-hoc analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Trial (PROVE IT-TIMI 22) (Miller 2008) wherein among patients receiving statin therapy after acute coronary syndrome (ACS), on treatment TG <150 mg/dL was associated with a lower risk of recurrent CHD events independent of the level of LDL-C. For each 10% lowering of TG attained during the first 30 days of treatment after an ACS event, the risk for death, MI, or recurrent ACS was reduced by 2.3% (p =0.035) after adjustment for high LDL-C (>70 mg/dL) and low HDL-C (<40 and 50 mg/dL in men and women, respectively).

Several large clinical studies have examined the effects of non-statin lipid-modifying agents (with TG-lowering effects) in combination with statin therapy versus statin monotherapy on CV events (see Table 2).

Table 2. Published Clinical Studies of the Effects of Lipid-modulating Agents Plus Statin Therapy versus Statin Monotherapy on Cardiovascular Events

Trial Pub. Year	CV Risk Profile (therapy) N	Stated Goal (as statin add-on)	Statin-treated TG Lower Limit (Upper Limit) (mg/dL)	Median Baseline TG (mg/dL) (IQR)	Primary Endpoint (*p*-value)	TG + HDL-C Subgroup Baseline Criterion (mg/dL) N (% full cohort)	TG + HDL-C Subgroup Endpoint (*p*-value)
ACCORD-Lipid Ginsberg 2010	Type II DM 1° & 2° Prevention (fenofibrate) N = 5,518	CV benefit of raising HDL-C & lowering TG	None (<400)	162 (113, 229) *Note: At BL ~40% of patients were statin-naive*	MACE HR 0.92 (0.32)	TG ≥204 HDL-C ≤34 N = 941 (17%)	-31% (0.057)
AIM-HIGH AIM-HIGH Investigators 2011	CVD 2° Prevention (ER Niacin) N = 3,414	CV benefit of raising HDL-C	≥100 (≤400)	163 (127, 218)	Expanded MACE HR 1.02 (0.79)	TG ≥198 HDL-C <33 N = 522 (15%) --- TG ≥200 HDL-C <32 N = 439 (13%)	-26% (0.073) --- -36% (0.032)
HPS2-THRIVE HPS2-THRIVE Collaborative Group 2014	CVD 2° Prevention (ER Niacin + Laropiprant) N = 25,673	CV benefit of raising HDL-C	None (None)	108 (Full IQR = 73)	MVE RR 0.96 (0.29)	TG ≥151 HDL-C: <40 (men) <51 (women) N = 4,362 (17%)	No significant difference between groups*

Table 2. Published Clinical Studies of the Effects of Lipid-modulating Agents Plus Statin Therapy versus Statin Monotherapy on Cardiovascular Events (Continued)

Trial Pub. Year	CV Risk Profile (therapy) N	Stated Goal (as statin add-on)	Statin-treated TG Lower Limit (Upper Limit) (mg/dL)	Median Baseline TG (mg/dL) (IQR)	Primary Endpoint (*p*-value)	TG + HDL-C Subgroup Baseline Criterion (mg/dL) N (% full cohort)	TG + HDL-C Subgroup Endpoint (*p*-value)
JELIS Yokoyama 2007	High Cholesterol 1^{o} & 2^{o} Prevention (EPA) N = 18,645	CV benefit of EPA therapy in Japanese with high cholesterol	None (None)	153 (109, 220) *Note: Statin therapy initiated at BL in all patients*	Expanded MACE HR 0.81 (0.011)	TG ≥150 HDL-C ≤40 N = 957 (5%) *Note: Only 1^{o} Prevention patients were analyzed*	-53% (0.043)

1^{o}: Primary, 2^{o}: Secondary, ACCORD: Action to Control Cardiovascular Risk in Diabetes; AIM-HIGH: Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes; BL: baseline; CVD: cardiovascular disease; DM: diabetes mellitus; EPA: eicosapentaenoic acid; ER: extended-release; HDL-C: high-density lipoprotein cholesterol; HPS2-THRIVE: Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events; HR: hazard ratio; IQR: interquartile range; JELIS: Japan Eicosapentaenoic Acid Lipid Intervention Study; MACE: major adverse coronary events ; MVE: major vascular events; RR: relative risk; TG: triglycerides.

The ACCORD-Lipid Study

The ACCORD-Lipid study, a substudy of ACCORD, was a randomized, double-blind study of fenofibrate+statin therapy vs placebo+statin therapy in 5518 patients with Type 2 diabetes mellitus with clinical CVD, anatomical evidence of CVD, or 2 additional risk factors (in addition to diabetes) for CVD (Ginsberg 2010). The study evaluated whether the use of fenofibrate and simvastatin to increase plasma HDL-C and reduce TG would provide an additional CV benefit compared to simvastatin alone, as determined by the rate of first occurrence of any of a composite of nonfatal MI, nonfatal stroke, or CV death. Baseline characteristics were similar between treatment groups. After a mean follow-up of 4.7 years, the annual rates of CV events were not significantly different between treatment groups (2.2% for fenofibrate and 2.4% for placebo; HR: 0.92, 95% CI: 0.79-1.08; p=0.32). In examined subgroups, there was a suggestion of heterogeneity according to baseline lipid levels. Although ACCORD-Lipid did not prospectively enroll patients specifically with high TG (baseline median 162 mg/dL; interquartile range [IQR] of 113-229 mg/dL), and 40% of patients were not on statin therapy at baseline, a non-significant numerical reduction in CV event rate with fenofibrate was observed in patients in the highest baseline TG tertile (11.1% for fenofibrate vs 12.8% for placebo). A more compelling trend toward benefit approached significance in a smaller subgroup of patients within both the highest baseline TG tertile (≥204 mg/dL) and lowest baseline HDL-C tertile (≤34 mg/dL), with fenofibrate vs placebo (12.4% vs 17.3%; p=0.057 for interaction). Although the results of ACCORD-Lipid suggest an association of TG reduction with reduction in CV events in patients with dyslipidemia, the facts that approximately 65% of patients had had baseline TG <200 mg/dL, and that 40% of patients were not on statin therapy at baseline, diminish the ability of the study to examine the effects of TG-lowering in patients with high TG levels despite stable statin therapy.

The AIM-HIGH Study

The AIM-HIGH Study was a randomized, blinded, placebo-controlled study of the effects of extended-release niacin 1500–2000 mg/day in 3414 CVD patients receiving simvastatin on the primary endpoint of incidence of CV events (first event of death from coronary heart disease, nonfatal MI, ischemic stroke, hospitalization for >23 hours from ACS, or symptom-driven coronary or cerebral revascularization) (AIM-HIGH Investigators 2011). The study was stopped early due to futility and safety concerns, which subsequently were determined not to be drug-related. In this trial, extended-release (ER) niacin plus simvastatin as compared with simvastatin alone was associated with significant increases in HDL–C levels and decreases in TG levels, but there was no significant reduction in the primary composite endpoint of CV events over a mean follow-up period of 36 months (HR=1.02, 95% CI=0.87-1.21, p=0.79). Although AIM-HIGH did not prospectively enroll patients with elevated TG levels (baseline median TG for the niacin arm was 164 mg/dL; IQR=127-218 mg/dL), when the effect of treatment on CV events by baseline lipid/lipoprotein tertiles was studied, for the 522 (15.3%) subjects who simultaneously had baseline TG levels in the highest tertile (>198 mg/dL) and HDL-C levels in the lowest tertile (<33 mg/dL), a nonsignificant trend toward reduction of CV risk was evident in the ER niacin group (HR: 0.74, p=0.073). In a smaller subgroup (n=439 [12.9%]) that met somewhat stricter criteria of TG levels >200 mg/dL and HDL-C levels <32 mg/dL, the reduction in events in the niacin group was significant (HR: 0.64, p=0.032). Although AIM-HIGH did not prospectively seek

to enroll statin-treated patients with persistently high TG, and therefore was not well suited to studying the benefit of TG-lowering in this patient population, the results of subgroup analyses are consistent with a CV benefit to TG-lowering therapy in patients with dyslipidemia despite statin-controlled LDL-C.

The HPS2-THRIVE Study

The HPS2-THRIVE Study was a randomized, double-blind, placebo-controlled study of niacin 2000 mg/day and laropiprant 40 mg/day in addition to statin therapy vs matching placebo added to statin therapy in 25,673 adult patients with occlusive arterial disease at high risk for CVD (HPS2-THRIVE Collaborative Group 2014). The primary endpoint was the first event of a composite of major vascular events (including nonfatal MI, coronary death, nonfatal or fatal stroke, coronary or non-coronary artery surgery or angioplasty [including amputation]). Mean follow-up was 3.9 years. The study did not demonstrate a benefit to niacin therapy added to statin vs statin alone in the full study population (HR=0.96; 95% CI = 0.90-1.03, p=0.29). An exploratory analysis of patients with high TG (≥151 mg/dL) and low HDL-C (<35 mg/dL) found no significant difference between the niacin/laropiprant group and the placebo group in the incidence of major vascular events (15.1% vs 15.5%, respectively, of patients with an event). Of note, an important consideration for this analysis is that there were no lipid inclusion criteria in HPS2-THRIVE and, as a result, the median baseline TG value was 108 mg/dL with a full interquartile range of 73 mg/dL (mean TG ± standard deviation was 125 ± 74 m g/dL), markedly lower than the median baseline TG values in ACCORD-Lipid and AIM-HIGH. In addition, the interquartile range is reflected in the fact that only 26% of patients in the HPS2-THRIVE trial had TG values at or above 151 mg/dL, and suggests that very few subjects had TG levels >200 mg/dL. Accordingly, it is difficult to glean from HPS2-THRIVE any conclusive information regarding the potential CV benefit of niacin therapy in subjects with high TG despite statin therapy.

The Japan EPA Lipid Intervention Study (JELIS)

While no outcome study to date has specifically tested the benefit of lowering TG in a statin-treated population with persistent HTG, JELIS has demonstrated the CV benefit of 1.8 g/day ethyl-EPA added to a statin in 18,645 patients with elevated cholesterol (Yokoyama 2007). JELIS was a prospective, randomized, open-label, blinded endpoint evaluation (PROBE design) study of ethyl-EPA 1.8 g/day added to statin therapy versus statin alone in Japanese patients with hypercholesterolemia. JELIS is the only completed cardiovascular outcomes trial (CVOT) that has looked specifically at the effects of ethyl-EPA therapy – without DHA or other omega-3 fatty acids – on CV risk reduction. The mean follow-up was 4.6 years. The primary endpoint was the occurrence of major coronary events, including sudden cardiac death, fatal and non-fatal MI, unstable angina pectoris, angioplasty, stenting, and coronary artery bypass grafting. JELIS demonstrated a 19% relative reduction in the risk of major coronary events (primary endpoint) in the ethyl-EPA plus statin group vs statin alone group (HR = 0.81, 95% CI = 0.69 to 0.95). In addition to the significant primary outcome, and as performed in the ACCORD-Lipid, AIM-HIGH, and HPS2-THRIVE trials, the JELIS investigators conducted a sub-analysis of primary prevention patients with abnormal lipid levels, defined as baseline (statin-naïve) TG ≥150 mg/dL and HDL-C <40 mg/dL. Compared to patients with normal baseline serum TG and HDL-C levels, those with abnormal levels

had a significantly higher risk of CAD, and ethyl-EPA treatment suppressed the risk of primary events by 53% (HR: 0.47, 95% CI: 0.23-0.98; p=0.043).

As the only major published CVOT administering ethyl-EPA-only co-therapy with statin, JELIS is most similar in design to the current REDUCE-IT study. Therefore, it is worthwhile to note some details of JELIS design and the resulting data that differ from REDUCE-IT. First, the baseline TG levels in JELIS were fairly low (153-154 mg/dL). Also of note, JELIS was conducted exclusively in Japanese patients, and the Japanese population is generally found to have lower CV risk rates and higher baseline EPA levels in comparison to Western populations; the latter, which is believed to be due to higher dietary intake. Baseline plasma EPA levels were high in JELIS, and yet despite the differences in EPA baseline levels, along with the dose and duration of treatment between JELIS (1.8 g/day in a Japanese population for a median follow-up of 4.6 years) and the ANCHOR study (4 g/day in a more diverse and Westernized population for 12 weeks), the final plasma EPA levels were similar between these studies. In addition, there are other aspects of the JELIS study that might limit its applicability to broader patient populations. The majority (69%) of patients enrolled in JELIS were women. Furthermore, treatment in JELIS was open-label (although endpoint adjudication was blinded), which could influence patient and physician behavior and reporting of symptoms, decisions regarding hospitalization, and referral of events for adjudication. This may be particularly relevant since the number of hospitalizations for unstable angina was a primary contributor to the overall positive result, and is considered a softer endpoint than fatal CV events. Finally, at baseline, statin-naïve patients had a high LDL-C and a dose of statins was administered that would be considered low in a more Westernized patient population, potentially limiting the generalizability of the JELIS study results to a broader, more aggressively-treated population. Therefore, overall it is unknown whether the positive treatment effects observed in JELIS would have persisted if patients had been more optimally treated with statins using contemporary LDL-C targets in the United States. Nonetheless, 80% of JELIS patients were primary prevention and the mean baseline LDL-C of 182 mg/dL was reduced by 25% with statin therapy, to approximately 136 mg/dL. For primary prevention Japanese patients at low risk for CAD death, an LDL-C <160 mg/dL would meet LDL-C treatment goals according to the Japanese Atherosclerosis Society (JAS) guidelines, and an LDL-C <140 mg/dL would meet treatment goals for primary prevention Japanese patients at moderate risk (Teramoto 2013). Therefore, while some higher risk JELIS subjects may not have been treated as aggressively as guidelines for a United States-based population would recommend, the mean LDL-C data and the patient distribution from JELIS would suggest that many of the low-to-moderate risk primary prevention subjects were treated to Japanese guidelines.

Overall, in the JELIS study, ethyl-EPA therapy added to statin therapy resulted in a coronary benefit beyond statin monotherapy in both the full cohort of patients with relatively normal TG levels (-19%; p=0.011) and a more dramatic benefit within a subgroup of higher risk patients with dyslipidemia (-53%; p=0.043). In contrast, there was a suggestion of CV benefit from fenofibrate or niacin co-therapy with statin only in subjects with dyslipidemia within ACCORD-Lipid (-31%; p=0.057) and AIM-HIGH (-36%; p=0.032). Taken together, these studies suggest that there may be a CV benefit to TG-lowering therapies in subjects with dyslipidemia despite statin-controlled LDL-C (sub-group analyses), and that ethyl-EPA therapy may have additional unique CV benefits beyond treatment of dyslipidemia (JELIS full cohort).

IMPROVE-IT

In addition to studies of TG-lowering agents as add-on to statins, the IMPROVE-IT study assessed the effect of ezetimibe on lipids via inhibition of cholesterol absorption in 18,144 patients with ACS. The study found reductions in LDL-C, along with TG and other lipid changes, corresponding to reduced incidence of a composite primary endpoint of CV events (median follow-up of 6 years). The reduction in the composite of CV death, nonfatal MI, unstable angina requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke suggests that CV benefit can be derived from add-on therapy to statin.

In contrast to the CV benefit of ezetimibe co-therapy with statin observed in IMPROVE-IT, many studies have co-administered therapies that reduce TG levels without CV benefit in the full study populations, despite reductions in TG levels and increases in HDL-C (Table 2). Importantly, these studies did not prospectively enroll subjects at risk due to high TG levels despite statin therapy, which resulted in mean/median baseline TG levels that were normal or only slightly elevated (108-163 mg/dL). Nonetheless, in subgroup analyses of patients with high TG and low HDL-C, three of the four studies in Table 2 suggest that patients with dyslipidemia may derive CV benefit from TG-lowering therapies.

Omega-3 Fatty Acids in Fish Oils

There is a growing body of evidence, encompassing molecular, cellular, animal and human studies defining the roles for O3FAs as bioactive agents for reducing the risks of and treating CVD (Torrejon 2007). Many epidemiological studies have demonstrated inverse associations between fish intake and CV death, and more specifically between the intake and blood levels of O3FAs and CV death. For example, when comparing blood levels of O3FAs among men who had died of sudden cardiac death with controls matched for age and smoking status, it was found that participants with the highest blood levels of EPA and DHA had a 90% risk reduction for sudden cardiac death compared with those with the lowest levels (Albert 2002).

Clinical trials and experimental studies, suggest important antiatherogenic and antithrombotic effects of O3FAs. These result from wide-ranging biological effects, including benefits on lipoprotein metabolism, blood pressure, endothelial function and vascular reactivity, inflammation, platelet and fibrinolytic function, cytokine production, coagulation and oxidative stress (Mori and Woodman 2006). Evidence suggests that increased consumption of O3FAs from fish or fish-oil supplements reduces the rates of all-cause mortality, cardiac and sudden death, and possibly stroke (Wang 2006). The effect was evident in both primary-prevention (general population without a history of CVD) and secondary-prevention (patients with a history of CVD) studies with a stronger effect in secondary prevention.

The Diet and Reinfarction Trial (DART) was one of the first randomized, controlled studies to demonstrate the beneficial effects of O3FAs in secondary prevention of CHD and reported a 29% reduction in all-cause mortality over a 2-year period in 2033 male MI survivors advised to increase their intake of oily fish (200 to 400 g of fatty fish per week, which provided 500 to 800 mg/day of O3FAs) (Burr 1989). While not statistically significant, there was also a trend toward a reduction in recurrent ischemic heart disease events with increased fatty fish consumption. A post hoc analysis of patients receiving fish oil capsules (900 mg/day of EPA+DHA) in DART suggested that the protective effect was attributable to

O3FAs (Burr 1994). The greatest benefit was seen in fatal MIs, and this observation led to the hypothesis that O3FAs might protect the myocardium against the adverse sequela of acute ischemic stress.

A cardioprotective effect for O3FAs derived from fish oil is also supported by other prospective studies demonstrating inverse associations between fish intake and coronary heart disease mortality, especially amongst high-risk individuals (Mori and Woodman 2006). Early separation of survival curves in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione study (GISSI-Prevenzione Investigators 1999; discussed below) and the DART trial support a reduction in ventricular fibrillation and a decreased incidence of myocardial infarction (Leaf 1996) as primary mechanisms through which O3FAs prevent CVD (Mori and Woodman 2006).

Many international bodies including the AHA, ACC, and the European Society of Cardiology have found the overall evidence for benefit sufficiently strong to make public recommendations for increased O3FA intake for both primary and secondary prevention (Harris 2007).

Omega-3 Fatty Acid Ethyl Esters

Most CV primary and secondary prevention outcomes trials utilizing OM3FA focused on mixtures predominantly comprised of EPA+DHA, while one focused on EPA alone. The largest prospective, randomized, controlled trial to test the efficacy of O3FAs for secondary prevention of CHD is the GISSI study (GISSI-Prevenzione Investigators 1999). In this study, 11,324 patients with preexisting CHD (experienced an MI and were receiving conventional cardiac pharmacotherapy) were randomized to either 300 mg of vitamin E, 850 mg of O3FA ethyl esters (as EPA and DHA), both, or neither. After 3.5 years of follow-up, the group given the O3FAs alone experienced a 15% reduction in the primary endpoint of death, nonfatal MI, and nonfatal stroke ($p < 0.02$). There was a 20% reduction in all-cause mortality ($p = 0.01$) and a 45% reduction in sudden death ($p < 0.001$) compared with the control group; vitamin E provided no additional benefit. TG decreased by 4% and LDL cholesterol levels increased by 2.5% after six months in the O3FA treatment groups compared with controls. This trial, although very large and carried out in a relatively "usual-care" setting, was not placebo controlled, dropout rates were high (>25%), and statin use was not required. A follow-up study (Marchioli 2002) assessed the time-course of the benefit of O3FAs on mortality in subjects in the GISSI-P Study and found that survival curves diverged early after randomization. Total mortality was significantly lowered by 28% after 3 months of treatment (RR =0.59), and by 4 months, the risk of sudden cardiac death was reduced by 45% (RR =0.47).

Since the completion of GISSI, several primary and secondary prevention studies failed to find a CV benefit to OM3FA therapy, especially beyond statin monotherapy. High-level tabulated summaries of eight major CV outcomes trials testing omega acid mixtures or ethyl-EPA alone are presented in Table 3. Of the seven trials utilizing mixtures of EPA and DHA, two demonstrated significant primary endpoint risk reduction, one demonstrated CV risk reduction only in the post hoc analysis of diabetic patients, and four did not demonstrate benefit. All seven of these trials had design limitations, but key consistent limitations were low OM3FA dosing (containing 376-850 mg/day EPA+DHA), possible underutilization of

statin therapy, and lack of statistical powering. It is also worth noting that of the six studies that reported baseline LDL-C, median levels were relatively low (95-137 mg/dL). Median baseline TG were also relatively low across the studies (106-185 mg/dL), with all seven studies being below 200 mg/dL. These patients therefore do not necessarily represent patients presenting with persistent HTG despite LDL-C being treated to goal, nor did they test the CV benefit of higher dose OM3FA therapy.

Ethyl-EPA

While no outcome study to date has specifically tested the benefit of lowering TG with ethyl-EPA in a statin-treated population with persistent HTG, JELIS has demonstrated the CV benefit of 1.8 g/day ethyl-EPA added to a statin in 18,645 pa tients with elevated cholesterol (Table 3). As discussed above, JELIS exhibited a 19% relative reduction in the risk of major coronary events (primary endpoint) in the EPA plus statin group vs statin alone group (HR = 0.81, 95% CI=0.69 to 0.95) (see Section 1.4, The Japan EPA Lipid Intervention Study). There is evidence supporting a benefit in both primary and secondary prevention, as there was a nonsignificant 18% decrease in CV events in the 80% of patients in the JELIS trial without documented CAD (p =0.13); with this effect size being essentially the same as that observed in the secondary prevention cohort (19%, p <0.05) (Lee 2008).

Unlike the other OM3FA studies presented in Table 3 that administered an EPA+DHA mixture, the JELIS trial established the safety and efficacy of combination therapy with ethyl-EPA and a statin versus statin therapy alone for improving CV prognosis. The JELIS trial was conducted with Epadel that contains the same active ingredient, ethyl-EPA, as AMR101. Ethyl-EPA was shown in the JELIS study to reduce CAD events even in a Japanese population with very high intakes of O3FAs due to the high fish consumption.

Table 3. Omega Acid Mixture or EPA-only Outcomes Trials

Study	Population	Baseline LDL-C [mg/dL]	Baseline TG [mg/dL]	Interventions	Statin Use (% at BL)	Duration (years)	Primary Endpoint	Outcomes (CI)
Omega acid mixture studies								
GISSI-P (GISSI-Prevenzione Investigators 1999)	11,324 pts recent MI (≤3 mon)	137	163	850 mg EPA+DHA vs. Vit E vs.n-3+Vit E vs. placebo	5% (EoS=46%)	3.5	Death+non-fatal MI/stroke	RR = 0.85 (0.74 to 0.98) [four-way analysis]
GISSI-HF (GISSI-HF Investigators 2008)	6975 pts symptomatic HF	Not provided	126	850 mg EPA+DHA vs. placebo	22-23%	3.9	Co-primary of death, and death or CV hospitalization	Death HR: 0.91 (0.833–0.998) Death or CV hospitalization HR: 0.92 (0.849–0.999)
OMEGA (Rauch 2010)	3851 pts recent MI (≤2 wks)	Not provided	Not provided	840 mg EPA+DHA vs. placebo	94-95%	1	SCD	OR = 0.95 (0.56 to 1.60)
Alpha-Omega (Hoogeveen 2014)	4837 pts history of MI (median 3.7 yrs)	99-102	144-150	376 mg EPA+DHA vs. placebo and ALA (1.9 g combined)	83%	3.4	MACE	HR = 1.01 (0.87–1.17)
SU.FOL.OM3 (Galan 2010)	2501 pts recent coronary or cervical ischemic event (median 101 d)	104	106	600 mg EPA+DHA vs. placebo and B vitamin	83-87% (lipid-lowering agents)	4.2	MACE	HR = 1.08 (0.79 to 1.47)
ORIGIN (ORIGIN Trial Investigators 2012)	12,536 pts dysglycemia	112	140-142	840 mg EPA+DHA vs. placebo	53-54%	6.2	CV death	HR = 0.98 (0.87–1.10)

Table 3. Omega Acid Mixture or EPA-only Outcomes Trials (Continued)

Study	Population	Baseline LDL-C [mg/dL]	Baseline TG [mg/dL]	Interventions	Statin Use (% at BL)	Duration (years)	Primary Endpoint	Outcomes (CI)
Risk & Prevention (Risk & Prevention Study Collaborative Group 2013)	12,505 pts high risk CVD	132	150	840 mg EPA+DHA vs. placebo	41%	5	CV death or CV hospital admission	HR = 0.98 (0.88–1.08)
Ethyl-EPA Study								
JELIS (Yokoyama 2007)	18,645 pts hyper-cholesterolemic	182	152-163	1800 mg ethyl-EPA + statin vs. statin	100%	4.6	Any major coronary event	HR = 0.81 (0.69–0.95)

BL: baseline; CI: confidence interval; CV: cardiovascular; CVD: cardiovascular disease; DHA: docosahexaenoic acid; EoS: end of study; EPA: eicosapentaenoic acid; GISSI-HF: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico – Heart Failure; GISSI-P: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico – Prevenzione; HF: heart failure; HR: hazard ratio; JELIS: Japan Eicosapentaenoic Acid Lipid Intervention Study; LDL-C: low density lipoprotein cholesterol; MACE: major adverse cardiovascular event; MI: myocardial infarction; OMEGA: Effect of Omega 3-Fatty Acids on the Reduction of Sudden Cardiac Death After Myocardial Infarction; OR: odds ratio; ORIGIN: Outcome Reduction With Initial Glargine Intervention; RR: relative risk; SCD: sudden cardiac death ; TC: total cholesterol; TG: triglycerides.

Pleiotropic Effects

In addition to lowering TG, OM3FA may lead to reduced CV risk through other potential non-cholesterol mechanisms, but the exact mechanisms by which OM3FA may exert such benefit are not completely understood. Some of the possible mechanisms have been reviewed by Mozaffarian et.al. (Mozaffarian 2011, Mozaffarian 2012) and Borow et. al (Borow 2015). These mechanisms include changes in lipid profiles (Harris 2008), lipid uptake into the arterial wall (Chang 2010), plaque stabilization (Thies 2003, Cawood 2010, Yamano 2015), endothelial function (Geleijnse 2002, M ozaffarian 2005, W ang 2012, Yamakawa 2012), vascular function (Sasaki 2012), arterial stiffness (Pase 2011), vasodilation (Tagawa 1999), carotid intima-media thickness (Mita 2007), platelet aggregation (Nomura 2009, Needleman 1979), heart rate and blood pressure (Morris 1993, Mori 2010), HF (Djousse 2012, Gissi-HF Investigators 2008, Yamagishi 2008), oxidative stress (Mori 2003), and anti-inflammatory properties (systemic and endothelial) (Cawood 2010, Calder 2010, Aaresetoey 2012, Serhan 2008 , W all 2010, DeCaterina 1994, C aughey 1996, Jinno 2011). Of note, EPA+DHA have been proposed to benefit arrhythmic properties (Leaf 2005, Mozaffarian 2004, Gillet 2011, Anand 2008), which has been supported by at least one meta-analysis (Costanzo 2013), but not by others (Khoueiry 2013, Cao 2012, A rmaganijan 2011), and may depend on t he specific patient populations being studied.

The vast majority of studies addressing the effects of omega acids on CV risk have studied mixtures of omega acids comprised primarily of EPA+DHA. The scientific literature also indicates that other omega fatty acids derived from fish oil have biological effects. For instance, the manufacturer of Lovaza, an FDA approved complex mixture of omega acids comprised primarily of EPA and DHA, noted that "experimental evidence suggests that the individual omega-3 fatty acids EPA, DHA, DPA, SDA, HPA, and ALA are each either biologically active or are metabolized in the body to form biologically active agents" (Citizen Petition 2009). How different omega acid components work together to produce clinical effects observed in patients is not completely understood. No studies have been conducted to elucidate the relative contribution of individual omega acid constituents within a mixture or any combination of various mixed constituents. Nonetheless, potential differential effects have been reviewed by Mozaffarian and Yu (Mozaffarian 2012) and distinctions in the effects of EPA and DHA on biologic pathways have been suggested.

Dose Selection

The dose regimen of AMR101 in this study is 4 g/day (4 capsules/day).

The effects of combination treatment with ethyl-EPA plus statins on clinical CV events has been studied previously in JELIS (Yokoyama 2007), wherein ethyl-EPA combined with low-dose pravastatin or simvastatin compared with statin therapy alone reduced major coronary events without altering rates of sudden cardiac death. These effects were achieved without any significant changes in total, LDL- or HDL-C and a statistically significant ($p < 0.0001$), but relatively small (5%) decrease in TG, suggesting that EPA can lower CVD risk by mechanisms other than lipid lowering (Yokoyama 2007). In a sub-analysis of this study, the addition of ethyl-EPA to pravastatin or simvastatin also reduced the incidence of CHD events in high-risk patients with metabolic syndrome and atherogenic dyslipidemia characterized by high TG and low HDL-C (Saito 2008). The JELIS study was performed in a large patient

population wherein an ethyl-EPA dose of 1.8 g/day translated to significant benefits on CV events beyond statin monotherapy.

In the ANCHOR study (Amarin-sponsored), both the 2 and 4 g/day dosing regimens of AMR101 resulted in statistically significant reductions of TGs (see Section1.2.2). However, the 4 g/day dose caused a larger reduction in TG and other lipid, lipoprotein and inflammatory markers. In addition, the JELIS study was conducted in an exclusively Japanese patient population with higher baseline plasma EPA levels than most patients that live in more Westernized countries, likely due to differences in diet and fish intake. Nonetheless, 12-week dosing of 4 g/day ethyl-EPA in the ANCHOR study in a Westernized patient population resulted in similar final plasma EPA levels as approximately 4.6-year dosing of 1.8 g/day ethyl-EPA in JELIS. Based on these changes in lipid and inflammatory parameters, and the resulting final plasma levels, the AMR101 4 g/day dose was selected for the present study.

1.5. Risk/Benefit

Across all completed Amarin-sponsored studies, the proportion of patients (based on the safety population from the randomized, double-blind periods of the studies) experiencing any adverse events was similar for patients on placebo (light paraffin oil) and patients on AMR101 (57.1% and 57.4% for placebo and AMR101, respectively). The proportion of patients experiencing a serious adverse event (SAE) was also similar for both treatment groups (5.2% and 6.0% for placebo and AMR101, respectively). The safety profile in the open-label extensions was similar to that observed in the double-blind treatment periods. There were no SAEs attributed to AMR101 during the open-label extension periods of the studies.

In summary, AMR101 is very well tolerated at daily doses up to 4 g. The side effects reported by the patients taking AMR101 were generally similar to those reported by the patients taking placebo. Ethyl-EPA is a pro-drug, and is rapidly and completely hydrolyzed to EPA. EPA is a natural substance found universally as a component of all cell membranes. It is classified as an essential fatty acid. Therefore, EPA is an essential component of normal tissue and is handled in normal metabolism, and human studies have demonstrated that it is safe. See the Investigator's Brochure for more information.

2. STUDY OBJECTIVES

The primary objective is, in patients at low-density lipoprotein cholesterol (LDL-C) goal while on statin therapy, with established cardiovascular disease (CVD) or at high risk for CVD, and hypertriglyceridemia (fasting triglycerides [TG] ≥200 mg/dL and <500 mg/dL [≥2.26 mmol/L and <5.64 mmol/L]), to evaluate the effect of 4 g/day AMR101 on the time from randomization to first occurrence of any component of the composite of the following major cardiovascular (CV) events:

- CV death;
- Nonfatal myocardial infarction (MI), including silent MI;
- Nonfatal stroke;
- Coronary revascularization; or
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

The secondary objectives of this study are the following:

The key secondary objective is to evaluate the effect of therapy on the time from randomization to the first occurrence of the composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke.

Other secondary objectives for this study are to evaluate the effect of therapy on time from randomization to the first occurence of:

- Composite of CV death or nonfatal MI (including silent MI);
- Fatal or nonfatal MI (including silent MI);
- Non-elective coronary revascularization represented as the composite of emergent or urgent classifications;
- CV death;
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Fatal or nonfatal stroke;
- Composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke;
- Total mortality.

The tertiary objectives for this study are to evaluate the effect of therapy on the following. Where applicable and unless specified otherwise, endpoints represent time from randomization to the first occurrence of the individual or composite endpoints.

- The total CV events analysis defined as the time from randomization to occurrence of the first and all recurrent major CV events defined as CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;

- Primary composite endpoint in the subset of patients with diabetes mellitus at baseline;
- Primary composite endpoint in the subset of patients with metabolic syndrome at baseline as defined in *A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and I nternational Association for the Study of Obesity* (Alberti 2009); with cut points of parameters as defined in Table 1 of Alberti *et al.* and waist circumference cut points further guided by Table 2 of Alberti *et al*. and specifically set at ≥35 inches (88 cm) for all women and Asian, Hispanic, or Latino men, and ≥40 inches (102 cm) for all other men (see Appendix D);
- Primary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG of 100-125 mg/dL);
- Key secondary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG 100-125 mg/dL);
- Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalization of ≥24 hours, or cardiac arrest;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or PVD requiring intervention, such as angioplasty, bypass surgery, or aneurism repair;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, PVD requiring intervention, or cardiac arrhythmia requiring hospitalization of ≥24 hours;
- New CHF;
- New CHF as the primary cause of hospitalization;
- Transient ischemic attack (TIA);
- Amputation for PVD;
- Carotid revascularization;
- All coronary revascularizations defined as the composite of emergent, urgent, elective, or salvage;
- Emergent coronary revascularizations;

- Urgent coronary revascularizations;
- Elective coronary revascularizations;
- Salvage coronary revascularizations;
- Cardiac arrhythmias requiring hospitalization of ≥24 hours;
- Cardiac arrest;
- Ischemic stroke;
- Hemorrhagic stroke;
- Fatal or nonfatal stroke in the subset of patients with a history of stroke prior to baseline;
- New onset diabetes, defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period;
- New onset hypertension, defined as blood pressure ≥140 mmHg systolic OR ≥90 mmHg diastolic newly diagnosed during the treatment/follow-up period;
- Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP (hsCRP and log[hsCRP]), hsTnT, and RLP-C (to be estimated from standard lipid panel, RLP-C = TC – HDL-C – LDL-C [Varbo 2014]), (based on ITT estimands):
    - Assessment of the relationship between baseline biomarker values and treatment effects within the primary and key secondary composite endpoints,
    - Assessment of the effect of AMR101 on each marker,
    - Assessment of the relationship between post-baseline biomarker values and treatment effects within the primary and key secondary composite endpoints by including post-baseline biomarker values (for example, at 4 months, or at 1 year) as a covariate;
- Change in body weight;
- Change in waist circumference.

3. STUDY DESIGN

3.1. Type of Study

Phase 3b, multi-center, multinational, prospective, randomized, double-blind, placebo-controlled, parallel-group study

3.2. Study Population

The population for this study is men and women ≥45 years of age with established CVD, or men and women ≥50 years of age with diabetes in combination with one additional risk factor for CVD. In addition, all patients will have atherogenic dyslipidemia defined as on treatment for hypercholesterolemia (but at treatment goal for LDL-C, by treatment with a statin) and HTG. More details are listed in the inclusion criteria.

The patients will need to provide consent to participate in the study and be willing and able to comply with the protocol and the study procedures.

3.3. Study Periods

This study consists of the following study periods:

- **Screening Period**: During the screening period, patients will be evaluated for inclusion/exclusion criteria.

