TITLE

METHODS OF REDUCING THE RISK OF A CARDIOVASCULAR EVENT IN A SUBJECT ON STATIN THERAPY

PRIORITY CLAIM

[0001] This application claims priority to U.S. provisional patent application serial no. 61/666,447, filed June 29, 2012, the entire contents of which are incorporated herein by reference.

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] 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

[0004] In various embodiments, the present invention provides methods of reducing the risk of a cardiovascular event in a subject on statin therapy. In one embodiment, the method comprises administering to the subject a pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester or a derivative thereof. In another embodiment, the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL. In another embodiment, the composition contains not more than 10%, by weight, docosahexaenoic acid or derivative thereof, substantially no docosahexaenoic acid or derivative thereof, or no docosahexaenoic acid or derivative thereof. In another embodiment, eicosapentaenoic acid ethyl ester comprises at least 96%, by weight, of all fatty acids present in the composition; the

composition contains not more than 4%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; and/or the composition contains about 0.1% to about 0.6% of at least one fatty acid other than eicosapentaenoic acid ethyl ester and docosahexaenoic acid.

[0005] In another embodiment, the invention provides a method of treating hypertriglyceridemia comprising administering a composition as described herein to a subject in need thereof one to about four times per day.

[0006] These and other embodiments of the present invention will be disclosed in further detail herein below.

DETAILED DESCRIPTION

[0007] While the present invention 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.

[0008] 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 invention.

Compositions

[0009] In one embodiment, a composition of the invention 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 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 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg, about 2500 mg, about 2525 mg, about 2550 mg, about 2575 mg, about 2600 mg, about 2625 mg, about 2650 mg, about 2675 mg, about 2700 mg, about 2725 mg, about 2750 mg, about 2775 mg, about 2800 mg, about 2825 mg, about 2850 mg, about 2875 mg, about 2900 mg, about 2925 mg, about 2950 mg, about 2975 mg, about 3000 mg, about 3025 mg, about 3050 mg, about 3075 mg, about 3100 mg, about 3125 mg, about 3150 mg, about 3175 mg, about 3200 mg, about 3225 mg, about 3250 mg, about 3275 mg, about 3300 mg, about 3325 mg, about 3350 mg, about 3375 mg, about 3400 mg, about 3425 mg, about 3450 mg, about 3475 mg, about 3500 mg, about 3525 mg, about 3550 mg, about 3575 mg, about 3600 mg, about 3625 mg, about 3650 mg, about 3675 mg, about 3700 mg, about 3725

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[0010] In one embodiment, a composition for use in methods of the invention 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.

[0011] 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.

[0012] 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.

[0013] In another embodiment, EPA is present in a composition useful in accordance with methods of the invention 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 2250 mg, about 2275 mg, about 2300 mg, about 2325 mg, about 2350 mg, about 2375 mg, about 2400 mg, about 2425 mg, about 2450 mg, about 2475 mg, about 2500 mg, about 2525 mg, about 2550 mg, about 2575 mg, about 2600 mg, about 2625 mg, about 2650 mg, about 2675 mg, about 2700 mg, about 2725 mg, about 2750 mg, about 2775 mg, about 2800 mg, about 2825 mg, about 2850 mg, about 2875 mg, about 2900 mg, about 2925 mg, about 2950 mg, about 2975 mg, about 3000 mg, about 3025 mg, about 3050 mg, about 3075 mg, about 3100 mg, about 3125 mg, about 3150 mg, about 3175 mg, about 3200 mg, about 3225 mg, about 3250 mg, about 3275 mg, about 3300 mg, about 3325 mg, about 3350 mg, about 3375 mg, about 3400 mg, about 3425 mg, about 3450 mg, about 3475 mg, about 3500 mg, about 3525 mg, about 3550 mg, about 3575 mg, about 3600 mg, about 3625 mg, about 3650 mg, about 3675 mg, about 3700 mg,

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[0014] In another embodiment, a composition useful in accordance with the invention 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 invention contains substantially no docosahexaenoic acid. In still another embodiment, a composition useful in the present invention contains no docosahexaenoic acid and/or derivative thereof.

[0015] 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 invention.

[0016] 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.

[0017] In another embodiment, a composition useful in accordance with methods of the invention 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 invention 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.

[0018] In another embodiment, a composition useful in accordance with the invention 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.

[0019] In another embodiment, compositions useful in accordance with methods of the invention 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.

[0020] A composition for use in accordance with the invention 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.

[0021] In one embodiment, compositions of the invention, 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

[0022] In one embodiment, the invention 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.

[0023] 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.

[0024] In various embodiments, the present invention 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.

[0025] 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, 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, or about 500 mg/dL.

[0026] 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.

[0027] 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.

[0028] 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).

[0029] In some embodiments, the subject or subject group being treated in accordance with methods of the invention 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 $\leq$ 40 mg/dL for men or $\leq$ 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 $\geq$ 2.5 mg/mmol, or an albumin excretion rate on timed collection of $\geq$ 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 $\geq$ 25 mg/mmol, or an albumin excretion rate on timed collection of $\geq$ 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.

[0030] 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.

[0031] 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.

[0032] 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. Thereafter, in some embodiments the subject exhibits one or more of

[0033] (a) reduced triglyceride levels compared to baseline;

[0034] (b) reduced Apo B levels compared to baseline;

[0035] (c) increased HDL-C levels compared to baseline;

[0036] (d) no increase in LDL-C levels compared to baseline;

[0037] (e) a reduction in LDL-C levels compared to baseline;

[0038] (f) a reduction in non-HDL-C levels compared to baseline;

[0039] (g) a reduction in VLDL levels compared to baseline;

[0040] (h) a reduction in total cholesterol levels compared to baseline;

[0041] (i) a reduction in high sensitivity C-reactive protein (hs-CRP) levels compared to baseline; and/or

[0042] (j) a reduction in high sensitivity troponin (hsTnT) levels compared to baseline.

[0043] In some embodiments, the subject exhibits one or more of: (a) a reduction in triglyceride level 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;

[0044] (b) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in non-HDL-C levels or 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;

[0045] (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%, or at least about 50% as compared to baseline; and/or

[0046] (d) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in LDL-C levels or 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.

[0047] 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.

[0048] 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 In some embodiments, the subject or subject group being treated in accordance with methods of the invention 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.

[0049] 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}.

[0050] 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.

[0051] In some embodiments, a biomarker assay associated with blood obtained from a subject includes hs-CRP, Apo B and hsTnT.

[0052] 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.

[0053] In some embodiments, demographic information associated with a subject includes day, month and year of birth, race, and gender.

[0054] 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).

[0055] 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.

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] In some embodiments, the present invention 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.

[0061] 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.

[0062] In some embodiments, the present invention 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.

[0063] In another embodiment, the present invention 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.

[0064] In some embodiments, the present invention 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.

[0065] In some embodiments, the present invention 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.

[0066] In some embodiments, the present invention 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.

[0067] 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 invention 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.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] In methods of the present invention 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.

[0076] 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.

[0077] In another embodiment, the invention 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.

EXAMPLES

[0078] A phase 3, multi-center, placebo-controlled randomized, double-blind, 12-week study with an open-label extension is performed to evaluate the efficacy and safety of AMR101 in patients with fasting triglyceride levels ≥ 150 mg/dL and < 500 mg/dL. The primary objective is, in patients at LDL-C goal while on statin therapy, with established cardiovascular disease (CVD) or at high risk for CVD, and hypertriglyceridemia (fasting triglycerides, TG, ≥200 mg/dL and <500 mg/dL, determine the efficacy of AMR101 4 g daily, compared to placebo, in preventing the occurrence of a first major cardiovascular event of the composite endpoint that includes:

- cardiovascular ("CV") death;
- nonfatal myocardial infarction ("MI");
- nonfatal stroke;

- coronary revascularization; and
- unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emertgent hospitalization.

[0079] The secondary objectives of this study are the following:

[0080] To evaluate the effect of therapy on the composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or peripheral CV disease requiring intervention, angioplasty, bypass surgery, and aneurysm repair;

[0081] To evaluate the effect of therapy on combinations of each of the clinical events listed in secondary objective #1, *supra*, in addition to cardiac arrhythmia requiring hospitalization, cardiac arrest, peripheral CV disease requiring intervention, angioplasty, bypass surgery, aneurysm repair, and total mortality;

[0082] To evaluate the effect of therapy on the occurrence of a second, third, fourth and fifth major cardiovascular event (*e.g.,* occurrence of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization after a first occurrence of any of same);

[0083] To evaluate the effect of therapy on the first occurrence of a major cardiovascular event in subgroups of patients including (a) those with diabetes mellitus, and (b) those with metabolic syndrome (*e.g.,* as defined by the NCEP ATP III or future criteria as may evolve therefrom);

[0084] To evaluate the effect of therapy on new congestive heart failure ("CHF"), on new CHF as a primary cause of hospitalization, on transient ischemic attack, on amputation for CV disease, and on carotid revascularization;

[0085] To evaluate the effect of therapy on occurrence of elective coronary revascularization and emergent coronary revascularization;

[0086] To evaluate the effects of therapy on lipids, lipoproteins and inflammatory markers including triglycerides, total cholesterol, low-density lipoprotein cholesterol ("LDL-C"), high-density lipoprotein cholesterol ("HDL-C"), non-HDL-C, very low-density lipoprotein cholesterol ("VLDL-C"), apoliporpotein B ("apo B"), high-sensitivity C-reactive protein ("hs-CRP"), and high-sensitivity troponin ("hsTnT") as follows:

[0087] Evaluation of the effect of therapy on each marker;

[0088] Evaluation of the effect of the baseline value of each marker on therapy effects; and

[0089] Evaluation of the effect of therapy for preventing clinical events as defined above among all patients in the study and in sub-groups such as patients with diabetes mellitus and patients with substantial on-treatment changes of any of the markers;

[0090] To evaluate the effect of therapy on new onset diabetes; and

[0091] To explore the effect of therapy on weight and waist circumference.

Study Population

[0092] The population for this study is men and women ≥45 years of age with established CVD, or men and women ≥50 years of age with diabetes in combination with one additional risk factor for CVD. In addition, all patients will have atherogenic dyslipidemia defined as on treatment for hypercholesterolemia (but at treatment goal for LDL-C, by treatment with a statin) and hypertriglyceridemia. More details are listed in the inclusion criteria.

[0093] The patients will need to provide consent to participate in the study and be willing and able to comply with the protocol and the study procedures.

Study Periods

[0094] This study consists of the following study periods:

[0095] Screening Period: During the screening period, patients will be evaluated for inclusion/exclusion criteria.

