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(54) **Title:** METHODS OF REDUCING THE RISK OF CARDIOVASCULAR EVENTS IN A SUBJECT WITH ATRIAL FIBRILLATION AND/OR ATRIAL FLUTTER

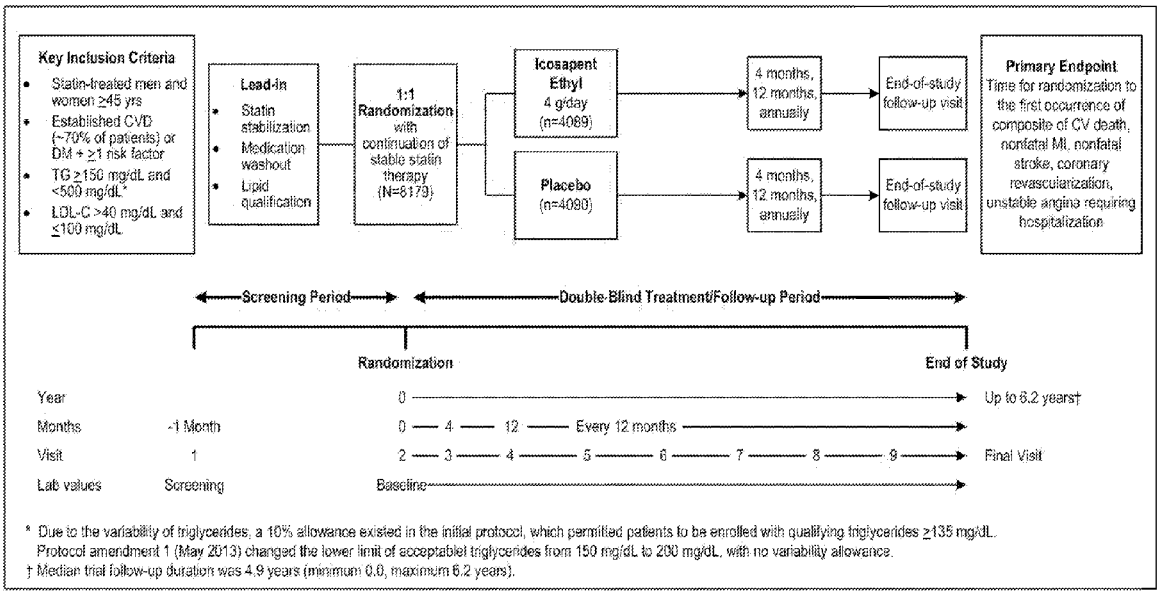


FIG. 1

(57) **Abstract:** In various embodiments, the present disclosure provides methods reducing the risk of cardiovascular events in a subject on statin therapy and having atrial fibrillation and/or flutter by administering to the subject a pharmaceutical composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester or a derivative thereof.

[Continued on next page]

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METHODS OF REDUCING THE RISK OF CARDIOVASCULAR EVENTS IN A SUBJECT WITH ATRIAL FIBRILLATION AND/OR ATRIAL FLUTTER

PRIORITY CLAIM

[0001] This application claims priority to U.S. Provisional Application No. 62/934,121 filed on November 12, 2019, U.S. Provisional Application No. 62/934,637 filed November 13, 2019, U.S. Provisional Application No. 62/934,952 filed November 13, 2019, U.S. Provisional Application No. 62/934,879 filed November 13, 2019, U.S. Provisional Application 62/976,683 filed February 14, 2020, U.S. Provisional Application No. 62/948,058 filed December 13, 2019, the entire contents of which are incorporated herein by reference and relied upon.

BACKGROUND

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

[0003] 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 disclosure provides methods of treating and preventing cardiovascular diseases and disorders.

[0005] In various embodiments, the present disclosure provides methods of treating and preventing cardiovascular diseases and disorders.

[0006] In one aspect, the present disclosure provides methods for treating a patient comprising: determining or having determined whether the patient has a triglyceride level of at least 150 mg/dl and a history of atrial fibrillation and/or atrial flutter by: obtaining or having obtained information which indicates that the patient has the triglyceride level of at least 150 mg/dl and has previously had symptoms of atrial fibrillation and/or atrial flutter and/or was previously diagnosed with atrial fibrillation and/or atrial flutter; and/or monitoring or having monitored the subject for the triglyceride level of at least 150 mg/dl and for symptoms of atrial fibrillation and/or atrial flutter; and (a) if the patient has previously had symptoms of atrial fibrillation and/or atrial flutter, was previously diagnosed with atrial fibrillation and/or atrial flutter, and/or had symptoms of atrial fibrillation and/or atrial flutter when monitored, then (i) determining whether a risk that the patient will experience symptoms of atrial fibrillation and/or atrial flutter if the patient were administered about 4 g of eicosapentaenoic acid (EPA) per day is greater than reducing a risk of one or more cardiovascular events in the patient; or (ii) determining whether reducing a risk of one or more cardiovascular events if the patient were administered about 4 g of EPA per day is greater than a risk that the patient will experience symptoms of atrial fibrillation and/or atrial flutter; and (b) if the risk is greater that the patient in (i) will experience symptoms of atrial fibrillation and/or atrial flutter, administering an atrial fibrillation flutter and/or atrial flutter therapeutic agent to the patient instead of about 4 g of EPA per day; and (c) if the risk is greater that the patient in (ii) will have a reduced risk of one or more cardiovascular events, administering about 4 g of EPA per day to the patient.

[0007] In some embodiments, the subject in (c) is likely to experience both (1) increased frequency of atrial fibrillation and/or atrial flutter symptoms, and (2) decreased frequency of cardiovascular events if administered about 4 g of EPA per day. In some embodiments, the subject is being treated with a statin and regardless if the subject is in (a) or (b), continuing to treat the subject with the statin.

[0008] In another aspect, the present disclosure provides methods for treating a subject comprising: determining or having determined whether the subject has a triglyceride level of at least 150 mg/dl and a history of atrial fibrillation and/or atrial flutter by: (i) obtaining or having obtained information which indicates that the subject has the triglyceride level of at least 150 mg/dl and has previously had symptoms of atrial fibrillation and/or atrial flutter and/or was previously diagnosed with atrial fibrillation and/or

atrial flutter; and/or (ii) monitoring or having monitored the subject for the triglyceride level of at least 150 mg/dl and symptoms of atrial fibrillation and/or atrial flutter; and (a) if the subject has previously had symptoms of atrial fibrillation and/or atrial flutter, was previously diagnosed with atrial fibrillation and/or atrial flutter, and/or symptoms of atrial fibrillation and/or atrial flutter were determined during the monitoring, then administering atrial fibrillation and/or atrial flutter therapeutic agent to the subject, and (b) if the subject has not previously had symptoms of atrial fibrillation and/or atrial flutter, was not previously diagnosed with atrial fibrillation and/or atrial flutter, and/or symptoms of atrial fibrillation and/or atrial flutter were not determined during the monitoring, then administering about 4 g of eicosapentaenoic acid (EPA) per day to the subject to reduce a risk for a cardiovascular event, wherein a risk of atrial fibrillation and/or atrial flutter for the subject in (a) is lower following administration of an atrial fibrillation flutter and/or atrial flutter therapeutic agent than it would be if the subject in (a) were administered about 4 g of EPA per day.

[0009] In some embodiments, the subject in (a) is likely to experience both (1) increased frequency of atrial fibrillation and/or atrial flutter symptoms, and (2) decreased frequency of cardiovascular events if administered about 4 g of EPA per day. In some embodiments, the subject is being treated with a statin and regardless if the subject is in (a) or (b), continuing to treat the subject with the statin.

[0010] In another aspect, the present disclosure provides methods of treatment comprising: identifying a subject whose measured triglyceride level is above 150 mg/dl and who has previously experienced symptoms of atrial fibrillation or atrial flutter; determining that individuals who have triglyceride levels above 150 mg/dl and who have previously experienced atrial fibrillation or atrial flutter episodes are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) decreased frequency of cardiovascular events other than atrial fibrillation or atrial flutter; and selecting a treatment according to either (a) or (b): (a) determining that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so treating the subject with 4 g EPA per day; or (b) determining that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is not worth a risk of

increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead treating the subject with a statin.

[0011] In some aspects, the present disclosure provides methods of treatment comprising: identifying a subject whose measured triglyceride level is above 150 mg/dl, who is being treated with a statin, and who has previously experienced symptoms of atrial fibrillation or atrial flutter; determining that individuals who have triglyceride levels above 150 mg/dl, who are being treated with a statin, and who have previously experienced atrial fibrillation or atrial flutter episodes are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) decreased frequency of cardiovascular events other than atrial fibrillation or atrial flutter; and selecting a treatment according to either (a) or (b): (a) determining that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so treating the subject with 4 g EPA per day and a statin; or (b) determining that decreasing a subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead continuing to treat the subject with a statin.

[0012] In yet another aspect, the present disclosure provides methods of treatment comprising: identifying a subject whose measured triglyceride level is above 150 mg/dl who is being treated with a statin, and who has a previous history of atrial fibrillation or atrial flutter; determining that individuals who have triglyceride levels above 150 mg/dl, who are being treated with a statin, and who have a previous history of atrial fibrillation or atrial flutter are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) cardiovascular benefits expected to result from the EPA treatment; and selecting a treatment according to either (a) or (b) below: (a) determining that the expected cardiovascular benefits are worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so treating the subject with 4 g EPA per day; or (b) determining that the expected cardiovascular benefits are not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead treating the subject with a statin.

[0013] In another aspect, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject having triglyceride levels of at least about 150 mg/dl, the method comprising administering to the subject at least about 4 g of eicosapentaenoic acid (EPA) per day for a period of time effective to reduce the cardiovascular event, wherein the subject develops atrial fibrillation and/or atrial flutter during the period of time effective to reduce the risk of the cardiovascular event.

[0014] In some aspects, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject having triglyceride levels of at least about 150 mg/dl and less than 65 years of age, the method comprising administering to the subject at least about 4 g of eicosapentaenoic acid (EPA) per day for a period of time effective to reduce the cardiovascular event, wherein the subject does not exhibit an increase in symptoms atrial fibrillation and/or atrial flutter.

[0015] In some embodiments, the atrial fibrillation flutter and/or atrial flutter therapeutic agent is one or more of warfarin, beta blocker, calcium channel blocker. In some embodiments, the warfarin is administered at a dose of about 25 mg per day.

[0016] In some embodiments, reducing the risk for the cardiovascular event for the subject further comprises determining that one or more cardiovascular benefits are expected to occur. In some embodiments, the cardiovascular event does not include atrial fibrillation and/or atrial flutter.

[0017] In some embodiments, the subject did does have a history of atrial fibrillation and/or flutter prior to administration of the 4 g of EPA. In some embodiments, the subject has established cardiovascular disease. In some embodiments, 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. In some embodiments, the subject does not have an established cardiovascular disease but at least two risk factors for cardiovascular disease.

[0018] In some embodiments, the EPA is administered to the subject in 1 to 4 dosage units per day. In some embodiments, the subject is administered the EPA for at least about 4 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, or at least about 5 years.

[0019] 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.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] Figure 1 is a schematic of the study design according to an embodiment of the present disclosure.

[0021] Figure 2 is a schematic showing disposition of patients according to an embodiment of the present disclosure.

[0022] Figures 3A and 3B are representative Kaplan-Meier event curves for the cumulative incidence of the primary composite endpoints. Figures 3A and 3B indicate a 25% relative risk reduction for the primary composite endpoint over the course of 5 years.

[0023] Figure 4 is a representative forest plot of individual components of primary endpoints analyzed as time to first event of each individual endpoint and indicates that each component, individually, was reduced.

[0024] Figures 5A and 5B are representative Kaplan-Meier event curves for the cumulative incidence of the key secondary composite endpoints. Figures 5A and 5B indicate that there was a 26% RRR for the key secondary composite endpoint over the course of 5 years.

[0025] Figure 6 is a representative forest plot analyses of individual components of the primary and key secondary endpoints for the ITT population.

[0026] Figures 7 and 8 are representative forest plots of primary efficacy outcomes in select prespecified subgroups. Figures 6 and 7 indicate that a subject's baseline triglyceride levels (e.g., ≥150 vs. <150 mg/dL or ≥200 or <200 mg/dL) did not influence the primary endpoint outcomes.

[0027] Figure 9 and 10 are representative forest plots of secondary efficacy outcomes in select prespecified subgroups. Figures 9 and 10 indicate that a subject's baseline triglyceride levels (e.g., ≥150 vs. <150 mg/dL or ≥200 or <200 mg/dL) did not influence the key secondary endpoint outcomes.

[0028] Figures 11A and 11B are representative Kaplan-Meier curves of primary and key secondary endpoints by achieved triglyceride level at 1 year. Figures 11A and 11B

indicate that patient's triglyceride levels had no influence on the efficacy of icosapent ethyl as compared with placebo with respect to the primary or key secondary efficacy endpoint outcomes.

[0029] Figure 12 is a representative forest plot of prespecified hierarchical testing of endpoints and indicates that all individual and composite ischemic endpoints were significantly reduced by icosapent ethyl (AMR101).

[0030] Figure 13 is a representative plot of median triglycerides over time for the ITT population.

[0031] Figure14 is a representative plot of median LDL-C (Hopkins Approximation) over time for the ITT population.

[0032] Figure 15 is a representative Kaplan-Meier curve of time to early termination from study from date of randomization for the ITT population.

[0033] Figure 16 is a schematic of the study design according to an embodiment of the present disclosure.

[0034] Figure 17 is a representative bar graph depicting the distribution of first, second, and recurrent ischemic events in patients. Figure 13 indicates that the first, second, and recurrent ischemic events were reduced in patients randomized to icosapent ethyl (IPE) compared to placebo.

[0035] Figure 18 is a representative overall cumulative event Kaplan-Meier event curve for the primary endpoint indicating that overall cumulative primary endpoints were reduced in patients randomized to icosapent ethyl.

[0036] Figure 19 is a representative cumulative event Kaplan-Meier event curve for the primary endpoint for patients in the secondary prevention cohort, which, similar to Figure 18, indicates that cumulative primary endpoints were also reduced in patients in the secondary prevention cohort randomized to icosapent ethyl.

[0037] Figure 20 is a representative cumulative event Kaplan-Meier event curve for the primary endpoint for patients in the primary prevention cohort, which, similar to Figures 18 and 19, indicates that cumulative primary endpoints were also reduced in patients in the primary prevention cohort randomized to icosapent ethyl.

[0038] Figure 21 is a representative forest plot of the total event for each occurrence of the primary endpoint. Figure 21 indicates that the times to first, second, third, or fourth occurrences of the primary composite endpoint were consistently reduced in the icosapent ethyl group as compared to placebo.

[0039] Figure 22 includes representative pie charts for the proportion of first and subsequent primary endpoint events, overall and by component.

[0040] Figure 23 is a representative graph depicting the risk difference in 100 patients treated for five years with icosapent ethyl versus placebo of the composite primary endpoint.

[0041] Figure 24 is a representative forest plot of the total event for each occurrence of the primary and key secondary efficacy endpoints. Figure 24 indicates that the total events for each component of the primary endpoint events were significantly reduced.

[0042] Figure 25 is a representative overall cumulative event Kaplan-Meier curve for the key secondary endpoint indicating that overall cumulative key secondary endpoints were reduced in patients randomized to icosapent ethyl.

[0043] Figure 26 is a representative cumulative event Kaplan-Meier curve for the key secondary endpoint for patients in the secondary prevention cohort, which similar to Figure 25 indicates that cumulative key secondary endpoints were also reduced in patients in the secondary prevention cohort randomized to icosapent ethyl.

[0044] Figure 27 is representative cumulative event Kaplan-Meier curve for the key secondary endpoint for patients in the primary prevention cohort, which, similar to Figures 25 and 26, indicates that cumulative primary endpoints were also reduced in patients in the primary prevention cohort randomized to icosapent ethyl.

[0045] Figure 28 is a representative overall cumulative Kaplan-Meier event curve as a function of years since randomization for the primary endpoint indicating that overall cumulative primary endpoints were reduced in patients randomized to icosapent ethyl.

[0046] Figure 29 is a representative overall cumulative event Kaplan-Meier curve as a function of years since randomization for the key secondary endpoint indicating that overall cumulative key secondary endpoints were reduced in patients randomized to icosapent ethyl.

[0047] Figure 30 is a representative Kaplan-Meier curve for recurrent events as a function of years since randomization of the primary endpoint for patients in the secondary prevention cohort indicating that cumulative primary endpoints were reduced in patients in the secondary prevention cohort randomized to icosapent ethyl.

[0048] Figure 31 is a representative Kaplan-Meier curve as a function of years since randomization for recurrent events of the key secondary endpoint for patients in the secondary prevention cohort indicating that cumulative key secondary endpoints were also reduced in patients in the secondary prevention cohort randomized to icosapent ethyl.

[0049] Figure 32 is a representative Kaplan-Meier curve as a function of years since randomization for recurrent events of the primary endpoint for patients in the primary prevention cohort indicating that cumulative primary endpoints were also reduced in patients in the primary prevention cohort randomized to icosapent ethyl.

[0050] Figure 33 is a representative Kaplan-Meier curve as a function of years since randomization for recurrent events of the key secondary endpoint for patients in the primary prevention cohort indicating that cumulative key secondary endpoints were reduced in patients in the primary prevention cohort randomized to icosapent ethyl.

[0051] Figure 34 are representative plots of the total events by number of events per patient for the primary composite endpoints and for each individual component for patients randomized to icosapent ethyl and placebo.

[0052] Figures 35A and 36B are representative flow charts of the total primary and secondary composite endpoint events for patients randomized to AMR101 and placebo, respectively.

[0053] Figure 36 includes representative pie charts for a proportion of first and subsequent primary endpoint events, overall and by component.

[0054] Figure 37A is a representative bar graphs depicting a distribution of total (i.e., first and subsequent) primary composite endpoint events in patients. Figure 37A indicates that there was a 30% relative risk reduction in total events for the primary composition endpoint in patients randomized to icosapent ethyl.

[0055] Figure 37B is a representative plot showing a Distribution of First and Subsequent Primary Composite Endpoint Events in the Full Dataset for Patients Randomized 1:1 to AMR101 Versus Placebo for the ITT Population.

[0056] Figures 38A and 38B are representative Kaplan-Meier curves over time for total (i.e., first and subsequent) and time to first primary composite events and secondary composite endpoint events, respectively. Figures 38A and 38B indicate that both primary and key secondary endpoints were significantly reduced in patients randomized to icosapent ethyl compare to placebo.

[0057] Figure 39 is a representative forest plot of total primary and key secondary composite endpoint events and indicates that times to first, second, and third occurrence of the primary and secondary endpoints were significantly reduced in patients randomized to icosapent ethyl compared placebo.

[0058] Figure 40 is a representative forest plot of total primary and key secondary composite endpoints and each individual component or endpoint for patients randomized to icosapent ethyl and placebo indicating that not only was there a significant reduction in the composite of the primary and key secondary endpoints, but also, each individual component was also significantly reduced.

[0059] Figure 41A and 41B are representative forest plots of total primary and secondary composite endpoints in selected subgroups by the negative binomial model, respectively, for patients randomized to icosapent ethyl and placebo.

[0060] Figure 42 is a representative graph depicting the risk difference in patients treated for five years with icosapent ethyl versus placebo for total components of the composite primary endpoint and indicates that approximately 159 total primary endpoint events could be prevented within that time frame to include 12 cardiovascular deaths, 42 myocardial infarctions, 14 strokes, 76 coronary revascularizations, and 16 episodes of hospitalization for unstable angina.

[0061] Figures 43 and 44 show the forest plot for total primary and key secondary composite endpoint events and first second, and third occurrences for the reduced dataset with unadjusted and adjusted values, respectively.

[0062] Figures 45 and 46 show the forest plots for the total primary composite endpoint events and total key secondary composite endpoint events and first, second, and third occurrences for the reduced data with unadjusted values, respectively.

[0063] Figures 47 and 48 show the total primary composite endpoint events and key secondary composite endpoint events and first, second, and third occurrences for the reduced data set with adjusted values, respectively.

[0064] Figures 49 and 50 show the total primary and key secondary composite endpoint events and first, second, and third occurrences for the full data set for the unadjusted and adjusted values, respectively.

[0065] Figure 51 is a representative bar graph showing risk differences for 1000 patients treated for 5 years with AMR101 versus placebo for the total components of the composite primary endpoint for the ITT Population.

[0066] Figure 52 is a representative forest plot depicting the reduction of total primary composite endpoint events in subjects as a function of triglyceride level. Figure 52 indicates that total primary composite endpoints were reduced in all patients across the entire triglyceride range and within each of the defined triglyceride tertiles.

[0067] Figure 53 is a representative forest plot depicting time to first event of primary composite endpoint events in subjects as a function of triglyceride level. Figure 53 demonstrates that the time to first event of the primary composite endpoint was reduced across the entire triglyceride range.

[0068] Figure 54 is a representative forest plot showing the effects of icosapent ethyl on the primary composite endpoint by LDL-C percent change from baseline at 1-year quartiles for the ITT population.

[0069] Figure 55 is a representative bar graph for a placebo-corrected reduction in blood pressure in patients administered icosapent ethyl 4 g per day.

[0070] Figure 56 is a representative bar graph for the study drug adherence overtime for each of the first, second, third, and fourth events.

[0071] Figures 57A and 57B are representative Kaplan-Meier curves of time to the primary endpoint and key secondary endpoint from date of randomization for AMR101 vs. placebo by an LDL-C increase or no change/a decreased at 1 year in the placebo group for the ITT population, respectively.

[0072] Figures 58A and 58B are representative Kaplan-Meier curves of time to the primary endpoint and key secondary endpoint from date of randomization for AMR101 vs. placebo by an hsCRP increase or no change/a decreased at 2 years in the placebo group for the ITT population, respectively.

[0073] Figure 59 is a representative forest plot analyses of the primary endpoint by subgroups (geographic region, cardiovascular risk category, baseline ezetimibe use, sex, and age group) for the ITT population.

[0074] Figure 60 is a representative forest plot analyses of the primary endpoint by subgroups (white vs. non-white, baseline diabetes, baseline statin intensity, TG ≥ 200 vs. < 200 mg/dL, TG ≥ 150 vs. < 150 mg/dL, and TG ≥ 200 and HDL-C ≤ 35 mg/dL) for the ITT population.

[0075] Figure 61 is a representative forest plot analyses of the primary endpoint by subgroups (US vs. non-US, hsCRP ≤ 2 vs. > 2 mg/L, hsCRP ≤ 3 vs. > 3 mg/L, baseline eGFR, LDL-C (derived) by tertiles, and HDL-C by tertiles) for the ITT population.

[0076] Figure 62 is a representative forest plot analyses for the primary endpoint by subgroups (Apo B by tertiles, Non-HDL-C b y tertiles, and TG by tertiles) for the ITT population.

[0077] Figure 63 is a representative forest plot of analyses of the key secondary endpoint by subgroups (geographic region, cardiovascular risk category, baseline ezetimibe use, sex, and age group) for the ITT Population)

[0078] Figure 64 is a representative forest plot analyses of the key secondary endpoint by subgroups (white vs. non-white, baseline diabetes, baseline statin intensity, TG ≥ 200 vs. < 200 mg/dL, TG ≥ 150 vs. < 150 mg/dL, and TG ≥ 200 and HDL-C ≤ 35 mg/dL) for the ITT population.

[0079] Figure 65 is a representative forest plot analyses of the key secondary endpoint by subgroups (US vs. non-US, hsCRP ≤ 2 vs. > 2 mg/L, hsCRP ≤ 3 vs. > 3 mg/L, baseline eGFR, LDL-C (derived) by tertiles, and HDL-C by tertiles) for the ITT population.

[0080] Figure 66 is a representative forest plot analyses for the key secondary endpoint by subgroups (Apo B by tertiles, Non-HDL-C b y tertiles, and TG by tertiles) for the ITT population.

[0081] Figure 67 is a representative forest plot showing the pre-specified hierarchical endpoint testing, emphasizing the relative risk reductions (RRR) for each of the endpoints.

[0082] Figure 68 is a representative forest plot showing patients from both the icosapent ethyl and placebo group who required hospitalization ≥ 24 hours from atrial fibrillation and/or flutter at baseline for the ITT population.

[0083] Figure 69A are representative plots showing the atrial fibrillation and/or flutter and bleeding overlap between the placebo and the icosapent ethyl groups as well as the risk difference between the two groups for the ITT population.

[0084] Figure 69B are representative plots showing the atrial fibrillation and/or flutter and bleeding overlap between the placebo and the icosapent ethyl groups for the secondary prevention cohort.

[0085] Figure 69C are representative plots showing the atrial fibrillation and/or flutter and bleeding overlap between the placebo and icosapent ethyl groups for the high-risk primary prevention cohort.

[0086] Figures 70A and 70B are representative Kaplan-Meier curves depicting the time to endpoint of atrial fibrillation and/or flutter requiring hospitalization of greater than 24 hours by treatment group for the ITT population.

[0087] Figure 71 is a representative forest plot summarizing the endpoints by history of atrial fibrillation and/or flutter for the ITT population.

[0088] Figure 72 is a representative forest plot showing endpoints by on-study atrial fibrillation and/or flutter for the ITT population.

[0089] Figure 73 is a representative forest plot summarizing the endpoints based on patients having a history of atrial fibrillation and/or flutter from the ITT population.

[0090] Figure 74 is a representative forest plot showing positively adjudicated atrial fibrillation or flutter by baseline history of atrial fibrillation and/or flutter for the high-risk primary prevention cohort.

[0091] Figure 75 is a representative forest plot showing positively adjudicated atrial fibrillation or flutter by baseline history of atrial fibrillation or flutter for the secondary prevention cohort.

[0092] Figure 76 is a forest plot showing atrial fibrillation an/d or flutter requiring hospitalization of greater than 24 hours by baseline for the ITT population.

[0093] Figure 77 is a representative bar graph showing the benefit and risk considerations for patients less than 65 years old and shows a decrease risk for onset of atrial fibrillation in the patient population.

[0094] Figure 78 is a representative bar graph showing the benefit and risk considerations for patients 65 years or older and shows an increase risk for onset of atrial fibrillation in the patient population.

[0095] Figure 79 is a representative plot showing the change in median hemoglobin levels over time for the safety population.

[0096] Figure 80 is a representative plot showing the change in median platelet count over time for the safety population.

[0097] Figure 81 is a representative plot showing the change the median alanine aminotransferase (ALT) over time for the safety population.

[0098] Figure 82 is a representative plot showing the change in the median aspartate aminotransferase (AST) over time for the safety population.

[0099] Figure 83 are representative plots showing the distribution of peak values of ALT or AST vs. peak values of total bilirubin for the evaluation of drug-induced serious hepatoxicity for the ITT population.

DETAILED DESCRIPTION

[0100] While the present disclosure is capable of being embodied in various forms, the description below of several embodiments is made with the understanding that the present disclosure is to be considered as an exemplification of the invention and is not intended to limit the invention to the specific embodiments illustrated. Headings are provided for convenience only and are not to be construed to limit the invention in any manner. Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

[0101] 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." It is to be understood, although not always explicitly stated, that all numerical designations are preceded by the term “about.” It is to be understood that such range format is used for convenience and brevity and should be understood flexibly to include numerical values explicitly specified as limits of a range, but also to include all individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range is explicitly specified. For example, a ratio in the range of about 1 to about 200 should be understood to include the explicitly recited limits of about 1 and about 200, but also to include individual ratios such as about 2, about 3, and about 4, and sub-ranges such as about 10 to about 50, about 20 to about 100, and so forth. It also is to be understood, although not always explicitly stated, that the reagents described herein are merely exemplary and that equivalents of such are known in the art.

[0102] The term “about,” as used herein when referring to a measurable value such as an amount or concentration and the like, is meant to encompass variations of 20%, 10%, 5%, 1%, 0.5%, or even 0.1% of the specified amount.

