METHODS OF REDUCING THE NEED FOR PERIPHERAL ARTERIAL REVASCULARIZATION IN A STATIN-TREATED SUBJECT

PRIORITY CLAIM

[0001] This application claims priority to U.S. Provisional Application No. 62/719,404 filed on August 17, 2018 the entire contents of which is incorporated herein by reference and relied upon.

BACKGROUND

[0002] Cardiovascular disease is one of the leading causes of death in the United States and most European countries. It is estimated that over 70 million people in the United States alone suffer from a cardiovascular disease or disorder including but not limited to high blood pressure, coronary heart disease, dyslipidemia, congestive heart failure and stroke.

[0003] Peripheral arterial disease is associated with cardiovascular morbidity and mortality. In Europe, more than 40 million people have peripheral arterial disease, and more than 200 million people have peripheral arterial disease worldwide. In the United States, at least 6.8 million people have peripheral arterial disease, with more than 13,000 deaths in 2015 and more than 100,000 people discharged a hospital in 2015. A better understanding of the prevalence, health burden, health care costs, and resource utilization associated with peripheral arterial disease is needed.

[0004] Lovaza®, a lipid regulating agent, is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with very high triglyceride levels. Unfortunately, Lovaza® can significantly increase LDL-C and/or non-HDL-C levels in some patients. A need exists for improved treatments for cardiovascular diseases and disorders.

SUMMARY

[0005] In some aspects, the present disclosure provides methods of reducing a need for peripheral arterial revascularization in a statin-treated subject, the method comprising: (a) identifying a statin-treated subject as having a fasting baseline

triglyceride level of at least about 150 mg/dL, and (b) administering to the statin-treated subject a pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester per day.

[0006] In other aspects, the present disclosure provides methods of diagnosing a subject having a need for peripheral arterial revascularization, the method comprising: (a) identifying the subject as being on a statin therapy; (b) measuring a fasting baseline triglyceride level of the subject; and (c) determining the need for peripheral arterial revascularization if the subject has a fasting baseline triglyceride level of at least about 150 mg/dL.

[0007] In yet other aspects, the present disclosure provides methods of treating a subject at risk for peripheral arterial revascularization, comprising administering to the subject a pharmaceutical composition, wherein the subject has been determined to be at risk for peripheral arterial revascularization by measuring a fasting baseline triglyceride level of the subject, and wherein the subject has a fasting baseline triglyceride level of at least about 150 mg/dL.

[0008] In some embodiments, the subject exhibits a reduction in a risk for cardiovascular death, coronary revascularization, unstable angina, stroke, and/or myocardial infarction.

[0009] In some embodiments, the composition is administered to the statin-treated subject in 1 to 4 dosage units per day.

[0010] In some embodiments, the eicosapentaenoic acid ethyl ester comprises at least about 96 wt.% of all omega-3 fatty acids in the pharmaceutical composition.

[0011] In some embodiments, the statin-treated subject has one or more of: a baseline non-HDL-C value of about 200 mg/dL to about 300 mg/dL; a baseline total cholesterol value of about 250 mg/dL to about 300 mg/dL; a baseline VLDL-C value of about 140 mg/dL to about 200 mg/dL; a baseline HDL-C value of about 10 to about 30 mg/dL; and/or a baseline LDL-C value of about 40 to about 100 mg/dL.

[0012] In some embodiments, the subject is on a statin therapy. In some embodiments, the statin-treated subject is on a stable statin therapy. In some embodiments, the statin therapy comprises administering to the statin-treated subject a statin and optionally ezetimibe.

[0013] In some embodiments, the methods further comprise identifying the statin-treated subject as having LDL-control.

[0014] In some embodiments, the statin-treated subject has a fasting baseline triglyceride level of about 200 mg/dL to about 499 mg/dL. In other embodiments, the statin-treated subject has a fasting baseline triglyceride levels of about 500 mg/dL to about 1500 mg/dL.

[0015] In some embodiments, the subject has been identified at least about 5 years from receiving a least one claim for the statin therapy.

[0016] In some embodiments, the pharmaceutical composition comprises about 1 g to about 4 g of eicosapentaenoic acid ethyl ester.

[0017] In some embodiments, the methods further comprise performing a peripheral arterial revascularization.

[0018] These and other embodiments of the present disclosure will be disclosed in further detail herein below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0019] Figure 1 is a schematic of the study design according to an embodiment of the present disclosure.

[0020] Figure 2 is a schematic showing disposition of patients according to an embodiment of the present disclosure.

[0021] Figures 3A and 3B are representative Kaplan-Meier event curves for the cumulative incidence of the primary composite endpoints. Figures 3A and 3B indicate a 25% relative risk reduction for the primary composite endpoint over the course of 5 years.

[0022] Figure 4 is a representative forest plot of individual components of primary endpoints analyzed as time to first event of each individual endpoint and indicates that each component, individually, was reduced.

[0023] Figures 5A and 5B are representative Kaplan-Meier event curves for the cumulative incidence of the key secondary composite endpoints. Figures 5A and 5B indicate that there was a 26% RRR for the key secondary composite endpoint over the course of 5 years.

[0024] Figures 6 and 7 are representative forest plots of primary efficacy outcomes in select prespecified subgroups. Figures 6 and 7 indicate that a subject's baseline triglyceride levels (e.g., ≥150 vs. <150 mg/dL or ≥200 or <200 mg/dL) did not influence the primary endpoint outcomes.

[0025] Figure 8 and 9 are representative forest plots of secondary efficacy outcomes in select prespecified subgroups. Figures 8 and 9 indicate that a subject's baseline triglyceride levels (e.g., ≥150 vs. <150 mg/dL or ≥200 or <200 mg/dL) did not influence the key secondary endpoint outcomes.

[0026] Figures 10A and 10B are representative Kaplan-Meier curves of primary and key secondary endpoints by achieved triglyceride level at 1 year. Figures 10A and 10B indicate that patient's triglyceride levels had no influence on the efficacy of icosapent ethyl as compared with placebo with respect to the primary or key secondary efficacy endpoint outcomes.

[0027] Figure 11 is a representative forest plot of prespecified hierarchical testing of endpoints and indicates that all individual and composite ischemic endpoints were significantly reduced by icosapent ethyl (AMR101).

[0028] Figure 12 is a schematic showing disposition of patients according to an embodiment of the present disclosure.

DETAILED DESCRIPTION

[0029] While the present disclosure is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention, and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any manner. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

[0030] The use of numerical values in the various quantitative values specified in this application, unless expressly indicated otherwise, are stated as approximations as though the minimum and maximum values within the stated ranges were both preceded by the word "about." Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values recited as well as

any ranges that can be formed by such values. Also disclosed herein are any and all ratios (and ranges of any such ratios) that can be formed by dividing a disclosed numeric value into any other disclosed numeric value. Accordingly, the skilled person will appreciate that many such ratios, ranges, and ranges of ratios can be unambiguously derived from the numerical values presented herein and in all instances such ratios, ranges, and ranges of ratios represent various embodiments of the present disclosure.

[0031] List of abbreviations: ANOVA, analysis of variance; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CV, cardiovascular; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome; ICD-9, International Classification of Diseases, Ninth Revision; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; non-HDL-C, non-high density lipoprotein cholesterol; PAD, peripheral artery disease; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; SD, standard deviation; TG, triglycerides; US$, United States dollars.

Compositions

[0032] In one embodiment, a composition of the disclosure is administered to a subject in an amount sufficient to provide a daily dose of eicosapentaenoic acid of about 1 mg to about 10,000 mg, 25 about 5000 mg, about 50 to about 3000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about

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[0033] In one embodiment, a composition for use in methods of the disclosure comprises eicosapentaenoic acid, or a pharmaceutically acceptable ester, derivative, conjugate or salt thereof, or mixtures of any of the foregoing, collectively referred to

herein as "EPA." The term "pharmaceutically acceptable" in the present context means that the substance in question does not produce unacceptable toxicity to the subject or interaction with other components of the composition.

[0034] In another embodiment, the EPA comprises an eicosapentaenoic acid ester. In another embodiment, the EPA comprises a C_1 – C_5 alkyl ester of eicosapentaenoic acid. In another embodiment, the EPA comprises eicosapentaenoic acid ethyl ester, eicosapentaenoic acid methyl ester, eicosapentaenoic acid propyl ester, or eicosapentaenoic acid butyl ester.

[0035] In another embodiment, the EPA is in the form of ethyl-EPA, lithium EPA, mono-, di- or triglyceride EPA or any other ester or salt of EPA, or the free acid form of EPA. The EPA may also be in the form of a 2-substituted derivative or other derivative which slows down its rate of oxidation but does not otherwise change its biological action to any substantial degree.

[0036] In another embodiment, EPA is present in a composition useful in accordance with methods of the disclosure in an amount of about 50 mg to about 5000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about

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[0037] In another embodiment, a composition useful in accordance with the disclosure contains not more than about 10%, not more than about 9%, not more than about 8%, not more than about 7%, not more than about 6%, not more than about 5%, not more than about 4%, not more than about 3%, not more than about 2%, not more than about 1%, or not more than about 0.5%, by weight, docosahexaenoic acid (DHA), if any. In another embodiment, a composition of the disclosure contains substantially no docosahexaenoic acid. In still another embodiment, a composition useful in the present disclosure contains no docosahexaenoic acid and/or derivative thereof.

[0038] In another embodiment, EPA comprises at least 70%, at least 80%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or 100%, by weight, of all fatty acids present in a composition that is useful in methods of the present disclosure.

[0039] In some embodiments, the composition comprises at least 96% by weight of eicosapentaenoic acid ethyl ester and less than about 2% by weight of a preservative. In some embodiments, the preservative is a tocopherol such as all-racemic α-tocopherol.

[0040] In another embodiment, a composition useful in accordance with methods of the disclosure contains less than 10%, less than 9%, less than 8%, less than 7%, less than 6%, less than 5%, less than 4%, less than 3%, less than 2%, less than 1%, less than 0.5% or less than 0.25%, by weight of the total composition or by weight of the total fatty acid content, of any fatty acid other than EPA. Illustrative examples of a "fatty acid other than EPA" include linolenic acid (LA), arachidonic acid (AA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), stearadonic acid (STA), eicosatrienoic acid (ETA) and/or docosapentaenoic acid (DPA). In another embodiment, a composition useful in accordance with methods of the disclosure contains about 0.1% to about 4%, about 0.5% to about 3%, or about 1% to about 2%, by weight, of total fatty acids other than EPA and/or DHA.

[0041] In another embodiment, a composition useful in accordance with the disclosure has one or more of the following features: (a) eicosapentaenoic acid ethyl ester represents at least about 96%, at least about 97%, or at least about 98%, by weight, of all fatty acids present in the composition; (b) the composition contains not more than about 4%, not more than about 3%, or not more than about 2%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; (c) the composition contains not more than about 0.6%, not more than about 0.5%, or not more than about 0.4% of any individual fatty acid other than eicosapentaenoic acid ethyl ester; (d) the composition has a refractive index (20 °C) of about 1 to about 2, about 1.2 to about 1.8 or about 1.4 to about 1.5; (e) the composition has a specific gravity (20 °C) of about 0.8 to about 1.0, about 0.85 to about 0.95 or about 0.9 to about 0.92; (e) the composition contains not more than about 20 ppm, not more than about 15 ppm or not more than about 10 ppm heavy metals, (f) the composition contains not more than about 5 ppm, not more than about 4 ppm, not more than about 3 ppm, or not more than about 2 ppm arsenic, and/or (g) the composition has a peroxide value of not more than about 5 meq/kg, not more than about 4 meq/kg, not more than about 3 meq/kg, or not more than about 2 meq/kg.

[0042] In another embodiment, compositions useful in accordance with methods of the disclosure are orally deliverable. The terms "orally deliverable" or "oral administration" herein include any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration. In one embodiment, the composition is present in a capsule, for example a soft gelatin capsule.

[0043] A composition for use in accordance with the disclosure can be formulated as one or more dosage units. The terms "dose unit" and "dosage unit" herein refer to a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single administration to provide a therapeutic effect. Such dosage units may be administered one to a plurality (i.e. 1 to about 10, 1 to 8, 1 to 6, 1 to 4 or 1 to 2) of times per day, or as many times as needed to elicit a therapeutic response.

[0044] In one embodiment, compositions of the disclosure, upon storage in a closed container maintained at room temperature, refrigerated (e.g. about 5 to about 5 -10 °C) temperature, or frozen for a period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, exhibit at least about 90%, at least about 95%, at least about 97.5%, or at least about 99% of the active ingredient(s) originally present therein.

Therapeutic Methods

[0045] In one embodiment, the disclosure provides a method for treatment and/or prevention of cardiovascular-related disease and disorders. The term "cardiovascular-related disease and disorders" herein refers to any disease or disorder of the heart or blood vessels (i.e. arteries and veins) or any symptom thereof. Non-limiting examples of cardiovascular-related disease and disorders include hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease, vascular disease, stroke, atherosclerosis, arrhythmia, hypertension, myocardial infarction, and other cardiovascular events.

[0046] The term "treatment" in relation a given disease or disorder, includes, but is not limited to, inhibiting the disease or disorder, for example, arresting the development of the disease or disorder; relieving the disease or disorder, for example, causing regression of the disease or disorder; or relieving a condition caused by or

resulting from the disease or disorder, for example, relieving, preventing or treating symptoms of the disease or disorder. The term "prevention" in relation to a given disease or disorder means: preventing the onset of disease development if none had occurred, preventing the disease or disorder from occurring in a subject that may be predisposed to the disorder or disease but has not yet been diagnosed as having the disorder or disease, and/or preventing further disease/disorder development if already present.

[0047] In various embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject on statin therapy. In some embodiments, the method comprises (a) identifying a subject on statin therapy and having a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, wherein said subject has established cardiovascular disease or has a high risk of developing cardiovascular disease; and (b) administering to the subject a pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester per day, wherein the composition contains substantially no docosahexaenoic acid.

[0048] In various embodiments, the present disclosure provides methods of reducing a need for peripheral arterial revascularization in a statin-treated subject. In some embodiments, the method comprises (a) identifying a statin-treated subject as having a fasting baseline triglyceride level of at least about 150 mg/dL; and (b) administering to the statin-treated subject a pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester per day. In some embodiments, the statin-treated subject has a fasting baseline triglyceride level of about 200 mg/dL to about 499 mg/dL. In some embodiments, the statin-treated subject has a fasting baseline triglyceride level of about 500 mg/dL to about 1500 mg/dL. In some embodiments, the statin-treated subject has been further identified as having peripheral arterial disease. In some embodiments, the statin-treated subject has been further identified has having LDL control, were LDL control means there are no clinical adverse changes in LDL levels during therapy. In another embodiment, the subject exhibits a reduction in a risk for cardiovascular death, coronary revascularization, unstable angina, stroke, and/or myocardial infarction.

[0049] In various embodiments, the present disclosure provides a method of diagnosing a subject having a need for peripheral arterial revascularization. In some embodiments, the method comprises (a) identifying the subject as being on a statin therapy; (b) measuring fasting baseline triglyceride level of the subject; and (c) determining the need for peripheral arterial revascularization if the subject has a fasting baseline triglyceride level of at least about 150 mg/dL. In some embodiments, the subject has been identified at least about 5 years from receiving at least one claim for the statin therapy. In some embodiments, the subject has been further identified as having LDL control. In some embodiments, the subject has fasting baseline triglyceride levels of about 200 mg/dL to about 499 mg/dL. In some embodiments, the subject has fasting baseline triglyceride levels of about 500 mg/dL to about 1500 mg/dL.

[0050] In various embodiments, the present disclosure provides a method of treating a subject at risk for peripheral arterial revascularization, comprising administering to the subject a pharmaceutical composition. In some embodiments, the subject has been previously determined to be at risk for peripheral arterial revascularization by measuring a fasting baseline triglyceride level of the subject, wherein the subject is considered at risk for arterial revascularization if the subject has a fasting baseline triglyceride level of at least about 150 mg/dL. In some embodiments, the subject is on a statin therapy. In some embodiments, the pharmaceutical composition comprises about 1 g to about 4 g of eicosapentaenoic acid ethyl ester. In some embodiments, the method of treating further comprises performing a peripheral arterial revascularization on the subject. In some embodiments, the subject has fasting baseline triglyceride levels of about 200 mg/dL to about 499 mg/dL. In some embodiments, the subject has fasting baseline triglyceride levels of about 500 mg/dL to about 1500 mg/dL. In yet another embodiment, the subject exhibits a reduction in a risk for cardiovascular death, coronary revascularization, unstable angina, stroke, and/or myocardial infarction.

[0051] In various embodiments, the present disclosure provides methods of improving blood vessel health (i.e., reducing endothelial dysfunction) in a subject having peripheral arterial disease and/or need for peripheral revascularization, comprising administering to the subject a pharmaceutical composition. In some embodiments, the blood vessel health is determined by measuring artery flow mediated dilation. Arterial flow mediated dilation can be measured by any method known to one of skill in the art.

In some embodiments, administration of the pharmaceutical composition, for example, about 1 g to about 4 g of eicosapentaenoic acid ethyl ester, increases artery flow mediated dilation. In another embodiment, the subject exhibits a reduction in a risk for cardiovascular death, coronary revascularization, unstable angina, stroke, and/or myocardial infarction.

[0052] In some embodiments, the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, for example 135 mg/dL to 500 mg/dL, 150 mg/dL to 500 mg/dL, 200 mg/dL to 499 mg/dL or 200 mg/dL to <500 mg/dL. In some embodiments, the subject or subject group has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of about 135 mg/dL, about 140 mg/dL, about 145 mg/dL, about 150 mg/dL, about 155 mg/dL, about 160 mg/dL, about 165 mg/dL, about 170 mg/dL, about 175 mg/dL, about 180 mg/dL, about 185 mg/dL, about 190 mg/dL, about 195 mg/dL, about 200 mg/dL, about 205 mg/dL, about 210 mg/dL, about 215 mg/dL, about 220 mg/dL, about 225 mg/dL, about 230 mg/dL, about 235 mg/dL, about 240 mg/dL, about 245 mg/dL, about 250 mg/dL, about 255 mg/dL, about 260 mg/dL, about 265 mg/dL, about 270 mg/dL, about 275 mg/dL, about 280 mg/dL, about 285 mg/dL, about 290 mg/dL, about 295 mg/dL, about 300 mg/dL, about 305 mg/dL, about 310 mg/dL, about 315 mg/dL, about 320 mg/dL, about 325 mg/dL, about 330 mg/dL, about 335 mg/dL, about 340 mg/dL, about 345 mg/dL, about 350 mg/dL, about 355 mg/dL, about 360 mg/dL, about 365 mg/dL, about 370 mg/dL, about 375 mg/dL, about 380 mg/dL, about 385 mg/dL, about 390 mg/dL, about 395 mg/dL, about 400 mg/dL, about 405 mg/dL, about 410 mg/dL, about 415 mg/dL, about 420 mg/dL, about 425 mg/dL, about 430 mg/dL, about 435 mg/dL, about 440 mg/dL, about 445 mg/dL, about 450 mg/dL, about 455 mg/dL, about 460 mg/dL, about 465 mg/dL, about 470 mg/dL, about 475 mg/dL, about 480 mg/dL, about 485 mg/dL, about 490 mg/dL, about 495 mg/dL, about 500 mg/dL, about 1000 mg/dL, about 1500 mg/dL, about 2000 mg/dL, about 2500 mg/dL, about 3000 mg/dL, about 3500 mg/dL, about 4000 mg/dL, about 4500 mg/dL, about 5000 mg/dL, or greater than about 5000 mg/dL. In some embodiments, the subject or subject group has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, greater than or equal to about 150 mg/dL, greater than or equal to about 175 mg/dL, greater than or equal to about 250 mg/dL, or greater than equal to about

500 mg/dL, for example about 200 mg/dL to about 500 mg/dL, about 300 mg/dL to about 1800 mg/dL, or about 500 mg/dL to about 1500 mg/dL.

[0053] In some embodiments, the subject or subject group is also on stable therapy with a statin (with or without ezetimibe). In some embodiments, the subject or subject group also has established cardiovascular disease, or is at high risk for establishing cardiovascular disease. In some embodiments, the subject's statin therapy includes administration of one or more statins. For example and without limitation, the subject's statin therapy may include one or more of: atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. In some embodiments, the subject is additionally administered one or more of: amlodipine, ezetimibe, niacin, and sitagliptin. In some embodiments, the subject's statin therapy includes administration of a statin and ezetimibe. In some embodiments, the subject's statin therapy includes administration of a statin without ezetimibe.

[0054] In some embodiments, the subject's statin therapy does not include administration of 200 mg or more per day of niacin and/or fibrates. In some embodiments, the subject is not on concomitant omega-3 fatty acid therapy (e.g., is not being administered or co-administered a prescription and/or over-the-counter composition comprising an omega-3 fatty acid active agent). In some embodiments, the subject is not administered or does not ingest a dietary supplement comprising an omega-3 fatty acid.

[0055] In some embodiments, the subject has established cardiovascular disease ("CV disease" or "CVD"). The status of a subject as having CV disease can be determined by any suitable method known to those skilled in the art. In some embodiments, a subject is identified as having established CV disease by the presence of any one of: documented coronary artery disease, documented cerebrovascular disease, documented carotid disease, documented peripheral arterial disease, or combinations thereof. In some embodiments, a subject is identified as having CV disease if the subject is at least 45 years old and: (a) has one or more stenosis of greater than 50% in two major epicardial coronary arteries; (b) has had a documented prior MI; (c) has been hospitalized for high-risk NSTE ACS with objective evidence of ischemia (e.g., ST-segment deviation and/or biomarker positivity); (d) has a documented prior ischemic stroke; (e) has symptomatic artery disease with at least 50%

carotid arterial stenosis; (f) has asymptomatic carotid artery disease with at least 70% carotid arterial stenosis per angiography or duplex ultrasound; (g) has an ankle-brachial index ("ABI") of less than 0.9 with symptoms of intermittent claudication; and/or (h) has a history of aorto-iliac or peripheral arterial intervention (catheter-based or surgical).

[0056] In some embodiments, the subject or subject group being treated in accordance with methods of the disclosure has a high risk for developing CV disease. For example and without limitation, a subject or subject group has a high risk for developing CV disease if the subject or subject in a subject group is age 50 or older, has diabetes mellitus (Type 1 or Type 2), and at least one of: (a) is a male age 55 or older or a female age 65 or older; (b) is a cigarette smoker or was a cigarette smoker who stopped less than 3 months prior; (c) has hypertension (e.g., a blood pressure of 140 mmHg systolic or higher, or greater than 90 mmHg diastolic); (d) has an HDL-C level of ≤ 40 mg/dL for men or ≤ 50 mg/dL for women; (e) has an hs-CRP level of > 3.0 mg/L; (f) has renal dysfunction (e.g., a creatinine clearance ("CrCL") of greater than 30 mL/min and less than 60 mL/min); (g) has retinopathy (e.g., defined as any of: non-proliferative retinopathy, preproliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease, or history of photocoagulation); (h) has microalbuminuria (e.g., a positive micral or other strip test, an albumin/creatinine ratio of ≥ 2.5 mg/mmol, or an albumin excretion rate on timed collection of ≥ 20 mg/min all on at least two successive occasions); (i) has macroalbuminuria (e.g., albumix or other dip stick evidence of gross proteinuria, an albumin/creatinine ratio of ≥ 25 mg/mmol, or an albumin excretion rate on timed collection of ≥ 200 mg/min all on at least two successive occasions); and/or (j) has an ankle-brachial index of < 0.9 without symptoms of intermittent claudication.

[0057] In some embodiments, the subject's baseline lipid profile is measured or determined prior to administering the pharmaceutical composition to the subject. Lipid profile characteristics can be determined by any suitable method known to those skilled in the art including, for example, by testing a fasting or non-fasting blood sample obtained from the subject using standard blood lipid profile assays. In some embodiments, the subject has one or more of: a baseline non-HDL-C value of about 200 mg/dL to about 300 mg/dL; a baseline total cholesterol value of about 250 mg/dL to about 300 mg/dL; a baseline VLDL-C value of about 140 mg/dL to about 200 mg/dL;

a baseline HDL-C value of about 10 to about 30 mg/dL; and/or a baseline LDL-C value of about 40 to about 100 mg/dL.