[0096] At the first visit to the Research Unit (Visit 1), study procedures will be performed for evaluation of patient's eligibility in the study. At this screening visit, patients will sign an informed consent form before any study procedure is performed; the informed consent form will cover the treatment/follow-up period. Based on the evaluation from Visit 1, the following situations may occur:

[0097] Patients who are eligible for participation based on the study procedures on Visit 1 will return to the Research Unit for Visit 2 (randomization visit) to start the treatment/follow-up period. This case includes, for example, patients at Visit 1who are on a stable dose of a statin, are planning to stay on the same statin and the same dose of the statin, and who not need to wash out any non-statin lipid-altering medications.

[0098] Patients who are not eligible for participation based on the study procedures on Visit 1 and are unlikely to become eligible in the next 28 days (for example: unlikely to stabilize statin dose, unable to wash out non-statin lipid-altering medications, etc.): these patients will be screen failed after Visit 1.

[0099] Patients not eligible for participation in the study based on the study procedures on Visit 1 may possibly become eligible in the next 28 days: these patients may return at the discretion of the investigator for a second optional screening visit (Visit 1.1) at which time the procedures needed for re-evaluation of the previously failed inclusion/exclusion criteria will be repeated. This case includes, for example, patients who are started on a statin at Visit 1, whose statin dose is changed at Visit 1, and/or needed to wash out non-statin lipid-altering medications. The following applies for these patients:

[0100] Patients with a change in the statin or statin dose on Visit 1 will need to be on a stable statin dose for at least 28 days before the lipid qualifying measurements at Visit 1.1. Other concomitant medications (antidiabetic therapy, for example) can be optimized or stabilized during this period.

[0101] Patients starting a washout at Visit 1 will have a washout period of at least 28 days (only 7 days for bile acid sequestrants) before the lipid qualifying measurements at Visit 1.1.

[0102] Patients at Visit 1 who are on a stable dose of a statin, are planning to stay on the same statin at the same dose, and who do not need any medication washout, but were asked to return for Visit 1.1 to repeat one or more of the other study procedures not related to concomitant medications

[0103] Patients who become eligible for participation based on the additional study procedures at Visit 1.1 will return to the Research Unit for Visit 2 (randomization visit) to start the treatment/follow-up period.

[0104] At the end of the screening period, patients will need to meet all inclusion/exclusion criteria before they can be randomized. Patients who are not eligible for participation after the screening period (based on study procedures at Visit 1 and/or Visit 1.1) may return at a later date for rescreening. These patients will need to re-start with all procedures starting with Visit 1. This includes patients who need more time to stabilize one or more conditions or therapies (for example: statin, antidiabetic, antihypertensive, thyroid hormone, HIV-protease inhibitor therapy).

[0105] Treatment/Follow-Up Period: Within 42 days after the first screening visit (Visit 1) or within 60 days after the first screening visit (Visit 1) for those patients that have a second screening visit (Visit 1.1), eligible patients will enter the treatment/follow-up period. During this period, the patients will receive study drug during the planned visits at the Research Site and take the study drug while away from the Research Site.

[0106] During the visits, study procedures will be performed for evaluation of efficacy and safety. A detailed schedule of procedures is provided in Table 1.

Study Duration

[0107] The estimated study duration includes a planned 18-month enrollment period followed by a follow-up period of approximately 3.5 years in expected duration

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

[0108] The total duration of the trial is based on a median 4-year follow-up period across patients. The first patient randomized would be followed for 4.75 years (the longest individual follow-up duration), and the last patient randomized would be followed for 3.25 year (the shortest individual follow-up duration).

Study Groups

[0109] At Visit 2 (Day 0), eligible study patients will be randomly assigned to the following treatment groups:

[0110] Group 1: AMR101 4 g daily (four 1000 mg capsules daily)

[0111] Group 2: placebo (four capsules daily)

[0112] The four AMR101 or placebo capsules daily will be taken as two capsules in the morning and two capsules in the evening (twice-per-day dosing regimen).

Number of Patients

[0113] This is an event-driven trial: It is expected that a minimum of 1612 primary efficacy endpoint events will be required during the study. A total of approximately 7990 patients will be entered into the study to either receive AMR101 or placebo (approximately 3995 patients per treatment group) in order to observe an estimated 1612 events that make up the primary composite endpoint for efficacy.

Number of Study Sites

[0114] Participants will be enrolled at multiple Research Sites in multiple countries.

Randomization

[0115] On Day 0, eligible patients will be randomized to one of 2 study groups using a computer-generated randomization schema. Randomized treatment assignment to either AMR101 or placebo in a 1:1 ratio will be provided using the internet (IWR).

Blinding

[0116] This is a double-blind study. Patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors supporting the study will be unaware of the randomization code (i.e., they will not know which study participants are receiving the experimental drug and which are receiving the placebo drug). The study medication AMR101 and placebo capsules will be similar in size and appearance to maintain blinding.

[0117] During the double-blind treatment/follow-up period, everyone (patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors managing/supporting the study), with the exception of the laboratory personnel performing the analysis, will be blinded to individual results of the efficacy laboratory measurements (including lipid values). Individual results from the lipid profile may be unblinded in the event of an emergency for a patient.

Stratification

[0118] Participants will be assigned to treatment groups stratified by CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries). There are two CV risk categories:

[0119] CV Risk Category 1: patients with established CVD defined in the inclusion criteria. Patients with diabetes and established CVD are included in this category.

[0120] CV Risk Category 2: patients with diabetes and at least one additional risk factor for CVD, but no established CVD.

[0121] Stratification will be recorded in the IWR at the time of enrollment. Approximately 70% of randomized patients will be in the CV Risk Category 1 and

approximately 30% of randomized patients will be in the CV Risk Category 2. Enrollment with patients of a CV risk category will be stopped when the planned number of patients in that risk category is reached.

STUDY POPULATION

Inclusion Criteria

[0122] Patients meeting the following criteria will be eligible to participate in the study:

[0123] Fasting TG levels of ≥200 mg/dL (2.26 mmol/L) and <500 mg/dL (5.64 mmol/L).

[0124] LDL-C >40 mg/dL (1.04 mmol/L) and ≤100 mg/dL (2.60 mmol/L) and on stable therapy with a statin (with or without ezetimibe) for at least 4 weeks prior to the LDL-C/TG baseline qualifying measurements for randomization

[0125] Stable therapy is defined as the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable, the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C). Patients who have their statin therapy or use of ezetimibe initiated at Visit 1, or have their statin, statin dose and/or ezetimibe dose changed at Visit 1, will need to go through a stabilization period of at least 28 days since initiation/change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).

[0126] Statins may be administered with or without ezetimibe.

[0127] If patients qualify at the first qualification visit (Visit 1) for TG and LDL-C, and meet all other inclusion/exclusion criteria, they may be randomized at Visit 2. If patients don't qualify at the first qualifying visit (Visit 1), a second re-qualifying visit (Visit 1.1) is allowed. For some patients, because they need to stabilize medications and/or need to washout medications, the second re-qualifying visit (Visit 1.1) will be needed after the stabilization/washout period.

[0128] Either having established CVD (in CV Risk Category 1) or at high risk for CVD (in CV Risk Category 2). The CV risk categories are defined as follows:

[0129] CV Risk Category 1: defined as men and women ≥45 years of age with one or more of the following:

[0130] Documented coronary artery disease (CAD; one or more of the following primary criteria must be satisfied):

[0131] Documented multivessel CAD (>50% stenosis in at least two major epicardial coronary arteries – with or without antecedent revascularization)

[0132] Documented prior MI

[0133] Hospitalization for high-risk NSTE-ACS (with objective evidence of ischemia: ST-segment deviation or biomarker positivity)

[0134] Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied):

[0135] Documented prior ischemic stroke

[0136] Symptomatic carotid artery disease with ≥50% carotid arterial stenosis

[0137] Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound

[0138] History of carotid revascularization (catheter-based or surgical)

[0139] Documented peripheral arterial disease (PAD; one or more of the following primary criteria must be satisfied):

[0140] ABI <0.9 with symptoms of intermittent claudication

[0141] History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical)

OR

[0142] CV Risk Category 2: defined as patients with:

[0143] Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication AND

[0144] Men and women ≥50 years of age AND

[0145] One of the following at Visit 1 (additional risk factor for CVD):

[0146] Men ≥55 years of age or women ≥65 years of age;

[0147] Cigarette smoker or stopped smoking within 3 months before Visit 1;

[0148] Hypertension (blood pressure ≥140 mmHg systolic OR ≥90 mmHg diastolic) or on antihypertensive medication;

[0149] HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women;

[0150] Hs-CRP >3.00 mg/L (0.3 mg/dL);

[0151] Renal dysfunction: CrCL >30 and <60 mL/min (>0.50 and <1.00 mL/sec);

[0152] Retinopathy, defined as any of the following: non-proliferative retinopathy, preproliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation;

[0153] 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;

[0154] ABI <0.9 without symptoms of intermittent claudication (patients with ABI <0.9 with symptoms of intermittent claudication are counted under CV Risk Category 1).

[0155] Patients with diabetes with CVD as defined above are eligible based on the CVD requirements and will be counted under CV Risk Category 1. Only patients with diabetes and no documented CVD as defined above need at least one additional risk factor as listed, and will be counted under CV Risk Category 2.

[0156] Women may be enrolled if all 3 of the following criteria are met:

[0157] They are not pregnant;

[0158] They are not breastfeeding;

[0159] They do not plan on becoming pregnant during the study.

[0160] Women of child-bearing potential must have a negative urine pregnancy test before randomization.

[0161] Women are not considered to be of childbearing potential if they meet one of the following criteria as documented by the investigator:

[0162] They have had a hysterectomy, tubal ligation or bilateral oophorectomy prior to signing the informed consent form;

[0163] They are post-menopausal, defined as ≥1 year since their last menstrual period or have a follicle-stimulating hormone (FSH) level in a menopausal range.

[0164] Women of childbearing potential must agree to use an acceptable method of avoiding pregnancy from screening to the end of the study, unless their sexual partner(s) is/are surgically sterile or the woman is abstinent.

[0165] Understanding of the study procedures, willing to adhere to the study schedules, and agreement to participate in the study by giving informed consent prior to screening.

[0166] Agree to follow a physician recommended diet and to maintain it through the duration of the study.

Exclusion Criteria

[0167] Patients are excluded from participation in the study if any of the following criteria apply:

[0168] Severe (class IV) heart failure.

[0169] Any life-threatening disease expected to result in death within the next 2 years (other than CVD).

[0170] Active severe liver disease (evaluated at Visit 1): cirrhosis, active hepatitis, ALT or AST >3 x ULN, or biliary obstruction with hyperbilirubinemia (total bilirubin >2 x ULN).