  At the first visit to the Research Unit (Visit 1), study procedures will be performed for evaluation of patient's eligibility in the study. At this screening visit, patients will sign an informed consent form before any study procedure is performed; the informed consent form will cover the treatment/follow-up period. Based on the evaluation from Visit 1, the following situations may occur:

  - Patients who are eligible for participation based on the study procedures on Visit 1 will return to the Research Unit for Visit 2 (randomization visit) to start the treatment/follow-up period. This case includes, for example, patients at Visit 1who are on a stable dose of a statin, are planning to stay on the same statin and the same dose of the statin, and who not need to wash out any non-statin lipid-altering medications.
  - Patients who are <u>not</u> eligible for participation based on the study procedures on Visit 1 and are <u>unlikely</u> to become eligible in the next 28 da ys (for example: unlikely to stabilize statin dose, unable to wash out non-statin lipid-altering medications, etc.): these patients will be screen failed after Visit 1.
  - Patients not eligible for participation in the study based on the study procedures on Visit 1 may possibly become eligible in the next 28 days: these patients may return at the discretion of the investigator for a second optional screening visit (Visit 1.1) at which time the procedures needed for re-evaluation of the previously failed inclusion/exclusion criteria will be repeated. This case includes, for example, patients who are started on a statin at Visit 1, whose statin dose is changed at Visit 1, and/or needed to wash out non-statin lipid-altering medications. The following applies for these patients:

- Patients with a change in the statin or statin dose on Visit 1 will need to be on a stable statin dose for at least 28 days before the lipid qualifying measurements at Visit 1.1. Other concomitant medications (antidiabetic therapy, for example) can be optimized or stabilized during this period.
- Patients starting a washout at Visit 1 will have a washout period of at least 28 days (only 7 days for bile acid sequestrants) before the lipid qualifying measurements at Visit 1.1.
- Patients at Visit 1 who are on a stable dose of a statin, are planning to stay on the same statin at the same dose, and who do not need any medication washout, but were asked to return for Visit 1.1 to repeat one or more of the other study procedures not related to concomitant medications

  - Patients who become eligible for participation based on the additional study procedures at Visit 1.1 will return to the Research Unit for Visit 2 (randomization visit) to start the treatment/follow-up period.

At the end of the screening period, patients will need to meet all inclusion/exclusion criteria before they can be randomized. Patients who are not eligible for participation after the screening period (based on study procedures at Visit 1 and/or Visit 1.1) may return at a later date for rescreening. These patients will need to re-start with all procedures starting with Visit 1. This includes patients who need more time to stabilize one or more conditions or therapies (for example: statin, antidiabetic, antihypertensive, thyroid hormone, HIV-protease inhibitor therapy).

- **Treatment/Follow-Up Period**: Within 42 days after the first screening visit (Visit 1) or within 60 days after the first screening visit (Visit 1) for those patients that have a second screening visit (Visit 1.1), eligible patients will enter the treatment/follow-up period. During this period, the patients will receive study drug during the planned visits at the Research Site and take the study drug while away from the Research Site.

During the visits, study procedures will be performed for evaluation of efficacy and safety. A detailed schedule of procedures is provided in Appendix A.

3.4. Study Duration

Patients will be randomized at different times during the enrollment period but will all end the study at approximately the same date (study end date) and, therefore, the duration of follow-up will differ based on date of randomization. It is planned that all randomized patients will receive study medication and be followed-up until the study end date. It is expected that a minimum of approximately 1612 primary endpoint events will be required during the study. Approximately 7990 patients will be randomized at multiple Research Sites worldwide over an estimated period of approximately 4.2 years. After randomization, patients will be treated and followed up to an estimated maximum of 6.5 years. The study end date is determined to be when approximately 1612 primary efficacy events have been adjudicated.

3.5. Study Groups

At Visit 2 (Day 0), eligible study patients will be randomly assigned to the following treatment groups:

- **Group 1**: AMR101 4 g daily (four 1 g capsules daily)
- **Group 2**: placebo (four capsules daily)

The four AMR101 or placebo capsules daily will be taken as two capsules in the morning and two capsules in the evening (twice-per-day dosing regimen).

3.6. Number of Patients

This is an event-driven trial: It is expected that a minimum of approximately 1612 primary endpoint events will be required during the study. A total of approximately 7990 patients will be entered into the study to either receive AMR101 or placebo (approximately 3995 patients per treatment group) in order to observe an estimated 1612 events that make up the primary composite endpoint for efficacy. Additional patients may be enrolled beyond the projected 7990 if the number of events contributing to the primary endpoint appears less than, and inconsistent with, projections (see Section 12.3).

3.7. Number of Study Sites

Participants will be enrolled at multiple Research Sites in multiple countries.

3.8. Randomization

On Day 0, eligible patients will be randomized to one of 2 study groups using a computer-generated randomization schema. Randomized treatment assignment to either AMR101 or placebo in a 1:1 ratio will be provided using the internet (via the Interactive Web Response System [IWRS]).

3.9. Blinding

This is a double-blind study. Patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors supporting the study will be unaware of the randomization code (i.e., they will not know which study participants are receiving the experimental drug and which are receiving the placebo drug). The study medication AMR101 and placebo capsules will be similar in size and appearance to maintain blinding.

During the double-blind treatment/follow-up period, everyone (patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors managing/supporting the study), with the exception of the laboratory personnel performing the analysis, will be blinded to individual results of the efficacy laboratory measurements (including lipid values). Individual results from the lipid profile may be unblinded in the event of an emergency for a patient.

3.10. Stratification

Participants will be assigned to treatment groups stratified by CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries). There are two CV risk categories:

- CV Risk Category 1: patients with established CVD defined in the inclusion criteria. Patients with diabetes and established CVD are included in this category.

- CV Risk Category 2: patients with diabetes and at least one additional risk factor for CVD, but no established CVD.

Stratification will be recorded in the IWRS at the time of enrollment. Approximately 70% of the planned 7990 randomized patients will be in the CV Risk Category 1 and approximately 30% of randomized patients will be in the CV Risk Category 2. Enrollment with patients of a CV risk category will be stopped when the planned number of patients in that risk category is reached. If total study enrollment exceeds 7990 patients, inclusion of new patients will be limited to CV Risk Category 1.

4. STUDY POPULATION

4.1. Inclusion Criteria

Patients meeting the following criteria will be eligible to participate in the study:

1. Fasting TG levels of ≥200 mg/dL (2.26 mmol/L) and <500 mg/dL (5.64 mmol/L).
2. LDL-C >40 mg/dL (1.04 mmol/L) and ≤100 mg/dL (2.60 mmol/L) and on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks prior to the LDL-C/TG baseline qualifying measurements for randomization
   - Stable therapy is defined as the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable, the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C). Patients who have their statin therapy or use of ezetimibe initiated at Visit 1, or have their statin, statin dose and/or ezetimibe dose changed at Visit 1, will need to go through a stabilization period of at least 28 days since initiation/change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).
   - Statins may be administered with or without ezetimibe.

   NOTE: If patients qualify at the first qualification visit (Visit 1) for TG and LDL-C, and meet all other inclusion/exclusion criteria, they may be randomized at Visit 2. If patients don't qualify at the first qualifying visit (Visit 1), a second re-qualifying visit (Visit 1.1) is allowed. For some patients, because they need to stabilize medications and/or need to washout medications, the second re-qualifying visit (Visit 1.1) will be needed after the stabilization/washout period.
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 are defined as follows:

   CV Risk Category 1: defined as men and women ≥45 years of age with one or more of the following:
   - Documented coronary artery disease (CAD; one or more of the following primary criteria must be satisfied):
     - Documented multivessel CAD (≥50% stenosis in at least two major epicardial coronary arteries – with or without antecedent revascularization)
     - Documented prior MI
     - Hospitalization for high-risk NSTE-ACS (with objective evidence of ischemia: ST-segment deviation or biomarker positivity)
   - Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied):
     - Documented prior ischemic stroke
     - Symptomatic carotid artery disease with ≥50% carotid arterial stenosis
     - Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound

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

o Documented peripheral arterial disease (PAD; one or more of the following primary criteria must be satisfied):

- ABI <0.9 with symptoms of intermittent claudication
- History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical)

OR

CV Risk Category 2: defined as patients with:

o Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication AND

o Men and women ≥50 years of age AND

o One 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: CrCL >30 and <60 mL/min (>0.50 and <1.00 mL/sec);
- Retinopathy, defined as any of the following: non-proliferative retinopathy, pre-proliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation;
- Micro- or macroalbuminuria. Microalbuminuria is defined as either a positive micral or other strip test (may be obtained from medical records), an albumin/creatinine ratio ≥2.5 mg/mmol or an albumin excretion rate on timed collection ≥20 mg/min all on at least two successive occasions; macroalbuminuria, defined as Albustix or other dipstick evidence of gross proteinuria, an albumin/creatinine ratio ≥25 mg/mmol or an albumin excretion rate on timed collection ≥200 mg/min all on at least two successive occasions;
- ABI <0.9 without symptoms of intermittent claudication (patients with ABI <0.9 with symptoms of intermittent claudication are counted under CV Risk Category 1).

Note: Patients with diabetes and CVD as defined above are eligible based on the CVD requirements and will be counted under CV Risk Category 1. Only patients with diabetes and no documented CVD as defined above need at least one additional risk factor as listed, and will be counted under CV Risk Category 2.

4. Women may be enrolled if all 3 of the following criteria are met:
   - They are not pregnant;
   - They are not breastfeeding;
   - They do not plan on becoming pregnant during the study.

5. Women of child-bearing potential must have a negative urine pregnancy test before randomization.

   Note: Women are not considered to be of childbearing potential if they meet one of the following criteria as documented by the investigator:

   - They have had a hysterectomy, tubal ligation or bilateral oophorectomy prior to signing the informed consent form;
   - They are post-menopausal, defined as ≥1 year since their last menstrual period or have a follicle-stimulating hormone (FSH) level in a menopausal range.

6. Women of childbearing potential must agree to use an acceptable method of avoiding pregnancy from screening to the end of the study, unless their sexual partner(s) is/are surgically sterile or the woman is abstinent.
7. Understanding of the study procedures, willing to adhere to the study schedules, and agreement to participate in the study by giving informed consent prior to screening.
8. Agree to follow a physician recommended diet and to maintain it through the duration of the study.

4.2. Exclusion Criteria

Patients are excluded from participation in the study if any of the following criteria apply:

1. Severe (New York Heart Association [NYHA] class IV) heart failure.
2. Any life-threatening disease expected to result in death within the next 2 years (other than CVD).
3. Active severe liver disease (evaluated at Visit 1): cirrhosis, active hepatitis, ALT or AST >3 × ULN, or biliary obstruction with hyperbilirubinemia (total bilirubin >2 × ULN).
4. Hemoglobin A_{1c} >10.0% (or >86 mmol/mol IFCC units) at screening (Visit 1). If patients fail this criterion (HbA_{1c} >10.0% or >86 mmol/mol IFCC units) at Visit 1, they may have their antidiabetic therapy optimized and be retested at Visit 1.1.
5. Poorly controlled hypertension: blood pressure ≥200 systolic mmHg OR ≥100 mmHg diastolic (despite antihypertensive therapy).
6. Planned coronary intervention (such as stent placement or heart bypass) or any non-cardiac major surgical procedure. Patients can be (re)evaluated for participation in the trial (starting with Visit 1.1) after their recovery from the intervention/surgery.
7. Known familial lipoprotein lipase deficiency (Fredrickson Type I), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type III)].
8. Participation in another clinical trial involving an investigational agent within 90 days prior to screening (Visit 1). Patients cannot participate in any other investigational medication or medical device trial while participating in this study (participation in a registry or observational study without an additional therapeutic intervention is allowed).
9. Intolerance or hypersensitivity to statin therapy.

10. Known hypersensitivity to any ingredients of the study product or placebo (refer to Table 5); known hypersensitivity to fish and or shellfish.
11. History of acute or chronic pancreatitis.
12. Malabsorption syndrome and/or chronic diarrhea (Note: patients who have undergone gastric/intestinal bypass surgery are considered to have malabsorption, hence are excluded; patients who have undergone gastric banding are allowed to enter the trial).
13. Non-study drug related, non-statin, lipid-altering medications, supplements or foods:
    - Patients are excluded if they used niacin >200 mg/day or fibrates during the during the screening period (after Visit 1) and/or plan to use during the study; patients who are taking niacin >200 mg/day or fibrates during the last 28 days before Visit 1 need to go through washout of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (Visit 1.1);
    - Patients are excluded if they take any omega-3 fatty acid medications (prescription medicines containing EPA and/or DHA) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking omega-3 fatty acid medications during the last 28 days before Visit 1 (except patients in the Netherlands), need to go through a washout period of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (at Visit 1.1);
    - Note: For patients in the Netherlands only: patients being treated with omega-3 fatty acid medications containing EPA and/or DHA are excluded; no washout is allowed.
    - Patients are excluded if they use dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking >300 mg/day omega-3 fatty acids (combined amount of EPA and DHA) within 28 days before Visit 1 (except patients in the Netherlands), need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);
    - Note: For patients in the Netherlands only: patients being treated with dietary supplements containing omega-3 fatty acids of >300 mg/day EPA and/or DHA are excluded; no washout is allowed.
    - Patients are excluded if they use bile acid sequestrants during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking bile acid sequestrants within 7 days before Visit 1, need to go through a washout period of at least 7 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);
    - Patients are excluded if they use PCSK9 inhibitors during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients cannot have taken a PCSK9 inhibitor within 90 days prior to their screening visit.

14. Other medications (not indicated for lipid alteration):
    - Treatment with tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are allowed), HIV-protease inhibitors that have not been stable for ≥28 days prior to the qualifying lipid measurements (TG and LDL-C) during screening. To be eligible for participation in the study, patients who are not taking a stable dose of these medications within 28 days before Visit 1, need to go through a stabilization period of at least 28 days since their last dose change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).
    - Patients are excluded if they use cyclophosphamide or systemic retinoids during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking these medications within 28 days before Visit 1, need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).
15. Known to have AIDS (patients who are HIV positive without AIDS are allowed).
16. Requirement for peritoneal dialysis or hemodialysis for renal insufficiency or creatinine clearance (CrCL) <30 mL/min (0.50 mL/sec).
17. Unexplained creatine kinase concentration >5 × ULN or creatine kinase elevation due to known muscle disease (e.g., polymyositis, mitochondrial dysfunction) at Visit 1.
18. Any condition or therapy which, in the opinion of the investigator, might pose a risk to the patient or make participation in the study not in the patient's best interest.
19. Drug or alcohol abuse within the past 6 months, and unable/unwilling to abstain from drug abuse and excessive alcohol consumption during the study or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking). Excessive alcohol consumption is on average >2 units of alcohol per day. A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.
20. Mental/psychological impairment or any other reason to expect patient difficulty in complying with the requirements of the study or understanding the goal and potential risks of participating in the study (evaluated at Visit 1).

5. STUDY COMMITTEES

5.1. Steering Committee

The Steering Committee (SC) will include the chairperson (the Principal Investigator [PI]) and medical/scientific specialists with expertise in clinical trials, cardiovascular outcomes and lipidology.

The SC has overall responsibility for:

- Scientific and strategic direction for the trial. The SC must address and resolve all scientific issues regarding the conduct of the trial. All sub-studies must be approved by the SC.
- The execution of the study protocol, and the reporting and publication of the study results.
- Logistical coordination of the different study committees.

The SC will meet at least twice per year, and the SC meetings will be conducted as defined within the SC Charter drafted and approved by the SC.

5.2. Study Operations Committee

The Study Operations Committee is responsible for ensuring that study execution and management is of the highest quality, and will monitor recruitment, compliance, and the adjudication process and address the day to day issues arising from the trial. This committee will be composed of representatives from the Sponsor and the organization(s) conducting the study (as delegated by the Sponsor). This committee will meet by telephone and/or in person on a periodic basis, and each meeting will be documented with minutes.

5.3. Clinical Endpoint Committee (CEC)

The CEC is composed of multidisciplinary medical experts. This committee will be responsible for blindly validating all primary, secondary, and tertiary efficacy outcome events reported by the investigators (event adjudication). The CEC will operate in accordance with a charter drafted and approved by the CEC that contains details of the adjudication process and methods based on the definitions of the events.

5.4. Data Monitoring Committee (DMC)

A DMC will be instituted for this study in order to ensure its ongoing safety and to oversee and review the interim and final analyses. Recommendation for trial continuation will be guided by monitoring boundaries at the interim analyses at which a formal efficacy analysis is performed as well as safety evaluations at all safety data reviews. Members of the DMC will not otherwise be participating in the trial. The committee will include at least one cardiologist and one independent statistician. The DMC meetings will be conducted as defined within the DMC Charter drafted and approved by the DMC and the SC. The Charter will provide details regarding the interim analysis and monitoring plan.

6. STUDY PROCEDURES

6.1. Assessment Schedule

A detailed schedule of procedures is provided in Appendix A. Study sites are to actively support patient progress and study protocol adherence (i.e., compliance with scheduled office and phone visit schedules).

6.1.1. Screening Period

6.1.1.1. Screening Visit (Visit 1)

Patients will come to the Research Site for Visit 1. They will be instructed to fast for at least 10 hours before their visit.

If patients qualify for randomization based on the procedures at Visit 1, they need to be randomized within 42 days after Visit 1. The following procedures will be performed at the screening visit:

- Obtain signed informed consent
- Assign the patient a patient number
- Obtain medical, surgical and family history
- Record demographics
- Obtain height, weight, and body mass index
- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)
- Obtain a 12-lead ECG
- Evaluate inclusion/exclusion criteria
- This includes procedures and (fasting) blood samples (for example, hs-CRP, calculated creatinine clearance) as needed to determine the CV risk category (see inclusion criteria)
- Obtain fasting blood samples for chemistry and hematology testing
- Obtain a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C)
- Perform a urine pregnancy test on women of childbearing potential
- Record concomitant medication(s)
- Instruct patient to fast for ≥10 hours prior to the next visit

6.1.1.2. Screening Visit (Visit 1.1)

Some patients will skip Visit 1.1: Patients who qualify for study participation after Visit 1 because they meet all inclusion criterion and none of the exclusion criteria, may return to the Research Site for Visit 2 to be randomized and to start the treatment/follow-up period of the study. For these patients, Visit 2 will occur soon after Visit 1.

Patients, who do not qualify at Visit 1, may return to the Research Site for a second qualifying visit (Visit 1.1) at the discretion of the investigator. At Visit 1.1, procedures that caused failure of eligibility at Visit 1 will be repeated. Patients will be eligible for randomization after Visit 1.1 if they meet all inclusion criteria and if they no longer fail the exclusion criteria. If patients are evaluated at Visit 1.1 and qualify for randomization based on the repeated procedures at Visit 1.1, they need to be randomized within 60 days after Visit 1.

For some patients, Visit 1.1 will be mandatory at least 28 days after Visit 1 in order to check eligibility. These are patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications (see inclusion/exclusion criteria for details). Any of these changes at Visit 1 may affect the qualifying lipid levels and therefore, patients will need to have Visit 1.1 to determine whether they qualify based on lipid level requirements (TG and LDL-C) determined at Visit 1. Other procedures that caused failure of eligibility at Visit 1 will also be repeated at Visit 1.1.

The following procedures will be performed at the screening visit:

- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)
- Evaluate inclusion/exclusion criteria; only those evaluations will be repeated that deemed the patient not eligible on Visit 1.
- Obtain fasting blood samples for chemistry and hematology testing. Only those samples will be obtained that deemed the patient not eligible on Visit 1.
- Obtain a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C) if the patient was deemed not eligible on Visit 1. This includes patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications (see inclusion/exclusion criteria for details). These patients will have a fasting blood sample collected at Visit 1.1 for the qualifying lipid values (TG and LDL-C), and the TG and LDL-C inclusion criteria will be evaluated.
- Record concomitant medication(s)

6.1.2. Treatment/Follow-Up Period

Every attempt should be made to complete the follow-up visits during the defined window periods.

6.1.2.1. Randomization visit (Visit 2; Day 0)

Qualified patients will return to the Research Site for Visit 2.

The following procedures will be performed at Visit 2:

- Perform physical examination
- Obtain weight

- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)
- Measure waist circumference (one of the 5 factors used to diagnose metabolic syndrome)
- Obtain a 12-lead ECG
- Evaluate inclusion/exclusion criteria
- Obtain fasting blood samples for:
  - Chemistry and hematology testing
  - Lipid profile (baseline)
  - Biomarker assays (baseline)
  - Genetic testing (optional blood sample)
  - Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)
- Perform a urine pregnancy test on w omen of childbearing potential (must be negative for randomization)
- Dispense study drug and record randomization number
- Instruct patient on how to take study drug
- Administer study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples
- Assess for and record adverse events
- Record concomitant medication(s)
- Instruct patient:
  - To bring all study supplies with them to the next visit
  - Not to take study drug on the morning of their next visit
  - To fast for ≥10 hours prior to the next visit

6.1.2.2. Visit 3 (Day 120; ~4 Months)

Patients will return to the Research Site for Visit 3 on Day 120 ±10 days.

The following procedures will be performed:

- Perform physical examination
- Obtain weight
- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)
- Obtain fasting blood samples for:
  - Chemistry and hematology testing
  - Lipid profile

- Review study drug compliance by unused capsule count; discuss with and counsel patients about compliance if needed
- Administer study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples
- Assess and record efficacy events
- Assess for and record adverse events
- Record concomitant medication(s)
- Instruct patient:
    - To bring all study supplies with them to the next visit
    - Not to take study drug on the morning of their next visit
    - To fast for ≥10 hours prior to the next visit

6.1.2.3. Visits 4, 5, 6, 7, 8 and 9

At Visit 4: Day 360 ± 10; Visit 5: Day 720 ± 10; Visit 6: Day 1080 ± 10; Visit 7: Day 1440 ± 10, Visit 8: Day 1800 ± 10, Visit 9: Day 2160 ± 10) the following procedures will be performed:

- Perform physical examination
- Obtain weight
- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)
- Measure waist circumference (collected at Visit 5 only)
- Obtain a 12-lead ECG
- Obtain fasting blood samples for:
    - Chemistry and hematology testing
    - Lipid profile
    - Biomarker assays (collected at Visit 5 only)
    - Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)
- Review study drug compliance by unused capsule count; discuss with and counsel patients about compliance if needed
- Administer study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples
- Assess and record efficacy events
- Assess for and record adverse events
- Record concomitant medication(s)
- Instruct patient:

- To bring all study supplies with them to the next visit
- Not to take study drug on the morning of their next visit
- To fast for ≥10 hours prior to the next visit

6.1.2.4. Additional Visits

The end date of the study is expected for Day 2160 but the actual end date will be dependent on the determination of the study end date by the DMC. The study end date is determined to be when approximately 1612 primary efficacy events have been adjudicated. If the actual study end date is later than the expected end date, additional visits will be planned between Visit 9 and the Last Visit with a maximum of 360 ±10 days between visits. If the actual study end date is sooner than the expected end date, fewer visits will occur, and the last visit (See Section 6.1.2.5) will occur sooner.

On additional visits the same procedures will be performed as listed in Section 6.1.2.3. Irrespective of the number of additional visits, after the DMC has established the end of the study date, there will be a last visit with procedures as listed in Section 6.1.2.5.

6.1.2.5. Last Visit – End of Study

All patients will complete the study at the same time (within a target of 30 days after the study end date), irrespective of the date that they were randomized. The end date of the study is planned for Day 2160 but the actual end date will be dependent on the determination of the study end date by the DMC when approximately 1612 primary efficacy events have been adjudicated (event-driven trial). For each patient, the last visit may occur within a target of 30 days after the actual study end date as determined by the DMC. However, for the efficacy endpoints based on CV events, only events occurring up to and including the scheduled actual study end date will be included in the efficacy analyses.

A final follow-up visit is required for all patients. In the rare cases that a final follow-up visit cannot occur within the targeted 30-day timeframe following the study end date, any attempt to contact the patient must be recorded on a special contact form, until/unless appropriate information is obtained.

At the Last Visit, the following procedures will be performed:

- Perform physical examination
- Obtain weight
- Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)
- Measure waist circumference
- Obtain a 12-lead ECG
- Obtain fasting blood samples for:
  - Chemistry and hematology testing
  - Lipid profile
  - Biomarker assays

  - Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)
- Determine study drug compliance by unused capsule count
- Assess and record efficacy events
- Assess for and record adverse events
- Record concomitant medication(s)

6.2. Telephone Follow-up Contact

Site personnel will contact each patient by telephone on the following study days:

- Day 60 ±3 days
- Day 180 ±5 days
- Day 270 ±5 days
- Day 450 ±5 days
- Day 540±5 days
- Day 630 ±5 days
- Day 810 ±5 days
- Day 900 ±5 days
- Day 990 ±5 days
- Day 1170 ±5 days
- Day 1260 ±5 days
- Day 1350 ±5 days
- Day 1530 ±5 days
- Day 1620 ±5 days
- Day 1710 ±5 days
- Day 1890 ±5 days
- Day 1980 ±5 days
- Day 2070 ±5 days

If the treatment/follow-up period of the study is extended beyond the expected end date (Day 2160), additional follow-up phone calls will be made every 90 days in-between additional visits ±5 days. See Section 6.1.2.4 for the timing of the additional visits. If the treatment/follow period of the study is shorter than the expected end date, less follow-up phone calls will be needed.

Every attempt will be made to talk to each patient within this time frame.

The following information will be collected from the patient:

- Possible efficacy endpoints related to CV events. Patients will be asked to return to the Research Site to assess for any endpoints or events identified.
- Adverse events
- Concomitant medications
- Current address and contact information (update if changed or will be changing)

Patients will be reminded about the following items:

- To take the study medication according to the dosing schedule assigned, with food
- When to return to the Research Center for the next visit
- To bring the unused study medication to the next visit
- To not take study drug on the morning of their next visit
- To fast for at least 10 hours prior to the next visit

6.3. Laboratory Procedures

6.3.1. Clinical Laboratory Procedures

All clinical laboratory determinations for screening and safety will be performed by a certified clinical laboratory under the supervision of the Sponsor or its designee.

Whenever possible and appropriate, samples for the clinical laboratory procedures will be collected after fasting for at least 10 hours. For the purposes of this study, fasting is defined as nothing by mouth except water (and any essential medications).

The investigator must review and sign all laboratory test reports. At screening, patients who have laboratory values that are outside the exclusionary limits specified in the exclusion criteria may not be enrolled in the study. After randomization, the investigator will be notified if laboratory values are outside of their normal range. In this case, the investigator will be required to conduct clinically appropriate follow-up procedures.

6.3.1.1. Safety Laboratory Tests

The safety laboratory tests include:

- Hematology with complete blood count (CBC), including RBC, hemoglobin (Hgb), hematocrit (Hct), white cell blood count (WBC), white cell differential, and platelet count
- Biochemistry panel including total protein, albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), total bilirubin, glucose, calcium, electrolytes (sodium, potassium, chloride), blood urea nitrogen (BUN), serum creatinine, uric acid, creatine kinase, and HbA_{1c}.

6.3.1.2. Fasting Lipid Profile

The fasting lipid panel includes: TG, TC, LDL-C, HDL-C, non-HDL-C, and VLDL-C.

At all visits, LDL-C will be calculated using the Friedewald equation if TG <400 mg/dL. At Visit 1 and Visit 1.1 Direct LDL-C will be used if at the same visit TG >400 mg/dL (4.52 mmol/L). These LDL-C values will be used for the evaluation of the LDL-C inclusion

criteria (LDL-C qualifying measurements for randomization) and for the assessment of changes in the statin therapy when LDL-C is not at goal. At all remaining visits LDL-C will be measured by Direct LDL-C or by Preparative Ultracentrifugation if at the same visit TG >400 mg/dL (4.52 mmol/L). In addition, irrespective of the TG levels, at Visit 2 (0 Months of Follow-up, baseline) and at Visit 4 (12 Months of Follow-up), LDL-C direct and LDL-C Preparative Ultracentrifugation will be taken. These Preparative Ultracentrifugation LDL-C measurements will be used in the statistical analysis including the calculation of the percent change from baseline (1 year versus baseline). Hopkins LDL-C (Martin 2013) will be calculated for each visit.

6.3.1.3. Genetic testing

A fasting blood sample will be stored for future genetic testing at the discretion of the sponsor. The specifics of this test will be determined at a later date. This sample is optional as local regulations may prohibit genetic samples to be collected or shipped outside the country, or patients may not consent.

Research on genetic testing will look for links between genes and certain diseases, including their treatment(s) such as medicines and medical care. The blood samples will be collected in the study center with the regular protocol-required labs. Each patient tube with sample for genetic testing will be labeled with patient number only. The site will maintain a Subject Code Identification List for cross-reference. The patient number does not contain any identifiable information (i.e. Patient initials, date of birth, etc.). Un-analyzed samples will be stored frozen by the sponsor for a period of up to 2 years following the end of the study, at which time they will be destroyed. If samples are tested, results will not be reported to the patient, parents, relatives, or attending physician and will not be recorded in the patient's medical records. There will be no follow-up contact with the sites or patients regarding this sample. The subject can withdraw their consent for genetic testing at any time up to analysis, even after the sample has been obtained. The subject can notify the site in writing that they withdraw their consent for the genetic testing portion of the study, and it will be documented by the site in the subject chart, as well as captured in the CRF. The lab will be notified to pull the sample and destroy it.

Potential genetic bioassays may be performed and may be as broad as a genome-wide association study (GWAS) or as limited as a single gene-target approach; potential target genes include, but are not limited to the genes encoding: Apo C3, Apo A5, CETP, LPL, PCSK9, TNFα, TNFβ, ALOX5, COX2, FABP genes, haptoglobin 1 and haptoglobin 2.

6.3.1.4. Biomarkers Assays

The biomarker assays include: hs-CRP, Apo B and hsTnT.

6.3.1.5. Additional laboratory tests

Additional laboratory tests include:

- A urine pregnancy test will be administered to women of childbearing potential at certain visits as listed in schedule of procedures (Appendix A). The urine pregnancy tests will be performed at the Research Site utilizing marketed test kits, or at a certified clinical laboratory.

- A fasting blood sample (10 mL) for serum archiving. This sample will be collected only at sites in countries where allowed by local regulations and at sites for which approved by the IRB or EC. The serum from the archiving sample will be stored frozen in 2 separate equal aliquots, and will be used at the Sponsor's discretion to perform repeat analyses described in the protocol or to perform other tests related to CV health.
    - Potential non-genetic bioassays may be performed, including but not limited to: Apo A1, Apo C3, Apo E, NMR lipid profile (particle size and number), oxidized LDL, Lp(a), Lp-PLA_2, serum fatty-acids concentrations, and gamma-glutamyltransferase (GGT).

6.3.1.6. Blinding of Laboratory Results

All efficacy laboratory results during the double-blind period of the trial will be blinded (values not provided) to patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors managing and/or supporting the study, with the exception of the laboratory personnel conducting the assays. To ensure patient safety, hsTnT values will be reported to the site.

6.3.1.7. Flagging of Critical Lab Values

Critical lab values are values that may warrant medical intervention to avoid possible harm to a patient. Critical lab values will be defined in the Laboratory Manual for the study, and the Research Site will be notified of the occurrence of a critical lab value (critical high or critical low) by a special annotation (flag) in the laboratory reports provided to the Research Sites. Although laboratory values that are part of the efficacy endpoints during the double-blind period of the study will not be provided to the Research Site (see Section 6.3.1.6), the sites will be notified when the TG value of a patient sample is >1000 mg/dL (11.29 mmol/L) (critical high TG value) or if the LDL-C values of a patient sample is >130 mg/dL (3.37 mmol/L) (critical high LDL-C value). These critical high values will need to be confirmed by a repeat measurement (new fasting blood sample) within 7 days. TG value of >2000 mg/dL (22.58 mmol/L) will also be flagged, so that appropriate medical action can be taken by the investigator as soon as possible.

If TG values are confirmed critically high, patients may be discontinued from study drug with the option to remain on study (see Section 11.1). The investigator should use the best clinical judgment for each patient which could include the use of approved TG-lowering medications after patients have been discontinued from study drug.

If LDL-C values are confirmed critically high, the investigator may need to take appropriate medical action which could include: reinforce/intensify therapeutic lifestyle changes (including diet and physical activity), increase the dose of the present statin therapy, add ezetimibe, or prescribe a more potent statin to lower LDL-C. The investigator should use the best clinical judgment for each patient.

6.3.2. Medical Procedures

6.3.2.1. Medical, Surgical and Family History

Medical history, including family history and details regarding all illnesses and allergies, date(s) of onset, status of current condition, and smoking and alcohol use will be collected on all patients.

6.3.2.2. Demographics

Demographic information including day, month, and year of birth, race, and gender will be collected for all patients.

6.3.2.3. Vital Signs

Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Blood pressure will be measured using a standardized process:

- Patient should sit for ≥5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level.
- Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery.

Blood pressure should be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device. A blood pressure reading should be repeated 1 to 2 minutes later, and the second reading should also be recorded to the nearest 2 mmHg mark or to the nearest whole number on an automatic device.

6.3.2.4. Physical Examination

A physical examination must include source documentation of general appearance, skin, and specific head and neck, heart, lung, abdomen, extremities, and neuromuscular assessments.

6.3.2.5. Height, Weight and Body Mass Index

Height and weight will be measured. Measurement of weight should be performed with the patient dressed in indoor clothing, with shoes removed, and bladder empty.

6.3.2.6. Waist Circumference

Waist circumference will be measured with a tape measure, as follows: Start at the top of the hip bone then bring the tape measure all the way around – level with the navel. Make sure the tape measure is snug, but without compressing the skin, and that it is parallel with the floor.

Patients should not hold their breath while measuring waist circumference.

6.3.2.7. 12-Lead ECG

ECGs (standard 12-lead) will be obtained annually. Site personnel should make every attempt to perform a patient's ECG using the same equipment at each visit. ECGs will be reviewed by the site for the detection of silent MI. Silent MIs will be sent for event adjudication. All post-randomization ECGs (protocol-specified and other) are to be sent to the CEC for evaluation of silent MI.

7. TREATMENT AND RESTRICTIONS

7.1. Treatment

7.1.1. Treatment Regimen, Dosage, and Duration

Eligible study patients will be randomly assigned on Day 0 to one of the 2 treatment groups. Patients in each group will receive either 4 g/day AMR101 or placebo as in Table 4 for up to approximately 6.5 years, depending on individual date of randomization and overall study stop date (see Section 3.4).

The daily dose of study drug is 4 capsules per day taken as two capsules taken on two occasions per day (2 capsules given twice daily).

Table 4. Dosing Schedule during the Treatment Period

Treatment Group	Daily Dose	Number of Capsules per Day
1	4 g	4 capsules of 1 g AMR101
2	Placebo	4 capsules of matching placebo

Patients will be instructed to take study drug with food (i.e., with or at the end of their morning and evening meals). On days that patients are scheduled for study visits, the daily dose of study drug will be administered by site personnel with food provided by the site following collection of all fasting blood samples. For the purposes of this study, fasting is defined as nothing by mouth except water (and any essential medications) for at least 10 hours.

7.1.2. Treatment Assignment

7.1.2.1. Identification number

A unique patient identification number (patient number) will be established for each patient at each site. The patient number will be used to identify the patient throughout the study and will be entered on all documentation. If a patient is not eligible to receive treatment, or if a patient discontinues from the study, the patient number cannot be reassigned to another patient. The patient number will be used to assign patients to one of the 2 treatment groups according to the randomization schedule.

7.1.2.2. Drug Randomization

Only qualified patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized and will receive study medication starting at Visit 2 (Day 0). Eligible patients will be randomly assigned to one of the 2 treatment groups. Randomization will be stratified by CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries) (See Section 3.10). Approximately 70% of randomized patients will be in the CV Risk Category 1, including patients with established CVD, and approximately 30% of randomized patients will be in the CV Risk Category 2, including patients with diabetes and at least one additional risk factor but no established CVD. Enrollment with patients of a CV risk category will be stopped

when the planned number of patients in that risk category is reached. If total study enrollment exceeds 7990 patients, enrollment of new patients will be limited to CV Risk Category 1.

7.1.2.3. Emergency Unblinding

In an emergency, when knowledge of the patient's treatment assignment is essential for the clinical management or welfare of the patient, the investigator may request the patient's treatment assignment for unblinding. Prior to unblinding the patient's individual treatment assignment, the investigator should assess the relationship of an adverse event to the administration of the study drug (Yes or No). If the blind is broken for any reason, the investigator must record the date and reason for breaking the blind on the appropriate Case Report Form (CRF) and source documents.

7.1.3. Compliance Control

It is recommended that, unless clear contraindications arise, patients be strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy should, if possible, be brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. While reduction in study drug dose to fewer than 4 capsules per day is discouraged, patients may remain on study medication at a reduced dose with approval by the Medical Monitor. Under such conditions, resumption of the dose of 4 capsules per day should be attempted when/if medically appropriate. Discontinuations will be discouraged as much as possible. Any discontinuations should be based on compelling clinical reasons.