[0058] In some embodiments, the cardiovascular event for which risk is reduced is one or more of: cardiovascular death; nonfatal myocardial infarction; nonfatal stroke; coronary revascularization; unstable angina (e.g., unstable angina determined to be caused by myocardial ischemia by, for example, invasive or non-invasive testing, and requiring hospitalization); cardiac arrest; peripheral cardiovascular disease requiring intervention, angioplasty, bypass surgery or aneurysm repair; death; and onset of new congestive heart failure.

[0059] In some embodiments, the subject has peripheral arterial disease. In various embodiments, the subject requires peripheral vascular intervention. The term peripheral vascular intervention in the present disclosure refers to a catheter-based or open surgical procedure designed to improve peripheral arterial or venous blood flow or otherwise modify or revise vascular conduits. Non-limiting examples of peripheral vascular intervention procedures include 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 some embodiments, peripheral vascular intervention procedures are a percutaneous peripheral vascular intervention, which refers to the insertion of a guide wire into a peripheral artery or vein.

[0060] In some embodiments, the subject requires a revascularization procedure, such as peripheral arterial revascularization. The term revascularization in the present disclosure refers to any arterial vascular intervention performed 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 do not constitute a revascularization procedure according to the present disclosure.

[0061] In some embodiments, the subject is administered about 1 g to about 4 g of the pharmaceutical composition per day for about 4 months, about 1 year, about 2 years, about 3 years, about 4 years, about 5 years, or more than about 5 years.

[0062] (a) a reduction in triglyceride levels compared to baseline or control;

[0063] (b) a reduction in Apo B levels compared to baseline or control;

[0064] (c) an increase in HDL-C levels compared to baseline or control;

[0065] (d) no increase or increase in LDL-C levels compared to baseline or control;

[0066] (e) a reduction in LDL-C levels compared to baseline;

[0067] (f) a reduction in non-HDL-C levels compared to baseline or control;

[0068] (g an increase in non-HDL-C levels compared to baseline or control;

[0069] (h) a reduction in VLDL-C levels compared to baseline or control;

[0070] (i) a reduction in total cholesterol levels compared to baseline or control;

[0071] (j) a reduction in high sensitivity C-reactive protein (hsCRP) levels compared to baseline or control;

[0072] (k) a reduction in high sensitivity troponin (hsTnT) levels compared to baseline or control;

[0073] (l) a reduction in a risk of cardiovascular death, coronary revascularization, unstable angina, myocardial infarction, and/or stroke as compared to baseline or control;

[0074] (m) a reduction in a risk of cardiac arrest as compared to baseline or control;

[0075] (n) a reduction in a risk of sudden death as compared to baseline or control;

[0076] (o) a reduction in a first, second, third, fourth, or more cardiovascular event as compared to baseline or placebo control;

[0077] (p) a reduction in total cardiovascular events as compared to baseline or control;

[0078] (q) a reduction in a 3-point composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke as compared to baseline or control;

[0079] (r) a reduction in a 5-point composite endpoint of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, coronary revascularization, or unstable angina as compared to baseline or control;

[0080] (s) an increase in atrial fibrillation and/or flutter as compared to baseline or control;

[0081] (t) an increase in symptoms of atrial fibrillation and/or flutter as compared to baseline or control;

[0082] (u) a reduction of total mortality (i.e., death from any cause) as compared to baseline or control;

[0083] (v) a reduction in a composite of total mortality, non-fatal myocardial infarction, and stroke as compared to baseline or placebo control;

[0084] (w) a reduction in new congestive heart failure (CHF) or new CHF as the primary cause of hospitalization as compared to baseline or control;

[0085] (x) a reduction in transient ischemic attack as compared to baseline or control;

[0086] (y) a reduction in a risk of amputation for peripheral vascular disease (PVD) as compared to baseline or control;

[0087] (z) a reduction in a risk of carotid revascularization as compared to baseline or control;

[0088] (aa) a reduction in cardiac arrhythmias as compared to baseline or control;

[0089] (bb) a reduction in hypertension as compared to baseline or control;

[0090] (cc) a reduction in type 1 or type 2 diabetes as compared to baseline or control; and/or

[0091] (dd) a reduction in body weight and/or weight circumference as compared to baseline or control; and/or

[0092] (ee) a reduction in a risk for peripheral arterial revascularization as compared to baseline or control.

[0093] In some embodiments, the subject exhibits one or more of:

[0094] (a) a reduction in triglyceride levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 55% as compared to baseline or control;

[0095] (b) a reduction in Apo B levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% as compared to baseline or control;

[0096] (c) an increase in HDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% as compared to baseline or control;

[0097] (d) no increase or an increase in LDL-C levels of less than 30%, less than 20%, less than 10%, less than 5% as compared to baseline or control; and/or

[0098] (e) a reduction in LDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 55% as compared to baseline or control.

[0099] (f) a reduction in non-HDL-C levels of at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% as compared to baseline or control;

[0100] (g) an increase in non-HDL-C levels of less than 30%, less than 20%, less than 10%, less than 5% (actual % change or median % change), or no increase in non-HDL-C levels as compared to baseline or control;

[0101] (h) a reduction in VLDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% compared to baseline or control;

[0102] (i) a reduction in total cholesterol levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% as compared to baseline or control; and/or

[0103] (j) a reduction in hsCRP levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least

about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% as compared to baseline or control;

[0104] (k) a reduction in high sensitivity troponin (hsTnT) levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% as compared to baseline or control;

[0105] (l) a reduction in a risk of cardiovascular death, coronary revascularization, unstable angina, myocardial infarction, and/or stroke of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0106] (m) a reduction in a risk of cardiac arrest of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0107] (n) a reduction in a risk of sudden cardiac death and/or sudden death of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0108] (o) a reduction in a first, second, third, fourth, or more cardiovascular event experienced by the subject of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0109] (p) a reduction in total cardiovascular events of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about

30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0110] (q) a reduction in a 3-point composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0111] (r) a reduction in a 5-point composite endpoint of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, coronary revascularization, or unstable angina of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0112] (s) an increase in atrial fibrillation and/or flutter of at least about 1%, at least about 1.5%, at least about 2%, at least about 2.5%, at least about 3%, at least about 3.5%, at least about 4%, at least about 4.5%, at least about 5%, at least about 5.5%, at least about 6%, at least about 6.5%, at least about 7%, at least about 7.5%, at least about 8%, at least about 8.5%, at least about 9%, at least about 9.5%, or at least about 10% as compared to baseline or control;

[0113] (t) an increase in symptoms of atrial fibrillation and/or flutter of at least about 1%, at least about 1.5%, at least about 2%, at least about 2.5%, at least about 3%, at least about 3.5%, at least about 4%, at least about 4.5%, at least about 5%, at least about 5.5%, at least about 6%, at least about 6.5%, at least about 7%, at least about 7.5%, at least about 8%, at least about 8.5%, at least about 9%, at least about 9.5%, or at least about 10% as compared to baseline or control;

[0114] (u) a reduction of total mortality (i.e., death from any cause) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least

about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0115] (v) a reduction in a composite of total mortality, non-fatal myocardial infarction, and stroke of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0116] (w) a reduction in new CHF or new CHF as the primary cause of hospitalization of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0117] (x) a reduction in transient ischemic attack of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0118] (y) a reduction in a risk of amputation for PVD of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0119] (z) a reduction in a risk of carotid revascularization of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%,

at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0120] (aa) a reduction in cardiac arrhythmias of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0121] (bb) a reduction in hypertension of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0122] (cc) a reduction in type 1 or type 2 diabetes of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0123] (dd) a reduction in body weight and/or weight circumference of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control; and/or

[0124] (ee) a reduction in a risk for peripheral arterial revascularization of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control.

[0125] In one embodiment, the subject or subject group being treated has a baseline EPA blood level on a (mol%) basis of less than 2.6, less than 2.5, less than 2.4, less than 2.3, less than 2.2, less than 2.1, less than 2, less than 1.9, less than 1.8, less than 1.7, less than 1.6, less than 1.5, less than 1.4, less than 1.3, less than 1.2, less than 1.1 or less than 1.

[0126] In another embodiment, the subject or subject group being treated has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of about 135 mg/dL to about 500 mg/dL. In some embodiments, the subject or subject group being treated in accordance with methods of the disclosure is on stable therapy with a statin (with or without ezetimibe). As used herein, the phrase "on stable therapy with a statin" means that the subject or subject group has been on the same daily dose of the same statin for at least 28 days and, if applicable, the same daily dose of ezetimibe for at least 28 days. In some embodiments, the subject or subject group on stable statin therapy has an LDL-C level of about 40 mg/dL to about 100 mg/dL.

[0127] In some embodiments, safety laboratory tests of subject blood samples include one or more of: hematology with complete blood count ("CBC"), including RBC, hemoglobin (Hgb), hematocrit (Hct), white cell blood count (WBC), white cell differential, 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 HbA_{1c}.

[0128] In some embodiments, a fasting lipid panel associated with a subject includes TG, TC, LDL-C, HDL-C, non-HDL-C, and VLDL-C. In some embodiments, LDL-C is calculated using the Friedewald equation, or is measured by preparative ultracentrifugation (Beta Quant) if the subject's triglyceride level is greater than 400 mg/dL. In some embodiments, LDL-C is measured by ultracentrifugation (Beta Quant) at randomization and again after about one year after randomization.

[0129] In some embodiments, a biomarker assay associated with blood obtained from a subject includes hs-CRP, Apo B and hsTnT.

[0130] In some embodiments, a medical history associated with a subject includes family history, details regarding all illnesses and allergies including, for example, date(s) of onset, current status of condition(s), and smoking and alcohol use.

[0131] In some embodiments, demographic information associated with a subject includes day, month and year of birth, race, and gender.

[0132] In some embodiments, vital signs associated with a subject include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (e.g., oral body temperature).

[0133] In some embodiments, a physical examination of a subject includes assessments of the subject's general appearance, skin, head, neck, heart, lung, abdomen, extremities, and neuromusculature.

[0134] In some embodiments, the subject's height and weight are measured. In some embodiments, the subject's weight is recorded with the subject wearing indoor clothing, with shoes removed, and with the subject's bladder empty.

[0135] In some embodiments, a waist measurement associated with the subject is measured. In some embodiments, the waist measurement is determined with a tape measure at the top of the subject's hip bone.

[0136] In some embodiments, an electrocardiogram associated with the subject is obtained. In some embodiments, an ECG is obtained every year during the treatment/follow-up portion of the study. In some embodiments, the ECG is a 12-lead ECG. In some embodiments, the ECG is analyzed for detection of silent MI.

[0137] In some embodiments, subjects randomly assigned to the treatment group receive 4 g per day of a composition comprising at least 96% by weight of eicosapentaenoic acid ethyl ester. In some embodiments, the composition is encapsulated in a gelatin capsule. In some embodiments, subjects in this treatment group continue to take 4 g per day of the composition for about 1 year, about 2 years, about 3 years, about 4 years, about 4.75 years, about 5 years, about 6 years, about 7 years, about 8 years, about 9 years, about 10 years, or more than about 10 years. In some embodiments, a median treatment duration is planned to be about 4 years.

[0138] In some embodiments, the present disclosure provides a method of reducing a risk of cardiovascular events in a subject. In some embodiments, the method

comprises administering to the subject a composition comprising at least 96% by weight of eicosapentaenoic acid ethyl ester. In some embodiments, the subject is administered about 1 g to about 4 g of the composition per day.

[0139] In some embodiments, the reduced risk of CV events is indicated or determined by comparing an amount of time (e.g., an average amount of time) associated with a subject or subject group from first dosing to a first CV event selected from the group consisting of: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization (e.g., emergent hospitalization) for unstable angina determined to be caused by myocardial ischemia (e.g., by invasive or non-invasive testing), to an amount of time (e.g., an average amount of time) associated with a placebo or untreated subject or group of subjects from first dosing with a placebo to a first CV event selected from the group consisting of: CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization (e.g., emergent hospitalization) for unstable angina determined to be caused by myocardial ischemia (e.g., by invasive or non-invasive testing), wherein said placebo does not include eicosapentaenoic acid ethyl ester. In some embodiments, the amount of time associated with the subject or group of subjects are compared to the amount of time associated with the placebo or untreated subject or group of subjects are compared using a log-rank test. In some embodiments, the log-rank test includes one or more stratification factors such as CV Risk Category, use of ezetimibe, and/or geographical region.

[0140] In some embodiments, the present disclosure provides a method of reducing risk of CV death in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

[0141] In another embodiment, the present disclosure provides a method of reducing risk of recurrent nonfatal myocardial infarction (including silent MI) in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the patient one or more compositions as disclosed herein.

[0142] In some embodiments, the present disclosure provides a method of reducing risk of nonfatal stroke in a subject on stable statin therapy and having CV

disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

[0143] In some embodiments, the present disclosure provides a method of reducing risk of coronary revascularization in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

[0144] In some embodiments, the present disclosure provides a method of reducing risk of developing unstable angina caused by myocardial ischemia in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

[0145] In another embodiment, any of the methods disclosed herein are used in treatment or prevention of a subject or subjects that consume a traditional Western diet. In one embodiment, the methods of the disclosure include a step of identifying a subject as a Western diet consumer or prudent diet consumer and then treating the subject if the subject is deemed a Western diet consumer. The term "Western diet" herein refers generally to a typical diet consisting of, by percentage of total calories, about 45% to about 50% carbohydrate, about 35% to about 40% fat, and about 10% to about 15% protein. A Western diet may alternately or additionally be characterized by relatively high intakes of red and processed meats, sweets, refined grains, and desserts, for example more than 50%, more than 60% or more or 70% of total calories come from these sources.

[0146] In another embodiment, a composition as described herein is administered to a subject once or twice per day. In another embodiment, 1, 2, 3 or 4 capsules, each containing about 1 g of a composition as described herein, are administered to a subject daily. In another embodiment, 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the morning, for example between about 5 am and about 11 am, and 1 or 2 capsules, each containing about 1 g of a composition as described herein, are administered to the subject in the evening, for example between about 5 pm and about 11 pm.

[0147] In some embodiments, the risk of a cardiovascular event in a subject is reduced compared to a control population. In some embodiments, a plurality of control subjects to a control population, wherein each control subject is on stable statin therapy,

has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, and has established cardiovascular disease or a high risk of developing cardiovascular disease, and wherein the control subjects are not administered the pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester per day.

[0148] In some embodiments, a first time interval beginning at (a) an initial administration of a composition as disclosed herein to the subject to (b) a first cardiovascular event of the subject is greater than or substantially greater than a first control time interval beginning at (a′) initial administration of a placebo to the control subjects to (b′) a first cardiovascular event in the control subjects. In some embodiments, the first cardiovascular event of the subject is a major cardiovascular event selected from the group consisting of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina caused by myocardial ischemia. In some embodiments, the first cardiovascular event of the control subjects is a major cardiovascular event selected from the group consisting of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina caused by myocardial ischemia. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death (from any cause), nonfatal myocardial infarction, or nonfatal stroke. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death from a cardiovascular cause, nonfatal myocardial infarction, coronary revascularization, unstable angina, peripheral cardiovascular disease, or cardiac arrhythmia requiring hospitalization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death from a cardiovascular cause, nonfatal myocardial infarction, and coronary revascularization, unstable angina. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death from a cardiovascular cause and nonfatal myocardial infarction. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is death (from any cause). In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: fatal myocardial infarction and nonfatal myocardial infarction (optionally including silent

MI). In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is coronary revascularization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is hospitalization (e.g. emergent hospitalization) for unstable angina (optionally unstable angina caused by myocardial ischemia). In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any one of: fatal stroke or nonfatal stroke. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any one of: new coronary heart failure, new coronary heart failure leading to hospitalization, transient ischemic attack, amputation for coronary vascular disease, and carotid revascularization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any one of: elective coronary revascularization and emergent coronary revascularization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is an onset of diabetes. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is cardiac arrhythmia requiring hospitalization. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is cardiac arrest.

[0149] In some embodiments, a second time interval beginning at (a) an initial administration of the pharmaceutical composition to the subject to (c) a second cardiovascular event of the subject is greater than or substantially greater than a second control time interval beginning at (a′) initial administration of a placebo to the control subjects to (c′) a second cardiovascular event in the control subjects. In some embodiments, the second cardiovascular event of the subject and the second cardiovascular event of the control subjects is a major cardiovascular event selected from the group consisting of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina caused by myocardial ischemia.

[0150] In some embodiments, the subject has diabetes mellitus and the control subjects each have diabetes mellitus. In some embodiments, the subject has metabolic syndrome and the control subjects each have metabolic syndrome.

[0151] In some embodiments, the subject exhibits one or more of (a) reduced triglyceride levels compared to the control population; (b) reduced Apo B levels compared to the control population; (c) increased HDL-C levels compared to the control population; (d) no increase in LDL-C levels compared to the control population; (e) a reduction in LDL-C levels compared to the control population; (f) a reduction in non-HDL-C levels compared to the control population; (g) a reduction in VLDL levels compared to the control population; (h) a reduction in total cholesterol levels compared to the control population; (i) a reduction in high sensitivity C-reactive protein (hs-CRP) levels compared to the control population; and/or (j) a reduction in high sensitivity troponin (hsTnT) levels compared to the control population.

[0152] In some embodiments, the subject's weight after administration of the composition is less than a baseline weight determined before administration of the composition. In some embodiments, the subject's waist circumference after administration of the composition is less than a baseline waist circumference determined before administration of the composition.

[0153] In methods of the present disclosure in which a time interval is determined or assessed, the time interval may be for example an average, a median, or a mean time interval. For example, in embodiments wherein a first control time interval is associated with a plurality of control subjects, the first control time interval is an average, a median, or a mean of a plurality of first control time intervals associated with each control subject. Similarly, in embodiments wherein a second control time interval is associated with a plurality of control subjects, the second control time interval is an average, a median, or a mean of a plurality of second control time intervals associated with each control subject.

[0154] In some embodiments, the reduced risk of cardiovascular events is expressed as a difference in incident rates between a study group and a control population. In some embodiments, the subjects in the study group experience a first major cardiovascular event after an initial administration of a composition as disclosed herein at a first incidence rate which is less than a second incidence rate, wherein the second incidence rate is associated with the rate of cardiovascular events in the subjects in the control population. In some embodiments, the first major cardiovascular event is any one of: cardiovascular death, nonfatal myocardial infarction, nonfatal

stroke, coronary revascularization, and hospitalization for unstable angina (optionally determined to be caused by myocardial ischemia). In some embodiments, the first and second incidence rates are determined for a time period beginning on the date of the initial administration and ending about 4 months, about 1 year, about 2 years, about 3 years, about 4 years, or about 5 years after the date of initial administration.

[0155] In another embodiment, the disclosure provides use of any composition described herein for treating hypertriglyceridemia in a subject in need thereof, comprising: providing a subject having a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL and administering to the subject a pharmaceutical composition as described herein. In one embodiment, the composition comprises about 1 g to about 4 g of eicosapentaenoic acid ethyl ester, wherein the composition contains substantially no docosahexaenoic acid.

EXAMPLE 1

[0156] Among patients with cardiovascular risk factors who are receiving treatment for secondary or primary prevention, the rates of cardiovascular events remain high. Even in patients receiving appropriate treatment with statins, a substantial residual cardiovascular risk remains. In such patients, an elevated triglyceride level serves as an independent marker for increased ischemic risk, as shown in epidemiological and mendelian randomization studies. In randomized trials, medications that reduce triglycerides, such as extended-release niacin and fibrates, have not reduced the rates of cardiovascular events when administered in addition to appropriate medical therapy, including statins. Further, contemporary trials and recent meta-analyses of omega-3 fatty acid products have not shown benefit in patients receiving statin therapy. Accordingly, the objective of the present study was to determine if and how icosapent ethyl (referenced interchangeably with AMR101 or VASCEPA®) reduced cardiovascular events in patients with elevated triglyceride levels on a statin therapy.

[0157] The following study, also referred to as the REDUCE-IT clinical trial, was a large cardiovascular (CV) outcome trial designed to assess CV risk reduction benefit of AMR101 treatment (commercially known as VASCEPA®) versus placebo on the 5-point primary composite endpoint: CV death, non-fatal stroke, non-fatal myocardial infarction (MI), coronary revascularizations, or unstable angina requiring hospitalization.

[0158] A multi-center, prospective, randomized, double-blind, placebo-controlled, parallel-group study was performed to evaluate the effect of AMR101 (4g per day) on cardiovascular health and mortality in hypertriglyceridemic patients with cardiovascular disease or at high risk for cardiovascular disease. The intended expanded indication of the study was 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.

[0159] The primary objective of this study was, in patients at LDL-C goal while on statin therapy, with established cardiovascular disease (CVD) or at high risk for CVD, and hypertriglyceridemia (e.g., fasting triglycerides(TG) ≥ 200 mg/dL and < 500 mg/dL), to evaluate the effect of AMR101 4 g daily on time from randomization to first occurrence of any component of the composite of the following major CV events: CV death; nonfatal MI; (including silent MI; electrocardiograms (ECGs) were performed annually for the detection of silent MIs); nonfatal stroke; coronary revascularization; and unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

[0160] The key secondary objective of this study was to evaluate the effect of AMR101 4 g daily on the time from randomization to the first occurrence of the composite of following major CV events: CV death, nonfatal MI (including silent MI), and nonfatal stroke.

[0161] Other secondary objectives for this study were to evaluate the effect of therapy on time from randomization to the first occurrence of the following individual or composite endpoints: 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; and total mortality.

[0162] The key tertiary objectives for this study were to evaluate the effect of AMR101 4 g daily from baseline and percent change form baseline in fasting triglycerides and LDL-C. Other tertiary objectives for this study were to evaluate the effect of therapy on the following in addition to supporting efficacy and safety analyses:

- 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 with waist circumference of ≥ 35 inches (88 cm) for all women and Asian, Hispanic, or Latino men, and ≥ 40 inches (102 cm) for all other men;
- Primary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 fasting blood glucose (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 peripheral vascular disease (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 congestive heart failure (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 triglycerides (TG), total cholesterol (TC), low dense lipoprotein cholesterol (LDL-C), high dense lipoprotein cholesterol (HDL-C), non-dense lipoprotein cholesterol (non-HDL-C), very low dense lipoprotein cholesterol

(VLDL-C), apolipoprotein B (apo B), high sensitivity-C reactive protein (hsCRP and log[hsCRP]), high-sensitivity troponin (hsTnT), and remnant like particle cholesterol (RLP-C; were 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; and
  - 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 from baseline and percent change from baseline in fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hsCRP, hsTnT, and RLP-C;
- Change in body weight; and
- Change in waist circumference.

Study Population

[0163] The population for this study were 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 had atherogenic dyslipidemia defined as on treatment for hypercholesterolemia (but at treatment goal for LDL-C, by treatment with a statin) and hypertriglyceridemia. More details regarding the patient population are listed in the inclusion criteria below. The patients needed to provide consent to participate in the study and were willing and able to comply with the protocol and the study procedures.

Study Periods

[0164] This study consisted of the following study periods:

[0165] Screening Period: During the screening period, patients were evaluated for inclusion and exclusion criteria.

[0166] At the first visit to the Research Unit (Visit 1), study procedures were performed for evaluation of patient's eligibility in the study. At this screening visit, patients signed an informed consent form before any study procedure was performed; the informed consent form covered the treatment/follow-up period. Based on the evaluation from Visit 1, the following situations occurred:

- Patients who were eligible for participation based on the study procedures on Visit 1 returned to the Research Unit for Visit 2 (randomization visit) to start the treatment/follow-up period. This case included, for example, patients at Visit 1 who were on a stable dose of a statin, were planning to stay on the same statin and the same dose of the statin, and who did not need to wash out any non-statin lipid-altering medications.
- Patients who were not eligible for participation based on the study procedures on Visit 1 and were 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 were screen failed after Visit 1.
- Patients that were not eligible for participation in the study based on the study procedures on Visit 1 could become eligible in the next 28 days: To become eligible, patients returned 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 were repeated. This case included, for example, patients who were started on a statin at Visit 1, whose statin dose was changed at Visit 1, and/or needed to wash out non-statin lipid-altering medications. The following applied for these patients:
    - Patients with a change in the statin or statin dose on Visit 1 needed 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) could have been optimized or stabilized during this period.
    - Patients starting a washout at Visit 1 had 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 were on a stable dose of a statin, were planning to stay on the same statin at the same dose, and who did 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 became eligible for participation based on the additional study procedures at Visit 1.1 returned to the Research Unit for Visit 2 (randomization visit) to start the treatment/follow-up period.