[0171] Hemoglobin A1c >10.0% (or 86 mmol/mol IFCC units) at screening (Visit 1). If patients fail this criterion (HbA1c >10.0% or 86 mmol/mol IFCC units) at Visit 1, they may have their antidiabetic therapy optimized and be retested at Visit 1.1.

[0172] Poorly controlled hypertension: blood pressure ≥200 systolic mmHg OR ≥100 mmHg diastolic (despite antihypertensive therapy).

[0173] Planned coronary intervention (such as stent placement or heart bypass) or any non-cardiac major surgical procedure. Patients can be (re)evaluated for participation in the trial (starting with Visit 1.1) after their recovery from the intervention/surgery.

[0174] Known familial lipoprotein lipase deficiency (Fredrickson Type I), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type III)].

[0175] Participation in another clinical trial involving an investigational agent within 90 days prior to screening (Visit 1). Patients cannot participate in any other investigational medication or medical device trial while participating in this study (participation in a registry or observational study without an additional therapeutic intervention is allowed).

[0176] Intolerance or hypersensitivity to statin therapy.

[0177] Known hypersensitivity to any ingredients of the study product or placebo; known hypersensitivity to fish and or shellfish.

[0178] History of acute or chronic pancreatitis.

[0179] Malabsorption syndrome and/or chronic diarrhea (Note: patients who have undergone gastric/intestinal bypass surgery are considered to have malabsorption, hence are excluded; patients who have undergone gastric banding are allowed to enter the trial).

[0180] Non-study drug related, non-statin, lipid-altering medications, supplements or foods:

[0181] Patients are excluded if they used niacin >200 mg/day or fibrates during the screening period (after Visit 1) and/or plan to use during the study; patients who are taking niacin >200 mg/day or fibrates during the last 28 days before Visit 1 need to go through washout of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (Visit 1.1);

[0182] Patients are excluded if they take any omega-3 fatty acid medications (prescription medicines containing EPA and/or DHA) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking omega-3 fatty acid medications during the last 28 days before Visit 1 (except patients in The Netherlands), need to go through a washout period of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (at Visit 1.1);

[0183] For patients in The Netherlands only: patients being treated with omega-3 fatty acid medications containing EPA and/or DHA are excluded; no washout is allowed.

[0184] Patients are excluded if they use dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils) during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be

eligible for participation in the study, patients who are taking >300 mg/day omega-3 fatty acids (combined amount of EPA and DHA) within 28 days before Visit 1 (except patients in The Netherlands), need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);

[0185] For patients in The Netherlands only: patients being treated with dietary supplements containing omega-3 fatty acids of >300 mg/day EPA and/or DHA are excluded; no washout is allowed.

[0186] Patients are excluded if they use bile acid sequestrants during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking bile acid sequestrants within 7 days before Visit 1, need to go through a washout period of at least 7 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1);

[0187] Other medications (not indicated for lipid alteration):

[0188] Treatment with tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are allowed), HIV-protease inhibitors that have not been stable for ≥28 days prior to the qualifying lipid measurements (TG and LDL-C) during screening. To be eligible for participation in the study, patients who are not taking a stable dose of these medications within 28 days before Visit 1, need to go through a stabilization period of at least 28 days since their last dose change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).

[0189] Patients are excluded if they use cyclophosphamide or systemic retinoids during the screening period (after Visit 1) and/or plan to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who are taking these medications within 28 days before Visit 1, need to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).

[0190] Known to have AIDS (patients who are HIV positive without AIDS are allowed).

[0191] Requirement for peritoneal dialysis or hemodialysis for renal insufficiency or if creatinine clearance (CrCL) <30 mL/min (0.50 mL/sec).

[0192] Unexplained creatine kinase concentration >5 × ULN or creatine kinase elevation due to known muscle disease (e.g., polymyositis, mitochondrial dysfunction) at Visit 1.

[0193] 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.

[0194] Drug or alcohol abuse within the past 6 months, and unable/unwilling to abstain from drug abuse and excessive alcohol consumption during the study or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking). Excessive alcohol consumption is on average >2 units of alcohol per day. A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.

[0195] 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

Assessment Schedule

[0196] Screening Period

[0197] Screening Visit (Visit 1)

[0198] Patients will come to the Research Site for Visit 1. They will be instructed to fast for at least 10 hours before their visit.

[0199] If patients qualify for randomization based on the procedures at Visit 1, they need to be randomized within 60 days after Visit 1. The following procedures will be performed at the screening visit:

[0200] Obtain signed informed consent

[0201] Assign the patient a patient number

[0202] Obtain medical, surgical and family history

[0203] Record demographics

[0204] Obtain height, weight, and body mass index

[0205] Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

[0206] Obtain a 12-lead electrocardiogram

[0207] Evaluate inclusion/exclusion criteria

[0208] This includes procedures and (fasting) blood samples (for example, hs-CRP, calculated creatinine clearance) as needed to determine the CV risk category (see inclusion criteria)

[0209] Obtain fasting blood samples for chemistry and hematology testing

[0210] Obtain a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C)

[0211] Perform a urine pregnancy test on women of childbearing potential

[0212] Record concomitant medication(s)

[0213] Instruct patient to fast for at least10 hours prior to the next visit

[0214] Screening Visit (Visit 1.1)

[0215] Some patients will skip Visit 1.1: Patients who qualify for study participation after Visit 1 because they meet all inclusion criterion and none of the exclusion criteria, may return to the Research Site for Visit 2 to be randomized and to start the treatment/follow-up period of the study. For these patients, Visit 2 will occur soon after Visit 1.

[0216] Patients, who do not qualify at Visit 1, may return to the Research Site for a second qualifying visit (Visit 1.1) at the discretion of the investigator. At Visit 1.1, procedures that caused failure of eligibility at Visit 1 will be repeated. Patients will be eligible for randomization after Visit 1.1 if they meet all inclusion criteria and if they no longer fail the exclusion criteria. If patients are evaluated at Visit 1.1 and qualify for randomization based on the repeated procedures at Visit 1.1, they need to be randomized within 60 days after Visit 1.

[0217] For some patients, Visit 1.1 will be mandatory at least 28 days after Visit 1 in order to check eligibility. These are patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications (see inclusion/exclusion criteria for details). Any of these changes at Visit 1 may affect the qualifying lipid levels and therefore, patients will need to have Visit 1.1 to determine whether they qualify based on lipid level requirements (TG and LDL-C) determined at Visit 1. Other procedures that caused failure of eligibility at Visit 1 will also be repeated at Visit 1.1.

[0218] The following procedures will be performed at the screening visit:

[0219] Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

[0220] Evaluate inclusion/exclusion criteria; only those evaluations will be repeated that deemed the patient not eligible on Visit 1.

[0221] Obtain fasting blood samples for chemistry and hematology testing. Only those samples will be obtained that deemed the patient not eligible on Visit 1.

[0222] Obtain a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C) if the patient was deemed not eligible on Visit 1. This includes patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications (see inclusion/exclusion criteria for details). These patients will have a fasting blood sample collected at Visit 1.1 for the qualifying lipid values (TG and LDL-C), and the TG and LDL-C inclusion criteria will be evaluated.

[0223] Record concomitant medication(s)

[0224] Treatment/Follow-Up Period

[0225] Every attempt should be made to complete the follow-up visits during the defined window periods.

[0226] Randomization visit (Visit 2; Day 0)

[0227] Qualified patients will return to the Research Site for Visit 2.

[0228] The following procedures will be performed at Visit 2:

[0229] Perform physical examination

[0230] Obtain weight

[0231] Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

[0232] Measure waist circumference (one of the factors to diagnose metabolic syndrome)

[0233] Obtain a 12-lead electrocardiogram

[0234] Evaluate inclusion/exclusion criteria

[0235] Obtain fasting blood samples for:

[0236] Chemistry and hematology testing

[0237] Lipid profile (baseline)

[0238] Biomarker assays (baseline)

[0239] Genetic testing (optional blood sample)

[0240] Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)

[0241] Perform a urine pregnancy test on women of childbearing potential (must be negative for randomization)

[0242] Dispense study drug and record randomization number

[0243] Instruct patient on how to take study drug

[0244] Administer study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples

[0245] Assess for and record adverse events

[0246] Record concomitant medication(s)

[0247] Instruct patient:

[0248] To bring all study supplies with them to the next visit

[0249] Not to take study drug on the morning of their next visit

[0250] To fast for $\geq$ 10 hours prior to the next visit

[0251] Visit 3 (Day 120; ~4 Months)

[0252] Patients will return to the Research Site for Visit 3 on Day 120 $\pm$10 days.

[0253] The following procedures will be performed:

[0254] Perform physical examination

[0255] Obtain weight

[0256] Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

[0257] Obtain fasting blood samples for:

[0258] Chemistry and hematology testing

[0259] Lipid profile

[0260] Review study drug compliance by unused capsule count; discuss with and counsel patients about compliance if needed

[0261] Administer study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples

[0262] Assess and record efficacy events

[0263] Assess for and record adverse events

[0264] Record concomitant medication(s)

[0265] Instruct patient:

[0266] To bring all study supplies with them to the next visit

[0267] Not to take study drug on the morning of their next visit

[0268] To fast for ≥10 hours prior to the next visit

[0269] Visits 4, 5, 6 and 7

[0270] At Visit 4: Day 360 ± 10; Visit 5: Day 720 ± 10; Visit 6: Day 1080 ± 10; and Visit 7: Day 1440 ± 10, the following procedures will be performed:

[0271] Perform physical examination

[0272] Obtain weight

[0273] Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

[0274] Measure waist circumference (collected at Visit 5 only)

[0275] Obtain a 12-lead electrocardiogram

[0276] Obtain fasting blood samples for:

[0277] Chemistry and hematology testing

[0278] Lipid profile

[0279] Biomarker assays (collected at Visit 5 only)

[0280] Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)

[0281] Review study drug compliance by unused capsule count; discuss with and counsel patients about compliance if needed

[0282] Administer study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples

[0283] Assess and record efficacy events

[0284] Assess for and record adverse events

[0285] Record concomitant medication(s)

[0286] Instruct patient:

[0287] To bring all study supplies with them to the next visit

[0288] Not to take study drug on the morning of their next visit

[0289] To fast for ≥10 hours prior to the next visit

Additional Visits

[0290] The end date of the study is expected for Day 1800 but the actual end date will be dependent on the determination of the study end date by the DMC. The study end date is determined to be when approximately 1612 primary efficacy events have occurred. If the actual study end date is later than the expected end date, additional visits will be planned between Visit 7 and the Last Visit with a maximum of 360 ±10 days between visits. If the actual study end date is sooner than the expected end date, fewer visits will occur, and the last visit (See Section 6.1.2.5) will occur sooner.