[0103] The term “derivative,” as used herein when referring to a fatty acid, is meant to encompass any modified form of the fatty acid that was derived for example, by a chemical reaction from the fatty acid in free acid form (i.e., terminal carboxylic acid functional group). Non-limiting examples of fatty acid derivatives as used herein include alkyl esters such as methyl esters, propyl esters, butyl esters, or ethyl esters, a salt of the fatty acid such as a lithium, sodium, or potassium salt, or glyceride form of the fatty acid such as a mono-, di-, or triglyceride fatty acid.

[0104] In one embodiment, where a derivative of EPA is administered instead of EPA, the amount of EPA derivative administered to the subject per day is an amount sufficient to substantially match the pharmacokinetic profile of EPA produced by administration of 4 g of E-EPA per day to a human subject with respect to maximum serum EPA concentration (C_{max}) and area under the curve (AUC), herein referred to as a “dose-equivalent amount of a derivative of EPA”. With respect to a dose of 3.7 g per day of EPA, a dose-equivalent amount of E-EPA is about 4 g of E-EPA per day.

[0105] In one embodiment, the free fatty acid of eicosapentaenoic acid is administered to the subject and the amount administered is the gram weight sufficient to substantially match the pharmacokinetic profile produced by administration of 4 g of E-EPA per day to a human subject. In another embodiment, a derivative of

eicosapentaenoic acid is administered to the subject and the amount administered is the gram weight sufficient to substantially match the pharmacokinetic profile produced by administration of 4 g of E-EPA per day to a human subject. With respect to a dose of 3.7 g per day of eicosapentaenoic acid, a dose-equivalent amount of E-EPA is about 4 g of E-EPA per day.

[0106] The phrase "control subject," as used herein refers to any subject used as a basis for comparison to the test subject. A control subject includes, but is not limited to, any subject who has not been administered the composition, administered a composition other than the test composition (e.g., Lovaza® comprised of 365 mg of E-EPA and 375 mg of E-DHA), or administered a placebo.

[0107] The phrase "cardiovascular risk category 1," as used herein refers to subjects categorized as having an established cardiovascular disease. Patients from cardiovascular risk category 1 were stratified to the secondary prevention cohort. The designations for patients defined by cardiovascular risk category 1 are collectively referred to as: secondary prevention stratum, secondary prevention cohort, and the primary risk category.

[0108] The phrase "cardiovascular risk category 2," as used herein refers to a subject categorized as having diabetes (which itself is a risk factor for cardiovascular disease) and at least one additional risk factor for cardiovascular disease but who does not have an established cardiovascular disease. Patients from cardiovascular risk category 2 were stratified to the primary prevention cohort. The designations for patients defined by cardiovascular risk category 1 are collectively referred to as: primary prevention stratum, primary prevention cohort, and secondary risk category.

[0109] Also, the disclosure of ranges is intended as a continuous range including every value between the minimum and maximum values recited as well as any ranges that can be formed by such values. Also disclosed herein are any and all ratios (and ranges of any such ratios) that can be formed by dividing a disclosed numeric value into any other disclosed numeric value. Accordingly, the skilled person will appreciate that many such ratios, ranges, and ranges of ratios can be unambiguously derived from the numerical values presented herein and in all instances such ratios, ranges, and ranges of ratios represent various embodiments of the present disclosure.

[0110] The phrase "statistical significance," as used herein refers to a result from data generated by testing or experimentation is not likely to occur randomly or by chance, but is instead likely to be attributable to a specific cause. Statistical significance is evaluated from a calculated probability (p-value), where the p-value is a function of the means and standard deviations of the data samples and indicates the probability under which a statistical result occurred by chance or by sampling error. A result is considered statistically significant if the p-value is 0.05 or less, corresponding to a confidence level of 95%.

[0111] Comprising" or "comprises" is intended to mean that the compositions and methods include the recited elements, but not excluding others. "Consisting essentially of" when used to define compositions and methods, shall mean excluding other elements of any essential significance to the combination for the stated purpose. Thus, a composition consisting essentially of the elements as defined herein would not exclude other materials or steps that do not materially affect the basic and novel characteristic(s) of the claimed invention. "Consisting of" shall mean excluding more than trace elements of other ingredients and substantial method steps. Embodiments defined by each of these transition terms are within the scope of this invention.

[0112] List of abbreviations: ANOVA, analysis of variance; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; RRR, relative risk reduction; HR, hazard ratio; CV, cardiovascular; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; HIV/AIDS, human immunodeficiency virus/acquired immune deficiency syndrome; ICD-9, International Classification of Diseases, Ninth Revision; TG, triglyceride; TC, total cholesterol; VLDL-C very low dense lipoprotein cholesterol, apo B, apolipoprotein B; hsCRP, high sensitivity-C reactive protein; hsTnT, high-sensitivity troponin; RLP-C, remnant like particle cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; non-HDL-C, non-high density lipoprotein cholesterol; PAD, peripheral artery disease; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial; SD, standard deviation; TG, triglycerides; and HLB; hydrophilic lipophilic balance.

Compositions

[0113] In one embodiment, a composition of the disclosure is administered to a subject in an amount sufficient to provide a daily dose of eicosapentaenoic acid of about

1 mg to about 10,000 mg, 25 about 5000 mg, about 50 to about 3000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 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 mg, about 3750 mg, about 3775 mg, about 3800 mg, about 3825 mg, about 3850 mg, about 3875 mg, about 3900 mg, about 3925 mg, about 3950 mg, about 3975 mg, about 4000 mg, about 4025 mg, about 4050 mg, about 4075 mg, about 4100 mg, about 4125 mg, about 4150 mg, about 4175 mg, about 4200 mg, about 4225 mg, about 4250 mg, about 4275 mg, about 4300 mg, about 4325

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[0114] In one embodiment, a composition for use in methods of the disclosure comprises eicosapentaenoic acid, or a pharmaceutically acceptable ester, derivative, conjugate or salt thereof, or mixtures of any of the foregoing, collectively referred to herein as "EPA." The term "pharmaceutically acceptable" in the present context means that the substance in question does not produce unacceptable toxicity to the subject or interaction with other components of the composition. In one embodiment, derivatives of EPA include, but are not limited to, methyl or other alkyl esters, re-esterified monoglycerides, re-esterified diglycerides and re-esterified triglycerides or mixtures thereof. In one embodiment, such derivatives of EPA are administered daily in amounts containing the same number of moles of EPA contained in 4 grams of ethyl icosapentate.

[0115] 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 (E-EPA), eicosapentaenoic acid methyl ester, eicosapentaenoic acid propyl ester, or eicosapentaenoic acid butyl ester.

[0116] In another embodiment, the EPA is in the form of ethyl-EPA, methyl-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. Where any particular form of EPA (e.g. eicosapentaenoic acid ethyl ester, icosapent ethyl or E-EPA) is referred to throughout this application, any pharmaceutically acceptable derivative of EPA can be substituted in

its place including icosapent methyl or eicosapentaenoic acid in free acid form. Eicosapentaenoic acid ethyl ester, icosapent ethyl, and E-EPA are referenced interchangeably.

[0117] In another embodiment, EPA is present in a composition useful in accordance with methods of the disclosure in an amount of about 50 mg to about 5000 mg, about 75 mg to about 2500 mg, or about 100 mg to about 1000 mg, for example about 75 mg, about 100 mg, about 125 mg, about 150 mg, about 175 mg, about 200 mg, about 225 mg, about 250 mg, about 275 mg, about 300 mg, about 325 mg, about 350 mg, about 375 mg, about 400 mg, about 425 mg, about 450 mg, about 475 mg, about 500 mg, about 525 mg, about 550 mg, about 575 mg, about 600 mg, about 625 mg, about 650 mg, about 675 mg, about 700 mg, about 725 mg, about 750 mg, about 775 mg, about 800 mg, about 825 mg, about 850 mg, about 875 mg, about 900 mg, about 925 mg, about 950 mg, about 975 mg, about 1000 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1100 mg, about 1025 mg, about 1050 mg, about 1075 mg, about 1200 mg, about 1225 mg, about 1250 mg, about 1275 mg, about 1300 mg, about 1325 mg, about 1350 mg, about 1375 mg, about 1400 mg, about 1425 mg, about 1450 mg, about 1475 mg, about 1500 mg, about 1525 mg, about 1550 mg, about 1575 mg, about 1600 mg, about 1625 mg, about 1650 mg, about 1675 mg, about 1700 mg, about 1725 mg, about 1750 mg, about 1775 mg, about 1800 mg, about 1825 mg, about 1850 mg, about 1875 mg, about 1900 mg, about 1925 mg, about 1950 mg, about 1975 mg, about 2000 mg, about 2025 mg, about 2050 mg, about 2075 mg, about 2100 mg, about 2125 mg, about 2150 mg, about 2175 mg, about 2200 mg, about 2225 mg, about 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 mg, about 3750

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[0118] In another embodiment, a composition useful in accordance with the disclosure contains not more than about 10%, not more than about 9%, not more than about 8%, not more than about 7%, not more than about 6%, not more than about 5%, not more than about 4%, not more than about 3%, not more than about 2%, not more than about 1%, or not more than about 0.5%, by weight, docosahexaenoic acid (DHA), if any. In another embodiment, a composition of the disclosure contains substantially no DHA. In still another embodiment, a composition useful in the present disclosure contains no DHA and/or derivative thereof. In one embodiment, derivatives of DHA include, but are not limited to, methyl or other alkyl esters, re-esterified monoglycerides, re-esterified diglycerides and re-esterified triglycerides or mixtures thereof.

[0119] In another embodiment, EPA comprises at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or 1 about 100%, by weight, of all fatty acids present in a composition that is useful in methods of the present disclosure.

[0120] 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.

[0121] In another embodiment, a composition useful in accordance with methods of the disclosure contains less than about 10%, less than about 9%, less than about 8%, less than about 7%, less than about 6%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, less than about 1%, less than about 0.5% or less than about 0.25%, by weight of the total composition or by weight of the total fatty acid

content, of any fatty acid other than EPA. Illustrative examples of a "fatty acid other than EPA" include linolenic acid (LA), arachidonic acid (AA), docosahexaenoic acid (DHA), alpha-linolenic acid (ALA), stearadonic acid (STA), eicosatrienoic acid (ETA) and/or docosapentaenoic acid (DPA). In another embodiment, a composition useful in accordance with methods of the disclosure contains about 0.1% to about 4%, about 0.5% to about 3%, or about 1% to about 2%, by weight, of total fatty acids other than EPA and/or DHA. In one embodiment, fatty acids other than EPA include derivatives of those fatty acids. Derivatives of the fatty acids include, but are not limited to, methyl or other alkyl esters, re-esterified monoglycerides, re-esterified diglycerides and re-esterified triglycerides or mixtures thereof of the fatty acids.

[0122] In another embodiment, a composition useful in accordance with the disclosure has one or more of the following features: (a) eicosapentaenoic acid ethyl ester represents at least about 96%, at least about 97%, or at least about 98%, by weight, of all fatty acids present in the composition; (b) the composition contains not more than about 4%, not more than about 3%, or not more than about 2%, by weight, of total fatty acids other than eicosapentaenoic acid ethyl ester; (c) the composition contains not more than about 0.6%, not more than about 0.5%, or not more than about 0.4% of any individual fatty acid other than eicosapentaenoic acid ethyl ester; (d) the composition has a refractive index (20 °C) of about 1 to about 2, about 1.2 to about 1.8 or about 1.4 to about 1.5; (e) the composition has a specific gravity (20 °C) of about 0.8 to about 1.0, about 0.85 to about 0.95 or about 0.9 to about 0.92; (e) the composition contains not more than about 20 ppm, not more than about 15 ppm or not more than about 10 ppm heavy metals, (f) the composition contains not more than about 5 ppm, not more than about 4 ppm, not more than about 3 ppm, or not more than about 2 ppm arsenic, and/or (g) the composition has a peroxide value of not more than about 5 meq/kg, not more than about 4 meq/kg, not more than about 3 meq/kg, or not more than about 2 meq/kg.

[0123] In some embodiments, a composition for use in accordance with the disclosure is a self-emulsifying composition. In some embodiments, the self-emulsifying composition comprises at least one compound selected from the group consisting of an omega-3 fatty acid and derivative thereof (e.g., pharmaceutically acceptable salt and/or ester). In another embodiment, the composition comprises an emulsifier. In some embodiments, the emulsifier has a hydrophilic lipophilic balance (HLB) of at least about 10. Non-limiting examples of emulsifiers include polyoxyethylene hydrogenated castor

oil, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene castor oil, polyethylene glycol fatty acid ester, polyoxyethylene polyoxypropylene glycol, sucrose fatty acid ester, and lecithin. In another embodiment, the omega-3 fatty acids or derivative thereof are present in an amount of about 50% to about 95% by weight of the total weight of the composition or by weight of the total fatty acids of the total composition. In some embodiments, the omega-3 fatty acid is EPA and/or DHA. In some embodiments, the EPA is present in amount at least about 95%, by weight, of all fatty acids present in the self-emulsifying composition. In another embodiment, the composition contains substantially no DHA. In yet another embodiment, the composition contains substantially no ethanol.

[0124] In another embodiment, the composition is a self-emulsifying composition comprising about 50% to about 95% by weight of the total weight of the composition at least one compound selected from the group consisting of omega-3 polyunsaturated fatty acids and derivative thereof (e.g., pharmaceutically acceptable salt and/or ester). In another embodiment, the composition comprises about 1% to about 20% by weight of the total weight of the composition, a sucrose fatty acid ester as an emulsifier having a hydrophilic lipophilic balance of at least about 10. In another embodiment, the composition comprises glycerin. In another embodiment, the composition comprises about 0% to about 5% by weight of the total composition, ethanol. In another embodiment, the self-emulsifying composition comprises about 50% to about 95% by weight of the total weight of the composition, at least one compound selected from the group consisting of omega-3 polyunsaturated fatty acids and derivative thereof; about 1% to about 20%, by weight of the total weight of the composition, a sucrose fatty acid ester as an emulsifier having a HLB of at least about 10; glycerin; and about 0% to about 4% by weight of the total weight of the composition, ethanol. In another embodiment, the sucrose fatty acid ester is one or more of: sucrose laurate, sucrose myristate, sucrose palmitate, sucrose stearate, or sucrose oleate. In another embodiment, the omega-3 polyunsaturated fatty acid is one or more of EPA, DHA, or derivative thereof. In yet another embodiment, the omega-3 polyunsaturated fatty acid is ethyl-EPA and/or ethyl-DHA.

[0125] In another embodiment, the composition is a self-emulsifying composition comprising about 50% to about 95% by weight of the total weight of the composition, at least one compound selected from the group consisting of omega-3 polyunsaturated fatty

acids and derivative thereof (e.g., pharmaceutically acceptable salt and ester); and about 5% to about 50%, by weight, of the total weight of the composition an emulsifier having a HLB of at least about 10; wherein ethanol content is up to about 4% by weight of the total weight of the composition. In some embodiments, the omega-3 polyunsaturated fatty acid is EPA and/or DHA. In another embodiment, the composition does not contain ethanol. In another embodiment, the emulsifier is at least one member selected from the group consisting of polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene castor oil, polyethylene glycol fatty acid ester, polyoxyethylene polyoxypropylene glycol, sucrose fatty acid ester, and lecithin. In another embodiment, the emulsifier is at least one member selected from the group consisting of polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene castor oil, and sucrose fatty acid ester.

[0126] In another embodiment, the hydrogenated castor oil is at least one member selected from the group consisting of include polyoxyethylene (20) hydrogenated castor oil, polyoxyethylene (40) hydrogenated castor oil, polyoxyethylene (50) hydrogenated castor oil, polyoxyethylene (60) hydrogenated castor oil, or polyoxyethylene (100) hydrogenated castor oil. In another embodiment, the polyoxyethylene sorbitan fatty acid ester is at least one member selected from the group consisting of polyoxyethylene sorbitan monooleate, polyoxyethylene sorbitan tristearate, polyoxyethylene sorbitan monostearate, polyoxyethylene sorbitan monopalmitate, and polyoxyethylene sorbitan monolaurate. In another embodiment, the sucrose fatty acid ester is at least one member selected from the group consisting of sucrose laurate, sucrose myristate, sucrose palmitate, sucrose stearate, and sucrose oleate.

[0127] In some embodiments, the composition contains a lecithin selected from the group consisting of soybean lecithin, enzymatically decomposed soybean lecithin, hydrogenated soybean lecithin, and egg yolk lecithin. In another embodiment, the composition contains a polyhydric alcohol, wherein the polyhydric alcohol is propylene glycol or glycerin. In another embodiment, the composition contains at least one member selected from the group consisting of EPA, DHA, and/or derivative thereof (e.g., their pharmaceutically acceptable salt and ester), wherein the composition contains ethyl-EPA and/or ethyl-DHA. In another embodiment, the composition comprises an emulsifier having a HLB of at least about 10 and is about 10 to about 100 parts by weight in relation to 100 parts by weight of the at least one compound selected from the group consisting

of omega-3 polyunsaturated fatty acids and/or derivative thereof (e.g., pharmaceutically acceptable salt and/or ester).

[0128] In another embodiment, the self-emulsifying composition comprises about 70% to about 90%, by weight, eicosapentaenoic acid ethyl ester as a first medicinal component. In some embodiments, the composition further comprises about 0.5 to about 0.6%, by weight, water. In some embodiments, the composition comprises about 1% to about 29%, by weight, polyoxyethylene sorbitan fatty acid ester as an emulsifier. In another embodiment, the composition comprises about 1 to about 25 parts, by weight, lecithin in relation to about 100 parts, by weight, eicosapentaenoic acid ethyl ester. In yet another embodiment, the composition comprises pitavastatin, rosuvastatin, or a salt thereof as a second medicinal component. In another embodiment, ethanol and/or polyhydric alcohol constitutes up to about 4% by weight of the total weight of the composition. In another embodiment, the composition comprises about 0.01 to about 1 part, by weight, of pitavastatin or its salt in relation to about 100 parts, by weight, of the eicosapentaenoic acid ethyl ester, or about 0.03 to about 5 parts, by weight, rosuvastatin or its salt in relation to about 100 parts, by weight, eicosapentaenoic acid ethyl ester as a second medicinal component. In some embodiments, the composition is encapsulated in a hard capsule and/or a soft capsule, wherein a capsule film of the soft capsule may contain gelatin. In another embodiment, the self-emulsifying composition further comprises polyoxyethylene hydrogenated castor oil and/or polyoxyethylene castor oil. In another embodiment, the emulsifier comprises polyoxyethylene sorbitan fatty acid ester and polyoxyethylene castor oil. In some embodiments, the pitavastatin, rosuvastatin, or a salt thereof is pitavastatin calcium or rosuvastatin calcium. In another embodiment, the lechtin is soybean lechtin. In another embodiment, the polyoxyethylene sorbitan fatty acid ester is polyoxyethylene (20) sorbitan monooleate.

[0129] In some embodiments, the self-emulsifying composition comprising E-EPA has improved bioavailability compared as compared to a standard E-EPA formulation. A standard E-EPA formulation is a formulation that is not self-emulsifying. In some embodiments, a self-emulsifying composition comprising about 1.8 to about 3.8 g of E-EPA has substantially equivalent bioavailability to about 4 g E-EPA that is not formulated as a self-emulsifying composition. In some embodiments, the self-emulsifying comprising E-EPA is assessed for a bioequivalence to about 4 g E-EPA that is not

formulated as a self-emulsifying using for example, U.S. Food and Drug Administration (FDA) guidelines.

[0130] In another embodiment, compositions useful in accordance with methods of the disclosure are orally deliverable. The terms "orally deliverable" or "oral administration" herein include any form of delivery of a therapeutic agent or a composition thereof to a subject wherein the agent or composition is placed in the mouth of the subject, whether or not the agent or composition is swallowed. Thus "oral administration" includes buccal and sublingual as well as esophageal administration. In one embodiment, the composition is present in a capsule, for example a soft gelatin capsule.

[0131] A composition for use in accordance with the disclosure can be formulated as one or more dosage units. The terms "dose unit" and "dosage unit" herein refer to a portion of a pharmaceutical composition that contains an amount of a therapeutic agent suitable for a single administration to provide a therapeutic effect. Such dosage units may be administered one to a plurality (i.e. 1 to about 10, 1 to 8, 1 to 6, 1 to 4 or 1 to 2) of times per day, or as many times as needed to elicit a therapeutic response.

[0132] In one embodiment, compositions of the disclosure, upon storage in a closed container maintained at room temperature, refrigerated (e.g. about 5 to about 5 -10 °C) temperature, or frozen for a period of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, exhibit at least about 90%, at least about 95%, at least about 97.5%, or at least about 99% of the active ingredient(s) originally present therein.

Therapeutic Methods

[0133] In one embodiment, the disclosure provides a method for treatment and/or prevention of cardiovascular-related disease and disorders. The term "cardiovascular-related disease and disorders" herein refers to any disease or disorder of the heart or blood vessels (i.e. arteries and veins) or any symptom thereof. Non-limiting examples of cardiovascular-related disease and disorders include hypertriglyceridemia, hypercholesterolemia, mixed dyslipidemia, coronary heart disease, vascular disease, stroke, atherosclerosis, arrhythmia, hypertension, myocardial infarction, and other cardiovascular events.

[0134] 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 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.

[0135] In various embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject on statin therapy. In some embodiments, the methods comprise (a) identifying a subject on statin therapy and having a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/d, wherein said subject has established cardiovascular disease or has a high risk of developing cardiovascular disease; and (b) administering to the subject a composition comprising about 1 g to about 4 g of eicosapentaenoic acid (free acid) or derivative thereof (ethyl or methyl ester) per day. The terms “composition” and “pharmaceutical composition” as provided herein are referenced interchangeably.

[0136] In various embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject, the methods comprising determining or having determined whether the subject has a triglyceride level of at least 150 mg/dl and a history of atrial fibrillation and/or atrial flutter.

[0137] In some embodiments, determining whether the subject has a triglyceride level of at least 150 mg/dl and a history of atrial fibrillation and/or atrial flutter comprises obtaining or having obtained information which indicates that the patient has the triglyceride level of at least 150 mg/dl and has previously had symptoms of atrial fibrillation and/or atrial flutter and/or was previously diagnosed with atrial fibrillation and/or atrial flutter. In another embodiment, determining whether the subject has a triglyceride level of at least 150 mg/dl and a history of atrial fibrillation and/or atrial flutter comprises monitoring or having monitored the subject for the triglyceride level of at least 150 mg/dl and for symptoms of atrial fibrillation and/or atrial flutter. In some embodiments, the subject is determined to have triglyceride levels of at least about 150 mg/dl by measuring triglyceride levels in a blood sample obtained from the subject. In some embodiments,

the subject is determined as having a history of atrial fibrillation and/or atrial flutter by identifying whether the subject has or has had symptoms of atrial fibrillation and/or flutter. Non-limiting examples of symptoms of atrial fibrillation and/or flutter include heart rate greater than about 100 beats per minute (bpm); heart palpitations; shortness of breath; pain, pressure, tightness or discomfort in chest; dizziness; lightheadedness; or fainting. In some embodiments the subject has a risk factor for atrial fibrillation and/or flutter including (a) heart failure; (b) previous heart attack; (c) heat valve abnormalities; (d) high blood pressure; (e) thyroid dysfunction; (f) chronic lung disease; (g) diabetes; (h) obesity; and (i) congenital heart disease. In some embodiments, the subject is monitored for symptoms of atrial fibrillation and/or flutter using one or more of: electrocardiograms (ECGs), implantable pacemakers, implantable cardioverter defibrillators, and/or subcutaneous implantable cardiac monitors.

[0138] In some embodiments, the methods further comprise determining a risk that the subject will experience symptoms of atrial fibrillation and/or atrial flutter if the subject has previously had symptoms of atrial fibrillation and/or atrial flutter, was previously diagnosed with atrial fibrillation and/or atrial flutter, and/or had symptoms of atrial fibrillation and/or atrial flutter when monitored. In some embodiments, the methods comprise determining a risk that the subject will experience symptoms of atrial fibrillation and/or atrial flutter if the subject is administered EPA. In some embodiments, the methods comprise determining whether a risk that the subject will experience symptoms of atrial fibrillation and/or atrial flutter if the subject is administered EPA is greater than reducing a risk of a cardiovascular event in the subject. In some embodiments, the methods comprise determining whether reducing a risk of one or more cardiovascular events if the subject were administered about 4 g of EPA per day is greater than a risk that the subject will experience symptoms of atrial fibrillation and/or atrial flutter

[0139] In some embodiments, determining whether a risk that the subject will experience symptoms of atrial fibrillation and/or atrial flutter if the subject is administered EPA is greater than reducing a risk of a cardiovascular event includes evaluating the risk benefits of reducing the one or more cardiovascular events as compared to a risk of increasing symptoms of atrial fibrillation and/or atrial flutter. Atrial fibrillation and/or flutter is caused by abnormal electrical signals that start in the upper chambers of the heart. As the abnormal signals move through the heart, a subject might experience heart flutter (e.g., rapid beating) in addition to shortness in breadth, tiredness, or light headiness.

However, while atrial fibrillation and/or flutter may cause chest discomfort if the heart is beating rapidly, atrial fibrillation and/or flutter is generally not as severe as compared to the subject experiencing a cardiovascular event (e.g., cardiovascular death, coronary revascularization, unstable angina, myocardial infarction, and/or stroke). As such, in some embodiments, the risk associated with increasing the symptoms of atrial fibrillation and/or atrial flutter is outweighed by the benefits of reducing a risk of one or more cardiovascular events in the subject. In some embodiments, when the benefits of administering EPA to the subject are greater as compared to an associated increase in symptoms of atrial fibrillation and/or atrial flutter experienced by the subject as a result of the administration of the EPA, the subject will be administered the EPA in order to reduce the risk of one or more cardiovascular events.

[0140] In some embodiments, if the benefits of administering EPA to the subject to reduce the one or more cardiovascular events is less than the risk of the subject experiencing symptoms associated with atrial fibrillation and/or atrial flutter, the subject will not be administered the EPA. For example, in some embodiments, the symptoms of atrial fibrillation and/or atrial flutter are so great that the symptoms suggest the subject will experience a cardiovascular event if the subject is administered the EPA. In some embodiments, if the risk associated with the increased symptoms of atrial fibrillation and/or atrial flutter are greater than the benefits of administering EPA to the subject, the subject will not be administered in the EPA. In some embodiments, the subject will instead, be administered a statin and/or continue to receive a statin if already on statin therapy.

[0141] In some embodiments, the risk associated with the symptoms of atrial fibrillation and/or atrial flutter is determined by monitoring the subject for symptoms of atrial fibrillation and/or atrial flutter and determining whether the symptoms are severe enough to cause a cardiovascular event if the subject is administered EPA. In some embodiments, the risk is based on evaluating the subject for heart rate consistency, heart contractions, blood pooling in the atria, increased risk in blood clotting, and/or increase in blood clots.

[0142] In some embodiments, if the patient has previously had symptoms of atrial fibrillation and/or atrial flutter, was previously diagnosed with atrial fibrillation and/or atrial flutter, and/or symptoms of atrial fibrillation and/or atrial flutter, the methods comprise

administering an atrial fibrillation flutter and/or atrial flutter therapeutic agent to the patient instead EPA. In some embodiments, a risk for atrial fibrillation and/or atrial flutter for the subject is lower following administration of atrial fibrillation flutter and/or atrial flutter therapeutic agent than it would be had the subject been administered EPA. In some embodiments, the risk for atrial fibrillation and/or atrial flutter is lower following administration of atrial fibrillation flutter and/or atrial flutter therapeutic agent than it would be had the subject been administered 4 g of EPA per day.

[0143] In some embodiments, if the risk is greater that the subject will experience symptoms of atrial fibrillation and/or atrial flutter, the methods comprise administering an atrial fibrillation flutter and/or atrial flutter therapeutic agent to the patient instead EPA. In some embodiments, the subject is administered an atrial fibrillation flutter and/or atrial flutter therapeutic agent instead of about 4 g of EPA per day.