[0167] At the end of the screening period, patients needed to meet all inclusion and exclusion criteria before they were randomized. Patients who were not eligible for participation after the screening period (based on study procedures at Visit 1 and/or Visit 1.1) could return at a later date for rescreening. These patients needed to re-start with all procedures starting with Visit 1. This included patients who need more time to stabilize one or more conditions or therapies (for example: statin, antidiabetic, antihypertensive, thyroid hormone, HIV-protease inhibitor therapy).

[0168] 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 had a second screening visit (Visit 1.1), eligible patients entered the treatment/follow-up period. During this period, the patients received study drug during the planned visits at the Research Site and took the study drug while away from the Research Site.

[0169] During the visits, study procedures were performed for evaluation of efficacy and safety. A detailed schedule of the procedures is provided below in Table 1.

[0170] Table 1. 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	0	120 ± 10	360 ± 10	720 ± 10	1080 ± 10	1440 ± 10	1800 + 30	2160 ± 10	Last Visit (LV)[15]

		before Day 0[2]								
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: hsCRP, apo B, hsTNT			X			X					X
Fasting blood sample for archiving [12]			X		X	X	X	X	X	X	X

[1] Includes procedures and (fasting) blood samples (for example, hsCRP, 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 were not eligible for participation based on data from Visit 1.
[3] Inclusion/exclusion criteria were re-evaluated for selected study procedures that were 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 were seated for at least 5 minutes before assessments of vital signs.
[6] For women of childbearing potential.
[7] The patients fasted at least 10 hours before arriving at the Research Site, when all fasting blood samples were obtained. After blood samples were obtained, patients were given drug with food.
[8] Review study drug compliance by unused capsule count, discussed with and counseled patients about compliance if needed; final study compliance at last visit.
[9] Safety Laboratories — Complete Blood Count: Included 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 were repeated as deemed necessary by the Investigator.
[10] TG, TC, HDL-C, LDL-C, non-HDL-C, and VLDL-C.
[11] Fasting blood sample were stored for future genetic testing at the discretion of the Sponsor. This sample was optional as local regulations may prohibit genetic samples to be collected or shipped outside the country, or patients may not have consented.
[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 contacted each patient by telephone in-between Visit 2 and Visit 3 and between Visit 3 and Visit 4. After Visit 4 contact was made every 3 months. The purpose of the contact was 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] Office visits continued at 360-day intervals and phone visits at 90-day intervals until study end date was determined.
[15] The last visit (LV) could have occurred within 30 days after the study end date as determined by the DMC; the study end date is tentatively schedule for Day 2160 but the actual date was determined by the DMC may be different.

Study Duration

[0171] Patients were randomized at different times during the enrollment period but all ended the study at approximately the same date (i.e., at the study end date) and, therefore, the duration of follow-up differed based on date of randomization. It was planned that all randomized patients received study medication and were followed-up

until the study end date. It was expected that a minimum of approximately 1612 primary endpoint events were required during the study. 8179 patients were randomized at multiple Research Sites worldwide over a period of approximately 4.2 years. After randomization, patients were treated and followed up to an estimated maximum of 6.5 years. The study end date was determined to be when approximately 1612 primary efficacy events had been adjudicated. Table 2 shows the study milestones from the first patient screened to the last patient visit and subsequent database lock.

[0172] Table 2. Study Milestones

Study Milestones	Date
First Patient Screened	21 November 2011
First Patient Randomized	28 November 2011
Last Patient Randomized	04 August 2016
SAP Finalization	08 July 2016
First DMC Interim Efficacy Review	09 September 2016
Second DMC Interim Efficacy Review	11 August 2017
First Patient Last Visit	01 Mar 2018
Last Patient Last Visit	31 May 2018
Database Lock	06 September 2018

Study Groups

[0173] At Visit 2 (Day 0), eligible study patients were randomly assigned to the following treatment groups:

- Group 1: AMR101 (>96% E-EPA) 4 g daily (four 1000 mg capsules daily)
- Group 2: placebo (four capsules daily)

[0174] The four AMR101 or placebo capsules daily were taken as two capsules in the morning and two capsules in the evening (twice-per-day dosing regimen).

Number of Patients

[0175] This was an event-driven trial and it was expected that a minimum of 1612 primary efficacy endpoint events were required during the study. A total of approximately 8179 patients entered into the study to either receive AMR101 or placebo (approximately 4089 patients per treatment group) in order to observe an estimated 1612 events that made up the primary composite endpoint for efficacy.

Randomization

[0176] On Day 0, eligible patients were randomized to one of the 2 study groups using a computer-generated randomization schema. Randomized treatment assignment to either AMR101 or placebo in a 1:1 ratio was provided using the internet (IWR).

Blinding

[0177] This was 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 were unaware of the randomization code (i.e., they did not know which study participants were receiving the experimental drug and which were receiving the placebo drug). The study medication AMR101 and placebo capsules were similar in size and appearance to maintain blinding.

[0178] 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, were blinded to individual results of the efficacy laboratory measurements (including lipid values). Individual results from the lipid profile could be unblinded in the event of an emergency for a patient.

Stratification

[0179] Participants were assigned to treatment groups stratified by CV risk category, use of ezetimibe and by geographical region (e.g., Westernized, Eastern European, and Asia Pacific countries). There were two CV risk categories:

- CV Risk Category 1: patients with established CVD defined in the inclusion criteria. Patients with diabetes and established CVD were included in this category. These patients are defined as the secondary prevention stratum, primary risk category, and/or secondary prevention cohort.
- CV Risk Category 2: patients with diabetes and at least one additional risk factor for CVD, but no established CVD. These patients are defined as the

primary prevention stratum, secondary risk category, and/or primary prevention cohort.

[0180] Stratification was recorded in the IWR at the time of enrollment. Approximately 70% of randomized patients were in the CV Risk Category 1 and approximately 30% of randomized patients were in the CV Risk Category 2. Enrollment with patients of a CV risk category was stopped when the planned number of patients in that risk category was reached.

Study Population

[0181] Inclusion Criteria. A detailed list of the inclusion criteria for this study is provided in Tables 3-5. Specifically, Table 3 outlines the inclusion criteria for patients in this study whereas Tables 4 and 5 further outline the inclusion criteria based on whether that patient is part of the primary prevention risk category or the secondary prevention risk category of patients, respectively.

[0182] Table 3. Patient Inclusion Criteria for this Study

	Study Inclusion Criteria
1	Men or women ≥45 years of age with established CVD (i.e., Primary Prevention Risk Category; see Table 4) or ≥50 years of age with diabetes in combination with one additional risk factor for CVD (i.e., Secondary Prevention Risk Category; see Table 5).
2	Fasting TG levels ≥150 mg/dL (2.26 mmol/L) and <500 mg/dL (5.64 mmol/L). Due to the variability of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglyceride levels ≥135 mg/dL. Protocol amendment made in May of 2013 changed the lower limit of acceptable triglyceride levels from 150 mg/dL to 200 mg/dL, with no variability allowance.
3	LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to the LDL-C and TG qualifying measurements for randomization.
4	Women who are not pregnant, not breastfeeding, not planning on becoming pregnant, and using an acceptable form of birth control during the study (if of child-bearing potential), unless their sexual partner(s) were surgically sterile or the woman was abstinent. Women of child bearing potential needed a negative urine pregnancy test prior to randomization.
5	Able to provide informed consent and adhere to study schedules.
6	Agree to follow and maintain a physician-recommended diet during the study.

[0183] Stable therapy was 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 had their statin therapy or use of ezetimibe initiated at Visit 1, or had their statin, statin dose and/or ezetimibe dose changed at Visit 1, needed to go through a stabilization period of at least 28 days since initiation/change and had their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1). Statins may have been administered with or without ezetimibe.

[0184] If patients qualified at the first qualification visit (Visit 1) for TG and LDL-C, and met all other inclusion/exclusion criteria, they were randomized at Visit 2. If patients did not qualify at the first qualifying visit (Visit 1), a second re-qualifying visit (Visit 1.1) was allowed. For some patients, because they needed to stabilize medications and/or needed to washout medications, the second re-qualifying visit (Visit 1.1) was needed after the stabilization/washout period.

[0185] Women were not considered to be of childbearing potential if they met one of the following criteria as documented by the investigator: they had a hysterectomy, tubal ligation or bilateral oophorectomy prior to signing the informed consent form; and/or they were post-menopausal, defined as ≥ 1 year since their last menstrual period or have a follicle-stimulating hormone (FSH) level in a menopausal range.

[0186] Patients having established CVD (in CV Risk Category 1) were defined as detailed in Table 4.

[0187] Table 4. Inclusion Criteria for the Primary Prevention Risk Category (i.e., CV Risk Category 1)

Primary Prevention Risk Category (i.e., Secondary Prevention Cohort)	
Defined as men and women ≥45 years of age with one or more of the following:	
1	Documented coronary artery disease (CAD; one or more of the following primary criteria must be satisfied): a. Documented multi vessel CAD (≥50% stenosis in at least two major epicardial coronary arteries – with or without antecedent revascularization). b. Documented prior MI. c. Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome (NSTE-ACS) (with objective evidence of ischemia: ST-segment deviation or biomarker positivity).
2	Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied):

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

[0188] Patients at high risk for CVD (in CV Risk Category 2) were defined as detailed in Table 5.

[0189] Table 5. Inclusion Criteria for the Secondary Prevention Risk Category (i.e., CV Risk Category 2)

Secondary Prevention Risk Category (i.e., Primary Prevention Cohort)	
Defined as having each of the following:	
1	Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication.
2	Men and women ≥50 years of age.
3	One of the following at Visit 1 (additional risk factor for CVD): a. Men ≥55 years of age and Women ≥65 years of age. b. Cigarette smoker or stopped smoking within 3 months before Visit 1. c. Hypertension (blood pressure ≥140 mmHg systolic OR ≥90 mmHg diastolic) or on antihypertensive medication. d. HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women. e. HsCRP >3.00 mg/L (0.3 mg/dL). f. Renal dysfunction: Creatinine clearance (CrCL) >30 and <60 mL/min. g. 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. h. 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. i. ABI <0.9 without symptoms of intermittent claudication (patients with ABI <0.9 with symptoms of intermittent claudication are counted under Secondary Prevention Risk Category).

Patients with diabetes and CVD as defined above are eligible based on the CVD requirements and will be counted under CV Risk Stratum 1. Only patients with diabetes and no documented CVD as defined above needed at least one additional risk factor as listed, and were counted under Primary Prevention Risk Category.

[0190] Exclusion Criteria: Patients meeting the following exclusion criteria enumerated in Table 6 were not eligible for the study.

[0191] Table 6. Patient Exclusion Criteria for this Study

	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	Diagnosis or laboratory evidence of active severe liver disease.
4	Hemoglobin A1c >10.0% (or 86 mmol/mol IFCC units) at screening (Visit 1). If patients failed this criterion (HbA1c >10.0% or 86 mmol/mol IFCC units) at Visit 1, they could have had their antidiabetic therapy optimized and be retested at Visit 1.1.
5	Poorly controlled hypertension: systolic blood pressure (SBP) ≥200 mmHg or diastolic blood pressure (DBP) ≥100 mmHg (despite antihypertensive therapy).
6	Planned coronary intervention or any non-cardiac major surgical procedure.
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 could not 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 was allowed).
9	Intolerance or hypersensitivity to statin therapy.
10	Known hypersensitivity to fish and/or shellfish, or ingredients of the study product or placebo.
11	History of acute or chronic pancreatitis.
12	Malabsorption syndrome and/or chronic diarrhea. (Note: patients who had undergone gastric/intestinal bypass surgery were considered to have malabsorption, hence were excluded; patients who had undergone gastric banding were allowed to enter the trial).
13	Use of non-study drug-related, non-statin, lipid-altering medications, dietary supplements, or foods during the screening period (after Visit 1) and/or plans for use during the treatment/follow-up period including: a. niacin >200 mg/day or fibrates during the screening period (after Visit 1) and/or planned to use during the study; patients who were taking niacin >200 mg/day or fibrates during the last 28 days before Visit 1 needed 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).

	b. any omega-3 fatty acid medications (prescription medicines containing EPA and/or DHA) during the screening period (after Visit 1) and/or planned to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who were taking omega-3 fatty acid medications during the last 28 days before Visit 1 (except patients in The Netherlands), needed 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). However, for patients in the Netherlands only being treated with omega-3 fatty acid medications containing EPA and/or DHA were excluded and no washout was allowed. c. dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils) during the screening period (after Visit 1) and/or planned to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who were 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), needed 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). However, for patients in the Netherlands only being treated with dietary supplements containing omega-3 fatty acids of >300 mg/day EPA and/or DHA were excluded and no washout was allowed. d. bile acid sequestrants during the screening period (after Visit 1) and/or planned to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who were taking bile acid sequestrants within 7 days before Visit 1, needed 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). e. proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors during the screening period (after Visit 1) and/or planned to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients could not have taken a PCSK9 inhibitor within 90 days prior to their screening visit.
14	Other medications (not indicated for lipid alteration): a. 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 were not taking a stable dose of these medications within 28 days before Visit 1, needed 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).

	b. Cyclophosphamide or systemic retinoids during the screening period (unless ≥28 day washout) and/or plans for use during the treatment/follow-up period. To be eligible for participation in the study, patients who were taking these medications within 28 days before Visit 1, needed 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 AIDS (HIV-positive patients without AIDS are allowed).
16	Requirement for peritoneal dialysis or hemodialysis for renal insufficiency or creatinine clearance <30 mL/min (0.50 mL/sec).
17	Unexplained elevated creatine kinase concentration >5 × ULN or 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 inability/unwillingness 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 was on average >2 units of alcohol per day. A unit of alcohol was 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 Procedures

[0192] The Screening Period for this study included two visits, Visit 1 and Visit 1.1.

[0193] Screening Visit (Visit 1): During Visit 1, patients came to the Research Site for and were instructed to fast for at least 10 hours before their visit. If patients qualified for randomization based on the procedures at Visit 1, they needed to be randomized within 42 days after Visit 1. The following procedures were performed at the screening Visit 1:

- Obtained signed informed consent;
- Assigned the patient a patient number;
- Obtained medical, surgical and family history;
- Recorded demographics;
- Obtained height, weight, and body mass index;

- Obtained vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Obtained a 12-lead electrocardiogram;
- Evaluated inclusion/exclusion criteria;
- This included procedures and (fasting) blood samples (for example, hsCRP, calculated creatinine clearance) as needed to determine the CV risk category (See inclusion criteria);
- Obtained fasting blood samples for chemistry and hematology testing;
- Obtained a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C);
- Performed a urine pregnancy test on women of childbearing potential;
- Recorded concomitant medication(s); and
- Instructed patient to fast for at least 10 hours prior to the next visit.

[0194] Screening Visit (Visit 1.1): Patients who qualified for study participation after Visit 1 because they meet all inclusion criterion and none of the exclusion criteria, skipped Visit 1.1 and returned 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 occurred soon after Visit 1. Patients, who did not qualify at Visit 1, returned 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 were repeated. Patients were eligible for randomization after Visit 1.1 if they meet all inclusion criteria and if they no longer failed the exclusion criteria. If patients were evaluated at Visit 1.1 and qualified for randomization based on the repeated procedures at Visit 1.1, they needed to be randomized within 60 days after Visit 1. For some patients, Visit 1.1 was mandatory at least 28 days after Visit 1 in order to check eligibility. These were 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 above for details). Any of these changes at Visit 1 may have affected the qualifying lipid levels and therefore, patients needed to have Visit 1.1 to determine whether they qualified based on lipid level

requirements (TG and LDL-C) determined at Visit 1. Other procedures that caused failure of eligibility at Visit 1 were also repeated at Visit 1.1. The following procedures were performed at the screening Visit 1.1:

- Obtained vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Evaluated inclusion/exclusion criteria; only those evaluations were repeated that deemed the patient not eligible on Visit 1;
- Obtained fasting blood samples for chemistry and hematology testing. Only those samples were obtained that deemed the patient not eligible on Visit 1;
- Obtained 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 included 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 had 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 were evaluated and
- Recorded concomitant medication(s).

[0195] The treatment/follow-up period for this study included Visit 2, Visit 3, and Visits 4-9. Every attempt was made to complete the follow-up visits during the defined window periods.

[0196] Randomization visit (Visit 2; Day 0): Qualified patients returned to the Research Site for Visit 2. The following procedures were performed at Visit 2:

- Performed physical examination;
- Obtained weight;
- Obtained vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Measured waist circumference (one of the factors to diagnose metabolic syndrome);

- Obtained a 12-lead electrocardiogram;
- Evaluated inclusion/exclusion criteria;
- Obtained fasting blood samples for:
    - Chemistry and hematology testing;
    - Lipid profile (baseline);
    - Biomarker assays (baseline);
    - Genetic testing (optional blood sample); and
    - Archived (in countries and at sites approved by IRB/IEC and dependent on country regulations).
- Performed a urine pregnancy test on women of childbearing potential (must be negative for randomization);
- Dispensed study drug and record randomization number;
- Instructed patient on how to take study drug;
- Administered study drug - Note: Study drug was taken orally with food following the collection of all fasting blood samples;
- Assessed for and recorded adverse events;
- Recorded concomitant medication(s); and
- Instructed patient:
    - To bring all study supplies with them to the next visit;
    - Not to take study drug on the morning of their next visit; and
    - To fast for ≥ 10 hours prior to the next visit.

[0197] Visit 3 (Day 120; ~4 Months): Patients returned to the Research Site for Visit 3 on Day 120 ±10 days. The following procedures were performed:

- Physical examination;
- Obtained weight;
- Obtained vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);

- Obtained fasting blood samples for:
    - Chemistry and hematology testing; and
    - Lipid profile.
- Reviewed study drug compliance by unused capsule count; discuss with and counsel patients about compliance if needed;
- Administered study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples;
- Assessed and record efficacy events;
- Assessed for and record adverse events;
- Recorded concomitant medication(s);
- Instructed patient:
    - To bring all study supplies with them to the next visit;
    - Not to take study drug on the morning of their next visit; and
    - To fast for ≥10 hours prior to the next visit.

[0198] Visits 4, 5, 6, 7, 8, and 9: At Visit 4: Day 360 ± 10; Visit 5: Day 720 ± 10; Visit 6: Day 1080 ± 10; and Visit 7: Day 1440 ± 10: Visit 8: Day 1800 ± 10, Visit 9: Day 2160 ± 10, the following procedures were performed:

- Physical examination;
- Obtained weight;
- Obtained vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Measured waist circumference (collected at Visit 5 only);
- Obtained a 12-lead electrocardiogram;
- Obtained fasting blood samples for:
    - Chemistry and hematology testing;
    - Lipid profile;
    - Biomarker assays (collected at Visit 5 only); and

- Archived (in countries and at sites approved by international review board (IRB)/independent ethics committee (IEC) and dependent on country regulations);

- Reviewed study drug compliance by unused capsule count; discussed with and counseled patients about compliance if needed;
- Administered study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples;
- Assessed and record efficacy events;
- Assessed for and record adverse events;
- Recorded concomitant medication(s); and
- Instructed patient:
  - To bring all study supplies with them to the next visit;
  - Not to take study drug on the morning of their next visit; and
  - To fast for ≥10 hours prior to the next visit.

[0199] Additional Visits: The end date of the study was expected for Day 2160 but the actual end date was dependent on the determination of the study end date by the DMC and when approximately 1612 primary efficacy events had occurred. If the actual study end date was later than the expected end date, additional visits were planned between Visit 7 and the Last Visit with a maximum of 360 ±10 days between visits. If the actual study end date was sooner than the expected end date, fewer visits occurred, and the last visit (See below, section titled Last Visit – End of Study) occurred sooner. On additional visits the same procedures were performed. Irrespective of the number of additional visits, after the DMC had established the end of the study date, there was a last visit with procedures as listed below in section titled Last Visit – End of Study.

[0200] Last Visit – End of Study: All patients completed 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 was planned for Day 2160 but the actual end date was dependent on the determination of the study end date by the DMC when approximately 1612 primary efficacy events had occurred (event-driven trial). For each patient, the last visit may have occurred within 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 were included in the efficacy analyses. A final follow-up visit was required for all patients. In a rare case that a final follow-up visit did not occur within the 30-day timeframe following the study end date, any attempt to contact the patient was recorded on a special contact form, until/unless appropriate information was obtained. At the Last Visit, the following procedures were performed:

- Physical examination;
- Obtained weight;
- Obtained vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Measured waist circumference;
- Obtained a 12-lead electrocardiogram;
- Obtained fasting blood samples for:
    - Chemistry and hematology testing;
    - Lipid profile;
    - Biomarker assays; and
    - Archived (in countries and at sites approved by IRB/IEC and dependent on country regulations).
- Determined study drug compliance by unused capsule count;
- Assessed and record efficacy events;
- Assessed for and record adverse events; and
- Recorded concomitant medication(s).

[0201] Telephoned Follow-up Contact: Site personnel contacted 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; and Day 2070 ±5 days.

[0202] If the treatment/follow-up period of the study was extended beyond the expected end date (Day 2160), additional follow-up phone calls were made every 3 months in-between additional visits ± 5 days. If the treatment/follow period of the study was shorter than the expected end date, less follow-up phone calls were needed. Every attempt was made to talk to each patient within this timeframe. The following information was collected from the patient:

- Possible efficacy endpoints related to CV events. Patients were asked to return to the Research Site to assess for any endpoints or events identified;
- Adverse events;
- Concomitant medications; and
- Current address and contact information.

[0203] Patients were 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; and
- To fast for at least 10 hours prior to the next visit.

Laboratory Procedures

[0204] Clinical Laboratory Procedures and Evaluations: All clinical laboratory determinations for screening and safety were 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 were collected after fasting for at least 10 hours. For the purposes of this study, fasting was defined as nothing by mouth except water (and any essential medications). The investigator reviewed and signed all laboratory test reports. At screening, patients who had laboratory values that are outside the exclusionary limits specified in the exclusion criteria were not enrolled

in the study (patients would have been considered for the study if values were classified as not clinically significant by the investigator). After randomization, the investigator was notified if laboratory values were outside of their normal range. In this case, the investigator was required to conduct clinically appropriate follow-up procedures.

[0205] Safety Laboratory Tests: The safety parameters were 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. The safety laboratory tests included:

- Hematology with complete blood count (CBC), including RBC, hemoglobin (Hgb), hematocrit (Hct), white cell blood count (WBC), white cell differential, 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.

[0206] Each laboratory result was classified as low (L), normal (N), and high (H) at each visit according to the laboratory-supplied normal range. The shift from baseline was presented for each post-baseline visit and overall post-baseline visits. If multiple measurements for a test parameter were available for a post-baseline patient-visit, the most extreme value was included in the shift table. For shift from baseline to overall post-baseline visits, values from all visits (including unscheduled measurements) were included. The chemistry shift table included fasting lipid parameters. The continuous lipid values were presented as part of the efficacy analysis.

[0207] Fasting Lipid Profile: The fasting lipid panel included: TG, TC, LDL-C, HDL-C, non-HDL-C, and VLDL-C. At all visits, LDL-C was calculated using the Friedewald equation. At Visit 1 and Visit 1.1 direct LDL-C were used if at the same visit TG >400 mg/dL (4.52 mmol/L). These LDL-C values were 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 was not at goal. At all remaining visits (except Visit 2 and Visit 4) LDL-C was 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 were measured by preparative ultracentrifugation. These preparative ultracentrifugation LDL-C measurements were used in the statistical analysis including the calculation of the percent change from baseline (1 year versus baseline). Hopkins LDL-C was calculated for each visit.