[0291] On additional visits the same procedures will be performed as listed in Section 6.1.2.3. Irrespective of the number of additional visits, after the DMC has established the end of the study date, there will be a last visit with procedures as listed in Section 6.1.2.5.

Last Visit – End of Study

[0292] All patients will complete the study at the same time (within a 30-day window after the study end date), irrespective of the date that they were randomized. The end date of the study is planned for Day 1800 but the actual end date will be dependent on the determination of the study end date when approximately 1612 primary efficacy events have occurred (event-driven trial). For each patient, the last visit may occur within 30 day after the actual study end date. However, for the efficacy endpoints based on CV events, only events occurring up to and including the scheduled actual study end date will be included in the efficacy analyses.

[0293] A final follow-up visit is required for all patients. In the rare cases that a final follow-up visit cannot occur within the 30-day timeframe following the study end date, any attempt to contact the patient must be recorded on a special contact form, until/unless appropriate information is obtained.

[0294] At the Last Visit, the following procedures will be performed:

[0295] Perform physical examination

[0296] Obtain weight

[0297] Obtain vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature)

[0298] Measure waist circumference

[0299] Obtain a 12-lead electrocardiogram

[0300] Obtain fasting blood samples for:

[0301] Chemistry and hematology testing

[0302] Lipid profile

[0303] Biomarker assays

[0304] Archiving (in countries and at sites approved by IRB/IEC and dependent on country regulations)

[0305] Determine study drug compliance by unused capsule count

[0306] Assess and record efficacy events

[0307] Assess for and record adverse events

[0308] Record concomitant medication(s)

[0309] Telephone Follow-up Contact

[0310] Site personnel will contact each patient by telephone on the following study days:

[0311] Day 60 ±3 days

[0312] Day 180 ±5 days

[0313] Day 270 ±5 days

[0314] Day 450 ±5 days

[0315] Day 540±5 days

[0316] Day 630 ±5 days

[0317] Day 810 ±5 days

[0318] Day 900 ±5 days

[0319] Day 990 ±5 days

[0320] Day 1170 ±5 days

[0321] Day 1260 ±5 days

[0322] Day 1350 ±5 days

[0323] Day 1530 ±5 days

[0324] Day 1620 ±5 days

[0325] Day 1710 ±5 days

[0326] If the treatment/follow-up period of the study is extended beyond the expected end date (Day 1800), additional follow-up phone calls will be made every 3 months in-between additional visits ±5 days. If the treatment/follow period of the study is shorter than the expected end date, less follow-up phone calls will be needed.

[0327] Every attempt will be made to talk to each patient within this time frame.

[0328] The following information will be collected from the patient:

[0329] Possible efficacy endpoints related to CV events. Patients will be asked to return to the Research Site to assess for any endpoints or events identified.

[0330] Adverse events

[0331] Concomitant medications

[0332] Current address and contact information (update if changed or will be changing)

[0333] Patients will be reminded about the following items:

[0334] To take the study medication according to the dosing schedule assigned, with food

[0335] When to return to the Research Center for the next visit

[0336] To bring the unused study medication to the next visit

[0337] To not take study drug on the morning of their next visit

[0338] To fast for at least 10 hours prior to the next visit

Laboratory Procedures

[0339] Clinical Laboratory Procedures

[0340] All clinical laboratory determinations for screening and safety will be performed by a certified clinical laboratory under the supervision of the Sponsor or its designee.

[0341] Whenever possible and appropriate, samples for the clinical laboratory procedures will be collected after fasting for at least 10 hours. For the purposes of this study, fasting is defined as nothing by mouth except water (and any essential medications).

[0342] The investigator must review and sign all laboratory test reports. At screening, patients who have laboratory values that are outside the exclusionary limits specified in the exclusion criteria may not be enrolled in the study (patients can be considered for the study if values are classified as not clinically significant by the investigator). After randomization, the investigator will be notified if laboratory values are outside of their normal range. In this case, the investigator will be required to conduct clinically appropriate follow-up procedures.

Safety Laboratory Tests

[0343] The safety laboratory tests include:

[0344] Hematology with complete blood count (CBC), including RBC, hemoglobin (Hgb), hematocrit (Hct), white cell blood count (WBC), white cell differential, and platelet count

[0345] 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.

Fasting Lipid Profile

[0346] The fasting lipid panel includes: TG, TC, LDL-C, HDL-C, non-HDL-C, and VLDL-C.

[0347] At all visits, LDL-C will be calculated using the Friedewald equation. At Visit 1 and Visit 1.1 Direct LDL-C will be used if at the same visit TG >400 mg/dL (4.52 mmol/L). These LDL-C values will be used for the evaluation of the LDL-C inclusion criterion (LDL-C qualifying measurements for randomization) and for the assessment of changes in the statin therapy when LDL-C is not at goal. At all remaining visits (except Visit 2 and Visit 4) LDL-C will be measured by Direct LDL Cholesterol or by Preparative Ultracentrifugation if at the same visit TG >400 mg/dL (4.52 mmol/L). In addition, irrespective of the TG levels, at Visit 2 (0 Months of Follow-up, baseline) and at Visit 4 (12 Months of Follow-up), LDL-C will be measured by Preparative Ultracentrifugation. These Preparative Ultracentrifugation LDL-C measurements will be used in the statistical analysis including the calculation of the percent change from baseline (1 year versus baseline).

Genetic testing

[0348] A fasting blood sample will be stored for future genetic testing at the discretion of the sponsor. The specifics of this test will be determined at a later date. This sample is optional as local regulations may prohibit genetic samples to be collected or shipped outside the country, or patients may not consent.

[0349] Research on genetic testing will look for links between genes and certain diseases, including their treatment(s) such as medicines and medical care. The blood samples will be collected in the study center with the regular protocol-required labs. Each patient tube with sample for genetic testing will be labeled with patient number only. The site will maintain a Subject Code Identification List for cross-reference. The patient number does not contain any identifiable information (i.e. Patient initials, date of birth, etc). Un-analyzed samples will be stored frozen by the sponsor for a period of up to 2 years following the end of the study, at which time they will be destroyed. If samples are tested, results will not be reported to the patient, parents, relatives, or attending physician and will not be recorded in the patient's medical records. There will be no follow-up contact with the sites or patients regarding this sample. The subject can withdraw their consent for genetic testing at any time up to analysis, even after the sample has been obtained. The subject can notify the site in writing that they withdraw their consent for the genetic testing portion of the study, and it will be documented by the site in the subject chart, as well as captured in the CRF. The lab will be notified to pull the sample and destroy it.

Biomarkers Assays

[0350] The biomarker assays include: hs-CRP, Apo B and hsTnT.

[0351] Additional laboratory tests

[0352] Additional laboratory tests include:

[0353] A urine pregnancy test will be administered to women of childbearing potential at certain visits as listed in schedule of procedures (Table 1). The urine pregnancy tests will be performed at the Research Site utilizing marketed test kits, or at a certified clinical laboratory.

[0354] A fasting blood sample (12 mL) for archiving. This sample will be collected only at sites in countries where allowed by local regulations and at sites for which approved by the IRB or IEC. The plasma from the archiving sample will be stored frozen in 2 separate equal aliquots, and will be used at the Sponsor's discretion to

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

[0355] Blinding of Laboratory Results

[0356] All efficacy laboratory results during the double-blind period of the trial will be blinded (values not provided) to patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors managing and/or supporting the study, with the exception of the laboratory personnel conducting the assays. To ensure patient safety, hsTnT values will be reported to the site.

[0357] Flagging of Critical Lab Values

[0358] Critical lab values are values that may warrant medical intervention to avoid possible harm to a patient. Critical lab values will be defined in the Laboratory Manual for the study, and the Research Site will be notified of the occurrence of a critical lab value (critical high or critical low) by a special annotation (flag) in the laboratory reports provided to the Research Sites. Although laboratory values that are part of the efficacy endpoints during the double-blind period of the study will not be provided to the Research Site (see Section 6.3.1.6), the sites will be notified when the TG value of a patient sample is >1000 mg/dL (11.29 mmol/L) (critical high TG value) or if the LDL-C values of a patient sample is >130 mg/dL (3.37 mmol/L) (critical high LDL-C value). These critical high values will need to be confirmed by a repeat measurement (new fasting blood sample) within 7 days. TG value of >2000 mg/dL (22.58 mmol/L) will also be flagged, so that appropriate medical action can be taken by the investigator as soon as possible.

[0359] If TG values are confirmed critically high, patients may be discontinued from study drug with the option to remain on study. The investigator should use the best clinical judgment for each patient which could include the use of approved TG-lowering medications after patients have been discontinued from study drug.

[0360] If LDL-C values are confirmed critically high, the investigator may need to take appropriate medical action which could include: reinforce/intensify therapeutic

lifestyle changes (including diet and physical activity), increase the dose of the present statin therapy, add ezetimibe, or prescribe a more potent statin to lower LDL-C. The investigator should use the best clinical judgment for each patient.

[0361] Medical Procedures

[0362] Medical, Surgical and Family History

[0363] Medical history, including family history and details regarding all illnesses and allergies, date(s) of onset, status of current condition, and smoking and alcohol use will be collected on all patients.

[0364] Demographics

[0365] Demographic information including day, month, and year of birth, race, and gender will be collected for all patients.

[0366] Vital Signs

[0367] Vital signs include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Blood pressure will be measured using a standardized process:

[0368] Patient should sit for ≥5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level.

[0369] Use a mercury sphygmomanometer or automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery.

[0370] Blood pressure should be recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device. A blood pressure reading should be repeated 1 to 2 minutes later, and the second reading should also be recorded to the nearest 2 mmHg mark.

[0371] Physical Examination

[0372] A physical examination must include source documentation of general appearance, skin, and specific head and neck, heart, lung, abdomen, extremities, and neuromuscular assessments.

[0373] Height, Weight and Body Mass Index

[0374] Height and weight will be measured. Measurement of weight should be performed with the patient dressed in indoor clothing, with shoes removed, and bladder empty.

[0375] Waist Circumference

[0376] Waist circumference will be measured with a tape measure, as follows: Start at the top of the hip bone then bring the tape measure all the way around – level with the navel. Make sure the tape measure is snug, but without compressing the skin, and that it is parallel with the floor.

[0377] Patients should not hold their breath while measuring waist circumference.