[0144] In some embodiments, the atrial fibrillation flutter and/or atrial flutter therapeutic agent administered to the subject is one or more of beta blockers, anticoagulants, antithrombics, calcium channel blockers, antiplatelets, sodium channel blockers, or potassium channel blockers. Non-limiting examples of beta blockers include acebutolol, metoprolol, nadolol, pindolol, betapace, propranolol. Non-limiting examples of anticoagulants include rivaroxaban, dabigatran, apixaban, and edoxaban. Non limiting examples of antithrombics including warfarin, heparin, aspirin, ticlopidine, and dipyridamole. Non-limiting examples of calcium channel blockers include diltiazem hydrochloride, verapamil hydrochloride, and verapamil hydrochloride. Non limiting examples of antiplatelets include aspirin, anagrelide, dipyridamole, vorapaxar, apixaban, rivaroxaban, dalteparin, and fondaparinux. Non-limiting examples of sodium channel blockers include procainamide, disopyramide, quinidine, and flecainide. Non-limiting examples of potassium channel blockers include dronedarone, ibutilide, and sotalol.

[0145] In some embodiments, the atrial fibrillation flutter and/or atrial flutter therapeutic agent administered to the subject at a dose of standard dose. In some embodiments, the subject is administered an about 20 mg to about 80 mg dose of a beta-blocker. In some embodiments, the subject is administered about a 2.5 mg to about 250 mg dose of an anticoagulant. In some embodiments, the subject is administered an about 2.5 mg to about 10 mg dose of a calcium channel blocker. In some embodiments, the subject is administered an about 30 mg to about 300 mg dose of an antiplatelet. In

some embodiments, the subject is administered an about 20 mg to about 150 mg dose of a sodium channel blocker. In some embodiments, the subject is administered an about 20 mg to about 150 mg dose of a potassium channel blocker. In some embodiments, the subject is administered a 25 mg dose of warfarin.

[0146] In yet another embodiment, if the subject has not previously had symptoms of atrial fibrillation and/or atrial flutter, was not previously diagnosed with atrial fibrillation and/or atrial flutter, and/or symptoms of atrial fibrillation and/or atrial flutter were not determined during the monitoring, the methods comprise administering EPA to the subject to reduce a risk for a cardiovascular event. In some embodiments, about 4 g of EPA is administered to the subject per day.

[0147] In some embodiments, if the risk is greater that the subject will have a reduced risk of one or more cardiovascular events, the methods comprise administering EPA to the subject. In some embodiments, the subject will experience both an increase frequency in atrial fibrillation and/or atrial flutter symptoms and a decreased frequency in cardiovascular events if the subject is administered EPA. In some embodiments, about 4 g of EPA is administered to the subject per day.

[0148] In some embodiments, regardless of whether the risk is greater that the subject will experience symptoms of atrial fibrillation and/or flutter, if the subject is being treated with a statin, the methods include continuing to treat the subject with a statin. In some embodiments, regardless of whether the risk is greater that the subject will have a reduced risk of one or more cardiovascular events, if the subject is being treated with a statin, the methods include continuing to treat the subject with a statin. In some embodiments, regardless of whether the subject is likely to experience and increase in atrial fibrillation and/or atrial flutter symptoms and decrease in frequency of cardiovascular events, if the subject is being treated with a statin, the methods include continuing to treat the subject with a statin.

[0149] In some embodiments, the methods comprise reduce a risk of a cardiovascular event in a subject comprising determining that individuals who have triglyceride levels above 150 mg/dl and who have previously experienced atrial fibrillation or atrial flutter episodes, upon treatment with 4 g EPA per day are likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes and (2) decreased frequency of cardiovascular events other than atrial fibrillation or atrial flutter.

In some embodiments, the methods further comprise identifying a subject whose measured triglyceride level is above 150 mg/dl and who has previously experienced symptoms of atrial fibrillation and/or atrial flutter.

[0150] In some embodiments, the methods further comprise determining that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject. In some embodiments, following this determination, the methods comprise administering to the subject EPA. In some embodiments, the methods comprise administering to the subject about 4 g of EPA per day.

[0151] In yet another embodiment, the methods further comprise determining that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the patient. In some embodiments, following this determination, the subject is not administered EPA, but instead, administered a statin. In some embodiments, the methods include continuing to administer a statin to the patient if the subject is already on statin therapy.

[0152] In some embodiments, the methods further comprise reducing a risk for one or more cardiovascular events by determining that one or more cardiovascular benefits are expected to occur. In some embodiments, the cardiovascular event does not include atrial fibrillation and/or atrial flutter. In some embodiments, the cardiovascular event is one or more of cardiovascular death, coronary revascularization, unstable angina, stroke, and myocardial infarction. In some embodiments, the cardiovascular event is sudden cardiac death, cardiac arrest, or both.

[0153] In some embodiments, the methods comprise reducing a risk of a cardiovascular event in a subject, wherein the subject develops atrial fibrillation and/or atrial flutter during the course of treatment. In some embodiments, the methods comprise administering EPA to the subject for a period of time effective to reduce the risk for a cardiovascular event, wherein the subject develops atrial fibrillation and/or flutter during the period of time effective to reduce the risk of the cardiovascular event. In some embodiments, prior to treatment, the subject is determined to not have previously had symptoms of atrial fibrillation and/or atrial flutter, not have been previously diagnosed with atrial fibrillation and/or atrial flutter, and/or not have exhibited symptoms of atrial

fibrillation and/or atrial flutter. In some embodiments, the subject is administered about 4 g of EPA per day.

[0154] In some embodiments, the methods comprise reducing a risk of a cardiovascular event in a subject that is less than 65 years of age. In some embodiments, the methods comprise administering to the subject EPA for a period of time effective to reduce the cardiovascular event, wherein the subject does not exhibit an increase in symptoms atrial fibrillation and/or atrial flutter. In some embodiments, prior to treatment, the subject less than 65 years of age is determined to not have previously had symptoms of atrial fibrillation and/or atrial flutter, not have been previously diagnosed with atrial fibrillation and/or atrial flutter, and/or not have exhibited symptoms of atrial fibrillation and/or atrial flutter. In some embodiments, the subject is administered about 4 g of EPA per day. In some embodiments, the subject is less than 65 years old, 60 years old, 55 years old, 50 years old, 45 years old, 40 years old, 35 years old, 30 years old, or less

[0155] In some embodiments, the methods include reducing a risk of sudden cardiac death in a subject having a history of atrial fibrillation and/or atrial flutter. In some embodiments, the methods include reducing a risk of cardiac arrest in a subject with a history of atrial fibrillation and/or atrial flutter. In some embodiments, the methods comprise determining if the subject has a history of atrial fibrillation and/or flutter based on whether the subject has previously had symptoms of atrial fibrillation and/or atrial flutter, was previously diagnosed with atrial fibrillation and/or atrial flutter, and/or had symptoms of atrial fibrillation and/or atrial flutter.

[0156] In various embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject on anti-thrombotic therapy. In some embodiments, the methods comprise (a) identifying a subject on anti-thrombotic therapy and having a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/d, wherein said subject has established cardiovascular disease or has a high risk of developing cardiovascular disease; and (b) administering to the subject a composition comprising about 1 g to about 4 g of eicosapentaenoic acid (free acid) or derivative thereof (ethyl or methyl ester) per day. The terms “composition” and “pharmaceutical composition” as provided herein are referenced interchangeably.

[0157] In various embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject on anti-thrombotic therapy. In some

embodiments, the methods comprise (a) identifying a subject on anti-thrombotic therapy and having a fasting baseline triglyceride level of about 80 mg/dL to about 1500 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 composition comprising about 1 g to about 4 g of eicosapentaenoic acid (free acid) or derivative thereof (ethyl or methyl ester) per day. In some embodiments, the reduction in a risk of a cardiovascular event is not correlated to a reduction in the subject's triglyceride levels.

[0158] In some embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject on anti-thrombotic therapy with or without an associated in reduction a baseline triglyceride level of the subject. As such, a reduction of cardiovascular events is not correlated to a reduction in the subject's triglyceride levels. Accordingly, regardless of whether the subject exhibits a reduction in triglyceride levels, the subject experiences a reduction in a risk of a cardiovascular event. In some embodiments, the methods comprise administering to the subject a composition comprising eicosapentaenoic acid or derivative thereof, wherein the subject does not exhibit a statistically significant change in fasting triglyceride levels for a period of time after administration of the composition. In some embodiments, the period of time is about 1 year to about 5 years, about 1 year to about 6 years, about 1 year to about 7 years, about 1 year to about 8 years, or about 1 year to about 9 years. In another embodiment, the subject exhibits a reduction in fasting triglycerides at a period time of greater than about 5 years, greater than about 6 years, greater than about 7 years, greater than about 8 years, greater than about 9 years, or greater than about 10 years.

[0159] In some embodiments, the present disclosure provides methods of reducing a risk of total cardiovascular events in a subject on anti-thrombotic therapy. In some embodiments, the methods comprise administering to the subject a composition comprising eicosapentaenoic acid or derivative thereof. Total cardiovascular events include a first, second, third, fourth, fifth, sixth, eight, ninth, tenth or more cardiovascular event. In some embodiments, the subject has not experienced a cardiovascular event, but is at a high risk for experiencing a cardiovascular event. In some embodiments, the subject has experienced multiple cardiovascular events (i.e., a second, third, fourth, or more) and a reduction in a risk of any subsequent cardiovascular event. In some embodiments, the total cardiovascular events are reduced by 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%. In some embodiments, the total cardiovascular events are reduced regardless of the subject's fasting baseline triglyceride level. For example, total cardiovascular events are reduced in a subject having a fasting baseline triglyceride level in a low, medium, or high tertile. Subjects in the low baseline fasting triglyceride tertile have triglyceride levels between about 80 mg/dL to about 190 mg/dL (median triglyceride level of 160 mg/dL), subjects in the medium baseline fasting triglyceride tertile have triglyceride levels between about 191 mg/dL to about 250 mg/dL (median triglyceride level of 215 mg/dL), and lastly, subjects in the high baseline fasting triglyceride tertile have triglyceride levels between about 251 mg/dL to about 1400 mg/dL (median triglyceride level of 304 mg/dL).

[0160] In some embodiments, the present disclosure provides methods of reducing a cardiovascular event in a subject on anti-thrombotic therapy, the methods comprising instructing or having instructed a caregiver of the subject to inquire if the subject has or previously has had atrial fibrillation and/or flutter, assessing or having assessed whether the subject has or has previously had symptoms of atrial fibrillation and/or flutter, monitoring or having monitored the subject for symptoms of atrial fibrillation and/or flutter, and/or providing or having provided guidance to a caregiver of the subject to monitor the subject for symptoms of atrial fibrillation and/or flutter. In some embodiments, the methods further comprise administering or having administered to the subject a composition comprising of eicosapentaenoic acid or derivative thereof per day.

[0161] In some embodiments, the present disclosure provides methods of reducing an incidence of a cardiovascular event in a subject on anti-thrombotic therapy. In some embodiments, the methods comprise administering to the subject a composition comprising eicosapentaenoic acid or derivative thereof per day, wherein the subject experiences atrial fibrillation and/or flutter and a reduction in or no cardiovascular event. For example, administration of the composition shifts the cardiovascular event to a less medically severe outcome of atrial fibrillation and/or flutter. As such, in some embodiments, the subject experiences atrial fibrillation and/or flutter instead of a cardiovascular event. In another embodiment, the subject exhibits an increase in the symptoms of atrial fibrillation and/or flutter and a reduction in a cardiovascular event as compared to baseline or a placebo control. In some embodiments, the increase in the symptoms of atrial fibrillation and/or flutter are statistically significant as compared to baseline or a placebo control. For example, the symptoms of atrial fibrillation and/or

flutter increase by at least about 1%, at least about 2%, at least about 3%, at least about 4%, or at least about 5%. In yet another embodiment, an incidence of atrial fibrillation and/or flutter requiring hospitalization is greater in the subject as compared to baseline or a placebo control. In some embodiments, the subject experiences a reduction in heart rate.

[0162] In various embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject on anti-thrombotic and/or statin therapy. In some embodiments, the methods comprise (a) identifying a subject on anti-thrombotic and/or statin therapy and having a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/d, wherein said subject has established cardiovascular disease or has a high risk of developing cardiovascular disease; and (b) administering to the subject a composition comprising about 1 g to about 4 g of eicosapentaenoic acid (free acid) or derivative thereof (ethyl or methyl ester) per day. The terms “composition” and “pharmaceutical composition” as provided herein are referenced interchangeably.

[0163] In various embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject on anti-thrombotic and/or statin therapy. In some embodiments, the methods comprise (a) identifying a subject on anti-thrombotic and/or statin therapy and having a fasting baseline triglyceride level of about 80 mg/dL to about 1500 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 composition comprising about 1 g to about 4 g of eicosapentaenoic acid (free acid) or derivative thereof (ethyl or methyl ester) per day. In some embodiments, the reduction in a risk of a cardiovascular event is not correlated to a reduction in the subject’s triglyceride levels.

[0164] In some embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject on anti-thrombotic and/or statin therapy with or without an associated in reduction a baseline triglyceride level of the subject. As such, a reduction of cardiovascular events is not correlated to a reduction in the subject’s triglyceride levels. Accordingly, regardless of whether the subject exhibits a reduction in triglyceride levels, the subject experiences a reduction in a risk of a cardiovascular event. In some embodiments, the methods comprise administering to the subject a composition comprising eicosapentaenoic acid or derivative thereof, wherein the subject does not

exhibit a statistically significant change in fasting triglyceride levels for a period of time after administration of the composition. In some embodiments, the period of time is about 1 year to about 5 years, about 1 year to about 6 years, about 1 year to about 7 years, about 1 year to about 8 years, or about 1 year to about 9 years. In another embodiment, the subject exhibits a reduction in fasting triglycerides at a period time of greater than about 5 years, greater than about 6 years, greater than about 7 years, greater than about 8 years, greater than about 9 years, or greater than about 10 years.

[0165] In some embodiments, the present disclosure provides methods of reducing a risk of total cardiovascular events in a subject on anti-thrombotic and/or statin therapy. In some embodiments, the methods comprise administering to the subject a composition comprising eicosapentaenoic acid or derivative thereof. Total cardiovascular events include a first, second, third, fourth, fifth, sixth, eight, ninth, tenth or more cardiovascular event. In some embodiments, the subject has not experienced a cardiovascular event, but is at a high risk for experiencing a cardiovascular event. In some embodiments, the subject has experienced multiple cardiovascular events (i.e., a second, third, fourth, or more) and a reduction in a risk of any subsequent cardiovascular event. In some embodiments, the total cardiovascular events are reduced by 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%. In some embodiments, the total cardiovascular events are reduced regardless of the subject's fasting baseline triglyceride level. For example, total cardiovascular events are reduced in a subject having a fasting baseline triglyceride level in a low, medium, or high tertile. Subjects in the low baseline fasting triglyceride tertile have triglyceride levels between about 80 mg/dL to about 190 mg/dL (median triglyceride level of 160 mg/dL), subjects in the medium baseline fasting triglyceride tertile have triglyceride levels between about 191 mg/dL to about 250 mg/dL (median triglyceride level of 215 mg/dL), and lastly, subjects in the high baseline fasting triglyceride tertile have triglyceride levels between about 251 mg/dL to about 1400 mg/dL (median triglyceride level of 304 mg/dL).

[0166] In some embodiments, the present disclosure provides methods of reducing a cardiovascular event in a subject on anti-thrombotic and/or statin therapy, the methods comprising instructing or having instructed a caregiver of the subject to inquire if the subject has or previously has had atrial fibrillation and/or flutter, assessing or having assessed whether the subject has or has previously had symptoms of atrial fibrillation

and/or flutter, monitoring or having monitored the subject for symptoms of atrial fibrillation and/or flutter, and/or providing or having provided guidance to a caregiver of the subject to monitor the subject for symptoms of atrial fibrillation and/or flutter. In some embodiments, the methods further comprise administering or having administered to the subject a composition comprising of eicosapentaenoic acid or derivative thereof per day.

[0167] In some embodiments, the present disclosure provides methods of reducing an incidence of a cardiovascular event in a subject on anti-thrombotic and/or statin therapy. In some embodiments, the methods comprise administering to the subject a composition comprising eicosapentaenoic acid or derivative thereof per day, wherein the subject experiences atrial fibrillation and/or flutter and a reduction in or no cardiovascular event. For example, administration of the composition shifts the cardiovascular event to a less medically severe outcome of atrial fibrillation and/or flutter. As such, in some embodiments, the subject experiences atrial fibrillation and/or flutter instead of a cardiovascular event. In another embodiment, the subject exhibits an increase in the symptoms of atrial fibrillation and/or flutter and a reduction in a cardiovascular event as compared to baseline or a placebo control. In some embodiments, the increase in the symptoms of atrial fibrillation and/or flutter are statistically significant as compared to baseline or a placebo control. For example, the symptoms of atrial fibrillation and/or flutter increase by at least about 1%, at least about 2%, at least about 3%, at least about 4%, or at least about 5%. In yet another embodiment, an incidence of atrial fibrillation and/or flutter requiring hospitalization is greater in the subject as compared to baseline or a placebo control. In some embodiments, the subject experiences a reduction in heart rate.

[0168] In some embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject on low, medium, or high statin therapy. In some embodiments, the methods comprise administering to the subject a composition comprising eicosapentaenoic acid or derivative thereof per day and a low, medium, or high intensity statin therapy. In some embodiments, the low intensity statin therapy includes about 5 mg to about 10 mg of simvastatin. In some embodiments, the medium intensity statin therapy includes about 5 mg to about 10 mg of rosuvastatin, about 10 mg to about 20 mg of atorvastatin, about 20 mg to 40 mg of simvastatin, or about 10 mg to about 20 mg of simvastatin plus about 5 mg to about 10 mg of ezetimibe. In some embodiments, the high intensity statin therapy includes about 20 mg to about 40 mg

rosuvastatin, about 40 mg to about 80 mg of atorvastatin, about 80 mg of simvastatin, or about 40 mg to about 80 mg of simvastatin plus about 5 mg to about 10 mg of ezetimibe. In some embodiments, the subject administered the high statin therapy a greater reduction in a cardiovascular event as compared to a subject in either a low or medium statin therapy. In some embodiments, the subject on a medium statin therapy exhibits a greater reduction in a cardiovascular event as compared to a subject on either a high or low statin therapy. In some embodiments, the subject on a low statin therapy exhibits a greater reduction in a cardiovascular evet as compared to a subject of a high or a medium statin therapy. In some embodiments, the greater reduction is a reduction of at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, or more.

[0169] In some embodiments, the antithrombotic therapy includes one or more antiplatelet therapies and/or one or more anticoagulant therapies. In some embodiments, the antiplatelet therapy is aspirin and/or clopidogrel. In some embodiments, the anticoagulant therapy is warfarin. In some embodiments, the aspirin, clopidogrel, or warfarin are antithrombotic monotherapies. In some embodiments, the antithrombotic therapy includes one or more antiplatelet therapies and one or more anticoagulant therapies. In some embodiments, the subject administered the one or more antiplatelet therapies exhibits a greater reduction in a cardiovascular event as compared to a subject in either an anticoagulant therapy or one or more antiplatelet therapies and an anticoagulant therapy. In some embodiments, the subject administered the one or more anticoagulant therapies exhibits a greater reduction in a cardiovascular event as compared to a subject in either an antiplatelet therapy or one or more antiplatelet therapies and an anticoagulant therapy. In some embodiments, the subject administered the one or more antiplatelet therapies and an anticoagulant therapy exhibits a greater reduction in a cardiovascular event as compared to a subject in either an anticoagulant therapy or an antiplatelet therapy. In some embodiments, the greater reduction is a reduction of at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, or more.

[0170] In various embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject on statin therapy. In some

embodiments, the methods comprise (a) identifying a subject on statin therapy and having a fasting baseline triglyceride level of about 80 mg/dL to about 1500 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 composition comprising about 1 g to about 4 g of eicosapentaenoic acid (free acid) or derivative thereof (ethyl or methyl ester) per day. In some embodiments, the reduction in a risk of a cardiovascular event is not correlated to a reduction in the subject's triglyceride levels.

[0171] In various embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject on statin therapy and having one or more of fasting of triglyceride levels, LDL-C levels, RLP-C levels, HDL-C levels, non-HDL-C levels, Apo B levels, hsCRP levels, or eGFR levels in a low, medium, or high tertile. In some embodiments, the subject exhibits a reduction in a cardiovascular event regardless of whether the subject's LDL-C levels, RLP-C levels, HDL-C levels, non-HDL-C levels, Apo B levels, hsCRP levels, and/or eGFR levels in a low, medium, or high tertile. For example, in some embodiments, the subject can have any combination of low, medium, or high LDL-C levels, RLP-C levels, HDL-C levels, non-HDL-C levels, Apo B levels, hsCRP levels, and/or eGFR levels and exhibit a reduction in a risk for a cardiovascular event.

[0172] In some embodiments, a risk for a cardiovascular event is reduced in a subject having a fasting baseline triglyceride level in a low, medium, or high tertile. Subjects in the low baseline fasting triglyceride tertile have triglyceride levels between about 80 mg/dL to about 190 mg/dL, subjects in the medium baseline fasting triglyceride tertile have triglyceride levels between about 191 mg/dL to about 250 mg/dL, and lastly, subjects in the high baseline fasting triglyceride tertile have triglyceride levels between about 251 mg/dL to about 1400 mg/dL. In some embodiments, the risk for a cardiovascular event is reduced by at least about 20%, at least about 30%, at least about 40%, or at least about 50%.

[0173] In some embodiments, a risk for a cardiovascular event is reduced in a subject having a fasting baseline LDL-C level in a low, medium, or high tertile. Subjects in the low baseline fasting LDL-C tertile have LDL-C levels between about 1 mg/dL to about 67 mg/dL, subjects in the medium baseline fasting LDL-C tertile have triglyceride levels between about 67 mg/dL to about 84 mg/dL, and lastly, subjects in the high

baseline LDL-C triglyceride tertile have triglyceride levels between about 84 mg/dL to about 208 mg/dL. In some embodiments, the risk for a cardiovascular event is reduced by at least about 20%, at least about 30%, at least about 40%, or at least about 50%.

[0174] In some embodiments, a risk for a cardiovascular event is reduced in a subject having a fasting baseline RLP-C levels in a low, medium, or high tertile. Subjects in the low baseline fasting RPL-C tertial have RPL-C levels between about 12 mg/dL to about 28 mg/dl, subjects in the medium baseline fasting RLP-C tertile have RLP-C levels between about 28 mg/dL to about 34 mg/dL, and lastly, subjects in the high baseline fasting RLP-C tertile have RLP-C levels between about 34 mg/dL to about 106 mg/dL. In some embodiments, the risk for a cardiovascular event is reduced by at least about 20%, at least about 30%, at least about 40%, or at least about 50%.

[0175] In some embodiments, a risk for a cardiovascular event is reduced in a subject having a fasting baseline HDL-C levels in a low, medium, or high tertile. Subjects in the low baseline fasting HDL-C tertile have HDL-C levels between about 17 mg/dL to about 36 mg/dl, subjects in the medium baseline fasting HDL-C tertile have HDL-C levels between about 36 mg/dL to about 43 mg/dL, and lastly, subjects in the high baseline fasting HDL-C tertile have HDL-C levels between about 43 mg/dL to about 107 mg/dL. In some embodiments, the risk for a cardiovascular event is reduced by at least about 20%, at least about 30%, at least about 40%, or at least about 50%.

[0176] In some embodiments, a risk for a cardiovascular event is reduced in a subject having a fasting baseline Apo B levels in a low, medium, or high tertile. Subjects in the low baseline fasting Apo B tertile have Apo B levels between about 17 mg/dL to about 76 mg/dl, subjects in the medium baseline fasting Apo B tertile have Apo B levels between about 76 mg/dL to about 89 mg/dL, and lastly, subjects in the high baseline fasting Apo B tertile have Apo B levels between about 89 mg/dL to about 207 mg/dL. In some embodiments, the risk for a cardiovascular event is reduced by at least about 20%, at least about 30%, at least about 40%, or at least about 50%.

[0177] In some embodiments, a risk for a cardiovascular event is reduced in a subject having a fasting baseline non-HDL-C levels in a low, medium, or high tertile. Subjects in the low baseline fasting non-HDL-C tertile have non-HDL-C levels between about 60 mg/dL to about 109 mg/dl, subjects in the medium baseline fasting non-HDL-C tertile have non-HDL-C levels between about 109 mg/dL to about 127 mg/dL, and lastly,

subjects in the high baseline fasting non-HDL-C tertile have non-HDL-C levels between about 127 mg/dL to about 244 mg/dL. In some embodiments, the risk for a cardiovascular event is reduced by at least about 20%, at least about 30%, at least about 40%, or at least about 50%.

[0178] In some embodiments, a risk for a cardiovascular event is reduced in a subject having a fasting baseline hsCRP levels in a low, medium, or high tertile. Subjects in the low baseline fasting hsCRP tertile have hsCRP levels between about 2 mg/dL to about 109 mg/dl, subjects in the medium baseline fasting hsCRP tertile have hsCRP levels between about 109 mg/dL to about 127 mg/dL, and lastly, subjects in the high baseline fasting hsCRP tertile have hsCRP levels between about 127 mg/dL to about 244 mg/dL. In some embodiments, the risk for a cardiovascular event is reduced by at least about 20%, at least about 30%, at least about 40%, or at least about 50%.

[0179] In some embodiments, a risk for a cardiovascular event is reduced in a subject having a fasting baseline eGFR levels in a low, medium, or high tertile. Subjects in the low baseline fasting eGFR tertile have eGFR levels less than 60 mL/min/1.73m^2, subjects in the medium baseline fasting eGFR tertile have eGFR levels between about 60 mL/min/1.73m^2 to about 90 mL/min/1.73m^2, and lastly, subjects in the high baseline fasting eGFR tertile have eGFR levels greater than about ≥90 mL/min/1.73m^2. In some embodiments, the risk for a cardiovascular event is reduced by at least about 20%, at least about 30%, at least about 40%, or at least about 50%.

[0180] In some embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject on statin therapy with or without an associated in reduction a baseline triglyceride level of the subject. As such, a reduction of cardiovascular events is not correlated to a reduction in the subject's triglyceride levels. Accordingly, regardless of whether the subject exhibits a reduction in triglyceride levels, the subject experiences a reduction in a risk of a cardiovascular event. In some embodiments, the methods comprise administering to the subject a composition comprising eicosapentaenoic acid or derivative thereof, wherein the subject does not exhibit a statistically significant change in fasting triglyceride levels for a period of time after administration of the composition. In some embodiments, the period of time is about 1 year to about 5 years, about 1 year to about 6 years, about 1 year to about 7 years, about 1 year to about 8 years, or about 1 year to about 9 years. In another embodiment,

the subject exhibits a reduction in fasting triglycerides at a period time of greater than about 5 years, greater than about 6 years, greater than about 7 years, greater than about 8 years, greater than about 9 years, or greater than about 10 years.

[0181] In some embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject on statin therapy with or without an associated in reduction a baseline LDL-C level of the subject. As such, a reduction of cardiovascular events is not correlated to a change in the subject's LDL-C levels. Accordingly, regardless of whether the subject exhibits a reduction in LDL-C levels or the subjects exhibits not statistically significant change in LDL-C levels, the subject experiences a reduction in a risk of a cardiovascular event. In some embodiments, the methods comprise administering to the subject a composition comprising eicosapentaenoic acid or derivative thereof, wherein the subject does not exhibit a statistically significant change in LDL-C levels for a period of time after administration of the composition. In some embodiments, the period of time is about 1 year to about 5 years, about 1 year to about 6 years, about 1 year to about 7 years, about 1 year to about 8 years, or about 1 year to about 9 years. In another embodiment, the subject exhibits a reduction in LDL-C levels at a period time of greater than about 5 years, greater than about 6 years, greater than about 7 years, greater than about 8 years, greater than about 9 years, or greater than about 10 years.