[0208] Genetic Testing: A fasting blood sample was stored for future genetic testing at the discretion of the Sponsor. The specifics of this test were determined at a later date. This sample was optional as local regulations may prohibit genetic samples to be collected or shipped outside the country, or patients may not have consented. Research on genetic testing looked for links between genes and certain diseases, including their treatment(s) such as medicines and medical care. The blood samples were collected in the study center with the regular protocol-required labs. Each patient tube with a sample for genetic testing were labeled with patient number only. The site maintained a Subject Code Identification List for cross-reference. The patient number did not contain any identifiable information (i.e., patient initials, date of birth, etc.). Un-analyzed samples were stored frozen by the Sponsor for a period of up to 2 years following the end of the study, at which time they were destroyed. If samples were tested, results were not reported to the patient, parents, relatives, or attending physician and were not recorded in the patient's medical records. There was no follow-up contact with the sites or patients regarding this sample. The subject could withdraw their consent for genetic testing at any time up to analysis, even after the sample had been obtained. The subject could notify the site in writing that they withdraw their consent for the genetic testing portion of the study, and it was documented by the site in the subject chart, as well as captured in the CRF. The lab was notified to pull the sample and destroy it. Potential genetic bioassays may have been performed and may have been 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.

[0209] Biomarkers Assays: The biomarker assays included: hsCRP, Apo B and hsTnT.

[0210] Additional laboratory tests: Additional laboratory tests were performed and included:

- A urine pregnancy test was administered to women of childbearing potential at certain visits as listed in schedule of procedures (Table 1). The urine pregnancy tests was performed at the Research Site utilizing marketed test kits, or at a certified clinical laboratory;
- A fasting blood sample (10 mL) for archiving. This sample was 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 was stored frozen in 2 separate equal aliquots, and was used at the Sponsor's discretion to perform repeat analyses described in the protocol or to perform other tests related to cardiovascular health; and
- Potential non-genetic bioassays were 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).

[0211] Blinding of Laboratory Results: All efficacy laboratory results during the double-blind period of the trial were 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 were reported to the site.

[0212] Flagging of Critical Lab Values: Critical lab values are values that may have warranted medical intervention to avoid possible harm to a patient. Critical lab values were defined in the Laboratory Manual for the study, and the Research Site was 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 were part of the efficacy endpoints during the double-blind period of the study were not provided to the Research Site, the sites were notified when the TG value of a patient sample was >1000 mg/dL (11.29 mmol/L) (critical high TG value) or if the LDL-C values of a patient sample was >130 mg/dL (3.37 mmol/L) (critical high

LDL-C value). These critical high values were confirmed by a repeat measurement (new fasting blood sample) within 7 days. TG value of >2000 mg/dL (22.58 mmol/L) were also flagged, so that appropriate medical action could be taken by the investigator as soon as possible.

[0213] If TG values were confirmed critically high, patients could be discontinued from study drug with the option to remain on study. The investigator used the best clinical judgment for each patient which included the use of approved TG-lowering medications after patients had discontinued from study drug. If LDL-C values were confirmed critically high, the investigator needed to take appropriate medical action which included: reinforcing/intensifying therapeutic lifestyle changes (including diet and physical activity), increasing the dose of the present statin therapy, adding ezetimibe, or prescribing a more potent statin to lower LDL-C. The investigator used the best clinical judgment for each patient.

Medical Procedures

[0214] 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 were collected on all patients.

[0215] Demographics: Demographic information including day, month, and year of birth, race, and gender were collected for all patients.

[0216] Vital Signs and Patient Measurements: Vital signs included systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Blood pressure was measured using a standardized process:

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

[0217] Blood pressure was recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device. A blood pressure reading was repeated 1 to 2 minutes later, and the second reading recorded to the nearest 2 mmHg mark.

[0218] The baseline value categories and post-baseline endpoint value categories shown in Table 6 were measured and presented. Definitions for potentially clinically significant (PCS) vital signs treatment-emergent values are defined below in Table 7.

[0219] Table 6. Vital Signs Value Categories

Vital Sign	Low	Normal	High
Systolic Blood Pressure	≤90 mmHg	>90 mmHg to <160 mmHg	≥160 mmHg
Diastolic Blood Pressure	≤50 mmHg	>50 mmHg to <100 mmHg	≥100 mmHg
Pulse	≤50 beats/min	>50 beats/min to <90 beats/min	≥90 beats/min

[0220] Table 7. Potentially Clinically Significant Vial 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

[0221] Number (%) of patients with any post-baseline PCS vital sign values was summarized by treatment group. A listing of patients who meet the threshold criteria was provided.

[0222] Physical Examination: A physical examination included source documentation of general appearance, skin, and specific head and neck, heart, lung, abdomen, extremities, and neuromuscular assessments.

[0223] Height, Weight and Body Mass Index: Height and weight were measured. Measurement of weight was performed with the patient dressed in indoor clothing, with shoes removed, and bladder empty.

[0224] Waist Circumference: Waist circumference was 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 have held their breath while measuring waist circumference.

[0225] 12-Lead Electrocardiogram (ECG): ECGs (standard 12-lead) were obtained annually. Site personnel made every attempt to perform a patient's ECG using the same equipment at each visit. ECGs were reviewed by the site for the detection of silent MI. Silent MIs were sent for event adjudication. All post-randomization ECGs (protocol-specified and other) were sent to the CEC for evaluation of silent MI. The 12-lead ECG parameters included Heart Rate (bpm), PR Interval (msec), QRS Interval (msec), QT Interval (msec), and QTc Interval (msec) were measured, and Overall Interpretation and Silent MI (Yes/No) were 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.

[0226] A treatment-emergent PCS high value at any time was 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 was 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 8 provides the PCS ECG values.

[0227] Table 8. Potentially Clinically Significant ECG Value Definitions

ECG Parameter	PCS Low	PCS High
PR Interval	<120 msec	>120 msec and increase of >20 msec from baseline
QRS Interval	N/A	>110 msec
QTc	N/A	>500 msec

[0228] Number (%) of patients with post-baseline PCS ECG values were presented by treatment group. A listing of subjects with potentially clinically significant changes in ECG values was included.

Treatment and Procedures

[0229] Treatment Regimen, Dosage, and Duration: Eligible study patients were randomly assigned on Day 0 to one of the 2 treatment groups. Patients in each group received either 4 g/day AMR101 or placebo for up to 6.5 years, depending on individual date of randomization and overall study stop date according to Table 9. The daily dose

of study drug was 4 capsules per day taken as two capsules taken on two occasions per day (2 capsules were given twice daily).

[0230] Table 9. 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

[0231] Patients were instructed to take study drug with food (i.e., with or at the end of their morning and evening meals). On days that patients were scheduled for study visits, the daily dose of study drug was administered by site personnel with food provided by the site following collection of all fasting blood samples. For the purposes of this study, fasting was defined as nothing by mouth except water (and any essential medications) for at least 10 hours. Treatment Assignment

[0232] Identification Number: A unique patient identification number (patient number) was established for each patient at each site. The patient number was used to identify the patient throughout the study and was entered on all documentation. If a patient was not eligible to receive treatment, or if a patient discontinued from the study, the patient number could not be reassigned to another patient. The patient number was used to assign patients to one of the 2 treatment groups according to the randomization schedule.

[0233] Drug Randomization: Only qualified patients who meet all of the inclusion criteria and none of the exclusion criteria were randomized and received study medication starting at Visit 2 (Day 0). Eligible patients were randomly assigned to one of the 2 treatment groups. Randomization was stratified by CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries). Approximately 70% of randomized patients were in the CV Risk Category 1, including patients with established CVD, and approximately 30% of randomized patients were 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 was stopped when the planned number of patients in that risk category was reached.

[0234] Emergency Unblinding: In an emergency, when knowledge of the patient's treatment assignment was essential for the clinical management or welfare of the

patient, the investigator could request the patient's treatment assignment for unblinding. Prior to unblinding the patient's individual treatment assignment, the investigator assessed the relationship of an adverse event to the administration of the study drug (Yes or No). If the blind was broken for any reason, the investigator recorded the date and reason for breaking the blind on the appropriate Case Report Form (CRF) and source documents.

[0235] Compliance Control: Unless clear contraindications arise, patients were strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy were, if possible, brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. Discontinuations were discouraged as much as possible. Any discontinuations were based on compelling clinical reasons. For every patient, an assessment of compliance to the study drug treatment regimen was obtained at each scheduled visit. Study medication was dispensed in amounts exceeding the amount required for the study. Patients were instructed to return all unused study medication at the next visit. Compliance to the study drug regimen was evaluated at each visit by counting unused capsules. Discrepancies were evaluated and discussed with each patient to assess compliance. If compliance was unsatisfactory, the patient was counseled about the importance of compliance to the dosing regimen. At the end of the study, the final study medication compliance was determined by unused capsule count.

Study Restrictions

[0236] Concomitant Medications during Treatment/Follow-Up Period: Any medications administered during the study period were documented on the Concomitant Medication CRF. Patients had not taken any investigational agent within 90 days prior to screening. Patients could not 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 were prohibited during the study (from Visit 1 until after the Last Visit-End of Study), except for compelling medical reasons in ODIS patients:

- 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; and
- systemic retinoids.

[0237] If any of these products were used during the treatment/follow-up period of the study, it was for compelling medical reasons in ODIS patients, and documented in the Concomitant Medication CRF. If the ODIS patient agreed to restart study medication, the use of excluded medication was discontinued. Foods enriched with omega-3 fatty acids were 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 ignored this request). The following products were allowed: statins, ezetimibe, and herbal products & dietary supplements not containing omega-3 fatty acids.

[0238] Statins:

- The same statin at the same dose was continued until the end of the study, unless deemed medically necessary to change because of an adverse event or lack of efficacy (LOE). It was preferred that if LOE was the determining factor that ezetimibe was added to the present dose;
- Switching between a brand name statin and the generic version of the same statin was allowed at any time during the study;
- Statins were administered with or without ezetimibe;
- Based on the FDA recommendation, simvastatin 80 mg was used only in patients who had been taking this dose for 12 months or more and had 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); and

- Changing of the type of statin or the statin dose during the treatment/follow-up period of the study was only done for compelling medical reasons and was documented in the CRF. Maintaining statin therapy throughout the study was important and, in the rare circumstance that it became medically compelling to discontinue statin use, the patient could remain in the study and on study medication with approval from the Medical Monitor. Under such conditions, resumption of statin therapy was attempted when/if medically appropriate.
- If the level of LDL-C exceeded 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 either increased the dose of the present statin therapy or added ezetimibe to lower LDL-C. The investigator used the best clinical judgment for each patient.

[0239] LDL-C Rescue: If the level of LDL-C exceeded 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 either increased the dose of the present statin therapy or added ezetimibe to lower LDL-C. The investigator used the best clinical judgment for each patient.

[0240] No data were available with regard to potential interactions between ethyl-EPA and oral contraceptives. There were no reports suggesting that omega-3 fatty acids, including ethyl-EPA, would decrease the efficacy of oral contraceptives.

[0241] Medications that were excluded if not at a stable dose for ≥28 days prior to screening, could be initiated post-randomization if medically warranted (i.e., tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids and HIV-protease inhibitors).

[0242] Patient Restrictions: Beginning at the screening visit, all patients were 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.

Investigational Product

[0243] Clinical Trial Material: The following clinical materials were supplied by the Sponsor:

- AMR101 1000 mg capsules
- Placebo capsules (to match AMR 101 1 g Capsules)

[0244] The Sponsor supplied sufficient quantities of AMR101 1000 mg capsules and placebo capsules to allow for completion of the study. The lot numbers of the drugs supplied were recorded in the final study report. Records were maintained indicating the receipt and dispensation of all drug supplies. At the conclusion of the study, any unused study drug was destroyed.

[0245] Pharmaceutical Formulations: AMR101 1000 mg and placebo capsules (paraffin) were provided in liquid-filled, oblong, gelatin capsules. Each capsule was filled with a clear liquid (colorless to pale yellow in color). The capsules were approximately 25.5 mm in length with a diameter of approximately 9.5 mm.

[0246] Labeling and Packaging: Study medication was packaged in high-density polyethylene bottles. Labeling and packaging was performed according to GMP guidelines and all applicable country-specific requirements. The bottles were 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 was used), corresponds to the number on the bottles. The bottle number for each patient was recorded in the Electronic Data Capture (EDC) system for the study.

Dispensing Procedures and Storage Conditions

[0247] Dispensing Procedures: At Visit 2 (Day 0), patients were assigned a study drug according to their treatment group determined by the randomization schedule. Once assigned to a treatment group, patients received study drug supplies. At each visit, patients brought unused drug supplies dispensed to them earlier. From the drug supplies assigned to each patient, site personnel administered the drug while the patients were at the Research Site. The investigator or designee contacted 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 were needed. During the last visit of the treatment period, patients brought the unused drug supplies for site personnel to calculate the final study medication compliance by unused capsule count.

[0248] Storage Conditions: At the Research Sites, study drugs were stored at room temperature, 68°F to 77°F (20°C to 25°C). Storage temperature did not go below 59°F (15°C) or above 86°F (30°C) and the drug was stored in the original package. Study drugs were 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 kept accurate dispensing records. At the conclusion of the study, study site personnel accounted for all used and unused study drug. Any unused study drug was destroyed. The investigator agreed not to distribute study drug to any patient, except those patients participating in the study.

Efficacy Assessments

[0249] Specification of Variables and Procedures: The primary endpoint and the majority of the secondary and tertiary endpoints were based on clinical events related to CVD and mortality. All events occurring between randomization and the study end date (inclusive) were recorded. Only adjudicated events were included in the final analyses.

[0250] Primary Efficacy Endpoint: The primary efficacy endpoint was time from randomization to the first occurrence of the composite of the following clinical events: CV death; nonfatal MI (including silent MI; ECGs were performed annually for the detection of silent MIs); nonfatal stroke; coronary revascularization; and 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 vascular events during the follow-up period of the study were included in the incidence.

[0251] Secondary Efficacy Endpoints: The key secondary efficacy endpoint was 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 were time from randomization to the first occurrence of the individual or composite endpoints as follows (tested in the order listed):

- The 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 and nonfatal stroke;
- The composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke; and/or
- Total mortality.

[0252] For the secondary endpoints that count a single event, the time from randomization to the first occurrence of this type of event was counted for each patient. For secondary efficacy endpoints that were 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 were counted for each patient.

[0253] Tertiary Efficacy Endpoints: The following tertiary endpoints were evaluated as supporting efficacy and safety analyses. Where applicable and unless specified otherwise, endpoint analyses were conducted as time from randomization to the first occurrence of the individual or composite endpoint as follows:

- 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 with waist circumference cut points 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;

- 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);
- The composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalization of ≥24 hours, or cardiac arrest;
- The composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina determined caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- The composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined 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;
- The composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined 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, hsCRP (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; and
    - 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; and
- Change in waist circumference.

[0254] 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 was counted in each patient. Similarly, where applicable and unless specified otherwise, for tertiary endpoints that were 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 was counted in each patient.

[0255] Other sensitivity, supportive, and exploratory analyses for the primary efficacy endpoint were carried out, namely, an on-treatment analysis which included primary event onset up to 0 and 30-days after the permanent discontinuation of the drug.

[0256] The following clinical events that were positively adjudicated by the Clinical Endpoint Committee were analyzed as tertiary endpoints for the ITT intent-to-treat (ITT) population:

- Composition of total mortality, or congestive heart failure (CHF);
- Composite of CV death, or new CHF;
- Sudden cardiac death;
- Peripheral artery disease (PAD); and
- Atrial fibrillation, or atrial flutter.

[0257] The above tertiary endpoints were analyzed similarly as the primary endpoint.

[0258] In addition, the following were analyzed as tertiary endpoints for the ITT population:

- Relationship between on-treatment high-sensitivity C-reactive protein (hsCRP) and the primary key secondary endpoints; and
- Relationship between on-treatment serum eicosapentaenoic acid (EPA) and the primary and key secondary endpoints.

[0259] To assess the relationship between on-treatment hsCRP and the primary and key secondary endpoints, subgroup analyses were 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 were produced for AMR101 treated patients grouped into tertiles based on their values at year 1 and were compared with the placebo-treated patients.

Safety Assessments

[0260] Specification of Variables and Procedures: Safety assessments included adverse events, clinical laboratory measurements (chemistry, hematology), 12-lead ECGs, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), weight, waist circumference, and physical examinations as per Study Procedures in Table 1. A complete medical, surgical and family history was completed at Visit 1. All laboratory test results were 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 were considered an adverse event.

[0261] 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, were recorded on the appropriate CRF. Each adverse event was evaluated for duration, intensity, and causal relationship with the study medication or other factors.

[0262] Adverse events, which included clinical laboratory test variables, were monitored from the time of informed consent until study participation was complete. Patients were instructed to report any adverse event that they experienced to the investigator. Beginning with Visit 2, investigators assessed for adverse events at each visit and recorded the event on the appropriate adverse event CRF.

[0263] Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms was identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom was not considered a component of a specific disease or syndrome by the investigator, it was recorded as a separate adverse event on the CRF.

[0264] Any medical condition that was present when a patient was screened or present at baseline that did not deteriorate were reported as an adverse event. However, medical conditions or signs or symptoms present at baseline and that changed in severity or seriousness at any time during the study were reported as an adverse event.

[0265] Clinically significant abnormal laboratory findings or other abnormal assessments that were detected during the study or were present at baseline and significantly worsened were reported as adverse events or SAEs. The investigator exercised his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment was clinically significant.

[0266] The investigator rated the severity (intensity) of each adverse event as mild, moderate, or severe, and also categorized each adverse event as to its potential relationship to study drug using the categories of Yes or No. The severity was defined as:

- 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.

[0267] Causality Assessment: The relationship of an adverse event to the administration of the study drug was 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 (related, probably related, possibly related) – 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.

[0268] The following factors were also considered:

- The temporal sequence from study medication administration;
- The event occurred after the study medication was given. The length of time from study medication exposure to event was evaluated in the clinical context of the event;
- Underlying, concomitant, intercurrent diseases;
- Each report was evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have had;
- Concomitant medication;
- The other medications the patient was taking or the treatment the patient received were examined to determine whether any of them might have caused the event in question;
- Known response pattern for this class of study medication;
- Clinical and/or preclinical data may have indicated whether a particular response was 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; and
- The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study medication were considered.

[0269] 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.

[0270] 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- 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. In general, hospitalization for treatment of a pre-existing condition(s) that did not worsen from baseline was not considered adverse events and was not reported as SAEs;
- Results in disability/incapacity;
- Is a congenital anomaly/birth defect; and
- Is an important medical event. Important medical events that may not result in death, be life threatening, or require hospitalization were considered an SAE when, based upon appropriate medical judgment, they may have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events included allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did not result in inpatient hospitalizations, or the development of drug dependency.

[0271] By design of this study SAEs that were endpoint events were only recorded for the endpoint determination and not captured as SAEs. The intention was that the endpoint events were reported to IRBs as SAEs, unless the IRB required that these were reported. Investigators specifically informed their institution/IRB of this plan and confirm whether or not they wanted the endpoint events reported. By agreement with the US FDA, these endpoints were also not reported to the US FDA as SAEs; rather they were reported as endpoint events. Following adjudication if the event was determined to not meet the criteria for an event, the event was evaluated as an SAE beginning with that day as Day 0.

[0272] 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) were summarized separately and compared between treatment groups.

Serious Adverse Event Reporting – Procedure for Investigators

[0273] Initial Reports: All SAEs occurring from the time of informed consent until 28 days following the last administration of study medication were 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 considered related to study medication occurring after the 28-day follow-up period were also reported to the Sponsor or designee. The investigator was 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) received any Suspected Unexpected Serious Adverse Reaction (SUSAR) reports for onward submission to their local IRB as required. All reports sent to investigators were blinded. In addition, regulatory agencies were notified of SAEs per the requirements of the specific regulatory jurisdiction regulations and laws.

[0274] Follow-Up Reports: The investigator followed the patient until the SAE subsided, or until the condition became chronic in nature, stabilized (in the case of persistent impairment), or the patient died. Within 24 hours of receipt of follow-up information, the investigator updated the SAE form electronically in the EDC system for the study and submitted any supporting documentation (e.g., laboratory test reports, patient discharge summary, or autopsy reports) to the Sponsor or designee via fax or email.

[0275] Reporting by the Sponsor: IRBs and IECs were informed of SUSARs according to local requirements. Cases were unblinded for reporting purposes as required.

[0276] Exposure *In Utero* During Clinical Trials: If a patient became pregnant during the study, the investigator reported the pregnancy to the Sponsor or designee within 24 hours of being notified. The Sponsor or designee then forwarded the Exposure *In Utero* form to the investigator for completion. The patient was followed by

the investigator until completion of the pregnancy. If the pregnancy ended for any reason before the anticipated date, the investigator notified the Sponsor or designee. At the completion of the pregnancy, the investigator documented the outcome of the pregnancy. If the outcome of the pregnancy met the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator followed the procedures for reporting an SAE.

Treatment Discontinuation/Patient Withdrawal

[0277] Patients could withdraw from the study at any time and for any reason. Study drug administration could also be discontinued at any time, at the discretion of the investigator. In any case, follow-up for efficacy and safety was continued in subjects that discontinued therapy, but remained in the study (i.e., ODIS patients).

[0278] Reasons for Early Study Drug Discontinuation: Study drug discontinuation was avoided as much as possible, but could have been done for any of the following reasons:

- Patient withdrew consent or requested early discontinuation from the study for any reason. Patients were 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 was notified if a patient was discontinued because of an adverse event or laboratory abnormality. It was recommended that, unless clear contraindications arise, patients were strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy were, if possible, brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. The following were considered a 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; and/or
- ALT > 3x ULN and cannot be monitored weekly for 4 weeks

- Any medical condition or personal circumstance that, in the opinion of the investigator, exposed the patient to risk by continuing in the study or precluded adherence to the protocol;
- Sponsor discontinued the study;
- Investigative site closure, in the event that:
  - Another investigative site cannot accommodate the patient, or
  - The patient was unable or unwilling to travel to another investigative site; and/or
- A TG value was 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 could be discontinued from study drug (with the option to remain ODIS) and other lipid-altering medications may be (re)initiated. If the TG value was flagged as >2000 mg/dL (22.58 mmol/L) then appropriate medical action was taken by the investigator as soon as possible.

[0279] Occurrence of an outcome event according to the judgment of the investigator was not considered a valid reason for study drug discontinuation. Patients whose treatment with study medication was discontinued early, and had not withdrawn consent, stayed in the study and were monitored until the end of the study. Patients that continued in the study after ≥30 days cessation of therapy were characterized as Off Drug In Study (ODIS). ODIS patients were asked to return to the study site for an interim visit once the patient had been off study drug for >30 days. Procedures at this visit were consistent with those at Visit 5. If not contraindicated, patients also had the option to restart study medication at any point once characterized as ODIS. For patients who discontinued study medication (e.g., for an AE that may or may not have been drug-related), a brief therapy interruption could have been 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 was recorded on the CRF.

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

[0280] Patients who prematurely discontinued study drug were not replaced. All randomized patients were followed up until the study end date or death, regardless of whether they discontinued study drug prematurely or not. Any event occurring after early study drug discontinuation was recorded up through the study end date. In order to follow the medical status of the patients, especially when they discontinued the study, investigators were encouraged to obtain information from the patient's primary care practitioner (physician or any other medical care provider). Investigators were 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 avoided lost to follow-up for the efficacy assessment. If patients were lost to follow-up, the CRF was completed up to the last visit or contact.

Statistics

[0281] Randomized Population: The randomized population included all patients who sign the informed consent form and are assigned a randomization number at Visit 2 (Day 0).

[0282] Intent-to-Treat Population: The ITT population included all patients who were randomized via the IRWS (Interactive Web Response System). All efficacy analyses were performed on the ITT population. Patients were analyzed according to the randomized treatment.