[0378] Electrocardiogram (ECG)

[0379] ECGs (standard 12-lead) will be obtained annually. Site personnel should make every attempt to perform a patient's ECG using the same equipment at each visit. ECGs will be reviewed by the site for the detection of silent MI. Silent MIs will be sent for event adjudication.

TREATMENT AND RESTRICTIONS

[0380] Treatment

[0381] Treatment Regimen, Dosage, and Duration

[0382] Eligible study patients will be randomly assigned on Day 0 to one of the 2 treatment groups. Patients in each group will receive either 4 g/day AMR101 or placebo for up to 4.75 years (4 years planned median treatment duration) according to Table 2.

[0383] The daily dose of study drug is 4 capsules per day taken as two capsules take on two occasions per day (2 capsules given twice daily).

Table 2. Dosing Schedule during the Treatment Period

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

[0384] Patients will be instructed to take study drug with food (i.e., with or at the end of their morning and evening meals). On days that patients are scheduled for study visits, the daily dose of study drug will be administered by site personnel with food provided by the site following collection of all fasting blood samples. For the purposes of this study, fasting is defined as nothing by mouth except water (and any essential medications) for at least 10 hours.

Treatment Assignment

[0385] Identification number

[0386] A unique patient identification number (patient number) will be established for each patient at each site. The patient number will be used to identify the patient throughout the study and will be entered on all documentation. If a patient is not eligible to receive treatment, or if a patient discontinues from the study, the patient number cannot be reassigned to another patient. The patient number will be used to assign patients to one of the 2 treatment groups according to the randomization schedule.

[0387] Drug Randomization

[0388] Only qualified patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized and will receive study medication starting at Visit 2 (Day 0). Eligible patients will be randomly assigned to one of the 2 treatment groups. Randomization will be stratified by CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries) (See

Section 3.10). Approximately 70% of randomized patients will be in the CV Risk Category 1, including patients with established CVD, and approximately 30% of randomized patients will be in the CV Risk Category 2, including patients with diabetes and at least one additional risk factor but no established CVD. Enrollment with patients of a CV risk category will be stopped when the planned number of patients in that risk category is reached.

[0389] Emergency Unblinding

[0390] In an emergency, when knowledge of the patient's treatment assignment is essential for the clinical management or welfare of the patient, the investigator may request the patient's treatment assignment for unblinding. Prior to unblinding the patient's individual treatment assignment, the investigator should assess the relationship of an adverse event to the administration of the study drug (Yes or No). If the blind is broken for any reason, the investigator must record the date and reason for breaking the blind on the appropriate Case Report Form (CRF) and source documents.

[0391] Compliance Control

[0392] It is recommended that, unless clear contraindications arise, patients be strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy should, if possible, be brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. Discontinuations will be discouraged as much as possible. Any discontinuations should be based on compelling clinical reasons.

[0393] For every patient, an assessment of compliance to the study drug treatment regimen must be obtained at each scheduled visit. Study medication will be dispensed in amounts exceeding the amount required for the study. Patients will be instructed to return all unused study medication at the next visit. Compliance to the study drug regimen will be evaluated at each visit by counting unused capsules. Discrepancies will be evaluated and discussed with each patient to assess compliance. If compliance is unsatisfactory, the patient will be counseled about the importance of compliance to the dosing regimen. At the end of the study, the final study medication compliance will be determined by unused capsule count.

[0394] Study Restrictions

[0395] Concomitant Medications during Treatment/Follow-Up Period

[0396] Any medications administered during the study period must be documented on the Concomitant Medication CRF. Patients must not have taken any investigational agent within 90 days prior to screening. Patients cannot participate in any other investigational medication trial while participating in this study.

[0397] The following non-study drug related, non-statin, lipid-altering medications and supplements, and foods are prohibited during the study (from Visit 1 until after the Last Visit-End of Study), except for compelling medical reasons in ODIS patients:

[0398] niacin >200 mg/day;

[0399] fibrates;

[0400] prescription omega-3 fatty acid medications;

[0401] dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils);

[0402] bile acid sequestrants;

[0403] cyclophosphamide;

[0404] systemic retinoids

[0405] If any of these products would be used during the treatment/follow-up period of the study, it should be for compelling medical reasons in ODIS patients, and it should be documented in the Concomitant Medication CRF. If the ODIS patient agrees to restart study medication, the use of excluded medication must be discontinued.

[0406] Foods enriched with omega-3 fatty acids are strongly discouraged after Visit 1 for the duration of the study (does not apply to The Netherlands or Canada only. Therefore, all centers in The Netherlands and Canada must ignore this request).

[0407] The following products are allowed: statins, ezetimibe, and herbal products & dietary supplements not containing omega-3 fatty acids.

[0408] Statins:

[0409] The same statin at the same dose should be continued until the end of the study, unless deemed medically necessary to change because of an adverse event or lack of efficacy (LOE). It is preferred that if LOE is the determining factor that ezetimibe be added to the present dose.

[0410] Switching between a brand name statin and the generic version of the same statin is allowed at any time during the study.

[0411] Statins may be administered with or without ezetimibe.

[0412] Based on the FDA recommendation, simvastatin 80 mg be used only in patients who have been taking this dose for 12 months or more and have not experienced any muscle toxicity. (See reference: FDA Drug Safety Communication: Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury. (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204882.htm)

[0413] Changing of the type of statin or the statin dose during the treatment/follow-up period of the study should only be done for compelling medical reasons and must be documented in the CRF.

[0414] LDL-C Rescue:

[0415] If the level of LDL-C exceeds 130 mg/dL (3.37 mmol/L) during the study (initial measurement and confirmed by a second determination at least 1 week later), the investigator may either increase the dose of the present statin therapy or may add ezetimibe to lower LDL-C. The investigator should use the best clinical judgment for each patient.

[0416] No data are available with regard to potential interactions between ethyl-EPA and oral contraceptives. There are no reports suggesting that omega-3 fatty acids, including ethyl-EPA, would decrease the efficacy of oral contraceptives.

[0417] Patient Restrictions

[0418] Beginning at the screening visit, all patients should be instructed to refrain from excessive alcohol consumption, to follow a physician recommended diet and to maintain it through the duration of the study. Excessive alcohol consumption is on average 2 units of alcohol per day or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking). A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.

INVESTIGATIONAL PRODUCT

[0419] Clinical Trial Material

[0420] The following will be supplied by the Sponsor:

[0421] AMR101 1000 mg capsules

[0422] Placebo capsules

[0423] The Sponsor will supply sufficient quantities of AMR101 1000 mg capsules and placebo capsules to allow for completion of the study. The lot numbers of the drugs supplied will be recorded in the final study report.

[0424] Records will be maintained indicating the receipt and dispensation of all drug supplies. At the conclusion of the study, any unused study drug will be destroyed.

[0425] Pharmaceutical Formulations

[0426] AMR101 1000 mg and placebo capsules (paraffin) are provided in liquid-filled, oblong, gelatin capsules. Each capsule is filled with a clear liquid (colorless to pale yellow in color). The capsules are approximately 25.5 mm in length with a diameter of approximately 9.5 mm.

[0427] Labeling and Packaging

[0428] Study medication will be packaged in high-density polyethylene bottles. Labeling and packaging will be performed according to GMP guidelines and all applicable country-specific requirements. The bottles will be numbered for each patient based on the randomization schedule. The patient randomization number assigned by IWR or a designee of the Sponsor for the study (if no IWR system is used), will correspond to the number on the bottles. The bottle number for each patient will be recorded in the Electronic Data Capture (EDC) system for the study.

[0429] Dispensing Procedures and Storage Conditions

[0430] Dispensing Procedures

[0431] At Visit 2 (Day 0), patients will be assigned study drug according to their treatment group determined by the randomization schedule. Once assigned to a treatment group, patients will receive study drug supplies. At each visit, patients will bring unused drug supplies dispensed to them earlier. From the drug supplies assigned to each patient, site personnel will administer drug while the patients are at the Research Site.

[0432] The investigator or designee must contact the IWR system or a designee of the Sponsor for the study (if no IWR system is used) when any unscheduled replacements of study medication are needed.

[0433] During the last visit during the treatment period, patients will bring the unused drug supplies for site personnel to calculate the final study medication compliance by unused capsule count.

[0434] Storage Conditions

[0435] At the Research Sites, study drugs must be stored at room temperature, 68°F to 77°F (20°C to 25°C). Do not allow storage temperature to go below 59°F (15°C) or above 86°F (30°C). Store in the original package.

[0436] Study drugs must be stored in a pharmacy or locked and secure storage facility, accessible only to those individuals authorized by the investigator to dispense the drug. The investigator or designee will keep accurate dispensing records. At the conclusion of the study, study site personnel will account for all used and unused study drug. Any unused study drug will be destroyed. The investigator agrees not to distribute study drug to any patient, except those patients participating in the study.

EFFICACY ASSESSMENTS

[0437] Specification of Variables and Procedures

[0438] The primary endpoint and the majority of the secondary and tertiary endpoints are based on clinical events related to CVD and mortality. All events occurring between randomization and the study end date (inclusive) must be recorded. Only adjudicated events will be included in the final analyses. Further details on the assessment of clinical events and their definitions will be found in the CEC charter.

[0439] Efficacy Endpoints

[0440] Primary Efficacy Endpoint

[0441] Time from randomization to the first occurrence of the composite of the following clinical events:

[0442] CV death,

[0443] Nonfatal MI (including silent MI; ECGs will be performed annually for the detection of silent MIs),

[0444] Nonfatal stroke,

[0445] Coronary revascularization

[0446] Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing.

[0447] The first occurrence of any of these major adverse vascular events during the follow-up period of the study will be included in the incidence.

[0448] Secondary Efficacy Endpoints

[0449] The key secondary efficacy endpoint is:

[0450] The composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or peripheral CVD requiring intervention, angioplasty, bypass surgery, or aneurysm repair.

[0451] Other secondary efficacy endpoints are as follows (to be tested in said order):

[0452] The composite of total mortality, nonfatal MI, or nonfatal stroke;

[0453] The composite of death from CV causes, nonfatal MI, coronary revascularization, unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, peripheral CVD requiring intervention, or cardiac arrhythmia requiring hospitalization;

[0454] The composite of death from CV causes, nonfatal MI, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;

[0455] The composite of death from CV causes or nonfatal MI;

[0456] Total mortality;

[0457] Fatal and nonfatal MI (including silent MI);

[0458] Coronary Revascularization;

[0459] Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing ;

[0460] Fatal and nonfatal stroke.

[0461] For the secondary endpoints that count a single event, the first occurrence of this type of event will be counted in each patient. For secondary endpoints that are composites of two or more types of events, the first occurrence of any of the event types included in the composite will be counted in each patient.