[0182] In some embodiments, the present disclosure provides methods of reducing a risk of total cardiovascular events in a subject on statin therapy. In some embodiments, the methods comprise administering to the subject a composition comprising eicosapentaenoic acid or derivative thereof. Total cardiovascular events include a first, second, third, fourth, fifth, sixth, eight, ninth, tenth or more cardiovascular event. In some embodiments, the subject has not experienced a cardiovascular event, but is at a high risk for experiencing a cardiovascular event. In some embodiments, the subject has experienced multiple cardiovascular events (i.e., a second, third, fourth, or more) and a reduction in a risk of any subsequent cardiovascular event. In some embodiments, the total cardiovascular events are reduced by 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%. In some embodiments, the total cardiovascular events are reduced regardless of the subject's fasting baseline triglyceride level. For example, total cardiovascular events are reduced in a subject having a fasting baseline triglyceride level

in a low, medium, or high tertile. Subjects in the low baseline fasting triglyceride tertile have triglyceride levels between about 80 mg/dL to about 190 mg/dL (median triglyceride level of 160 mg/dL), subjects in the medium baseline fasting triglyceride tertile have triglyceride levels between about 191 mg/dL to about 250 mg/dL (median triglyceride level of 215 mg/dL), and lastly, subjects in the high baseline fasting triglyceride tertile have triglyceride levels between about 251 mg/dL to about 1400 mg/dL (median triglyceride level of 304 mg/dL).

[0183] In some embodiments, the present disclosure provides methods of reducing a cardiovascular event in a subject on statin therapy, the methods comprising instructing or having instructed a caregiver of the subject to inquire if the subject has or previously has had atrial fibrillation and/or flutter, assessing or having assessed whether the subject has or has previously had symptoms of atrial fibrillation and/or flutter, monitoring or having monitored the subject for symptoms of atrial fibrillation and/or flutter, and/or providing or having provided guidance to a caregiver of the subject to monitor the subject for symptoms of atrial fibrillation and/or flutter. In some embodiments, the methods further comprise administering or having administered to the subject a composition comprising of eicosapentaenoic acid or derivative thereof per day.

[0184] In some embodiments, the present disclosure provides methods of reducing an incidence of a cardiovascular event in a subject on statin therapy. In some embodiments, the methods comprise administering to the subject a composition comprising eicosapentaenoic acid or derivative thereof per day, wherein the subject experiences atrial fibrillation and/or flutter and a reduction in or no cardiovascular event. For example, administration of the composition shifts the cardiovascular event to a less medically severe outcome of atrial fibrillation and/or flutter. As such, in some embodiments, the subject experiences atrial fibrillation and/or flutter instead of a cardiovascular event. In another embodiment, the subject exhibits an increase in the symptoms of atrial fibrillation and/or flutter and a reduction in a cardiovascular event as compared to baseline or a placebo control. In some embodiments, the increase in the symptoms of atrial fibrillation and/or flutter are statistically significant as compared to baseline or a placebo control. For example, the symptoms of atrial fibrillation and/or flutter increase by at least about 1%, at least about 2%, at least about 3%, at least about 4%, or at least about 5%. In yet another embodiment, an incidence of atrial fibrillation and/or flutter requiring hospitalization is greater in the subject as compared to baseline

or a placebo control. In some embodiments, the subject experiences a reduction in heart rate.

[0185] In some embodiments, the present disclosure provides methods of reducing a risk of a cardiovascular event in a subject on low, medium, or high statin therapy. In some embodiments, the methods comprise administering to the subject a composition comprising eicosapentaenoic acid or derivative thereof per day and a low, medium, or high intensity statin therapy. In some embodiments, the low intensity statin therapy includes about 5 mg to about 10 mg of simvastatin. In some embodiments, the medium intensity statin therapy includes about 5 mg to about 10 mg of rosuvastatin, about 10 mg to about 20 mg of atorvastatin, about 20 mg to 40 mg of simvastatin, or about 10 mg to about 20 mg of simvastatin plus about 5 mg to about 10 mg of ezetimibe. In some embodiments, the high intensity statin therapy includes about 20 mg to about 40 mg rosuvastatin, about 40 mg to about 80 mg of atorvastatin, about 80 mg of simvastatin, or about 40 mg to about 80 mg of simvastatin plus about 5 mg to about 10 mg of ezetimibe. In some embodiments, the subject administered the high statin therapy a greater reduction in a cardiovascular event as compared to a subject in either a low or medium statin therapy. In some embodiments, the subject on a medium statin therapy exhibits a greater reduction in a cardiovascular event as compared to a subject on either a high or low statin therapy. In some embodiments, the subject on a low statin therapy exhibits a greater reduction in a cardiovascular evet as compared to a subject of a high or a medium statin therapy. In some embodiments, the greater reduction is a reduction of at least about 5%, at least about 10%, at least about 20%, at least about 30%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 100%, or more.

[0186] In some embodiments, the present disclosure provides methods of delaying an onset of: (a) non-fatal myocardial infarction; (b) fatal or non-fatal stroke; (c) cardiovascular death; (d) unstable angina; (e) coronary revascularization; (f) hospitalization for unstable angina; (g) composite of cardiovascular death or nonfatal myocardial infarction; (h) fatal or nonfatal myocardial infarction; (i) non-elective coronary revascularization represented the composite of emergent or urgent classifications; (j) cardiovascular death; (k) unstable angina determined to be caused by myocardial ischemia by invasive or non invasive testing and requiring emergent hospitalization; and/or (l) a composite of total mortality, nonfatal myocardial infarction, and/or nonfatal

stroke. An onset of a disease and/or cardiovascular event refers to a first appearance of a sign and/or symptom of the cardiovascular event. In some embodiments, delaying an onset of a cardiovascular event prevents the subject from experiencing the cardiovascular event and/or developing any further symptoms of the cardiovascular event. In some embodiments, the methods comprise administering a composition comprising eicosapentaenoic acid or derivative thereof per day.

[0187] In yet another embodiment, the present disclosure provides methods of reducing risk of occurrence of one or more components of a 3-point composite endpoint composed of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke in a subject on statin therapy or reducing risk occurrence of one or more components of a 5-point composite endpoint composed of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, coronary revascularization, or unstable angina requiring hospitalization in a subject on statin therapy. In some embodiments, each of the individual components of 3-point composite and 5-poinst composite endpoints is reduced. For example, each of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke are reduced within the combination. In some embodiments, the methods comprise administering a composition comprising eicosapentaenoic acid or derivative thereof per day. In some embodiments, the 3-point composite endpoint or the 5-point composite endpoint is reduced by at least about 20%, at least about 30%, at least about 40%, or at least about 50%. In some embodiments, each of the individual components of the 3-point composite endpoint or the 5-point composite endpoint is reduced by at least about 20%, at least about 30%, at least about 40%, or at least about 50%.

[0188] In another embodiment, the present disclosure provides methods of reducing a cardiovascular event, the methods comprising administering a composition comprises EPA or derivative thereof that is formulated such that when administered to the subject, the composition provides an amount of EPA or derivative thereof effective to achieve an efficacy equivalent dose to about a 4 g dose of EPA or derivative thereof but at a lower daily dose of EPA or derivative thereof. In some embodiments, the lower daily dose of the EPA or derivative thereof of is not more than about 3.8 g, not more than about 3.6 g, not more than about 3.4 g, not more than about 3.2 g, not more than about 3 g, not more than about 2.8 g, not more than about 2.6 g, or not more than about 2.5 g. In some embodiments, the lower daily dose of the EPA or derivative thereof is reduced by at least about 10%, at least about 20%, at least about 30%, at least about 40% in the subject as

compared to a baseline or placebo control. In one embodiment, administering the composition to the subject results in an improved pharmacokinetic profile in the subject as compared a control subject, wherein the subject and control subject are in either or fed or fasting state, and wherein the pharmacokinetic profile is defined by maximum serum concentration (C_{max}) and area under the curve (AUC). In some embodiments, the control subject is on a statin therapy and administered a placebo or other fatty acid composition such as Lovaza comprised of 365 mg of E-EPA and 375 mg of E-DHA.

[0189] In some embodiments, the present disclosure provides methods of reducing a cardiovascular event in a subject on a statin therapy, the methods comprising administering a composition comprising EPA or derivative thereof, wherein the subject does not experience an adverse event. Non-limiting examples of adverse events include back pain, nasopharyngitis, arthralgia, bronchitis, oedema peripheral, dyspnea, osteoarthritis, cataract, fatigue, constipation, musculoskeletal pain, gout, fall, type 2 diabetes mellitus, gastroesophageal reflux disease, insomnia, acute kidney injury, hepatic disorders, bleeding related disorders (e.g., gastrointestinal or central nervous system bleeding), newly diagnosed diabetes, newly diagnosed neoplasms (e.g., benign or malignant neoplasms), upper respiratory tract infection, chest pain, peripheral edema, pneumonia, influenza, urinary tract infection, cough, dizziness, pain in an extremity, angina pectoris, and anemia.

[0190] In yet another embodiment, the present disclosure provides methods of reducing a cardiovascular event in a subject on a statin therapy and less than about 65 years of age or greater than about 65 years of age, the method comprising administering to the subject a composition comprising EPA or derivative thereof. In some embodiments, the degree by which the cardiovascular event is reduced is dependent upon the age of the subject. For example, in some embodiments, the subject less than about 65 years of age exhibits a statistically significant reduction in a cardiovascular event as compared to a subject greater than about 65 years of age. Conversely, in some embodiments, the subject greater than about 65 years of age exhibits a statistically significant reduction in a cardiovascular event as compared to a subject less than about 65 years of age. As such, in some embodiments, the methods for reducing a cardiovascular event are correlated to the age of the subject.

[0191] In some embodiments, the present disclosure provides methods of reducing a cardiovascular event in a subject on a statin therapy, the methods comprising administering to the subject a self-emulsifying composition. In some embodiments, the self-emulsifying composition comprises at least one compound selected from the group consisting of an omega-3 fatty acid and derivative thereof (e.g., pharmaceutically acceptable salt and/or ester). In another embodiment, the composition comprises an emulsifier. In some embodiments, the emulsifier has a hydrophilic lipophilic balance (HLB) of at least about 10. Non-limiting examples of emulsifiers include polyoxyethylene hydrogenated castor oil, polyoxyethylene sorbitan fatty acid ester, polyoxyethylene castor oil, polyethylene glycol fatty acid ester, polyoxyethylene polyoxypropylene glycol, sucrose fatty acid ester, and lecithin. In another embodiment, the omega-3 fatty acids or derivative thereof are present in an amount of about 50% to about 95% by weight of the total weight of the composition or by weight of the total fatty acids of the total composition. In some embodiments, the omega-3 fatty acid is EPA and/or DHA. In some embodiments, the EPA is present in amount at least about 95%, by weight, of all fatty acids present in the self-emulsifying composition. In another embodiment, the composition contains substantially no DHA. In yet another embodiment, the composition contains substantially no ethanol.

[0192] In some embodiments, the subject has symptoms of atrial fibrillation and/or flutter. Non-limiting examples of symptoms of atrial fibrillation and/or flutter include heart rate greater than about 100 beats per minute (bpm); heart palpitations; shortness of breath; pain, pressure, tightness or discomfort in chest; dizziness; lightheadedness; or fainting. In some embodiments the subject has a risk factor for atrial fibrillation and/or flutter including (a) heart failure; (b) previous heart attack; (c) heat valve abnormalities; (d) high blood pressure; (e) thyroid dysfunction; (f) chronic lung disease; (g) diabetes; (h) obesity; and (i) congenital heart disease.

[0193] In some embodiments, the methods further comprising monitoring a subject for atrial fibrillation and/or flutter or for symptoms of atrial fibrillation and/or flutter. Non-limiting examples for methods to monitor atrial fibrillation and/or flutter include electrocardiograms (ECGs), implantable pacemakers, implantable cardioverter defibrillators, and/or subcutaneous implantable cardiac monitors.

[0194] In some embodiments, the subject has atrial fibrillation and/or flutter or has symptoms of atrial fibrillation and/or flutter and has been determined to have a heart rate of about 80 bpm, about 85, bpm, about 90 bpm, about 95 bpm, about 100 bpm, about 105 bpm, about 110 bpm, about 115 bpm, about 120 bpm, about 125 bpm, about 130 bpm, about 135 bmp, about 140 bmp, about 145 bmp, about 150 bpm, about 155 bpm, about 160 bpm, about 165 bpm, about 170 bpm, about 175 bpm, about 180 bpm, about 185, bpm, about 190 bpm or a heart rate between about 80 bpm to about 100 bpm, about 90 bpm to about 200 bpm, about 100 bpm to about 175 bpm, about 120 bpm to about 180 bpm, or about 85 bpm to about 200 bpm.

[0195] In some embodiments, the present disclosure provides methods of reducing blood pressure in a subject. In one embodiment, administration of 4 g per day of comprising EPA or derivative thereof (E-EPA) for a period at least 1, 2, 3 or 4 year reduces systolic blood pressure by at least about 1 mm Hg and reduces diastolic blood pressure aby at least about 0.5 mm Hg, compared to baseline or a placebo control subject.

[0196] In some embodiments, the subject has a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL, for example about 135 mg/dL to about 500 mg/dL, about 150 mg/dL to about 500 mg/dL, about 200 mg/dL to about 499 mg/dL or about 200 mg/dL to <500 mg/dL. In some embodiments, the subject has a fasting baseline triglyceride level of about 50 mg/dL to about 1500 mg/dL, for example about 50 mg/dL to about 1500 mg/dL, about 80 mg/dL to about 1500 mg/dL, about 50 mg/dL to about 190 mg/dl, about 80 mg/dL to about 190 mg/dl, about 190 mg/dL to about 250 mg/dL, about 250 mg/dL to about 1400 mg/dL. In one embodiment, the subject has a fasting baseline triglyceride level of about 80 mg/dL to about 1400 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 50 mg/dL, about 55 mg/dL, about 60 mg/dL, about 65 mg/dL, about 70 mg/dL, about 75 mg/dL, about 80 mg/dL, about 85 mg/dL, about 90 mg/dL, about 95 mg/dL, about 100 mg/dL, about 105 mg/dL, about 110 mg/dL, about 115 mg/dL, about 120 mg/dL, about 125 mg/dL, about 130 mg/dL, about 135 mg/dL, about 140 mg/dL, about 145 mg/dL, about 150 mg/dL, about 155 mg/dL, about 160 mg/dL, about 165 mg/dL, about 170 mg/dL, about 175 mg/dL, about 180 mg/dL, about 185 mg/dL, about 190 mg/dL, about 195 mg/dL, about 200 mg/dL, about 205 mg/dL, about 210 mg/dL, about 215 mg/dL, about 220 mg/dL, about

225 mg/dL, about 230 mg/dL, about 235 mg/dL, about 240 mg/dL, about 245 mg/dL, about 250 mg/dL, about 255 mg/dL, about 260 mg/dL, about 265 mg/dL, about 270 mg/dL, about 275 mg/dL, about 280 mg/dL, about 285 mg/dL, about 290 mg/dL, about 295 mg/dL, about 300 mg/dL, about 305 mg/dL, about 310 mg/dL, about 315 mg/dL, about 320 mg/dL, about 325 mg/dL, about 330 mg/dL, about 335 mg/dL, about 340 mg/dL, about 345 mg/dL, about 350 mg/dL, about 355 mg/dL, about 360 mg/dL, about 365 mg/dL, about 370 mg/dL, about 375 mg/dL, about 380 mg/dL, about 385 mg/dL, about 390 mg/dL, about 395 mg/dL, about 400 mg/dL, about 405 mg/dL, about 410 mg/dL, about 415 mg/dL, about 420 mg/dL, about 425 mg/dL, about 430 mg/dL, about 435 mg/dL, about 440 mg/dL, about 445 mg/dL, about 450 mg/dL, about 455 mg/dL, about 460 mg/dL, about 465 mg/dL, about 470 mg/dL, about 475 mg/dL, about 480 mg/dL, about 485 mg/dL, about 490 mg/dL, about 495 mg/dL, about 500 mg/dL, about 1000 mg/dL, about 1100 mg/dL, about 1200 mg/dL, about 1300 mg/dL, about 1400 mg/dL, about 1500 mg/dL, about 2000 mg/dL, about 2500 mg/dL, about 3000 mg/dL, about 3500 mg/dL, about 4000 mg/dL, about 4500 mg/dL, about 5000 mg/dL, or greater than about 5000 mg/dL. In some embodiments, the subject or subject group has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, greater than or equal to 80 mg/dL, greater than or equal to about 100 mg/dL, greater than or equal to about 120 mg/dL greater than or equal to about 150 mg/dL, greater than or equal to about 175 mg/dL, greater than or equal to about 250 mg/dL, or greater than equal to about 500 mg/dL, for example about 190 mg/dL to about 250 mg/dL, about 80 mg/dL to about 190 mg/dL, about 250 mg/dL to about 1400 mg/dL, about 200 mg/dL to about 500 mg/dL, about 300 mg/dL to about 1800 mg/dL, about 500 mg/dL to about 1500 mg/dL, or about 80 mg/dL to about 1500 mg/dL.

[0197] 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.

[0198] In some embodiments, the statin therapy is classified as monotherapies, combinations, and or 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG CoA) reductase inhibitor combinations. In some embodiments, the monotherapies include simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin, or pitavastatin. In some embodiments, the combinations include lovastatin and nicotinic acid, simvastatin and ezetimibe, pravastatin and fenofibrate, simvastatin and fenofibrate, atorvastatin and ezetimibe, or rosuvastatin and ezetimibe. In some embodiments, the HMG CoA inhibitor combinations include simvastatin and acetylsalicylic acid; pravastatin and acetylsalicylic acid; atorvastatin and amlodipine; simvastatin, acetylsalicylic acid, and ramipril; rosuvastatin and acetylsalicylic acid; atorvastatin, acetylsalicylic acid, and ramipril; rosuvastatin, amlodipine, and lisinopril; atorvastatin and acetylsalicylic acid; rosuvastatin and amlodipine; rosuvastatin and valsartan; atorvastatin, amlodipine, and perindopril; atorvastatin, acetylsalicylic acid, and perindopril; rosuvastatin, perindopril, and indapamide; rosuvastatin, amlodipine, and perindopril; or atorvastatin and perindopril.

[0199] In some embodiments, the statin therapy is a low, medium (i.e., moderate), or high intensity statin therapy. In some embodiments, the low intensity statin therapy includes about 5 mg to about 10 mg of simvastatin. In some embodiments, the medium intensity statin therapy includes about 5 mg to about 10 mg of rosuvastatin, about 10 mg to about 20 mg of atorvastatin, about 20 mg to about 40 mg of simvastatin, or about 10 mg to about 20 mg of simvastatin plus about 5 mg to about 10 mg of ezetimibe. In some embodiments, the high intensity statin therapy includes about 20 mg to about 40 mg rosuvastatin, about 40 mg to about 80 mg of atorvastatin, about 80 mg of simvastatin, or about 40 mg to about 80 mg of simvastatin plus about 5 mg to about 10 mg of ezetimibe.

[0200] 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.

[0201] In some embodiments, the subject has established cardiovascular (CV) 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).

[0202] In some embodiments, the subject or subject group being treated in accordance with methods of the disclosure has a high risk for developing CV disease. For example and without limitation, a subject or subject group has a high risk for developing CV disease if the subject or subject in a subject group is age about 50 or older, has diabetes mellitus (Type 1 or Type 2), and at least one of: (a) is a male age about 55 or older or a female age about 65 or older; (b) is a cigarette smoker or was a cigarette smoker who stopped less than about 3 months prior; (c) has hypertension (e.g., a blood pressure of about 140 mmHg systolic or higher, or greater than about 90 mmHg diastolic); (d) has an HDL-C level of ≤ about 40 mg/dL for men or ≤ about 50 mg/dL for women; (e) has an hsCRP level of > about 3.0 mg/L; (f) has renal dysfunction (e.g., a creatinine clearance ("CrCL") of greater than about 30 mL/min and less than about 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 ≥ about 2.5 mg/mmol, or an albumin excretion rate on timed collection of ≥ about 20 mg/min all on at least two successive occasions); (i) has macroalbuminuria (e.g., Albustix or other dip stick

evidence of gross proteinuria, an albumin/creatinine ratio of ≥ about 25 mg/mmol, or an albumin excretion rate on timed collection of ≥ about 200 mg/min all on at least two successive occasions); and/or (j) has an ankle-brachial index of < about 0.9 without symptoms of intermittent claudication.

[0203] In some embodiments, the subject's baseline lipid profile is measured or determined prior to administering the 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 mg/dL to about 30 mg/dL; a baseline LDL-C value of about 40 mg/dL to about 100 mg/dL; and/or a baseline hsCRP level of about 2 mg/dL or less.

[0204] 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; sudden cardiac death, sudden death, and onset of new congestive heart failure. In some embodiments, the cardiovascular event is a first, second, third, fourth, or more cardiovascular event experienced by the subject.

[0205] In some embodiments, the subject is administered about 1 g to about 4 g of the composition per day for about 4 months, about 1 year, about 1.25 years, about 1.5 years, about 1.75 years, about 2 years, about 2.25 years, about 2.5 years, about 2.75 years, about 3 years, about 3.25 years, about 3.5 years, about 3.75 years, about 4 years, about 4.25 years, about 4.5 years, about 4.75 years, about 5 years, or more than about 5 years. Thereafter, in some embodiments the subject exhibits one or more of

[0206] (a) a reduction in triglyceride levels compared to baseline or control;

[0207] (b) a reduction in Apo B levels compared to baseline or control;

[0208] (c) an increase in HDL-C levels compared to baseline or control;

[0209] (d) no increase or increase in LDL-C levels compared to baseline or control;

[0210] (e) a reduction in LDL-C levels compared to baseline;

[0211] (f) a reduction in non-HDL-C levels compared to baseline or control;

[0212] (g an increase in non-HDL-C levels compared to baseline or control;

[0213] (h) a reduction in VLDL-C levels compared to baseline or control;

[0214] (i) a reduction in total cholesterol levels compared to baseline or control;

[0215] (j) a reduction in high sensitivity C-reactive protein (hsCRP) levels compared to baseline or control;

[0216] (k) a reduction in high sensitivity troponin (hsTnT) levels compared to baseline or control;

[0217] (l) a reduction in a risk of cardiovascular death, coronary revascularization, unstable angina, myocardial infarction, and/or stroke as compared to baseline or control;

[0218] (m) a reduction in a risk of cardiac arrest as compared to baseline or control;

[0219] (n) a reduction in a risk of sudden death as compared to baseline or control;

[0220] (o) a reduction in a first, second, third, fourth, or more cardiovascular event as compared to baseline or placebo control;

[0221] (p) a reduction in total cardiovascular events as compared to baseline or control;

[0222] (q) a reduction in a 3-point composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke as compared to baseline or control;

[0223] (r) a reduction in a 5-point composite endpoint of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, coronary revascularization, or unstable angina as compared to baseline or control;

[0224] (s) an increase in atrial fibrillation and/or flutter as compared to baseline or control;

[0225] (t) an increase in symptoms of atrial fibrillation and/or flutter as compared to baseline or control;

[0226] (u) a reduction of total mortality (i.e., death from any cause) as compared to baseline or control;

[0227] (v) a reduction in a composite of total mortality, non-fatal myocardial infarction, and stroke as compared to baseline or placebo control;

[0228] (w) a reduction in new congestive heart failure (CHF) or new CHF as the primary cause of hospitalization as compared to baseline or control;

[0229] (x) a reduction in transient ischemic attack as compared to baseline or control;

[0230] (y) a reduction in a risk of amputation for peripheral vascular disease (PVD) as compared to baseline or control;

[0231] (z) a reduction in a risk of carotid revascularization as compared to baseline or control;

[0232] (aa) a reduction in cardiac arrhythmias as compared to baseline or control;

[0233] (bb) a reduction in hypertension as compared to baseline or control;

[0234] (cc) a reduction in type 1 or type 2 diabetes as compared to baseline or control;

[0235] (dd) a reduction in body weight and/or weight circumference as compared to baseline or control; and/or

[0236] (ee) a reduction in eGFR levels as compared to baseline or control

[0237] In one embodiment, methods of the present disclosure comprise measuring baseline levels of one or more markers set forth in (a) – (ee) above prior to dosing the subject or subject group. In another embodiment, the methods comprise administering a composition as disclosed herein to the subject after baseline levels of one or more markers set forth in (a) – (ee) are determined, and subsequently taking an additional measurement of said one or more markers.

[0238] In another embodiment, upon treatment with a composition of the present disclosure, the subject exhibits one or more of:

[0239] (a) a reduction in triglyceride levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least

about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 55% as compared to baseline or control;

[0240] (b) a reduction in Apo B levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% as compared to baseline or control;

[0241] (c) an increase in HDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% as compared to baseline or control;

[0242] (d) no increase or an increase in LDL-C levels of less than 30%, less than 20%, less than 10%, less than 5% as compared to baseline or control; and/or

[0243] (e) a reduction in LDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 55% as compared to baseline or control.

[0244] (f) a reduction in non-HDL-C levels of at least about 1%, at least about 3%, at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50% as compared to baseline or control;

[0245] (g) an increase in non-HDL-C levels of less than 30%, less than 20%, less than 10%, less than 5% (actual % change or median % change), or no increase in non-HDL-C levels as compared to baseline or control;

[0246] (h) a reduction in VLDL-C levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% compared to baseline or control;

[0247] (i) a reduction in total cholesterol levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55% or at least about 75% as compared to baseline or control; and/or

[0248] (j) a reduction in hsCRP levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% as compared to baseline or control;

[0249] (k) a reduction in high sensitivity troponin (hsTnT) levels of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, or at least about 100% as compared to baseline or control;

[0250] (l) a reduction in a risk of cardiovascular death, coronary revascularization, unstable angina, myocardial infarction, and/or stroke of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0251] (m) a reduction in a risk of cardiac arrest of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0252] (n) a reduction in a risk of sudden cardiac death and/or sudden death of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0253] (o) a reduction in a first, second, third, fourth, or more cardiovascular event experienced by the subject of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0254] (p) a reduction in total cardiovascular events of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0255] (q) a reduction in a 3-point composite endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0256] (r) a reduction in a 5-point composite endpoint of cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, coronary revascularization, or unstable angina of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0257] (s) an increase in atrial fibrillation and/or flutter of at least about 1%, at least about 1.5%, at least about 2%, at least about 2.5%, at least about 3%, at least about 3.5%, at least about 4%, at least about 4.5%, at least about 5%, at least about 5.5%, at least about 6%, at least about 6.5%, at least about 7%, at least about 7.5%, at least about 8%, at least about 8.5%, at least about 9%, at least about 9.5%, or at least about 10% as compared to baseline or control;

[0258] (t) an increase in symptoms of atrial fibrillation and/or flutter of at least about 1%, at least about 1.5%, at least about 2%, at least about 2.5%, at least about 3%, at least about 3.5%, at least about 4%, at least about 4.5%, at least about 5%, at least about 5.5%, at least about 6%, at least about 6.5%, at least about 7%, at least about 7.5%, at least about 8%, at least about 8.5%, at least about 9%, at least about 9.5%, or at least about 10% as compared to baseline or control;

[0259] (u) a reduction of total mortality (i.e., death from any cause) of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0260] (v) a reduction in a composite of total mortality, non-fatal myocardial infarction, and stroke of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0261] (w) a reduction in new CHF or new CHF as the primary cause of hospitalization of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0262] (x) a reduction in transient ischemic attack of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0263] (y) a reduction in a risk of amputation for PVD of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0264] (z) a reduction in a risk of carotid revascularization of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about

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

[0265] (aa) a reduction in cardiac arrhythmias of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0266] (bb) a reduction in hypertension of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0267] (cc) a reduction in type 1 or type 2 diabetes of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control;

[0268] (dd) a reduction in body weight and/or weight circumference of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control; and/or

[0269] (ee) a reduction in body weight and/or weight circumference of at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, or at least about 100% as compared to baseline or control.

[0270]

[0271] 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.