[0283] Modified Intent-to-Treat Population: The Modified Intent-to-Treat (mITT) population included all randomized patients who had the study drug dispensed after randomization. Groups were defined based on the randomized treatment.

[0284] Per-Protocol Population: The per-protocol (PP) population included 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 was 90 days.

[0285] Safety Population: All safety analyses were conducted based on the safety population, which is defined as all randomized patients. This was the same as the ITT population.

[0286] Statistical Methods: Safety and efficacy variables were analyzed using appropriate statistical methods that were described in detail in a separate Statistical Analysis Plan (SAP). The SAP was finalized before study unblinding.

[0287] Patient Disposition and Demographic/Baseline Characteristics: The number and percentage of patients was 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 completed 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); and
- 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.

[0288] For randomized patients who discontinued treatment with study drug, the primary reason for discontinuation was 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 were summarized using descriptive statistics by treatment group in the ITT population.

[0289] Demographic data and baseline characteristics were compared among treatment groups for the ITT and PP population. Differences in demographic and baseline characteristics were tested using a chi-square test (for categorical variables) or t-test (for continuous variables). The p-values used were considered descriptive, primarily as an assessment of the balance between the two groups. Age in years was calculated using the date of randomization (Visit 2) and the date of birth.

[0290] Study Medication Exposure and Compliance: Study drug exposure was summarized by treatment group using descriptive statistics for each time point and overall. Overall study drug compliance was calculated as the number of doses assumed to be taken relative to scheduled dosing period as follows:

$$\text{Compliance (\%)} = \frac{(\text{\# Capsules of total dispensed} - \text{\# Capsules of total returned})}{(\text{last dose date} - \text{first dose date} + 1) \times 4 \text{ capsules/day}} \times 100$$

[0291] Overall percent compliance was calculated per patient in the ITT and Modified ITT populations and summarized by treatment group using descriptive statistics.

[0292] Concomitant Therapies: Concomitant medication/therapy verbatim terms were 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 were summarized. All verbatim descriptions and coded terms were listed for all non-study medications.

[0293] Analysis of Efficacy: For efficacy endpoints including CV events, only adjudicated events were included in the final statistical analyses.

[0294] 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 were presented by treatment group and by visit for all efficacy variables analyzed. The summary statistics included changes in body weight and body mass index from baseline by treatment group and by visit.

[0295] Primary Endpoint Analyses: The analysis of the primary efficacy endpoint was 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. The two-sided alpha level for the primary analysis was 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) for treatment group (AMR101 vs. placebo) from a Cox proportional hazard model that included the stratification factor was also reported, along with the associated 95% confidence interval (CI). Kaplan-Meier estimates from randomization to the time to the primary efficacy endpoint were plotted.

[0296] The size and direction of the treatment effects of the individual components of the composite endpoint and their relative contribution to the composite endpoint were determined as well. All observed data that were positively adjudicated by the CEC, including data after discontinuation of study treatment for patients who discontinued study drug prematurely, were included in the primary analysis. Patients who did 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 were censored at the date of their last visit/phone contact. The longest prespecified interval between visits (onsite or phone) was 90 days. In view of the up to 90-day monitoring period for CV events, the primary endpoint for patients who had a non-CV death within 90 days of last contact without having had an earlier CV event was censored at the time of death. The primary endpoint for patients who had a non-CV death more than 90 days after last contact without having had an earlier CV event were censored at the time of last contact.

[0297] The primary analysis assumed that all silent MIs occurred on the date of the first tracing indicative of a silent MI; a second (sensitivity) analysis assumed that all silent MIs occurred on the day after the last prior normal ECG; and a third (sensitivity) analysis assumed 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" were combined with those adjudicated as "CV deaths" for the primary analysis. A sensitivity analysis of the CV death category was performed that excluded the "undetermined cause of death" cohort.

[0298] The primary efficacy analysis was performed on the ITT population. A sensitivity analysis was performed using the mITT and PP populations. As a sensitivity analysis, patients who discontinued study drug prematurely were censored for the primary composite endpoint analysis on the date of drug discontinuation. The primary analysis was repeated using this censoring rule for the mITT population. As a supportive analysis, a multivariable, stratified Cox proportional hazards model was constructed for the primary endpoint to evaluate the treatment effect adjusting for important covariates.

[0299] Secondary Endpoint Analyses: The key secondary hypothesis was tested as part of the confirmatory process only if the primary analysis was statistically significant. For the analysis of secondary efficacy endpoints, the Type 1 error was controlled by testing each endpoint sequentially, starting with the key endpoint. Testing was done at a significance level consistent with that used for the primary endpoint and ceased when a secondary endpoint was found for which treatments did not significantly differ. P-values were presented for all analyses, but they were considered descriptive after the first non-significant result was obtained. Each of the secondary endpoints were analyzed by the same methods described for the primary efficacy endpoint. Kaplan-Meier estimated, 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, were summarized by treatment group. In view of the 90-day monitoring period for CV events, the key secondary endpoint for patients who had a non-CV death within 90 days of last contact without having had an earlier CV event was censored at the time of death. The key secondary endpoint for patients who had a non-CV death more than 90 days after last contact without having had an earlier CV event was censored at the time of last contact. Kaplan-Meier curves stratified by each stratification factor were presented. These analyses were conducted for the ITT population.

[0300] Tertiary Endpoints Analyses: Time-to-event tertiary endpoints were 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, were summarized by treatment group. In view of the 90-day monitoring period for CV events, if applicable, tertiary endpoints for patients who had a non-CV death within 90 days of last contact without having had an earlier CV event were censored at the time of death. If applicable, tertiary endpoints for patients who gad a non-CV death more than 90 days after last contact without having had an earlier CV event were censored at the time of last contact. Kaplan-Meier curves stratified by each of the stratification factors were presented.

[0301] The fasting lipid panel was 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 were analyzed, unless this value was missing. If the LDL-C preparative ultracentrifugation values were missing, then another LDL-C value was 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 SS, Blaha MJ, Elshazly MB, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. JAMA. 2013; 310:2061-8.). In addition, change from baseline to day 120 in LDL-C utilizing Friedewald's and Hopkins methods was analyzed, 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 was missing, the single available LDL-C value was used. LDL-C according to Hopkins was calculated at each visit.

[0302] The randomization visit was considered Baseline. If a baseline value was not available from the randomization visit, then the latest screening value was used. For measurements of lipids, lipoproteins and inflammatory markers, the change and the percent change were summarized at each visit. Since these biomarkers are typically not normally distributed, the Wilcoxon rank-sum test was used for treatment comparisons of the percent change from baseline, and medians and quartiles were

provided for each treatment group. The medians of the differences between the treatment groups and 95% CIs were estimated with the Hodges-Lehmann method. In addition, shift –tables were generated as appropriate.

[0303] As an additional exploratory analysis, the relationship between post-baseline biomarker values and treatment effects with the primary and key secondary endpoints were assessed by adding biomarker values (for example, at 4 months, or at 1 year, etc.) as time-dependent covariates in the Cox proportional hazards model. Diagnostic plots for the proportional hazards assumption were evaluated. Weight was measured at the screening visit and at all follow-up visits, including the last visit of the study. Waist circumference was measured at the randomization visit (Visit 2; Day 0), Visit 5 (Day 720) and the last visit of the study. Descriptive statistics were presented by visit and treatment group for baseline, post-treatment change from baseline, and the percent change from baseline. Analysis methods for repeated measurements were used to compare percent change from baseline between treatments.

[0304] Additional prespecified efficacy endpoints and analyses of this study are listed below. These endpoints and analyses were exploratory in nature and were not included in the original testing scheme:

- Time-to-event analyses as done for the primary analysis were carried out at 1-year and 2-year landmarks for the ITT Population;
- For the recurrent CV events analyses based on the 5-component MACE (CV death, non-fatal MI, non-fatal stroke, unstable angina requiring hospitalization, or coronary revascularization), a total CV event was performed using a Negative Binomial Model analysis;
- An on treatment sensitivity analysis was performed including primary events with onset up to 0 and 30 days after permanent discontinuation of study drug;
- As done for the primary analysis, time-to-event analyses at 1-year and 2-year landmarks for the key secondary endpoints for the ITT Population;
- An analysis of the following clinical events that are positively adjudicated as tertiary endpoints for the ITT Population:
    - Composite of total mortality, or new CHF;
    - Composite of CV death, or new CHF;
    - Sudden cardiac death;

- Peripheral artery disease (PAD); and
- Atrial fibrillation, or atrial flutter.

- An analysis of the following as tertiary endpoints for the ITT Population:
  - Relationship between on-treatment hsCRP and primary and key secondary endpoints; and
  - Relationship between on-treatment serum EPA and primary and key secondary endpoints.
- To assess relationships between on-treatment hsCRP and primary and key secondary endpoints, subgroup analyses as done for the ITT population for patients grouped according to (1) values greater or equal to or (2) less than 2 mg/dL at baseline and at 2 years;
- To assess relationships between on-treatment serum EPA and primary and key secondary endpoints, Kaplan Meier curves for AMR101 patients grouped into tertiles based on values at year 1 compared with placebo patients;
- The following were added to the subgroup analyses:
  - Baseline HbA1c value (<6.5%, ≥6.5%);
  - Baseline PAD; and
  - Baseline TG ≥ 150mg/dL with HDL-C ≤ 40 mg/dL for males and ≤ 50 mg/dL for females.

[0305] The following list presents additional pre-specified exploratory efficacy analyses that are of particular interest to the general clinical and scientific community that were also explored in this study:

- Non-fatal myocardial infarction (MI) (including both clinical manifestation and silent MI categorizations) for the ITT Population;
- Evaluation of effect of time-weighted (or area under the curve [AUC]) EPA data on the primary and key secondary composite endpoints for the ITT Population;
- Sensitivity analyses on 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 for the ITT Population;
- Two silent MI (SMI) sensitivity analyses on primary and key secondary composite endpoints – ITT Population:

    - Counting all potential SMIs identified by CEC 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 for the 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; and
    - Treatment effect on change from baseline in renal function (eGFR) at 1 and 5 years.
- Sensitivity analyses on primary and key secondary composite endpoints by excluding patients with post-randomization LDL-C values >100 mg/dL; and another for >70 mg/dL for the ITT Population;
- Analyses of hospitalization data (pooled positively adjudicated unstable angina requiring hospitalization, congestive heart failure [CHF] requiring hospitalization, and cardiac arrhythmia requiring hospitalization) for the ITT Population;
    - Time from randomization to first hospitalization; and
    - Recurrent event analysis on hospitalizations.
- Additional subgroup analyses (US versus Non-US) on the primary and key secondary composite endpoints; also potentially other endpoints for the 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 for the ITT Population;

- Sensitivity analyses for 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 myocardial infarctions excluding 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) endpoint(s) among the following cohorts:
    - High risk patients with "the hypertriglyceridemic waist" (obese patients at high CV risk);
    - High risk subgroup defined by baseline hsTNT level (and potentially by NT-proBNP from archived frozen samples); and
    - High TG/low LDL-C phenotypes;
    - High-risk patients as defined by their atherothrombotic risk score.
- Treatment effect on:
    - Peripheral arterial events (e.g., major adverse limb events [MALE]); and
    - Hypertension, using BP as a continuous variable.
- Using archived frozen serum biosamples, additional analyses of fatty-acid levels (and ratios), including baseline and on-treatment effects on EPA, DHA, DPA, AA (and associated ratios) and relationships between fatty-acid levels and cardiovascular outcomes;
    - Relationship between on-treatment fatty-acid levels;
    - Baseline fatty-acid levels; and
    - Study medication compliance.

- Using archived frozen biosamples (e.g., 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:
    - LDL-P;
    - RLP-C (measured);
    - LDL-TG;
    - Ox-LDL;
    - Galectin-3;
    - Lp(a) at baseline, as a predictor of CVD benefit;
    - LpPLA2;
    - HDL2, HDL3, apo A-I, apo A-II, HDL-P, apo C-III (and apo C-III in apo-B containing proteins), apo A-V, Apo E subtypes (2, 3, 4), IL-6, lipoprotein lipase (LPL); and
    - Analyses may include change (and percent change) from baseline, 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;
    - Erectile dysfunction; and
    - Ischemic cardiomyopathy (as indicated by hospitalization for CHF, ICD placement etc.).
- Additional genetic bioassays including genes which may relate to triglyceride, lipid metabolism, and CVD; and
- Effects of potential mediators identified *post hoc* on primary/key secondary outcome measures.

[0306] In this study, new onset diabetes was defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period (i.e. patients with no history of diabetes at randomization). For purposes of this study, a diagnosis of diabetes was made based on the observation of:

- HbA_{1c} ≥6.5%. The test was 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. In the absence of unequivocal hyperglycemia, HbA_{1c} ≥6.5% was confirmed by repeat testing;
- Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting was defined as no caloric intake for at least 8 hr. In the absence of unequivocal hyperglycemia, FPG ≥126 mg/dL (7.0 mmol/L) was confirmed by repeat testing;
- 2-hr plasma glucose ≥200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT). The test was performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. In the absence of unequivocal hyperglycemia, 2-hr plasma glucose ≥200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT) were confirmed by repeat testing; and/or
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

[0307] In the absence of unequivocal hyperglycemia, the first three criteria were confirmed by repeat testing.

[0308] Exploratory Subgroup Analyses: Analyses of the effects that patients off study drug and withdrawn from study have on the primary endpoint were performed. Subgroup analyses of the primary and key secondary endpoints were 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 was a stratification factor), and HRs and CIs from the Cox proportional hazards model as specified for the primary efficacy endpoint, were summarized by treatment group. Demographic, disease, treatment, and baseline lipid and lipoproteins parameters were explored.

[0309] Demographic parameters included: 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).

[0310] Disease parameters included: 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.

[0311] Treatment Parameters included: Statin intensity at baseline (statin type and regimen); and statin intensity categories as defined in ACC/AHA Cholesterol Guidelines (Stone 2013) and patient's 10-year CV Risk Score (Goff 2013).

[0312] Baseline Lipid and Lipoprotein Parameter included: 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; hsCRP (≤3 mg/L and >3 mg/L) and by gender; hsCRP (≤2 mg/L and >2 mg/L) and by gender; Apo B (by tertile); non-HDL-C (by tertile); baseline hemoglobin A1c (Hb1c) value (<6.5%, ≥6.5%); baseline PAD; and baseline TG levels ≥150 mg/dL with high-density lipoprotein cholesterol (HDL-C) levels ≤ 40 mg/dL for males and ≤50 mg/dL for females.

[0313] A Cox proportional hazard (PH) model as mentioned above but additionally with baseline TG as a covariate were fitted to the data at each interim. Diagnostic plots for the PH assumption were evaluated. The consistency of the treatment effects in subgroups was 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 were performed.

The main treatment effect was tested with this model. P-values for testing the interaction terms < 0.15 were considered significant. Results were presented in a Forest plot.

[0314] Subgroup analyses of the primary and key secondary endpoints were 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 was a stratification factor), and HRs and CIs from the Cox proportional hazards model as specified for the primary efficacy endpoint, were summarized by treatment group. All subgroup analyses were conducted for the ITT, mITT and PP populations.

[0315] Interim Efficacy Analysis: Two interim analyses were 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) was reached. The planned interim analyses were based on a group-sequential design.

[0316] The interim results of the study were monitored by an independent Data Monitoring Committee (DMC). The analyses were performed by the independent statistical team who was unblinded to the treatment assignment and reported only to the DMC. If the study was terminated early following interim analysis, patients were notified promptly and brought in for their final close-out visit, and the final analyses of efficacy and safety included all data through their final visit. All suspected events were adjudicated in a blinded manner by the CEC. The time to event was 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 were still in the trial were considered censored at the time of their last regular contact before the interim data cutoff.

[0317] The alpha-levels for the two protocol prespecified interim analyses and the final analysis are based on a group sequential design (GSD) with O'Brien-Fleming boundaries generated using the Lan-DeMets alpha spending function. The one-sided alpha-levels and boundaries based on a Z-test and the achieved p-values for each of the two interim analyses and the final analysis are given in Table 10.

[0318] Table 10. Group Sequential P-Values Boundaries According to Two Actual Interim Analyses Information Fractions

Look	Analysis	No. of Events	Information Fraction	Efficacy Boundary (1-sided α-level)	Efficacy Boundary (2-sided α-level)	Achieved P-value (2-sided)
1	IA#1	953	59.3%	0.00356	0.0071	**0.0000463**
2	IA#2	1218	75.8%	0.00885	0.0177	**0.00000082**
3	Final	1606	100%	0.02186	0.0437	**0.00000001**

[0319] Analysis of Safety: All analyses of safety were conducted on the safety population, which was defined as all randomized patients. The safety assessment was based on the frequency of adverse events, 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 last dose of study drug for each patient was considered treatment-emergent (TEAEs). This included any AE with onset prior to initiation of study drug and increased severity after the treatment initiation.

[0320] Treatment-emergent adverse events were summarized by system organ class and preferred term, and by treatment. This included 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 (for ≥30 days) were presented through data listings. Patients who restarted study drug were included in the summary of AEs leading to discontinuation. Safety laboratory tests and vital signs were summarized by post-treatment change from baseline for each of the parameters using descriptive statistics by treatment group. Those patients with significant laboratory abnormalities were identified in data listings. Additional safety parameters were summarized in data listings.

[0321] In addition to the treatment-emergent adverse events analyses, analyses on all AEs (serious and non-serious) and all serious AEs were performed.

[0322] All AEs included: treatment-emergent adverse event (TEAE) by high level group term (HLGT); TEAE by high level term (HLT); and TEAE by system organ class (SOC), HLGT, HLT, and preferred term (PT) (4-level table).

[0323] All SAEs included: treatment emergent SAE by HLGT; treatment emergent SAE by HLT; and treatment emergent SAE by SOC, HLGT, HLT, and PT (4-level table).

Clinical Laboratory Evaluation

[0324] The criteria for potentially clinically significant (PCS) laboratory values are provided in Table 11 and Table 12. A treatment-emergent PCS high value at any time was defined as a change from a value less than or equal to the upper reference limit at baseline to a PCS high value at any post-baseline measurement. A treatment-emergent PCS low value at any time was defined as a change from a value greater than or equal to the lower reference limit at baseline to a PCS low value at any post-baseline measurement. Number (%) of patients with any post-baseline PCS laboratory values was summarized by treatment group. A listing of patients with PCS laboratory values at any time, i.e., baseline or at any post-baseline visit, were included.

[0325] Table 11. Potentially Clinically Significant Chemistry Values

Parameter	PCS Low	PCS High
Albumin	≤3.3 g/dL	≥5.8 g/dL
Alkaline Phosphate	Not Applicable (N/A)	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
ALT	N/A	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
AST	N/A	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
Bilirubin	N/A	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
ALT + Bilirubin	N/A	>3x ULN + 2x ULN (Bilirubin)
AST + Bilirubin	N/A	>3x ULN + 2x ULN (Bilirubin)
Calcium	≤7 mg/dL	≥11 g/dL ≤12 mg/dL
Chloride	<70 mmol/L	>120 mmol/L
Creatinine	<0.5 mg/dL (Female) <0.65 mg/dL (Male)	>1.6 mg/dL (Female) >2.0 mg/dL (Male); ≥ 50% increase from baseline
Creatine Kinase	<30 U/L (Female)	>1x ULN to 5x ULN

	<0.55 U/L (Male)	>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	≥150 mEq/L
Total Protein	<5.0 g/dL	≥9.5 g/dL
Urea Nitrogen (BUN)	N/A	≥31 mg/dL
Uric Acid	<1.9 mg/dL (Female) <2.5 mg/dL (Male)	>7.5 mg/dL (Female) >8 mg/dL (Male)

[0326] Table 12. Potentially Clinically Significant Hematology Values

Parameter	PCS Low	PCS High
Red Blood Cell (RBC)	<3.5 × 10^6/μL (Female) <3.8 × 10^6/μL (Male)	>3.5 × 10^6/μL (Female) >3.8 × 10^6/μL (Male)
Hemoglobin (Hgb)	<10.0 g/dL (Female) < 10.0 g/dL (Male)	> >
Hematocrit (Hct)	<37% (Female) <42% (Male)	> >
White Blood Cells (WBC)	<1.5 × 10^3/μL	N/A
White Cell Differential	Segmented neutrophils <50% Lymphocytes <30% Monocytes N/A Basophils N/A Eosinophils N/A	Segmented neutrophils >70% Lymphocytes >45% Monocytes >6% Basophils >1% Eosinophils >3%
Platelet Count	<100 × 10^3/μL	>500 × 10^3/μL

Drug-Induced Liver Injury (DILI)

[0327] DILI cases were 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 was prepared, using a logarithmic scale. In the graph, for each patient, the peak TBL times the Upper Limit of Normal (ULN) were plotted against the peak ALT times the ULN, where the peak TBL and peak ALT may or may not have happened on the same day of liver testing. The graph was 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

was referred to as the potential Hy's Law quadrant, including potentially DILI cases.

- A similar graph was plotted with respect to aspartate aminotransferase (AST).
- The individual patient profile of liver function tests (ALT, AST, alkaline phosphatase [ALP] and TBL) over time was 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 was provided for the following:
    - ALT or AST >3x ULN;
    - ALT or AST >3x ULN and TBL >2x ULN; and
    - ALT or AST >3x ULN and TBL >2x ULN, and ALP < 2x ULN.

Study Design

Study Design

[0328] This was a Phase 3b, multi-center, multi-national, prospective, randomized, double-blind, placebo-controlled, parallel-group study. This was also an event-driven trial comparing the effect of AMR101 vs. placebo in terms of the composite endpoint listed above as the primary endpoint. The placebo contained mineral oil to mimic the color and consistency of icosapent ethyl in AMR101 and was administered in the same capsule fill volume and count as the AMR101. The study accrued a total of 1612 efficacy endpoint events with two planned interim analyses when approximately 967 (60%) and 1290 (80%) of the events had been adjudicated. The study included 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). Randomization was stratified by cardiovascular risk stratum which included the secondary-prevention cohort (i.e., CV Risk Category 1) or primary-prevention cohort (i.e., CV Risk Category 2), with the primary prevention cohort capped at 30% of enrolment, use or no use of ezetimibe, and by geographical region. Details of the study design are shown in Figure 1.

[0329] Sample size calculation was based on the assumption of constant hazard, asymmetric recruitment rate overtime and without factoring for dropouts. A risk

reduction corresponding to a HR of 0.85 (AMR101 vs. placebo) was assumed. 1612 events were required to detect this HR with approximately 90% power with one-sided alpha-level at 2.5% and with two interim analyses. The operating characteristics of this design were identical to those of a corresponding group sequential design with a two-sided alpha level of 0.05.

[0330] The recruitment period was 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 was 6.5 years unless the trial was terminated early for efficacy or safety issues. A one-year event rate of 5.2% (hazard = 0.053) in the control arm was also assumed. Under these assumptions the number of patients enrolled was N = 7990.

[0331] Since this was an events-driven trial, the 'sample size' was the number of events rather than the number of patients. The number of events that occurred depends primarily on three factors: how many patients were enrolled; the combined group event rate; and how long the patients were followed. Because of the difficulty in predicting the combined event rate, the Sponsor monitored the event rate as the trial progressed. If the combined event rate was less than anticipated, either increasing the number of patients, extending the length of follow-up, or a balance of adjusting both factors was necessary to achieve the sample size of 1612 events.

[0332] At completion of study enrollment, the actual number of patients randomized may have varied 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.

Completion of Study

[0333] The end of the study was at the time the last patient-last visited of the follow-up period of the study. The IRB and IEC were notified about the end of the study according to country-specific regulatory requirements.

Standardized Definitions for the Cardiovascular Trial Endpoint Events

[0334] In assessing patients in this clinical trial, the follow definitions were used:

[0335] 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.

[0336] Death due to acute myocardial infarction: refers to a death by any mechanism (e.g., 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 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.

[0337] Sudden Cardiac Death: refers to a death that occurs unexpectedly, not within 30 days of an acute MI, and includes the following deaths: death witnessed and instantaneous without new or worsening symptoms; death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest an acute MI; 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); death after unsuccessful resuscitation from cardiac arrest; death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology; and/or unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

[0338] General Considerations for Sudden Cardiac Death: 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" are classified as "death due to other cardiovascular causes". (See Definition of Undetermined Cause of Death, for full details below).