[0462] Tertiary Efficacy Endpoints:

[0463] The second, third, fourth, and fifth major CV event of the primary composite endpoint. The type of (nonfatal) events may occur in any order.

[0464] Primary endpoint in subset of patients with diabetes mellitus;

[0465] Primary endpoint in subset of patients with metabolic syndrome;

[0466] New CHF, new CHF leading to hospitalization, transient ischemic attack, amputation for CVD and carotid revascularization;

[0467] Elective coronary revascularization and emergent coronary revascularization;

[0468] New onset diabetes;

[0469] Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hs-CRP, and hsTnT: effect of baseline and on-treatment change of biomarkers on primary and key secondary endpoints;

[0470] CV mortality;

[0471] Cardiac Arrhythmias requiring hospitalization;

[0472] Cardiac Arrest;

[0473] To explore the effect of AMR101 on weight and waist circumference.

[0474] For the tertiary endpoints that count a single event, the first occurrence of this type of event will be counted in each patient. For tertiary endpoints that are composites of two or more types of events, the first occurrence of any of the event

types included in the composite will be counted in each patient (except when stated otherwise, for the second, third, fourth, and fifth major CV event).

SAFETY ASSESSMENTS

[0475] Specification of Variables and Procedures

[0476] Safety assessments will include adverse events, clinical laboratory measurements (chemistry, hematology), 12-lead ECGs, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), and physical examinations as per Study Procedures/Table 1.

[0477] A complete medical, surgical and family history will be completed at Visit 1.

[0478] All laboratory test results must be evaluated by the investigator as to their clinical significance. Any observations at physical examinations or laboratory values considered by the investigator to be clinically significant should be considered an adverse event.

[0479] Adverse Events

[0480] An adverse event is defined as any untoward medical occurrence, which does not necessarily have a causal relationship with the medication under investigation. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medication product, whether or not related to the investigational medication product. All adverse events, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate CRF. Each adverse event is to be evaluated for duration, intensity, and causal relationship with the study medication or other factors.

[0481] Adverse events, which include clinical laboratory test variables, will be monitored from the time of informed consent until study participation is complete. Patients should be instructed to report any adverse event that they experience to the

investigator. Beginning with Visit 2, investigators should assess for adverse events at each visit and record the event on the appropriate adverse event CRF.

[0482] Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the investigator, it should be recorded as a separate adverse event on the CRF.

[0483] Any medical condition that is present when a patient is screened or present at baseline that does not deteriorate should not be reported as an adverse event. However, medical conditions or signs or symptoms present at baseline and that change in severity or seriousness at any time during the study should be reported as an adverse event.

[0484] Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen will be reported as adverse events or SAEs. The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

[0485] The investigator will rate the severity (intensity) of each adverse event as mild, moderate, or severe, and will also categorize each adverse event as to its potential relationship to study drug using the categories of Yes or No.

[0486] Severity:

[0487] Mild – An event that is usually transient in nature and generally not interfering with normal activities.

[0488] Moderate – An event that is sufficiently discomforting to interfere with normal activities.

[0489] Severe – An event that is incapacitating with inability to work or do usual activity or inability to work or perform normal daily activity.

[0490] Causality Assessment:

[0491] The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

[0492] 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.

[0493] Yes – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

[0494] The following factors should also be considered:

[0495] The temporal sequence from study medication administration

[0496] The event should occur after the study medication is given. The length of time from study medication exposure to event should be evaluated in the clinical context of the event.

[0497] Underlying, concomitant, intercurrent diseases

[0498] Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.

[0499] Concomitant medication

[0500] The other medications the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.

[0501] Known response pattern for this class of study medication

[0502] Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

[0503] Exposure to physical and/or mental stresses

[0504] The exposure to stress might induce adverse changes in the patient and provide a logical and better explanation for the event.

[0505] The pharmacology and pharmacokinetics of the study medication

[0506] The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study medication should be considered.

[0507] 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.

[0508] Serious Adverse Events

[0509] A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

[0510] Results in death

[0511] Is life-threatening- Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

[0512] Requires hospitalization or prolongation of existing hospitalization- Note: In general, hospitalization for treatment of a pre-existing condition(s) that did not worsen from baseline is not considered adverse events and should not be reported as SAEs.

[0513] Results in disability/incapacity

[0514] Is a congenital anomaly/birth defect;

[0515] Is an important medical event- Note: Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed

above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

[0516] By design of this study SAEs that are endpoint events will only be recorded for the endpoint determination and not captured as SAEs. The intention is that the endpoint events are not reported to IRBs as SAEs, unless the IRB requires that these are reported. Investigators should specifically inform their institution/IRB of this plan and confirm whether or not they want the endpoint events reported. By agreement with the US FDA, these endpoints will also not be reported to the US FDA as SAEs; rather they will be reported as endpoint events. Following adjudication if the event is determined to not meet the criteria for an event, the event will be evaluated as an SAE beginning with that day as Day 0.

[0517] Serious Adverse Event Reporting – Procedure for Investigators

[0518] Initial Reports

[0519] All SAEs occurring from the time of informed consent until 28 days following the last administration of study medication must be reported to the Sponsor or designee within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). SAEs that the investigator considers related to study medication occurring after the 28-day follow-up period will also be reported to the Sponsor or designee.

[0520] The investigator is required to submit SAE reports to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local requirements. All investigators involved in studies using the same investigational medicinal product (IMP) will receive any Suspected Unexpected Serious Adverse Reaction (SUSAR) reports for onward submission to their local IRB as required. All reports sent to investigators will be blinded.

[0521] In addition, regulatory agencies will be notified of SAEs per the requirements of the specific regulatory jurisdiction regulations and laws.

[0522] Follow-Up Reports

[0523] The investigator must continue to follow the patient until the SAE has subsided, or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., laboratory test reports, patient discharge summary, or autopsy reports) to the Sponsor or designee via fax or email.

[0524] Reporting by the Sponsor

[0525] IRBs and IECs will be informed of SUSARs according to local requirements. Cases will be unblinded for reporting purposes as required.

[0526] Exposure In Utero During Clinical Trials

[0527] If a patient becomes pregnant during the study, the investigator should report the pregnancy to the Sponsor or designee within 24 hours of being notified. The Sponsor or designee will then forward the Exposure In Utero form to the investigator for completion.

[0528] The patient should be followed by the investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify the Sponsor or designee. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

TREATMENT DISCONTINUATION/PATIENT WITHDRAWAL

[0529] Patients may withdraw from the study at any time and for any reason. Study drug administration may also be discontinued at any time, at the discretion of the investigator. In any case, follow-up for efficacy and safety should be continued.

[0530] Reasons for Early Study Drug Discontinuation

[0531] Study drug discontinuation should be avoided as much as possible, but may be done for any of the following reasons:

[0532] Patient withdraws consent or requests early discontinuation from the study for any reason. Patients should be encouraged to continue to participate in the study for the entire duration of the study even if they choose not to take study medication any longer.

[0533] Occurrence of a clinical or laboratory adverse event, either serious or non-serious, at the discretion of the investigator. The Sponsor or designee should be notified if a patient is discontinued because of an adverse event or laboratory abnormality. It is recommended that, unless clear contraindications arise, patients be strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy should, if possible, be brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. The following should be considered reason for discontinuation:

[0534] ALT > 3x ULN and bilirubin > 1.5x ULN

[0535] ALT >5x ULN

[0536] ALT >3x ULN and appearance or worsening of hepatitis

[0537] ALT > 3x ULN persisting for >4weeks

[0538] ALT > 3x ULN and cannot be monitored weekly for 4 weeks

[0539] Any medical condition or personal circumstance that, in the opinion of the investigator, exposes the patient to risk by continuing in the study or precludes adherence to the protocol.

[0540] Sponsor discontinues the study.

[0541] A TG value that is flagged as critically high, i.e., >1000 mg/dL (11.29 mmol/L), and confirmed as critically high by a repeat measurement (new fasting blood

sample) within 7 days. In this case, a patient may be discontinued from study drug (with the option to remain ODIS) and other lipid-altering medications may be (re)initiated. If the TG value is flagged as >2000 mg/dL (22.58 mmol/L) then appropriate medical action can be taken by the investigator as soon as possible.

[0542] Occurrence of an outcome event according to the judgment of the investigator is not considered a valid reason for study drug discontinuation.

[0543] Patients whose treatment with study medication is discontinued early, and have not withdrawn consent, will stay in study and will be monitored until the end of the study. Patients that continue in the study after indefinite cessation of therapy will be characterized as Off Drug In Study (ODIS). ODIS patients should be asked to return to the study site for an interim visit once the patient has been off study drug for >30 days. Procedures at this visit are consistent with those at Visit 5. If not contraindicated, patients will also have the option to restart study medication at any point once characterized as ODIS.

[0544] The reason for study drug discontinuation or interruption will be recorded on the CRF.

[0545] Follow-Up after Early Study Drug Discontinuation/Lost to Follow-Up

[0546] Patients who prematurely discontinue study drug are not to be replaced.

[0547] All randomized patients must be followed up according to the study flowchart until the study end date or death, regardless of whether they discontinue study drug prematurely or not. Any event occurring after early study drug discontinuation will be recorded up through the study end date.

[0548] In order to follow the medical status of the patients, especially when they discontinued the study, investigators are encouraged to obtain information from the patient's primary care practitioner (physician or any other medical care provider). Investigators are also requested to try as much as possible to re-contact those patients at the end of the trial to obtain at least their vital status as well as their status with

respect to the primary endpoint, and thus avoid lost to follow-up for the efficacy assessment.

[0549] If patients are lost to follow-up, the CRF must be completed up to the last visit or contact.

STATISTICS

[0550] Analysis Populations

[0551] Randomized Population

[0552] The randomized population will include all patients who sign the informed consent form and are assigned a randomization number at Visit 2 (Day 0).

[0553] Intent-to-Treat Population

[0554] The Intent-to-Treat (ITT) population will consist of all randomized patients who take at least one dose of study drug. The ITT population is the primary analysis population. All efficacy analyses will be performed on the ITT population.

[0555] Per-Protocol Population

[0556] The per-protocol (PP) population will include all ITT patients without any major protocol deviations, and who had ≥80% compliance with study drug while on treatment (up to discontinuation for patients whose treatment is terminated early). The per-protocol efficacy analysis for CV events will be restricted to each patient's time on study drug plus 30 days thereafter.

[0557] Safety Population

[0558] All safety analyses will be conducted based on the safety population, which is defined as all randomized patients who receive at least one dose of study drug. This is the same as the ITT population.