[0272] In another embodiment, the subject or subject group being treated has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of about 135 mg/dL to about 500 mg/dL. In some embodiments, the subject or subject group being treated has a baseline triglyceride level (or median baseline triglyceride level in the case of a subject group), fed or fasting, of about 80 mg/dL to about 1500 mg/dL. In some embodiments, the subject or subject group being treated in accordance with methods of the disclosure is on stable therapy with a statin (with or without ezetimibe). As used herein, the phrase "on stable therapy with a statin" means that the subject or subject group has been on the same daily dose of the same statin for at least 28 days and, if applicable, the same daily dose of ezetimibe for at least 28 days. In some embodiments, the subject or subject group on stable statin therapy has an LDL-C level of about 40 mg/dL to about 100 mg/dL.

[0273] 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}.

[0274] 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.

[0275] In some embodiments, a biomarker assay associated with blood obtained from a subject includes hsCRP, Apo B and hsTnT.

[0276] 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.

[0277] In some embodiments, demographic information associated with a subject includes day, month and year of birth, race, and gender.

[0278] 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).

[0279] 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.

[0280] 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.

[0281] 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.

[0282] 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.

[0283] 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.

[0284] In some embodiments, the present disclosure provides a method of reducing a risk of cardiovascular events in a subject. In some embodiments, the method comprises administering to the subject a composition comprising at least 96% by weight of eicosapentaenoic acid ethyl ester. In some embodiments, the subject is administered about 1 g to about 4 g of the composition per day.

[0285] 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.

[0286] In some embodiments, the present disclosure provides a method of reducing risk of CV death in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

[0287] In another embodiment, the present disclosure provides a method of reducing risk of recurrent nonfatal myocardial infarction (including silent MI) in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the patient one or more compositions as disclosed herein.

[0288] In some embodiments, the present disclosure provides a method of reducing risk of nonfatal stroke in a subject on stable statin therapy and having CV disease or at

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

[0289] In some embodiments, the present disclosure provides a method of reducing risk of coronary revascularization in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

[0290] In some embodiments, the present disclosure provides a method of reducing risk of developing unstable angina caused by myocardial ischemia in a subject on stable statin therapy and having CV disease or at high risk for developing CV disease, comprising administering to the subject a composition as disclosed herein.

[0291] In some embodiments, the present disclosure provides a method of reducing risk of cardiac arrest 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.

[0292] In some embodiments, the present disclosure provides a method of reducing risk of sudden cardiac death and/or sudden 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.

[0293] In some embodiments, the present disclosure provides a method of reducing risk of first, second, third, fourth, or more cardiovascular event 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

[0294] In another embodiment, any of the methods disclosed herein are used in treatment or prevention of a subject or subjects that consume a traditional Western diet. In one embodiment, the methods of the disclosure include a step of identifying a subject as a Western diet consumer or prudent diet consumer and then treating the subject if the subject is deemed a Western diet consumer. The term "Western diet" herein refers generally to a typical diet consisting of, by percentage of total calories, about 45% to about 50% carbohydrate, about 35% to about 40% fat, and about 10% to about 15% protein. A Western diet may alternately or additionally be characterized by relatively high intakes of red and processed meats, sweets, refined grains, and desserts, for example

more than 50%, more than 60% or more or 70% of total calories come from these sources.

[0295] 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.

[0296] 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 composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester per day.

[0297] 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 80 mg/dL to about 1500 mg/dL, and has established cardiovascular disease or a high risk of developing cardiovascular disease, and wherein the control subjects are not administered the composition comprising about 1 g to about 4 g of eicosapentaenoic acid ethyl ester per day.

[0298] 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. In some embodiments, the first cardiovascular event of the subject and the first cardiovascular event of the control subjects is sudden cardiac death and/or sudden death.

[0299] In some embodiments, a second time interval beginning at (a) an initial administration of the 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. In some embodiments, the major cardiovascular event(s) is further selected from the group consisting of: cardiac arrest, sudden cardiac death, and/or sudden death.

[0300] 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.

[0301] 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 (hsCRP) levels compared to the control population; and/or (j) a reduction in high sensitivity troponin (hsTnT) levels compared to the control population.

[0302] 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.

[0303] In methods of the present disclosure in which a time interval is determined or assessed, the time interval may be for example an average, a median, or a mean time interval. For example, in embodiments wherein a first control time interval is associated with a plurality of control subjects, the first control time interval is an average, a median, or a mean of a plurality of first control time intervals associated with each control subject. Similarly, in embodiments wherein a second control time interval is associated with a plurality of control subjects, the second control time interval is an average, a median, or a mean of a plurality of second control time intervals associated with each control subject.

[0304] 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.

[0305] In another embodiment, the disclosure provides use of any composition described herein for treating hypertriglyceridemia in a subject in need thereof, comprising: providing a subject having a fasting baseline triglyceride level of about 135 mg/dL to about 500 mg/dL and administering to the subject a 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.

[0306] In yet another embodiment, the disclosure provides use of any composition described herein for treating hypertriglyceridemia in a subject in need thereof, comprising: providing a subject having a fasting baseline triglyceride level of about 80 mg/dL to about 1500 mg/dL and administering to the subject a 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

EXAMPLE 1: Impact of Icosapent Ethyl on Reducing Cardiovascular Events in High Risk Statin-Treated Patients

[0307] Among patients with cardiovascular risk factors who are receiving treatment for secondary or primary prevention, the rates of cardiovascular events remain high. Even in patients receiving appropriate treatment with statins, a substantial residual cardiovascular risk remains. In such patients, an elevated triglyceride level serves as an independent marker for increased ischemic risk, as shown in epidemiological and mendelian randomization studies. In randomized trials, medications that reduce triglycerides, such as extended-release niacin and fibrates, have not reduced the rates of cardiovascular events when administered in addition to appropriate medical therapy, including statins. Further, contemporary trials and recent meta-analyses of omega-3 fatty acid products have not shown benefit in patients receiving statin therapy. Accordingly, the objective of the present study was to determine if and how icosapent ethyl (referenced interchangeably with AMR101 or VASCEPA®) reduced cardiovascular events in patients with elevated triglyceride levels on a statin therapy.

[0308] The following study, also referred to as the REDUCE-IT clinical trial, was a large cardiovascular (CV) outcome trial designed to assess CV risk reduction benefit of AMR101 treatment (commercially known as VASCEPA®) versus placebo on the 5-point primary composite endpoint: CV death, non-fatal stroke, non-fatal myocardial infarction (MI), coronary revascularizations, or unstable angina requiring hospitalization.

[0309] A multi-center, prospective, randomized, double-blind, placebo-controlled, parallel-group study was performed to evaluate the effect of AMR101 (4g per day) on

cardiovascular health and mortality in hypertriglyceridemic patients with cardiovascular disease or at high risk for cardiovascular disease. The intended expanded indication of the study was treatment with AMR101 as an add-on to statin therapy to reduce the risk of cardiovascular events in patients with clinical cardiovascular disease or with multiple risk factors for cardiovascular disease.

[0310] The primary objective of this study was, in patients at LDL-C goal while on statin therapy, with established cardiovascular disease (CVD) or at high risk for CVD, and hypertriglyceridemia (e.g., fasting triglycerides(TG) ≥ 200 mg/dL and < 500 mg/dL), to evaluate the effect of AMR101 4 g daily on time from randomization to first occurrence of any component of the composite of the following major CV events: CV death; nonfatal MI; (including silent MI; electrocardiograms (ECGs) were performed annually for the detection of silent MIs); nonfatal stroke; coronary revascularization; and unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.

[0311] The key secondary objective of this study was to evaluate the effect of AMR101 4 g daily on the time from randomization to the first occurrence of the composite of following major CV events: CV death, nonfatal MI (including silent MI), and nonfatal stroke.

[0312] Other secondary objectives for this study were to evaluate the effect of therapy on time from randomization to the first occurrence of the following individual or composite endpoints: composite of CV death or nonfatal MI (including silent MI); fatal or nonfatal MI (including silent MI); non-elective coronary revascularization represented as the composite of emergent or urgent classifications; CV death; unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization; fatal or nonfatal stroke; composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke; and total mortality.

[0313] The key tertiary objectives for this study were to evaluate the effect of AMR101 4 g daily from baseline and percent change from baseline in fasting triglycerides and LDL-C. Other tertiary objectives for this study were to evaluate the effect of therapy on the following in addition to supporting efficacy and safety analyses:

- Total CV events analysis defined as the time from randomization to occurrence of the first and all recurrent major CV events defined as CV death, nonfatal MI

(including silent MI), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;

- Primary composite endpoint in the subset of patients with diabetes mellitus at baseline;
- Primary composite endpoint in the subset of patients with metabolic syndrome at baseline as defined with waist circumference of ≥ 35 inches (88 cm) for all women and Asian, Hispanic, or Latino men, and ≥ 40 inches (102 cm) for all other men;
- Primary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 fasting blood glucose (FBG) of 100-125 mg/dL);
- Key secondary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG 100-125 mg/dL);
- Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalization of ≥ 24 hours, or cardiac arrest;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or peripheral vascular disease (PVD) requiring intervention, such as angioplasty, bypass surgery, or aneurism repair;
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, PVD requiring intervention, or cardiac arrhythmia requiring hospitalization of ≥ 24 hours;

- New congestive heart failure (CHF);
- New CHF as the primary cause of hospitalization;
- Transient ischemic attack (TIA);
- Amputation for PVD;
- Carotid revascularization;
- All coronary revascularizations defined as the composite of emergent, urgent, elective, or salvage;
- Emergent coronary revascularizations;
- Urgent coronary revascularizations;
- Elective coronary revascularizations;
- Salvage coronary revascularizations;
- Cardiac arrhythmias requiring hospitalization of ≥24 hours;
- Cardiac arrest;
- Ischemic stroke;
- Hemorrhagic stroke;
- Fatal or nonfatal stroke in the subset of patients with a history of stroke prior to baseline;
- New onset diabetes, defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period;
- New onset hypertension, defined as blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic newly diagnosed during the treatment/follow-up period;
- Fasting triglycerides (TG), total cholesterol (TC), low dense lipoprotein cholesterol (LDL-C), high dense lipoprotein cholesterol (HDL-C), non-dense lipoprotein cholesterol (non-HDL-C), very low dense lipoprotein cholesterol (VLDL-C), apolipoprotein B (apo B), high sensitivity-C reactive protein (hsCRP and log[hsCRP]), high-sensitivity troponin (hsTnT), and remnant like particle cholesterol (RLP-C; were estimated from standard lipid panel, RLP-C = TC – HDL-C – LDL-C [Varbo 2014]), (based on ITT estimands):

- Assessment of the relationship between baseline biomarker values and treatment effects within the primary and key secondary endpoints;
- Assessment of the effect of AMR101 on each marker; and
- Assessment of the relationship between post-baseline biomarker values and treatment effects within the primary and key secondary composite endpoints by including post-baseline biomarker values (for example, at 4 months, or at 1 year) as a covariate.

- Change from baseline and percent change from baseline in fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hsCRP, hsTnT, and RLP-C;
- Change in body weight; and
- Change in waist circumference.

Study Population

[0314] The population for this study were men and women ≥45 years of age with established CVD, or men and women ≥50 years of age with diabetes in combination with one additional risk factor for CVD. In addition, all patients had atherogenic dyslipidemia defined as on treatment for hypercholesterolemia (but at treatment goal for LDL-C, by treatment with a statin) and hypertriglyceridemia. More details regarding the patient population are listed in the inclusion criteria below. The patients needed to provide consent to participate in the study and were willing and able to comply with the protocol and the study procedures.

Study Periods

[0315] This study consisted of the following study periods:

[0316] Screening Period: During the screening period, patients were evaluated for inclusion and exclusion criteria.

[0317] At the first visit to the Research Unit (Visit 1), study procedures were performed for evaluation of patient's eligibility in the study. At this screening visit, patients signed an informed consent form before any study procedure was performed; the informed consent form covered the treatment/follow-up period. Based on the evaluation from Visit 1, the following situations occurred:

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

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

[0318] At the end of the screening period, patients needed to meet all inclusion and exclusion criteria before they were randomized. Patients who were not eligible for participation after the screening period (based on study procedures at Visit 1 and/or Visit 1.1) could return at a later date for rescreening. These patients needed to re-start with all procedures starting with Visit 1. This included patients who need more time to stabilize one or more conditions or therapies (for example: statin, antidiabetic, antihypertensive, thyroid hormone, HIV-protease inhibitor therapy).

[0319] Treatment/Follow-Up Period: Within 42 days after the first screening visit (Visit 1) or within 60 days after the first screening visit (Visit 1) for those patients that had a second screening visit (Visit 1.1), eligible patients entered the treatment/follow-up period. During this period, the patients received study drug during the planned visits at the Research Site and took the study drug while away from the Research Site.

[0320] During the visits, study procedures were performed for evaluation of efficacy and safety. A detailed schedule of the procedures is provided below in Table 1.

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	2160 ± 10	Last Visit (LV)[15]
Months of FU			0	4	12	24	36	48	60	72	Varies
Years of FU			0	0.33	1	2	3	4	5	6	Varies
Visit #	1	1.1	2	3	4	5	6	7	8	9[14]	LV
Study Procedures:											

Informed Consent	X										
Medical, Surgical & Family History	X										
Demographics	X										
Evaluate inclusion / exclusion criteria	X[1]	X[3]	X								
Physical Examination			X	X	X	X	X	X	X	X	X
Weight, Height[4]	X		X	X	X	X	X	X	X	X	X
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X	X
Waist Circumference			X			X					X
12-Lead ECG	X		X		X	X	X	X	X	X	X
Urine pregnancy test[6]	X		X								
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X
Randomization			X								
Dosing at the Research Site[7]			X	X	X	X	X	X	X	X	
Efficacy events				X	X	X	X	X	X	X	X
AE Evaluations			X	X	X	X	X	X	X	X	X
Compliance Check[8]				X	X	X	X	X	X	X	X
Chemistry and hematology[9]	X	X[3]	X	X	X	X	X	X	X	X	X
Fasting lipid profile[10]	X	X[3]	X	X	X	X	X	X	X	X	X

Genetic testing[11]			X								
Biomarkers: hsCRP, apo B, hsTNT			X			X					X
Fasting blood sample for archiving [12]			X		X	X	X	X	X	X	X

[1] Includes procedures and (fasting) blood samples (for example, hsCRP, calculated creatinine clearance) as needed to determine the CV risk category (see inclusion criteria).
[2] Screening visit to re-evaluate inclusion/exclusion criteria for patients who were not eligible for participation based on data from Visit 1.
[3] Inclusion/exclusion criteria were re-evaluated for selected study procedures that were performed on Visit 1.1 because patients failed to meet them at Visit 1.
[4] Height at first screening visit only.
[5] Vital signs, including systolic and diastolic blood pressure (mmHg), heart rate, respiratory rate and body temperature. Participants were seated for at least 5 minutes before assessments of vital signs.
[6] For women of childbearing potential.
[7] The patients fasted at least 10 hours before arriving at the Research Site, when all fasting blood samples were obtained. After blood samples were obtained, patients were given drug with food.
[8] Review study drug compliance by unused capsule count, discussed with and counseled patients about compliance if needed; final study compliance at last visit.
[9] Safety Laboratories — Complete Blood Count: Included RBC, Hgb, Hct, WBC and differential, and platelet count. Biochemistry includes total protein, albumin, alkaline phosphatase, ALT, AST, total bilirubin, glucose, calcium, electrolytes (sodium, potassium, chloride), blood urea nitrogen (BUN), serum creatinine, uric acid, creatine kinase, HbA1c. Safety labs were repeated as deemed necessary by the Investigator.
[10] TG, TC, HDL-C, LDL-C, non-HDL-C, and VLDL-C.
[11] Fasting blood sample were stored for future genetic testing at the discretion of the Sponsor. This sample was optional as local regulations may prohibit genetic samples to be collected or shipped outside the country, or patients may not have consented.
[12] Used at the Sponsor's discretion to perform repeat analyses described in the protocol or to perform other tests related to cardiovascular health.
[13] Site personnel contacted each patient by telephone in-between Visit 2 and Visit 3 and between Visit 3 and Visit 4. After Visit 4 contact was made every 3 months. The purpose of the contact was to collect information about efficacy events, adverse events, concomitant medications, confirm patient's current address and contact information and remind patients about taking their study medication and logistics for the next visit.
[14] Office visits continued at 360-day intervals and phone visits at 90-day intervals until study end date was determined.
[15] The last visit (LV) could have occurred within 30 days after the study end date as determined by the DMC; the study end date is tentatively schedule for Day 2160 but the actual date was determined by the DMC may be different.

Study Duration

[0321] Patients were randomized at different times during the enrollment period but all ended the study at approximately the same date (i.e., at the study end date) and, therefore, the duration of follow-up differed based on date of randomization. It was planned that all randomized patients received study medication and were followed-up until the study end date. It was expected that a minimum of approximately 1612 primary endpoint events were required during the study. 8179 patients were randomized at multiple Research Sites worldwide over a period of approximately 4.2 years. After randomization, patients were treated and followed up to an estimated maximum of 6.5 years. The study end date was determined to be when approximately 1612 primary

efficacy events had been adjudicated. Table 2 shows the study milestones from the first patient screened to the last patient visit and subsequent database lock.

Table 2. Study Milestones

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

Study Groups

[0322] At Visit 2 (Day 0), eligible study patients were randomly assigned to the following treatment groups:

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

[0323] The four AMR101 or placebo capsules daily were taken as two capsules in the morning and two capsules in the evening (twice-per-day dosing regimen).

Number of Patients

[0324] This was an event-driven trial and it was expected that a minimum of 1612 primary efficacy endpoint events were required during the study. A total of approximately 8179 patients entered into the study to either receive AMR101 or placebo (approximately 4089 patients per treatment group) in order to observe an estimated 1612 events that made up the primary composite endpoint for efficacy.

Randomization

[0325] On Day 0, eligible patients were randomized to one of the 2 study groups using a computer-generated randomization schema. Randomized treatment assignment to either AMR101 or placebo in a 1:1 ratio was provided using the internet (IWR).

Blinding

[0326] This was a double-blind study. Patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors supporting the study were unaware of the randomization code (i.e., they did not know which study participants were receiving the experimental drug and which were receiving the placebo drug). The study medication AMR101 and placebo capsules were similar in size and appearance to maintain blinding.

[0327] During the double-blind treatment/follow-up period, everyone (patients, investigators, pharmacists and other supporting staff at the Research Sites, personnel and designees of the Sponsor, study administrators and personnel at the organization(s) and vendors managing/supporting the study), with the exception of the laboratory personnel performing the analysis, were blinded to individual results of the efficacy laboratory measurements (including lipid values). Individual results from the lipid profile could be unblinded in the event of an emergency for a patient.

Stratification

[0328] Participants were assigned to treatment groups stratified by CV risk category, use of ezetimibe and by geographical region (e.g., Westernized, Eastern European, and Asia Pacific countries). There were two CV risk categories:

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

[0329] Stratification was recorded in the IWR at the time of enrollment. Approximately 70% of randomized patients were in the CV Risk Category 1 and approximately 30% of randomized patients were in the CV Risk Category 2. Enrollment

with patients of a CV risk category was stopped when the planned number of patients in that risk category was reached.

Study Population

[0330] Inclusion Criteria. A detailed list of the inclusion criteria for this study is provided in Tables 3-5. Specifically, Table 3 outlines the inclusion criteria for patients in this study whereas Tables 4 and 5 further outline the inclusion criteria based on whether that patient is part of the primary prevention risk category or the secondary prevention risk category of patients, respectively.

Table 3. Patient Inclusion Criteria for this Study

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

[0331] Stable therapy was defined as the same daily dose of the same statin for at least 28 days before the lipid qualification measurements (TG and LDL-C) and, if applicable, the same daily dose of ezetimibe for at least 28 days before the lipid qualification measurements (TG and LDL-C). Patients who had their statin therapy or use of ezetimibe initiated at Visit 1, or had their statin, statin dose and/or ezetimibe dose changed at Visit 1, needed to go through a stabilization period of at least 28 days since initiation/change and had their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1). Statins may have been administered with or without ezetimibe.

[0332] If patients qualified at the first qualification visit (Visit 1) for TG and LDL-C, and met all other inclusion/exclusion criteria, they were randomized at Visit 2. If patients did not qualify at the first qualifying visit (Visit 1), a second re-qualifying visit (Visit 1.1) was allowed. For some patients, because they needed to stabilize medications and/or needed to washout medications, the second re-qualifying visit (Visit 1.1) was needed after the stabilization/washout period.

[0333] Women were not considered to be of childbearing potential if they met one of the following criteria as documented by the investigator: they had a hysterectomy, tubal ligation or bilateral oophorectomy prior to signing the informed consent form; and/or they were post-menopausal, defined as ≥ 1 year since their last menstrual period or have a follicle-stimulating hormone (FSH) level in a menopausal range.

[0334] Patients having established CVD (in CV Risk Category 1) were defined as detailed in Table 4.

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

Primary Prevention Risk Category (i.e., Secondary Prevention Cohort)	
Defined as men and women ≥45 years of age with one or more of the following:	
1	Documented coronary artery disease (CAD; one or more of the following primary criteria must be satisfied): a. Documented multi vessel CAD (≥50% stenosis in at least two major epicardial coronary arteries – with or without antecedent revascularization). b. Documented prior MI. c. Hospitalization for high-risk non-ST-segment elevation acute coronary syndrome (NSTE-ACS) (with objective evidence of ischemia: ST-segment deviation or biomarker positivity).
2	Documented cerebrovascular or carotid disease (one of the following primary criteria must be satisfied): a. Documented prior ischemic stroke. b. Symptomatic carotid artery disease with ≥50% carotid arterial stenosis. c. Asymptomatic carotid artery disease with ≥70% carotid arterial stenosis per angiography or duplex ultrasound. d. History of carotid revascularization (catheter-based or surgical).
3	Documented peripheral arterial disease (PAD; one or more of the following primary criteria must be satisfied): a. Ankle-brachial index (ABI) <0.9 with symptoms of intermittent claudication. b. History of aorto-iliac or peripheral arterial intervention (catheter-based or surgical).

[0335] Patients at high risk for CVD (in CV Risk Category 2) were defined as detailed in Table 5.

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

Secondary Prevention Risk Category (i.e., Primary Prevention Cohort)	
Defined as having each of the following:	
1	Diabetes mellitus (Type 1 or Type 2) requiring treatment with medication.
2	Men and women ≥50 years of age.
3	One of the following at Visit 1 (additional risk factor for CVD): a. Men ≥55 years of age and Women ≥65 years of age. b. Cigarette smoker or stopped smoking within 3 months before Visit 1. c. Hypertension (blood pressure ≥140 mmHg systolic OR ≥90 mmHg diastolic) or on antihypertensive medication. d. HDL-C ≤40 mg/dL for men or ≤50 mg/dL for women. e. HsCRP >3.00 mg/L (0.3 mg/dL). f. Renal dysfunction: Creatinine clearance (CrCL) >30 and <60 mL/min. g. Retinopathy, defined as any of the following: non-proliferative retinopathy, pre-proliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation. h. Micro- or macroalbuminuria. Microalbuminuria is defined as either a positive micral or other strip test (may be obtained from medical records), an albumin/creatinine ratio ≥2.5 mg/mmol or an albumin excretion rate on timed collection ≥20 mg/min all on at least two successive occasions; macroalbuminuria, defined as Albustix or other dipstick evidence of gross proteinuria, an albumin/creatinine ratio ≥25 mg/mmol or an albumin excretion rate on timed collection ≥200 mg/min all on at least two successive occasions. i. ABI <0.9 without symptoms of intermittent claudication (patients with ABI <0.9 with symptoms of intermittent claudication are counted under Secondary Prevention Risk Category).
Patients with diabetes and CVD as defined above are eligible based on the CVD requirements and will be counted under CV Risk Stratum 1. Only patients with diabetes and no documented CVD as defined above needed at least one additional risk factor as listed, and were counted under Primary Prevention Risk Category.	

[0336] Exclusion Criteria: Patients meeting the following exclusion criteria enumerated in Table 6 were not eligible for the study.

Table 6. Patient Exclusion Criteria for this Study

Study Exclusion Criteria	
1	Severe (New York Heart Association [NYHA] class IV) heart failure.

2	Any life-threatening disease expected to result in death within the next 2 years (other than CVD).
3	Diagnosis or laboratory evidence of active severe liver disease.
4	Hemoglobin A1c >10.0% (or 86 mmol/mol IFCC units) at screening (Visit 1). If patients failed this criterion (HbA1c >10.0% or 86 mmol/mol IFCC units) at Visit 1, they could have had their antidiabetic therapy optimized and be retested at Visit 1.1.
5	Poorly controlled hypertension: systolic blood pressure (SBP) ≥200 mmHg or diastolic blood pressure (DBP) ≥100 mmHg (despite antihypertensive therapy).
6	Planned coronary intervention or any non-cardiac major surgical procedure.
7	Known familial lipoprotein lipase deficiency (Fredrickson Type I), apolipoprotein C-II deficiency, or familial dysbetalipoproteinemia (Fredrickson Type III).
8	Participation in another clinical trial involving an investigational agent within 90 days prior to screening (Visit 1). Patients could not participate in any other investigational medication or medical device trial while participating in this study (participation in a registry or observational study without an additional therapeutic intervention was allowed).
9	Intolerance or hypersensitivity to statin therapy.
10	Known hypersensitivity to fish and/or shellfish, or ingredients of the study product or placebo.
11	History of acute or chronic pancreatitis.
12	Malabsorption syndrome and/or chronic diarrhea. (Note: patients who had undergone gastric/intestinal bypass surgery were considered to have malabsorption, hence were excluded; patients who had undergone gastric banding were allowed to enter the trial).
13	Use of non-study drug-related, non-statin, lipid-altering medications, dietary supplements, or foods during the screening period (after Visit 1) and/or plans for use during the treatment/follow-up period including: a. niacin >200 mg/day or fibrates during the screening period (after Visit 1) and/or planned to use during the study; patients who were taking niacin >200 mg/day or fibrates during the last 28 days before Visit 1 needed to go through washout of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (Visit 1.1). b. any omega-3 fatty acid medications (prescription medicines containing EPA and/or DHA) during the screening period (after Visit 1) and/or planned to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who were taking omega-3 fatty acid medications during the last 28 days before Visit 1 (except patients in The Netherlands), needed to go through a washout period of at least 28 days after their last use and have their qualifying lipids measured (TG and LDL-C) after the washout period (at Visit 1.1). However, for patients in the Netherlands only being treated with omega-3 fatty acid medications containing EPA and/or DHA were excluded and no washout was allowed. c. dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils) during the screening period (after Visit 1) and/or planned to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who were

	taking >300 mg/day omega-3 fatty acids (combined amount of EPA and DHA) within 28 days before Visit 1 (except patients in The Netherlands), needed to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1). However, for patients in the Netherlands only being treated with dietary supplements containing omega-3 fatty acids of >300 mg/day EPA and/or DHA were excluded and no washout was allowed. d. bile acid sequestrants during the screening period (after Visit 1) and/or planned to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients who were taking bile acid sequestrants within 7 days before Visit 1, needed to go through a washout period of at least 7 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1). e. proprotein convertase subtilisin kexin 9 (PCSK9) inhibitors during the screening period (after Visit 1) and/or planned to use during the treatment/follow-up period of the study. To be eligible for participation in the study, patients could not have taken a PCSK9 inhibitor within 90 days prior to their screening visit.
14	Other medications (not indicated for lipid alteration): a. Tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids (local, topical, inhalation, or nasal corticosteroids are allowed), HIV-protease inhibitors that have not been stable for ≥28 days prior to the qualifying lipid measurements (TG and LDL-C) during screening. To be eligible for participation in the study, patients who were not taking a stable dose of these medications within 28 days before Visit 1, needed to go through a stabilization period of at least 28 days since their last dose change and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1). b. Cyclophosphamide or systemic retinoids during the screening period (unless ≥28 day washout) and/or plans for use during the treatment/follow-up period. To be eligible for participation in the study, patients who were taking these medications within 28 days before Visit 1, needed to go through a washout period of at least 28 days since their last use and have their qualifying lipid measurements measured (TG and LDL-C) after the washout period (at Visit 1.1).
15	Known AIDS (HIV-positive patients without AIDS are allowed).
16	Requirement for peritoneal dialysis or hemodialysis for renal insufficiency or creatinine clearance <30 mL/min (0.50 mL/sec).
17	Unexplained elevated creatine kinase concentration >5 × ULN or elevation due to known muscle disease (e.g., polymyositis, mitochondrial dysfunction) at Visit 1.
18	Any condition or therapy which, in the opinion of the investigator, might pose a risk to the patient or make participation in the study not in the patient's best interest.
19	Drug or alcohol abuse within the past 6 months, and inability/unwillingness to abstain from drug abuse and excessive alcohol consumption during the study or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking).