[0339] 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, for full details below). Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

[0340] 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, for full details below).

[0341] Death due to Cardiovascular Procedures: refers to death caused by the immediate complications of a cardiac procedure.

[0342] 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, for full details below), non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

[0343] 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).

[0344] 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.

- 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; and/or
- Prescription Drug Error (e.g., prescribed drug overdose, use of inappropriate drug, or drug-drug interaction); and
- Neurological process that is not a stroke or hemorrhage.

- Malignancy: Malignancy is coded as 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; and
  - Death results from an illness that is not a consequence of a cancer.

[0345] 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.

[0346] Definition of 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 was not readily apparent (e.g., found dead at home), the cause was assumed to be cardiovascular in origin, unless one of the following 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.

[0347] Definition of Myocardial Infarction: The term myocardial infarction (MI) is 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.

[0348] 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.

[0349] The Criteria for myocardial infarction include clinical presentation, biomarker evaluation, and ECG changes.

[0350] Clinical Presentation: The clinical presentation is 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.

[0351] Biomarker Evaluation: 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 were required. The specific criteria were 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 were made.

[0352] 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.

[0353] Criteria for acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)) include:

- 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.

[0354] 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.

[0355] Criteria for pathological Q-wave include: 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); and 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.

[0356] The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

[0357] Criteria for Prior Myocardial Infarction include: pathological Q-waves, as defined above; and 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.

[0358] Myocardial Infarction Subtypes: Several MI subtypes are commonly reported in clinical investigations and each is defined below:

1. Spontaneous MI:

- 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; and/or
    - Autopsy evidence of acute MI
- If biomarkers are elevated from a prior infarction, then a spontaneous myocardial infarction is defined as 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; and/or
    - Autopsy evidence of acute MI; and
- Both of the Following:

- Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI (note: If biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent MI is generally not possible); and
- ≥ 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.

2. Percutaneous Coronary Intervention-Related Myocardial Infarction: 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:

- Symptoms suggestive of myocardial ischemia (i.e., prolonged ischemia ≥ 20 min);
- New ischemic changes on ECG or new LBBB;
- Angiographic loss of patency of a major coronary artery or a side branch or persistent slow flow or no flow or embolization; and/or
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

3. Coronary Artery Bypass Grafting-Related (CABG) Myocardial Infarction: is defined by the following criteria. Symptoms of cardiac ischemia were not required and data was collected in such a way that analyses using ≥ 20% or ≥ 50% could both be performed.

- 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 are true:
    - ≥ 50% increase in the cardiac biomarker result; and

- Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI; and

- One of the following are true:
    - 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; or
    - Imaging evidence of new loss of viable myocardium.
- Autopsy evidence of acute MI.

4. Silent Myocardial Infarction: is defined by the following:

- No evidence of acute myocardial infarction; and
- 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; and/or
    - Autopsy evidence of a healed or healing MI.

[0359] In the case of evanescent Q waves, the last ECG determines whether a silent infarction has occurred.

[0360] Sub-classification of Myocardial Infarction: The universal MI definition includes clinical classification of different types of MI, electrocardiographic features, and by biomarker evaluation, with the definition of each provided below.

[0361] Clinical Classification of Different Types of Myocardial Infarction include the following:

- 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 Percutaneous Coronary Intervention (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; and
- Type 5: Myocardial infarction associated with CABG.

[0362] By Electrocardiographic Features include:

- ST-Elevation MI (STEMI). The additional categories of STEMI include: Q wave, non-Q-wave, or unknown (no ECG or ECG non-interpretable);
- Non-ST-Elevation MI (NSTEMI). The additional categories NSTEMI may include: Q wave, non-Q-wave, or unknown (no ECG or ECG non-interpretable); and
- Unknown (no ECG or ECG not interpretable).

[0363] All events adjudicated as MI were 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.

[0364] 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.

[0365] Definition of Hospitalize of Unstable Angina: Unstable angina requiring hospitalization is defined as:

- 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;
- 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
- At least one of the following:
    - New or worsening ST or T wave changes on resting ECG (in 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.
    - 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 at least one of the following: stress echocardiography (reversible wall motion

abnormality); myocardial scintigraphy (reversible perfusion defect); or MRI (myocardial perfusion deficit under pharmacologic stress.

- 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; and
- 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;

- Negative cardiac biomarkers and no evidence of acute MI.

[0366] General Considerations include:

[0367] 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.

[0368] If subjects were admitted with suspected unstable angina, and subsequent testing revealed a noncardiac or non-ischemic etiology, this event should not have been recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for myocardial infarction should not have been adjudicated as unstable angina.

[0369] Planned hospitalization or re-hospitalization for performance of an elective revascularization in patients who did not fulfill the criteria for unstable angina should not have been 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; or 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.

[0370] A patient who underwent an elective catheterization where incidental coronary artery disease was found and who subsequently underwent coronary revascularization was not be considered as meeting the hospitalization for unstable angina endpoint.

[0371] 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.

[0372] Stroke: Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

[0373] 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.

[0374] 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. However, microhemorrhages seen on T2-weighted MRI imaging, subdural and epidural hemorrhages are not considered hemorrhagic strokes.

[0375] 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.

[0376] 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 show below in Table 13 may be used to address this requirement:

[0377] Table 13. Rankin Scaled Used to Assess Stroke Disability in Patients

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 and attention.
6	Dead

[0378] 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.

[0379] Definition of Heart Failure Event: is defined as an event that meets all of the following criteria:

- The patient is admitted to the hospital with a primary diagnosis of HF;
- 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);
- The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least one of the following: dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea), decreased exercise tolerance, fatigue, or other symptoms of worsened end-organ perfusion or volume overload (must be specified and described by the protocol);
- 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:
    - Physical examination findings considered to be due to heart failure, including new or worsened: Peripheral edema, increasing abdominal

distention or ascites (in the absence of primary hepatic disease), S_3 gallop, clinically significant or rapid weight gain thought to be related to fluid retention; or

- Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including: 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, radiological evidence of pulmonary congestion, or 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.

- The patient receives initiation or intensification of treatment specifically for HF, including at least one of the following: significant augmentation in oral diuretic therapy, intravenous diuretic, inotrope, or vasodilator therapy, or Mechanical or surgical intervention. The mechanical or surgical intervention including mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device) and/or mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis).

[0380] New Heart Failure/Heart Failure Not Requiring Hospitalization*:* is defined as an event that meets all of the following: 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; all signs and symptoms for HF hospitalization must be met as defined in A Heart Failure Hospitalization above; and 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 was not sufficient.

Interventional Cardiology Definitions

[0381] Clinical Definitions:

[0382] 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 history of angina pectoris, presumably related to the target vessel; objective signs of ischemia at rest (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel; and abnormal results of any invasive functional diagnostic test (e.g., coronary flow reserve [CFR] or fractional flow reserve [FFR]).

[0383] 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.

[0384] 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.

[0385] Percutaneous Coronary Intervention (PCI) Status includes:

- 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.
- 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.

- 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.
- 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).

[0386] 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 was not considered PCI.

[0387] Peripheral Vascular Intervention Definitions:

[0388] Peripheral Vascular Intervention Definition*:* 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.

[0389] Procedural Status includes:

- 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).
- 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.

[0390] 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.

[0391] 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:

- Atrial arrhythmia – atrial fibrillation, atrial flutter, supraventricular tachycardia that requires cardio-version, drug therapy, or is sustained for greater than 1 minute;
- Ventricular arrhythmia – Ventricular tachycardia or ventricular fibrillation requiring cardio-version and/or intravenous antiarrhythmics; and/or
- 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.

[0392] 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 is further sub-classified into either: witnessed, occurring within 60 min from the onset of new symptoms, in the absence of a clear cause other than cardiovascular; or unwitnessed, within 24 hours of being observed alive, in the absence of pre-existing other non-cardiovascular causes of death;

[0393] Non-cardiac causes of cardiac arrest, such as drug overdose, suicide, drowning, hypoxia, exsanguination, cerebrovascular accident, subarachnoid hemorrhage, or trauma must not be present.

[0394] Definition of Resuscitated Cardiac Arrest: Resuscitated Cardiac Arrest is present when there is restoration of both: organized electrical activity and 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).

[0395] 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 with cut points of parameters as defined in Table 1 and listed below, and waist circumference cut points further guided by the Table 14.

- 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; and
- Elevated fasting glucose (fasting glucose ≥100 mg/dL, or on drug therapy for elevated glucose.

[0396] Table 14. Current Recommended Waist Circumference Thresholds for Abdominal Obesity by Organization and Population.

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)*	US	≥102	≥88
Health Canada	Canada	≥102	≥88
European Cardiovascular Societies	European	≥102	≥88
IDF	Asian (including Japanese)	≥90	≥80
WHO	Asian	≥90	≥80
Japanese Obesity Society	Japanese	≥85	≥90
Cooperative Task Force	China	≥85	≥80
IDF	Middle East, Mediterranean	≥94	≥80
IDF	Sub-Saharan African	≥94	≥80
IDF	Ethnic Central & South American	≥90	≥80

Organization	Population (Reference)	Waist Circumference Threshold	
		Men(cm)	Women (cm)
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.			

[0397] Statistical Analysis

[0398] In this event-driven trial, it was estimated that approximately 1612 adjudicated primary endpoint events would be necessary to provide 90% power to detect a 15% lower risk of the primary composite endpoint in the AMR101 group than in the placebo group. This resulted in an estimated sample size of approximately 7990 patients to reach the number of primary endpoints. The primary efficacy analysis was based on the time from randomization to the first occurrence of any component of the primary composite endpoint. If the relative risk reduction with administration of AMR101 in the primary endpoint was significant (final two-sided alpha level = 0.0437; determined from O'Brien-Fleming boundaries generated using the Lan-DeMets alpha-spending function after accounting for two protocol pre-specified interim efficacy analyses), in a hierarchical fashion, the key secondary endpoint and other prespecified secondary endpoints were to be tested at the same final alpha level of 0.0437. All primary efficacy analyses followed the intent-to-treat principle. HRs and 95% CI were generated using a Cox proportional hazard model with treatment as covariate, and stratified by cardiovascular risk category, geographic region, and use of ezetimibe. Log-rank P values were reported from a Kaplan–Meier analysis, stratified by the three randomization factors, to evaluate the timing of events in the two treatment groups.

[0399] **Results**

[0400] Subject Disposition*:* The subject disposition by treatment group is depicted in Figure 2. A total of 19,212 patients were screened of whom 8,179 (43%) were randomized. At the time of database lock, vital status was available in 99.8%; 152 (1.9%) patients did not complete final study visits and 578 (7.1%) patients withdrew consent. Demographic and Baseline Disease Characteristics: Among the patients who underwent randomization, 70.7% were enrolled on the basis of secondary prevention (i.e., patients had established cardiovascular disease) and 29.3% for primary prevention (i.e., patients had diabetes mellitus and at least one additional risk factor). The median

age was 64 years, 28.8% were female, and 38.5% were from the United States. At baseline, the median LDL-cholesterol was 75.0 mg/dL, HDL-cholesterol was 40.0 mg/dL, and triglycerides were 216.0 mg/dL. The baseline characteristics of the patients are provided below in Table 16.

[0401] Table 16. Demographic and Randomization Stratification Information of the ITT Population

	Icosapent ethyl (N=4089)	Placebo (N=4090)
Age (years), Median (Q1-Q3)	64.0 (57.0 - 69.0)	64.0 (57.0 - 69.0)
Female, (n %)	1162 (28.4%)	1195 (29.2%)
Non-White, (n %)	398 (9.7%)	401 (9.8%)
Age ≥65 years, n (%)	1857 (45.4%)	1906 (46.6%)
Male, n (%)	2927 (71.6%)	2895 (70.8%)
White, n (%)[1]	3691 (90.3%)	3688 (90.2%)
BMI (kg/m^2), Median (Q1-Q3)	30.8 (27.8 - 34.5)	30.8 (27.9 - 34.7)
BMI ≥30 (kg/M^2), n (%)	2331 (57.0%)	2362 (57.8%)
Geographic Region, n (%)		
Westernized [2]	2906 (71.1%)	2905 (71.0%)
Eastern Europe [3]	1053 (25.8%)	1053 (25.7%)
Asia Pacific [4]	130 (3.2%)	132 (3.2%)
CV Risk Category, n (%)		
Secondary Prevention	2892 (70.7%)	2893 (70.7%)
Primary Prevention	1197 (29.3%)	1197 (29.3%)
Ezetimibe Use, n (%)	262 (6.4%)	262 (6.4%)
Statin Intensity, n (%)		
Low	254 (6.2%)	267 (6.5%)
Moderate	2533 (61.9%)	2575 (63.0%)
High	1290 (31.5%)	1226 (30.0%)
Missing	12 (0.3%)	22 (0.5%)
Diabetes, n (%)		

Type I Diabetes	27 (0.7%)	30 (0.7%)
Type II Diabetes	2367 (57.9%)	2363 (57.8%)
No Diabetes at Baseline	1695 (41.5%)	1694 (41.4%)
Data Missing	0	3 (0.1%)
hsCRP (mg/L), Median (Q1-Q3)	2.2 (1.1 - 4.5)	2.1 (1.1 - 4.5)
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5 - 46.0)	40.0 (35.0 - 46.0)
LDL-C (mg/dL), Median (Q1-Q3)	74.0(61.5-88.0)	76.0 (63.0 - 89.0)
Triglycerides Category		
<150 mg/dL	412 (10.1%)	429 (10.5%)
150 to < 200 mg/dL	1193 (29.2%)	1191 (29.1%)
≥ 200 mg/dL	2481 (60.7%)	2469 (60.4%)
Triglycerides ≥ 200 mg/dL and HDL-C ≤ 35 mg/dL	823 (20.1%)	794 (19.4%)
EPA (µg/mL), Median (Q1-Q3)	26.1 (17.1 - 40.1)	26.1 (17.1 - 39.9)

In general, the baseline value is defined as the last non-missing measurement obtained prior to the randomization. The baseline LDL-C value obtained via Preparative Ultracentrifugation was used, unless this value was missing. If the LDL-C Preparative Ultracentrifugation value was missing, then another LDL-C value was be used, with prioritization of values obtained from LDL-C Direct measurements, followed by LDL-C derived by the Friedewald calculation (only for patients with TG < 400 mg/dL), and finally LDL-C derived using the calculation published by Johns Hopkins University investigators.22 At Visit 1 and Visit 1.1 Direct LDL-C was used if at the same visit TG >400 mg/dL At alll remaining visits LDL-C was measured by Direct LDL-C or by Preparative Ultracentrifugation if at the same visit TG >400 mg/dL. For all other lipid and lipoprotein marker parameters, wherever possible, baseline was 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 was available, the single available value was used as baseline. The only significant baseline between group difference with $p < 0.05$ was LDL-C ($p= 0.03$).
[1] Race as reported by the investigators.
[2] Westernized region includes Australia, Canada, Netherlands, New Zealand, United States, and South Africa.
[3] Eastern European region includes Poland, Romania, Russian Federation, and Ukraine.
[4] Asia Pacific region includes India.

[0402] The median trial follow-up duration was 4.9 years with a maximum of 6.2 years. The median change in triglycerides from baseline to one year was –18.3% (–39.0 mg/dL) in the AMR101 group and +2.2% (4.5 mg/dL) in the placebo group; the median reduction from baseline (as estimated with the use of the Hodges–Lehmann approach) was 19.7% greater in the AMR101 group than in the placebo group (a 44.5 mg/dL [0.50 mmol/L] greater reduction; P<0.001). The median change in LDL cholesterol level from

baseline was an increase of 3.1% (2.0 mg/dL [0.05 mmol/L]) in the AMR101 group and an increase of 10.2% (7.0 mg /dL [0.18 mmol/L]) in the placebo group — a 6.6% (5.0 mg/dL [0.13 mmol/L]) lower increase with AMR101 than with placebo (P<0.001).

[0403] Analyses of Primary Composite Endpoint:

[0404] There were a total of 1606 adjudicated primary endpoint first events. Figure 3A shows the Kaplan-Meier event curves for the primary efficacy endpoint of time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in the AMR101 and placebo groups with the inset showing the data on an expanded y axis. All patients were included in the analysis and patients experiencing more than one type of endpoint event were counted for their first occurrence in each event type. The primary endpoint as shown in Figure 3A occurred in 17.2% of AMR101 patients versus in 22.0% of placebo patients (HR, 0.75; 95% CI, 0.68-0.83; P<0.001) for an absolute risk reduction (AAR) of 4.8% (95% CI, 3.1-6.5%) and number needed to treat (NNT) of 21 (95% CI, 15-33) over median follow up 4.9 years. Similarly, Figure 3B shows the Kaplan-Meier estimates of the cumulative incidence of the primary composition endpoints over time. Significantly, Figure 3B indicates a 25% relative risk reduction for the primary composite endpoint over the course of 5 years.

[0405] Figure 4 lists the individual components of the primary endpoint analyzed as time to first event of each individual endpoint. Shown first in Figure 4 is the HR and 95% CI for the primary composite endpoint event (time to first occurrence of either cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina). Shown separately beneath Figure 4 are HRs and 95% CIs for time to first occurrence of each type of individual primary endpoint component event, irrespective of whether contributing to the primary composite endpoint event or not.

[0406] Analyses of Key Secondary Endpoints:

[0407] Figure. 5A shows the Kaplan-Meier event curves for the key secondary efficacy endpoint of time to first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the AMR101 and placebo groups with the inset showing the data on an expanded y axis. All patients were included in the analysis and patients experiencing more than one type of endpoint event were counted for their first

occurrence in each event type. The key secondary efficacy endpoint as shown in Figure 5A occurred in 11.2% of AMR101 patients versus 14.8% of placebo patients (HR, 0.74, 95% CI 0.65-0.83, P<0.001) for an absolute risk reduction of 3.6% (95% CI, 2.1-5.0%) and a number needed to treat of 28 (95% CI, 20-47) over median follow up 4.9 years. Similarly, Figure 5B shows the Kaplan-Meier estimates of the cumulative incidence of the key secondary composition endpoints over time. Significantly, Figure 5B indicates a 26% relative risk reduction for the key secondary composite endpoint over the course of 5 years.

[0408] Analysis of Prespecified Subgroups

[0409] The primary efficacy outcomes in select prespecified subgroups are shown in Figures 6 and 7 with corresponding HRs and 95% CIs for the primary efficacy endpoint of time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina from select prespecified subgroups in the AMR101 and placebo groups. The key secondary efficacy outcomes in select prespecified subgroups are shown in Figures 8 and 9 with corresponding HRs and 95% CIs for the key secondary efficacy endpoint of time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina from select prespecified subgroups in the AMR101 and placebo groups. Significantly, Figures 6-9 indicate that a subject's baseline triglyceride levels (e.g., ≥150 vs. <150 mg/dL or ≥200 or <200 mg/dL) had no influence on the primary or key secondary efficacy endpoints.

[0410] This conclusion is further substantiated by the combination of Figures 10A and 10B which show that achievement of on-treatment triglyceride levels above or below 150 mg/dL at one year did not influence the efficacy of AMR101 versus placebo. In particular, Figures 10A and 10B show the primary and key secondary endpoints by achieved triglyceride level (e.g., above or below 150 mg/dL) at 1 year (e.g., patients with a triglyceride level above or below 150 mg/dL after 1 year of having received the AMR101). Figure 10A are the Kaplan-Meier curves for the primary endpoint of time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in the AMR101 treatment group for patients with achieved triglycerides, and the placebo group at year 1. Conversely, Figure 10B are the Kaplan-Meier event curves for the key secondary endpoint of time

to first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the AMR101 treatment group for patients with achieved triglycerides, and the placebo group at year 1. Importantly, Figures 10A and 10B indicate that regardless of the subject's triglyceride levels at year 1, the subject experienced a statistically significant reduction in time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The attainment of triglyceride levels of 150 mg/dL or higher or below 150 mg/dL at 1 year after randomization also had no influence on the efficacy of AMR101 as compared with placebo with respect to the primary or key secondary efficacy endpoint. In a *post hoc* analysis, no substantial difference in the benefit of AMR101 as compared with placebo was observed with respect to the primary endpoint according to whether the patients who received placebo had an increase in LDL cholesterol levels at 1 year or had no change or a decrease in LDL cholesterol levels.

[0411] Figure 11 depicts the prespecified hierarchical testing of the endpoints; except for the last hierarchical secondary endpoint of death from any cause (also referred to as total mortality), all other individual and composite ischemic endpoints were significantly reduced by AMR101, including cardiovascular death (4.3% versus 5.2%; HR, 0.80; 95% CI, 0.66-0.98; P=0.03). Total mortality was 6.7% versus 7.6% (HR, 0.87; 95% CI, 0.74-1.02; P=0.09) in the AMR101 and placebo groups, respectively. For each of the prespecified endpoints in Figure 11, icosapent ethyl 4g per day provide a RRR of 25% for the primary composite endpoint, 26% for the secondary composite endpoint, 25% for the composite of cardiovascular death or nonfatal myocardial infarction, 31% for fatal or nonfatal myocardial infarction, 35% for urgent or emergent revascularization, 20% for cardiovascular death, 32% for hospitalization for unstable angina, 28% for fatal or nonfatal stroke, 23% reduction in the composite of total mortality, nonfatal myocardial infarction, or nonfatal stroke, and lastly, a 13% reduction in total mortality.

[0412] Results for selected tertiary outcomes are shown in Table 17. A tertiary endpoint, adjudicated sudden cardiac death was 2.1% versus 1.5% (HR, 0.69; 95% CI, 0.50-0.96).

[0413] Table 17. Selected Prespecified Adjudicated Tertiary Endpoints

Tertiary Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)
Primary Endpoint in Patients with Diabetes at Baseline	433/2394 (18.1%)	536/2393 (22.4%)	0.77 (0.68, 0.87)
New Heart Failure	169/4089 (4.1%)	176/4090 (4.3%)	0.95 (0.77, 1.17)
New Heart Failure Requiring Hospitalization	141/4089 (3.4%)	144/4090 (3.5%)	0.97 (0.77, 1.22)
Transient Ischemic Attack	64/4089 (1.6%)	48/4090 (1.2%)	1.32 (0.91, 1.92)
Amputation for PVD	22/4089 (0.5%)	21/4090 (0.5%)	1.04 (0.57, 1.89)
Carotid Revascularization	31/4089 (0.8%)	26/4090 (0.6%)	1.18 (0.70, 1.98)
Coronary Revascularization	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58, 0.76)
Emergent Revascularization	41/4089 (1.0%)	65/4090 (1.6%)	0.62 (0.42, 0.92)
Urgent Revascularization	181/4089 (4.4%)	268/4090 (6.6%)	0.66 (0.54, 0.79)
Elective Revascularization	194/4089 (4.7%)	278/4090 (6.8%)	0.68 (0.57, 0.82)
Salvage Revascularization	0/4089 (0.0%)	2/4090 (0.0%)	0.00 (0.00, -)
Cardiac Arrhythmias Requiring Hospitalization of ≥ 24 Hours	188/4089 (4.6%)	154/4090 (3.8%)	1.21 (0.97, 1.49)
Cardiac Arrest	22/4089 (0.5%)	42/4090 (1.0%)	0.52 (0.31, 0.86)
Sudden Cardiac Death	61/4089 (1.5%)	87/4090 (2.1%)	0.69 (0.50, 0.96)
Ischemic Stroke	80/4089 (2.0%)	122/4090 (3.0%)	0.64 (0.49, 0.85)

Tertiary Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)
Hemorrhagic Stroke	13/4089 (0.3%)	10/4090 (0.2%)	1.28 (0.56, 2.93)
New Onset of Diabetes[1]	65/1695 (3.8%)	63/1697 (3.7%)	1.04 (0.73, 1.47)

[1] Patents with diabetes at baseline are excluded from this endpoint analysis.

[0414] Analysis of Additional Biomarker from Baseline:

[0415] The effects on additional biomarkers to year 1 are shown in Table 18.