[0559] Statistical Methods

[0560] Safety and efficacy variables will be analyzed using appropriate statistical methods to be described in detail in a separate Statistical Analysis Plan (SAP). The SAP will be finalized before study unblinding.

[0561] Patient Disposition and Demographic/Baseline Characteristics

[0562] The numbers of patients screened, the number of patients randomized per treatment group (randomized population), and the number of patients in the ITT and PP populations by treatment group will be listed.

[0563] For randomized patients who discontinued treatment with study drug, the primary reason for discontinuation will be listed and summarized by treatment group.

[0564] Summary statistics (mean, standard deviation, median, minimum and maximum) will be provided by treatment group for demographic characteristics (e.g., age, sex, race, and ethnicity) and baseline characteristics (e.g., body weight, height, and body mass index) in the ITT and PP populations.

[0565] Demographic data and baseline characteristics will be compared among treatment groups for the ITT and PP population. Differences in demographic and baseline characteristics will be tested using a chi-square test (for categorical variables) or a 1-way analysis of variance model with treatment as a factor (for continuous variables). The p-values will be used as descriptive statistics, primarily as an assessment of the adequacy of randomization.

[0566] Study Medication Exposure and Compliance

[0567] The final compliance to study drug will be calculated as the percent of doses taken relative to doses scheduled to be taken. Overall percent compliance will be calculated per patient in the ITT and PP populations and summarized by treatment group using summary statistics (n, mean, standard deviation, median, minimum, and maximum).

[0568] Concomitant Therapies

[0569] Concomitant medication/therapy verbatim terms will be coded using the latest version of the World Health Organization Drug Dictionary. The numbers and percentages of patients in each treatment group taking concomitant medications will be summarized by anatomic and therapeutic chemical classification and preferred term.

[0570] Analysis of Efficacy

[0571] For efficacy endpoints including CV events, only adjudicated events will be included in the final statistical analyses.

[0572] Summary Statistics

[0573] Summary statistics (n, mean, standard deviation, median, minimum, and maximum) for the baseline and post-baseline measurements, the percent changes, or changes from baseline will be presented by treatment group and by visit for all efficacy variables to be analyzed. The summary statistics will include changes in body weight and body mass index from baseline by treatment group and by visit.

[0574] Primary Endpoint

[0575] The primary efficacy endpoint is the time from randomization to the first occurrence of any component of the composite of the following clinical events:

[0576] CV death,

[0577] Nonfatal MI (including silent MI),

[0578] Nonfatal stroke,

[0579] Coronary revascularization,

[0580] Hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing.

[0581] The analysis of the primary efficacy endpoint will be performed using the log-rank test comparing the 2 treatment groups (AMR101 and placebo) and including the stratification factor "CV risk category", use of ezetimibe and geographical region (Westernized, Eastern European, and Asia Pacific countries) (each as recorded in the

IWR at the time of enrollment) as covariates. Treatment difference will be tested at alpha level of 0.0476 accounting for one interim efficacy analysis. The hazard ratio for treatment group (AMR101 vs. placebo) from a Cox proportional hazard model that includes the stratification factor will also be reported, along with the associated 95% confidence interval. Kaplan-Meier estimates from randomization to the time to the primary efficacy endpoint will be plotted.

[0582] The size and direction of the treatment effects of the individual components of the composite endpoint and their relative contribution to the composite endpoint will be determined as well.

[0583] Secondary Endpoints

[0584] The statistical analyses of the secondary endpoints will be analyzed by the same log-rank test specified above for the primary efficacy endpoint. Treatment differences will be tested at alpha level of 0.05 using a sequential procedure for controlling type 1 error starting with the key secondary variable. The remaining secondary variables will be tested in the order specified in Section 9.2.2. Estimates of the hazard ratios from the Cox proportional hazard model and the associated 95% confidence intervals will also be provided. Kaplan-Meier estimates from randomization the time to the secondary efficacy endpoints will be plotted.

[0585] Tertiary Endpoints

[0586] For event rates, the statistical analyses of the tertiary endpoints will be similar to the analysis of the secondary efficacy endpoints. All tertiary analyses will be conducted for the ITT population. No adjustments for multiple testing will be made.

[0587] For measurements of lipids, lipoproteins and inflammatory markers the change from baseline will be analyzed in the units of each marker, and the percent change from baseline. Since these biomarkers are typically not normally distributed, the Wilcoxon rank-sum test will be used for treatment comparisons of the percent change from baseline, and medians and quartiles will be provided for each treatment group. The medians of the differences between the treatment groups and 95% confidence intervals will be estimated with the Hodges-Lehmann method.

[0588] New onset diabetes is defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period (i.e. patients with no history of diabetes at randomization).

[0589] For purposes of this study, a diagnosis of diabetes is made based on the observation of:

[0590] 1. HbA_{1c} ≥6.5%. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay. In the absence of unequivocal hyperglycemia, HbA_{1c} ≥6.5% should be confirmed by repeat testing.

OR

[0591] 2. Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hr. In the absence of unequivocal hyperglycemia, FPG ≥126 mg/dL (7.0 mmol/L) should be confirmed by repeat testing.

OR

[0592] 3. 2-hr plasma glucose ≥200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT). The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water. In the absence of unequivocal hyperglycemia, 2-hr plasma glucose ≥200 mg/dL (11.1 mmol/L) during an Oral Glucose Tolerance Test (OGTT) should be confirmed by repeat testing.

OR

[0593] 4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

[0594] Exploratory Subgroup Analyses

[0595] Subgroup analyses of the primary and key secondary endpoints (as defined in the Statistical Analysis Plan) will be performed. All subgroup analyses will be conducted for the ITT population. No adjustments for multiple testing will be made.

[0596] Log-rank tests, treatment effects and the associated 95% confidence intervals for the primary and key secondary efficacy endpoints within each subgroup will be provided using the Cox proportional hazard model with treatment (AMR101 or placebo), and stratification as a factor (with the exception of the subgroup analyses of those subgroup variables related to the stratification factors, i.e., CV risk category that will not have stratification as a factor).

[0597] Subgroups including, but not limited to the following, will be explored. A complete list will be prospectively defined in the Statistical Analysis Plan.

[0598] Demographics:

[0599] Gender,

[0600] age (<65 yr and ≥65 yr),

[0601] race (white and nonwhite, or any other subset with at least 10% of the total number of patients),

[0602] geography (western vs. non-western)

[0603] Disease Parameters:

[0604] CV risk category,

[0605] the presence/absence of diabetes at baseline,

[0606] renal impairment

[0607] Treatment Parameters:

[0608] by statin intensity (statin type and regimen),

[0609] relevant concomitant medications,

[0610] Baseline Lipid and Lipoprotein Parameters:

[0611] LDL-C (by tertile),

[0612] HDL-C (by tertile),

[0613] TG (by tertile),

[0614] TG ≥150 mg/dL,

[0615] TG ≥200 mg/dL and TG <200 mg/dL, combined highest tertile for TG and lowest tertile for HDL-C,

[0616] hs-CRP (≤3 mg/L and >3 mg/L),

[0617] Apo B (by tertile),

[0618] non-HDL-C (by tertile)

[0619] The consistency of the treatment effects in subgroups will be assessed for the primary and key secondary efficacy endpoints. For each subgroup variable, a Cox proportional hazard model with terms for treatment, stratification factors (with the exception of those subgroup variables related to the stratification factors, i.e., CV risk category), subgroup, and treatment-by-subgroup interaction will be performed. The main treatment effect will not be tested with this model. P-values for testing the interaction terms will be provided.

[0620] Interim Efficacy Analysis

[0621] One interim analysis will be performed for the primary efficacy endpoint using best available data (adjudicated events and site reported endpoints) based on data when approximately 60% of the total number of primary endpoint events is reached. The interim analysis will be based on a group sequential design that includes early stopping rules for benefit while preserving the overall Type I error rate (O'Brien-Fleming). This allows for interim analysis and preserves the overall Type I error probability of α=0.05 for the primary endpoint.

[0622] Approximately 1612 primary efficacy endpoint events are planned to be observed during the trial, based on sample size calculation assumptions. Therefore, the interim analysis will occur after at least 967 primary efficacy endpoint events have been observed. According to this boundary, the critical p-value at the interim analysis has to be $p \leq 0.0076$, resulting in the final evaluation p-value of 0.0476.

[0623] The interim results of the study will be monitored by an independent DMC. The analyses will be performed by the independent statistical group unblinded to the treatment assignment. The results will be reported only to the DMC. The unblinded information will not be released to sponsor under any circumstance before the completion of the study. Specific statistical guidelines for data monitoring will be discussed and formalized in a separate Interim Statistical Analysis Plan and DMC Charter.

[0624] Analysis of Safety

[0625] All analyses of safety will be conducted on the safety population, which is defined as all randomized patients who receive at least one dose of study drug. The safety assessment will be based on the frequency of adverse events, physical exams, vital signs and safety laboratory tests.

[0626] Adverse events with new onset during the study between the initiation of study drug and 30 days after the last dose of study drug for each patient will be considered treatment-emergent (TEAEs). This will include any AE with onset prior to initiation of study drug and increased severity after the treatment initiation.

[0627] Treatment-emergent adverse events will be summarized by system organ class and preferred term, and by treatment. This will include overall incidence rates (regardless of severity and relationship to study drug), and incidence rates for moderate or severe adverse events. A summary of SAEs and adverse events leading to early discontinuation from the study will be presented through data listings.

[0628] Safety laboratory tests and vital signs will be summarized by post-treatment change from baseline for each of the parameters using descriptive statistics by treatment group. Those patients with significant laboratory abnormalities will be

identified in data listings. Additional safety parameters will be summarized in data listings.

[0629] Sample Size Determination

[0630] Sample size estimation is based on the assumption that the primary composite endpoint (time from randomization to the first occurrence of CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina requiring hospitalization) would be relatively reduced by 15%, from an event rate by 4 years of 23.6% in the placebo group to 20.5% in the AMR101 group. It is expected that a minimum of 1612 primary efficacy endpoint events will be required during the study. A total of approximately 6990 patients are needed to be able to detect this difference at 4.76% significance level (because of the interim analysis described in Section 12.2.4.6) and with 90% power, assuming an 18-month enrollment period and a median follow-up of 4 years. The current sample size calculation is based on an estimated placebo yearly event rate of 5.9% (23.6% over 4 years). To protect against the possibility that the actual placebo event rate is lower than estimated, an extra 1000 patients will be enrolled (approximately 7990 patients in total). By adding the extra 1000 patients, the event rate in the placebo group could be 5.2% per year (20.8% over 4 years) without having to modify the other sample size assumptions.