	Excessive alcohol consumption was on average >2 units of alcohol per day. A unit of alcohol was defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.
20	Mental/psychological impairment or any other reason to expect patient difficulty in complying with the requirements of the study or understanding the goal and potential risks of participating in the study (evaluated at Visit 1).

Study Procedures

[0337] The Screening Period for this study included two visits, Visit 1 and Visit 1.1.

[0338] Screening Visit (Visit 1): During Visit 1, patients came to the Research Site for and were instructed to fast for at least 10 hours before their visit. If patients qualified for randomization based on the procedures at Visit 1, they needed to be randomized within 42 days after Visit 1. The following procedures were performed at the screening Visit 1:

- Obtained signed informed consent;
- Assigned the patient a patient number;
- Obtained medical, surgical and family history;
- Recorded demographics;
- Obtained height, weight, and body mass index;
- Obtained vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Obtained a 12-lead electrocardiogram;
- Evaluated inclusion/exclusion criteria;
- This included procedures and (fasting) blood samples (for example, hsCRP, calculated creatinine clearance) as needed to determine the CV risk category (See inclusion criteria);
- Obtained fasting blood samples for chemistry and hematology testing;
- Obtained a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C);
- Performed a urine pregnancy test on women of childbearing potential;

- Recorded concomitant medication(s); and
- Instructed patient to fast for at least 10 hours prior to the next visit.

[0339] Screening Visit (Visit 1.1): Patients who qualified for study participation after Visit 1 because they meet all inclusion criterion and none of the exclusion criteria, skipped Visit 1.1 and returned to the Research Site for Visit 2 to be randomized and to start the treatment/follow-up period of the study. For these patients, Visit 2 occurred soon after Visit 1. Patients, who did not qualify at Visit 1, returned to the Research Site for a second qualifying visit (Visit 1.1) at the discretion of the investigator. At Visit 1.1, procedures that caused failure of eligibility at Visit 1 were repeated. Patients were eligible for randomization after Visit 1.1 if they meet all inclusion criteria and if they no longer failed the exclusion criteria. If patients were evaluated at Visit 1.1 and qualified for randomization based on the repeated procedures at Visit 1.1, they needed to be randomized within 60 days after Visit 1. For some patients, Visit 1.1 was mandatory at least 28 days after Visit 1 in order to check eligibility. These were patients who at Visit 1 started treatment with a statin, changed their statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications (See inclusion/exclusion criteria above for details). Any of these changes at Visit 1 may have affected the qualifying lipid levels and therefore, patients needed to have Visit 1.1 to determine whether they qualified based on lipid level requirements (TG and LDL-C) determined at Visit 1. Other procedures that caused failure of eligibility at Visit 1 were also repeated at Visit 1.1. The following procedures were performed at the screening Visit 1.1:

- Obtained vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Evaluated inclusion/exclusion criteria; only those evaluations were repeated that deemed the patient not eligible on Visit 1;
- Obtained fasting blood samples for chemistry and hematology testing. Only those samples were obtained that deemed the patient not eligible on Visit 1;
- Obtained a fasting blood sample for the lipid profile (TG, TC, HDL-C, LDL-C, non-HDL-C, VLDL-C) if the patient was deemed not eligible on Visit 1. This included patients who at Visit 1 started treatment with a statin, changed their

statin, changed the daily dose of their statin, started to washout prohibited medications or started a stabilization period with certain medications (See inclusion/exclusion criteria for details). These patients had a fasting blood sample collected at Visit 1.1 for the qualifying lipid values (TG and LDL-C), and the TG and LDL-C inclusion criteria were evaluated and

- Recorded concomitant medication(s).

[0340] The treatment/follow-up period for this study included Visit 2, Visit 3, and Visits 4-9. Every attempt was made to complete the follow-up visits during the defined window periods.

[0341] Randomization visit (Visit 2; Day 0): Qualified patients returned to the Research Site for Visit 2. The following procedures were performed at Visit 2:

- Performed physical examination;
- Obtained weight;
- Obtained vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Measured waist circumference (one of the factors to diagnose metabolic syndrome);
- Obtained a 12-lead electrocardiogram;
- Evaluated inclusion/exclusion criteria;
- Obtained fasting blood samples for:
    - Chemistry and hematology testing;
    - Lipid profile (baseline);
    - Biomarker assays (baseline);
    - Genetic testing (optional blood sample); and
    - Archived (in countries and at sites approved by IRB/IEC and dependent on country regulations).
- Performed a urine pregnancy test on women of childbearing potential (must be negative for randomization);

- Dispensed study drug and record randomization number;
- Instructed patient on how to take study drug;
- Administered study drug - Note: Study drug was taken orally with food following the collection of all fasting blood samples;
- Assessed for and recorded adverse events;
- Recorded concomitant medication(s); and
- Instructed patient:
    - To bring all study supplies with them to the next visit;
    - Not to take study drug on the morning of their next visit; and
    - To fast for ≥ 10 hours prior to the next visit.

[0342] Visit 3 (Day 120; ~4 Months): Patients returned to the Research Site for Visit 3 on Day 120 ±10 days. The following procedures were performed:

- Physical examination;
- Obtained weight;
- Obtained vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Obtained fasting blood samples for:
    - Chemistry and hematology testing; and
    - Lipid profile.
- Reviewed study drug compliance by unused capsule count; discuss with and counsel patients about compliance if needed;
- Administered study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples;
- Assessed and record efficacy events;
- Assessed for and record adverse events;
- Recorded concomitant medication(s);

- Instructed patient:
    - To bring all study supplies with them to the next visit;
    - Not to take study drug on the morning of their next visit; and
    - To fast for ≥10 hours prior to the next visit.

[0343] Visits 4, 5, 6, 7, 8, and 9: At Visit 4: Day 360 ± 10; Visit 5: Day 720 ± 10; Visit 6: Day 1080 ± 10; and Visit 7: Day 1440 ± 10: Visit 8: Day 1800 ± 10, Visit 9: Day 2160 ± 10, the following procedures were performed:

- Physical examination;
- Obtained weight;
- Obtained vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature);
- Measured waist circumference (collected at Visit 5 only);
- Obtained a 12-lead electrocardiogram;
- Obtained fasting blood samples for:
    - Chemistry and hematology testing;
    - Lipid profile;
    - Biomarker assays (collected at Visit 5 only); and
    - Archived (in countries and at sites approved by international review board (IRB)/independent ethics committee (IEC) and dependent on country regulations);
- Reviewed study drug compliance by unused capsule count; discussed with and counseled patients about compliance if needed;
- Administered study drug - Note: Study drug should be taken orally with food following the collection of all fasting blood samples;
- Assessed and record efficacy events;
- Assessed for and record adverse events;
- Recorded concomitant medication(s); and

- Instructed patient:
    - To bring all study supplies with them to the next visit;
    - Not to take study drug on the morning of their next visit; and
    - To fast for ≥10 hours prior to the next visit.

[0344] Additional Visits: The end date of the study was expected for Day 2160 but the actual end date was dependent on the determination of the study end date by the DMC and when approximately 1612 primary efficacy events had occurred. If the actual study end date was later than the expected end date, additional visits were planned between Visit 7 and the Last Visit with a maximum of 360 ±10 days between visits. If the actual study end date was sooner than the expected end date, fewer visits occurred, and the last visit (See below, section titled Last Visit – End of Study) occurred sooner. On additional visits the same procedures were performed. Irrespective of the number of additional visits, after the DMC had established the end of the study date, there was a last visit with procedures as listed below in section titled Last Visit – End of Study.

[0345] Last Visit – End of Study: All patients completed the study at the same time (within a 30-day window after the study end date), irrespective of the date that they were randomized. The end date of the study was planned for Day 2160 but the actual end date was dependent on the determination of the study end date by the DMC when approximately 1612 primary efficacy events had occurred (event-driven trial). For each patient, the last visit may have occurred within 30 days after the actual study end date as determined by the DMC. However, for the efficacy endpoints based on CV events, only events occurring up to and including the scheduled actual study end date were included in the efficacy analyses. A final follow-up visit was required for all patients. In a rare case that a final follow-up visit did not occur within the 30-day timeframe following the study end date, any attempt to contact the patient was recorded on a special contact form, until/unless appropriate information was obtained. At the Last Visit, the following procedures were performed:

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

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

[0346] Telephoned Follow-up Contact: Site personnel contacted each patient by telephone on the following study days: Day 60 ±3 days; Day 180 ±5 days; Day 270 ±5 days; Day 450 ±5 days; Day 540±5 days; Day 630 ±5 days; Day 810 ±5 days; Day 900 ±5 days; Day 990 ±5 days; Day 1170 ±5 days; Day 1260 ±5 days; Day 1350 ±5 days; Day 1530 ±5 days; Day 1620 ±5 days; Day 1710 ±5 days; Day 1890 ±5 days; Day 1980 ±5 days; and Day 2070 ±5 days.

[0347] If the treatment/follow-up period of the study was extended beyond the expected end date (Day 2160), additional follow-up phone calls were made every 3 months in-between additional visits ± 5 days. If the treatment/follow period of the study was shorter than the expected end date, less follow-up phone calls were needed. Every attempt was made to talk to each patient within this timeframe. The following information was collected from the patient:

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

- Current address and contact information.

[0348] Patients were reminded about the following items:

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

Laboratory Procedures

[0349] Clinical Laboratory Procedures and Evaluations: All clinical laboratory determinations for screening and safety were performed by a certified clinical laboratory under the supervision of the Sponsor or its designee. Whenever possible and appropriate, samples for the clinical laboratory procedures were collected after fasting for at least 10 hours. For the purposes of this study, fasting was defined as nothing by mouth except water (and any essential medications). The investigator reviewed and signed all laboratory test reports. At screening, patients who had laboratory values that are outside the exclusionary limits specified in the exclusion criteria were not enrolled in the study (patients would have been considered for the study if values were classified as not clinically significant by the investigator). After randomization, the investigator was notified if laboratory values were outside of their normal range. In this case, the investigator was required to conduct clinically appropriate follow-up procedures.

[0350] Safety Laboratory Tests: The safety parameters were analyzed by a certified clinical laboratory at screening (Visit 1 or Visit 1.1), Randomization visit (Visit 2; Day 0), Visit 3 (Day 120; ~4 Months) and all other follow-up visits including the Last Visit. The safety laboratory tests included:

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

- Biochemistry panel including total protein, albumin, alkaline phosphatase, alanine aminotransferase (ALT/SGPT), aspartate aminotransferase (AST/SGOT), total bilirubin, glucose, calcium, electrolytes (sodium, potassium, chloride), blood urea nitrogen (BUN), serum creatinine, uric acid, creatine kinase, and HbA1c.

[0351] Each laboratory result was classified as low (L), normal (N), and high (H) at each visit according to the laboratory-supplied normal range. The shift from baseline was presented for each post-baseline visit and overall post-baseline visits. If multiple measurements for a test parameter were available for a post-baseline patient-visit, the most extreme value was included in the shift table. For shift from baseline to overall post-baseline visits, values from all visits (including unscheduled measurements) were included. The chemistry shift table included fasting lipid parameters. The continuous lipid values were presented as part of the efficacy analysis.

[0352] Fasting Lipid Profile: The fasting lipid panel included: TG, TC, LDL-C, HDL-C, non-HDL-C, and VLDL-C. At all visits, LDL-C was calculated using the Friedewald equation. At Visit 1 and Visit 1.1 direct LDL-C were used if at the same visit TG >400 mg/dL (4.52 mmol/L). These LDL-C values were used for the evaluation of the LDL-C inclusion criterion (LDL-C qualifying measurements for randomization) and for the assessment of changes in the statin therapy when LDL-C was not at goal. At all remaining visits (except Visit 2 and Visit 4) LDL-C was measured by direct LDL cholesterol or by preparative ultracentrifugation if at the same visit TG >400 mg/dL (4.52 mmol/L). In addition, irrespective of the TG levels, at Visit 2 (0 Months of Follow-up, baseline) and at Visit 4 (12 Months of Follow-up), LDL-C were measured by preparative ultracentrifugation. These preparative ultracentrifugation LDL-C measurements were used in the statistical analysis including the calculation of the percent change from baseline (1 year versus baseline). Hopkins LDL-C was calculated for each visit.

[0353] Genetic Testing: A fasting blood sample was stored for future genetic testing at the discretion of the Sponsor. The specifics of this test were determined at a later date. This sample was optional as local regulations may prohibit genetic samples to be collected or shipped outside the country, or patients may not have consented. Research on genetic testing looked for links between genes and certain diseases, including their treatment(s) such as medicines and medical care. The blood samples were collected in

the study center with the regular protocol-required labs. Each patient tube with a sample for genetic testing were labeled with patient number only. The site maintained a Subject Code Identification List for cross-reference. The patient number did not contain any identifiable information (i.e., patient initials, date of birth, etc.). Un-analyzed samples were stored frozen by the Sponsor for a period of up to 2 years following the end of the study, at which time they were destroyed. If samples were tested, results were not reported to the patient, parents, relatives, or attending physician and were not recorded in the patient's medical records. There was no follow-up contact with the sites or patients regarding this sample. The subject could withdraw their consent for genetic testing at any time up to analysis, even after the sample had been obtained. The subject could notify the site in writing that they withdraw their consent for the genetic testing portion of the study, and it was documented by the site in the subject chart, as well as captured in the CRF. The lab was notified to pull the sample and destroy it. Potential genetic bioassays may have been performed and may have been as broad as a genome-wide association study (GWAS) or as limited as a single gene-target approach; potential target genes include, but are not limited to the genes encoding: Apo C3, Apo A5, CETP, LPL, PCSK9, TNFα, TNFβ, ALOX5, COX2, FABP genes, haptoglobin 1 and haptoglobin 2.

[0354] Biomarkers Assays: The biomarker assays included: hsCRP, Apo B and hsTnT.

[0355] Additional laboratory tests: Additional laboratory tests were performed and included:

- A urine pregnancy test was administered to women of childbearing potential at certain visits as listed in schedule of procedures (Table 1). The urine pregnancy tests were performed at the Research Site utilizing marketed test kits, or at a certified clinical laboratory;
- A fasting blood sample (10 mL) for archiving. This sample was collected only at sites in countries where allowed by local regulations and at sites for which approved by the IRB or IEC. The plasma from the archiving sample was stored frozen in 2 separate equal aliquots, and was used at the Sponsor's discretion to perform repeat analyses described in the protocol or to perform other tests related to cardiovascular health; and

- Potential non-genetic bioassays were performed, including but not limited to: Apo A1, Apo C3, Apo E, NMR lipid profile (particle size and number), oxidized LDL, Lp(a), Lp-PLA_2, serum fatty-acids concentrations, and gamma-glutamyltransferase (GGT).

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

[0357] Flagging of Critical Lab Values: Critical lab values are values that may have warranted medical intervention to avoid possible harm to a patient. Critical lab values were defined in the Laboratory Manual for the study, and the Research Site was notified of the occurrence of a critical lab value (critical high or critical low) by a special annotation (flag) in the laboratory reports provided to the Research Sites. Although laboratory values that were part of the efficacy endpoints during the double-blind period of the study were not provided to the Research Site, the sites were notified when the TG value of a patient sample was >1000 mg/dL (11.29 mmol/L) (critical high TG value) or if the LDL-C values of a patient sample was >130 mg/dL (3.37 mmol/L) (critical high LDL-C value). These critical high values were confirmed by a repeat measurement (new fasting blood sample) within 7 days. TG value of >2000 mg/dL (22.58 mmol/L) were also flagged, so that appropriate medical action could be taken by the investigator as soon as possible.

[0358] If TG values were confirmed critically high, patients could be discontinued from study drug with the option to remain on study. The investigator used the best clinical judgment for each patient which included the use of approved TG-lowering medications after patients had discontinued from study drug. If LDL-C values were confirmed critically high, the investigator needed to take appropriate medical action which included: reinforcing/intensifying therapeutic lifestyle changes (including diet and physical activity), increasing the dose of the present statin therapy, adding ezetimibe, or prescribing a more potent statin to lower LDL-C. The investigator used the best clinical judgment for each patient.

Medical Procedures

[0359] Medical, Surgical and Family History: Medical history, including family history and details regarding all illnesses and allergies, date(s) of onset, status of current condition, and smoking and alcohol use were collected on all patients.

[0360] Demographics: Demographic information including day, month, and year of birth, race, and gender were collected for all patients.

[0361] Vital Signs and Patient Measurements: Vital signs included systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Blood pressure was measured using a standardized process:

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

[0362] Blood pressure was recorded to the nearest 2 mmHg mark on the manometer or to the nearest whole number on an automatic device. A blood pressure reading was repeated 1 to 2 minutes later, and the second reading recorded to the nearest 2 mmHg mark.

[0363] The baseline value categories and post-baseline endpoint value categories shown in Table 7A were measured and presented. Definitions for potentially clinically significant (PCS) vital signs treatment-emergent values are defined below in Table 7B.

Table 7A. Vital Signs Value Categories

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

Table 7B. Potentially Clinically Significant Vial Signs Value Definitions

Vital Sign	PCS Low	PCS High
Systolic Blood Pressure	≤90 mmHg AND decrease of ≥20 mmHg; ≤90 mmHg; decrease of ≥20 mmHg	≥160 mmHg AND increase of ≥20 mmHg; ≥ 160 mmHg; increase of ≥20 mmHg

Diastolic Blood Pressure	≤50 mmHg AND decrease of ≥10 mmHg; ≤50 mmHg; decrease of >10 mmHg	≥100 mmHg AND increase of >10 mmHg; ≥100 mmHg; increase of 10 mmHg
Pulse	≤50 beats/min AND decrease of ≥15 beats/min; ≤50 beats/min; decrease of ≥15 beats/min	≥90 beats/min AND increase of ≥15 beats/min; ≥90 beats/min; increase of ≥15 beats/min

[0364] Number (%) of patients with any post-baseline PCS vital sign values was summarized by treatment group. A listing of patients who meet the threshold criteria was provided.

[0365] Physical Examination: A physical examination included source documentation of general appearance, skin, and specific head and neck, heart, lung, abdomen, extremities, and neuromuscular assessments.

[0366] Height, Weight and Body Mass Index: Height and weight were measured. Measurement of weight was performed with the patient dressed in indoor clothing, with shoes removed, and bladder empty.

[0367] Waist Circumference: Waist circumference was measured with a tape measure, as follows: Start at the top of the hip bone then bring the tape measure all the way around – level with the navel. Make sure the tape measure is snug, but without compressing the skin, and that it is parallel with the floor. Patients should not have held their breath while measuring waist circumference.

[0368] 12-Lead Electrocardiogram (ECG): ECGs (standard 12-lead) were obtained annually. Site personnel made every attempt to perform a patient's ECG using the same equipment at each visit. ECGs were reviewed by the site for the detection of silent MI. Silent MIs were sent for event adjudication. All post-randomization ECGs (protocol-specified and other) were sent to the CEC for evaluation of silent MI. The 12-lead ECG parameters included Heart Rate (bpm), PR Interval (msec), QRS Interval (msec), QT Interval (msec), and QTc Interval (msec) were measured, and Overall Interpretation and Silent MI (Yes/No) were summarized for all patients at Screening (Visit 1), Randomization visit (Visit 2; Day 0) and all other follow-up visits including the last visit of the study.

[0369] A treatment-emergent PCS high value at any time was defined as a change from a value less than or equal to the defined PCS value at baseline to a PCS high value

at any post-baseline measurement. A treatment-emergent PCS low value at any time was defined as a change from a value greater than or equal to the lower PCS value at baseline to a PCS low value at any post-baseline measurement. Table 8 provides the PCS ECG values.

Table 8. Potentially Clinically Significant ECG Value Definitions

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

[0370] Number (%) of patients with post-baseline PCS ECG values were presented by treatment group. A listing of subjects with potentially clinically significant changes in ECG values was included.

Treatment and Procedures

[0371] Treatment Regimen, Dosage, and Duration: Eligible study patients were randomly assigned on Day 0 to one of the 2 treatment groups. Patients in each group received either 4 g/day AMR101 or placebo for up to 6.5 years, depending on individual date of randomization and overall study stop date according to Table 9. The daily dose of study drug was 4 capsules per day taken as two capsules taken on two occasions per day (2 capsules were given twice daily).

Table 9. Dosing Schedule during the Treatment Period

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

[0372] Patients were instructed to take study drug with food (i.e., with or at the end of their morning and evening meals). On days that patients were scheduled for study visits; the daily dose of study drug was administered by site personnel with food provided by the site following collection of all fasting blood samples. For the purposes of this study, fasting was defined as nothing by mouth except water (and any essential medications) for at least 10 hours. Treatment Assignment

[0373] Identification Number: A unique patient identification number (patient number) was established for each patient at each site. The patient number was used to identify the patient throughout the study and was entered on all documentation. If a patient was not eligible to receive treatment, or if a patient discontinued from the study, the patient number could not be reassigned to another patient. The patient number was used to assign patients to one of the 2 treatment groups according to the randomization schedule.

[0374] Drug Randomization: Only qualified patients who meet all of the inclusion criteria and none of the exclusion criteria were randomized and received study medication starting at Visit 2 (Day 0). Eligible patients were randomly assigned to one of the 2 treatment groups. Randomization was stratified by CV risk category, use of ezetimibe and by geographical region (Westernized, Eastern European, and Asia Pacific countries). Approximately 70% of randomized patients were in the CV Risk Category 1, including patients with established CVD, and approximately 30% of randomized patients were in the CV Risk Category 2, including patients with diabetes and at least one additional risk factor but no established CVD. Enrollment with patients of a CV risk category was stopped when the planned number of patients in that risk category was reached.

[0375] Emergency Unblinding: In an emergency, when knowledge of the patient's treatment assignment was essential for the clinical management or welfare of the patient, the investigator could request the patient's treatment assignment for unblinding. Prior to unblinding the patient's individual treatment assignment, the investigator assessed the relationship of an adverse event to the administration of the study drug (Yes or No). If the blind was broken for any reason, the investigator recorded the date and reason for breaking the blind on the appropriate Case Report Form (CRF) and source documents.

[0376] Compliance Control: Unless clear contraindications arise, patients were strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy were, if possible, brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. Discontinuations were discouraged as much as possible. Any discontinuations were based on compelling clinical reasons. For every patient, an assessment of compliance to the study drug treatment regimen was obtained at each scheduled visit. Study medication was

dispensed in amounts exceeding the amount required for the study. Patients were instructed to return all unused study medication at the next visit. Compliance to the study drug regimen was evaluated at each visit by counting unused capsules. Discrepancies were evaluated and discussed with each patient to assess compliance. If compliance was unsatisfactory, the patient was counseled about the importance of compliance to the dosing regimen. At the end of the study, the final study medication compliance was determined by unused capsule count.

Study Restrictions

[0377] Concomitant Medications during Treatment/Follow-Up Period: Any medications administered during the study period were documented on the Concomitant Medication CRF. Patients had not taken any investigational agent within 90 days prior to screening. Patients could not participate in any other investigational medication trial while participating in this study. The following non-study drug related, non-statin, lipid-altering medications and supplements, and foods were prohibited during the study (from Visit 1 until after the Last Visit-End of Study), except for compelling medical reasons in ODIS patients:

- niacin >200 mg/day;
- fibrates;
- prescription omega-3 fatty acid medications;
- dietary supplements containing omega-3 fatty acids (e.g., flaxseed, fish, krill, or algal oils);
- bile acid sequestrants;
- PCSK9 inhibitors;
- cyclophosphamide; and
- systemic retinoids.

[0378] If any of these products were used during the treatment/follow-up period of the study, it was for compelling medical reasons in ODIS patients, and documented in the Concomitant Medication CRF. If the ODIS patient agreed to restart study medication, the use of excluded medication was discontinued. Foods enriched with omega-3 fatty acids were strongly discouraged after Visit 1 for the duration of the study (does not apply

to The Netherlands or Canada only. Therefore, all centers in The Netherlands and Canada ignored this request). The following products were allowed: statins, ezetimibe, and herbal products & dietary supplements not containing omega-3 fatty acids.

[0379] Statins:

- The same statin at the same dose was continued until the end of the study, unless deemed medically necessary to change because of an adverse event or lack of efficacy (LOE). It was preferred that if LOE was the determining factor that ezetimibe was added to the present dose;
- Switching between a brand name statin and the generic version of the same statin was allowed at any time during the study;
- Statins were administered with or without ezetimibe;
- Based on the FDA recommendation, simvastatin 80 mg was used only in patients who had been taking this dose for 12 months or more and had not experienced any muscle toxicity. (See reference: FDA Drug Safety Communication: Ongoing safety review of high-dose Zocor (simvastatin) and increased risk of muscle injury. (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm204882.htm); and
- Changing of the type of statin or the statin dose during the treatment/follow-up period of the study was only done for compelling medical reasons and was documented in the CRF. Maintaining statin therapy throughout the study was important and, in the rare circumstance that it became medically compelling to discontinue statin use, the patient could remain in the study and on study medication with approval from the Medical Monitor. Under such conditions, resumption of statin therapy was attempted when/if medically appropriate.
- If the level of LDL-C exceeded 130 mg/dL (3.37 mmol/L) during the study (initial measurement and confirmed by a second determination at least 1 week later), the investigator either increased the dose of the present statin therapy or added ezetimibe to lower LDL-C. The investigator used the best clinical judgment for each patient.

[0380] LDL-C Rescue: If the level of LDL-C exceeded 130 mg/dL (3.37 mmol/L) during the study (initial measurement and confirmed by a second determination at least 1 week later), the investigator either increased the dose of the present statin therapy or added ezetimibe to lower LDL-C. The investigator used the best clinical judgment for each patient.

[0381] No data were available with regard to potential interactions between ethyl-EPA and oral contraceptives. There were no reports suggesting that omega-3 fatty acids, including ethyl-EPA, would decrease the efficacy of oral contraceptives.

[0382] Medications that were excluded if not at a stable dose for ≥28 days prior to screening, could be initiated post-randomization if medically warranted (i.e., tamoxifen, estrogens, progestins, thyroid hormone therapy, systemic corticosteroids and HIV-protease inhibitors).

[0383] Patient Restrictions: Beginning at the screening visit, all patients were instructed to refrain from excessive alcohol consumption, to follow a physician recommended diet and to maintain it through the duration of the study. Excessive alcohol consumption is on average 2 units of alcohol per day or drinking 5 units or more for men or 4 units or more for women in any one hour (episodic excessive drinking or binge drinking). A unit of alcohol is defined as a 12-ounce (350 mL) beer, 5-ounce (150 mL) wine, or 1.5-ounce (45 mL) of 80-proof alcohol for drinks.

Investigational Product

[0384] Clinical Trial Material: The following clinical materials were supplied by the Sponsor:

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

[0385] The Sponsor supplied sufficient quantities of AMR101 1000 mg capsules and placebo capsules to allow for completion of the study. The lot numbers of the drugs supplied were recorded in the final study report. Records were maintained indicating the receipt and dispensation of all drug supplies. At the conclusion of the study, any unused study drug was destroyed.

[0386] Pharmaceutical Formulations: AMR101 1000 mg and placebo capsules (paraffin) were provided in liquid-filled, oblong, gelatin capsules. Each capsule was filled with a clear liquid (colorless to pale yellow in color). The capsules were approximately 25.5 mm in length with a diameter of approximately 9.5 mm.