[0416] Table 18. Effect on Biomarkers from Baseline to Year 1

	Icosapent Ethyl (N=4089) Median		**Placebo (N=4090) Median**		**Median Between Group Difference at Year 1**		
Biomarker	**Baseline**	**Year 1**	**Baseline**	**Year 1**	**Absolute Change from Baseline**	**% Change from Baseline**	**% Change P-value**
Triglycerides (mg/dL)	216.5	175.0	216.0	221.0	-44.5	-19.7	<0.0001
Non-HDL-C (mg/dL)	118.0	113.0	118.5	130.0	-15.5	-13.1	<0.0001
LDL-C (mg/dL)	74.5	77.0	76.0	84.0	-5.0	-6.6	<0.0001
HDL-C (mg/dL)	40.0	39.0	40.0	42.0	-2.5	-6.3	<0.0001
Apo B (mg/dL)	82.0	80.0	83.0	89.0	-8.0	-9.7	<0.0001
hsCRP (mg/L)	2.2	1.8	2.1	2.8	-0.9	-39.9	<0.0001
EPA (µg/mL)	26.1	144.0	26.1	23.3	114.9	358.8	<0.0001

[0417] The effects on lipid, lipoprotein, and inflammatory marker overtime for the ITT population are shown in Table 19.

[0418] Table 19. Lipid, Lipoprotein, and Inflammatory Marker Data Over Time for the ITT Population

		Icosapent Ethyl (N=4089)				**Placebo (N=4090)**				**Between Group Difference**		
Biomarker	**Visit**	**Median Observed Value**	**Median Absolute Change from Baseline**	**Median % Change from Baseline**	**Median % Change P-value[1]**	**Median Observed Value**	**Median Absolute Change from Baseline**	**Median % Change from Baseline**	**Median % Change P-value[1]**	**Median Absolute Change from Baseline[2]**	**Median % Change from Baseline[2]**	**Median % Change P value[3]**
Triglycerides (mg/dL)	Baseline	216.5				216.0						
	Month 4	177.0	-37.5	-18.6	<0.001	221.0	5.5	2.7	<0.001	-45.5	-20.1	<0.001
	Year 1	175.0	-39.0	-18.3	<0.001	221.0	4.5	2.2	<0.001	-44.5	-19.7	<0.001
	Year 2	173.0	-38.5	-18.9	<0.001	220.0	4.3	2.1	<0.001	-43.8	-19.7	<0.001
	Year 3	167.0	-44.0	-21.7	<0.001	212.0	1.0	0.4	<0.001	-45.5	-20.3	<0.001

	Year 4	163.0	-42.5	-21.7	<0.001	200.0	-7.0	-3.7	>0.99	-38.0	-17.4	<0.001
	Year 5	158.0	-38.0	-20.0	<0.001	193.0	-3.0	-1.5	0.23	-33.5	-16.7	<0.001
	Last Visit	170.0	-45.0	-21.6	<0.001	202.0	-13.0	-6.5	<0.001	-32.0	-14.1	<0.001
Non-HDL-C (mg/dL)	Baseline	118.0				118.5						
	Month 4	113.0	-4.5	-4.0	<0.001	128.0	9.5	8.2	<0.001	-14.3	-12.2	<0.001
	Year 1	113.0	-4.0	-3.6	<0.001	130.0	12.0	10.4	<0.001	-15.5	-13.1	<0.001
	Year 2	113.0	-3.5	-3.1	0.002	129.0	11.5	9.8	<0.001	-14.5	-12.5	<0.001
	Year 3	112.0	-4.8	-4.2	<0.001	128.0	10.5	9.2	<0.001	-14.5	-12.4	<0.001
	Year 4	110.5	-5.0	-4.2	<0.001	126.0	9.5	8.1	<0.001	-14.0	-12.0	<0.001
	Year 5	109.0	-5.0	-4.4	0.004	123.0	7.0	6.1	<0.001	-11.0	-9.9	<0.001
	Last Visit	112.0	-5.0	-4.4	<0.001	124.0	6.0	5.1	<0.001	-10.0	-8.6	<0.001
LDL-C derived (mg/dL)[4]	Baseline	74.0				76.0						
	Year 1	77.0	2.0	3.1	<0.001	84.0	7.0	10.2	<0.001	-5.0	-6.6	<0.001
	Last Visit	77.0	2.0	3.1	<0.001	84.0	7.0	10.2	<0.001	-5.0	-6.6	<0.001
LDL-C Hopkins (mg/dL)	Baseline	85.8				86.7						
	Month 4	83.6	-1.6	-2.0	0.01	93.7	7.3	8.7	<0.001	-8.7	-10.3	<0.001
	Year 1	85.3	-1.1	-1.2	0.06	95.8	9.3	10.9	<0.001	-9.6	-11.4	<0.001
	Year 2	85.5	-0.1	-0.2	<0.001	96.1	9.5	11.4	<0.001	-9.4	-11.1	<0.001
	Year 3	84.6	-1.0	-1.2	0.01	95.7	9.0	10.5	<0.001	-8.7	-10.4	<0.001
	Year 4	83.6	-0.5	-0.6	0.07	94.7	8.8	10.1	<0.001	-8.9	-10.6	<0.001
	Year 5	82.2	-0.8	-0.7	0.23	91.6	6.2	6.9	<0.001	-6.6	-8.0	<0.001
	Last Visit	84.0	-1.0	-1.2	0.14	92.1	5.7	6.5	<0.001	-6.2	-7.4	<0.001
HDL-C (mg/dL)	Baseline	40.0				40.0						
	Month 4	39.0	-1.0	-2.8	<0.001	42.0	2.0	4.7	<0.001	-3.0	-7.2	<0.001
	Year 1	39.0	-1.0	-2.6	<0.001	42.0	1.5	3.8	<0.001	-2.5	-6.3	<0.001
	Year 2	40.0	0.0	0.0	0.21	42.0	1.5	4.2	<0.001	-2.0	-4.6	<0.001
	Year 3	40.0	0.0	0.0	0.006	42.0	1.5	4.0	<0.001	-1.5	-3.8	<0.001
	Year 4	40.5	0.5	1.0	<0.001	43.0	2.0	4.8	<0.001	-1.5	-3.9	<0.001
	Year 5	41.0	0.0	0.0	0.02	43.0	1.5	3.0	<0.001	-1.5	-3.0	<0.001
	Last Visit	41.0	1.0	2.5	<0.001	42.0	2.0	5.7	<0.001	-1.0	-3.0	<0.001
Apo B (mg/dL)	Baseline	82.0				83.0						
	Year 2	80.0	-2.0	-2.5	0.05	89.0	6.0	7.8	<0.001	-8.0	-9.7	<0.001
	Last Visit	80.0	-2.0	-2.5	0.06	86.0	4.0	4.5	<0.001	-5.0	-6.7	<0.001
hsCRP (mg/L)	Baseline	2.2				2.1						
	Year 2	1.8	-0.2	-13.9	0.04	2.8	0.5	32.3	<0.001	-0.9	-39.9	<0.001
	Last Visit	1.8	-0.2	-12.6	0.75	2.8	0.4	29.9	<0.001	-0.8	-37.6	<0.001
Log hsCRP (mg/L)	Baseline	0.8				0.8						
	Year 2	0.6	-0.1	-21.8	<.0001	1.0	0.3	0.0	0.9203	-0.4	-22.5	<.0001
	Last Visit	0.6	-0.1	-23.1	<.0001	1.0	0.3	-4.0	0.0481	-0.4	-21.2	<.0001
EPA (µg/mL)[5]	Baseline	26.1				26.1						
	Year 1	144.0	112.6	393.5	<0.001	23.3	-2.9	-12.8	<0.001	114.9	358.8	<0.001

Safety Results

[0419] The results from this study showed no new or unexpected important adverse effects were observed in the safety population for this study as shown below in Tables 20 and 21. These conclusions are consistent with the independent DMC review conclusions and with quarterly safety review conclusions.

[0420] Table 20. Overview of Treatment-Emergent Adverse Events of the Safety Population

	AMR101 (N=4089)	Placebo (N=4090)	p-value[1]
Subjects with at Least One TEAE [2], n(%)	3343 (81.8%)	3326 (81.3%)	0.63
Serious TEAE	1252 (30.6%)	1254 (30.7%)	0.98
TEAE Leading to Withdrawal of Study Drug [3]	321 (7.9%)	335 (8.2%)	0.60

	AMR101 (N=4089)	Placebo (N=4090)	p-value[1]
Serious TEAE Leading to Withdrawal of Study Drug [3]	88 (2.2%)	88 (2.2%)	1.00
Serious TEAE Leading to Death[4]	94 (2.3%)	102 (2.5%)	0.61

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
[1] P-value from Fisher's Exact test.
[2] All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
[3] Withdrawal of study drug excludes patients who were off drug in study (ODIS) for 30 days or more, and restarted study drug.
[4] The most common serious TEAEs leading to death by system organ class were neoplasms (1.1%); infections and infestations (0.4%); respiratory, thoracic, and mediastinal disorders (0.2%); cardiac disorders (0.2%); and vascular disorders (0.1%). No serious TEAEs leading to death by system organ class were statistically significant across treatment groups except for cardiac disorders, which occurred in 3 (0.1%) of VASCEPA® patients and 15 (0.4%) of placebo patents (p=0.008).

[0421] Table 21. Serious Bleeding Treatment-Emergent Adverse Events by Preferred term.

Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	p-value [1]
Bleeding related disorders	111 (2.7%)	85 (2.1%)	0.06
Gastrointestinal bleeding	62 (1.5%)	47 (1.1%)	0.15
Central nervous system bleeding	14 (0.3%)	10 (0.2%)	0.42
Other bleeding	41 (1.0%)	30 (0.7%)	0.19

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
[1] Fishers Exact test.

[0422] Adverse events occurring in ≥5% are reported in Table 22. Compared with placebo, AMR101 was associated with a significantly higher rate of atrial fibrillation (5.3% versus 3.9%), and peripheral edema (6.5% vs 5%), but a lower rate of diarrhea (9% vs 11.1 %), anemia (4.7% vs 5.8%), and gastrointestinal adverse events (33.0% to 35.1%). There was no significant difference in the prespecified adjudicated tertiary endpoint of heart failure (4.1% vs 4.3%). The prespecified adjudicated tertiary endpoint of atrial fibrillation or flutter requiring hospitalization was more common with the AMR101 group than the placebo group (3.1% vs 2.1%; P=0.004).

[0423] Table 22. Number (%) Patients with Most Frequent Treatment-Emergent Adverse Events (≥5%) in Either Treatment Group By Preferred Term for the Safety Population

Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value [1]
Diarrhea	367 (9.0%)	453 (11.1%)	0.002
Back pain	335 (8.2%)	309 (7.6%)	0.29
Hypertension	320 (7.8%)	344 (8.4%)	0.35
Nasopharyngitis	314 (7.7%)	300 (7.3%)	0.56
Arthralgia	313 (7.7%)	310 (7.6%)	0.90
Upper respiratory tract infection	312 (7.6%)	320 (7.8%)	0.77
Bronchitis	306 (7.5%)	300 (7.3%)	0.80
Chest pain	273 (6.7%)	290 (7.1%)	0.48
Peripheral edema	267 (6.5%)	203 (5.0%)	0.002
Pneumonia	263 (6.4%)	277 (6.8%)	0.56
Influenza	263 (6.4%)	271 (6.6%)	0.75
Dyspnea	254 (6.2%)	240 (5.9%)	0.52
Urinary tract infection	253 (6.2%)	261 (6.4%)	0.75
Cough	241 (5.9%)	241 (5.9%)	1.00
Osteoarthritis	241 (5.9%)	218 (5.3%)	0.27
Dizziness	235 (5.7%)	246 (6.0%)	0.64
Pain in extremity	235 (5.7%)	241 (5.9%)	0.81
Cataract	233 (5.7%)	208 (5.1%)	0.22
Fatigue	228 (5.6%)	196 (4.8%)	0.11
Constipation	221 (5.4%)	149 (3.6%)	<0.001
Atrial fibrillation	215 (5.3%)	159 (3.9%)	0.003
Angina pectoris	200 (4.9%)	205 (5.0%)	0.84
Anemia	191 (4.7%)	236 (5.8%)	0.03

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
[1] P-value from Fishers Exact test.

[0424] Serious treatment-emergent events occurring in ≥2% are reported in Table 23.

[0425] Table 23. Number (%) Patients with Serious Treatment-Emergent Adverse Events (≥2%) in Either Treatment Group) By Preferred Term

Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	p-value [1]
Pneumonia	105 (2.6%)	118 (2.9%)	0.42

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
[1] Fishers Exact test.

[0426] Adjudicated events from hospitalization for arterial fibrillation or atrial flutter are reported in Table 24.

[0427] Table 24. Number (%) Patients with Serious Treatment-Emergent Adverse Events (≥2%) in Either Treatment Group) By Preferred Term

Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	p-value [1]
Positively Adjudicated Atrial Fibrillation/Flutter [1]	127 (3.1%)	84 (2.1%)	0.0037

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
[1] Fishers Exact test.

[0428] Tolerability of gastrointestinal TEAS in either treatment group are reported are reported in Table 25.

[0429] Table 25. Tolerability of gastrointestinal TEAS

Primary System Organ Class Preferred Term	**Icosapent Ethyl (N=4089)**	**Placebo (N=4090)**	**P-value [1]**
Gastrointestinal disorders	1350 (33.0%)	1437 (35.1%)	0.04
Diarrhea	367 (9.0%)	453 (11.1%)	0.002
Constipation	221 (5.4%)	149 (3.6%)	<0.001
Nausea	190 (4.6%)	197 (4.8%)	0.75
Gastroesophageal Reflux Disease	124 (3.0%)	118 (2.9%)	0.70

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
[1] P value from Fisher's Exact test.

[0430] When grouping treatment-emergent serious adverse events for bleeding, the rate was 2.7% in the AMR101 group versus 2.1% in the placebo group (P=0.06),

although there were no fatal bleeding events in either group, and no significant increases in adjudicated hemorrhagic stroke (0.3% vs 0.2 %; P=0.55), serious central nervous system bleeding (0.3% versus 0.2%; P=0.42), or gastrointestinal bleeding (1.5% versus 1.1%; P=0.15). Table 26 enumerates the serious bleeding treatment-emergent adverse events by preferred term.

[0431] Table 26. Assessment of Serious Bleeding Treatment-Emergent Adverse Events by Category and by Preferred Term.

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P Value[1]
Patients with Bleeding-Related Disorders[2]	111 (2.7%)	85 (2.1%)	0.06
By Category			
Gastrointestinal Bleeding[3]	62 (1.5%)	47 (1.1%)	0.15
Central Nervous System Bleeding[4]	14 (0.3%)	10 (0.2%)	0.42
Other Bleeding[5]	41 (1.0%)	30 (0.7%)	0.19
By Preferred Term			
Gastrointestinal Hemorrhage	26 (0.6%)	20 (0.5%)	0.38
Rectal Hemorrhage	10 (0.2%)	6 (0.1%)	0.33
Subdural Hematoma	9 (0.2%)	5 (0.1%)	0.30
Hematuria	8 (0.2%)	4 (0.1%)	0.27
Epistaxis	7 (0.2%)	4 (0.1%)	0.39
Lower Gastrointestinal Hemorrhage	5 (0.1%)	4 (0.1%)	0.75
Post Procedural Hemorrhage	5 (0.1%)	3 (0.1%)	0.51
Hemorrhagic Anemia	4 (0.1%)	1 (0.0%)	0.22
Gastric Ulcer Hemorrhage	3 (0.1%)	1 (0.0%)	0.37
Hematemesis	3 (0.1%)	0 (0.0%)	0.12
Hemorrhoidal Hemorrhage	3 (0.1%)	1 (0.0%)	0.37
Melaena	3 (0.1%)	4 (0.1%)	>0.99
Upper Gastrointestinal Hemorrhage	3 (0.1%)	3 (0.1%)	>0.99
Diverticulum Intestinal Hemorrhagic	3 (0.1%)	3 (0.1%)	>0.99
Shock Hemorrhagic	2 (0.0%)	0 (0.0%)	0.25
Cystitis Hemorrhagic	2 (0.0%)	0 (0.0%)	0.25
Subarachnoid Hemorrhage	2 (0.0%)	1 (0.0%)	0.62
Subdural Hemorrhage	2 (0.0%)	1 (0.0%)	0.62

Traumatic Hematoma	2 (0.0%)	1 (0.0%)	0.62
Duodenal Ulcer Hemorrhage	2 (0.0%)	0 (0.0%)	0.25
Aortic Aneurysm Rupture	1 (0.0%)	1 (0.0%)	>0.99
Ecchymosis	1 (0.0%)	0 (0.0%)	0.50
Extravasation Blood	1 (0.0%)	0 (0.0%)	0.50
Gastric Hemorrhage	1 (0.0%)	3 (0.1%)	0.62
Gastrointestinal Angiodysplasia Hemorrhagic	1 (0.0%)	0 (0.0%)	0.50
Genital Hemorrhage	1 (0.0%)	0 (0.0%)	0.50
Hematochezia	1 (0.0%)	2 (0.0%)	>0.99
Hematoma	1 (0.0%)	1 (0.0%)	>0.99
Hemoptysis	1 (0.0%)	0 (0.0%)	0.50
Hemorrhagic Transformation Stroke	1 (0.0%)	0 (0.0%)	0.50
Hemothorax	1 (0.0%)	1 (0.0%)	>0.99
Intra-Abdominal Hemorrhage	1 (0.0%)	0 (0.0%)	0.50
Large Intestinal Hemorrhage	1 (0.0%)	1 (0.0%)	>0.99
Mallory-Weiss Syndrome	1 (0.0%)	0 (0.0%)	0.50
Menorrhagia	1 (0.0%)	0 (0.0%)	0.50
Pancreatitis Hemorrhagic	1 (0.0%)	0 (0.0%)	0.50
Peptic Ulcer Hemorrhage	1 (0.0%)	0 (0.0%)	0.50
Post Procedural Hematoma	1 (0.0%)	1 (0.0%)	>0.99
Retinal Hemorrhage	1 (0.0%)	1 (0.0%)	>0.99
Retroperitoneal Hemorrhage	1 (0.0%)	0 (0.0%)	0.50
Ulcer Hemorrhage	1 (0.0%)	0 (0.0%)	0.50
Urinary Bladder Hemorrhage	1 (0.0%)	1 (0.0%)	>0.99
Hemarthrosis	0 (0.0%)	1 (0.0%)	>0.99
Brain Contusion	0 (0.0%)	2 (0.0%)	0.50
Intracranial Hemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Immune Thrombocytopenic Purpura	0 (0.0%)	1 (0.0%)	>0.99
Catheter Site Hemorrhage	0 (0.0%)	1 (0.0%)	>0.99

Mouth Hemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Esophageal Hemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Cerebral Hemorrhage	0 (0.0%)	2 (0.0%)	0.50
Pericardial Hemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Post Procedural Hematuria	0 (0.0%)	1 (0.0%)	>0.99
Renal Hemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Retroperitoneal Hematoma	0 (0.0%)	1 (0.0%)	>0.99
Traumatic Intracranial Hemorrhage	0 (0.0%)	1 (0.0%)	>0.99
Diverticulitis Intestinal Hemorrhagic	0 (0.0%)	1 (0.0%)	>0.99
Hemorrhagic Duodenitis	0 (0.0%)	1 (0.0%)	>0.99

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1). [1] P value from Fisher's Exact test.
[2] Bleeding related events are identified using the Hemorrhage terms (excl laboratory terms), a Standard MedDRA Query (SMQ).
[3] Gastrointestinal (GI) related bleeding events are identified using the Gastrointestinal hemorrhage SMQ.
[4] Central nervous system (CNS) related bleeding events are identified using the Central Nervous System hemorrhages and cerebrovascular conditions SMQs.
[5] Other bleeding events are identified from the Hemorrhage terms (excl laboratory terms) SMQ excluding GI bleeding and CNS bleeding.

[0432] Among the 8,179 patients (70.7% secondary prevention) followed for a median 4.9 years, the primary endpoint occurred in 17.2% of AMR101 patients versus 22.0% of placebo (HR, 0.75; 95% CI, 0.68-0.83; P<0.001) and the key secondary endpoint in 11.2% versus 14.8% (HR, 0.74; 95% CI, 0.65-0.83; P<0.001). Additional ischemic endpoints, assessed according to a prespecified hierarchical schema, were significantly reduced, including cardiovascular death (4.3% versus 5.2%; HR, 0.80; 95% CI, 0.66-0.98; P=0.03). Atrial fibrillation or flutter hospitalization was more common with the AMR101 patients than the placebo patients (3.1% versus 2.1%; P=0.004); serious bleeding occurred in 2.7% of the AMR101 patients versus 2.1% in the placebo patients (P=0.06). There were no significant differences between treatments in the overall rate of treatment emergent adverse events or serious adverse events leading to withdrawal of study drug as shown in Table 20. The only serious adverse event occurring at a frequency ≥2% was pneumonia at 2.6% in the AMR101 group versus 2.9% in the placebo group (P=0.42).

Conclusion

[0433] In this study, the risk of the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, assessed in a time-to-event analysis, was significantly lower, by 25%, among the patients who received 2 g of icosapent ethyl twice daily than among those who received placebo, corresponding to an absolute between-group difference of 4.8 percentage points in the rate of the endpoint and a number needed to treat of 21. The risk of the key secondary composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis was also significantly lower, by 26%, in patients who received 2 g of icosapent ethyl twice daily than among those who received placebo, corresponding to an absolute between-group difference of 3.6 percentage points in the rate of the endpoint and a number needed to treat of 28. Prespecified hierarchical testing of other secondary endpoints revealed that the risks of a variety of fatal and nonfatal ischemic events were lower in the AMR101 group than in the placebo group, including a 20% lower risk of cardiovascular death. The benefits were observed against a background of appropriate statin use among patients who had a median LDL cholesterol level of 75.0 mg/dL at baseline.

[0434] Overall adverse event rates were similar across treatment groups. There were numerically more serious adverse events related to bleeding, though overall rates were low, with no fatal bleeding observed in either group and no significant increase in adjudicated hemorrhagic stroke or serious central nervous system or gastrointestinal bleeding. There was a significantly higher rate of hospitalization for atrial fibrillation or flutter, though rates were low in those patients who received 2 g of icosapent ethyl twice daily. Adverse event and serious adverse event rates leading to study drug discontinuation were similar to placebo. The rates of adverse events and serious adverse events leading to discontinuation of trial drug were similar in the two groups.

[0435] The results from this study stand apart from the negative findings of several recent trials of other agents that also lower triglyceride levels, such as other omega-3 fatty acids, extended-release niacin, fenofibrate, and cholesteryl ester transfer protein-inhibitors. It is not known whether the lack of benefit of omega-3 fatty acids in previous trials might be attributable to the low dose or the low ratio of EPA to DHA. Both the formulation (a highly purified and stable EPA acid ethyl ester) and dose (4 grams daily) used in this study are different from all prior omega-3 outcome trials. Despite utilizing a standard PROBE design limitation of those previous trials included an open label

design without placebo, use of a low-intensity statin, and conducted in a single country; in contrast to the present report, patients in those trials had higher baseline LDL-C levels (182 mg/dL prior to statin initiation) and lower triglyceride values (151 mg/dL). In contrast, the present study provides robust, multinational data showing significant reductions in ischemic events with administration of icosapent ethyl in patients with well-controlled LDL-C. Metabolic data support that icosapent ethyl does not raise LDL cholesterol levels, which DHA containing formulations do.

[0436] A triglyceride level ≥150 mg/dL was required for inclusion in this study however, owing to initial allowance for variability in these levels and differences between qualifying and randomization measurements, 10.3% of enrolled patients had triglycerides less than 150 mg/dL on study entry. Cardiovascular benefits appeared similar across baseline levels of triglycerides (e.g., 135-149, 150 to 199, and 200 mg/dL or greater). Additionally, the robust reduction in major adverse cardiovascular events with administration of icosapent ethyl appeared to occur irrespective of an achieved triglyceride level above or below 150 mg/dL at one year, suggesting that the cardiovascular risk reduction was not tied to achieving a more normal (i.e., <150 mg/dL) triglyceride level. These observations suggest that at least some of the impact of icosapent ethyl on the reduction in ischemic events may be explained by metabolic effects other than triglyceride lowering.