For every patient, an assessment of compliance to the study drug treatment regimen must be obtained at each scheduled visit. Study medication will be dispensed in amounts exceeding the amount required for the study. Patients will be instructed to return all unused study medication at the next visit. Compliance to the study drug regimen will be evaluated at each visit by counting unused capsules. Discrepancies will be evaluated and discussed with each patient to assess compliance. If compliance is unsatisfactory, the patient will be counseled about the importance of compliance to the dosing regimen. At the end of the study, the final study medication compliance will be determined by unused capsule count (see Section 12.2.2).

7.2. Study Restrictions

7.2.1. Concomitant Medications during Treatment/Follow-Up Period

Any medications administered during the study period must be documented on the Concomitant Medication CRF. Patients must not have taken any investigational agent within 90 days prior to screening. Patients cannot participate in any other investigational medication trial while participating in this study.

The following non-study drug related, non-statin, lipid-altering medications and supplements, and foods are prohibited during the study (from Visit 1 until after the Last Visit-End of Study), except for compelling medical reasons in patients characterized as being Off Drug in Study (ODIS). A detailed description of ODIS is provided in Section 11.1:

- niacin >200 mg/day;
- fibrates;

- prescription omega-3 fatty acid medications;
- dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils);
- bile acid sequestrants;
- PCSK9 inhibitors;
- cyclophosphamide;
- systemic retinoids

If any of these products would be used during the treatment/follow-up period of the study, it should be for compelling medical reasons in ODIS patients, and it should be documented in the Concomitant Medication CRF. If the ODIS patient agrees to restart study medication, the use of excluded medication must be discontinued.

Foods enriched with omega-3 fatty acids are strongly discouraged after Visit 1 for the duration of the study (does not apply to the Netherlands or Canada only. Therefore, all centers in the Netherlands and Canada must ignore this request).

The following products are allowed: statins, ezetimibe, and herbal products & dietary supplements not containing omega-3 fatty acids.

Statins:

- The same statin at the same dose should be continued until the end of the study, unless deemed medically necessary to change because of an adverse event or lack of efficacy (LOE). It is preferred that if LOE is the determining factor that ezetimibe be added to the present dose.
- Switching between a brand name statin and the generic version of the same statin is allowed at any time during the study.
- Statins may be administered with or without ezetimibe.
- Based on the FDA recommendation, simvastatin 80 mg may be used only in patients who have been taking this dose for 12 months or more and have not experienced any muscle toxicity. (See reference: FDA Drug Safety Communication: Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury. (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204882.htm)
- Changing of the type of statin or the statin dose during the treatment/follow-up period of the study should only be done for compelling medical reasons and must be documented in the CRF. Maintaining statin therapy throughout the study is important and, in the rare circumstance that it becomes medically compelling to discontinue statin use, the patient may remain in the study and on study medication with approval from the Medical Monitor. Under such conditions, resumption of statin therapy should be attempted when/if medically appropriate.

LDL-C Rescue:

- If the level of LDL-C exceeds 130 mg/dL (3.37 mmol/L) during the study (initial measurement and confirmed by a second determination at least 1 week later), the investigator may either increase the dose of the present statin therapy or may add ezetimibe to lower LDL-C. The investigator should use the best clinical judgment for each patient.

No data are available with regard to potential interactions between ethyl-EPA and oral contraceptives. There are no reports suggesting that omega-3 fatty acids, including ethyl-EPA, would decrease the efficacy of oral contraceptives.

Medications that were excluded if not at a stable dose for ≥28 days prior to screening (see Section 4.2, Criterion 14), may be initiated post-randomization if medically warranted (i.e., tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids and HIV-protease inhibitors).

7.2.2. Patient Restrictions

Beginning at the screening visit, all patients should be instructed to refrain from excessive alcohol consumption, to follow a physician recommended diet and to maintain it through the duration of the study. Excessive alcohol consumption is on average >2 units of alcohol per day or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking). A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.

8. INVESTIGATIONAL PRODUCT

8.1. Clinical Trial Material

The following will be supplied by the Sponsor:

- AMR101 1 g Capsules
- Placebo Capsules (to match AMR101 1 g Capsules)

The Sponsor will supply sufficient quantities of AMR101 1 g Capsules and Placebo Capsules to allow for completion of the study. The lot numbers of the drugs supplied will be recorded in the final study report.

Records will be maintained indicating the receipt and dispensation of all drug supplies. At the conclusion of the study, any unused study drug will be destroyed.

8.2. Pharmaceutical Formulations

AMR101 1 g Capsules and Placebo Capsules are provided in liquid-filled, oblong, soft gelatin capsules. Each capsule is filled with a clear liquid (colorless to pale yellow in color). The capsules are approximately 25.5 mm in length with a diameter of approximately 9.5 mm.

Table 5 summarizes the components of each capsule.

Table 5. Components of AMR101 1 g Capsules and Placebo Capsules

Component	AMR101 1 g Capsules Quantity (mg/capsule)	Placebo Capsules Quantity (mg/capsule)	Function
Capsule Fill			
Icosapent ethyl	998	-	Active
Paraffin, light liquid	-	932	Inactive
All-rac-α-tocopherol	2	1.86	Antioxidant
Capsule Shell[a]			
Gelatin	285	285	Capsule shell material
Sorbitol	80	80	Plasticizer
Glycerol	45	45	Plasticizer
Purified Water	38	38	Solvent
Maltitol	29	29	Plasticizer

[a] The capsule shell quantities represent a nominal "dry shell" formula weight.

8.3. Labeling and Packaging

Study medication will be packaged in high-density polyethylene bottles. Labeling and packaging will be performed according to GMP guidelines and all applicable country-specific requirements. The bottles will be numbered for each patient based on the randomization schedule. The patient randomization number assigned by IWRS or a designee of the Sponsor for the study (if no IWRS is used), will correspond to the number on the

bottles. The bottle number for each patient will be recorded in the Electronic Data Capture (EDC) system for the study.

8.4. Dispensing Procedures and Storage Conditions

8.4.1. Dispensing Procedures

At Visit 2 (Day 0), patients will be assigned study drug according to their treatment group determined by the randomization schedule. Once assigned to a treatment group, patients will receive study drug supplies. At each visit, patients will bring unused drug supplies dispensed to them earlier. From the drug supplies assigned to each patient, site personnel will administer drug while the patients are at the Research Site.

The investigator or designee must contact the IWRS or a designee of the Sponsor for the study (if no IWRS is used) when any unscheduled replacements of study medication are needed.

During the last visit during the treatment period, patients will bring the unused drug supplies for site personnel to calculate the final study medication compliance by unused capsule count (see Section 12.2.2).

8.4.2. Storage Conditions

At the Research Sites, study drugs must be stored at room temperature, 68°F to 77°F (20°C to 25°C). Do not allow storage temperature to go below 59°F (15°C) or above 86°F (30°C). Store in the original package.

Study drugs must be stored in a pharmacy or locked and secure storage facility, accessible only to those individuals authorized by the investigator to dispense the drug. The investigator or designee will keep accurate dispensing records. At the conclusion of the study, study site personnel will account for all used and unused study drug. Any unused study drug will be destroyed. The investigator agrees not to distribute study drug to any patient, except those patients participating in the study.

9. EFFICACY ASSESSMENTS

9.1. Specification of Variables and Procedures

The primary endpoint and the majority of the secondary and tertiary endpoints are based on clinical events related to CVD and mortality. All events occurring between randomization and the study end date (inclusive) must be recorded. Only adjudicated events will be included in the final analysis. Further details on the assessment of clinical events and their definitions will be found in the CEC charter. Important definitions are listed in Appendix B and Appendix C of this protocol.

9.2. Efficacy Endpoints

9.2.1. Primary Endpoint

The primary efficacy endpoint is the time from randomization to the first occurrence of any component of the composite of the following clinical events:

- CV death;
- Nonfatal MI (including silent MI; ECGs will be performed annually for the detection of silent MIs);
- Nonfatal stroke;
- Coronary revascularization;
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

The first occurrence of any of these major adverse cardiovascular events during the follow-up period of the study will be included in the incidence.

9.2.2. Secondary Endpoints

The key secondary efficacy endpoint is the time from randomization to the first occurrence of the composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke.

Other secondary efficacy endpoints are time from randomization to the first occurrence of the individual or composite endpoints as follows (to be tested in the order listed):

- Composite of CV death or nonfatal MI (including silent MI);
- Fatal or nonfatal MI (including silent MI);
- Non-elective coronary revascularization represented as the composite of emergent or urgent classifications;
- CV death;
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Fatal or nonfatal stroke;
- Composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke;
- Total mortality.

For the secondary efficacy endpoints that count a single event, the time from randomization to the first occurrence of this type of event will be counted for each patient. For secondary efficacy endpoints that are composites of two or more types of events, the time from randomization to the first occurrence of any of the event types included in the composite will be counted for each patient.

9.2.3. Tertiary Endpoints

The following tertiary endpoints will be evaluated as supporting efficacy and safety analyses. Where applicable and unless specified otherwise, endpoint analyses will be conducted as time from randomization to the first occurrence of the individual or composite endpoints.

- Total CV events analysis defined as the time from randomization to occurrence of the first and all recurrent major CV events defined as CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Primary composite endpoint in subset of patients with diabetes mellitus at baseline;
- Primary composite endpoint in the subset of patients with metabolic syndrome at baseline as defined in *A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and I nternational Association for the Study of Obesity* (Alberti 2009); with cut points of parameters as defined in Table 1 of Alberti *et. al.* and waist circumference cut points further guided by Table 2 and specifically set at ≥35 inches (88 cm) for all women and Asian, Hispanic, or Latino men, and ≥40 inches (102 cm) for all other men (see Appendix D);
- Primary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG of 100-125 mg/dL);
- Key secondary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG 100-125 mg/dL);
- Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalization of ≥24 hours, or cardiac arrest;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or PVD requiring intervention, such as angioplasty, bypass surgery, or aneurism repair;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and

requiring emergent hospitalization, PVD requiring intervention, or cardiac arrhythmia requiring hospitalization of ≥24 hours;

- New CHF;
- New CHF as the primary cause of hospitalization;
- Transient ischemic attack (TIA);
- Amputation for PVD;
- Carotid revascularization;
- All coronary revascularizations defined as the composite of emergent, urgent, elective, or salvage;
- Emergent coronary revascularizations;
- Urgent coronary revascularizations;
- Elective coronary revascularizations;
- Salvage coronary revascularizations;
- Cardiac arrhythmias requiring hospitalization of ≥24 hours;
- Cardiac arrest;
- Ischemic stroke;
- Hemorrhagic stroke;
- Fatal or nonfatal stroke in the subset of patients with a history of stroke prior to baseline;
- New onset diabetes, defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period;
- New onset hypertension, defined as blood pressure ≥140 mmHg systolic OR ≥90 mm Hg diastolic newly diagnosed during the treatment/follow-up period;
- Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP (hsCRP and log[hsCRP]), hsTnT, and RLP-C (to be estimated from standard lipid panel, RLP-C = TC – HDL-C – LDL-C [Varbo 2014]), (based on ITT estimands):
    - Assessment of the relationship between baseline biomarker values and treatment effects within the primary and key secondary composite endpoints,
    - Assessment of the effect of AMR101 on each marker,
    - Assessment of the relationship between post-baseline biomarker values and treatment effects within the primary and key secondary composite endpoints by including post-baseline biomarker values (for example, at 4 months, or at 1 year) as a covariate;
- Change in body weight;
- Change in waist circumference.

Where applicable and unless specified otherwise, for the tertiary endpoints that count a single event, the time from randomization to the first occurrence of this type of event will be counted in each patient. Similarly, where applicable and unless specified otherwise, for tertiary endpoints that are composites of two or more types of events, the time from

randomization to the first occurrence of any of the event types included in the composite will be counted in each patient.

10. SAFETY ASSESSMENTS

10.1. Specification of Variables and Procedures

Safety assessments will include adverse events (AEs), clinical laboratory measurements (chemistry, hematology), 12-lead electrocardiograms (ECGs), vital signs (seated systolic and diastolic blood pressures, heart rate, respiration rate, and body temperature), weight, waist circumference, and physical examinations as per Study Procedures/Appendix A.

A complete medical, surgical and family history will be completed at Visit 1.

A list of the analytes to be measured for the safety evaluation is found in Section 6.3.1.1. All laboratory test results must be evaluated by the investigator as to their clinical significance. Any observations at physical examinations or laboratory values considered by the investigator to be clinically significant should be considered an AE.

10.2. AEs

An AE is defined as any untoward medical occurrence, which does not necessarily have a causal relationship with the medication under investigation. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medication product, whether or not related to the investigational medication product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate CRF. Each AE is to be evaluated for duration, intensity, and causal relationship with the study medication or other factors.

AEs, which include clinical laboratory test variables, will be monitored from the time of informed consent until study participation is complete. Patients should be instructed to report any AE that they experience to the investigator. Beginning with Visit 2, investigators should assess for AEs at each visit and record the event on the appropriate AE CRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate AE on the CRF.

Any medical condition that is present when a patient is screened or present at baseline that does not deteriorate should not be reported as an AE. However, medical conditions or signs or symptoms present at baseline and that change in severity or seriousness at any time during the study should be reported as an AE.

Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen will be reported as AEs or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

The investigator will rate the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug using the categories of Yes or No.

Severity:

- Mild – An event that is usually transient in nature and generally not interfering with normal activities.
- Moderate – An event that is sufficiently discomforting to interfere with normal activities.
- Severe – An event that is incapacitating with inability to work or do usual activity or inability to work or perform normal daily activity.

Causality Assessment:

The relationship of an AE to the administration of the study drug is to be assessed according to the following definitions:

- No (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the AE rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.
- Yes (related, probably related, possibly related) – The time course between the administration of study drug and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

- The temporal sequence from study medication administration
- The event should occur after the study medication is given. The length of time from study medication exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases
- Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication
- The other medications the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study medication
- Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses
- The exposure to stress might induce adverse changes in the patient and provide a logical and better explanation for the event.
- The pharmacology and pharmacokinetics of the study medication
- The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study medication should be considered.

Unexpected AEs – An unexpected AE is an AE either not previously reported or where the nature, seriousness, severity, or outcome is not consistent with the current Investigator's Brochure.

10.2.1. Serious Adverse Events

A serious adverse event (SAE) is defined as an AE that meets **any** of the following criteria:

- Results in death;
- Is life-threatening- Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization- Note: In general, hospitalization for treatment of a pre-existing condition(s) that did not worsen from baseline is not considered an AE(s) and should not be reported as a SAE(s).
- Results in disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is an important medical event- Note: Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

By design of this study SAEs that are endpoint events will only be recorded for the endpoint determination and not captured as SAEs. The intention is that the endpoint events are not reported to IRBs as SAEs, unless the IRB requires that these are reported. Investigators should specifically inform their institution/IRB of this plan and confirm whether or not they want the endpoint events reported. By agreement with the US FDA, these endpoints will also not be reported to the US FDA as SAEs; rather they will be reported as endpoint events. Following adjudication if the event is determined to not meet the criteria for an event, the event will be evaluated as an SAE beginning with that day as Day 0.

10.3. Serious Adverse Event Reporting – Procedure for Investigators

10.3.1. Initial Reports

All SAEs occurring from the time of informed consent until 28 days following the last administration of study medication (or until 28 days following study completion for ODIS patients) must be reported to the Sponsor or designee **within 24 hours** of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). SAEs that the investigator considers related to study medication occurring after the 28-day follow-up period will also be reported to the Sponsor or designee.

The investigator is required to submit SAE reports to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local requirements. All investigators involved in studies using the same investigational medicinal product (IMP) will receive any Suspected Unexpected Serious Adverse Reaction (SUSAR) reports for onward submission to their local IRB as required. All reports sent to investigators will be blinded.

In addition, regulatory agencies will be notified of SAEs per the requirements of the specific regulatory jurisdiction regulations and laws.

10.3.2. Follow-Up Reports

The investigator must continue to follow the patient until the SAE has subsided, or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., laboratory test reports, patient discharge summary, or autopsy reports) to the Sponsor or designee via fax or email.

10.3.3. Reporting by the Sponsor

IRBs and IECs will be informed of SUSARs according to local requirements. Cases will be unblinded for reporting purposes as required.

10.4. Exposure *in Utero* During Clinical Trials

If a patient becomes pregnant during the study, the investigator should report the pregnancy to the Sponsor or designee within 24 hours of being notified. The Sponsor or designee will then forward the Exposure *in Utero* form to the investigator for completion.

The patient should be followed by the investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the Sponsor or designee. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

11. TREATMENT DISCONTINUATION/PATIENT WITHDRAWAL

Patients may withdraw from the study at any time and for any reason. Study drug administration may also be discontinued at any time, at the discretion of the investigator. In any case, follow-up for efficacy and safety should be continued in subjects that discontinue therapy, but remain in the study (i.e., ODIS patients).

11.1. Reasons for Early Study Drug Discontinuation

Study drug discontinuation should be avoided as much as possible, but may be done for any of the following reasons:

- Patient withdraws consent or requests early discontinuation from the study for any reason. Patients should be encouraged to continue to participate in the study for the entire duration of the study even if they choose not to take study medication any longer.
- Occurrence of a clinical or laboratory AE, either serious or non-serious, at the discretion of the investigator. The Sponsor or designee should be notified if a patient discontinues study drug because of an AE or laboratory abnormality. It is recommended that, unless clear contraindications arise, patients be strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy should, if possible, be brief (e.g., <4 weeks) and only for clinically indicated reasons, such as AEs. The following should be considered reasons 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 cannot be monitored weekly for 4 weeks
- Any medical condition or personal circumstance that, in the opinion of the investigator, exposes the patient to risk by continuing in the study or precludes adherence to the protocol.
- Sponsor discontinues the study.
- Investigative site closure, in the event that:
    - Another investigative site cannot accommodate the patient, or
    - The patient is unable or unwilling to travel to another investigative site.
- A TG value that is flagged as critically high, i.e., >1000 mg/dL (11.29 mmol/L), and confirmed as critically high by a repeat measurement (new fasting blood sample) within 7 days. In this case, a patient may be discontinued from study drug (with the option to remain ODIS) and other lipid-altering medications may be (re)initiated. If the TG value is flagged as >2000 mg/dL (22.58 mmol/L) then appropriate medical action can be taken by the investigator as soon as possible.

Occurrence of an outcome event according to the judgment of the investigator is not considered a valid reason for study drug discontinuation.

Patients whose treatment with study medication is discontinued early, and have not withdrawn consent, will stay in study and will be monitored until the end of the study. Patients who continue in the study after ≥30 days after cessation of therapy will be characterized as ODIS. ODIS patients should be asked to return to the study site for an interim visit once the patient has been off study drug for >30 days. Procedures at this visit are consistent with those at Visit 5. If not contraindicated, patients will also have the option to restart study medication at any point once characterized as ODIS. For patients who discontinue study medication (e.g., for an AE that may or may not be drug-related), a brief therapy interruption can be followed with a re-challenge (re-initiating study medication) as soon as clinically appropriate; thereby allowing a causative role for study medication to be confirmed or ruled out and continuing a patient in the study and on study drug if appropriate.

The reason for study drug discontinuation or interruption will be recorded on the CRF.

11.2. Follow-Up after Early Study Drug Discontinuation/Lost to Follow-Up

- Patients who prematurely discontinue study drug are not to be replaced.
- All randomized patients must be followed up a ccording to the study schedule of procedures until the study end date or death, regardless of whether they discontinue study drug prematurely or not. Any event occurring after early study drug discontinuation will be recorded up through the study end date.
- In order to follow the medical status of the patients, especially when they discontinued the study, investigators are encouraged to obtain information from the patient's primary care practitioner (physician or any other medical care provider). Investigators are also requested to try as much as possible to re-contact those patients at the end of the trial to obtain at least their vital status as well as their status with respect to the primary endpoint, and thus avoid lost to follow-up for the efficacy assessment.
- If patients are lost to follow-up, the CRF must be completed up to the last visit or contact.

12. STATISTICS

12.1. Analysis Populations

12.1.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all patients who are randomized via the IWRS. All efficacy analyses, including the primary analysis, will be performed on the ITT population. Patients will be analyzed according to the randomized treatment.

12.1.2. Modified Intent-to-Treat Population

The Modified Intent-to-Treat (mITT) population will include all randomized patients who have study drug dispensed after randomization. Groups will be defined based on the randomized treatment.

12.1.3. Per-Protocol Population

The Per-Protocol (PP) population will include all mITT patients without any major protocol deviations, and who had ≥80% compliance while on treatment. To be included in the PP population the minimum time on therapy is 90 days.

12.1.4. Safety Population

All safety analyses will be conducted based on the Safety population, which is defined as all randomized patients. This is the same as the ITT population.

12.2. Statistical Methods

Safety and efficacy variables will be analyzed using appropriate statistical methods to be described in detail in a separate Statistical Analysis Plan (SAP). The SAP will be finalized before study unblinding.

12.2.1. Patient Disposition and Demographic/Baseline Characteristics

The number and percentage of patients will be tabulated for each of the following categories for each treatment group:

- Screened (total only);
- Re-screened and reasons for re-screening (total only);
- ITT overall and by stratification factors (CV risk, ezetimibe use, and geographical region);
- mITT population; overall and by stratification factors (CV risk, ezetimibe use, and geographical region);
- PP population; overall and by stratification factors (CV risk, ezetimibe use, and geographical region);
- Safety population;
- Patients who complete the study;
- Patients who terminated from the trial early and the primary reason for early termination.
- Patients who terminated the trial early; prior to having a confirmed primary endpoint event.

- Patients with complete follow-up, defined as those for whom all components of the primary endpoint have been ascertained during the entire observation period (or until death).
- Patients who, at the time of study completion, were discontinued from study drug prematurely, but continued within the study (i.e. ODIS patients), along with the primary reason.

For randomized patients who discontinued treatment with study drug, the primary reason for discontinuation will be listed and summarized by treatment group.

Demographic and baseline characteristics, including age, gender, ethnicity, race, height, body weight, BMI, diabetes, hypertension, metabolic syndrome, overweight/obese/normal according to BMI, and diabetes plus obesity will be summarized using descriptive statistics by treatment group in the ITT population.

Demographic data and baseline characteristics will be also compared between treatment groups for the mITT population and PP population. Differences in demographic and baseline characteristics will be tested using a chi-square test (for categorical variables) or t-test (for continuous variables). The p-values will be considered descriptive, primarily as an assessment of the balance between groups. Age in years will be calculated using the date of randomization (Visit 2) and the date of birth.

12.2.2. Study Medication Exposure and Compliance

Study drug exposure will be summarized by treatment group using descriptive statistics for each time point and overall. Overall study drug compliance will be calculated as the number of doses assumed to be taken relative to scheduled dosing period as follows:

$$\text{Compliance (\%)} = \frac{\text{\# Capsules of total dispensed - \# Capsules of total returned}}{\text{(last dose date – first dose date + 1)} \times \text{4 capsules/day}} \times 100$$

Overall percent compliance will be calculated per patient in the ITT and Modified ITT populations and summarized by treatment group using descriptive statistics.

12.2.3. Concomitant Therapies

Concomitant medication/therapy verbatim terms will be coded using the latest available version, prior to data base lock, of the World Health Organization Drug Dictionary and the Anatomical Therapeutic Chemical classification system. The numbers and percentages of patients in each treatment group taking concomitant medications will be summarized. All verbatim descriptions and coded terms will be listed for all non-study medications.

12.2.4. Analysis of Efficacy

For efficacy endpoints including CV events, only adjudicated events will be included in the final statistical analyses.

12.2.4.1. Summary Statistics

Summary statistics (n, mean, standard deviation, median, minimum, and maximum) for the baseline and post-baseline measurements, the percent changes, or changes from baseline will be presented by treatment group and by visit for all efficacy variables to be analyzed. The

summary statistics will include changes in body weight and BMI from baseline by treatment group and by visit.

12.2.4.2. Primary Endpoint Analyses

The primary endpoint is described in Section 9.2.1. The analysis of the primary endpoint will be performed using the log-rank test comparing the 2 treatment groups (AMR101 and placebo) and including the stratification factor "CV risk category", use of ezetimibe and geographical region (Westernized, Eastern European, and Asia Pacific countries) (each as recorded in the IWRS at the time of enrollment) as covariates. The two-sided alpha level for the primary analysis will be reduced from 0.05 to account for the interim analyses based on a group sequential design with O'Brien-Fleming boundaries generated using the Lan-DeMets alpha-spending function. The hazard ratio for treatment group (AMR101 vs. placebo) from a Cox proportional hazard model that includes the stratification factor will also be reported, along with the associated 95% confidence interval. Kaplan-Meier estimates from randomization to the time to the primary endpoint will be plotted.

The size and direction of the treatment effects of the individual components of the composite endpoint and their relative contribution to the composite endpoint will be determined as well.

All observed data that are positively adjudicated by the CEC, including data after discontinuation of study treatment for patients who discontinue study drug prematurely, will be included in the primary analysis.

Patients who do not experience a primary efficacy event prior to the end of the study or who withdraw from the study early without a preceding primary efficacy event will be censored at the date of their last visit/phone contact.

The longest prespecified interval between visits (onsite or phone) is 90 days. In view of the up to 90-day monitoring period for CV events, the primary endpoint for patients who have a non-CV death within 90 days of last contact without having had an earlier CV event will be censored at the time of death. The primary endpoint for patients who have a non-CV death more than 90 days after last contact without having had an earlier CV event will be censored at the time of last contact.

The primary analysis will assume that all silent MIs occurred on the date of the first tracing indicative of a silent MI; a second (sensitivity) analysis will assume that all silent MIs occurred on the day after the last prior normal ECG; and a third (sensitivity) analysis will assume that all silent MIs occurred at the mid-point between the last normal ECG and the ECG with the new MI.

All deaths causally adjudicated as "undetermined" will be combined with those adjudicated as "CV deaths" for the primary analysis. A sensitivity analysis of the CV death category will be performed that excludes the "undetermined cause of death" cohort.

The primary efficacy analysis will be performed on the ITT population. A sensitivity analysis will be performed using the mITT and PP populations.

As a sensitivity analysis, patients who discontinue study drug prematurely will be censored for the primary composite endpoint analysis on the date of drug discontinuation. The primary analysis will be repeated using this censoring rule for the mITT population.

As a supportive analysis, a multivariable, stratified Cox proportional hazards model will be constructed for the primary endpoint to evaluate the treatment effect adjusting for important covariates.

12.2.4.3. Secondary Endpoint Analyses

The key and other secondary endpoints are listed in Section 9.2.2. The key secondary hypothesis will be tested as part of the confirmatory process only if the primary analysis is statistically significant. For the analysis of secondary efficacy endpoints, the Type 1 error will be controlled by testing each endpoint sequentially, starting with the key endpoint. Testing will be done at a significance level consistent with that used for the primary endpoint and will cease when a secondary endpoint is found for which treatments do not significantly differ. P-values will be presented for all analyses, but they will be considered descriptive after the first non-significant result is obtained.

Each of the secondary endpoints will be analyzed by the same methods described for the primary efficacy endpoint. Kaplan-Meier estimates, the log-rank test stratified by stratification factors used at randomization, and the Cox proportional hazards model including the stratification factors as specified above for the primary efficacy endpoint, will be summarized by treatment group. In view of the 90-day monitoring period for CV events, the key secondary endpoint for patients who have a non-CV death within 90 days of last contact without having had an earlier CV event will be censored at the time of death. The key secondary endpoint for patients who have a non-CV death more than 90 days after last contact without having had an earlier CV event will be censored at the time of last contact. Kaplan-Meier curves stratified by each stratification factor will be presented. These analyses will be conducted for the ITT population.

12.2.4.4. Tertiary Endpoint Analyses

The tertiary endpoints are listed in Section 9.2.3. Time-to-event tertiary endpoints will be analyzed by the same methods as described for the primary efficacy endpoint. Kaplan-Meier estimates, the log-rank test stratified by stratification factors used at randomization, and the Cox proportional hazards model as specified for the primary efficacy endpoint, will be summarized by treatment group. In view of the 90-day monitoring period for CV events, if applicable, tertiary endpoints for patients who have a non-CV death within 90 days of last contact without having had an earlier CV event will be censored at the time of death. If applicable, tertiary endpoints for patients who have a non-CV death more than 90 days after last contact without having had an earlier CV event will be censored at the time of last contact. Kaplan-Meier curves stratified by each of the stratification factors will be presented.

The fasting lipid panel is tested at Screening (Visit 1 or Visit 1.1), Randomization visit (Visit 2; Day 0), Visit 3 (Day 120; ~4 Months) and all other follow-up visits including the last visit. For change from baseline to 1 year preparative ultracentrifugation measurements for LDL-C will be analysed, unless this value is missing. If the LDL-C preparative ultracentrifugation values are missing, then another LDL-C value will be used, with prioritization of values obtained from LDL-C Direct measurements, followed by LDL-C derived by the Friedewald calculation (only for subjects with TG <400 mg/dL), and finally LDL-C derived using the calculation published by Hopkins University investigators (Martin 2013). In addition, change from baseline to day 120 in LDL-C utilizing Friedewald's and Hopkins methods will be analysed, using the arithmetic mean of LDL-C obtained at Visit 2

(Day 0) and the preceding Visit 1 (or Visit 1.1). If one of these values is missing, the single available LDL-C value will be used. LDL-C according to Hopkins will be calculated at each visit.

The randomization visit will be considered Baseline. If a baseline value is not available from the randomization visit, then the latest screening value will be used.

For measurements of lipids, lipoproteins, and inflammatory markers, the change from baseline and the percent change will be summarized at each visit. Since these parameters are typically not normally distributed, the Wilcoxon rank-sum test will be used for treatment comparisons of the percent change from baseline, and medians and quartiles will be provided for each treatment group. The medians of the differences between the treatment groups and 95% CIs will be estimated with the Hodges-Lehman method. In addition, shift –tables may be generated as appropriate.

As an additional exploratory analysis, the relationship between post-baseline biomarker values and treatment effects with the primary and key secondary endpoints will be assessed by adding biomarker values (for example, at 4 month, or at 1 year, etc.) as time-dependent covariates in the Cox proportional hazards model. Diagnostic plots for the proportional hazards assumption will be evaluated

Weight is measured at the screening visit and at all follow-up visits, including the last visit of the study. Waist circumference will be measured at the randomization visit (Visit 2; Day 0), Visit 5 (Day 720) and the last visit of the study. Descriptive statistics will be presented by visit and treatment group for baseline, post-treatment change from baseline, and the percent change from baseline. Analysis methods for repeated measurements will be used to compare percent change from baseline between treatments.

New onset diabetes is defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period (i.e. patients with no history of diabetes at randomization, with the test as listed in Appendix C).

12.2.4.5. Exploratory Subgroup Analyses

Analyses of the effects that patients off study drug and withdrawn from study have on the primary endpoint will be performed.

Subgroup analyses of the primary and key secondary endpoints will be performed as described for the primary endpoint. For each subgroup, Kaplan-Meier estimates, the log-rank test stratified by stratification factors used at randomization (except where the subgroup is a stratification factor), and HRs and CIs from the Cox proportional hazards model as specified for the primary efficacy endpoint, will be summarized by treatment group.

The following subgroups will be explored:

Demographics:

- gender;
- age at baseline (<65 years and ≥65 years);
- race (white and nonwhite, or any other subset with at least 10% of the total number of patients);
- geographical region (Westernized, Eastern European, and Asia Pacific countries); and

- baseline ezetimibe use (yes/no).

Disease Parameters:

- CV risk category;
- the presence/absence of diabetes at baseline; and
- renal dysfunction at baseline (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as follows:

$$eGFR = 141 \times \min (S_{cr} /\kappa, 1)^{\alpha} \times \max(S_{cr} /\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

Where:

S_{cr} is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of S_{cr} /κ or 1, and
max indicates the maximum of S_{cr} /κ or 1 (Levey 2009).

Treatment Parameters:

- statin intensity at baseline (statin type and regimen)

  Statin intensity categories as defined in ACC/AHA Cholesterol Guidelines (Stone 2013) and patient's 10-year CV Risk Score (Goff 2013).

Baseline Lipid and Lipoprotein Parameters:

- LDL-C (by tertile);
- HDL-C (by tertile, and tertile by gender);
- TG (by tertile, and tertile by gender);
- RLP-C (by tertile)
- TG ≥150 mg/dL and TG <150 mg/dL;
- TG ≥200 mg/dL and TG <200 mg/dL;
- TG ≥ median, TG < median;
- combined highest tertile for TG and lowest tertile for HDL-C;
- gender-specific highest tertile for TG and lowest tertile for HDL-C;
- TG ≥ 200 mg/dL with HDL-C ≤35 mg/dL;
- hs-CRP (≤3 mg/L and >3 mg/L) and by gender;
- hs-CRP (≤2 mg/L and >2 mg/L) and by gender;
- Apo B (by tertile); and
- non-HDL-C (by tertile).

A Cox proportional hazard (PH) model as mentioned above but additionally with baseline TG as a covariate will be fitted to the data at each interim. Diagnostic plots for the PH assumption will be evaluated.

The consistency of the treatment effects in subgroups will be assessed for the primary and key secondary efficacy endpoints. For each subgroup variable, a Cox PH model with terms for treatment, stratification factors (with the exception of those subgroup variables related to the stratification factors, i.e., CV risk category), subgroup, and treatment-by-subgroup interaction will be performed. The main treatment effect will not be tested with this model. P-values for testing the interaction terms < 0.15 will be considered significant. Results will be presented in a Forest plot.

All subgroup analyses will be conducted for the ITT, mITT and PP populations.

12.2.4.6. Interim Efficacy Analyses

Two interim analyses are planned for the primary efficacy endpoint using adjudicated events when approximately 60% (967 events) and approximately 80% (1290 events) of the total number of primary endpoint events planned (1612) is reached. The planned interim analyses are based on a group-sequential design and are described in the Interim Statistical Analysis Plan (included as an appendix to the SAP) which will be finalized prior to performing the unblinded interim analyses.

The interim results of the study will be monitored by an independent Data Monitoring Committee (DMC). The analyses will be performed by the independent statistical team who is unblinded to the treatment assignment and reported only to the DMC. Unblinded information will not be released to the Sponsor before the completion of the study unless extraordinary circumstances arise and, under such circumstances, procedures for maintaining confidentiality will be described in a written agreement with the DMC. If the study is terminated early following interim analysis, patients will be notified promptly and brought in for their final close-out visit, and the final analyses of efficacy and safety will include all data through their final visit.

All suspected events will be adjudicated in a blinded manner by the CEC.

The time to event will be calculated as the time from randomization to the onset date of the event (as determined by the CEC). Patients who do not experience any of the above events at the time of data cutoff for the interim but are still in the trial will be considered censored at the time of their last regular contact before the interim data cutoff.

12.2.5. Analysis of Safety

All analyses of safety will be conducted on the safety population, which is defined as all randomized patients. The safety assessment will be based on the frequency of AEs, physical exams, vital signs and safety laboratory tests.

AEs with new onset during the study between the initiation of study drug and 30 days after the completion or withdrawal from study will be considered treatment-emergent (TEAEs). This will include any AE with onset prior to initiation of study drug and increased severity after the treatment initiation.

Treatment-emergent adverse events will be summarized by system organ class and preferred term, and by treatment. This will include overall incidence rates (regardless of severity and

relationship to study drug), and incidence rates for moderate or severe AEs. A summary of SAEs and AEs leading to early study drug discontinuation (for ≥30 days) will be presented through data listings. Patients who restart study drug will not be included in the summary of AEs leading to discontinuation.

Safety laboratory tests and vital signs will be summarized by post-treatment change from baseline for each of the parameters using descriptive statistics by treatment group. Those patients with significant laboratory abnormalities will be identified in data listings. Additional safety parameters will be summarized in data listings.

12.3. Sample Size Determination

This is an event-driven trial comparing the effect of AMR101 vs. placebo in terms of the composite endpoint listed above as the primary endpoint. The study has been planned to accrue a total of 1612 efficacy endpoint events with two planned interim analyses when approximately 967 (60%) and 1290 (80%) of the events have been adjudicated.