[0387] Labeling and Packaging: Study medication was packaged in high-density polyethylene bottles. Labeling and packaging was performed according to GMP guidelines and all applicable country-specific requirements. The bottles were numbered for each patient based on the randomization schedule. The patient randomization number assigned by IWR or a designee of the Sponsor for the study (if no IWR system was used), corresponds to the number on the bottles. The bottle number for each patient was recorded in the Electronic Data Capture (EDC) system for the study.

Dispensing Procedures and Storage Conditions

[0388] Dispensing Procedures: At Visit 2 (Day 0), patients were assigned a study drug according to their treatment group determined by the randomization schedule. Once assigned to a treatment group, patients received study drug supplies. At each visit, patients brought unused drug supplies dispensed to them earlier. From the drug supplies assigned to each patient, site personnel administered the drug while the patients were at the Research Site. The investigator or designee contacted the IWR system or a designee of the Sponsor for the study (if no IWR system is used) when any unscheduled replacements of study medication were needed. During the last visit of the treatment period, patients brought the unused drug supplies for site personnel to calculate the final study medication compliance by unused capsule count.

[0389] Storage Conditions: At the Research Sites, study drugs were stored at room temperature, 68°F to 77°F (20°C to 25°C). Storage temperature did not go below 59°F (15°C) or above 86°F (30°C) and the drug was stored in the original package. Study drugs were stored in a pharmacy or locked and secure storage facility, accessible only to those individuals authorized by the investigator to dispense the drug. The investigator or designee kept accurate dispensing records. At the conclusion of the study, study site personnel accounted for all used and unused study drug. Any unused study drug was destroyed. The investigator agreed not to distribute study drug to any patient, except those patients participating in the study.

Efficacy Assessments

[0390] Specification of Variables and Procedures: The primary endpoint and the majority of the secondary and tertiary endpoints were based on clinical events related to CVD and mortality. All events occurring between randomization and the study end date (inclusive) were recorded. Only adjudicated events were included in the final analyses.

[0391] Primary Efficacy Endpoint: The primary efficacy endpoint was time from randomization to the first occurrence of the composite of the following clinical events: CV death; nonfatal MI (including silent MI; ECGs were performed annually for the detection of silent MIs); nonfatal stroke; coronary revascularization; and unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization. The first occurrence of any of these major adverse vascular events during the follow-up period of the study were included in the incidence.

[0392] Secondary Efficacy Endpoints: The key secondary efficacy endpoint was the time from randomization to the first occurrence of the composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke. Other secondary efficacy endpoints were time from randomization to the first occurrence of the individual or composite endpoints as follows (tested in the order listed):

- The composite of CV death or nonfatal MI (including silent MI);
- Fatal or nonfatal MI (including silent MI);
- Non-elective coronary revascularization represented as the composite of emergent or urgent classifications;
- CV death;
- Unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Fatal and nonfatal stroke;
- The composite of total mortality, nonfatal MI (including silent MI), or nonfatal stroke; and/or
- Total mortality.

[0393] For the secondary endpoints that count a single event, the time from randomization to the first occurrence of this type of event was counted for each patient. For secondary efficacy endpoints that were composites of two or more types of events, the time from randomization to the first occurrence of any of the event types included in the composite were counted for each patient.

[0394] Tertiary Efficacy Endpoints: The following tertiary endpoints were evaluated as supporting efficacy and safety analyses. Where applicable and unless specified otherwise, endpoint analyses were conducted as time from randomization to the first occurrence of the individual or composite endpoint as follows:

- Total CV events analysis defined as the time from randomization to occurrence of the first and all recurrent major CV events defined as CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;
- Primary composite endpoint in subset of patients with diabetes mellitus at baseline;
- Primary composite endpoint in the subset of patients with metabolic syndrome at baseline with waist circumference cut points specifically set at ≥35 inches (88 cm) for all women and Asian, Hispanic, or Latino men, and ≥40 inches (102 cm) for all other men;
- Primary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG of 100-125 mg/dL);
- Key secondary composite endpoint in the subset of patients with impaired glucose metabolism at baseline (Visit 2 FBG 100-125 mg/dL);
- The composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalization of ≥24 hours, or cardiac arrest;
- The composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina determined caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization;

- The composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, nonfatal stroke, or PVD requiring intervention, such as angioplasty, bypass surgery, or aneurism repair;
- The composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, PVD requiring intervention, or cardiac arrhythmia requiring hospitalization of ≥24 hours;
- New CHF;
- New CHF as the primary cause of hospitalization;
- Transient ischemic attack (TIA);
- Amputation for PVD;
- Carotid revascularization;
- All coronary revascularizations defined as the composite of emergent, urgent, elective, or salvage;
- Emergent coronary revascularizations;
- Urgent coronary revascularizations;
- Elective coronary revascularizations;
- Salvage coronary revascularizations;
- Cardiac arrhythmias requiring hospitalization of ≥24 hours;
- Cardiac arrest;
- Ischemic stroke;
- Hemorrhagic stroke;
- Fatal or nonfatal stroke in the subset of patients with a history of stroke prior to baseline;

- New onset diabetes, defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period;
- New onset hypertension, defined as blood pressure ≥ 140 mmHg systolic OR ≥ 90 mm Hg diastolic newly diagnosed during the treatment/follow-up period;
- Fasting TG, TC, LDL-C, HDL-C, non-HDL-C, VLDL-C, apo B, hsCRP (hsCRP and log[hsCRP]), hsTnT, and RLP-C (to be estimated from standard lipid panel, RLP-C = TC – HDL-C – LDL-C [Varbo 2014]), (based on ITT estimands):
    - Assessment of the relationship between baseline biomarker values and treatment effects within the primary and key secondary composite endpoints;
    - Assessment of the effect of AMR101 on each marker; and
    - Assessment of the relationship between post-baseline biomarker values and treatment effects within the primary and key secondary composite endpoints by including post-baseline biomarker values (for example, at 4 months, or at 1 year) as a covariate.
- Change in body weight; and
- Change in waist circumference.

[0395] Where applicable and unless specified otherwise, for the tertiary endpoints that count a single event, the time from randomization to the first occurrence of this type of event was counted in each patient. Similarly, where applicable and unless specified otherwise, for tertiary endpoints that were composites of two or more types of events, the time from randomization to the first occurrence of any of the event types included in the composite was counted in each patient.

[0396] Other sensitivity, supportive, and exploratory analyses for the primary efficacy endpoint were carried out, namely, an on-treatment analysis which included primary event onset up to 0 and 30-days after the permanent discontinuation of the drug.

[0397] The following clinical events that were positively adjudicated by the Clinical Endpoint Committee were analyzed as tertiary endpoints for the ITT intent-to-treat (ITT) population:

- Composition of total mortality, or congestive heart failure (CHF);

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

[0398] The above tertiary endpoints were analyzed similarly as the primary endpoint.

[0399] In addition, the following were analyzed as tertiary endpoints for the ITT population:

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

[0400] To assess the relationship between on-treatment hsCRP and the primary and key secondary endpoints, subgroup analyses were carried out as done for the ITT population for patients grouped according to values greater or equal to or less than 2 mg/dL at baseline and at 2 years. To assess the relationship between on-treatment serum EPA and the primary and key secondary endpoints, Kaplan-Meier (KM) curves were produced for AMR101 treated patients grouped into tertiles based on their values at year 1 and were compared with the placebo-treated patients.

Safety Assessments

[0401] Specification of Variables and Procedures: Safety assessments included adverse events, clinical laboratory measurements (chemistry, hematology), 12-lead ECGs, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature), weight, waist circumference, and physical examinations as per Study Procedures in Table 1. A complete medical, surgical and family history was completed at Visit 1. All laboratory test results were evaluated by the investigator as to their clinical significance. Any observations at physical examinations or laboratory values considered by the investigator to be clinically significant were considered an adverse event.

[0402] Adverse Events: An adverse event is defined as any untoward medical occurrence, which does not necessarily have a causal relationship with the medication under investigation. An adverse event can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medication product, whether or not related to the investigational medication product. All adverse events, including observed or volunteered problems, complaints, or symptoms, were recorded on the appropriate CRF. Each adverse event was evaluated for duration, intensity, and causal relationship with the study medication or other factors.

[0403] Adverse events, which included clinical laboratory test variables, were monitored from the time of informed consent until study participation was complete. Patients were instructed to report any adverse event that they experienced to the investigator. Beginning with Visit 2, investigators assessed for adverse events at each visit and recorded the event on the appropriate adverse event CRF.

[0404] Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms was identified by the investigator and recorded on the CRF. However, if an observed or reported sign or symptom was not considered a component of a specific disease or syndrome by the investigator, it was recorded as a separate adverse event on the CRF.

[0405] Any medical condition that was present when a patient was screened or present at baseline that did not deteriorate were reported as an adverse event. However, medical conditions or signs or symptoms present at baseline and that changed in severity or seriousness at any time during the study were reported as an adverse event.

[0406] Clinically significant abnormal laboratory findings or other abnormal assessments that were detected during the study or were present at baseline and significantly worsened were reported as adverse events or SAEs. The investigator exercised his or her medical and scientific judgment in deciding whether an abnormal laboratory finding, or other abnormal assessment was clinically significant.

[0407] The investigator rated the severity (intensity) of each adverse event as mild, moderate, or severe, and also categorized each adverse event as to its potential relationship to study drug using the categories of Yes or No. The severity was defined as:

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

[0408] Causality Assessment: The relationship of an adverse event to the administration of the study drug was assessed according to the following definitions:

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

[0409] The following factors were also considered:

- The temporal sequence from study medication administration;
- The event occurred after the study medication was given. The length of time from study medication exposure to event was evaluated in the clinical context of the event;
- Underlying, concomitant, intercurrent diseases;
- Each report was evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have had;
- Concomitant medication;
- The other medications the patient was taking or the treatment the patient received were examined to determine whether any of them might have caused the event in question;
- Known response pattern for this class of study medication;

- Clinical and/or preclinical data may have indicated whether a particular response was likely to be a class effect;
- Exposure to physical and/or mental stresses;
- The exposure to stress might induce adverse changes in the patient and provide a logical and better explanation for the event;
- The pharmacology and pharmacokinetics of the study medication; and
- The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study medication were considered.

[0410] 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.

[0411] Serious Adverse Events: A serious adverse event (SAE) is defined as an adverse event that meets any of the following criteria:

- Results in death;
- Is life-threatening- The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;
- Requires hospitalization or prolongation of existing hospitalization. In general, hospitalization for treatment of a pre-existing condition(s) that did not worsen from baseline was not considered adverse events and was not reported as SAEs;
- Results in disability/incapacity;
- Is a congenital anomaly/birth defect; and
- Is an important medical event. Important medical events that may not result in death, be life threatening, or require hospitalization were considered an SAE when, based upon appropriate medical judgment, they may have jeopardized the patient and may have required medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events included

allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did not result in inpatient hospitalizations, or the development of drug dependency.

[0412] By design of this study SAEs that were endpoint events were only recorded for the endpoint determination and not captured as SAEs. The intention was that the endpoint events were reported to IRBs as SAEs, unless the IRB required that these were reported. Investigators specifically informed their institution/IRB of this plan and confirm whether or not they wanted the endpoint events reported. By agreement with the US FDA, these endpoints were also not reported to the US FDA as SAEs; rather they were reported as endpoint events. Following adjudication if the event was determined to not meet the criteria for an event, the event was evaluated as an SAE beginning with that day as Day 0.

[0413] Adverse Events of Special Interest: Bleeding-related adverse events, glucose control (fasting blood glucose and HbA1c), and indicators of hepatic disorders (e.g., ALT or AST increases >3 × ULN, total bilirubin increases of ≥2 × ULN) were summarized separately and compared between treatment groups.

Serious Adverse Event Reporting – Procedure for Investigators

[0414] Initial Reports: All SAEs occurring from the time of informed consent until 28 days following the last administration of study medication were reported to the Sponsor or designee within 24 hours of the knowledge of the occurrence (this refers to any adverse event that meets any of the aforementioned serious criteria). SAEs that the investigator considered related to study medication occurring after the 28-day follow-up period were also reported to the Sponsor or designee. The investigator was required to submit SAE reports to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local requirements. All investigators involved in studies using the same investigational medicinal product (IMP) received any Suspected Unexpected Serious Adverse Reaction (SUSAR) reports for onward submission to their local IRB as required. All reports sent to investigators were blinded. In addition, regulatory agencies were notified of SAEs per the requirements of the specific regulatory jurisdiction regulations and laws.

[0415] Follow-Up Reports: The investigator followed the patient until the SAE subsided, or until the condition became chronic in nature, stabilized (in the case of

persistent impairment), or the patient died. Within 24 hours of receipt of follow-up information, the investigator updated the SAE form electronically in the EDC system for the study and submitted any supporting documentation (e.g., laboratory test reports, patient discharge summary, or autopsy reports) to the Sponsor or designee via fax or email.

[0416] Reporting by the Sponsor: IRBs and IECs were informed of SUSARs according to local requirements. Cases were unblinded for reporting purposes as required.

[0417] Exposure *In Utero* During Clinical Trials: If a patient became pregnant during the study, the investigator reported the pregnancy to the Sponsor or designee within 24 hours of being notified. The Sponsor or designee then forwarded the Exposure *In Utero* form to the investigator for completion. The patient was followed by the investigator until completion of the pregnancy. If the pregnancy ended for any reason before the anticipated date, the investigator notified the Sponsor or designee. At the completion of the pregnancy, the investigator documented the outcome of the pregnancy. If the outcome of the pregnancy met the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator followed the procedures for reporting an SAE.

Treatment Discontinuation/Patient Withdrawal

[0418] Patients could withdraw from the study at any time and for any reason. Study drug administration could also be discontinued at any time, at the discretion of the investigator. In any case, follow-up for efficacy and safety was continued in subjects that discontinued therapy, but remained in the study (i.e., ODIS patients).

[0419] Reasons for Early Study Drug Discontinuation: Study drug discontinuation was avoided as much as possible, but could have been done for any of the following reasons:

- Patient withdrew consent or requested early discontinuation from the study for any reason. Patients were encouraged to continue to participate in the study for the entire duration of the study even if they choose not to take study medication any longer;

- Occurrence of a clinical or laboratory adverse event, either serious or non-serious, at the discretion of the investigator. The Sponsor or designee was notified if a patient was discontinued because of an adverse event or laboratory abnormality. It was recommended that, unless clear contraindications arise, patients were strongly encouraged to adhere to their treatment regimen with the study drug for the duration of the trial. Any interruptions of therapy were, if possible, brief (e.g., <4 weeks) and only for clinically indicated reasons, such as adverse events. The following were considered a reason for discontinuation:
    - ALT > 3x ULN and bilirubin > 1.5x ULN;
    - ALT >5x ULN;
    - ALT >3x ULN and appearance or worsening of hepatitis;
    - ALT > 3x ULN persisting for >4weeks; and/or
    - ALT > 3x ULN and cannot be monitored weekly for 4 weeks
- Any medical condition or personal circumstance that, in the opinion of the investigator, exposed the patient to risk by continuing in the study or precluded adherence to the protocol;
- Sponsor discontinued the study;
- Investigative site closure, in the event that:
    - Another investigative site cannot accommodate the patient, or
    - The patient was unable or unwilling to travel to another investigative site; and/or
- A TG value was flagged as critically high, i.e., >1000 mg/dL (11.29 mmol/L) and confirmed as critically high by a repeat measurement (new fasting blood sample) within 7 days. In this case, a patient could be discontinued from study drug (with the option to remain ODIS) and other lipid-altering medications may be (re)initiated. If the TG value was flagged as >2000 mg/dL (22.58 mmol/L) then appropriate medical action was taken by the investigator as soon as possible.

[0420] Occurrence of an outcome event according to the judgment of the investigator was not considered a valid reason for study drug discontinuation. Patients whose treatment with study medication was discontinued early, and had not withdrawn consent, stayed in the study and were monitored until the end of the study. Patients that continued in the study after ≥30 days cessation of therapy were characterized as Off Drug In Study (ODIS). ODIS patients were asked to return to the study site for an interim visit once the patient had been off study drug for >30 days. Procedures at this visit were consistent with those at Visit 5. If not contraindicated, patients also had the option to restart study medication at any point once characterized as ODIS. For patients who discontinued study medication (e.g., for an AE that may or may not have been drug-related), a brief therapy interruption could have been followed with a re-challenge (re-initiating study medication) as soon as clinically appropriate; thereby allowing a causative role for study medication to be confirmed or ruled out and continuing a patient in the study and on study drug if appropriate. The reason for study drug discontinuation or interruption was recorded on the CRF.

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

[0421] Patients who prematurely discontinued study drug were not replaced. All randomized patients were followed up until the study end date or death, regardless of whether they discontinued study drug prematurely or not. Any event occurring after early study drug discontinuation was recorded up through the study end date. In order to follow the medical status of the patients, especially when they discontinued the study, investigators were encouraged to obtain information from the patient's primary care practitioner (physician or any other medical care provider). Investigators were also requested to try as much as possible to re-contact those patients at the end of the trial to obtain at least their vital status as well as their status with respect to the primary endpoint, and thus avoided lost to follow-up for the efficacy assessment. If patients were lost to follow-up, the CRF was completed up to the last visit or contact.

Statistics

[0422] Randomized Population: The randomized population included all patients who sign the informed consent form and are assigned a randomization number at Visit 2 (Day 0).

[0423] Intent-to-Treat Population: The ITT population included all patients who were randomized via the IRWS (Interactive Web Response System). All efficacy analyses were performed on the ITT population. Patients were analyzed according to the randomized treatment.

[0424] Modified Intent-to-Treat Population: The Modified Intent-to-Treat (mITT) population included all randomized patients who had the study drug dispensed after randomization. Groups were defined based on the randomized treatment.

[0425] Per-Protocol Population: The per-protocol (PP) population included all mITT patients without any major protocol deviations, and who had ≥80% compliance while on treatment. To be included in the PP population the minimum time on therapy was 90 days.

[0426] Safety Population: All safety analyses were conducted based on the safety population, which is defined as all randomized patients. This was the same as the ITT population.

[0427] Statistical Methods: Safety and efficacy variables were analyzed using appropriate statistical methods that were described in detail in a separate Statistical Analysis Plan (SAP). The SAP was finalized before study unblinding.

[0428] Patient Disposition and Demographic/Baseline Characteristics: The number and percentage of patients was tabulated for each of the following categories for each treatment group:

- Screened (total only);
- Re-screened and reasons for re-screening (total only);
- ITT overall and by stratification factors (CV risk, ezetimibe use, and geographical region);
- mITT population; overall and by stratification factors (CV risk, ezetimibe use, and geographical region);
- PP population; overall and by stratification factors (CV risk, ezetimibe use, and geographical region);
- Safety population;

- Patients who completed the study;
- Patients who terminated from the trial early and the primary reason for early termination;
- Patients who terminated the trial early prior to having a confirmed primary endpoint event;
- Patients with complete follow-up, defined as those for whom all components of the primary endpoint have been ascertained during the entire observation period (or until death); and
- Patients who, at the time of study completion, were discontinued from study drug prematurely, but continued within the study (i.e. ODIS patients), along with the primary reason.

[0429] For randomized patients who discontinued treatment with study drug, the primary reason for discontinuation was listed and summarized by treatment group. Demographic and baseline characteristics, including age, gender, ethnicity, race, height, body weight, BMI, diabetes, hypertension, metabolic syndrome, overweight/obese/normal according to BMI, and diabetes plus obesity were summarized using descriptive statistics by treatment group in the ITT population.

[0430] Demographic data and baseline characteristics were compared among treatment groups for the ITT and PP population. Differences in demographic and baseline characteristics were tested using a chi-square test (for categorical variables) or t-test (for continuous variables). The p-values used were considered descriptive, primarily as an assessment of the balance between the two groups. Age in years was calculated using the date of randomization (Visit 2) and the date of birth.

[0431] Study Medication Exposure and Compliance: Study drug exposure was summarized by treatment group using descriptive statistics for each time point and overall. Overall study drug compliance was calculated as the number of doses assumed to be taken relative to scheduled dosing period as follows:

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

[0432] Overall percent compliance was calculated per patient in the ITT and Modified ITT populations and summarized by treatment group using descriptive statistics.

[0433] Concomitant Therapies: Concomitant medication/therapy verbatim terms were coded using the latest available version, prior to data base lock, of the World Health Organization Drug Dictionary and the Anatomical Therapeutic Chemical classification system. The numbers and percentages of patients in each treatment group taking concomitant medications were summarized. All verbatim descriptions and coded terms were listed for all non-study medications.

[0434] Analysis of Efficacy: For efficacy endpoints including CV events, only adjudicated events were included in the final statistical analyses.

[0435] Summary Statistics: Summary statistics (n, mean, standard deviation, median, minimum, and maximum) for the baseline and post-baseline measurements, the percent changes, or changes from baseline were presented by treatment group and by visit for all efficacy variables analyzed. The summary statistics included changes in body weight and body mass index from baseline by treatment group and by visit.

[0436] Primary Endpoint Analyses: The analysis of the primary efficacy endpoint was performed using the log-rank test comparing the 2 treatment groups (AMR101 and placebo) and including the stratification factor "CV risk category", use of ezetimibe and geographical region (Westernized, Eastern European, and Asia Pacific countries) (each as recorded in the IWR at the time of enrollment) as covariates. The two-sided alpha level for the primary analysis was reduced from 0.05 to account for the interim analyses based on a group sequential design with O'Brien-Fleming boundaries generated using the Lan-DeMets alpha-spending function. The hazard ratio (HR) for treatment group (AMR101 vs. placebo) from a Cox proportional hazard model that included the stratification factor was also reported, along with the associated 95% confidence interval (CI). Kaplan-Meier estimates from randomization to the time to the primary efficacy endpoint were plotted.

[0437] The size and direction of the treatment effects of the individual components of the composite endpoint and their relative contribution to the composite endpoint were determined as well. All observed data that were positively adjudicated by the CEC, including data after discontinuation of study treatment for patients who discontinued study drug prematurely, were included in the primary analysis. Patients who did not

experience a primary efficacy event prior to the end of the study or who withdraw from the study early without a preceding primary efficacy event were censored at the date of their last visit/phone contact. The longest prespecified interval between visits (onsite or phone) was 90 days. In view of the up to 90-day monitoring period for CV events, the primary endpoint for patients who had a non-CV death within 90 days of last contact without having had an earlier CV event was censored at the time of death. The primary endpoint for patients who had a non-CV death more than 90 days after last contact without having had an earlier CV event were censored at the time of last contact.

[0438] The primary analysis assumed that all silent MIs occurred on the date of the first tracing indicative of a silent MI; a second (sensitivity) analysis assumed that all silent MIs occurred on the day after the last prior normal ECG; and a third (sensitivity) analysis assumed that all silent MIs occurred at the mid-point between the last normal ECG and the ECG with the new MI. All deaths causally adjudicated as "undetermined" were combined with those adjudicated as "CV deaths" for the primary analysis. A sensitivity analysis of the CV death category was performed that excluded the "undetermined cause of death" cohort.

[0439] The primary efficacy analysis was performed on the ITT population. A sensitivity analysis was performed using the mITT and PP populations. As a sensitivity analysis, patients who discontinued study drug prematurely were censored for the primary composite endpoint analysis on the date of drug discontinuation. The primary analysis was repeated using this censoring rule for the mITT population. As a supportive analysis, a multivariable, stratified Cox proportional hazards model was constructed for the primary endpoint to evaluate the treatment effect adjusting for important covariates.

[0440] Secondary Endpoint Analyses: The key secondary hypothesis was tested as part of the confirmatory process only if the primary analysis was statistically significant. For the analysis of secondary efficacy endpoints, the Type 1 error was controlled by testing each endpoint sequentially, starting with the key endpoint. Testing was done at a significance level consistent with that used for the primary endpoint and ceased when a secondary endpoint was found for which treatments did not significantly differ. P-values were presented for all analyses, but they were considered descriptive after the first non-significant result was obtained. Each of the secondary endpoints were analyzed by the same methods described for the primary efficacy endpoint. Kaplan-Meier estimated, the

log-rank test stratified by stratification factors used at randomization, and the Cox proportional hazards model including the stratification factors as specified above for the primary efficacy endpoint, were summarized by treatment group. In view of the 90-day monitoring period for CV events, the key secondary endpoint for patients who had a non-CV death within 90 days of last contact without having had an earlier CV event was censored at the time of death. The key secondary endpoint for patients who had a non-CV death more than 90 days after last contact without having had an earlier CV event was censored at the time of last contact. Kaplan-Meier curves stratified by each stratification factor were presented. These analyses were conducted for the ITT population.

[0441] Tertiary Endpoints Analyses: Time-to-event tertiary endpoints were analyzed by the same methods as described for the primary efficacy endpoint. Kaplan-Meier estimates, the log-rank test stratified by stratification factors used at randomization, and the Cox proportional hazards model as specified for the primary efficacy endpoint, were summarized by treatment group. In view of the 90-day monitoring period for CV events, if applicable, tertiary endpoints for patients who had a non-CV death within 90 days of last contact without having had an earlier CV event were censored at the time of death. If applicable, tertiary endpoints for patients who gad a non-CV death more than 90 days after last contact without having had an earlier CV event were censored at the time of last contact. Kaplan-Meier curves stratified by each of the stratification factors were presented.

[0442] The fasting lipid panel was tested at Screening (Visit 1 or Visit 1.1), Randomization visit (Visit 2; Day 0), Visit 3 (Day 120; ~4 Months) and all other follow-up visits including the last visit. For change from baseline to 1 year preparative ultracentrifugation measurements for LDL-C were analyzed, unless this value was missing. If the LDL-C preparative ultracentrifugation values were missing, then another LDL-C value was used, with prioritization of values obtained from LDL-C Direct measurements, followed by LDL-C derived by the Friedewald calculation (only for subjects with TG <400 mg/dL), and finally LDL-C derived using the calculation published by Hopkins University investigators (Martin SS, Blaha MJ, Elshazly MB, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. JAMA. 2013; 310:2061-8.). In addition, change from baseline to day 120 in LDL-C utilizing Friedewald's and Hopkins

methods was analyzed, using the arithmetic mean of LDL-C obtained at Visit 2 (Day 0) and the preceding Visit 1 (or Visit 1.1). If one of these values was missing, the single available LDL-C value was used. LDL-C according to Hopkins was calculated at each visit.

[0443] The randomization visit was considered Baseline. If a baseline value was not available from the randomization visit, then the latest screening value was used. For measurements of lipids, lipoproteins and inflammatory markers, the change and the percent change were summarized at each visit. Since these biomarkers are typically not normally distributed, the Wilcoxon rank-sum test was used for treatment comparisons of the percent change from baseline, and medians and quartiles were provided for each treatment group. The medians of the differences between the treatment groups and 95% CIs were estimated with the Hodges-Lehmann method. In addition, shift –tables were generated as appropriate.

[0444] As an additional exploratory analysis, the relationship between post-baseline biomarker values and treatment effects with the primary and key secondary endpoints were assessed by adding biomarker values (for example, at 4 months, or at 1 year, etc.) as time-dependent covariates in the Cox proportional hazards model. Diagnostic plots for the proportional hazard's assumption was evaluated. Weight was measured at the screening visit and at all follow-up visits, including the last visit of the study. Waist circumference was measured at the randomization visit (Visit 2; Day 0), Visit 5 (Day 720) and the last visit of the study. Descriptive statistics were presented by visit and treatment group for baseline, post-treatment change from baseline, and the percent change from baseline. Analysis methods for repeated measurements were used to compare percent change from baseline between treatments.