[0437] Mechanisms responsible for the benefit in the present study are currently not known. The timing of divergence of the Kaplan-Meier event curves suggests a delayed onset to benefit, which may reflect the time to benefit from triglyceride reduction or other mechanisms. The modestly higher rate of bleeding suggests that there might be an anti-thrombotic mechanism of action. However, it is unlikely that an anti-thrombotic effect would reduce elective revascularization. Also, if the full explanation were an antiplatelet or anticoagulant effect, one might expect a large increase in major bleeding, which was not seen. Potentially, membrane-stabilizing effects could explain part of the benefit. Stabilization and/or regression of coronary plaque may also play a part. The observation in the present study of a lower rate of sudden cardiac death might support that mechanism, though this finding should be viewed as exploratory. It is also possible that the 40% reduction in hsCRP observed in patients from this trial may contribute to benefit. Samples (e.g., serum and plasma) from patients who participated

in this trial have been banked for biomarker and genetic analyses, which may provide more information regarding mechanisms of action.

[0438] Regarding higher rates of diarrhea in the mineral oil placebo group, a *post hoc* analysis excluding patients with diarrhea still resulted in a significant risk reduction of 25% in the primary endpoint. Also, there were no differences in the primary or key secondary endpoints for placebo patients with an increase in LDL-C compared to those with no change or a decrease in LDL-C.

[0439] In conclusion, AMR101 4 grams daily demonstrated similar overall adverse event rates as placebo, and reduced important ischemic events, including cardiovascular death, in statin-treated patients with elevated triglycerides. Compared with placebo, icosapent ethyl 4 g per day significantly reduced cardiovascular events by 25% including: a 31% reduction in heart attack, 28% reduction in stroke, 31% reduction in myocardial infarction, and a 20% reduction in death due to cardiovascular events.

[0440] The following are key conclusions obtained from this trial that indicate a very favorable risk-benefit profile (1) significant reduction in primary endpoint with a RRR of 24.8%, ARR of 4.8%, NNT of 21, and a p-value of 0.00000001, (2) significant reduction in key secondary endpoint with a RRR of 26.5%, ARR of 3.6%, NNT of 28, and a p-value of 0.0000062, (3) consistent results across subgroups to include triglycerides and secondary and primary prevention, (4) consistent results across hierarchical secondary endpoints to include cardiovascular death, (5) consistent results across recurrent events, and (6) safety with a small but insignificant increase in atrial fibrillation/flutter with low event rates and non-significant increase in serious bleeding with low event rates.

EXAMPLE 2. DIAGNOSING A NEED FOR PERIPHERAL ARTERIAL REVASCULARIZATION IN A STATIN-TREATED SUBJECT

[0441] This study analyzed real-world data and determined the occurrence and/or risk of peripheral arterial revascularization in high-risk, statin-treated patients with and without elevated triglyceride levels. The purpose of the study was to perform a retrospective analysis of a large medical claims database (e.g., the Optum Research Database with over 160 million individuals) to evaluate the real-world impact of elevated

triglycerides levels on freedom from peripheral arterial revascularization in the high-risk statin-treated patients. In the context of this study, the phrase "freedom from peripheral arterial revascularization" refers to a statistically derived metric used to predict if a subject has a need for and/or requires peripheral arterial revascularization.

[0442] *Subjects*: Patients analyzed were at least about 45 years of age, had diabetes and/or CV disease, such as atherosclerotic CV disease, filled a statin prescription in 2010 (i.e., had at least one claim for statin therapy between January 2, 2010 to December 31, 2010), had continuous medical and/or pharmacy coverage, and had baseline data from 6 months pre-index and at least 6 months from the index date (or less if due to death) up to March 2016. An "index date" in the context of this study refers to the date of the patient received a prescription for a statin therapy. The patients were divided into two cohorts, an elevated triglyceride cohort and a comparator cohort. Patients in the elevated triglyceride cohort had triglyceride levels of at least about 150 mg/dL (i.e., ≥ 150 mg/dL, median 2.23 mmol/L). The elevated triglyceride cohort also included patients with triglyceride levels between about 200 mg/dL to about 500 mg/dL (i.e., 200-500 mg/dL) and patients with triglycerides at least about 500 mg/dL to about 1500 mg/dL (i.e., ≥ 1500 mg/dL). Patients in the comparator cohort had triglyceride levels less than 150 mg/dL (i.e., < 150 mg/dL, median 1.11 mmol/L) and had HDL-C levels greater than 40 mg/dL (i.e., > 150 mg/dL, 1.04 mmol/L). Figure 12 shows the disposition of the patients in the elevated triglyceride and comparator cohorts and Table 27 enumerates the inclusion and exclusion criteria for the patients of the two cohorts. Importantly, there were few clinically important differences between the elevated triglyceride and comparator cohorts except for the baseline lipid levels, consistent with the inclusion criteria for each cohort (i.e., ≥ 150 mg/dL vs < 150 mg/dL). (Shown in Table 28). The two cohorts also had similar baseline comorbidities. (Shown in Table 5).

[0443] Table 27. Patient Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Age ≥45 years • ≥1 prescription claim for a statin medication in 2010 • ≥1 medical claim with a diagnosis or procedure code representing ASCVD* and/or diabetes • Known gender, insurance type, and geographic region • Continuous enrolment with medical and pharmacy benefits during the baseline period and ≥6 months starting on the index date, or death within 6 months of the index date • **Elevated TG cohort:** TG ≥1.69 mmol/L (≥150 mg/dL) at most recent laboratory test prior to index date • **Comparator cohort:** TG <1.69 mmol/L (<150 mg/dL) and HDL-C >1.04 mmol/L (>40 mg/dL)	• Niacin on hand at index date • ICD-9 codes indicating the presence of any of the following conditions during the 6-month baseline period: – Pregnancy – Severe liver disease – Acute or chronic pancreatitis – Malabsorption syndrome or gastric/ intestinal bypass surgery – HIV/AIDS – End-stage renal disease, hemodialysis, or peritoneal dialysis – Myositis, polymyositis, or rhabdomyolysis – Drug or alcohol abuse

*ASCVD included acute coronary syndrome, myocardial infarction, angina, coronary or other arterial revascularisation, stroke, transient ischaemic attack, or peripheral arterial disease.

[0444] Table 28. Patient Demographics and Characteristics of the Elevated Triglyceride and Comparator Cohorts

	Elevated-TG Cohort* **n=23,181**	**Comparator Cohort†** **n=23,181**	***P* Value**
Age, mean (SD), years	62.2 (9.6)	62.6 (9.9)	<0.001
Female, n (%)	11,518 (49.7)	11,467 (49.5)	0.244
Insurance type, n (%)			
Commercial	15,823 (68.3)	15,855 (68.4)	0.461
Medicare	7358 (31.7)	7326 (31.6)	0.461
Duration of follow-up, mean (SD), months	41.4 (23.7)	42.5 (23.9)	<0.001
Baseline‡ lipid profile, mean (SD), mmol/L			
TG	2.49 (0.87)	1.11 (0.33)	<0.001
LDL-C	2.71 (1.06)	2.61 (0.91)	<0.001
HDL-C	1.10 (0.26)	1.43 (0.32)	<0.001
Total cholesterol	4.93 (1.21)	4.54 (1.00)	<0.001
Non-HDL-C§	3.83 (1.14)	3.12 (0.95)	<0.001

Rao-Scott test was used for binary measures. Robust standard errors were used for continuous measures.
*Elevated-TG cohort: TG ≥1.69 mmol/L (≥150 mg/dL).
†Comparator cohort: TG <1.69 mmol/L (<150 mg/dL) and HDL-C >1.04 mmol/L (>40 mg/dL).
‡Baseline period excludes index date.
§Calculated by subtracting HDL-C result from total cholesterol. This value was not calculated unless patients had both HDL-C and total cholesterol laboratory result in period.
To convert from International System unit of mmol/L to mg/dL, multiply cholesterol by 38.6 and multiply TG by 88.5.

[0445] Table 29. Baseline Comorbidities of Elevated Triglyceride and Comparator Cohorts

Comorbidity, n (%)	**Elevated-TG Cohort*** **n=23,181**	**Comparator Cohort†** **n=23,181**	***P* Value**
Diabetes	19,392 (83.7)	19,478 (84.0)	0.017
ASCVD	6915 (29.8)	6800 (29.3)	0.009

MI	495 (2.1)	411 (1.8)	0.003
Stroke	750 (3.2)	674 (2.9)	0.005
Angina	1225 (5.3)	1179 (5.1)	0.284
Coronary revascularization	600 (2.6)	506 (2.2)	0.002
Peripheral artery disease	3384 (14.6)	3317 (14.3)	0.104
Heart failure	1258 (5.4)	1088 (4.7)	<0.001
Atrial fibrillation	1133 (4.9)	989 (4.3)	0.001
Hypertension	18,346 (79.1)	18,375 (79.3)	0.462
Transient ischaemic attack	895 (3.9)	905 (3.9)	0.796
Renal disease	2832 (12.2)	2782 (12.0)	0.196

Rao-Scott test was used for binary measures; robust standard errors were used for continuous measures.
*Elevated-TG cohort: TG ≥1.69 mmol/L (≥150 mg/dL).
†Comparator cohort: TG <1.69 mmol/L (<150 mg/dL) and HDL-C >1.04 mmol/L (>40 mg/dL).

[0446] *Objectives*: The primary objective of this study was to measure the occurrence of major cardiovascular events defined as a composite of cardiovascular-related death, non-fatal myocardial infraction, non-fatal stroke, coronary revascularization, and/or unstable angina in the follow-up period. The secondary objective was to quantify the health care costs and resource utilization in the follow-up period. The "follow-up period" in the context of this study refers to a time period that is greater than 6 months, which began on the index date and ended on the earliest of any of the following: the date of disenrollment from the plan, the date of death, or the end of the study on 31 March 2016.

[0447] *Statistical Analyses*: All variables obtained from the study were analyzed descriptively and reported for the overall study sample as well as stratified and statistically compared by cohort. The mean and standard deviation were provided for all continuous variables; descriptive techniques that account for the length of observation time, such as per-patient-per-month, were used for analyses of health care cost and resource utilization. Statistical comparison tests included using a Rao-Scott test and chi-square test (for categorical measures) and the t-test and ANOVA (for continuous measures). Multivariate pre-match analyses used a Cox proportional hazard model to calculate hazard ratios for time-to-event analyses, and generalized linear model with gamma distribution and log link to calculate cost ratios. Clustered P-values were calculated using Cox proportional hazard model with cohort as independent variable (α, 0.05). Health care costs and resource utilization were assessed on a per-patient-per-month basis. Kaplan-Meier analyses were used to calculate time-to-event

probabilities for peripheral arterial revascularization. A *P* value < 0.05 was considered statistically significant. In this study, the findings for peripheral arterial revascularization are from Kaplan-Meier analyses.

[0448] *Results*: Freedom from peripheral arterial revascularization was significantly higher in patients from the comparator cohort (i.e., triglycerides < 150 mg/dL) vs patients from the elevated triglyceride cohort (i.e., triglycerides ≥ 150 mg/dL). At 5 years, the probability of peripheral arterial revascularization was 4.9% in the comparator cohort whereas the probability of peripheral arterial revascularization was 6.9% in the elevated triglyceride cohort. In a multivariate analysis controlled for patient characteristics and comorbidities, the rate of occurrence of peripheral arterial revascularization per unit time was 37% higher in the elevated triglyceride cohort vs the comparator cohort. (Shown in Table 30)

[0449] Table 30. Freedom From Peripheral Arterial Revascularization in High-CV Risk Statin Treated Patients (Kaplan-Meier Analysis)

Cohort		.5 yr	1 yr	2 yr	3 yr	4 yr	5 yr	*P* Value
Elevated TG*	Probability‡	.9873	.9783	.9637	.9525	.9420	.9308	<0.001
	n	22,795	19,265	14,678	11,723	7942	6096	
Comparator†	Probability‡	.9913	.9849	.9752	.9652	.9574	.9512	
	n	22,884	19,566	15,149	12,319	8514	6664	

*Elevated-TG cohort: TG ≥1.69 mmol/L (≥150 mg/dL).
†Comparator cohort: TG ≥1.69 mmol/L (<150 mg/dL) and HDL-C >1.04 mmol/L (40 mg/dL).
‡Probability of freedom from peripheral arterial revascularization.

[0450] *Impact of Elevated Triglycerides on CV Events, and Health Care Utilization*: A composite of major CV events (controlled for patient characteristics and comorbidities) revealed a 25.8% higher rate of occurrence of a major CV event per unit time in the elevated triglyceride cohort versus the comparator cohort. The increased CV risk in the elevated triglyceride cohort versus the comparator cohort was maintained even with the addition of non-HDL-C values to the multivariate model and when analyzing high and low HDL-C subgroups. A cost ratio indicated a nearly 12% higher average total health care cost in the elevated triglyceride cohort vs the comparator cohort. In addition, patients in the elevated triglyceride cohort had higher mean ± SD total monthly health care costs (US $1438 ± 3214) versus the matched comparator cohort (US $1270 ± 2516, P < 0.001). Based on the per-patient-per-month average total health care costs across the variable follow-up time in this study, this extrapolates

to an approximate average difference of US $47 million per year in these study populations and US $200 million per year per 100,000 patients. Controlling for patient characteristics, patients in the elevated triglyceride cohort had a 13.4% higher rate of occurrence of an inpatient visit per unit time than the comparator cohort. (Shown in Table 31).

[0451] Table 31. Effects of Elevated Triglycerides on Major CV Events, Total Health Care costs, and Initial Inpatient Hospital State (Multivariate Analysis)*†

	Hazard or Cost Ratio for Cohort Variable	**95% CI**	***P* Value**
Initial major CV event‡	1.258	1.185 – 1.335	<0.001
Total health care costs§	1.118	1.080 – 1.159	<0.001
Initial inpatient hospital stay‡	1.134	1.101 – 1.169	<0.001

*Elevated-TG pre-match cohort: TG ≥1.69 mmol/L (≥150 mg/dL) (n=25,452 patients); comparator pre-match cohort: TG <1.69 mmol/L (<150 mg/dL) and HDL-C >1.04 mmol/L (>40 mg/dL) (n=31,805 patients).
†Separate multivariate analyses of major CV events, total health care costs, and initial inpatient stay were performed. Covariates included TG cohort, as represented here along with age (45-54, 55-64, 65+ years), gender, insurance coverage type, geographic region of enrolment, baseline clinical characteristics (diabetes, ASCVD, LDL-C laboratory result in relation to median), and baseline medication use (fibrate, prescription omega-3, both, and neither).
‡Multivariate analysis using Cox proportional hazard model.
§Generalised linear model (gamma distribution, log link).

[0452] *Conclusions*: Statin-treated patients at high CV risk with elevated triglycerides levels of ≥ 150 mg/dL and generally controlled LDL-C had worse CV and health economic outcomes than patients with well-managed triglycerides of < 150 mg/dL and HDL-C levels > 40 mg/dL in a real-world setting. Similar results were observed in patients with triglycerides between 200–499 mg/dL. Patients in the elevated triglyceride cohort had a higher probability of peripheral arterial revascularization estimated at 5 years than patients with well-managed triglycerides in the comparator cohort with an absolute difference of 2% between the two cohorts or about 40% higher probability in the elevated triglyceride cohort to the comparator cohort in relative terms.

[0453] Various embodiments of the present disclosure are set forth herein below.

[0454] Para. A. A method of reducing a need for peripheral arterial revascularization in a statin-treated subject, the method comprising: (a) identifying a statin-treated subject as having a fasting baseline triglyceride level of at least about 150

mg/dL, and (b) administering to the statin-treated subject a pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester per day.

[0455] Para. B. The method of Para. A, wherein the composition is administered to the statin-treated subject in 1 to 4 dosage units per day.

[0456] Para. C. The method of Para. A or Para. B, wherein the eicosapentaenoic acid ethyl ester comprises at least about 96 wt.% of all omega-3 fatty acids in the pharmaceutical composition.

[0457] Para. D. The method as in any one of Paras. A to C, wherein the statin-treated subject has one or more of: a baseline non-HDL-C value of about 200 mg/dL to about 300 mg/dL; a baseline total cholesterol value of about 250 mg/dL to about 300 mg/dL; a baseline VLDL-C value of about 140 mg/dL to about 200 mg/dL; a baseline HDL-C value of about 10 to about 30 mg/dL; and/or a baseline LDL-C value of about 40 to about 100 mg/dL.

[0458] Para. E. The method as in any one of Paras. A to D, wherein the statin-treated subject is on a stable statin therapy.

[0459] Para. F. The method of Para. E, wherein the statin therapy comprises administering to the statin-treated subject a statin and optionally ezetimibe.

[0460] Para. G. The method as in any one of Paras. A to F, further comprising identifying the statin-treated subject as having LDL-control.

[0461] Para. H. The method as in any one of Paras. A to G, wherein the statin-treated subject has a fasting baseline triglyceride level of about 200 mg/dL to about 499 mg/dL.

[0462] Para. I. The method as in any one of Paras. A to G, wherein the statin-treated subject has a fasting baseline triglyceride levels of about 500 mg/dL to about 1500 mg/dL.

[0463] Para. J. The method as in any one of Paras. A to I. wherein the subject exhibits a reduction in a risk for cardiovascular death, coronary revascularization, unstable angina, stroke, and/or myocardial infarction.

[0464] Para. K. A method of diagnosing a subject having a need for peripheral arterial revascularization, the method comprising: (a) identifying the subject as being on

a statin therapy; (b) measuring a fasting baseline triglyceride level of the subject; and (c) determining the need for peripheral arterial revascularization if the subject has a fasting baseline triglyceride level of at least about 150 mg/dL.

[0465] Para. L. The method of Para. K, wherein the subject has been identified at least about 5 years from receiving a least one claim for the statin therapy.

[0466] Para. M. The method of Para. K or L, further comprising identifying the subject as having LDL-control.

[0467] Para. N. The method as in any one of Paras. K to M, wherein the subject has a fasting baseline triglyceride level of about 200 mg/dL to about 499 mg/dL.

[0468] Para. O. The method as in any one of Paras. K to N, wherein the subject has a fasting triglyceride level of about 500 mg/dL to about 1500 mg/dL.

[0469] Para. P. The method as in any one of Paras. K to O, wherein the subject exhibits a reduction in a risk for cardiovascular death, coronary revascularization, unstable angina, stroke, and/or myocardial infarction.

[0470] Para. Q. A method of treating a subject at risk for peripheral arterial revascularization, comprising administering to the subject a pharmaceutical composition, wherein the subject has been determined to be at risk for peripheral arterial revascularization by measuring a fasting baseline triglyceride level of the subject, and wherein the subject has a fasting baseline triglyceride level of at least about 150 mg/dL.

[0471] Para. R. The method of Para. Q, wherein the subject is on a statin therapy.

[0472] Para. S. The method of Para. Q or R, wherein the pharmaceutical composition comprises about 1 g to about 4 g of eicosapentaenoic acid ethyl ester.

[0473] Para. T. The method as in any one of Paras. Q to S, wherein the eicosapentaenoic acid ethyl ester comprises at least about 96 wt.% of all omega-3 fatty acids in the pharmaceutical composition.

[0474] Para. U. The method as in any one of Paras. Q to T, further comprising performing a peripheral arterial revascularization.

[0475] Para. V. The method as in any one of Paras. Q to U, wherein the subject has a fasting baseline triglyceride level of about 200 mg/dL to about 499 mg/dL.

[0476] Para. W. The method as in any one of Paras. Q to U, wherein the subject has a fasting triglyceride level of about 500 mg/dL to about 1500 mg/dL.

[0477] Para. X. The method as in any one of Paras. Q to W, wherein the subject exhibits a reduction in a risk for cardiovascular death, coronary revascularization, unstable angina, stroke, and/or myocardial infarction.

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CLAIMS

What is claimed is:

1. A method of reducing a need for peripheral arterial revascularization in a statin-treated subject, the method comprising:

(a) identifying a statin-treated subject as having a fasting baseline triglyceride level of at least about 150 mg/dL, and

(b) administering to the statin-treated subject a pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester per day for a period sufficient to reduce the need for peripheral arterial revascularization.

2. The method of claim 1, wherein the composition is administered to the statin-treated subject in 1 to 4 dosage units per day.

3. The method of claim 1 or claim 2, wherein the eicosapentaenoic acid ethyl ester comprises at least about 96 wt.% of all omega-3 fatty acids in the pharmaceutical composition.

4. The method as in any one of the preceding claims, wherein the statin-treated subject has one or more of: a baseline non-HDL-C value of about 200 mg/dL to about 300 mg/dL; a baseline total cholesterol value of about 250 mg/dL to about 300 mg/dL; a baseline VLDL-C value of about 140 mg/dL to about 200 mg/dL; a baseline HDL-C value of about 10 to about 30 mg/dL; and/or a baseline LDL-C value of about 40 to about 100 mg/dL.

5. The method as in any one of the preceding claims, wherein the statin-treated subject is on a stable statin therapy.

6. The method of claim 5, wherein the statin therapy comprises administering to the statin-treated subject a statin and optionally, ezetimibe.

7. The method as in any one of the preceding claims, further comprising identifying the statin-treated subject as having LDL-control.

8. The method as in any one of the preceding claims, wherein the statin-treated subject has a fasting baseline triglyceride level of about 200 mg/dL to about 499 mg/dL.

9. The method as in any one of claims 1 to 7, wherein the statin-treated subject has a fasting baseline triglyceride levels of about 500 mg/dL to about 1500 mg/dL.

10. The method as in any one of claims 1 to 7, wherein the subject exhibits a reduction in a risk for cardiovascular death, coronary revascularization, unstable angina, stroke, and/or myocardial infarction.

11. A method of diagnosing a subject having a need for peripheral arterial revascularization, the method comprising:

(a) identifying the subject as being on a statin therapy;

(b) measuring a fasting baseline triglyceride level of the subject; and

(c) determining the need for peripheral arterial revascularization if the subject has a fasting baseline triglyceride level of at least about 150 mg/dL.

12. The method of claim 11, wherein the subject has been identified at least about 5 years from receiving a least one claim for the statin therapy.

13. The method of claim 11 or claim 12, further comprising identifying the subject as having LDL-control.

14. The method as in any one of claims 11 to 13, wherein the subject has a fasting baseline triglyceride level of about 200 mg/dL to about 499 mg/dL.

15. The method as in any one of claims 11 to 13, wherein the subject has a fasting triglyceride level of about 500 mg/dL to about 1500 mg/dL.

16. The method as in any one of claims 11 to 15, wherein the subject exhibits a reduction in a risk for cardiovascular death, coronary revascularization, unstable angina, stroke, and/or myocardial infarction.

17. A method of treating a subject at risk for peripheral arterial revascularization, comprising administering to the subject a pharmaceutical composition, wherein the subject has been determined to be at risk for peripheral arterial revascularization by measuring a fasting baseline triglyceride level of the subject, and wherein the subject has a fasting baseline triglyceride level of at least about 150 mg/dL.

18. The method of claim 17, wherein the subject is on a statin therapy.

19. The method of claim 17 or claim 18, wherein the pharmaceutical composition comprises about 1 g to about 4 g of eicosapentaenoic acid ethyl ester.

20. The method as in any one of claims 17 to 19, wherein the eicosapentaenoic acid ethyl ester comprises at least about 96 wt.% of all omega-3 fatty acids in the pharmaceutical composition.

21. The method as in any one of claims 17 to 20, further comprising performing a peripheral arterial revascularization.

22. The method as in any one of claims 17 to 21, wherein the subject has a fasting baseline triglyceride level of about 200 mg/dL to about 499 mg/dL.

23. The method as in any one of claims 17 to 21, wherein the subject has a fasting triglyceride level of about 500 mg/dL to about 1500 mg/dL.

24. The method as in any one of claims 15 to 23, wherein the subject exhibits a reduction in a risk for cardiovascular death, coronary revascularization, unstable angina, stroke, and/or myocardial infarction.