Sample size calculation was based on assumptions of constant hazard, asymmetric recruitment rate over time and without factoring for dropouts. A risk reduction corresponding to a hazard ratio of 0.85 (AMR101 vs. placebo) is assumed. 1612 events would be required to detect this hazard ratio with approximately 90% power with one-sided alpha-level at 2.5% and with two interim analyses. The operating characteristics of this design are identical to those of a corresponding group sequential design with a two-sided alpha level of 0.05.

The recruitment period is assumed to be 4.2 years with 20% recruitment in the first year, 40% in the second year, 20% in the third year, 19% in the fourth year and the remaining 1% in the last 0.2 years. The estimated maximum study duration is 6.5 years unless the trial is terminated early for efficacy or safety issues. A one-year event rate of 5.2% (hazard = 0.053) in the control arm is also assumed. Under these assumptions the number of patients to be enrolled is N = 7990.

Since this is an events-driven trial, the 'sample size' is the number of events rather than the number of patients. The number of events that occur depends primarily on three factors: how many patients are enrolled, the combined group event rate, and how long the patients are followed. Because of the difficulty in predicting the combined event rate, the sponsor will monitor that event rate as the trial progresses. If the combined event rate is less than anticipated, either increasing the number of patients, extending the length of follow-up, or a balance of adjusting both factors may be necessary to achieve the sample size of 1612 events.

Before completing the enrollment phase of the trial, *i.e.* approximately 3- to 6-months prior to the projected enrollment of the 7990th patient, the actual event rate based on pooled, blinded accumulation of primary efficacy endpoint events would be calculated and plotted. If those analyses suggested the number of patients with at least 1 adjudicated, primary event (and appropriately accounting for patients with potential primary events for which the adjudication process is then incomplete) was consistent with projections, then the study could continue toward the protocol-specified target enrollment of 7990 patients. However, if the number of such events appeared less than, and inconsistent with projections, the Sponsor would consider (under blinded conditions) re-calculating the number of patients needed to achieve the target number of events within the desired timeline or extend the follow-up period. If the projected increase in number of patients was ≤25% of the original 7990 target

population, the Sponsor could, with documented approval of both the REDUCE-IT Steering Committee and the Data Monitoring Committee, extend enrollment to the revised target number without need for an additional protocol amendment. Under those conditions, all principal investigators, ethics committees, and regulatory authorities associated with the protocol will be promptly notified of the action. If the projected increase in number of patients was more than 25% above the original 7990 target (*i.e.* more than 1998 additional patients) a formal protocol amendment would be initiated.

Consistent with the plan stated above, an analysis and modeling of pooled, blinded primary efficacy endpoint events across the remainder of the trial was performed prior to the projected enrollment of the 7990th patient. Based on this analysis, the sample size of 7990 randomized patients is with 95% confidence likely to result in the target 1,612 adjudicated primary efficacy events within 2018. The results of this analysis were shared with and approved by the REDUCE-IT Steering Committee and Data Monitoring Committee.

As of the completion of study enrollment, the actual number of patients randomized will vary from the target number (either original or revised) as a result of the inherent lag between the date the last patient started screening and the date the last patient was randomized.

13. MONITORING, DATA MANAGEMENT, AND RECORD KEEPING

13.1. Data Management

13.1.1. Data Handling

Data will be recorded at the site on CRFs. All entries on a CRF are ultimately the responsibility of the Investigator, who is expected to review each form for completeness and accuracy before signing. A CRF must be completed for each randomized patient. The CRFs and source documents must be made available to the Sponsor and/or its designee.

13.2. Record Keeping

The Investigator must maintain all documents and records, originals or certified copies of original records, relating to the conduct of this trial, and necessary for the evaluation and reconstruction of the clinical trial. This documentation includes, but is not limited to protocol, CRFs, AE reports, patient source data (including records of patients, patient visit logs, clinical observations and findings), correspondence with health authorities and IRB, consent forms, inventory of study product, Investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures, and laboratory director curriculum vitae.

The Investigator and affiliated institution should maintain the trial documents as required by the applicable regulations. The Investigator and affiliated institution should take measures to prevent accidental or premature destruction of documents. Clinical trial documents must be kept in the clinical site's archives indefinitely, unless written authorization is obtained from the Sponsor.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator and research institution agree that the Sponsor, their representatives and designees, the IRB or IEC, and representatives from worldwide regulatory agencies will have the right, both during and after the clinical trial, to review and inspect pertinent medical records related to the clinical trial.

15. QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor and/or its designee(s) will perform quality control and quality assurance checks of all clinical trials that it sponsors. Before the enrollment of any patient in this study, the Sponsor or its designee will review with the investigator and site personnel the following documents: protocol, Investigator's Brochure, CRFs and procedures for their completion, the informed consent process, and the procedure for reporting SAEs. Site visits will be performed by the Sponsor and/or its designees. During these visits, information recorded on the CRFs will be verified against source documents and requests for clarification or correction may be made. After the CRF data is entered by the site, the Sponsor or designee will review for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical trial. If necessary, requests for clarification or correction will be sent to investigators.

By signing the protocol, the Sponsor agrees directly or through its designee(s) to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice (GCP), International Conference on Harmonisation (ICH) and other applicable regulations.

16. ETHICS AND GOOD CLINICAL PRACTICE COMPLIANCE

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human patients. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial patients are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. In this study, the 2008 version of the Declaration of Helsinki will be adhered to. It can be found on the website of The World Medical Association:

http://www.wma.net/en/30publications/10policies/b3/17c.pdf

17. INFORMED CONSENT

Prior to participation in a study, the participant, or participant's legal representative/impartial witness must sign an IRB/IEC-approved written informed consent form (ICF). The approved written informed consent must abide to all applicable laws in regards to the safety and confidentiality of the patients. To obtain and document informed consent, the Investigator should comply with applicable regulations; adhere to GCP standards and the ethical principles in the Declaration of Helsinki (see Section 16).

The language in the oral and written information about the trial, including the written informed consent form should be as non-technical as practical and should be understandable to the participant or participant's legal representative/impartial witness, where applicable. Before informed consent is obtained, the Investigator should provide the participant, or participant's legal representative/impartial witness ample time and opportunity to inquire about the trial and to decide whether or not to participate.

All questions about the trial should be answered to the satisfaction of the participant, or the participant's legal representative/impartial witness. The written ICF should be signed and personally dated by the participant or participant's legal representative/impartial witness, and by the person who conducted the informed consent discussion. Participants will be informed that participation is voluntary and that he/she can withdraw from the study at any time. A signed copy of the consent form must be given to the participant, and this fact will be documented in the CRF.

Of special concern regarding informed consent is the collection of blood samples for genetic analysis. Local regulations may not allow the collection of blood samples for genetic testing or the shipment of blood samples for genetic testing outside the region. In these cases, blood samples for genetic testing will not be collected, and the portion of the ICF describing the genetic component of the study will not be included. If blood samples for genetic testing will be collected, the ICF will clearly indicate that a sample will be drawn for this purpose, but that the participant has the right to refuse this procedure.

18. PUBLICATION POLICY

The SC is responsible for the reporting and publication of the study results. The Sponsor will be provided a reasonable opportunity to review such manuscripts prior to journal submission. The results of the study will be published irrespective of whether the endpoints are met, or whether the results are regarded positive or negative.

Confidentiality, publication, and patent applications related to unpublished study-related information and unpublished information given to the site investigators by the Sponsor and/or its designee(s) shall be handled as set forth in the Clinical Trial Agreement.

19. FINANCING AND INSURANCE

19.1. Finances

Prior to starting the study, the Principal Investigator and/or institution will sign a Clinical Trial Agreement with the Sponsor and/or its designee(s). This agreement will include the financial information agreed upon by the parties.

19.2. Insurance Compensation

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the investigator and the other collaborators from maintaining their own liability insurance policy. An insurance certificate will be provided to the IRB/IEC and Competent Authority according to country specific regulatory requirements.

20. COMPLETION OF STUDY

The end of the study will be at the time of the last patient-last visit of the follow-up period of the study. The IRB and IEC will be notified about the end of the study according to country-specific regulatory requirements.

21. STUDY ADMINISTRATIVE INFORMATION

21.1. Protocol Amendments

Any amendments to the study protocol considered to be a substantial amendment will be communicated to the investigator by the Sponsor or its designee. All substantial protocol amendments will undergo the same review and approval process as the original protocol and may be implemented after it has been approved by the IRB/IEC and Competent Authority, unless immediate implementation of the change is necessary for patient safety. In this case, the situation must be documented and reported to the IRB/IEC and Competent Authority according to all relevant country-specific regulatory requirements.

A protocol amendment is considered to be a substantial amendment if it is likely to affect the safety, physical, or mental integrity of patients in the study; the scientific value of the study; the conduct or management of the study; or the quality or safety of any investigational medicinal product (IMP) used in the study.

Any other minor changes to the protocol not considered to be substantial amendments will not need prior approval of the IRB/EC and Competent Authority and will be communicated to the investigator by the Sponsor or its designee.

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23. INVESTIGATOR'S AGREEMENT

This document is a confidential communication of Amarin. The authorized investigators agree to personally conduct or supervise the conduct of this investigational study in compliance with the current protocol, good clinical practices, and all applicable laws, regulations, and guidelines. No changes will be made to the protocol without prior notification to Amarin, except to protect the safety, rights, and welfare of the study patients, and always in compliance with all applicable laws, regulations, and guidelines. Acceptance of this document constitutes the agreement by the Investigator that no unpubl ished information contained herein or related to the study will be published or disclosed without prior written approval from Amarin.

I have read this protocol in its entirety and agree to conduct the study accordingly.

_____ _____

Signature Date
Principal Investigator

_____

Printed Name

APPENDIX A: SCHEDULE OF PROCEDURES

Study Day	Screening		Follow-Up (FU) [13]								
	Up to 42 days before Day 0	**If a Visit 1.1 takes place, Visit 1 may occur up to 60 days before Day 0[2]**	**0**	**120 ± 10**	**360 ± 10**	**720 ± 10**	**1080 ± 10**	**1440 ± 10**	**1800 ± 10**	**2160 ± 10**	**Last Visit (LV)[15]**
Months of FU			**0**	**4**	**12**	**24**	**36**	**48**	**60**	**72**	**(varies)**
Years of FU			**0**	**0.33**	**1**	**2**	**3**	**4**	**5**	**6**	**(varies)**
Visit #	**1**	**1.1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 [14]**	**LV**
Study Procedures:											
Informed Consent	X										
Medical, Surgical & Family History	X										
Demographics	X										
Evaluate inclusion / exclusion criteria	X [1]	X [3]	X								
Physical Examination			X	X	X	X	X	X	X	X	X
Weight, Height [4]	X		X	X	X	X	X	X	X	X	X
Vital Signs [5]	X	X	X	X	X	X	X	X	X	X	X
Waist Circumference			X			X					X
12-Lead ECG	X		X		X	X	X	X	X	X	X
Urine pregnancy test [6]	X		X								
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X
Randomization			X								
Dosing at the Research Site [7]			X	X	X	X	X	X	X	X	
Efficacy events				X	X	X	X	X	X	X	X
AE Evaluations			X	X	X	X	X	X	X	X	X
Compliance Check [8]				X	X	X	X	X	X	X	X
Chemistry and hematology [9]	X	X [3]	X	X	X	X	X	X	X	X	X
Fasting lipid profile [10]	X	X [3]	X	X	X	X	X	X	X	X	X
Genetic testing [11]			X								
Biomarkers: hs-CRP, apo B, hsTNT			X			X					X

Study Day	Screening		Follow-Up (FU) [13]								
	Up to 42 days before Day 0	If a Visit 1.1 takes place, Visit 1 may occur up to 60 days before Day 0[2]	0	120 ± 10	360 ± 10	720 ± 10	1080 ± 10	1440 ± 10	1800 ± 10	2160 ± 10	Last Visit (LV)[15]
Months of FU			**0**	**4**	**12**	**24**	**36**	**48**	**60**	**72**	**(varies)**
Years of FU			**0**	**0.33**	**1**	**2**	**3**	**4**	**5**	**6**	**(varies)**
Visit #	**1**	**1.1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9 [14]**	**LV**
Fasting blood sample for archiving [12]			X		X	X	X	X	X	X	X

1. Includes procedures and (fasting) blood samples (for example, hs-CRP, calculated creatinine clearance) as needed to determine the CV risk category (see inclusion criteria).
2. Screening visit to re-evaluate inclusion/exclusion criteria for patients who are not eligible for participation based on data from Visit 1.
3. Inclusion/exclusion criteria will be re-evaluated for selected study procedures that are performed on Visit 1.1 because patients failed to meet them at Visit 1.
4. Height at first screening visit only.
5. Vital signs, including systolic and diastolic blood pressure (mmHg), heart rate, respiratory rate and body temperature. Participants must be seated for at least 5 minutes before assessments of vital signs.
6. For women of childbearing potential.
7. The patients will fast of at least 10 hours before arriving at the Research Site, when all fasting blood samples will be obtained. After blood samples are obtained, patients will be given drug with food.
8. Review study drug compliance by unused capsule count, discuss with and counsel patients about compliance if needed; final study compliance at last visit.
9. Safety Laboratories — Complete Blood Count: Includes RBC, Hgb, Hct, WBC and differential, and platelet count. Biochemistry includes total protein, albumin, alkaline phosphatase, ALT, AST, total bilirubin, glucose, calcium, electrolytes (sodium, potassium, chloride), blood urea nitrogen (BUN), serum creatinine, uric acid, creatine kinase, HbA1c. Safety labs may be repeated as deemed necessary by the Investigator.
10. TG, TC, HDL-C, LDL-C, non-HDL-C, and VLDL-C.
11. Fasting blood sample that will be stored for future genetic testing at the discretion of the sponsor. This sample is optional as local regulations may prohibit genetic samples to be collected or shipped outside the country, or patients may not consent.
12. Used at the sponsor's discretion to perform repeat analyses described in the protocol or to perform other tests related to cardiovascular health.
13. Site personnel will contact each patient by telephone in-between Visit 2 and Visit 3 and between Visit 3 and Visit 4. After Visit 4 contact will be made every 3 months. The purpose of the contact is to collect information about efficacy events, AEs, concomitant medications, confirm patient's current address and contact information and remind patients about taking their study medication and logistics for the next visit.
14. Office visits will continue at 360-day intervals and phone visits at 90-day intervals until study end date is determined.
15. The last visit (LV) will be targeted to occur within 30 days after the study end date as determined by the DMC; the study end date is tentatively scheduled for Day 2160 but the actual date as determined by the DMC may be different.

APPENDIX B: STANDARDIZED DEFINITIONS FOR REDUCE-IT CARDIOVASCULAR TRIAL ENDPOINT EVENTS

NOTE: The following definitions are based on the publications referenced below for the standardized definitions of endpoint events in cardiovascular trials. They have been edited to only include the endpoints relevant to this study.

References:

Karen A. Hicks, H. M. James Hung, Kenneth W. Mahaffey, Roxana Mehran, Steven E. Nissen, Norman L. Stockbridge, Shari L. Targum, Robert Temple; on be half of the Standardized Data Collection for Cardiovascular Trials Initiative. Standardized Definitions for End Point Events in Cardiovascular Trials, May 31, 2011.

Karen A. Hicks, James E Tcheng, Biykem Bozkurt, Bernard R. Chaitman, Donald E. Cutlip, Andrew Farb, Gregg C. Fonarow, Jeffrey P. Jacobs, Michael R. Jaff, Judith H. Lichtman, Marian C. Limacher, Kenneth W. Mchaffey, Roxana Mehran, Steven E. Nissen, Eric E. Smith, Shari L. Targum. 2014 A CC/AHA Key Data Elements and Definitions for Cardiovascular Endpoint Events in Clinical Trials. Circulation 2015;132:302-361

23.1. Definition of Cardiovascular Death

Cardiovascular death includes death resulting from an acute myocardial infarction, sudden cardiac death, death due to congestive heart failure (CHF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other cardiovascular causes.

1. **Death due to Acute Myocardial Infarction** refers to a d eath by any mechanism (arrhythmia, CHF) within 30 da ys after a MI related to the immediate consequences of the MI, such as progressive CHF or recalcitrant arrhythmia.

   Mortal events that occur after a "break" (e.g., a CHF and arrhythmia-free period of at least a week) should be classified as CV or non-CV death, and if classified as a CV death, should be attributed to the immediate cause, even though the MI may have increased the risk of that event (e.g., the risk of arrhythmic death is increased for many months after an acute MI).

   Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI (see Definition of MI) or by autopsy findings showing recent MI or recent coronary thrombosis.

   Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)), or to treat a complication resulting from MI, should also be considered death due to acute MI.

   Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.
2. **Sudden Cardiac Death** refers to a death that occurs unexpectedly, not within 30 days of an acute MI, and includes the following deaths:

a. Death witnessed and instantaneous without new or worsening symptoms
b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest an acute MI
c. Death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review)
d. Death after unsuccessful resuscitation from cardiac arrest
e. Death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology
f. Unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

General Considerations

A subject seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death."
Deaths for which there is no information beyond "patient found dead at home" will be classified as "death due to other cardiovascular causes". Please see Definition of Undetermined Cause of Death, for full details.

3. **Death due to Congestive Heart Failure** refers to a death in association with clinically worsening symptoms and/or signs of heart failure (see Definition of Heart Failure Event). Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.
4. **Death due to Stroke** refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke (see Definition of Transient Ischemic Attack and Stroke).
5. **Death due to Cardiovascular Procedures** refers to death caused by the immediate complications of a cardiac procedure.
6. **Death due to Cardiovascular Hemorrhage** refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage (see Definition of Transient Ischemic Attack and Stroke), non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.
7. **Death due to Other Cardiovascular Causes** refers to a CV death not included in the above categories (e.g., pulmonary embolism or peripheral arterial disease).

23.2. Definition of Non-Cardiovascular Death

Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. The following is a suggested list of non-cardiovascular causes of death for this trial.

23.2.1. Non-malignant, Non-cardiovascular Death

- Pulmonary

- Renal
- Gastrointestinal
- Hepatobiliary
- Pancreatic
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS))
- Hemorrhage that is neither cardiovascular bleeding nor a stroke
- Accidental (e.g., physical accidents or drug overdoses) or trauma
- Suicide
- Prescription Drug Error (e.g., prescribed drug overdose, use of inappropriate drug, or drug-drug interaction)
- Neurological process that is not a stroke or hemorrhage
- Other non-CV, specify: _____

23.2.2. Malignancy

Malignancy should be coded as the cause of death if:

- Death results directly from the cancer; or
- Death results from a concurrent illness that could be a consequence of a cancer or
- Death results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer
- Death results from an illness that is not a consequence of a cancer

Cancer deaths may arise from cancers that were present prior to randomization or which developed subsequently. It may be helpful to distinguish these two scenarios (i.e. worsening of prior malignancy; new malignancy).

- Suggested categorization includes the following organ systems; Lung/larynx, breast, leukemia/lymphoma, upper GI, melanoma, central nervous system, colon/rectum, renal, bladder, prostate, other/unspecified, or unknown.

23.3. Definition of Undetermined Cause of Death

Undetermined Cause of Death refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause. The inability to classify the cause of death is generally due to lack of information (e.g., the only available information is "patient died") or when there is insufficient supporting information or detail to assign the cause of death. In this trial, when a cause of death is not readily apparent (e.g., found dead at home), the cause will be assumed to be cardiovascular in origin, unless one of the following two scenarios occur:

1. There is no information or data available regarding the circumstances of death other than that a death has occurred.

2. The available data are conflicting regarding whether the death was cardiovascular or non-cardiovascular.

23.4. Definition of Myocardial Infarction

1. **General Considerations**

   The term myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. In general, the diagnosis of MI requires the combination of:

   - Evidence of myocardial necrosis (either changes in cardiac biomarkers or postmortem pathological findings); and
   - Supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging

   The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

2. **Criteria for Myocardial Infarction**

   a. Clinical Presentation

   The clinical presentation should be consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be take into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, congestive heart failure, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.

   b. Biomarker Elevation

   For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory

performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. CK-MB and troponin are preferred, but CK may be used in the absence of CK-MB and troponin.

For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin will be required. The specific criteria will be referenced to the URL.

In this study, patients may present acutely to hospitals which are not participating sites, it is not practical to stipulate the use of a single biomarker or assay, and the locally available results are to be used as the basis for adjudication.
Since the prognostic significance of different types of myocardial infarctions (e.g., periprocedural myocardial infarction versus spontaneous myocardial infarction) may be different, considerations evaluating outcomes for these subsets of patients separately will be made.

c. ECG Changes

ECG changes can be used to support or confirm a MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

- **Criteria for acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB))**:
  - ST elevation

    New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.
  - ST depression and T-wave changes New horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

- **Criteria for pathological Q-wave**
  - Any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3
  - Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF)
  - R-wave 0.04 s in V1–V2 and R/S ratio >1 with a concordant positive T-wave in the absence of a conduction defect

The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

- **Criteria for Prior Myocardial Infarction**
  - Pathological Q-waves, as defined above
  - R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect

3. **Myocardial Infarction Subtypes**

Several MI subtypes are commonly reported in clinical investigations and each is defined below:

a. Spontaneous MI

i. Detection of rise and/or fall of cardiac biomarkers with at least one value above the URL with at least one of the following:

- Clinical presentation consistent with ischemia
- ECG evidence of acute myocardial ischemia
- New pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Autopsy evidence of acute MI

ii. If biomarkers are elevated from a prior infarction, then a spontaneous myocardial infarction is defined as:

1. One of the following:

- Clinical presentation consistent with ischemia
- ECG evidence of acute myocardial ischemia
- New pathological Q waves
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Autopsy evidence of acute MI

AND

2. Both of the following:

- Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI*
- ≥ 20% increase (and > URL) in troponin or CK-MB between a measurement made at the time of the initial presentation and a further sample taken 3-6 hours later

*If biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent MI is generally not possible.

b. Percutaneous Coronary Intervention-Related Myocardial Infarction

Peri-PCI MI is defined by any of the following criteria. MI associated with and occurring within 48 hours of PCI, with elevation of cardiac biomarker

values to > 5 x 99th percentile of the URL in patients with normal baseline values (≤99th percentile URL), or a rise of [cardiac biomarker] values ≥20% if baseline values are elevated and are stable or falling. This classification also requires at least 1 of the following:

a) Symptoms suggestive of myocardial ischemia (i.e., prolonged ischemia ≥ 20 min)
b) New ischemic changes on ECG or new LBBB
c) Angiographic loss of patency of a major coronary artery or a side branch or persistent slow flow or no flow or embolization
d) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

c. Coronary Artery Bypass Grafting-Related Myocardial Infarction

Peri-coronary artery bypass graft surgery (CABG) MI is defined by the following criteria. Symptoms of cardiac ischemia are not required.

i. Biomarker elevations within 48 hours of CABG:

- Troponin or CK-MB (preferred) > 10 x 99th percentile of the URL and
- No evidence that cardiac biomarkers were elevated prior to the procedure;

OR

- Both of the following must be true:
  - ≥ 50%[2] increase in the cardiac biomarker result
  - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI.

AND

ii. One of the following:

- New pathological Q-waves persistent through 30 days
- New persistent non-rate-related LBBB
- Angiographically documented new graft or native coronary artery occlusion Other complication in the operating room resulting in loss of myocardium
- Imaging evidence of new loss of viable myocardium

Data should be collected in such a way that analyses using ≥ 20% or ≥ 50% could both be performed.

OR

iii. Autopsy evidence of acute MI

d. Silent Myocardial Infarction

Silent MI is defined by the following:

i. No evidence of acute myocardial infarction

AND

ii. Any one of the following criteria:

- New pathological Q-waves. A confirmatory ECG is recommended if there have been no clinical symptoms or history of myocardial infarction.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a n on-ischemic cause
- Autopsy evidence of a healed or healing MI

(NOTE: In the case of evanescent Q waves, the last ECG will determine whether a silent infarction has occurred.)

23.5. Sub-classification of Myocardial Infarction

1. **By the Universal MI Definition:**

a. Clinical Classification of Different Types of Myocardial Infarction

- Type 1

  Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
- Type 2

  Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension
- Type 3

  Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
- Type 4a

  Myocardial infarction associated with PCI
- Type 4b

  Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
- Type 4c

  Myocardial infarction associated with stent restenosis as detected by angiography or at autopsy
- Type 5

  Myocardial infarction associated with CABG

b. Sample Clinical Trial Tabulation of Randomized Patients by Types of Myocardial Infarction

Types of MI	Treatment A Number of patients (N =)	Treatment B Number of patients (N =)
MI Type 1	n, %	n, %
MI Type 2	n, %	n, %
MI Type 3	n, %	n, %
MI Type 4	n, %	n, %
MI Type 5	n, %	n, %
Total number	n, %	n, %
N = total number of patients; n = number of patients with a particular MI.		

2. **By Electrocardiographic Features:**

- **ST-Elevation MI (STEMI)**
  - Additional subcategories may include:
    - Q-wave
    - Non-Q-wave
    - Unknown (no ECG or ECG not interpretable)
- **Non-ST-Elevation MI (NSTEMI)**
  - Additional subcategories may include:
    - Q-wave
    - Non-Q-wave
    - Unknown (no ECG or ECG not interpretable)
- **Unknown (no ECG or ECG not interpretable)**

  **All events adjudicated as MI will be classified as STEMI, NSTEMI, or Unknown; however, it is acknowledged that a significant proportion of periprocedural (PCI or CABG) events may have missing, inadequate or uninterpretable ECG documentation.*

3. **By Biomarker Elevation (per Universal MI Definition[1]):**

The magnitude of cardiac biomarker elevation can be calculated as a ratio of the peak biomarker value divided by the 99th percentile URL.
The biomarker elevation can be provided for various MI subtypes, as shown in the example below.

Multiples X 99%	MI Type 1 (Spontaneous)	MI Type 2 (Secondary)	MI Type 3* (Sudden death)	MI Type 4** (PCI)	MI Type 5** (CABG)	Total Number
1-2 X						
2-3 X						
3-5 X						
5-10 X						
>10 X						
Total Number						

*Biomarkers are not available for this type of myocardial infarction since the patients expired before biomarker determination could be performed.
**For the sake of completeness, the total distribution of biomarker values should be reported. The hatched areas represent biomarker elevations below the decision limit used for these types of myocardial infarction.

23.6. Definition of Hospitalization for Unstable Angina

Unstable angina requiring hospitalization is defined as:

1. Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥ 10 minutes in duration occurring
   - at rest, or
   - in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity.

   AND
2. Prompting an unscheduled hospitalization **within 24 hours** of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 2 4* hour stay (or a date change if the time of admission/discharge is not available).

   AND
3. At least one of the following:
   a. New or worsening ST or T wave changes on resting ECG **(**in the absence of confounders, such as LBBB or LVH)
      - Transient ST elevation (duration <20 minutes)

        New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥0.2 mV in men (>0.25 mV in men <40 years) or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads
      - ST depression and T-wave changes

        New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads; and/or new T inversion ≥0.1 mV in two contiguous leads.

   b. Definite evidence of inducible myocardial ischemia as demonstrated by:
      - An early positive exercise stress test, defined as ST elevation or ≥2 mm ST depression prior to 5 mets

      OR
      - Stress echocardiography (reversible wall motion abnormality) **OR**
      - Myocardial scintigraphy (reversible perfusion defect), **OR**
      - MRI (myocardial perfusion deficit under pharmacologic stress).

   c. Angiographic evidence of new or worse ≥70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.

d. Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge.

AND

4. Negative cardiac biomarkers and no evidence of acute MI

General Considerations

1. Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β-blockers, should be considered supportive of the diagnosis of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3, would be insufficient alone to support classification as hospitalization for unstable angina.
2. If subjects are admitted with suspected unstable angina, and subsequent testing reveals a noncardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for myocardial infarction should not be adjudicated as unstable angina.
3. Planned hospitalization or re-hospitalization for performance of an elective revascularization in patients who do not fulfill the criteria for unstable angina should not be considered a hospitalization for unstable angina. For example,
    - Hospitalization of a patient with stable exertional angina for coronary angiography and PCI that is prompted by a positive outpatient stress test should not be considered hospitalization for unstable angina.
    - Re-hospitalization of a patient meeting the criteria for unstable angina who was stabilized, discharged, and subsequently readmitted for revascularization, does not constitute a second hospitalization for unstable angina
4. A patient who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina endpoint.

23.7. Definition of Transient Ischemic Attack and Stroke

Transient Ischemic Attack

Transient ischemic attack (TIA) is defined as a transient episode (< 24 hours) of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

Stroke

Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

Classification:

1. **Ischemic Stroke**

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.
Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

2. **Hemorrhagic Stroke**

   Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.
   NOTE: Microhemorrhages seen on T2-weighted MRI imaging, subdural and epidural hemorrhages are not considered hemorrhagic strokes.

3. **Undetermined Stroke**

   Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as ischemic or hemorrhagic.

Stroke Disability

Stroke disability should be measured by a reliable and valid scale in all cases, typically at each visit and 90 days after the event. For example, the modified Rankin Scale may be used to address this requirement:

Scale	Disability
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability; unable to perform all previous activities but able to look after own affairs without assistance.
3	Moderate disability; requiring some help but able to walk without assistance.
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention.
6	Dead

Additional Considerations

Evidence of vascular central nervous system injury without recognized neurological dysfunction may be observed. Examples include micro-hemorrhage, silent infarction, and silent hemorrhage.

Subdural hematomas are intracranial hemorrhagic events and not strokes.

The distinction between a Transient Ischemic Attack and an Ischemic Stroke is the presence of Infarction. Persistence of symptoms is an acceptable indicator of acute infarction.

23.8. Definition of Heart Failure Event

A Heart Failure Event may consist of a hospitalization (a required component of this end point and defined below), as well as urgent outpatient visits.

A Heart Failure Hospitalization is defined as an event that meets **ALL** of the following criteria:

1) The patient is admitted to the hospital with a primary diagnosis of HF
2) The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable)
3) The patient exhibits documented new or worsening symptoms due to HF on presentation, including **at least ONE** of the following:
    a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea)
    b. Decreased exercise tolerance
    c. Fatigue
    d. Other symptoms of worsened end-organ perfusion or volume overload (must be specified and described by the protocol)
4) The patient has objective evidence of new or worsening HF, consisting of **at least TWO** physical examination findings **OR** one physical examination finding and **at least ONE** laboratory criterion), including:
    a. Physical examination findings considered to be due to heart failure, including new or worsened:
        i. Peripheral edema
        ii. Increasing abdominal distention or ascites (in the absence of primary hepatic disease)
        iii. Pulmonary rales/crackles/crepitations
        iv. Increased jugular venous pressure and/or hepatojugular reflux
        v. S_3 gallop
        vi. Clinically significant or rapid weight gain thought to be related to fluid retention
    b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
        i. Increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a s ignificant increase should be noted above baseline.
        ii. Radiological evidence of pulmonary congestion
        iii. Non-invasive or invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' >

15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral [TVI]) **OR** right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m^2

Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

5) The patient receives initiation or intensification of treatment specifically for HF, including **at least ONE** of the following:
   a. Significant augmentation in oral diuretic therapy
   b. Intravenous diuretic, inotrope, or vasodilator therapy
   c. Mechanical or surgical intervention, including:
      i. Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device)
      ii. Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

New Heart Failure/Heart Failure Not Requiring Hospitalization:

An **Urgent Heart Failure Visit** is defined as an event that meets all of the following:

1) The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization.
2) All signs and symptoms for HF hospitalization must be met as defined in A Heart Failure Hospitalization above.
3) The patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which will not be sufficient.

23.9. Interventional Cardiology Definitions

A. **Clinical Definitions**

1. **Clinically-Driven Target Lesion Revascularization**: Revascularization is clinically-driven if the target lesion diameter stenosis is > 50% by quantitative coronary angiography (QCA) and the subject has clinical or functional ischemia which cannot be explained by another native coronary or bypass graft lesion. Clinical or functional ischemia includes any of the following:
   a. A history of angina pectoris, presumably related to the target vessel
   b. Objective signs of ischemia at rest (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel
   c. Abnormal results of any invasive functional diagnostic test (e.g., coronary flow reserve [CFR] or fractional flow reserve [FFR])

Comment: *Target lesion revascularization of a > 70% diameter stenosis by QCA in the absence of the above signs or symptoms may be considered clinically-driven.*

Comment: *In the absence of QCA data or if a ≤ 50% stenosis is present, TLR may be considered clinically-driven by the Clinical Endpoint Committee (CEC) if severe ischemic signs and symptoms attributed to the target lesion are present.*

2. **Non-Target Lesion and Non-Target Lesion Revascularization**: A lesion for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.
3. **Non-Target Vessel and Non-Target Vessel Revascularization**: A vessel for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.
4. **Percutaneous Coronary Intervention (PCI) Status**:

    a. **Elective**: The procedure can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of myocardial infarction (MI) or death. For stable in-patients, the procedure is being performed during this hospitalization for convenience and ease of scheduling and NOT because the patient's clinical situation demands the procedure prior to discharge.

    b. **Urgent:** The procedure should be performed on an inpatient basis and prior to discharge because of significant concerns that there is risk of myocardial ischemia, MI, and/or death. Patients who are outpatients or in the emergency department at the time that the cardiac catheterization is requested would warrant hospital admission based on their clinical presentation.

    c. **Emergency**: The procedure should be performed as soon as possible because of substantial concerns that ongoing myocardial ischemia and/or MI could lead to death. "As soon as possible" refers to a patient who is of sufficient acuity that one would cancel a scheduled case to perform this procedure immediately in the next available room during business hours, or one would activate the on-call team were this to occur during off-hours.

    d. **Salvage:** The procedure is a last resort. The patient is in cardiogenic shock when the PCI begins (i.e., the time at which the first guide wire or intracoronary device is introduced into a coronary artery or bypass graft for the purpose of mechanical revascularization) OR within the last ten minutes prior to the start of the case or during the diagnostic portion of the case, the patient has also received chest compressions or has been on unanticipated circulatory support (e.g., intra-aortic balloon pump, extracorporeal mechanical oxygenation, or cardiopulmonary support).

5. **Percutaneous Coronary Intervention (PCI):** Placement of an angioplasty guide wire, balloon, or other device (e.g., stent, atherectomy catheter, brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or coronary artery bypass graft for the purpose of mechanical coronary revascularization. In the

assessment of the severity of coronary lesions with the use of intravascular ultrasound, CFR, or FFR, insertion of a guide wire will NOT be considered PCI.

23.10. Definition of Peripheral Vascular Intervention

1. **Peripheral Vascular Intervention (PVI):** Peripheral vascular intervention is a catheter-based or open surgical procedure designed to improve peripheral arterial or venous blood flow or otherwise modify or revise vascular conduits. Procedures may include, but are not limited to, balloon angioplasty, stent placement, thrombectomy, embolectomy, atherectomy, dissection repair, aneurysm exclusion, treatment of dialysis conduits, placement of various devices, intravascular thrombolysis or other pharmacotherapies, and open surgical bypass or revision.

   In general, the intention to perform *percutaneous* peripheral vascular intervention is denoted by the insertion of a guide wire into a peripheral artery or vein.

   The target vessel(s) and the type of revascularization procedure (e.g., surgical bypass, thrombectomy, endarterectomy, percutaneous angioplasty, stent placement, thromboembolectomy, and thrombolysis) should be specified and recorded. For the sake of simplicity, this definition applies to the extracranial carotid artery and other non-cardiac arteries and veins and excludes the intracranial vessels and lymphatics.

2. **Procedural Status: Non-Elective and Elective:**

   a. **Non-Elective**: Non-elective procedures include emergent and urgent procedures. A non-elective procedure is a procedure that is performed without delay, because there is clinical consensus that the procedure should occur imminently. Non-elective procedures imply a degree of instability of the patient, urgency of the medical condition, or instability of the threatening lesion.

      - **Emergent:** A procedure that is performed immediately because of the acute nature of the medical condition (e.g., acute limb ischemia, acute aortic dissection), and the increased morbidity or mortality associated with a temporal delay in treatment.

      - **Urgent**: An urgent procedure is one that is not emergent but required to be performed on a timely basis (≤ 24 hrs) (e.g., a patient who has been stabilized following initial treatment of acute limb ischemia, and there is clinical consensus that a definitive procedure should occur within the next 24 hours).

   b. **Elective**: An elective procedure is one that is scheduled and is performed on a patient with stable disease, or in whom there is no urgency and/or increased morbidity or mortality associated with a planned procedure.