[0631] Since this is an events-driven trial, the 'sample size' is the number of events rather than the number of patients. The number of events that occur depends primarily on three factors: how many patients are enrolled, the combined group event rate, and how long the patients are followed. Because of the difficulty in predicting the combined event rate, the sponsor will monitor that event rate as the trial progresses. If the combined event rate is less than anticipated, either increasing the number of patients, extending the length of follow-up, or a balance of adjusting both factors may be necessary to achieve the sample size of 1612 events.

[0632] Before completing the enrollment phase of the trial, i.e. approximately 3- to 6-months prior to the projected enrollment of the 7990th patient, the actual event rate based on pooled, blinded accumulation of primary efficacy endpoint events will be calculated and plotted. If those analyses suggest the number of patients with at least 1

adjudicated, primary event (and appropriately accounting for patients with potential primary events for which the adjudication process is then incomplete) is consistent with projections, then the study could continue toward the protocol-specified target enrollment of 7990 patients. However, if the number of such events appears less than, and inconsistent with projections, the Sponsor will consider (under blinded conditions) re-calculating the number of patients needed to achieve the target number of events within the desired timeline or extend the follow-up period. If the projected increase in number of patients is ≤ 25% of the original 7990 target population, the Sponsor may, with documented approval of both the REDUCE-IT Steering Committee (SC) and the Data Monitoring Committee (DMC), extend enrollment to the revised target number without need for an additional protocol amendment. Under those conditions, all principal investigators, ethics committees, and regulatory authorities associated with the protocol will be promptly notified of the action. Should the projected increase in number of patients be more than 25% above the original 7990 target (i.e. more than 1998 additional patients) a formal protocol amendment will be initiated.

[0633] If the number of patients to be studied is increased, the enrollment phase will be extended to allow enrollment of the additional patients.

[0634] At completion of study enrollment, the actual number of patients randomized may vary from the target number (either original or revised) as a result of the inherent lag between the date the last patient started screening and the date the last patient was randomized.

MONITORING, DATA MANAGEMENT, AND RECORD KEEPING

[0635] Data Management

[0636] Data Handling

[0637] Data will be recorded at the site on CRFs. All entries on a CRF are ultimately the responsibility of the Investigator, who is expected to review each form for completeness and accuracy before signing. A CRF must be completed for each randomized patient. The CRFs and source documents must be made available to the Sponsor and/or its designee.

[0638] Record Keeping

[0639] The Investigator must maintain all documents and records, originals or certified copies of original records, relating to the conduct of this trial, and necessary for the evaluation and reconstruction of the clinical trial. This documentation includes, but is not limited to protocol, CRFs, AE reports, patient source data (including records of patients, patient visit logs, clinical observations and findings), correspondence with health authorities and IRB, consent forms, inventory of study product, Investigator's curriculum vitae, monitor visit logs, laboratory reference ranges and laboratory certification or quality control procedures, and laboratory director curriculum vitae.

[0640] The Investigator and affiliated institution should maintain the trial documents as required by the applicable regulations. The Investigator and affiliated institution should take measures to prevent accidental or premature destruction of documents. Clinical trial documents must be kept in the clinical site's archives indefinitely, unless written authorization is obtained from the Sponsor.

DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

[0641] The investigator and research institution agree that the Sponsor, their representatives and designees, the IRB or IEC, and representatives from worldwide regulatory agencies will have the right, both during and after the clinical trial, to review and inspect pertinent medical records related to the clinical trial.

QUALITY CONTROL AND QUALITY ASSURANCE

[0642] The Sponsor and/or its designee(s) will perform quality control and quality assurance checks of all clinical trials that it sponsors. Before the enrollment of any patient in this study, the Sponsor or its designee will review with the investigator and site personnel the following documents: protocol, Investigator's Brochure, CRFs and procedures for their completion, the informed consent process, and the procedure for reporting SAEs. Site visits will be performed by the Sponsor and/or its designees. During these visits, information recorded on the CRFs will be verified against source documents and requests for clarification or correction may be made. After the CRF data is entered by the site, the Sponsor or designee will review for safety information,

completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical trial. If necessary, requests for clarification or correction will be sent to investigators.

[0643] By signing the protocol, the Sponsor agrees directly or through its designee(s) to be responsible for implementing and maintaining quality control and quality assurance systems with written standard operating procedures to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice (GCP), International Conference on Harmonization (ICH) and other applicable regulations.

COMPLETION OF STUDY

[0644] The end of the study will be at the time of the last patient-last visit of the follow-up period of the study. The IRB and IEC will be notified about the end of the study according to country-specific regulatory requirements.

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

1. Includes procedures and (fasting) blood samples (for example, hs-CRP, calculated creatinine clearance) as needed to determine the CV risk category (see inclusion criteria).
2. Screening visit to re-evaluate inclusion/exclusion criteria for patients who are not eligible for participation based on data from Visit 1.
3. Inclusion/exclusion criteria will be re-evaluated for selected study procedures that are performed on Visit 1.1 because patients failed to meet them at Visit 1.

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

What is claimed is:

1. A method of reducing a risk of a cardiovascular event in a subject on statin therapy, the method comprising:

(a) identifying a subject on statin therapy and having a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, optionally 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.

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

3. The method of claim 1 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 of claim 1, wherein the established cardiovascular disease is determined by the presence of any one of: documented coronary artery disease, documented cerebrovascular disease, documented carotid disease, documented peripheral arterial disease, or combinations thereof.

5. The method of claim 1 further comprising a step of measuring the subject's baseline lipid profile prior to administering the pharmaceutical composition to the subject.

6. The method of claim 1 wherein 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.

7. The method of claim 1 wherein the statin therapy comprises administering to the subject a statin and optionally ezetimibe.

8. The method of claim 1 wherein the subject: (a) has not been administered 200 mg or more per day of niacin and/or fibrates for at least 28 days before step (a); (b) has not been administered omega-3 fatty acid prescription for a period of time beginning 28 days prior to step (a); (c) has not ingested dietary supplements comprising omega-3 fatty acids for a period of time beginning 28 days prior to step (a).

9. The method of any of claim 8, wherein the period of time ends no earlier than about 6 months after a first administration of the pharmaceutical composition in step (b).

10. The method of claim 8, wherein the period of time ends about 6 months, about 1 year, about 2 years, about 3 years, about 4 years, about 5 years, or more than about 5 years after the first administration of the pharmaceutical composition in step (b).

11. The method of claim 1 wherein the cardiovascular event is one or more of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina.

12. The method of claim 1 wherein the cardiovascular event is one or more of: cardiac arrhythmia; cardiac arrest; peripheral cardiovascular disease requiring intervention, angioplasty, bypass surgery or aneurysm repair; and death.

13. The method of claim 1 wherein the cardiovascular event is onset of new congestive heart failure.

14. The method of claim 1 wherein 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, or about 5 years in step (b).

15. The method of claim 14 wherein, after administering the pharmaceutical composition in step (b), the subject exhibits one or more of (a) reduced triglyceride levels compared to baseline; (b) reduced Apo B levels compared to baseline; (c) increased HDL-C levels compared to baseline; (d) no increase in LDL-C levels compared to baseline; (e) a reduction in LDL-C levels compared to baseline; (f) a reduction in non-HDL-C levels compared to baseline; (g) a

reduction in VLDL levels compared to baseline; (h) a reduction in total cholesterol levels compared to baseline; (i) a reduction in high sensitivity C-reactive protein (hs-CRP) levels compared to baseline; and/or (j) a reduction in high sensitivity troponin (hsTnT) levels compared to baseline.

16. The method of claim 14, wherein the subject exhibits one or more of: (a) a reduction in triglyceride level 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; (b) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in non-HDL-C levels or 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; (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%, or at least about 50% as compared to baseline; and/or (d) a less than 30% increase, less than 20% increase, less than 10% increase, less than 5% increase or no increase in LDL-C levels or 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.

17. The method of claim 1 further comprising assigning 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.

18. The method of claim 17, wherein a first time interval beginning at an initial administration of the pharmaceutical composition to the subject in step (b) to a first cardiovascular event of the subject is greater than or substantially greater than a first control time interval beginning at initial administration of a placebo to the control subjects to a first cardiovascular event in the control subjects.

19. The method of claim 18, wherein 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.

20. The method of claim 18 or 19, wherein 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.

21. The method of claim 18, wherein 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.

22. The method of claim 18, wherein 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.

23. The method of claim 18, wherein 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.

24. The method of claim 18, wherein 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.

25. The method of claim 18, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is any of: death (from any cause).

26. The method of claim 18, wherein 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.

27. The method of claim 26, wherein nonfatal myocardial infarction includes silent myocardial infarction.

28. The method of claim 18, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is coronary revascularization.

29. The method of claim 18, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is hospitalization for unstable angina.

30. The method of claim 29, wherein the unstable angina is caused by myocardial ischemia.

31. The method of claim 18, wherein 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.

32. The method of claim 1 or claim 18, wherein a second time interval beginning at an initial administration of the pharmaceutical composition to the subject in step (b) to a second cardiovascular event of the subject is greater than or substantially greater than a second control time interval beginning at initial administration of a placebo to the control subjects to a second cardiovascular event in the control subjects.

33. The method of claim 32, wherein 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.

34. The method of claim 18, wherein the subject has diabetes mellitus and the control subjects each have diabetes mellitus.

35. The method of claim 18, wherein the subject has metabolic syndrome and the control subjects each have metabolic syndrome.

36. The method of claim 18, wherein 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.

37. The method of claim 18, wherein 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.

38. The method of claim 18, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is an onset of diabetes.

39. The method of claim 18, wherein, after an initial administration of the pharmaceutical composition in step (b), 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.

40. The method of claim 18, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is cardiac arrhythmia requiring hospitalization.

41. The method of claim 18, wherein the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is cardiac arrest.

42. The method of claim 14, wherein a first weight of the subject determined after step (b) is less than a baseline weight of the subject determined before step (b).

43. The method of claim 14, wherein a first waist circumference of the subject determined after step (b) is less than a baseline waist circumference of the subject determined before step (b).

44. The method of any one of claims 18 to 38 or 40 to 43, wherein 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.

45. The method of claim 32 or claim 33, wherein 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.

46. The method of claim 17, wherein a plurality of subjects experience a first major cardiovascular event after an initial administration of the pharmaceutical composition in step (b) at a first incidence rate, and wherein the control subjects experience a first major cardiovascular event after an initial administration of a placebo at a second incidence rate,

wherein the first incidence rate is less than the second incidence rate.

47. The method of claim 46, wherein the first major cardiovascular event is any one of: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina.

48. The method of claim 47, wherein the unstable angina is determined to be caused by myocardial ischemia.

49. The method of claim 46, wherein 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.