23.11. Definition of Any Revascularization Procedure

Any revascularization includes any arterial vascular intervention done to treat ischemia or prevent major ischemic events, including percutaneous or surgical intervention of the coronary, peripheral, or carotid arteries. Aneurysm repairs, dissection repairs, arterial-venous fistula or graft placement or repairs, or renal arterial intervention for hypertension or renal dysfunction are not included.

23.12. 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 cardio-version and/or intravenous antiarrhythmics

3. Bradyarrhythmia - 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 < 30 bpm). The bradycardia must require temporary or permanent pacing.

23.13. Definition of Cardiac Arrest (Sudden Cardiac Death)

A sudden, unexpected death due to the cessation of cardiac mechanical activity, confirmed by the absence of a detectable pulse, unresponsiveness, and apnea (or agonal, gasping respirations) of presumed cardiac etiology. An arrest is presumed to be cardiac (i.e., related to heart disease) if this is likely, based on the available information, including hospital records and autopsy data. The cardiac arrest will be further sub-classified into either:

a) witnessed, occurring within 60 min from the onset of new symptoms, in the absence of a clear cause other than cardiovascular; or

b) unwitnessed, within 24 hours of being observed alive, in the absence of pre-existing other non-cardiovascular causes of death;

Note: Non-cardiac causes of cardiac arrest, such as drug overdose, suicide, drowning, hypoxia, exsanguination, cerebrovascular accident, subarachnoid hemorrhage, or trauma must not be present.

23.14. Definition of Resuscitated Cardiac Arrest[2]

Resuscitated Cardiac Arrest is present when there is restoration of both:

1. Organized electrical activity, and

2. Organized mechanical activity resulting in restoration of spontaneous circulation (defined as the documented presence of a measurable pulse and blood pressure at any time after initiation of resuscitative efforts).

References:

1. Thygesen K., Alpert J., Jaffe A., et al. Third Universal Definition of Myocardial Infarction. *J Am Coll Cardiol.* 2012;60(16):1581-1598.

2. Becker LB, Aufderheide TP, Geocadin RG, Callaway CW, Lazar RM, Donnino MW, Nadkarni VM, Abella BS, Adrie C, Berg RA, Merchant RM, O'Connor RE, Meltzer DO, Holm MB, Longstreth WT, Halperin HR. AHA Consensus Statement: Primary Outcomes for Resuscitation Science Sturdies: A Consensus Statement From the American Heart

Association. *Circulation* 2011; CIR. 0b013e3182340239 published online before print October 3 2011, doi:10.1161/CIR.0b013e3182340239

APPENDIX C: CRITERIA FOR THE DIAGNOSIS OF DIABETES

Reference:
American Diabetes Association. Classification and diagnosis of diabetes mellitus. Sec. 2. In Standards of Medical Care in Diabetes - 2015. Diabetes Care 2015; 38 (Suppl. 1):S8-S16.

1. HbA_{1c} ≥6.5%. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.*

OR

2. Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hr.*

OR

3. 2-hr plasma glucose ≥200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

OR

4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

* In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

APPENDIX D: CRITERIA FOR THE DIAGNOSIS OF METABOLIC SYNDROME

The diagnosis of metabolic syndrome requires the presence of three out of the following five specific components using the following criteria (Alberti 2009) with cut points of parameters as defined in Table 1 of Alberti *et. al.* and listed below, and waist circumference cut points further guided by the Table 6 below:

- A waist circumference ≥35 inches (88 cm) for all women, and Asian, Hispanic, or Latino men, and waist circumference ≥40 inches (102 cm) for all other men;
- Elevated TG (TG ≥150 mg/dL);
- Reduced HDL-C (HDL-C <40 mg/dL if male; HDL-C <50 mg/dL if female);
- Elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg, OR an antihypertensive therapy with medical history of hypertension;
- Elevated fasting glucose (fasting glucose ≥100 mg/dL, OR on drug therapy for elevated glucose.

Table 6. Current Recommended Waist Circumference Thresholds for Abdominal Obesity by Organization and Population (Alberti *et. al.* Table 2)

Organization	Population (Reference)	Waist Circumference Threshold	
		Men (cm)	Women (cm)
IDF (4)	Europid	≥94	≥80
WHO (7)	Caucasian	≥94 (increased risk)	≥80
		≥102 (still higher risk)	≥88
AHA/NHLBI (ATP III)* (5)	US	≥102	≥88
Health Canada (8,9)	Canada	≥102	≥88
European Cardiovascular Societies (10)	European	≥102	≥88
IDF (4)	Asian (including Japanese)	≥90	≥80
WHO (11)	Asian	≥90	≥80
Japanese Obesity Society	Japanese	≥85	≥90
Cooperative Task Force (13)	China	≥85	≥80
IDF (4)	Middle East, Mediterranean	≥94	≥80
IDF (4)	Sub-Saharan African	≥94	≥80
IDF (4)	Ethnic Central & South American	≥90	≥80

IDF=International Diabetes Federation; WHO=World Health Organization; AHA/NHLBI (ATP III)=American Heart Association/National Heart, Lung, and Blood Institute Adult Treatment Panel III; *Recent AHA/NHLBI guidelines for metabolic syndrome recognize an increased risk for cardiovascular disease and diabetes at waist-circumference thresholds of ≥94 cm in men and ≥80 cm in women and identify these as optional cut points for individuals or populations with increased insulin resistance.

EXPLANATION OF CHANGES DOCUMENT

STUDY NUMBER: AMR-01-01-0019

AMENDMENT NUMBER 1

PROTOCOL 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: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

AMENDMENT 1 DATE: 16 May 2013

REASON FOR CHANGES:

This protocol amendment includes changes based on feedback and comments from regi onal regulatory agencies (including US FDA-approved labeling), ethics comm ittees, investigators, and the RE DUCE-IT Steering Committee. Major protocol changes are included in the summary of changes. Editorial ch anges, clarifications, and corrections were also made throughout the protocol, but have not been included in this summary.

Protocol Location	Summary of Change	Reason for Change
• Throughout Protocol • Synopsis Objectives • Inclusion Criteria #1 and #2	Laboratory data changes or additions: • Fasting TG level ≥200 mg/dL (2.26 mmol/L) and <500 mg/dL (5.64 mmol/L) • Deletion of the lower end fasting TG level requirement.	Increase in the required fasting TG level at screening to increase the overall proportion of patients enrolled with TG at or above the 200 mg/dL level. Added SI Units for all laboratory values. The lower end fasting TG level information is no longer relevant.
• Secondary Objectives and Endpoints	Clarified secondary efficacy statements regarding unstable angina by adding "determined to be caused by myocardial	Further clarify objective and endpoints.

Protocol Location	Summary of Change	Reason for Change
	ischemia by invasive/non-invasive testing and requiring emergent hospitalization".	
• Inclusion Criterion #3, CV Risk Category 1	Deletion of "one or more" and addition of "≥50%" and "at least" two major epicardial coronary arteries.	Further clarify and define inclusion criteria.
• Inclusion Criterion #6	"Effective" was deleted and "acceptable" was added to define the method of birth control. Last sentence was deleted "Effective methods of avoiding pregnancy are….etc".	Required change as per Canada regulators.
• Inclusion Criterion #8 • Section 7.2.2. Patient Restrictions	The wording changed to "Agree to follow a physician recommended diet and to maintain it through the duration of the study."	Required change as per Canada regulators.
• Exclusion Criterion #10	Updated to read: "Known hypersensitivity to any ingredients of the study product or placebo. Known hypersensitivity to fish and or shell fish."	Canada and the Netherlands required the exclusion of patients with allergies to the study product, placebo or seafood. This will be adopted across the entire study. Modification to better conform with FDA-approved label.
• Exclusion Criterion #12	Added "malabsorption syndrome and/or chronic diarrhea (Note: patients who have undergone gastric/intestinal bypass surgery are considered to have malabsorption, hence are excluded; patients who have undergone gastric banding are allowed to enter the trial)."	Added clarity for investigators.
• Exclusion Criterion #13	Additional details of a wash-out were added for patients taking niacin or fibrates.	Added clarity for investigators.

Protocol Location	Summary of Change	Reason for Change
	Added Netherlands specific exclusion for patients currently taking >300 mg/day of EPA/DHA.	Required change as per The Netherlands regulators.
• Exclusion Criterion #17	Creatine kinase exclusion changed to >5 x ULN (from >10 x ULN previously).	Required change as per Canada regulators and adopted for all countries.
• Sample Size Determination Synopsis • Section 12.3. Sample Size Determination	Updated with additional text.	Added to clearly define conditions under which the addition of patients would require a protocol amendment.
• Section 1.3. Study AMR-01-01-0017 (ANCHOR Study)	Included the ANCHOR study results and data table.	Updated with ANCHOR study results; at the time the original REDUCE-IT protocol was written, ANCHOR clinical study report was not available.
• Section 1.4. Clinical Safety	Updated the most commonly reported adverse events in hypertriglyceridemia studies completed by Amarin.	Update with current expected adverse events; at the time the original REDUCE-IT protocol was written, the expected events were taken from a combination of past Amarin CNS population studies and hypertriglyceride population studies. As all the hypertriglyceridemia population data are available, new expected events have been added, consistent with FDA-approved label.
• Section 6.1.1.2. Screening Visit (Visit 1.1)	Extended length of the screening Visit 1 to randomization, from 42 days to 60, for patients that have had a Visit 1.1.	Increased to include time to send and receive laboratory sample results and to then schedule next visits for patients with multiple screening visits.
• Section 6.2. Telephone Follow-up Contact	Additional phone contact with patients at Day 270 +/- 5 days.	Ensure patients are contacted at least every 3 months throughout study.
• Section 6.3.1.3. Genetic Testing	Additional information added on anonymity of genetic testing and the ability for patients to decline testing prior to sample analysis.	Added for clarity.
• Section 6.3.1.6. Blinding of Laboratory	Added the allowance for the central	Added for enhanced patient safety.

Protocol Location	Summary of Change	Reason for Change
Results	laboratory to notify sites of all hsTnT results.	
• Section 6.3.1.7. Flagging of Critical Lab Values • Section 11.1. Reasons for Early Study Drug Discontinuation	Added an additional flag from the central laboratory to site of TG values >2000 mg/dL (22.58 mmol/L) during the blinded phase of the study.	Added for enhanced patient safety.
• Section 10.2.1. Serious Adverse Events	Further definition added around endpoint event reporting and site responsibility to inquire with their institution/IRB about their specific reporting requirements for these events.	Added for clarity.
• Section 12.2.4.4. Tertiary Endpoints	Added "All tertiary analyses will be conducted for the ITT population. No multiple testing adjustments will be made."	Further define tertiary endpoints.
• Section 12.2.4.5. Exploratory Subgroup Analyses	Updated subgroup analyses detail for primary and key secondary endpoints.	Further define planned exploratory subgroup analyses.
• Section 18 Publication Policy	Paragraph was updated to conform to Steering Committee publication policies.	Updated based on Steering Committee feedback.
• APPENDIX B: Standardized definitions for endpoint events in cardiovascular trials.	The appendix was replaced with a section from the CEC charter.	Updated to reflect the Clinical Event Committee Charter (updated FDA guidelines).

EXPLANATION OF CHANGES DOCUMENT

STUDY NUMBER: AMR-01-01-0019

AMENDMENT NUMBER 2

PROTOCOL 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: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

PROTOCOL AMENDMENT 2 FINAL; DATE: 8 July 2016

REASON FOR CHANGES:

This protocol amendment includes changes to update the content with newly available scientific background information and feedback and comments from the United States Food and Drug Administration (FDA), ethics committees, investigators, and the REDUCE-IT Steering Committee. Major protocol changes are included in the summary of changes table below. Editorial changes, clarifications, and corrections were also made throughout the protocol, but have not been included in this summary.

Protocol Location	Summary of Change	Reason for Change
• Section 1 (Introduction and Background Information)	Updated the regulatory status of AMR101 in the US.	Provided updated background information
• Section 1.2 (Summary of Completed Amarin-Sponsored Clinical Studies of AMR101 in Patients with Hypertriglyceridemia)	Removed summary of previous Amarin-sponsored studies in patients with central nervous system disorders; added a summary of the MARINE study.	Provided updated and relevant information related to clinical development
• Section 1.4 (Rationale)	Updated medical need with statistics from 2016 AHA publications. Updated the results from recent genetic studies and recently completed relevant cardiovascular outcomes studies.	Provided updated background information

Protocol Location	Summary of Change	Reason for Change
• Section 2 (Study Objectives), • Section 9.2.1 (Primary Endpoint) and • *Synopsis*	The following wording "to evaluate the effect of 4 g/day AMR101 for preventing the occurrence of a first major cardiovascular event of the composite endpoint that includes:", was rewritten as follows: "to evaluate the effect of 4 g/day AMR101 on the time from randomization to first occurrence of any component of the composite of the following major cardiovascular (CV) events:". Included silent MI under nonfatal myocardial infarction (MI).	Clarification
• Section 2 (Study Objectives), • Section 9.2.2 (Secondary Endpoints) and • *Synopsis*	Per FDA comments, the composite of hard major adverse coronary event (MACE) endpoints (CV death, non-fatal MI, non-fatal stroke) was designated as the "key secondary endpoint" and secondary endpoints were streamlined and re-ordered to further elucidate primary and key secondary findings. Again in concert with FDA comments, several former secondary endpoints were moved to tertiary endpoints with definitions of such tertiary endpoints around metabolic syndrome and new-onset hypertension provided. The "other" secondary objectives were designated and re-ordered as follows: • Composite of CV death or nonfatal MI (including silent MI); • Fatal or nonfatal MI (including silent MI); • Non-elective coronary revascularization represented as the composite of emergent or urgent classifications; • CV death; • Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization; • Fatal or nonfatal stroke; • Composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke; • Total mortality.	For consistency with Statistical Analysis Plan (SAP)

Protocol Location	Summary of Change	Reason for Change
• Section 2 (Study Objectives), • Section 9.2.3 (Tertiary Endpoints), and • *Synopsis*	The tertiary objectives and endpoints were designated, re-ordered, and in some cases more clearly defined. Examples include: Adding remnant lipoprotein cholesterol to the list of lipids, lipoproteins, and inflammatory markers to be assessed. Added tertiary endpoints: Ischemic stroke, hemorrhagic stroke, incidence of new onset hypertension, primary endpoint in the subset of patients with impaired glucose metabolism, key secondary endpoint in the subset of patients with impaired glucose metabolism and specifically classified revascularization procedures. Definition was provided around metabolic syndrome as part of a composite. Some components of composite endpoints which were previously secondary were moved to tertiary and reordered.	For consistency with the SAP
• Section 3.4 (Study Duration) • Section 7.1.1 (Treatment Regimen, Dosage, and Duration) • Synopsis Study Design and Duration	Updated enrollment duration (approximately 4.2 years) and total study duration (approximately 6.5 years).	Extension of the expected enrollment period and total study period and for consistency with the SAP and iSAP
• Section 3.6 (Number of Patients)	Clarified that additional patients may be enrolled beyond the projected 7990 if the number of events contributing to the primary endpoint appears less than, and inconsistent with, projections.	Clarification
• Section 3.10 (Stratification) • Section 7.1.2.2 (Drug Randomization)	Added condition to stratification: If the enrollment exceeds 7990 patients, new patients will be limited to Cardiovascular Risk Category 1.	For clarification if enrollment exceeds pre-specified 7990 patients
• Section 4.2 and • *Synopsis*	Added the following bullet point to Exclusion Criterion 13: Patients are excluded if they use proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up periods of the study. To be eligible for participation in the study, patients cannot have taken a PCSK9 inhibitor within 90 days prior to their screening visit.	For clarification of patients who would be excluded from study participation on the basis of concurrent medication usage.
• Section 5.1 (Steering Committee)	Revised description of the composition of the Steering Committee.	Clarification

Protocol Location	Summary of Change	Reason for Change
• Section 5.2 (Study Operations Committee)	Updated meeting frequency from monthly/bimonthly to periodic.	For flexibility of meeting schedule
• Section 5.3 (Clinical Endpoints Committee [CEC])	Change the name of the CEC from "Clinical Events Committee" to "Clinical Endpoints Committee" and added requirement of adjudication of events for tertiary endpoints.	For consistency with CEC Charter
• Section 5.4 (Data Monitoring Committee [DMC])	Clarification of description of Data Monitoring Committee (DMC) activities.	For consistency with DMC Charter, SAP and iSAP
• Section 6.1 (Assessment Schedule)	Added statement on supporting patient protocol adherence (compliance with office and phone visit schedule).	Advisement to investigators to promote protocol adherence
• Section 6.1.2.3 (Visits 4, 5, 6, 7, 8, and 9) • Appendix A: Schedule of Procedures	Added procedures for Visit 8 and 9	Extension of the expected study period
• Sections 6.1.2.4 (Additional Visits) • Section 6.1.2.5 (Last Visit – End of Study) • Section 6.2 (Telephone Follow-up Contact) • Appendix A: Schedule of Procedures	Changed expected end of study date to Day 2160.	Extension of the expected study period
• Section 6.1.2.5 (Last Visit – End of Study)	Changed study completion window for all patients of 30 days from study end date to a target of 30 days from study end date	Clarification
• Section 6.2 (Telephone Follow-up Contact)	Added timing of additional planned telephone contacts; Clarified the frequency of additional telephone contacts to occur every 90 days	Extension of the expected study period; Clarification
• Section 6.3.1 (Clinical Laboratory Procedures)	Deletion of allowance for eligibility if exclusion criteria are deemed not clinically significant by the investigator	Clarification of requirement
• Section 6.3.1.2 (Fasting Lipid Profile)	Direct measurement of low-density lipoprotein cholesterol (LDL-C) was added to Visits 2 and 4	Added measurement to existing biosamples
• Section 6.3.1.2 (Fasting Lipid Profile) • Section 12.2.4.4 (Tertiary Endpoints)	Addition of calculation of Hopkins LDL-C	Additional analysis variable based on LDL-C measurements
• Section 6.3.1.3 (Genetic testing)	Added list of potential genetic tests	Inclusion of detail on genetic tests
• Section 6.3.1.5 (Additional Laboratory Tests)	Changed 12 mL blood draw to 10 mL blood draw; Clarified that serum will be archived. Added list of potential bioassays (non-genetic and genetic).	Correction of blood sample volume; Clarification Description of potential bioassay uses of samples

Protocol Location	Summary of Change	Reason for Change
• Section 6.3.2.7 (Electrocardiogram [ECG])	Added instruction that all post-randomization ECG results are to be sent to the CEC for assessment of silent myocardial infarction (MI).	Clarification of process
• Section 7.1.3 (Compliance Control)	Added instruction on study drug dose decrease: If dose is decreased for a patient (with Medical Monitor [MM] approval), the study drug dose should be increased back to 4 capsules as soon as medically appropriate.	Clarification of process
• Section 7.2.1 (Concomitant Medications during Treatment/Follow-Up Period)	Added instruction on statin discontinuation: If it becomes necessary to discontinue statin therapy, patients may (with MM approval) remain in the study and on study medication; statin therapy should be resumed when medically appropriate. Added instruction on post randomization initiation of medications that were excluded for non-stable dosage ≥28 days prior to screening, if medically warranted. Added PCSK9 inhibitors to the list of non-study drug related, non-statin, lipid-altering medications and supplements, and foods are prohibited during the study.	Clarification of process Clarification of process Clarification of process
• Section 8.2 (Pharmaceutical Formulations)	Update the capsule shell components of AMR101 1 g capsules and placebo capsules.	Update capsule shell components to represent nominal “dry shell” formula weight
• Section 9.1 (Specification of Variables and Procedures)	Clarification added that only adjudicated events will be used in the final efficacy statistical analysis. Also added reference to Appendix C for metabolic syndrome.	Clarification and to provide a location of additional relevant information
• Section 10.2 (Adverse Events)	For causality assessments, clarified definition of “Yes” as (related, probably related, possibly related).	Clarification of definition
• Section 10.3.1 (Initial Reports)	Specified follow-up period for SAE reporting for patients who are Off Drug In Study (ODIS) (28 days following study completion).	Clarification of process
• Section 11 (Treatment discontinuation/patient withdrawal)	Clarified that follow-up for efficacy and safety should be continued “i*n subjects that discontinued therapy, but remain in the study (i.e., ODIS patients)*”.	Clarification of process

Protocol Location	Summary of Change	Reason for Change
• Section 11.1 (Reasons for Early Study Drug Discontinuation)	Added reason for early study drug discontinuation: Investigative site closure. Added requirement of ≥30 days discontinuation of study drug for patient to qualify as ODIS. Added description of re-challenge (re-initiating study drug) after study drug discontinuation as soon as clinically appropriate.	Clarification of process Clarification of process Clarification of process
• Section 12.1.1 (Intent-to-Treat Population)	Renamed the Randomized Population to the Intent-to-Treat population; clarified definition.	For consistency with the population description and SAP
• Section 12.1.2 (Modified Intent-to-Treat Population)	Added definition of Modified Intent-to-Treat (mITT) population.	For consistency with SAP
• Section 12.1.3 (Per-Protocol Population)	Updated definition of Per-Protocol population.	Following the addition of the mITT population and for consistency with SAP
• Section 12.1.4 (Safety Population)	Updated definition of Safety Population: patients will be analyzed based on treatment received if different from that assigned by randomization.	Clarification
• Section 12.2.1 (Patient Disposition/Baseline Characteristics)	Modified or added descriptions of variables to be analyzed, methods, and analysis populations.	For consistency with SAP
• Section 12.2.2 (Study Medication Exposure and Compliance)	Clarified the methods for calculating study medication exposure and compliance.	For consistency with SAP
• Section 12.2.3 (Concomitant Therapies)	Clarified the codes to be used for summary and presentation of concomitant medications.	For consistency with SAP

Protocol Location	Summary of Change	Reason for Change
• Section 12.2.4.2 (Primary Endpoint)	Revised statistical methods for primary endpoint analysis to account for change in interim analyses: the 2-sided alpha level for the log-rank test will be reduced from 0.05 to account for the interim analyses based on a group sequential design.	For consistency with SAP
	Added information on analysis populations for the primary and sensitivity analyses of the primary endpoint.	For consistency with SAP
	Added a paragraph that describes how patients who have a non-CV death within 90 days versus patients who have a non-CV death more than 90 days after last contact without having had an earlier CV event will be censored.	For consistency with SAP
	Added a paragraph defining the analysis and sensitivity analysis for silent MI.	Clarification of process
	Added language which specifies that all observed data will be included in the primary analysis.	Clarification of process
	Added language explaining that all deaths adjudicated as “undetermined” will be combined with those adjudicated as “CV deaths” for the primary analysis. Additionally, a sensitivity analysis of the CV death category will be done excluding “undetermined” deaths.	Clarification of process
• Section 12.2.4.3 (Secondary Endpoints)	Revised statistical methods for analysis of secondary endpoints to describe sequential testing and updated methods.	For consistency with SAP
	Added a paragraph that describes how patients who have a non-CV death within 90 days versus patients who have a non-CV death more than 90 days after last contact without having had an earlier CV event will be censored.	For consistency with SAP

Protocol Location	Summary of Change	Reason for Change
• Section 12.2.4.4 (Tertiary Endpoints)	Added calculation of Hopkins LDL-C to tertiary endpoint analyses. Added a paragraph that describes how patients who have a non-CV death within 90 days versus patients who have a non-CV death more than 90 days after last contact without having had an earlier CV event will be censored. Added an explanation of an additional exploratory analysis on the relationship between post-baseline biomarker values and treatment effect with the primary and key secondary endpoint.	Additional analysis variable based on LDL-C measurements For consistency with SAP For consistency with SAP
• Section 12.2.4.5 (Exploratory Subgroup Analyses	Updated the analysis populations (mITT and PP) for the subgroup analyses. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was designated as the equation that would be used to evaluate renal dysfunction with an estimated glomerular filtration rate [eGFR] of 60 mL/min/1.73m^2 set as the lower limit of normal.	For consistency with SAP For consistency with SAP
• Section 12.2.4.6 (Interim Efficacy Analyses)	Added an additional interim analysis to occur after approximately 80% of the total primary endpoint events are reached. Added condition for unblinded information to be released to the Sponsor before completion of the study under extraordinary circumstances. Added description of statistical methods to be used for the interim analyses.	For consistency with iSAP Clarification of process For consistency with SAP
• Section 12.2.5 (Analysis of Safety)	Clarified definition of TEAEs to be consistent with SAP. Revised text to describe planned safety analysis for patients who discontinued study drug for at least 30 days due to AE/SAE. Patients who restart drug will not be included in the summary.	Clarification of planned safety analysis
• Section 12.3 (Sample Size Determination) and *Synopsis*	Clarified sample size calculation and assumptions. Provided a brief update on the analysis completed.	For consistency with iSAP Updated information
• Section 22 (References)	Updated the references cited in the main body of the protocol.	Revised set of references according to content changes

Protocol Location	Summary of Change	Reason for Change
• Appendix A: Schedule of Procedures	Added columns to describe Day 2160 Visit and Last Visit.	Extension of the expected study period
• Appendix B: Standardized Definitions for Endpoint Events in Cardiovascular Trials	Updated per new version of Standardized Definitions for Endpoint Events in Cardiovascular Trials (Hicks 2015). Consistent with FDA comments, the definitions were updated to make them specific to the REDUCE-IT study by removing ambiguous language and deleting definitions that do not apply to the study (i.e., some interventional cardiology definitions). Also, language clarifying that undetermined deaths will be classified as death due to cardiovascular causes unless one of two scenarios occur: there is no information or data available regarding the circumstances of death other than that a death has occurred; or the available data are conflicting regarding whether the death was cardiovascular or non-cardiovascular.	Updated to the current definitions for standardized cardiovascular endpoint events Clarification of definitions and for consistency with SAP
• Appendix C: Criteria for the Diagnosis of Diabetes	Updated source to new version of guideline.	Update of current source
• Appendix D: Criteria for the Diagnosis of Metabolic Syndrome	This appendix was added to provide the criteria and waist circumference cut-points for abdominal obesity used for the diagnosis of metabolic syndrome as published by Alberti *et al.* in 2009.	Addition of a new resource related to evaluation of certain tertiary endpoints.

STATISTICAL ANALYSIS PLAN

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:
REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

Investigational Product: AMR101 (icosapent ethyl [ethyl-EPA])

Protocol Number: AMR-01-01-0019

Sponsor:
Amarin Pharma Inc.
1430 Route 206
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Final: 8 July 2016
Version Number: Final v 1.0

SIGNATURE PAGE

TRIAL 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: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

We, the undersigned, have reviewed and approved this Statistical Analysis Plan for Protocol AMR-01-01-0019.

Signature	Date
[Name / signature redacted]	[Signed (11 July 2016)]
Senior Director, Biostatistics and Data Management Amarin Pharma Inc.	
[Name / signature redacted]	[Signed (11 July 2016)]
Executive Director, Clinical Development Amarin Pharma Inc.	
[Name / signature redacted]	[Signed (11 July 2016)]
Executive Director, Clinical Development Amarin Pharma Inc.	
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President of R&D and Chief Scientific Officer, SVP Amarin Pharma Inc.	
[Name / signature redacted]	[Signed (19 July 2016)]
Principal Investigator	

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
apo B	Apolipoprotein B
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CBC	Complete blood count
CEC	Clinical Endpoint Committee
CHF	Congestive heart failure
CI	Confidence interval
CRF	Case Report Form
CV	Cardiovascular
CVD	Cardiovascular disease
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EPA	Eicosapentaenoic acid
Hct	Hematocrit
HDL-C	High-density lipoprotein cholesterol
Hgb	Hemoglobin
HR	Hazard ratio
hs-CRP	High-sensitivity C-reactive protein
hsTnT	High-sensitivity troponin T
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ITT	Intent-to-treat
IWRS	Interactive Web Response System
iSAP	Interim Statistical Analysis Plan

Abbreviation or Term	Definition
LDL-C	Low-density lipoprotein cholesterol
MI	Myocardial infarction
mITT	Modified Intent-to-Treat
NCEP	National Cholesterol Education Program
PP	Per Protocol
PTCA	Percutaneous transluminal coronary angioplasty
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
SOC	System Organ Class
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TIA	Transient Ischemic Attack
WBC	White blood cell

2. INTRODUCTION

This Statistical Analysis Plan (SAP) has been developed based on Protocol AMR-01-01-0019 (Amendment #2 Final Version 3.0 dated 8 July 2016). The SAP describes the statistical methods to be used for the final analysis and reporting of efficacy and safety data collected during the entire conduct of Protocol AMR-01-01-0019, and has been developed and finalized prior to database lock and unblinding of the clinical database for Study AMR-01-01-0019. A separate Interim Statistical Analysis Plan (iSAP) (Appendix A) describes the planned interim analyses that will be solely used for interim decision making by the independent Data Monitoring Committee (DMC). If additional analyses are required to supplement the planned analyses described in this SAP, they will be identified in the Clinical Study Report (CSR).

This SAP is being written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

3. STUDY OBJECTIVES AND TRIAL DESIGN

3.1 Study Objective(s)

The primary objective is, in patients at low-density lipoprotein cholesterol (LDL-C) goal while on statin therapy, with established cardiovascular disease (CVD) or at high risk for CVD, and hypertriglyceridemia (fasting triglycerides [TG] ≥200* mg/dL and <500 mg/dL [≥2.26 mmol/L and <5.64 mmol/L]), to evaluate the effect of 4 g/day AMR101 on the time from randomization to first occurrence of any component of the composite of the following major cardiovascular (CV) events:

- CV death;
- Nonfatal myocardial infarction (MI), (including silent MI; electrocardiograms [ECGs] will be performed annually for the detection of silent MIs);
- Nonfatal stroke;
- Coronary revascularization; or
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

(*The fasting TG lower limit of ≥150 mg/dL, as defined in the original protocol, was changed via protocol amendment #1 dated 16 May 2013 to ≥200 mg/dL. All randomized patients will be included in the final analyses).

The secondary objectives of this study are the following:

The key secondary objective is to evaluate the effect of therapy on the time from randomization to the first occurrence of the composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke.

Other secondary objectives for this study are to evaluate the effect of therapy on time from randomization to the first occurrence of:

- Composite of CV death or nonfatal MI (including silent MI);
- Fatal or nonfatal MI (including silent MI);
- Non-elective coronary revascularization represented as the composite of emergent or urgent classifications;
- CV death;
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Fatal or nonfatal stroke;
- Composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke;
- Total mortality.

The tertiary objectives for this study are to evaluate the effect of therapy on the following. Where applicable and unless specified otherwise, endpoints represent time from randomization to the first occurrence of the individual or composite endpoints:

- The total CV events analysis defined as the time from randomization to occurrence of the first and all recurrent major CV events defined as CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;

- Primary composite endpoint in the subset of patients with diabetes mellitus at baseline;

- Primary composite endpoint in the subset of patients with metabolic syndrome at baseline as defined in *A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity* (Alberti 2009); with cut points of parameters as defined in Table 1 of Alberti *et al.* and waist circumference cut points further guided by Table 2 of Alberti et. al. and specifically set at ≥35 inches (88 cm) for all women and Asian, Hispanic, or Latino men, and ≥40 inches (102 cm) for all other men (see Appendix C in Section 6.3);

- Primary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG of 100-125 mg/dL);

- Key secondary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG 100-125 mg/dL);

- Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalization of ≥24 hours, or cardiac arrest;

- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;

- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or PVD requiring intervention, such as angioplasty, bypass surgery, or aneurism repair;

- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, PVD requiring intervention, or cardiac arrhythmia requiring hospitalization of ≥24 hours;

- New CHF;
- New CHF as the primary cause of hospitalization;
- Transient ischemic attack (TIA);
- Amputation for PVD;
- Carotid revascularization;
- All coronary revascularizations defined as the composite of emergent, urgent, elective, or salvage;
- Emergent coronary revascularizations;
- Urgent coronary revascularizations;
- Elective coronary revascularizations;
- Salvage coronary revascularizations;
- Cardiac arrhythmias requiring hospitalization of ≥24 hours;
- Cardiac arrest;
- Ischemic stroke;
- Hemorrhagic stroke;
- Fatal or nonfatal stroke in the subset of patients with a history of stroke prior to baseline;
- New onset diabetes, defined as Type 2 di abetes newly diagnosed during the treatment/follow-up period;
- New onset hypertension, defined as blood pressure ≥140 mmHg systolic OR ≥90 mmHg diastolic newly diagnosed during the treatment/follow-up period;
- Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP (hsCRP and log[hsCRP]), hsTnT, and RLP-C (to be estimated from standard lipid panel, RLP-C = TC – HDL-C – LDL-C [Varbo 2014]) (based on ITT estimands):
    - Assessment of the relationship between baseline biomarker values and treatment effects within the primary and key secondary composite endpoints,
    - Assessment of the effect of AMR101 on each marker,

- Assessment of the relationship between post-baseline biomarker values and treatment effects within the primary and key secondary composite endpoints by including post-baseline biomarker values (for example, at 4 months, or at 1 year) as a covariate;

- Change in body weight;

- Change in waist circumference.

3.2 Study Design

This is a Phase 3b, multi-center, multi-national, prospective, randomized, double-blind, placebo-controlled, parallel-group study.

This is an event driven trial comparing the effect of AMR101 vs. control, in terms of the composite endpoint listed above as the primary efficacy endpoint. The study has been planned to accrue a total of 1612 efficacy endpoint events with two planned interim analyses when approximately 967 (60%) and 1290 (80%) of the events have occurred and been adjudicated. The study includes patients with established CVD (CV Risk Category 1) and patients ≥50 years old with diabetes and at least one additional risk factor for CVD but with CVD not established (CV Risk Category 2).

Sample size calculation was based on assumptions of constant hazard, asymmetric recruitment rate over time and without factoring for dropouts. A risk reduction corresponding to a hazard ratio of 0.85 (AMR101 vs. control) is assumed. 1612 events would be required to detect this hazard ratio with approximately 90% power with one-sided alpha-level at 2.5% and with two interim analyses.

The recruitment period is assumed to be approximately 4.2 years with 20% recruitment in the first year, 40% in the second year, 20% in the third year, 19% in the fourth year and the remaining 1% in the last 0.2 years. The expected maximum study duration is estimated at 6.5 years unless the trial is terminated early for efficacy or safety issues. A one-year event rate of 5.2% (hazard = 0.053) in the control arm is also assumed. Under these assumptions the number of patients to be enrolled is N = 7990.

Randomized treatment assignment to either 4 g/day AMR101 or placebo in a 1:1 ratio will be provided using the internet via an interactive web response system (IWRS). Randomization will be stratified by CV Risk Category 1 or 2 (defined in the inclusion criteria of the study protocol), use of ezetimibe, and by geographical region (Westernized, Eastern European, and Asia Pacific countries).

Approximately 70% of randomized patients will be in CV Risk Category 1, and approximately 30% of randomized patients will be in CV Risk Category 2. Enrollment of patients within a CV risk category will be stopped when the planned number of patients in that risk category is reached or, if the enrollment target is extended beyond 7990 patients (as

described in Section 4.1), then only CV Risk Category 1 will be included in further enrollment.

Study drug AMR101 or placebo capsules will be taken daily (with food) as two capsules in the morning and two capsules in the evening (twice-per-day dosing regimen).

The study schedule and assessments to be performed are described in the study protocol.

3.2.1 Efficacy Assessments

The primary endpoint and the majority of the secondary and tertiary endpoints are based on clinical events related to CVD and mortality. All events occurring between randomization and the study end date (inclusive) will be recorded. All suspected efficacy endpoint events will be adjudicated by a Clinical Endpoints Committee (CEC) based on the criteria detailed in the CEC Charter. The CEC members are blinded to study treatment allocation. For efficacy endpoints including CV events, only adjudicated events will be included in the final statistical analyses.

3.2.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the time from randomization to the first occurrence of the composite of the following clinical events:

- CV death;
- Nonfatal MI (including silent MI; ECGs will be performed annually for the detection of silent MIs);
- Nonfatal stroke;
- Coronary revascularization;
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

The first occurrence of any of these major adverse cardiovascular events during the follow-up period of the study will be included in the incidence.

All deaths casually adjudicated as “undetermined” will be combined with those adjudicated as “CV deaths” for the primary analysis. A sensitivity analysis of the CV death category will be performed that excludes the “undetermined cause of death” cohort.

For silent MIs, the primary analysis will assume that all silent MIs occurred on the date of the first tracing indicative of a silent MI; a second (sensitivity) analysis will assume that all silent MIs occurred on the day after the last prior normal ECG; and a third (sensitivity) analysis will assume that all silent MIs occurred at the mid-point between the last normal ECG and the ECG with the new MI.

3.2.1.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoint is the time from randomization to the first occurrence of the composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke.

Other secondary efficacy endpoints are time from randomization to the first occurrence of the individual or composite endpoints as follows (to be tested in the order listed):

- Composite of CV death or nonfatal MI (including silent MI);
- Fatal or nonfatal MI (including silent MI);
- Non-elective coronary revascularization represented as the composite of emergent or urgent classifications;
- CV death;
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Fatal or nonfatal stroke;
- Composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke;
- Total mortality.

For the secondary endpoints that count a single event, the time to first occurrence of this type of event will be counted for each patient. For secondary endpoints that are composites of two or more types of events, the time to first occurrence of any of the event types included in the composite will be counted for each patient.

For the secondary endpoints as well as the tertiary endpoints mentioned below, the main analysis will combine all deaths casually adjudicated as "undetermined" with those adjudicated as "CV deaths" and use the date of the first tracing indicative of a silent MI as the onset date for silent MI, similar to the primary efficacy analysis described above. Similarly, the sensitivity analyses as described for the primary composite endpoint will also be carried out for the secondary and tertiary endpoints.

3.2.1.3 Tertiary Efficacy Endpoints

The following tertiary endpoints will be evaluated as supporting efficacy analyses. Where applicable and unless specified otherwise, endpoint analyses will be conducted as time from randomization to the first occurrence of the individual or composite endpoints.

- Total CV events analysis defined as the time from randomization to occurrence of the first and all recurrent major CV events defined as CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Primary composite endpoint in subset of patients with diabetes mellitus at baseline;

- Primary composite endpoint in the subset of patients with metabolic syndrome at baseline as defined in A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity (Alberti 2009); with cut points of parameters as defined in Table 1 of Alberti et al. and waist circumference cut points further guided by Table 2 of Alberti et al. and specifically set at ≥35 inches (88 cm) for all women and Asian, Hispanic, or Latino men, and ≥40 inches (102 cm) for all other men (see Appendix C in Section 6.3);
- Primary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG of 100-125 mg/dL);
- Key secondary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG 100-125 mg/dL);
- Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalization of ≥24 hours, or cardiac arrest;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or PVD requiring intervention, such as angioplasty, bypass surgery, or aneurism repair;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, PVD requiring intervention, or cardiac arrhythmia requiring hospitalization of ≥24 hours;
- New CHF;
- New CHF as the primary cause of hospitalization;
- Transient ischemic attack (TIA);
- Amputation for PVD;
- Carotid revascularization;
- All coronary revascularizations defined as the composite of emergent, urgent, elective, or salvage;
- Emergent coronary revascularizations;
- Urgent coronary revascularizations;

- Elective coronary revascularizations;
- Salvage coronary revascularizations;
- Cardiac arrhythmias requiring hospitalization of ≥24 hours;
- Cardiac arrest;
- Ischemic stroke;
- Hemorrhagic stroke;
- Fatal or nonfatal stroke in the subset of patients with a history of stroke prior to baseline;
- New onset diabetes, defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period;
- New onset hypertension, defined as blood pressure ≥140 mmHg systolic OR ≥90 mm Hg diastolic newly diagnosed during the treatment/follow-up period;
- Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP (hsCRP and log[hsCRP]), hsTnT, and RLP-C (to be estimated from standard lipid panel, RLP-C = TC – HDL-C – LDL-C [Varbo 2014]) (based on ITT estimands):
  - Assessment of the relationship between baseline biomarker values and treatment effects within the primary and key secondary composite endpoints,
  - Assessment of the effect of AMR101 on each marker,
  - Assessment of the relationship between post-baseline biomarker values and treatment effects within the primary and key secondary composite endpoints by including post-baseline biomarker values (for example, at 4 months, or at 1 year) as a covariate;
- Change in body weight;
- Change in waist circumference.

Where applicable and unless specified otherwise, for the tertiary endpoints that count a single event, the time from randomization to the first occurrence of this type of event will be counted in each patient. Similarly, where applicable and unless specified otherwise, for tertiary endpoints that are composites of two or more types of events, the time from randomization to the first occurrence of any of the event types included in the composite will be counted for each patient.

3.2.2 Safety Endpoints

Safety assessments will include adverse events (AEs), clinical laboratory measurements (chemistry, hematology), 12-lead electrocardiograms (ECGs), vital signs (seated systolic and diastolic blood pressures, heart rate, respiration rate, and body temperature), weight, waist circumference, and physical examinations as per the study protocol.

A complete medical, surgical and family history will be completed at Visit 1.

4. STATISTICAL METHODOLOGY

4.1 Determination of Sample Size

The initial sample size estimation (protocol v1.0) was based on the assumption that the primary composite endpoint (time from randomization to the first occurrence of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina requiring hospitalization) would be relatively reduced by approximately 15% with AMR101 from an event rate by 4 years of 20.8% (5.2% per year) in the placebo group (which corresponds to a hazard ratio of 0.85). The updated sample size calculation is based on assumptions of constant hazard, asymmetric recruitment rate over time and without factoring for dropouts. A risk reduction corresponding to a hazard ratio of 0.85 (AMR101 vs. control) is assumed. 1612 events would be required to detect this hazard ratio with approximately 90% power with two-sided alpha-level at 5% and with two interim analyses.

The recruitment period is assumed to be approximately 4.2 years with 20% recruitment in the first year, 40% in the second year, 20% in the third year, 19% in the fourth year and the remaining 1% in the last 0.2 years. The expected maximum study duration is estimated at 6.5 years unless the trial is terminated early for efficacy or safety issues. A one-year event rate of 5.2% (hazard = 0.053) in the control arm is also assumed. Under these assumptions the number of patients to be enrolled is N = 7990.

Two interim analyses are planned after approximately 60% (967) and approximately 80% (1290) of the primary events have occurred (see iSAP in Section 6.1 [Appendix A] for description of the interim analyses).

Since this is an events-driven trial, the 'sample size' is the number of events rather than the number of patients. The number of events that occur depends primarily on three factors: how many patients are enrolled, the combined group event rate, and how long the patients are followed. Because of the difficulty in predicting the combined event rate, the sponsor will monitor that event rate as the trial progresses. If the combined event rate is less than anticipated, either increasing the number of patients, extending the length of follow-up, or a balance of adjusting both factors may be necessary to achieve the sample size of 1612 events.

Before completing the enrollment phase of the trial, *i.e.* approximately 3 to 6 months prior to the projected enrollment of the 7990th patient, the actual event rate based on pooled, blinded accumulation of primary efficacy endpoint events would be calculated and plotted. If those analyses suggested the number of patients with at least 1 adjudicated, primary event (and appropriately accounting for patients with potential primary events for which the adjudication process is then incomplete) was consistent with projections, then the study could continue toward the protocol-specified target enrollment of 7990 patients. However, if the number of such events appeared less than and inconsistent with projections, the Sponsor would consider (under blinded conditions) re-calculating the number of patients needed to achieve the target

number of events within the desired timeline or extend the follow-up period. If the projected increase in number of patients was ≤25% of the original 7990 target population, the Sponsor could, with documented approval of both the REDUCE-IT Steering Committee and the DMC, extend enrollment to the revised target number without need for an additional protocol amendment. Under those conditions, all principal investigators, ethics committees, and regulatory authorities associated with the protocol will be promptly notified of the action. If the projected increase in number of patients was more than 25% above the original 7990 target (*i.e.* more than 1998 additional patients) a formal protocol amendment would have been initiated.

Consistent with the plan stated above, an analysis and modeling of pooled, blinded primary efficacy endpoint events across the remainder of the trial was performed prior to the projected enrollment of the 7990th patient. Based on this analysis, the sample size of 7990 randomized patients is with 95% confidence likely to result in the target 1,612 adjudicated primary efficacy events within 2018. The results of this analysis were shared with and approved by the REDUCE-IT Steering Committee and DMC.

As of the completion of study enrollment, the actual number of patients randomized will vary from the target number as a result of the inherent lag between the date the last patient started screening and the date the last patient was randomized.

4.2 Analysis Sets

4.2.1 Intent-to-Treat Population (ITT)

The Intent-to-Treat (ITT) population will include all patients who are randomized via the IWRS. All efficacy analyses, including the primary analysis, will be performed on the ITT population. Patients will be analysed according to the randomized treatment.

4.2.2 Modified Intent-to-Treat Population (mITT)

The Modified Intent-to-Treat (mITT) population will include all randomized patients who have study drug dispensed after randomization. Groups will be defined based on the randomized treatment.

4.2.3 Per Protocol Population (PP)

The Per-Protocol (PP) population will include all mITT patients without any major protocol deviations, and who had ≥80% compliance while on treatment. To be included in the PP population the minimum time on therapy is 90 days.

4.2.4 Safety Population

All safety analyses will be conducted based on the Safety population, which is defined as all randomized patients. This is the same as the ITT population.

4.3 Statistical Considerations

4.3.1 General Statistical Considerations

All statistical analyses and data summaries are to be generated according to this SAP. Any deviations from this SAP will be documented in the CSR.

All null hypotheses will be defined as no treatment difference. All statistical tests for the efficacy outcomes will be performed at the two-sided 5% significance level, unless otherwise noted. The iSAP will utilize one-sided testing for efficacy at the 0.025 level for interim analyses, the operating characteristics of which are identical to those of a corresponding group sequential design with a two-sided alpha level of 0.05.

Summary statistics will be presented by treatment group and by visit where appropriate. Data will be presented "as-observed", unless otherwise specified. Continuous data will be summarized with descriptive statistics: count (n), number of missing values (n-missing), mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be described using frequencies and percentages, including a category for missing values where appropriate. Percentages are based on the number of patients in the analysis set. All meaningful patient data collected in the database will be listed. Listings will be sorted by patient within center/site.

4.3.2 Missing Data

Only measurements obtained at each study visit will be used in presenting tabular data summaries, unless otherwise stated. Unless otherwise stated, observed data will be presented in tables and listings without imputation of missing values. All measurements, including unscheduled or repeated assessments, will be presented in data listings.

Medications, except study drug, with missing stop dates will be considered in concurrent use with study drug during the study period and counted in the summary table of concomitant medications unless the start date of the medication was after study completion or after discontinuation from study.

Adverse events with missing onset dates will be considered treatment-emergent for randomized patients if the adverse event stop date is after randomization. Adverse events with missing stop dates will be considered treatment-emergent for randomized patients. If only the year is present for AE stop dates, then December 31 will be used as the month and day, respectively. If only the day is missing, the first of the month will be used for all start dates and the last day of the month will be used for all end dates.

Missing AE relationship will be presented as 'related' in tables and missing in listings. In addition, tables that describe the collected data and that include a 'missing' relationship category where appropriate will be presented. Missing AE intensity/severity will be presented in a 'missing' category in tables and as missing in listings.

Event or censoring dates used in the time-to-event analysis of efficacy endpoints will be imputed to the first of the month only if the day is missing and the month and year are both known. However, for events that occurred in the same month as randomization, the day will be imputed as the date of randomization. For event or censoring with missing months or years, the event or censoring date will be imputed to the last known date without a previous event, or January 1 if only year is known, whichever is later.

4.3.3 Baseline

In general, the baseline value will be defined as the last non-missing measurement obtained prior to the dispensing drug, unless otherwise specified. If the baseline value is missing, the value obtained at the screening visit will be used as the baseline value.

Lipid, lipoprotein, and inflammatory marker baseline values will be derived variables. LDL-C may be obtained by various methods at each visit; therefore, the baseline value obtained via Preparative Ultracentrifugation will be used, unless this value is missing. If the LDL-C Preparative Ultracentrifugation value is missing, then another LDL-C value will be used, with prioritization of values obtained from LDL-C Direct measurements, followed by LDL-C derived by the Friedewald calculation (only for subjects with TG < 400 mg/dL), and finally LDL-C derived using the calculation published by Hopkins University investigators (Martin 2013). For all other lipid, lipoprotein, and inflammatory marker parameters, wherever possible, baseline will be derived as the arithmetic mean of the Visit 2 (Day 0) value and the preceding Visit 1 (or Visit 1.1) value. If only one of these values is available, the single available value will be used as baseline.

4.3.4 Study Day

For purposes of calculating study day, the day of randomization is defined as Day 0. Study Day will be calculated as [date of event – date of randomization + 1].

4.3.5 Visit Windows

Nominal study visits (days or weeks relative to Baseline) as collected per the protocol schedule of events will be used to summarize data. Ranges for study day intervals (“windows”) will not be used to re-assign visit numbers in relation to the start of therapy. If there is more than one valid measurement for a selected visit after the baseline visit, the average of the values collected will be used. However, for any safety analyses intended to identify outliers (including, but not limited to, shift tables), the most extreme value instead of the average of the values collected will be used; and values from all visits (including unscheduled measurements) will be included in these analyses.

4.3.6 Multiplicity

There is a single primary efficacy endpoint (a composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina) and one primary comparison (Placebo vs. 4 g /day AMR101) defined in the primary objective. Formal

statistical testing for key and other secondary endpoints will be performed for the final analysis, either at the planned completion at 1612 primary events or in case of an early stop for efficacy at one of the two interim analyses, and will be carried out in a hierarchical fashion if and only if the primary endpoint meets statistical significance. The hierarchy of secondary endpoints is given in Section 3.2.1.2.

The planned interim analyses are based on a group sequential design with O'Brien-Fleming boundaries generated using the Lan-DeMets alpha-spending function at approximately 60% and 80% of the targeted 1612 events. The use of the spending-function allows for possible deviations from the planned event number at the time of the interim. If the interim analyses are carried out exactly at the planned 60% and 80% milestones, then the resulting one-sided alpha-levels at each of the two interim analyses and the final analysis are:

- 0.0038 at the 60% milestone (967 events),
- 0.0110 at the 80% milestone (1290 events), and
- 0.0211 at the 100% milestone (1612 events).

A complete description of the group sequential design details is described in the iSAP (Appendix A).

The alpha level for the final analysis either at the planned completion at 1612 primary events or in case of an early stop for efficacy will be obtained from the O'Brien-Fleming boundaries generated using the Lan-DeMets alpha-spending function. If the primary efficacy endpoint test described in Section 4.7.1.1 meets statistical significance at this alpha-level, then the testing will be carried out hierarchically for the key secondary and the other secondary endpoints at the same alpha level used for the primary endpoint. All analysis beyond the primary or the last endpoint meeting statistical significance at this alpha-level will be considered as exploratory. Further details on the alpha-level to be used for the final analysis are given in Section 4.5.

Since the results from the analysis of the tertiary endpoints are intended to be supportive rather than pivotal evidence of drug efficacy and safety, all tertiary efficacy endpoint analysis will be considered exploratory and statistical testing will be carried out at the nominal 5% level without adjustment.

4.4 Interim Analyses

Two interim analyses are planned for the primary efficacy endpoint using adjudicated events when adjudication of approximately 60% (967 events) and approximately 80% (1290 events) of the total number of primary endpoint events planned (1612) is reached. The planned interim analyses are based on a group-sequential design and are described in the iSAP (Appendix A).

The interim results of the study will be monitored by an independent DMC. The analyses will be performed by an independent statistical team that is unblinded to the treatment assignment and will be reported only to the DMC. The unblinded information will not be released to the

Sponsor before the completion of the study unless extraordinary circumstances arise and, under such circumstances, procedures for maintaining confidentiality will be described in a written agreement with the DMC.

If the study is terminated early following an interim analysis, patients will be notified promptly and brought in for their final close-out visit, and the final analyses of efficacy and safety will include all data through their final visit. Further details are given in Section 4.5.

4.5 Final Analysis Following an Interim Analysis Early Stop Decision

If the decision is taken to terminate the study at one of the two planned interim analyses, the study will enter the closeout phase. During this phase, which extends from the DMC interim analysis meeting until the final database lock, additional adjudicated events may arrive. The final analysis, being based on the totality of the evidence, will include these additional events, resulting in an increase in the information fraction (of the pre-specified 1612 events) from what the information was at the time of the interim decision making. The significance level for the formal hypothesis testing at the final analysis will then be recomputed from the Lan-DeMets error spending function at the new information fraction while ignoring the look at which the efficacy boundary was crossed for the DMC decision-making purpose (Whitehead, 1992). A few examples of the recomputed alpha level used for the final analysis are given in the Table below:

Table 1. Examples of Recomputed Alpha Levels for Final Analysis

Early Stop IA Number	Number of Events at IA Decision	Number of Additional Events at Closeout	Final Analysis	
			Total Number of Events	α Level
1	967	33	1000	0.0088
1	967	50	1017	0.0095
2	1290	40	1330	0.0272
2	1290	60	1350	0.0286
IA=interim analysis				

4.6 Summary of Study Population Data

4.6.1 Patient Disposition

The number and percentage of patients will be tabulated for each of the following categories for each treatment group:

- Screened (total only);
- Re-screened and reasons for re-screening (total only);
- ITT overall and by stratification factors (CV risk, ezetimibe use, and geographical region);

- mITT population; overall and by stratification factors (CV risk, ezetimibe use, and geographical region);
- PP population; overall and by stratification factors (CV risk, ezetimibe use, and geographical region);
- Safety population;
- Patients who complete the study;
- Patients who terminated from the trial early and the primary reason for early termination.
- Patients who terminated the trial early; prior to having a confirmed primary endpoint event.
- Patients with complete follow-up, defined as those for whom all components of the primary endpoint have been ascertained during the entire observation period (or until death).
- Patients who, at the time of study completion, were discontinued from study drug prematurely, but continued within the study (i.e. ODIS patients), along with the primary reason.

4.6.2 Protocol Deviations

All instances of protocol non-compliance will be tracked during the study and a list of protocol deviations will be reviewed in a blinded manner by the Sponsor prior to database lock. Major deviations resulting in exclusion of the patient from the Per Protocol population will be determined. Protocol deviations will be presented in a data listing and summarized by type using counts and percentages by treatment group.

4.6.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics, including age, gender, ethnicity, race, height, body weight, body mass index (BMI), diabetes, hypertension, metabolic syndrome, overweight/obese/normal according to BMI, and diabetes plus obesity will be summarized using descriptive statistics by treatment group in the ITT population.

Demographic data and baseline characteristics will be also compared between treatment groups for the mITT population and PP population. Differences in demographic and baseline characteristics will be tested using a ch i-square for categorical variables and a t-test for continuous measures. The p-values will be considered descriptive, primarily as an assessment of the balance between groups. Age in years will be calculated using the date of randomization (Visit 2) and the date of birth.

4.6.4 Cardiovascular Risk Category

Factors determining the cardiovascular risk category (1 or 2) at randomization will be summarized by treatment group using counts and percentages for the ITT and Modified ITT populations.

4.6.5 Smoking and Alcohol History

Smoking status (Never/Former/Current) and Alcohol use (Never/Former/Current) will be presented by treatment group using counts and percentages for the ITT and mITT populations. In addition, the average number of drinks per day for former and current alcohol users will be summarized with descriptive statistics. The number and percentage of patients with a history of alcoholism, previous treatment for alcoholism, and number of years since treatment was completed will be presented.

4.6.6 Cardiovascular History and Procedures, Family History, and Other Significant Medical History

Counts and percentages of patients with each type of cardiovascular disease history will be presented by treatment group for the ITT and Modified ITT populations.

Counts and percentages of patients with a history of cardiovascular procedures (percutaneous transluminal coronary angioplasty [PTCA]/stent, coronary artery bypass graft [CABG], Implantable Cardioverter/Defibrillator, Permanent Pacemaker, Carotid Revascularization and Aorto-iliac or Peripheral Arterial Intervention) will be presented by treatment group for the ITT population. For PTCA/Stent and CABG, whether the procedure was emergent and whether it was successful will be reported. For Carotid Revascularization and Aorto-iliac or Peripheral Arterial Intervention, whether it was performed with a catheter or surgically will be presented.

The number and percentage of patients with a family history of premature coronary heart disease will be summarized by treatment group for the ITT and mITT populations. For patients with a family history, the number and percentage with a male first degree relative < 55 years, female first degree relative < 65 years, or both male and female will be presented.

Other significant medical history will be listed by patient.

4.6.7 Study Medication Administration and Compliance

Study drug exposure will be summarized by treatment group using descriptive statistics for each time point and overall.

Overall study drug compliance will be calculated as the number of doses assumed to be taken relative to scheduled dosing period as follows:

$$\text{Compliance (\%)} = \frac{(\#\text{ Capsules of total dispensed} - \#\text{ Capsules of total returned}) \times 100}{(\text{last dose date} - \text{first dose date} + 1) \times 4 \text{ capsules/day}}$$

Overall percent compliance will be calculated per patient in the ITT and mITT populations and summarized by treatment group using descriptive statistics.

4.6.8 Discontinuation of Study Drug

A Kaplan-Meier analysis of the time to premature discontinuation of study drug will be presented by treatment arm. A temporary discontinuation followed by re-starting study drug will not be considered a discontinuation in this analysis. Event probabilities at 6-month intervals and the median time to event (if estimable) will be presented. The log-rank test will be used to compare treatment groups.

4.6.9 Early Termination from the Study

A Kaplan-Meier analysis of the time to early termination will be presented by treatment arm. The date of termination for patients who do not complete the study due to any reason besides death will be used as the event date. Patients who do not terminate early or who terminate due to death will be censored at the date of death or last contact. Event probabilities at 6-month intervals and the median time to event (if estimable) will be presented. The log-rank test will be used to compare treatment groups.

4.6.10 Medications of Special Interest

At each scheduled visit (on site or by phone contact), information on changes in ezetimibe, statins, angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs)/beta blockers, and anti-diabetic drugs will be collected. For each medication type, the number and percentage of patients who started a new medication, discontinued a medication, increased the dose or decreased the dose of a medication will be presented by visit/phone contact. The overall number of patients with at least one of the above changes during the study will also be summarized by medication type.

4.6.11 Prior and Concomitant Medications

Non-study medications will be coded using the latest available version prior to database lock of the World Health Organization Drug Dictionary (WHO-DRUG) and the Anatomical Therapeutic Chemical (ATC) classification system. Coding includes the anatomical main group (ATC 1st Level), therapeutic class (ATC 3rd Level), and preferred term. All verbatim descriptions and coded terms will be listed for all non-study medications.

Prior medications are defined as non-study medications with a stop date before the randomization date.

Concomitant medications are defined as non-study medications with a stop date on or after the date of randomization. Medications that started prior to randomization but continued during study will also be defined as concomitant. Ongoing medications without stop dates are considered concomitant.

Medications with partial onset/stop dates that indicate that the medication could be concomitant in relation to the date of randomization are classified as concomitant. Otherwise, they are classified as prior medications.

The numbers and percentages of patients in each treatment group taking concomitant medications will be summarized by ATC therapeutic class and preferred term. For each patient, multiple records of the same concomitant medication will be counted only once within each therapeutic class and preferred term.

Listings will be provided for both prior and concomitant medications.

4.7 Efficacy Analyses

4.7.1 Primary Efficacy Endpoint

4.7.1.1 Primary Analysis

The primary efficacy endpoint is the time from randomization to the first occurrence of any component of the composite of the following adjudicated clinical events:

- CV death,
- Nonfatal MI (including silent MI; ECGs will be performed annually for the detection of silent MIs),
- Nonfatal stroke,
- Coronary revascularization,
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

All observed data that are positively adjudicated by the CEC, including data after discontinuation of study treatment for patients who discontinue study drug prematurely, will be included in the primary analysis.

Suspected endpoint events are adjudicated by the CEC without knowledge of the treatment. Counts and Kaplan-Meier estimates of the percentage of patients experiencing each type of adjudicated event by study completion, along with overall counts for each type, will be presented by treatment arm. A separate table of the number of events that are ruled out by the CEC will also be displayed.

The event time will be calculated as the (date of first event – date of randomization + 1 day) for patients who experience one or more of the primary endpoint events. The following provides detailed considerations for determining the date of event/date of censoring:

- Patients who do not experience a primary efficacy event prior to the end of the study or withdrawal from the study early without a preceding primary efficacy event will be censored at the date of their last visit/phone contact.
- Patients who die with an adjudicated undetermined cause of death and without a preceding endpoint event will be considered to have an adjudicated CV death and this will be included as an event in the primary analysis.

- In view of the 90-day monitoring period for CV events, patients who have a non-CV death within 90 days of last contact without having had an earlier CV event will be censored at the time of death. Patients who have a non-CV death more than 90 days after last contact without having had an earlier CV event will be censored at the date of their last visit/phone contact.
- The primary analysis of silent MI will assume that all silent MIs occurred on the date of the first tracing indicative of a silent MI.

Kaplan-Meier estimates will be used to summarize the time to the first event of the composite endpoint. Event probabilities at 6-month intervals and the median time to event (if estimable) will be presented. The log-rank test, stratified by stratification variables at randomization (CV risk category, use of ezetimibe, and geographical region [Westernized, Eastern European, and Asia Pacific countries]), will be used to compare the time-to-event between treatment groups. The two-sided alpha level for the primary analysis will be reduced from 0.05 to account for the interim analyses based on a group sequential design with O'Brien-Fleming boundaries generated using the Lan-DeMets alpha-spending function.

The hazard ratio (HR) comparing the two treatment groups along with a confidence interval (CI) adjusted for the interim analyses and p-value will be calculated from a stratified Cox proportional hazards (PH) model with treatment as the only covariate, and stratified by CV risk category at baseline, use of ezetimibe at baseline, and geographical region (Westernized, Eastern European, and Asia Pacific countries). Kaplan-Meier curves stratified by each of the stratification variables will be presented.

The primary efficacy analysis will be performed on the ITT population. A corresponding sensitivity analysis will be performed using the mITT and PP populations.

4.7.1.2 Other Sensitivity, Supportive, and Exploratory Analyses for the Primary Efficacy Endpoint

As a sensitivity analysis, patients who discontinue study drug prematurely will be censored for the composite endpoint analysis on the date of drug discontinuation. The primary analysis will be repeated using this censoring rule for the mITT population.

In the primary analysis, the date of first ECG indicative of a silent MI will be taken as the date for that silent MI. The following sensitivity analyses regarding this definition will be carried out both on the ITT and mITT populations:

1. Date of silent MI = Date of last normal ECG + 1; and
2. Date of silent MI = Mid-point between date of last normal ECG and date of first indicative ECG.

In the primary analysis, deaths with undetermined cause and without a preceding primary endpoint event constituent will be regarded as CV deaths. A sensitivity analysis where patients are censored for these cases will be carried out both on the ITT and the mITT populations.

Since the primary efficacy endpoint is a composite of five cardiovascular events, recurrence of such events within each patient is possible. For this reason, a supportive analysis using a Cox proportional-hazard with the counting-process formulation of Andersen and Gill (Andersen and Gill, 1982) will be carried out to model the recurrent cardiovascular events. Since death is a terminating event, the modified Wei-Lin-Weissfeld (WLW) method (Wei, Lin, and Weissfeld, 1989) for analysis of recurrent events in presence of death proposed by Li and Lagakos (Li and Lagakos, 1997) will also be carried out as a supportive analysis. Both analyses will be carried out for the ITT and mITT populations.

As an exploratory and supportive analysis, a stratified Cox proportional hazards model will be constructed for the primary endpoint to evaluate the treatment effect adjusting for important baseline covariates. Stratification variables will include CV risk category at baseline, use of ezetimibe at baseline, and geographical region (Westernized, Eastern European, and Asia Pacific countries). The model will include treatment and any of the following variables that are identified by a stepwise selection procedure:

- Gender;
- Age at baseline (<65 or ≥65 years);
- Race (White and non-White);
- Presence/absence of diabetes at baseline;
- Baseline LDL-C (by tertile);
- Baseline HDL-C (by tertile);
- Baseline non-HDL-C (by tertile);
- Baseline TG (by tertile);
- Baseline hs-CRP (≤3 mg/L and >3 mg/L);
- Baseline Apo B (by tertile);
- Baseline RLP-C (by tertile);
- Hopkins calculated LDL-C at baseline (by tertile);
- Waist/height ratio at baseline; and
- Waist circumference at baseline.

The minimum p-value to enter will be 0.05 and selected variables with $p < 0.10$ will remain in the model. The hazard ratio (HR), 95% confidence interval (CI) and p-value comparing the two treatment groups, and the hazard ratio, 95% CI and p-value for each covariate in the final model will be presented.

4.7.2 Components of Primary Endpoint

The time to first occurrence of each of the five component events of the primary endpoint will be analyzed by the same methods described for the primary endpoint. Kaplan-Meier

estimates, the log-rank test stratified by stratification factors used at randomization, and the Cox proportional hazards model including the stratification factors as specified above for the primary efficacy endpoint, will be summarized by treatment group. Kaplan-Meier curves stratified by each stratification factor will be presented. These analyses will be conducted for the ITT, mITT and PP populations.

Similarly, the rules for determining date of event/date of censoring for the primary efficacy endpoint (Section 4.7.1) will be applied to the components of primary endpoints. For the CV death endpoint, patients who do not die from CV causes will be censored at death from non-CV causes or last visit/phone contact as described in Section 4.7.1.1. For all other events (nonfatal MI [including silent MI], nonfatal stroke, coronary revascularization, and hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing), patients who do not experience the event will be censored at death or last visit/phone contact, consistent with that described in Section 4.7.1.1.

In addition, a recurrent event analysis using Andersen-Gill and Li-Lagakos methods will be carried out for the individual primary event constituents other than CV death.

4.7.3 Analysis of Secondary Efficacy Endpoints

The key secondary hypothesis will be tested as part of the confirmatory process only if the primary analysis is statistically significant. For the analysis of secondary efficacy endpoints, the Type 1 error will be controlled by testing each endpoint sequentially, starting with the key endpoint. Testing will be done at a significance level consistent with that used for the primary endpoint and will cease when a secondary endpoint is found for which treatments do not significantly differ. P-values will be presented for all analyses, but they will be considered descriptive after the first non-significant result is obtained.

Each of the secondary endpoints will be analyzed by the same methods described for the primary efficacy endpoint. Kaplan-Meier estimates, the log-rank test stratified by stratification factors used at randomization, and the Cox proportional hazards model including the stratification factors as specified above for the primary efficacy endpoint, will be summarized by treatment group. Kaplan-Meier curves stratified by each stratification factor will be presented. Similarly, the rules for determining date of event/date of censoring for the primary efficacy endpoint (Section 4.7.1) will be applied to the secondary endpoints. These analyses will be conducted for the ITT population.

4.7.3.1 Key Secondary Efficacy Endpoint

If the primary analysis is statistically significant, then the key secondary efficacy endpoint, which is the time from randomization to the first occurrence of the composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke will be tested first.

4.7.3.2 Other Secondary Efficacy Endpoints

Other secondary efficacy endpoints are the time from randomization to the first occurrence of each of the events described below. If the primary and key secondary endpoints are statistically significant, the remaining secondary endpoints will be tested in the following order:

- Composite of CV death or nonfatal MI (including silent MI);
- Fatal or nonfatal MI (including silent MI);
- Non-elective coronary revascularization represented as the composite of emergent or urgent classifications;
- CV death;
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Fatal or nonfatal stroke;
- Composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke;
- Total mortality.

4.7.4 Analysis of Tertiary Endpoints

All tertiary analyses will be conducted for the ITT population. No multiple testing adjustments will be made. Time-to-event tertiary endpoints will be analyzed by the same methods as described for the primary efficacy endpoint. Kaplan-Meier estimates, the log-rank test stratified by stratification factors used at randomization, and the Cox proportional hazards model as specified for the primary efficacy endpoint, will be summarized by treatment group. Kaplan-Meier curves stratified by each of the stratification factors will be presented. Similarly, the rules for determining date of event/date of censoring for the primary efficacy endpoint (Section 4.7.1) will be applied to the tertiary endpoints. The following are the tertiary time-to-event endpoints:

- Total CV events analysis defined as the time from randomization to occurrence of the first and all recurrent major CV events defined as CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Primary composite endpoint in subset of patients with diabetes mellitus at baseline;
- Primary composite endpoint in the subset of patients with metabolic syndrome at baseline as defined in *A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity* (Alberti

2009); with cut points of parameters as defined in Table 1 of Alberti *et al.* and waist circumference cut points further guided by Table 2 of Alberti *et al.* and specifically set at ≥35 inches (88 cm) for all women and Asian, Hispanic, or Latino men, and ≥40 inches (102 cm) for all other men (see Appendix C in Section 6.3);

- Primary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG of 100-125 mg/dL);
- Key secondary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG 100-125 mg/dL);
- Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalization of ≥24 hours, or cardiac arrest;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or PVD requiring intervention, such as angioplasty, bypass surgery, or aneurism repair;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, PVD requiring intervention, or cardiac arrhythmia requiring hospitalization of ≥24 hours;
- New CHF;
- New CHF as the primary cause of hospitalization;
- Transient ischemic attack (TIA);
- Amputation for PVD;
- Carotid revascularization;
- All coronary revascularizations defined as the composite of emergent, urgent, elective, or salvage;
- Emergent coronary revascularizations;
- Urgent coronary revascularizations;
- Elective coronary revascularizations;
- Salvage coronary revascularizations;
- Cardiac arrhythmias requiring hospitalization of ≥24 hours;

- Cardiac arrest;
- Ischemic stroke;
- Hemorrhagic stroke;
- Fatal or nonfatal stroke in the subset of patients with a history of stroke prior to baseline;
- New onset diabetes, defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period;
- New onset hypertension, defined as blood pressure ≥140 mmHg systolic OR ≥90 mmHg diastolic newly diagnosed during the treatment/follow-up period;
- Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP (hsCRP and log[hsCRP]), hsTnT, and RLP-C (to be estimated from standard lipid panel, RLP-C = TC – HDL-C – LDL-C [Varbo 2014]) (based on ITT estimands):
    - Assessment of the relationship between baseline biomarker values and treatment effects within the primary and key secondary composite endpoints,
    - Assessment of the relationship between post-baseline biomarker values and treatment effects within the primary and key secondary composite endpoints by including post-baseline biomarker values (for example, at 4 months, or at 1 year) as a covariate.

Continuous tertiary endpoints include:

- Change from baseline and percent change from baseline in fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP (hsCRP and log[hsCRP]), hsTnT, and RLP-C (to be estimated from standard lipid panel, RLP-C = TC – HDL-C – LDL-C [Varbo 2014]) (based on ITT estimands);
- Change in body weight;
- Change in waist circumference.

The fasting lipid panel is tested at Screening (Visit 1 or Visit 1.1), Randomization visit (Visit 2; Day 0), Visit 3 (Day 120; ~4 Months) and all other follow-up visits including the last visit. For change from baseline to 1-year Preparative Ultracentrifugation measurements for LDL-C will be analysed, unless this value is missing. As described in Section 4.3.3, if the LDL-C Preparative Ultracentrifugation values is missing, then another LDL-C value will be used, with prioritization of values obtained from LDL-C Direct measurements, followed by LDL-C derived by the Friedewald calculation (only for subjects with TG <400 mg/dL), and finally LDL-C derived using the calculation published by Hopkins University investigators (Martin 2013). In addition, change from baseline to day 120 in LDL-C utilizing Friedewald's and Hopkins methods will be analysed, using the arithmetic mean of LDL-C obtained at Visit 2 (Day 0) and the preceding Visit 1 (or Visit 1.1). If one of these values is missing, the single available LDL-C value will be used. LDL-C according to Hopkins will be calculated at each visit.

The randomization visit will be considered Baseline. If a baseline value is not available from the randomization visit, then the latest screening value will be used.

For measurements of lipids, lipoproteins, and inflammatory markers, the change from baseline and the percent change will be summarized at each visit. Since these parameters are typically not normally distributed, the Wilcoxon rank-sum test will be used for treatment comparisons of the percent change from baseline, and medians and quartiles will be provided for each treatment group. The medians of the differences between the treatment groups and 95% CIs will be estimated with the Hodges-Lehman method. In addition, shift–tables may be generated as appropriate.

As an additional exploratory analysis, the relationship between post-baseline biomarker values and treatment effects with the primary and key secondary composite endpoints will be assessed by adding biomarker values (for example, at 4 month, or at 1 year, etc.) as time-dependent covariates in the Cox proportional hazards model. Diagnostic plots for the proportional hazards assumption will be evaluated.

Weight is measured at the screening visit and at all follow-up visits, including the last visit of the study. Waist circumference will be measured at the randomization visit (Visit 2; Day 0), Visit 5 (Day 720) and the last visit of the study. Descriptive statistics will be presented by visit and treatment group for baseline, post-treatment change from baseline, and the percent change from baseline. Analysis methods for repeated measurements will be used to compare percent change from baseline between treatments.

4.7.5 Exploratory Analysis of Subgroups

Analyses of the effects of patients off study drug and withdrawn from study have on primary endpoint will be performed.

Subgroup analyses of the primary and key secondary endpoints will be performed as described for the primary endpoint. For each subgroup, Kaplan-Meier estimates, the log-rank test stratified by stratification factors used at randomization (except where the subgroup is a stratification factor), and HRs and CIs from the Cox proportional hazards model as specified for the primary efficacy endpoint, will be summarized by treatment group.

The following subgroups will be explored:

Demographic Parameters:

- gender;
- age (<65 years and ≥65 years);
- race (white and non-white, or any other subset with at least 10% of the total number of patients);
- geography (Westernized, Eastern European, and Asia Pacific countries); and

- baseline ezetimibe use (yes/no).

Disease Parameters:

- CV risk category;
- the presence/absence of diabetes at baseline; and
- renal dysfunction (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as follows:

$$eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

Where:

S_{cr} is serum creatinine in mg/dL,
κ is 0.7 for females and 0.9 for males,
α is -0.329 for females and -0.411 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1.

Treatment Parameters:

- statin intensity at baseline (statin type and regimen)

Statin intensity categories as defined in ACC/AHA Cholesterol Guidelines (Stone 2013) and patient's 10-year CV Risk Score (Goff 2013) will be considered.

Baseline Lipid and Lipoprotein Parameters:

- LDL-C (by tertile);
- HDL-C (by tertile, and tertile by gender);
- TG (by tertile, and tertile by gender);
- RLP-C (by tertile);
- TG ≥150 mg/dL and TG <150 mg/dL;
- TG ≥200 mg/dL and TG <200 mg/dL;
- TG ≥ median, TG < median;
- combined highest tertile for TG and lowest tertile for HDL-C;
- gender-specific highest tertile for TG and lowest tertile for HDL-C;

- TG ≥ 200 mg/dL with HDL-C ≤35 mg/dL;
- hs-CRP (≤3 mg/L and >3 mg/L) and by gender;
- hs-CRP (≤2 mg/L and >2 mg/L) and by gender;
- Apo B (by tertile); and
- non-HDL-C (by tertile).

Adjustment for Baseline TG Level: Following a protocol amendment, dated May 2013, only patients with qualifying TG ≥200 mg/dL were enrolled in the study. Prior to this, patients with qualifying TG levels as low as approximately 135 mg/dL were enrolled. In order to account and adjust for the fact the follow-up times may be different depending on the baseline TG level, a Cox PH model as mentioned above but additionally with baseline TG as a covariate will be fitted to the data at each interim. Diagnostic plots for the PH assumption will be evaluated.

The consistency of the treatment effects in subgroups will be assessed for the primary and key secondary efficacy endpoints. For each subgroup variable, a Cox proportional hazards model with terms for treatment, stratification factors (with the exception of those subgroup variables related to the stratification factors, i.e., CV risk category), subgroup, and treatment-by-subgroup interaction will be performed. The main treatment effect will not be tested with this model. P-values for testing the interaction terms <0.15 will be considered significant. Results will be presented in a Forest plot.

All subgroup analyses will be conducted for the ITT, mITT and PP populations.

4.8 Safety Analyses

All safety analysis summaries will be tabulated by treatment received (if different from randomized treatment assignment) and based on the Safety Analysis population. The baseline values for all safety variables are from assessments obtained on Day 0 (the randomization visit). If the value on Day 0 is not available, the nearest prior assessment at Screening will be used as baseline value. No formal statistical comparisons of treatment groups will be made for safety data.

A list of potential biomarker assays (genetic and non-genetic) to be analysed is included in Appendix B.

4.8.1 Adverse Events

AEs are recorded from the time the informed consent is signed until study participation is complete. Adverse events with onset on or after the date of dispensing study drug for each patient will be considered treatment-emergent (TEAEs). This will include any AE with onset prior to initiation of study drug and increased severity after the treatment initiation.

By design of this study, serious AEs (SAEs) that are endpoint events will only be recorded for the endpoint determination and not captured as SAEs. Following adjudication, if the event is determined to not meet the criteria for an event, the event will be evaluated as an SAE.

Adverse events will be coded using the most recent available Medical Dictionary for Regulatory Activities (MedDRA) Version. Coding includes system organ class (SOC) and preferred term (PT). All AEs will be listed by patient and by SOC and PT; these listings will present detailed information concerning adverse events, including the verbatim description, time of onset and resolution, severity, relationship to study drug, action taken, and outcome.

Pre-treatment AEs:

Pre-treatment-emergent AEs will be defined as any AE that started before the patient's randomization. (An AE that was ongoing at the time of randomization and subsequently increased in severity is also considered treatment-emergent.) Pre-treatment AEs will be listed separately from TEAEs.

Treatment-emergent AEs:

For each patient, the following AEs will be defined as TEAEs:

- AEs occurring after randomization;
- AEs occurring within 30 days after the completion or withdrawal from study;
- AEs started prior to randomization but worsened in severity following randomization;
- AEs with partial onset dates if the AE stop date is after randomization and the dates do not definitively place the AE start date before randomization; and
- AEs with completely missing onset dates.

The frequency and percentage of patients with any TEAEs will be summarized. TEAEs will be presented by SOC and PT. At each summary level, a patient will be counted only once for each TEAE he/she experiences within that level, regardless of how many occurrences of that TEAE that patient experienced. The percentage of patients having had at least one TEAE at each level will be calculated.

An overall summary of patients with at least one TEAE, severe TEAE, related TEAE, SAE, related SAE, TEAE leading to discontinuation of study drug, adjudicated as a clinical event, and leading to death will be presented by treatment group. Tabular summaries by SOC and preferred term will include all AEs, severe TEAEs, related TEAEs, serious TEAEs (SAEs), related SAEs, TEAEs leading to permanent study drug discontinuation, TEAEs that were adjudicated as events, and TEAEs leading to death.

For the purpose of analysis, TEAEs with a reported relatedness of related, probably related, or possibly related will be characterized as "Related". AEs assessed as "Not Related" will be classified as not related to study drug. In instances where a patient may have had multiple TEAEs with differing levels of severity or relatedness, the most severe or most related event,

respectively, will be reported for the severity and relatedness tables. For the purpose of analysis, missing AE relationship will be presented as 'related' in tables and missing in listings. In addition, tables that describe the collected data and that include a 'missing' relationship category where appropriate will be presented. Missing AE severity will be presented in a 'missing' category in tables and as missing in listings.

Pre-randomization AEs and TEAEs will be listed separately. In addition, listings will be provided of SAEs and AEs meeting criteria for adjudication (including whether the event was adjudicated as an endpoint or ruled out). Deaths will be presented in a listing that includes the AE leading to death, demographic data, details of study treatment, and relationship of the AE leading to death to the study drug.

4.8.2 Clinical Laboratory Evaluation

Samples for the clinical laboratory procedures will be collected after fasting for at least 10 hours. For the purposes of this study, fasting is defined as nothing by mouth except water (and any essential medications).

The safety parameters are analyzed by a certified clinical laboratory at screening (Visit 1 or Visit 1.1), Randomization visit (Visit 2; Day 0), Visit 3 (Day 120; ~4 Months) and all other follow-up visits including the last visit:

- Hematology with complete blood count (CBC), including red blood cell (RBC) count, hemoglobin (Hgb), hematocrit (Hct), white blood cell (WBC) count, white cell differentials (Neutrophils, Lymphocytes, Monocytes, Eosinophils and Basophils), and platelet count; and
- Biochemistry panel including total protein, albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), total bilirubin, glucose, calcium, electrolytes (sodium, potassium, chloride), blood urea nitrogen (BUN), serum creatinine, uric acid, creatine kinase, and HbA1c.

Clinical laboratory parameters will be summarized using descriptive statistics. Mean and mean change from baseline values will be presented at each study visit. Change from baseline will be calculated as post-baseline measurement minus baseline measurement. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary.

Each laboratory result will be classified as low (L), normal (N), and high (H) at each visit according to the laboratory-supplied normal range. The shift from baseline will be presented for each post-baseline visit and overall post-baseline visits. If multiple measurements for a test parameter are available for a post-baseline patient-visit, the most extreme value will be included in the shift table. For shift from baseline to overall post-baseline visits, values from all visits (including unscheduled measurements) will be included. The chemistry shift table will include fasting lipid parameters. (The continuous lipid values are presented as part of the efficacy analysis.)

All laboratory results will be listed by patient, parameter, and time point.

4.8.3 Adverse Events of Special Interest

Bleeding-related adverse events, glucose control (fasting blood glucose and HbA1c), and indicators of hepatic disorders (e.g., ALT or AST increases >3 × ULN, total bilirubin increases of ≥2 × ULN) will be summarized separately and compared between treatment groups.

4.8.4 Vital Signs and Patient Measurements

Vital signs include systolic and diastolic blood pressures (mmHg), heart rate, respiration rate, and body temperature. Blood pressure should be measured for all patients at screening (Visit 1/ Visit 1.1), Randomization visit (Visit 2; Day 0) and all other follow-up visits including the last visit (end of the study. The end of the study will be at the time of the last patient's last visit of the follow-up period of the study).

Height is measured only at the screening visit (Visit 1). Vital signs (respiration, heart rate, temperature, systolic and diastolic blood pressure), height, and BMI by gender will be summarized descriptively at each scheduled visit. Mean and mean change from baseline values will be presented in a similar manner as for laboratory variables. Change from baseline will be calculated as post-baseline measurement minus baseline measurement. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary. If there is more than one valid measurement for a selected visit after the baseline visit, the average of the values collected will be used.

All vital signs, height, and BMI, will be listed by patient, parameter, and time point.

4.8.5 12-Lead ECG

Twelve-lead ECG parameters including Heart Rate (bpm), PR Interval (msec), QRS Interval (msec), QT Interval (msec), and QTc Interval (msec) are measured, and Overall Interpretation and Silent MI (Yes/No) are summarized for all patients at Screening (Visit 1), Randomization visit (Visit 2; Day 0) and all other follow-up visits including the last visit of the study.

ECG parameters will be summarized using descriptive statistics. Mean and mean change from baseline values will be presented for every scheduled assessment. Change from baseline will be calculated as the post-baseline measurement minus the baseline measurement. If either the baseline or post-baseline value is missing, the observation will not be included in the change from baseline summary. In addition, counts and percentages for ECG overall interpretation (normal, abnormal, clinically significant and not clinically significant) and whether MI was present will be presented for each scheduled assessment.

ECG results will be listed by patient, parameter and time point.

4.8.6 Physical Examination

The physical examination includes assessment of general appearance, skin, and specific head and neck, heart, lung, abdomen, extremities, and neuromuscular systems. A physical examination is performed at Randomization Visit (Visit 2; Day 0) and all other follow-up visits including the last visit of the study.

The results (normal, abnormal, or not done) by body system of the full physical examination at the Randomization visit (Visit 2; Day 0) and follow-up visits will be summarized with descriptive statistics by treatment group and visit. For physical examinations performed at post-randomization time points, the number and percent of patients with no change or any significant changes since the previous examination will be presented by treatment received. In addition, a shift table will be included to summarize the number and percent of patients with changes from Day 0 to each post-randomization visit by body system for each treatment group. The number and percent of patients with normal and abnormal results (clinically significant vs. not clinically significant) for each body system will be presented by treatment group.

All physical examinations will be presented in a data listing.

4.8.7 Childbearing Potential and Pregnancy Tests

A urine pregnancy test will be administered to women of childbearing potential at the screening and randomization visits. The urine pregnancy tests will be performed at the Research Site utilizing marketed test kits, or at a certified clinical laboratory. Childbearing potential and urine pregnancy test results will be included in a data listing.

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6. APPENDICES

6.1 Appendix A: Interim Statistical Analysis Plan (iSAP)

INTERIM STATISTICAL ANALYSIS PLAN (iSAP)

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:
REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

Investigational Product: AMR101 (icosapent ethyl [ethyl-EPA])
Protocol Number: AMR-01-01-0019

Sponsor:
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Final: 8 July 2016
Version Number: Final v 1.0

SIGNATURE PAGE

TRIAL 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: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

We, the undersigned, have reviewed and approved this Interim Statistical Analysis Plan for protocol AMR-01-01-0019.

Signature	Date
[Name / signature redacted] Biostatistician, Data Management Service Cytel, Inc.	[Signed (8 July 2016)]
[Name / signature redacted] President, Executive Management Cytel, Inc.	[Signed (8 July 2016)]
[Name / signature redacted] Senior Director, Biostatistics and Data Management Amarin Pharma Inc.	[Signed (11 July 2016)]
[Name / signature redacted] President of R&D and Chief Scientific Officer, SVP Amarin Pharma Inc.	[Signed (15 July 2016)]
[Name / signature redacted] Principal Investigator	[Signed (19 July 2016)]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse event
CEC	Clinical Endpoint Committee
CP	Conditional power
CV	Cardiovascular
CVD	Cardiovascular disease
DMC	Data Monitoring Committee
GSD	Group-sequential design
HR	Hazard ratios
IA	Interim analyses
iSAP	interim Statistical Analysis Plan
ITT	Intent-to-Treat
K-M	Kaplan-Meier
LDL-C	Low density lipoprotein cholesterol-C
MACE	Major adverse cardiovascular events
MI	Myocardial infarction
PH	Proportional hazards
PP	Predictive power
SAP	Statistical Analysis Plan
TG	Triglycerides

1 INTRODUCTION

This interim Statistical Analysis Plan (iSAP) has been developed based on the Protocol AMR-01-01-0019 (Amendment #2 Final Version 3.0 da ted: 8 July 2016 and the Statistical Analysis Plan (SAP), Final Version 1.0 dated: 8 July 2016). This iSAP describes analysis methods to be used by the independent Data Monitoring Committee (DMC) and the independent statistical team for carrying out unblinded efficacy and safety analysis at the two planned interim analyses (IA) during a group sequential trial. Unblinded data will only be available to the DMC and the independent statistical team supporting the interim analyses. Unblinded information will not be released to the Sponsor before the completion of the study unless extraordinary circumstances arise and, under such circumstances, procedures for maintaining confidentiality will be described in a written agreement with the DMC. The analyses described in this iSAP are only to be used for interim decision making for early stop or continuation of the trial to the planned completion and not to be used for supporting efficacy and safety claims. A separate SAP has been developed that describes the final analysis that would support such claims.

Clinical trial REDUCE-IT (protocol AMR-01-01-0019) is a multi-center, prospective, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the effect of AMR101 (icosapent ethyl [ethyl-EPA], 4 g/day) vs. control in patients at low density lipoprotein-cholesterol (LDL-C) goal while on statin therapy with established cardiovascular disease (CVD) or at high risk for CVD. The primary efficacy endpoint will be evaluated in terms of the time from randomization to first occurrence of the composite major cardiovascular (CV) event that includes:

1. CV death;
2. Nonfatal myocardial infarction (MI), including silent MI;
3. Nonfatal stroke;
4. Coronary revascularization; or
5. Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

In this document, components 1-3 above are referred to as “hard” major adverse cardiovascular events (MACE) components while components 4 and 5 are referred to as “other” MACE components

This is an event driven trial, i.e. targeting a fixed number of major CV events listed above and follows a group sequential design (GSD) with two planned interim analyses at approximately 60% and 80% of the targeted major CV events.

2 TRIAL DESIGN

This is an event driven trial comparing the effect of AMR101 vs. control, in terms of the composite endpoint listed above as the primary efficacy endpoint. The study has been planned to accrue a total of 1612 efficacy endpoint events with two planned interim analyses when approximately 967 (60%) and 1290 (80%) of the events have occurred and been adjudicated. The study includes patients with established CVD (CV Risk Category-1) and patient ≥ 50 years old with diabetes and at least one additional risk factor for CVD but with CVD not established (CV Risk Category-2).

Sample size calculation was based on assumptions of constant hazard, asymmetric recruitment rate over time and without factoring for dropouts. A risk reduction corresponding to a hazard ratio (HR) of 0.85 (AMR101 vs. control) is assumed. 1612 events would be required to detect this HR with approximately 90% power with one-sided alpha-level at 2.5% and with two interim analyses.

The recruitment period is assumed to be approximately 4.2 years with 20% recruitment in the first year, 40% in the second year, 20% in the third year, 19% in the fourth year and the remaining 1% in the last 0.2 years. The expected maximum study duration is estimated at 6.5 years unless the trial is terminated early for efficacy or safety issues. A one-year event rate of 5.2% (hazard = 0.053) in the control arm is also assumed. Under these assumptions the number of patients to be enrolled is N=7990.

2.1 Group Sequential Design Details

The planned interim analyses are based on a GSD with O'Brien-Fleming boundaries generated using the Lan-DeMets (DeMets 1994) alpha-spending function. The use of the spending-function allows for possible deviations from the planned event number at the time of the IA. If the interim analyses are carried out exactly at the planned 60% and 80% milestones, then the resulting one-sided alpha-levels and boundaries based on a Z-test and corresponding HR for each of the two interim analyses and the final analysis are given in Table 1. In case of a deviation, as an example, if the first interim is carried out after 58% of the events and the second at 80% then the one-sided alpha-levels will be 0.0032 and 0.009 respectively with corresponding upper bounds on HRs being 0.837 and 0.881 respectively. For reference, Table 2 and Table 3 provide examples of possible deviation, if the planned 60% interim (Table 1) occurs at 50% (Table 2) or 55% (Table 3) of primary events with completed adjudication.

Table 1: Group Sequential Boundaries according to planned interim analyses, power = 0.897

Look	Information Fraction	No. of Events	Cumulative Alpha (1-sided) Spent	Efficacy Boundary (Z-score)	Efficacy Boundary (HR)	Efficacy Boundary (1-sided P-value)
1	0.60	967	0.0038	-2.669	0.842	0.0038
2	0.80	1290	0.0122	-2.289	0.880	0.0110
3	1.00	1612	0.0250	-2.031	0.904	0.0211

Table 2: Group Sequential Boundaries according to minor deviation from planned interim analyses - example 1, power = 0.898

Look	Information Fraction	No. of Events	Cumulative Alpha (1-sided) Spent	Efficacy Boundary (Z-score)	Efficacy Boundary (HR)	Efficacy Boundary (1-sided P-value)
1	0.50	806	0.0015	-2.963	0.812	0.0015
2	0.80	1290	0.0122	-2.266	0.881	0.0117
3	1.00	1612	0.0250	-2.028	0.904	0.0213

Table 3: Group Sequential Boundaries according to minor deviation from planned interim analyses - example 2, power = 0.897

Look	Information Fraction	No. of Events	Cumulative Alpha (1-sided) Spent	Efficacy Boundary (Z-score)	Efficacy Boundary (HR)	Efficacy Boundary (1-sided P-value)
1	0.55	887	0.0025	-2.805	0.828	0.0025
2	0.80	1290	0.0122	-2.276	0.881	0.0114
3	1.00	1612	0.0250	-2.029	0.904	0.0212

3 ANALYSIS POPULATION

All interim data analysis will be carried out on the Intent-to-Treat (ITT) population except for the safety analysis where all analysis will be based on the safety population. Each of the ITT and safety populations will be as defined in the protocol/SAP.

4 INTERIM DATA ANALYSIS PLAN AT THE 60% AND 80% MILESTONES

Described here is an analysis plan consisting of a sequence of analyses to be performed at each IA time point, in order to aid decision making regarding whether the trial should continue or be terminated. However, the entire sequence of analyses described below in Sections 4.1 through 4.3, and the predictive power (PP) calculation in Section 5, will be performed and presented to the DMC irrespective of the result of the singular formal hypothesis test. Figure 1 in Section 6 provides a graphical display of the hierarchical sequence of analyses and serves as a guide for the DMC in making its recommendation to either continue or stop the trial.

4.1 Safety Analysis

Safety analyses will be carried at the interim analyses based on the safety population.

All adverse events (AEs) will be tabulated by treatment with summary measures. P-values from tests of independence using Fisher's exact test or the Chi-square test will be provided for flagging purpose. No multiplicity adjustment is needed here. The definition of AEs and their classification is defined in the SAP for the final analysis.

Summary measures at each visit and change from baseline will be presented for other safety parameters: electrocardiogram, vital signs including systolic and diastolic blood pressure, hematology and biochemistry clinical laboratory parameters. Summary tables will be accompanied by appropriate plots to best visualize the data.

The safety analyses could result in three possible outcomes as shown in Figure 1.

- The DMC has safety concerns that warrant immediate termination of the trial;
- The DMC has safety concerns that warrant continuing the trial for additional safety follow-up regardless of the efficacy outcomes; or
- The DMC has no safety concerns currently warranting action.

4.2 Efficacy Analysis

In this section we provide details of the analysis methods to be used for the different efficacy analyses at each of the two IA time points.

4.2.1 Formal Test for the Primary Efficacy Endpoint

This is the only formal hypothesis testing that will be carried out as part of the two interim analyses. All other analyses described in this iSAP are either supportive to the primary analysis or for the purpose of informal consistency and robustness check. The formal hypothesis test results will only be used for the purpose of DMC's decision making. The final efficacy analysis is described in Sections 4.5 and 4.7 in the SAP and consists of a hierarchical sequence of formal hypothesis tests with strong alpha control, to be performed in a hierarchical fashion on the secondary endpoints should the primary endpoint demonstrate statistical significance.

The primary efficacy endpoint is the time to first occurrence of any component of the composite of the following adjudicated events

1. CV death;
2. Nonfatal MI (including silent MI; electrocardiograms [ECGs] will be performed annually for the detection of silent MIs);
3. Nonfatal stroke;
4. Coronary revascularization; or
5. Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

In this document, components 1-3 above are referred to as "hard" MACE components while components 4 and 5 are referred to as "other" MACE components.

All suspected events will be adjudicated in a blinded manner by the Clinical Endpoint Committee (CEC) and only events that are confirmed by the CEC will be included in this analysis.

The following are detailed considerations for determining the date of event/date of censoring for the primary analysis:

- Patients who withdraw from the study early and do not experience any of the primary efficacy events prior to withdrawal will be considered censored at the last visit/phone contact before withdrawal.
- Patients who do not experience any of the primary efficacy events prior to the interim cutoff date but are still in the trial will be considered censored at the date of their last visit/phone contact before the interim data cutoff.
- Patients who die with an adjudicated undetermined cause of death and without a preceding endpoint event will be considered to have an adjudicated CV death and this will be included as an event in the primary analysis.
- In view of the 90-day monitoring period for CV events, patients who have a non-CV death within 90 days of last contact without having had an earlier CV event will be censored at the time of death. Patients who have a non-CV death more than 90 days after last contact without having had an earlier CV event will be censored at the date of their last visit/phone contact.
- The primary analysis of silent MI will assume that all silent MIs occurred on the date of the first tracing indicative of a silent MI.

In order to test the hypothesis of superiority of the AMR101 group vs. the control group, an unblinded analysis will consist of fitting Kaplan-Meier (K-M) curves to the time to composite event and using a stratified log-rank test to test for the difference. The one-sided alpha-level corresponding to the IA will be used as the significance level for the log-rank test here. Thus, for example, if the first interim is conducted after 60% of the events then the above test will meet statistical significance if the one-sided stratified log-rank test p-value <0.0038 as reflected in Table 1.

The following randomization stratification factors will be used in the stratified log-rank test:

1. Geographical location (Western, Eastern European and Asia Pacific);
2. CV risk group: Patients with established CVD (CV Risk Category-1) and Patients ≥ 50 years old with diabetes and at least one additional risk factor for CVD but CVD not established (CV Risk Category-2); and,
3. Use of ezetimibe.

All stratified analyses mentioned in this document will be based on the above three variables.

4.2.2 Supportive Analyses for Primary Efficacy Analysis

4.2.2.1 Estimation of Hazard Ratio

In addition to the stratified log-rank test described in Section 4.2.1 and in order to provide an estimate of the treatment effect, we will estimate the corresponding HR (point estimate and confidence interval) between the AMR101 and the control groups for the primary composite event. Since this is not part of a formal hypothesis test, a 95% two-sided confidence interval will be presented. Estimation will be carried out using a stratified Cox proportional hazards (PH) model fitted to the time to composite event, stratified by the factors mentioned in Section 4.2.1, and with treatment as the only covariate. Diagnostic plots for the proportional hazards assumption will be evaluated.

4.2.2.2 Adjustment for Baseline Triglyceride (TG) Level

Following a protocol amendment, dated May 2013, only patients with a qualifying TG level ≥200 mg/dL were enrolled in the study. Prior to this, patients with qualifying TG levels as low as approximately 135 mg/dL were permitted to enroll. In order to account and adjust for the fact the follow-up times may be different depending on the baseline TG level, a Cox PH model as mentioned above but additionally with baseline TG as a covariate will be fitted to the data at each interim. Diagnostic plots for the proportional hazards assumption will be evaluated.

4.2.2.3 Adjustments for Unadjudicated Events

A data cut-off date prior to the IA will be decided on by the sponsors and the DMC. Certain events may remain unadjudicated at this point. Summary measures by treatment group and investigators' classification (primary or otherwise) of these unadjudicated events will be presented to the DMC. Additionally, adjusted survival curves (Cook 2000) and corresponding log-rank test and hazard estimation will be provided.

Cook's methodology (Cook 2000) is based on assuming that the probability that a reported event will be adjudicated as primary event constituent depends only on its investigator-reported classification and is unrelated to treatment, time of event or the subject's prior event history. Under these assumptions, the results of adjudication for all events for which the adjudication is complete are used to estimate the probability of an unadjudicated event to be adjudicated as a primary event constituent. Once these

probabilities are estimated, the data with only confirmed events (as used for the primary efficacy analysis above) will be augmented with the unadjudicated events data while allocating the events according to the estimated probabilities. Then a valid analysis using the K-M estimator, the log-rank statistic, and the Cox PH model can be performed using the augmented data. As an alternative, the estimated probabilities can be used as weights in the generalized K-M estimator, the generalized log-rank test and in the weighted Cox PH model. Technical details are available in (Cook 2000, Cook 2004). The estimates of the survival probabilities and regression parameters are shown to be unbiased in Cook and Kosorok (Cook 2004).

4.2.3 Hazard Ratio for Composite "Hard" MACE and Individual Components of the Composite Primary Endpoint

Hazard ratios for AMR101 vs. control will be estimated separately for the 3-component "hard" MACE composite endpoint as well as for each of the "hard" and the "other" MACE individual components using a stratified Cox PH model with treatment as the only covariate. 95% confidence intervals will be used.

4.2.4 Analysis within Subgroups Defined by Stratification Factors

The Cox PH models to be used for the previous analyses use the stratification variables to fit separate baseline hazard functions for each stratum while assuming that the stratum-wise HRs between the AMR101 and the control groups are the same. Here we consider an analysis where HRs are estimated individually for each marginal stratum level of each of the three stratification factors. Thus we estimate the HRs with 95% confidence intervals for each stratum within:

1. Each of the three geographical regions;
2. For each of the two CV risk groups; and
3. For each of the two groups based on ezetimibe use.

Thus seven HR estimates will be obtained, each from a stratified Cox PH model with treatment as the only covariate. Stratification in this case will be based on the other two stratification variables. For marginal stratum, where the cell-size is small, an unstratified analysis will be carried out as an alternative.

4.2.5 Progress in the Control Group

One of the inclusion criteria of this trial is that the patients be on a stable dose of statin therapy (with or without ezetimibe) prior to randomization and following randomization. In view of the importance of the statin-alone group response being consistent with expectations, two methods of comparing the control group in terms of the primary composite event endpoint and in terms of the composite of CV death, non-fatal MI and nonfatal stroke (hard MACE) with historical data will be employed. The historical data will be obtained from different studies having at least one of the two CV-risk populations (Section 4.2.1) on statin therapy.

First, the annualized (time-averaged) control group event rates will be compared to that from the historical data stratified by CV-risk group. This will be done both in terms of the

composite primary endpoint as well as its five individual components, whenever the required information is available from the historical data. Pooling of historical data from different studies will not be carried out.

Second, cumulative incidence (%) of the primary composite endpoint and that of the composite "hard" MACE endpoint will be plotted for the control group arm alongside the corresponding cumulative incidence (%) plots that are available from peer-reviewed literature on individual historical studies. Variations in primary endpoint definitions will be allowed and pooling of data from individual studies will not be carried out.

At minimum, the following articles (studies) will be considered for the historical data:

1. Intensive Blood Glucose and Vascular Outcomes in Patients with Type 2 Diabetes, the ADVANCE collaborative group (Patel 2008)
2. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus, The ACCORD study group (Ginsberg 2010)
3. Intensive versus Moderate Lipid Lowering with Statins after Acute Coronary Syndromes (Cannon 2004)
4. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events (Bhatt 2006)
5. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial (Colhoun 2004)
6. Impact of Triglyceride Levels Beyond Low-Density Lipoprotein Cholesterol After Acute Coronary Syndrome in the PROVE IT-TIMI 22 Trial (M. Miller et al. [2008])
7. Angiotensin-Converting–Enzyme Inhibition in Stable Coronary Artery Disease, The PEACE trial investigators (Braunwald 2004)
8. High-Dose Atorvastatin vs. Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction, The IDEAL Study: A Randomized Controlled Trial (Pedersen 2005)

Other studies completed before the time of the interim analyses may also be included. A detailed explanation for inclusion/exclusion of studies will be provided in the interim data analysis report.

In addition to the above analyses comparing the entire REDUCE-IT control group responses (by CV-risk category and overall) to historical outcomes data, other potential analyses may employ case-matched subsets from the control group in REDUCE-IT for comparison to populations with similar attributes from published historical data.

4.3 Lipid and Lipoprotein Parameters

Descriptive analysis of these parameters will be included as part of the IA and may be used for interim decision-making only at the discretion of the DMC.

These parameters will be summarized by treatment group and visit in terms of the raw data and also expressed as change and percent-change from baseline. Tables will be accompanied by plots where appropriate.

5 THE USE OF CONDITIONAL AND PREDICTIVE POWER

As a means to predict the future of the trial, given the interim data, we consider calculation of conditional power (CP) and predictive power (PP). While the CP provides a frequentist means to this, the PP is based on Bayesian calculations where one starts with a prior belief on the effect of the treatment which is then updated once the data is available. Through these calculations one can study the impact of departures from design assumptions, such as lags in efficacy response, loss to follow-up, or differences in stratum-wise HRs, into predicting the probability of success given the interim data. In this section we describe how PP may be incorporated into the interim decision-making for possibly overruling an early efficacy-stopping decision despite meeting all the necessary efficacy criteria.

Figure 1 shows that stopping at an IA for efficacy may be possible if there is strong and clear evidence in support of the efficacy and safety of AMR101. However, in spite of having such evidence, it may be worthwhile to continue the trial if the results at the final analysis are expected to provide even stronger evidence of efficacy, for example, in terms of one or more of the three individual components of the "hard" MACE composite endpoint meeting statistical significance. This situation could be expected if the predictive power calculated at the interim for an individual hard MACE component is sufficiently high (>90%).

In the remainder of this section we summarize how CP and PP are computed. Additional technical details are provided in the Appendix. In the context of this iSAP, HR for the composite event and that for its five individual components will be used to estimate the effect of AMR101 compared to control. We describe the PP calculation process in terms of the composite event, calculations for the individual components are similar.

The hazard functions for the two arms are assumed to be piece-wise constant, i.e., constant over a small time interval but allowed to change from one time interval to the next. A prior distribution for each of the piece-wise constant hazards are assumed. For this we propose to use the Gamma-process priors (Nieto-Barajas 2002). Priors reflecting different HRs between the two treatment arms will be considered in order to assess the sensitivity of the predictive power to prior assumptions. Other scenarios such as lag in treatment response and different stratum-wise HRs will also be considered.

Once the unblinded interim data is obtained, the posterior (updated prior) distribution of the piece-wise constant hazards will be obtained. A Monte-Carlo simulation will follow where at each run, hazard functions will be sampled for each of the treatment groups using the posterior distributions. These hazard functions will then be used to generate the part of the data that is yet to be observed. The interim data and the generated data will then be considered as a "proxy" for the final data and will be used to test the primary efficacy hypothesis. Using the proxy data if the hypothesis is rejected the decision value will be 1, otherwise 0. This generation of the missing or incomplete data will be carried out several times for each set of sampled hazard functions. The average of the binary decision variable over all these runs is then the Bayesian CP. Averaging the Bayesian CP

over several sets of hazard functions sampled from the posterior is then the Bayesian PP. Details of this computation are given in the Section 9 (Appendix).

At interim analyses, the DMC may conduct/request additional analyses at their discretion, such as conditional power analyses, as estimations of possible power at study completion.

6 DECISIONS FOLLOWING THE INTERIM ANALYSES

At each IA, one of the following recommendations may be given by the DMC:

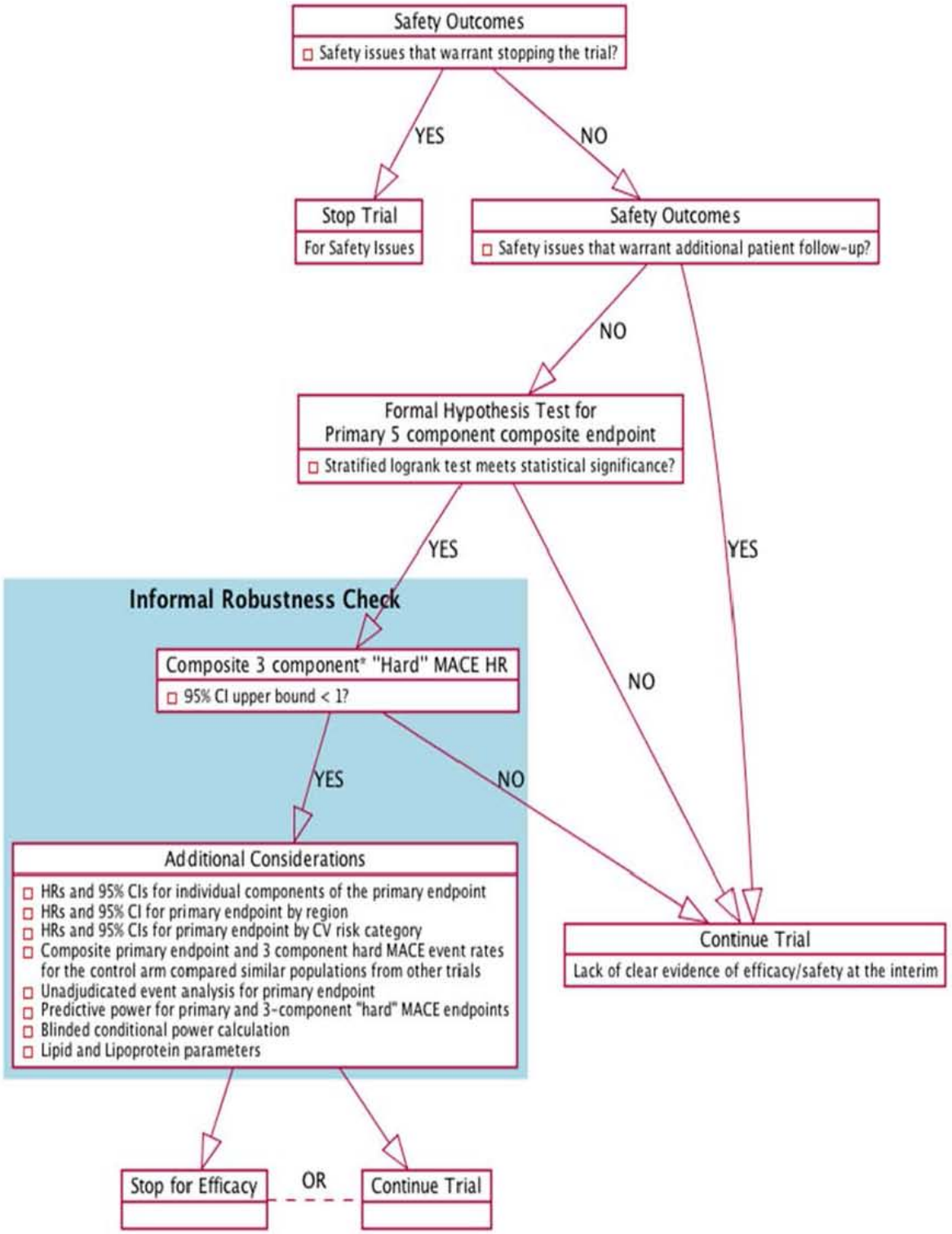
1. Continue trial as planned;
2. Stop for success; or
3. Stop for safety issues.

In Figure 1, we outline the hierarchy of analysis results that is intended to be followed for interim decision-making by the DMC. This sequence of analyses is discussed in Section 4 and Section 5. It consists of the safety analysis (Section 4.1), Efficacy Analysis (Section 4.2) which includes one formal hypothesis test, and computation of Predictive Power (Section 5). Descriptive analysis of Lipid and Lipoprotein parameters (Section 4.3) may additionally be used for interim decision-making at the discretion of the DMC.

6.1 Decision Tree

The following decision tree in Figure 1 is provided to aid the DMC members for decision-making based on the interim analyses. Thus if the results from the safety analysis described in Section 4.1 do not warrant stopping the trial for safety issues or additional follow-up of patients then the interim decision rule is based on interim results of the efficacy analysis described in Section 4.2. If the formal hypothesis test for efficacy meets statistical significance at the corresponding interim alpha-level (Section 2.1) and other supportive analyses depicted in Figure 1 provide strong and consistent efficacy results, then the DMC may recommend early stopping for efficacy.

Figure 1: Flow Chart to Guide Interim Decision-Making



7 STATISTICAL INFERENCE FOLLOWING AN STOP EARLY AT AN INTERIM ANALYSIS

If the decision is taken to terminate the study at one of the two planned interim analyses, the study will enter the closeout phase. During this phase that extends from the interim analysis meeting of DMC until the final database lock, additional adjudicated events may arrive. The final analysis, being based on the totality of the evidence, will include these additional events, resulting in an increase in the information fraction (of the pre-specified 1612 events) from what the information was at the time of the IA. The significance level for the formal hypothesis testing at the final analysis will then be recomputed from the Lan-DeMets error spending function at the new information fraction. Stage-wise adjusted p-values and confidence intervals consistent with group sequential boundaries computed using the Lan-DeMets spending function (Tsiatis 1984, Kim 1987) will be calculated.

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9 APPENDIX

9.1 Predictive Probability Calculation

The PP calculation proposed here involves assuming (nonparametric) priors for the two hazard functions corresponding to the two treatment groups.

Denote the data for the i-th subject as $y_i = (t_i, \delta_i, z_i)$, where t_i is the time of the occurrence of composite event, δ_{i} is the censoring indicator and z_i is the set of stratification and other covariates including the randomized treatment regimen. At the time of the interim analysis, some patients would already have had the primary event of interest and some would have completed the planned follow-up (y_{obs}), while some patients enrolled prior to the interim would not have experienced the event of interest and would not have completed their follow-up (y^1_{miss}). Data for patients to be enrolled after the interim in case the trial continues is denoted as y^2_{miss}. Also let $y_{miss} = (y^1_{miss}, y^2_{miss})$. This notation can be generalized to more than one interim analysis.

The PP will be calculated following the methods outlined in Schmidli, Bretz, and Racine-Poon (2007). The main difference in our approach is that we base our decision-making (R) on the log-rank test where as in Schmidli, Bretz, and Racine-Poon (2007) it is based on the test for proportion of events in each treatment arm.

$$PP = \int CP(\theta \mid y_{obs}) p(\theta \mid (y_{obs}, y^1_{miss})) d\theta,$$

where, $\theta = (h_1, h_2)$ the hazard functions for the two groups, $p(\theta \mid y_{obs}, y^1_{miss})$ is the posterior distribution of θ given the interim data and CP is the conditional power given by

$$CP(\theta \mid y_{\mathrm{obs}}) = \int R(y_{\mathrm{obs}}, y_{\mathrm{miss}}) p(y_{\mathrm{miss}} \mid \theta, y_{obs}) dy_{\mathrm{miss}},$$

where, $R(y)$ defines a decision function based on the log-rank test with $R(y) = 1$ if the result based on the data y is statistically significant and 0 otherwise.

9.2 Simulations to calculate CP and PP

Extensive simulations to characterize the proposed PP calculation method will be taken up prior to the interim analysis.

Within the current setup, we start by assuming priors for the two hazard functions using Gamma processes (Nieto-Barajas [2002]). Using such priors facilitates modeling of the hazard function in terms of piece-wise constant hazards, λ_{k} in the time interval $(\tau_{k-1}, \tau_k]$. Thus the hazard function is given by

$$h(t) = \sum_{k=1}^{K} \lambda_k \, I_{(\tau_{k-1}, \tau_k]}(t).$$

Gamma-priors are imposed on each λ_{k}. Further, the dependency between $\lambda_{\mathrm{k-1}}$ and λ_{k} is modeled using a latent-variable which is conditionally independent of $\{\lambda_k\}$ given the

interim data. The dependency consideration results in a smooth estimate of the hazard function (Nieto-Barajas [2002]).

For the REDUCE-IT trial, Gamma-priors can be constructed using data from other recent similar trials.

Once the posterior distributions are obtained for the piece-wise components for the two hazard functions, the posterior is sampled several times: $\theta(1), \theta(2), \ldots, \theta(M)$. For each θ(k), several samples $y_{miss}(1), y_{miss}(2), \ldots, y_{miss}(N)$ are drawn from the likelihood $p(y_{miss} \mid \theta(k))$. Then the CP is calculated at θ(k) as

$$CP(\theta(k) \mid y_{obs}) = \frac{1}{N}\sum_{j=1}^{N} R\,(y_{obs}, y_{miss}(j)).$$

Next the Predictive Power is calculated as

$$PP = \frac{1}{M}\sum_{i=1}^{M} C\,P(\theta(i) \mid y_{obs}).$$

6.2 Appendix B: Potential Genetic and Non-Genetic Bioassays

Potential bioassays for archived blood samples are as follows:

a. Potential non-genetic bioassays (this list may not be all-inclusive):

   Apo A1, Apo C3, Apo E, NMR lipid profile (particle size and number), oxidized LDL, Lp(a), Lp-PLA_2, serum fatty-acid concentrations, gamma-glutamyltransferase (GGT).

b. Potential genetic bioassays: Genetic testing may potentially be as broad as a GWAS (genome-wide association study) or as specific as a target gene approach. Potential target genes may include but may not be limited to Apo C3, Apo E, Apo A5, CETP, LPL, PCSK9, TNFα, TNFβ, ALOX5, COX2, IL-6, FABPs, haptoglobin 1 vs. 2.

The markers would be analyzed for effects of treatment on change from baseline (for the marker), as well as for relationships between baseline biomarker values and outcome response to treatment (primary and key secondary endpoints).

6.3 Appendix C: Criteria for the Diagnosis of Metabolic Syndrome

The diagnosis of metabolic syndrome requires the presence of three out of the following five specific components using the following criteria (Alberti 2009) with cut points of parameters as defined in Table 1 of Alberti *et. al.* and listed below, and waist circumference cut points further guided by the Table 2 below (adapted from Table 2 within Alberti *et. al.*):

- A waist circumference ≥35 inches (88 cm) for all women, and Asian, Hispanic, or Latino men, and waist circumference ≥40 inches (102 cm) for all other men;
- Elevated TG (TG ≥150 mg/dL);
- Reduced HDL-C (HDL-C <40 mg/dL if male; HDL-C <50 mg/dL if female);
- Elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg, OR an antihypertensive therapy with medical history of hypertension;
- Elevated fasting glucose (fasting glucose ≥100 mg/dL, OR on drug therapy for elevated glucose.

Table 2. Current Recommended Waist Circumference Thresholds for Abdominal Obesity by Organization and Population (adapted from Alberti et. al. Table 2)

Organization	Population (Reference)	Waist Circumference Threshold	
		Men (cm)	Women (cm)
IDF (4)	Europid	≥94	≥80
WHO (7)	Caucasian	≥94 (increased risk)	≥80
		≥102 (still higher risk)	≥88
AHA/NHLBI (ATP III)* (5)	US	≥102	≥88
Health Canada (8,9)	Canada	≥102	≥88
European Cardiovascular Societies (10)	European	≥102	≥88
IDF (4)	Asian (including Japanese)	≥90	≥80
WHO (11)	Asian	≥90	≥80
Japanese Obesity Society	Japanese	≥85	≥90
Cooperative Task Force (13)	China	≥85	≥80
IDF (4)	Middle East, Mediterranean	≥94	≥80
IDF (4)	Sub-Saharan African	≥94	≥80
IDF (4)	Ethnic Central & South American	≥90	≥80

IDF=International Diabetes Federation; WHO=World Health Organization; AHA/NHLBI (ATP III)=American Heart Association/National Heart, Lung, and Blood Institute Adult Treatment Panel III; *Recent AHA/NHLBI guidelines for metabolic syndrome recognize an increased risk for cardiovascular disease and diabetes at waist-circumference thresholds of ≥94 cm in men and ≥80 cm in women and identify these as optional cut points for individuals or populations with increased insulin resistance.

STATISTICAL ANALYSIS PLAN (SAP) ADDENDUM
REDUCE-IT STUDY

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:
REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

Investigational Product: AMR101 (icosapent ethyl [ethyl-EPA])

Protocol Number: AMR-01-01-0019

Sponsor:
Amarin Pharma Inc.
1430 Route 206
Bedminster, New Jersey 07921, USA
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Date: 15 August 2018
Version Number: Final 1.0

SIGNATURE PAGE

TRIAL 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: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

We, the undersigned, have reviewed and approved this SAP Addendum for Protocol AMR-01-01-0019.

Signature	Date
[Name / signature redacted] Executive Director, Biostatistics and Data Management Amarin Pharma Inc.	[Signed (15 August 2018]
[Name / signature redacted] Executive Director, Clinical Development Amarin Pharma Inc.	[Signed (15 August 2018]
[Name / signature redacted] VP, Clinical Research and Development Amarin Pharma Inc.	[Signed (15 August 2018]
[Name / signature redacted] Chief Medical Officer, SVP Amarin Pharma Inc.	[Signed (15 August 2018]
[Name / signature redacted] President of R&D and Chief Scientific Officer, SVP Amarin Pharma Inc.	[Signed (15 August 2018]
[Name / signature redacted] Principal Investigator	[Signed (20 August 2018]

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CEC	Clinical Endpoint Committee
CHF	Congestive Heart Failure
CI	Confidence Interval
CSR	Clinical Study Report
CV	Cardiovascular
DILI	Drug-Induced Liver Injury
ECG	Electrocardiogram
EPA	Eicosapentaenoic Acid
FDA	Food and Drug Administration
HbA1c	Hemoglobin A1c
HDL-C	High-Density Lipoprotein Cholesterol
HLGT	High Level Group Term
HLT	High Level Term
HMG CoA	β-hydroxy β-methylglutaryl coenzyme A
HR	Hazard Ratio
hsCRP	High-Sensitivity C-Reactive Protein
ITT	Intent-to-Treat
KM	Kaplan-Meier
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
PAD	Peripheral Artery Disease
PCS	Potentially Clinically Significant
PLAA	Pre-specified List of Additional Analyses
PT	Preferred Term
SAP	Statistical Analysis Plan
SOC	System Organ Class
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TG	Triglycerides

2. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) Addendum is to describe and document additional pre-specified statistical analyses and specifications beyond those that were pre-specified in the approved SAP version dated 08 July 2016, which will be included in the final analysis and reporting of clinical data collected during the conduct of Protocol AMR-01-01-0019. As discussed and agreed with the Food and Drug Administration (FDA) in relation to a pre-sNDA meeting on 07 March 2018, this SAP Addendum has been developed and will be finalized and submitted to the AMR101 investigational new drug application prior to database lock and unblinding. Importantly, the additional efficacy endpoints and analyses outlined below in this SAP Addendum are exploratory in nature and will not be included in the formal SAP testing scheme. Results from the exploratory analyses described herein will be included in the AMR-01-01-0019 clinical study report (CSR). Analyses associated with a separate document, entitled "pre-specified list of additional analyses (PLAA)", that will be approved by the sponsor prior to database lock and unblinding but that may or may not be performed and the results of which may or may not appear in the CSR.

For each section below, the relevant section of the SAP will be identified.

3. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

This section relates to Section 4.6.3 of version 1 of the SAP dated 08 July 2016.

For the statin-related analyses, the following medications will be classified as statins:

Monotherapies:

C10AA β-hydroxy β-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors

- C10AA01 simvastatin
- C10AA02 lovastatin
- C10AA03 pravastatin
- C10AA04 fluvastatin
- C10AA05 atorvastatin
- C10AA06 cerivastatin
- C10AA07 rosuvastatin
- C10AA08 pitavastatin

Combinations

C10BA HMG CoA reductase inhibitors in combination with other lipid-modifying agents

- C10BA01 lovastatin and nicotinic acid
- C10BA02 simvastatin and ezetimibe
- C10BA03 pravastatin and fenofibrate
- C10BA04 simvastatin and fenofibrate
- C10BA05 atorvastatin and ezetimibe
- C10BA06 rosuvastatin and ezetimibe

C10BX HMG CoA reductase inhibitors, other combinations

- C10BX01 simvastatin and acetylsalicylic acid
- C10BX02 pravastatin and acetylsalicylic acid
- C10BX03 atorvastatin and amlodipine
- C10BX04 simvastatin, acetylsalicylic acid, and ramipril
- C10BX05 rosuvastatin and acetylsalicylic acid
- C10BX06 atorvastatin, acetylsalicylic acid, and ramipril
- C10BX07 rosuvastatin, amlodipine, and lisinopril
- C10BX08 atorvastatin and acetylsalicylic acid
- C10BX09 rosuvastatin and amlodipine
- C10BX10 rosuvastatin and valsartan
- C10BX11 atorvastatin, amlodipine, and perindopril
- C10BX12 atorvastatin, acetylsalicylic acid, and perindopril
- C10BX13 rosuvastatin, perindopril, and indapamide
- C10BX14 rosuvastatin, amlodipine, and perindopril
- C10BX15 atorvastatin and perindopril

4. OTHER SENSITIVITY, SUPPORTIVE AND EXPLORATORY ANALYSES FOR THE PRIMARY EFFICACY ENDPOINT

This section relates to Section 4.7.1.2 of version 1 of the SAP dated 08 July 2016.

Time-to-event analyses as done for the primary analysis will be carried out at 1-year and 2-year landmarks for the intent-to-treat (ITT) Population. For each landmark, the log-rank test, stratified by stratification variables at randomization (cardiovascular [CV] risk category, use of ezetimibe, and geographical region [Westernized, Eastern European, and Asia Pacific countries]), will be used to compare the time-to-event between treatment groups. Similarly, hazard ratios and 95% confidence intervals will be determined using Cox proportional hazards modelling. Patients without events prior to the landmark time will be censored.

For the recurrent CV events analyses based on 5-component Major Adverse Cardiovascular Events (MACE) (CV death, non-fatal myocardial infarction [MI], non-fatal stroke, unstable angina requiring hospitalization, or coronary revascularization), in addition to the Anderson and Gill and the Li and Lagakos methods specified in the SAP dated 08 July 2016, the total CV event counts will be analyzed using a Negative Binomial Model (Rogers 2012, Rogers 2014, and Claggett 2018). It will be implemented using SAS Proc Genmod with a log link function, log exposure time as offset, and treatment group and randomization strata as factors.

As additional sensitivity analysis for the primary composite endpoint will be carried out, namely, an on-treatment analysis which includes primary event onset up to 0 and 30-days after permanent discontinuation of study drug.

All SAP Addendum efficacy analyses are considered exploratory and are not included in the formal SAP testing scheme.

5. ANALYSIS OF SECONDARY EFFICACY ENDPOINTS

This section relates to Section 4.7.3 of version 1 of the SAP dated 08 July 2016.

As done for the primary analysis, time-to-event analyses will be carried out at 1-year and 2-year landmarks for the key secondary endpoints for the ITT Population.

6. ANALYSIS OF TERTIARY ENDPOINTS

This section relates to Section 4.7.4 of version 1 of the SAP dated 08 July 2016.

The following clinical events that are positively adjudicated by the Clinical Endpoint Committee (CEC) will be analyzed as tertiary endpoints for the ITT Population:

- Composite of total mortality, or new congestive heart failure (CHF)
- Composite of CV death, or new CHF
- Sudden cardiac death
- Peripheral artery disease (PAD)
- Atrial fibrillation, or atrial flutter

These tertiary endpoints will be analysed similarly as for the primary composite endpoint.

In addition, the following will be analysed as tertiary endpoints for the ITT Population:

- Relationship between on-treatment high-sensitivity C-reactive protein (hsCRP) and the primary and key secondary endpoints
- Relationship between on-treatment serum eicosapentaenoic acid (EPA) and the primary and key secondary endpoints

To assess the relationship between on-treatment hsCRP and the primary and key secondary endpoints, subgroup analyses will be carried out as done for the ITT population for patients grouped according to values greater or equal to or less than 2 mg/dL at baseline and at 2 years.

To assess the relationship between on-treatment serum EPA and the primary and key secondary endpoints, Kaplan-Meier (KM) curves will be produced for AMR101 treated patients grouped into tertiles based on their values at year 1 and will be compared with the placebo-treated patients.

7. EXPLORATORY ANALYSIS OF SUBGROUPS

This section relates to Section 4.7.5 of version 1 of the SAP dated 08 July 2016.

The following will be added to the subgroup analyses:

- Baseline Hemoglobin A1c (HbA1c) value (<6.5%, ≥6.5%)

- Baseline PAD
- Baseline triglyceride (TG) levels ≥ 150 mg/dL with high-density lipoprotein cholesterol (HDL-C) levels ≤ 40 mg/dL for males and ≤ 50 mg/dL for females

Subgroup analyses of the primary and key secondary endpoints will be performed as described for the primary endpoint. For each subgroup, Kaplan-Meier estimates, the log-rank test stratified by stratification factors used at randomization (except where the subgroup is a stratification factor), and hazard ratios (HRs) and confidence intervals (CIs) from the Cox proportional hazards model as specified for the primary efficacy endpoint, will be summarized by treatment group.

8. ADVERSE EVENTS

This section relates to Section 4.8.1 of version 1 of the SAP dated 08 July 2016.

In addition to the treatment-emergent adverse events analyses specified in the SAP dated 08 Jul 2016, the following analyses will be performed:

- All adverse events (AEs) (serious and non-serious)
    - Treatment-emergent adverse event (TEAE) by high level group term (HLGT)
    - TEAE by high level term (HLT)
    - TEAE by system organ class (SOC), HLGT, HLT, and preferred term (PT) (4-level table)
- All serious AEs (SAEs)
    - Treatment emergent SAE by HLGT
    - Treatment emergent SAE by HLT
    - Treatment emergent SAE by SOC, HLGT, HLT, and PT (4-level table)

9. CLINICAL LABORATORY EVALUATION

This section relates to Section 4.8.2 of version 1 of the SAP dated 08 July 2016.

The criteria for potentially clinically significant (PCS) laboratory values are provided in Table 1 and Table 2 of Appendix A. A treatment-emergent PCS high value at any time will be 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 will be 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. Number (%) of patients with any post-baseline PCS laboratory values will be summarized by treatment group. A listing of patients with PCS laboratory values at any time, i.e., baseline or at any post-baseline visit, will be included.

Drug-Induced Liver Injury (DILI)

Potential DILI cases will be investigated through the following analyses:

- A graph of distribution of peak values of alanine aminotransferase (ALT) versus peak values of total bilirubin (TBL) during the treatment period will be presented, using a logarithmic scale. In the graph, for each patient, the peak TBL times the Upper Limit of Normal (ULN) will be plotted against the peak ALT times the ULN, where the peak TBL and peak ALT may or may not happen on the same day of liver testing. The graph will be divided into 4 quadrants with a vertical line corresponding to 3x ULN for ALT and a horizontal line corresponding to 2x ULN for TBL. The upper right quadrant will be referred to as the potential Hy's Law quadrant, including potentially DILI cases.
- A similar graph will be plotted with respect to aspartate aminotransferase (AST).
- The individual patient profile of liver function tests (ALT, AST, alkaline phosphatase [ALP] and TBL) over time will be provided through a graph for all patients with peak value of ALT >3x ULN and peak value of TBL >2x ULN during the treatment period.
- Number (%) of patients will be provided for the following:
    - ALT or AST >3x ULN
    - ALT or AST >3x ULN and TBL >2x ULN
    - ALT or AST >3x ULN and TBL >2x ULN, and ALP < 2x ULN.

10. VITAL SIGNS AND PATIENT MEASUREMENTS

This section relates to Section 4.8.4 of version 1 of the SAP dated 08 July 2016.

Shift tables will present baseline value categories and post-baseline endpoint value categories as defined in Table 3 of Appendix A. The definitions for potentially clinically significant treatment-emergent values are defined in Table 4 of Appendix A.

Number (%) of patients with any post-baseline PCS vital sign values will be summarized by treatment group. A listing of patients who meet the threshold criteria will be provided.

11. 12-LEAD ELECTROCARDIOGRAMS (ECGS)

This section relates to Section 4.8.5 of version 1 of the SAP dated 08 July 2016.

A treatment-emergent PCS high value at any time will be defined as a change from a value less than or equal to the defined PCS value at baseline to a PCS high value at any post-baseline measurement. A treatment-emergent PCS low value at any time will be defined as a change from a value greater than or equal to the lower PCS value at baseline to a PCS low value at any post-baseline measurement. Table 5 of Appendix A provides the PCS ECG values.

Number (%) of patients with post-baseline PCS ECG values will be presented by treatment group. A listing of subjects with potentially clinically significant changes in ECG values will be included.

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13. APPENDICES

13.1 Appendix A. Potentially Clinically Significant Lab, Vital Signs, and ECG Values

Table 1: Potentially Clinically Significant Chemistry Values

Parameter	PCS Low	PCS High
Albumin	≤3.3 g/dL	≥5.8 g/dL
Alkaline Phosphatase	Not Applicable (NA)	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
ALT	NA	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
AST	NA	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
Bilirubin	NA	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
ALT + Bilirubin	NA	>3x ULN (ALT) + 2 x ULN (Bilirubin)
AST + Bilirubin	NA	>3x ULN (AST) + 2x ULN (Bilirubin)
Calcium	≤7 mg/dL	≥11 mg/dL; ≥12 mg/dL
Chloride	<70 mmol/L	>120mmol/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)	>1x ULN to 5x ULN >5x ULN to 10x ULN >10x ULN
Glucose (fasting)	≤36 mg/dL; ≤70 mg/dL	≥126 mg/dL; ≥130 mg/dL
Potassium (K)	≤3.0 mEq/L	≥5.5 mEq/L
Sodium (Na)	≤130 mEq/L	≥150 mEq/L

Table 1: Potentially Clinically Significant Chemistry Values (continued)

Parameter	PCS Low	PCS High
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)

Table 2: Potentially Clinically Significant Hematology Values

Parameter	PCS Low	PCS High
Red Blood Cell (RBC)	<3.5 x 10^6/uL (Female) <3.8 x 10^6/uL (Male)	>5.5 x 10^6/uL (Female) >6.0 x 10^6/uL (Male)
Hemoglobin (Hgb)	<10.0 g/dL (Female) <10.0 g/dL (Male)	>16.5 g/dL(Female) >18.0 g/dL (Male)
Hematocrit (Hct)	<37% (Female) <42% (Male)	>42% (Female) >50% (Male)
White Blood Cells (WBC)	<1.5 x 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 x 10^3/uL	>500 x 10^3/uL

Table 3: Vital Signs Value Categories

Vital Sign	Low	Normal	High
Systolic Blood Pressure	≤90 mmHg	>90 mmHg to <160mmHg	≥160 mmHg
Diastolic Blood Pressure	≤50 mmHg	>50 mmHg to <100mmHg	≥100 mmHg
Pulse	≤50 beats/min	>50 beats/min to <90 beat/min	≥90 beats/min

Table 4: Potentially Clinically Significant Vital Signs Value Definitions

Vital Sign	PCS Low	PCS High
Systolic Blood Pressure	≤90 mmHg AND decrease of ≥20 mmHg; ≤90 mmHg; decrease of ≥20 mmHg	≥160 mmHg AND increase of ≥20 mmHg; ≥160 mmHg; increase of ≥20 mmHg
Diastolic Blood Pressure	≤50 mmHg AND decrease of >10 mmHg; ≤50 mmHg; decrease of >10 mmHg	≥100 mmHg AND increase of >10 mmHg; ≥100 mmHg; increase of >10 mmHg
Pulse	≤50 beats/min AND decrease of ≥15 beats/min; ≤50 beats/min; decrease of ≥15 beats/min	≥90 beats/min AND increase of ≥15 beats/min; ≥90 beats/min; increase of ≥15 beats/min

Table 5: Potentially Clinically Significant ECG Value Definitions

ECG Parameter	PCS Low	PCS High
PR Interval	<120 msec	>120 msec and increase >20 msec from baseline
QRS Interval	NA	>110 msec
QTc	NA	>500 msec

PRE-SPECIFIED LIST OF ADDITIONAL ANALYSES
REDUCE-IT STUDY

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:
REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

Investigational Product: AMR101 (icosapent ethyl [ethyl-EPA])
Protocol Number: AMR-01-01-0019

Sponsor:
Amarin Pharma Inc.
1430 Route 206
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Date: 15 August 2018
Version Number: Final 1.0

SIGNATURE PAGE

TRIAL 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: REDUCE-IT (Reduction of Cardiovascular Events with EPA – Intervention Trial)

We, the undersigned, have reviewed and approved this pre-specified list of additional exploratory analyses for Protocol AMR-01-01-0019.

Signature	Date
[Name / signature redacted] Executive Director, Biostatistics and Data Management Amarin Pharma Inc.	[Signed (15 August 2018)]
[Name / signature redacted] Executive Director, Clinical Development Amarin Pharma Inc.	[Signed (15 August 2018)]
[Name / signature redacted] VP, Clinical Research and Development Amarin Pharma Inc.	[Signed (15 August 2018)]
[Name / signature redacted] Chief Medical Officer, SVP Amarin Pharma Inc.	[Signed (15 August 2018)]
[Name / signature redacted] President of R&D and Chief Scientific Officer, SVP Amarin Pharma Inc.	[Signed (15 August 2018)]
[Name / signature redacted] Principal Investigator	[Signed (20 August 2018)]

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Term	Definition
AA	Arachidonic acid
AE	Adverse Event
ALT	Alanine Aminotransferase
Apo A-I	Apolipoprotein A-I
Apo A-1I	Apolipoprotein A-II
Apo A-V	Apolipoprotein A-V
Apo B	Apolipoprotein B
Apo C-III	Apolipoprotein C-III
Apo E	Apolipoprotein E
AUC	Area under the curve
BP	Blood Pressure
CEC	Clinical Endpoint Committee
CHF	Congestive Heart Failure
CV	Cardiovascular
CVD	Cardiovascular Disease
DHA	Docosahexaenoic acid
DPA	Docosapentaenoic acid
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
EPA	Eicosapentaenoic Acid
HDL2	High Density Lipoprotein subfraction HDL2
HDL3	High Density Lipoprotein subfraction HDL3
HDL-P	High Density Lipoprotein Particle Number
hsCRP	High-Sensitivity C-Reactive Protein
hsTNT	High-sensitivity troponin T
ICD	Implantable Cardioverter Defibrillator
IL-6	Interleukin 6
ITT	Intent-to-Treat
LDL-C	Low Density Lipoprotein Cholesterol
LDL-P	Low Density Lipoprotein Particle Number
LDL-TG	Low Density Lipoprotein Trigyceride
Lp(a)	Lipoprotein a
LPL	Lipoprotein Lipase
LpPLA2	Lipoprotein-associated Phospholipase-A2

Abbreviation or Term	Definition
AA	Arachidonic acid
MALE	Major Adverse Limb Event
MI	Myocardial Infarction
NAFLD	Nonalcoholic Fatty Liver Disease
NFS	NAFLD Fibrosis Score
NT-proBNP	N-terminal-pro-brain Natriuretic Peptide
Ox-LDL	Oxidized Low Density Lipoprotein
RLP-C	Remnant Lipoprotein Cholesterol
SAP	Statistical Analysis Plan
SMI	Silent Myocardial Infarction
TG	Triglycerides
ULN	Upper Limit of Normal
US	United States

2. INTRODUCTION

This purpose of this Pre-Specified List of Additional Analyses (PLAA) is to document any additional pre-specified exploratory statistical analyses that may be carried out beyond those that were pre-specified in the approved statistical analysis plan (SAP) version dated 08 July 2016 as well as the SAP Addendum dated 15 August 2018. This PLAA identifies pre-specified analyses that may or may not be performed and the results of which may or may not appear in the CSR depending upon overall results from the trial. This PLAA will be finalized and signed off prior to database lock and unblinding.

3. ADDITIONAL EXPLORATORY EFFICACY ANALYSES

The following list presents additional pre-specified exploratory efficacy analyses that could be of interest to the general clinical and scientific community:

- Non-fatal myocardial infarction (MI) (including both clinical manifestation and silent MI categorizations) – intent-to-treat (ITT) Population
- Evaluation of effect of time-weighted (or area under the curve [AUC]) eicosapentaenoic acid (EPA) data on the primary and key secondary composite endpoints – ITT Population
- Sensitivity analyses on the primary and key secondary composite endpoints by excluding elective coronary artery revascularizations if onset is <3 months post randomization; and also excluding peri-procedural MIs – ITT Population
- Two silent MI (SMI) sensitivity analyses on the primary and key secondary composite endpoints – ITT Population:
  - counting all potential SMIs identified by Clinical Endpoint Committee (CEC) electrocardiogram (ECG) reviewer, whether confirmed at final ECG or not; and,
  - counting only potential SMIs that have at least one confirmatory ECG showing persistence of Q-waves (even if not present at final ECG)
- Non-alcoholic fatty liver disease (NAFLD) analyses using NAFLD Fibrosis Score (NFS), assessing – ITT Population:
  - effect on primary and key secondary composite endpoints by baseline NFS category; and,
  - treatment effect on change from baseline in NFS at 1 and 5 years
- Individual and combined on-treatment goal achievement of triglyceride (TG) ≤ 150 mg/dL and hsCRP ≤ 2 mg/L at 2 years, and end of study – ITT Population
- Additional renal function (eGFR) analyses – ITT Population:
  - primary and key secondary composite endpoints for patients with baseline renal dysfunction [eGFR] ≥60 and <90 mL/min/1.73m^2

  - treatment effect on change from baseline in renal function (eGFR) at 1 and 5 years

- Sensitivity analyses on the primary and key secondary composite endpoints by excluding patients with post-randomization low density lipoprotein cholesterol (LDL-C) values >100 mg/dL; and another for >70 mg/dL – ITT Population

- Analyses of hospitalization data (pooled positively adjudicated unstable angina requiring hospitalization, congestive heart failure [CHF] requiring hospitalization, and cardiac arrhythmia requiring hospitalization) – ITT Population

  - Time from randomization to first hospitalization
  - Recurrent event analysis on hospitalization

- Additional subgroup analyses (United States [US] versus Non-US) on the primary and key secondary composite endpoints; also potentially other endpoints – ITT Population

- Additional subgroup analyses for patients with very high-risk cardiovascular disease (CVD) (defined as recurrent cardiovascular [CV] events or CV events in more than one vascular bed, i.e., polyvascular disease) on the primary and key secondary composite endpoints; also potentially other endpoints – ITT Population

- Sensitivity analyses for apolipoprotein B (apo B) to assess whether subgroup(s) with apo B reductions from baseline beyond certain threshold(s) have corresponding incremental reductions in clinical endpoint events

- Sensitivity analyses for endpoints comprised of myocardial infarctions which exclude peri-procedural MIs (Type 4a)

  - Additional analyses factoring for recency and number of prior MIs

- Sensitivity analyses for stroke, factoring for patients with history of stroke

- Sensitivity analyses for heart failure, factoring for patients with history of heart failure

- Sensitivity analyses for endpoints comprised of coronary revascularizations which exclude early elective revascularizations (e.g., within 30-90 days post-randomization)

- Subgroup analyses of primary and potentially key secondary endpoints among the following cohorts:

  - High risk patients with “the hypertriglyceridemic waist” (obese patients at high CV risk)
  - High risk subgroup defined by baseline high-sensitivity troponin T (hsTNT) level (and potentially by N-terminal-pro-brain Natriuretic Peptide [NT-proBNP] from archived frozen samples)
  - High TG/low LDL-C phenotypes beyond those currently specified in the SAP and SAP Addendum

  - High-risk patients as defined by their atherothrombotic risk score (Bohula 2016)

- Treatment effect on:
  - Peripheral arterial events (e.g., major adverse limb [MALE] events)
  - Hypertension, using blood pressure (BP) as a continuous variable

- Using archived frozen serum biosamples, additional analyses of fatty-acid levels (and ratios) not currently specified in the SAP Addendum, including baseline and on-treatment effects on EPA, docosahexaenoic acid (DHA), docosapentaenoic acid (DPA), arachidonic acid (AA) (and associated ratios) and relationships between fatty-acid levels and cardiovascular outcomes.
  - Relationship between on-treatment fatty-acid levels and
    - baseline fatty-acid levels and
    - study medication compliance

- Using archived frozen biosamples (serum and whole blood); potential analyses of treatment effects on biomarkers and genetic markers and associations with outcomes, including but not limited to the following:
  - Low density lipoprotein particle number (LDL-P)
  - Remnant lipoprotein cholesterol (RLP-C) (measured)
  - Low density lipoprotein triglyceride (LDL-TG)
  - Oxidized low density lipoprotein (Ox-LDL)
  - Galectin-3
  - Lipoprotein a (Lp(a)) at baseline, as a predictor of CVD benefit
  - Lipoprotein-associated phospholipase-A2 (LpPLA2)
  - High density lipoprotein subfraction 2 (HDL2), high density lipoprotein subfraction 3 (HDL3), apolipoprotein A-I (apo A-I), apolipoprotein A-II (apo A-II), high density lipoprotein particle number (HDL-P), apolipoprotein C-III (apo C-III) (and apo C-III in apo-B containing proteins), apolipoprotein A-V (apo A-V), apolipoprotein E (Apo E) subtypes (2, 3, 4), interleukin 6 (IL-6), lipoprotein lipase (LPL)
  - Analyses may include change (and percent change) from baseline, and on-treatment comparisons between treatment groups with testing as predictors of CV risk

- Exploratory analyses of differential treatment effects for potential benefit (from adverse event reports) of:
  - ophthalmologic changes (e.g., incidence of age-related macular degeneration, progression of diabetic retinopathy)

  - cognitive impairment (Schwarz 2018)
  - erectile dysfunction (Shim 2016)
  - ischemic cardiomyopathy (as indicated by hospitalization for CHF, implantable cardioverter defibrillator [ICD] placement etc.)

- Additional genetic bioassays not included in the REDUCE-IT SAP including genes which may relate to triglyceride, lipid metabolism, and CVD

- Effects of potential mediators identified *post hoc* on primary/key secondary outcome measures (Inzucchi 2018)

4. ADDITIONAL EXPLORATORY SAFETY ANALYSES

The following list presents additional pre-specified exploratory safety analyses that could be of interest to the general clinical and scientific community:

- Number and percent of patients with the following liver function abnormalities – Safety Population:
  - Alanine aminotransferase (ALT) >/=3x Upper Limit of Normal (ULN) + Total Bilirubin >1.5x ULN
  - ALT >/=5x ULN
  - ALT >/=3x ULN with an appearance of rash or worsening hepatitis symptoms
- Number and percent of patients with treatment-emergent cancer (overall, Lung Cancer, and Prostate Cancer) reported as adverse event (AE); each in 2 populations (ITT and hsCRP ≥2 mg/L) – Safety Population

- Number and percent of patients with treatment-emergent depression and social dysfunction reported as AE – Safety Population

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