[0445] Additional prespecified efficacy endpoints and analyses of this study are listed below. These endpoints and analyses were exploratory in nature and were not included in the original testing scheme:

- Time-to-event analyses as done for the primary analysis were carried out at 1-year and 2-year landmarks for the ITT Population;
- For the recurrent CV events analyses based on the 5-component MACE (CV death, non-fatal MI, non-fatal stroke, unstable angina requiring hospitalization,

or coronary revascularization), a total CV event was performed using a Negative Binomial Model analysis;

- An on treatment sensitivity analysis was performed including primary events with onset up to 0 and 30 days after permanent discontinuation of study drug;
- As done for the primary analysis, time-to-event analyses at 1-year and 2-year landmarks for the key secondary endpoints for the ITT Population;
- An analysis of the following clinical events that are positively adjudicated as tertiary endpoints for the ITT Population:
    - Composite of total mortality, or new CHF;
    - Composite of CV death, or new CHF;
    - Sudden cardiac death;
    - Peripheral artery disease (PAD); and
    - Atrial fibrillation, or atrial flutter.
- An analysis of the following as tertiary endpoints for the ITT Population:
    - Relationship between on-treatment hsCRP and primary and key secondary endpoints; and
    - Relationship between on-treatment serum EPA and primary and key secondary endpoints.
- To assess relationships between on-treatment hsCRP and primary and key secondary endpoints, subgroup analyses as done for the ITT population for patients grouped according to (1) values greater or equal to or (2) less than 2 mg/dL at baseline and at 2 years;
- To assess relationships between on-treatment serum EPA and primary and key secondary endpoints, Kaplan Meier curves for AMR101 patients grouped into tertiles based on values at year 1 compared with placebo patients;
- The following were added to the subgroup analyses:
    - Baseline HbA1c value (<6.5%, ≥6.5%);
    - Baseline PAD; and
    - Baseline TG ≥ 150mg/dL with HDL-C ≤ 40 mg/dL for males and ≤ 50 mg/dL for females.

[0446] The following list presents additional pre-specified exploratory efficacy analyses that are of particular interest to the general clinical and scientific community that were also explored in this study:

- Non-fatal myocardial infarction (MI) (including both clinical manifestation and silent MI categorizations) for the ITT Population;
- Evaluation of effect of time-weighted (or area under the curve [AUC]) EPA data on the primary and key secondary composite endpoints for the ITT Population;
- Sensitivity analyses on primary and key secondary composite endpoints by excluding elective coronary artery revascularizations if onset is <3 months post randomization; and also excluding peri-procedural MIs for the ITT Population;
- Two silent MI (SMI) sensitivity analyses on primary and key secondary composite endpoints – ITT Population:
    - Counting all potential SMIs identified by CEC ECG reviewer, whether confirmed at final ECG or not; and
    - Counting only potential SMIs that have at least one confirmatory ECG showing persistence of Q-waves (even if not present at final ECG).
- Non-alcoholic fatty liver disease (NAFLD) analyses using NAFLD Fibrosis Score (NFS), assessing – ITT Population:
    - Effect on primary and key secondary composite endpoints by baseline NFS category; and
    - Treatment effect on change from baseline in NFS at 1 and 5 years.
- Individual and combined on-treatment goal achievement of triglyceride (TG) ≤ 150 mg/dL and hsCRP ≤ 2 mg/L at 2 years, and end of study for the ITT Population;
- Additional renal function (eGFR) analyses – ITT Population:
    - Primary and key secondary composite endpoints for patients with baseline renal dysfunction [eGFR] ≥60 and <90 mL/min/1.73m^2; and
    - Treatment effect on change from baseline in renal function (eGFR) at 1 and 5 years.
- Sensitivity analyses on primary and key secondary composite endpoints by excluding patients with post-randomization LDL-C values >100 mg/dL; and another for >70 mg/dL for the ITT Population;
- Analyses of hospitalization data (pooled positively adjudicated unstable angina requiring hospitalization, congestive heart failure [CHF] requiring hospitalization, and cardiac arrhythmia requiring hospitalization) for the ITT Population;

- Time from randomization to first hospitalization; and
- Recurrent event analysis on hospitalizations.

- Additional subgroup analyses (US versus Non-US) on the primary and key secondary composite endpoints; also potentially other endpoints for the ITT Population;
- Additional subgroup analyses for patients with very high-risk cardiovascular disease (CVD) (defined as recurrent cardiovascular [CV] events or CV events in more than one vascular bed, i.e., polyvascular disease) on the primary and key secondary composite endpoints; also potentially other endpoints for the ITT Population;
- Sensitivity analyses for apo B to assess whether subgroup(s) with apo B reductions from baseline beyond certain threshold(s) have corresponding incremental reductions in clinical endpoint events;
- Sensitivity analyses for myocardial infarctions excluding peri-procedural MIs (Type 4a);
  - Additional analyses factoring for recency and number of prior MIs
- Sensitivity analyses for stroke, factoring for patients with history of stroke
- Sensitivity analyses for heart failure, factoring for patients with history of heart failure
- Sensitivity analyses for endpoints comprised of coronary revascularizations which exclude early elective revascularizations (e.g., within 30-90 days post-randomization)
- Subgroup analyses of primary (and potentially key secondary) endpoint(s) among the following cohorts:
  - High risk patients with “the hypertriglyceridemic waist” (obese patients at high CV risk);
  - High risk subgroup defined by baseline hsTNT level (and potentially by NT-proBNP from archived frozen samples); and
  - High TG/low LDL-C phenotypes;
  - High-risk patients as defined by their atherothrombotic risk score.
- Treatment effect on:
  - Peripheral arterial events (e.g., major adverse limb events [MALE]); and
  - Hypertension, using BP as a continuous variable.

- Using archived frozen serum biosamples, additional analyses of fatty-acid levels (and ratios), including baseline and on-treatment effects on EPA, DHA, DPA, AA (and associated ratios) and relationships between fatty-acid levels and cardiovascular outcomes;
    - Relationship between on-treatment fatty-acid levels;
    - Baseline fatty-acid levels; and
    - Study medication compliance.
- Using archived frozen biosamples (e.g., serum and whole blood); potential analyses of treatment effects on biomarkers and genetic markers and associations with outcomes, including but not limited to the following:
    - LDL-P;
    - RLP-C (measured);
    - LDL-TG;
    - Ox-LDL;
    - Galectin-3;
    - Lp(a) at baseline, as a predictor of CVD benefit;
    - LpPLA2;
    - HDL2, HDL3, apo A-I, apo A-II, HDL-P, apo C-III (and apo C-III in apo-B containing proteins), apo A-V, Apo E subtypes (2, 3, 4), IL-6, lipoprotein lipase (LPL); and
    - Analyses may include change (and percent change) from baseline, on-treatment comparisons between treatment groups with testing as predictors of CV risk.
- Exploratory analyses of differential treatment effects for potential benefit (from adverse event reports) of:
    - Ophthalmologic changes (e.g., incidence of age-related macular degeneration, progression of diabetic retinopathy);
    - Cognitive impairment;
    - Erectile dysfunction; and
    - Ischemic cardiomyopathy (as indicated by hospitalization for CHF, ICD placement etc.).
- Additional genetic bioassays including genes which may relate to triglyceride, lipid metabolism, and CVD; and

- Effects of potential mediators identified *post hoc* on primary/key secondary outcome measures.

[0447] In this study, new onset diabetes was defined as Type 2 diabetes newly diagnosed during the treatment/follow-up period (i.e. patients with no history of diabetes at randomization). For purposes of this study, a diagnosis of diabetes was made based on the observation of:

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

[0448] In the absence of unequivocal hyperglycemia, the first three criteria were confirmed by repeat testing.

[0449] Exploratory Subgroup Analyses: Analyses of the effects that patients off study drug and withdrawn from study have on the primary endpoint were performed. Subgroup analyses of the primary and key secondary endpoints were performed as described for the primary endpoint. For each subgroup, Kaplan-Meier estimates, the log-rank test stratified by stratification factors used at randomization (except where the subgroup was a stratification factor), and HRs and CIs from the Cox proportional hazards model as specified for the primary efficacy endpoint, were summarized by treatment

group. Demographic, disease, treatment, and baseline lipid and lipoproteins parameters were explored.

[0450] Demographic parameters included: Gender; age at baseline (<65 years and ≥65 years); race (white and nonwhite, or any other subset with at least 10% of the total number of patients); geographical region (Westernized, Eastern European, and Asia Pacific countries); and baseline ezetimibe use (yes/no).

[0451] Disease parameters included: CV risk category; the presence/absence of diabetes at baseline; and renal dysfunction at baseline (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73m^2) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation as follows:

$$eGFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ [if female]} \times 1.159 \text{ [if black]}$$

Where:

S_{cr} is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

α is -0.329 for females and -0.411 for males,

min indicates the minimum of S_{cr}/κ or 1, and

max indicates the maximum of S_{cr}/κ or 1.

[0452] Treatment Parameters included: Statin intensity at baseline (statin type and regimen); and statin intensity categories as defined in ACC/AHA Cholesterol Guidelines (Stone 2013) and patient's 10-year CV Risk Score (Goff 2013).

[0453] Baseline Lipid and Lipoprotein Parameter included: LDL-C (by tertile); HDL-C (by tertile, and tertile by gender); TG (by tertile, and tertile by gender); RLP-C (by tertile); TG ≥150 mg/dL and TG <150 mg/dL; TG ≥200 mg/dL and TG <200 mg/dL; TG ≥ median, TG < median; combined highest tertile for TG and lowest tertile for HDL-C; gender-specific highest tertile for TG and lowest tertile for HDL-C; TG ≥ 200 mg/dL with HDL-C ≤35 mg/dL; hsCRP (≤3 mg/L and >3 mg/L) and by gender; hsCRP (≤2 mg/L and >2 mg/L) and by gender; Apo B (by tertile); non-HDL-C (by tertile); baseline hemoglobin A1c (Hb1c) value (<6.5%, ≥6.5%); baseline PAD; and baseline TG levels ≥150 mg/dL with high-density lipoprotein cholesterol (HDL-C) levels ≤ 40 mg/dL for males and ≤50 mg/dL for females.

[0454] A Cox proportional hazard (PH) model as mentioned above but additionally with baseline TG as a covariate were fitted to the data at each interim. Diagnostic plots for the PH assumption were evaluated. The consistency of the treatment effects in subgroups was assessed for the primary and key secondary efficacy endpoints. For each subgroup variable, a Cox PH model with terms for treatment, stratification factors (with the exception of those subgroup variables related to the stratification factors, i.e., CV risk category), subgroup, and treatment-by-subgroup interaction were performed. The main treatment effect was tested with this model. P-values for testing the interaction terms < 0.15 were considered significant. Results were presented in a Forest plot.

[0455] Subgroup analyses of the primary and key secondary endpoints were performed as described for the primary endpoint. For each subgroup, Kaplan-Meier estimates, the log-rank test stratified by stratification factors used at randomization (except where the subgroup was a stratification factor), and HRs and CIs from the Cox proportional hazards model as specified for the primary efficacy endpoint, were summarized by treatment group. All subgroup analyses were conducted for the ITT, mITT and PP populations.

[0456] Interim Efficacy Analysis: Two interim analyses were planned for the primary efficacy endpoint using adjudicated events when approximately 60% (967 events) and approximately 80% (1290 events) of the total number of primary endpoint events planned (1612) was reached. The planned interim analyses were based on a group-sequential design.

[0457] The interim results of the study were monitored by an independent Data Monitoring Committee (DMC). The analyses were performed by the independent statistical team who was unblinded to the treatment assignment and reported only to the DMC. If the study was terminated early following interim analysis, patients were notified promptly and brought in for their final close-out visit, and the final analyses of efficacy and safety included all data through their final visit. All suspected events were adjudicated in a blinded manner by the CEC. The time to event was calculated as the time from randomization to the onset date of the event (as determined by the CEC). Patients who do not experience any of the above events at the time of data cutoff for the interim but were still in the trial were considered censored at the time of their last regular contact before the interim data cutoff.

[0458] The alpha-levels for the two protocol prespecified interim analyses and the final analysis are based on a group sequential design (GSD) with O'Brien-Fleming boundaries generated using the Lan-DeMets alpha spending function. The one-sided alpha-levels and boundaries based on a Z-test and the achieved p-values for each of the two interim analyses and the final analysis are given in Table 10.

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

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

[0459] Analysis of Safety: All analyses of safety were conducted on the safety population, which was defined as all randomized patients. The safety assessment was based on the frequency of adverse events, physical exams, vital signs and safety laboratory tests. AEs with new onset during the study between the initiation of study drug and 30 days after the last dose of study drug for each patient was considered treatment-emergent (TEAEs). This included any AE with onset prior to initiation of study drug and increased severity after the treatment initiation.

[0460] Treatment-emergent adverse events were summarized by system organ class and preferred term, and by treatment. This included overall incidence rates (regardless of severity and relationship to study drug), and incidence rates for moderate or severe adverse events. A summary of SAEs and adverse events leading to early discontinuation (for ≥30 days) were presented through data listings. Patients who restarted study drug were included in the summary of AEs leading to discontinuation. Safety laboratory tests and vital signs were summarized by post-treatment change from baseline for each of the parameters using descriptive statistics by treatment group. Those patients with significant laboratory abnormalities were identified in data listings. Additional safety parameters were summarized in data listings.

[0461] In addition to the treatment-emergent adverse events analyses, analyses on all AEs (serious and non-serious) and all serious AEs were performed.

[0462] All AEs included: treatment-emergent adverse event (TEAE) by high level group term (HLGT); TEAE by high level term (HLT); and TEAE by system organ class (SOC), HLGT, HLT, and preferred term (PT) (4-level table).

[0463] All SAEs included: treatment emergent SAE by HLGT; treatment emergent SAE by HLT; and treatment emergent SAE by SOC, HLGT, HLT, and PT (4-level table).

Clinical Laboratory Evaluation

[0464] The criteria for potentially clinically significant (PCS) laboratory values are provided in Table 11 and Table 12. A treatment-emergent PCS high value at any time was defined as a change from a value less than or equal to the upper reference limit at baseline to a PCS high value at any post-baseline measurement. A treatment-emergent PCS low value at any time was defined as a change from a value greater than or equal to the lower reference limit at baseline to a PCS low value at any post-baseline measurement. Number (%) of patients with any post-baseline PCS laboratory values was summarized by treatment group. A listing of patients with PCS laboratory values at any time, i.e., baseline or at any post-baseline visit, were included.

Table 11. Potentially Clinically Significant Chemistry Values

Parameter	PCS Low	PCS High
Albumin	≤3.3 g/dL	≥5.8 g/dL
Alkaline Phosphate	Not Applicable (N/A)	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
ALT	N/A	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
AST	N/A	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
Bilirubin	N/A	>1x ULN to 2x ULN >2x ULN to 3x ULN >3x ULN
ALT + Bilirubin	N/A	>3x ULN + 2x ULN (Bilirubin)
AST + Bilirubin	N/A	>3x ULN + 2x ULN (Bilirubin)
Calcium	≤7 mg/dL	≥11 g/dL

		≤12 mg/dL
Chloride	<70 mmol/L	>120 mmol/L
Creatinine	<0.5 mg/dL (Female) <0.65 mg/dL (Male)	>1.6 mg/dL (Female) >2.0 mg/dL (Male); ≥ 50% increase from baseline
Creatine Kinase	<30 U/L (Female) <0.55 U/L (Male)	>1x ULN to 5x ULN >5x ULN to 10x ULN >10x ULN
Glucose (fasting)	≤36 mg/dL; ≤70 mg/dL	≥126 mg/dL; ≥130 mg/dL
Potassium (K)	≤3.0 mEq/L	≥150 mEq/L
Total Protein	<5.0 g/dL	≥9.5 g/dL
Urea Nitrogen (BUN)	N/A	≥31 mg/dL
Uric Acid	<1.9 mg/dL (Female) <2.5 mg/dL (Male)	>7.5 mg/dL (Female) >8 mg/dL (Male)

Table 12. Potentially Clinically Significant Hematology Values

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

Drug-Induced Liver Injury (DILI)

[0465] DILI cases were investigated through the following analyses:

- A graph of distribution of peak values of alanine aminotransferase (ALT) versus peak values of total bilirubin (TBL) during the treatment period was prepared, using a logarithmic scale. In the graph, for each patient, the peak

TBL times the Upper Limit of Normal (ULN) were plotted against the peak ALT times the ULN, where the peak TBL and peak ALT may or may not have happened on the same day of liver testing. The graph was divided into 4 quadrants with a vertical line corresponding to 3x ULN for ALT and a horizontal line corresponding to 2x ULN for TBL. The upper right quadrant was referred to as the potential Hy's Law quadrant, including potentially DILI cases.

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

Study Design

[0466] This was a Phase 3b, multi-center, multi-national, prospective, randomized, double-blind, placebo-controlled, parallel-group study. This was also an event-driven trial comparing the effect of AMR101 vs. placebo in terms of the composite endpoint listed above as the primary endpoint. The placebo contained mineral oil to mimic the color and consistency of icosapent ethyl in AMR101 and was administered in the same capsule fill volume and count as the AMR101. The study accrued a total of 1612 efficacy endpoint events with two planned interim analyses when approximately 967 (60%) and 1290 (80%) of the events had been adjudicated. The study included patients with established CVD (CV Risk Category 1) and patients ≥50 years old with diabetes and at least one additional risk factor for CVD but with CVD not established (CV Risk Category 2). Randomization was stratified by cardiovascular risk stratum which included the secondary-prevention cohort (i.e., CV Risk Category 1) or primary-prevention cohort (i.e., CV Risk Category 2), with the primary prevention cohort capped at 30% of enrolment, use or no use of ezetimibe, and by geographical region. Details of the study design are shown in Figure 1.

[0467] Sample size calculation was based on the assumption of constant hazard, asymmetric recruitment rate overtime and without factoring for dropouts. A risk reduction corresponding to a HR of 0.85 (AMR101 vs. placebo) was assumed. 1612 events were required to detect this HR with approximately 90% power with one-sided alpha-level at 2.5% and with two interim analyses. The operating characteristics of this design were identical to those of a corresponding group sequential design with a two-sided alpha level of 0.05.

[0468] The recruitment period was assumed to be 4.2 years with 20% recruitment in the first year, 40% in the second year, 20% in the third year, 19% in the fourth year and the remaining 1% in the last 0.2 years. The estimated maximum study duration was 6.5 years unless the trial was terminated early for efficacy or safety issues. A one-year event rate of 5.2% (hazard = 0.053) in the control arm was also assumed. Under these assumptions the number of patients enrolled was N = 7990.

[0469] Since this was an events-driven trial, the 'sample size' was the number of events rather than the number of patients. The number of events that occurred depends primarily on three factors: how many patients were enrolled; the combined group event rate; and how long the patients were followed. Because of the difficulty in predicting the combined event rate, the Sponsor monitored the event rate as the trial progressed. If the combined event rate was less than anticipated, either increasing the number of patients, extending the length of follow-up, or a balance of adjusting both factors was necessary to achieve the sample size of 1612 events.

[0470] At completion of study enrollment, the actual number of patients randomized may have varied from the target number (either original or revised) as a result of the inherent lag between the date the last patient started screening and the date the last patient was randomized.

Completion of Study

[0471] The end of the study was at the time the last patient-last visited of the follow-up period of the study. The IRB and IEC were notified about the end of the study according to country-specific regulatory requirements.

Standardized Definitions for the Cardiovascular Trial Endpoint Events

[0472] In assessing patients in this clinical trial, the follow definitions were used:

[0473] Definition of Cardiovascular Death: Cardiovascular death includes death resulting from an acute myocardial infarction, sudden cardiac death, death due to congestive heart failure (CHF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other cardiovascular causes.

[0474] Death due to acute myocardial infarction: refers to a death by any mechanism (e.g., arrhythmia, CHF) within 30 days after a MI related to the immediate consequences of the MI, such as progressive CHF or recalcitrant arrhythmia. Mortal events that occur after a "break" (e.g., a CHF and arrhythmia-free period of at least a week) should be classified as CV or non-CV death, and if classified as a CV death, should be attributed to the immediate cause, even though the MI may have increased the risk of that event (e.g., the risk of arrhythmic death is increased for many months after an acute MI). Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI (see Definition of MI) or by autopsy findings showing recent MI or recent coronary thrombosis. Death resulting from a procedure to treat a MI (percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG)), or to treat a complication resulting from MI, should also be considered death due to acute MI. Death resulting from an elective coronary procedure to treat myocardial ischemia (i.e., chronic stable angina) or death due to a MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered as a death due to a CV procedure.

[0475] Sudden Cardiac Death: refers to a death that occurs unexpectedly, not within 30 days of an acute MI, and includes the following deaths: death witnessed and instantaneous without new or worsening symptoms; death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest an acute MI; death witnessed and attributed to an identified arrhythmia (e.g., captured on an electrocardiographic (ECG) recording, witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator review); death after unsuccessful resuscitation from cardiac arrest; death after successful resuscitation from cardiac arrest and without identification of a non-cardiac etiology; and/or unwitnessed death without other cause of death (information regarding the patient's clinical status preceding death should be provided, if available)

[0476] General Considerations for Sudden Cardiac Death: A subject seen alive and clinically stable 12-24 hours prior to being found dead without any evidence or information of a specific cause of death should be classified as "sudden cardiac death." Deaths for which there is no information beyond "patient found dead at home" are classified as "death due to other cardiovascular causes". (See Definition of Undetermined Cause of Death, for full details below).

[0477] Death due to Congestive Heart Failure: refers to a death in association with clinically worsening symptoms and/or signs of heart failure (See Definition of Heart Failure Event, for full details below). Deaths due to heart failure can have various etiologies, including single or recurrent myocardial infarctions, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.

[0478] Death due to Stroke: refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke (See Definition of Transient Ischemic Attack and Stroke, for full details below).

[0479] Death due to Cardiovascular Procedures: refers to death caused by the immediate complications of a cardiac procedure.

[0480] Death due to Cardiovascular Hemorrhage: refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage (see Definition of Transient Ischemic Attack and Stroke, for full details below), non-procedural or non-traumatic vascular rupture (e.g., aortic aneurysm), or hemorrhage causing cardiac tamponade.

[0481] Death due to Other Cardiovascular Causes: refers to a CV death not included in the above categories (e.g., pulmonary embolism or peripheral arterial disease).

[0482] Definition of Non-Cardiovascular Death: Non-cardiovascular death is defined as any death that is not thought to be due to a cardiovascular cause. The following is a suggested list of non-cardiovascular causes of death for this trial.

- Non-malignant, Non-cardiovascular Death:
  - Pulmonary;
  - Renal;

- Gastrointestinal;
- Hepatobiliary;
- Pancreatic;
- Infection (includes sepsis)
- Non-infectious (e.g., systemic inflammatory response syndrome (SIRS));
- Hemorrhage that is neither cardiovascular bleeding nor a stroke;
- Accidental (e.g., physical accidents or drug overdoses) or trauma;
- Suicide; and/or
- Prescription Drug Error (e.g., prescribed drug overdose, use of inappropriate drug, or drug-drug interaction); and
- Neurological process that is not a stroke or hemorrhage.

- Malignancy: Malignancy is coded as cause of death, if:
  - Death results directly from the cancer; or
  - Death results from a concurrent illness that could be a consequence of a cancer; or
  - Death results from withdrawal of other therapies because of concerns relating to the poor prognosis associated with the cancer; and
  - Death results from an illness that is not a consequence of a cancer.

[0483] Cancer deaths may arise from cancers that were present prior to randomization or which developed subsequently. It may be helpful to distinguish these two scenarios (i.e. worsening of prior malignancy; new malignancy). Suggested categorization includes the following organ systems; Lung/larynx, breast, leukemia/lymphoma, upper GI, melanoma, central nervous system, colon/rectum, renal, bladder, prostate, other/unspecified, or unknown.

[0484] Definition of Undetermined Cause of Death: refers to a death not attributable to one of the above categories of cardiovascular death or to a non-cardiovascular cause. The inability to classify the cause of death is generally due to lack of information (e.g., the only available information is “patient died”) or when there is insufficient supporting

information or detail to assign the cause of death. In this trial, when a cause of death was not readily apparent (e.g., found dead at home), the cause was assumed to be cardiovascular in origin, unless one of the following two scenarios occur: there is no information or data available regarding the circumstances of death other than that a death has occurred; or the available data are conflicting regarding whether the death was cardiovascular or non-cardiovascular.

[0485] Definition of Myocardial Infarction: The term myocardial infarction (MI) is used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. In general, the diagnosis of MI requires the combination of: evidence of myocardial necrosis (either changes in cardiac biomarkers or postmortem pathological findings); and supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging.

[0486] The totality of the clinical, electrocardiographic, and cardiac biomarker information should be considered to determine whether or not a MI has occurred. Specifically, timing and trends in cardiac biomarkers and electrocardiographic information require careful analysis. The adjudication of MI should also take into account the clinical setting in which the event occurs. MI may be adjudicated for an event that has characteristics of a MI, but which does not meet the strict definition because biomarker or electrocardiographic results are not available.

[0487] The Criteria for myocardial infarction include clinical presentation, biomarker evaluation, and ECG changes.

[0488] Clinical Presentation: The clinical presentation is consistent with diagnosis of myocardial ischemia and infarction. Other findings that might support the diagnosis of MI should be take into account because a number of conditions are associated with elevations in cardiac biomarkers (e.g., trauma, surgery, pacing, ablation, congestive heart failure, hypertrophic cardiomyopathy, pulmonary embolism, severe pulmonary hypertension, stroke or subarachnoid hemorrhage, infiltrative and inflammatory disorders of cardiac muscle, drug toxicity, burns, critical illness, extreme exertion, and chronic kidney disease). Supporting information can also be considered from myocardial imaging and coronary imaging. The totality of the data may help differentiate acute MI from the background disease process.

[0489] Biomarker Evaluation: For cardiac biomarkers, laboratories should report an upper reference limit (URL). If the 99th percentile of the upper reference limit (URL) from the respective laboratory performing the assay is not available, then the URL for myocardial necrosis from the laboratory should be used. If the 99th percentile of the URL or the URL for myocardial necrosis is not available, the MI decision limit for the particular laboratory should be used as the URL. Laboratories can also report both the 99th percentile of the upper reference limit and the MI decision limit. Reference limits from the laboratory performing the assay are preferred over the manufacturer's listed reference limits in an assay's instructions for use. CK-MB and troponin are preferred, but CK may be used in the absence of CK-MB and troponin. For MI subtypes, different biomarker elevations for CK, CK-MB, or troponin were required. The specific criteria were referenced to the URL. In this study, patients may present acutely to hospitals which are not participating sites, it is not practical to stipulate the use of a single biomarker or assay, and the locally available results are to be used as the basis for adjudication. Since the prognostic significance of different types of myocardial infarctions (e.g., periprocedural myocardial infarction versus spontaneous myocardial infarction) may be different, considerations evaluating outcomes for these subsets of patients separately were made.

[0490] ECG Changes: ECG changes can be used to support or confirm a MI. Supporting evidence may be ischemic changes and confirmatory information may be new Q waves.

[0491] Criteria for acute myocardial ischemia (in absence of left ventricular hypertrophy (LVH) and left bundle branch block (LBBB)) include:

- ST elevation: New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥ 0.2 mV in men (> 0.25 mV in men < 40 years) or ≥ 0.15 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads.
- ST depression and T-wave changes new horizontal or down-sloping ST depression ≥ 0.05 mV in two contiguous leads; and/or new T inversion ≥ 0.1 mV in two contiguous leads.

[0492] The above ECG criteria illustrate patterns consistent with myocardial ischemia. In patients with abnormal biomarkers, it is recognized that lesser ECG

abnormalities may represent an ischemic response and may be accepted under the category of abnormal ECG findings.

[0493] Criteria for pathological Q-wave include: any Q-wave in leads V2-V3 ≥ 0.02 seconds or QS complex in leads V2 and V3; Q-wave ≥ 0.03 seconds and ≥ 0.1 mV deep or QS complex in leads I, II, aVL, aVF, or V4-V6 in any two leads of a contiguous lead grouping (I, aVL, V6; V4-V6; II, III, and aVF); and R-wave 0.04 s in V1–V2 and R/S ratio >1 with a concordant positive T-wave in the absence of a conduction defect.

[0494] The same criteria are used for supplemental leads V7-V9, and for the Cabrera frontal plane lead grouping.

[0495] Criteria for Prior Myocardial Infarction include: pathological Q-waves, as defined above; and R-wave ≥ 0.04 seconds in V1-V2 and R/S ≥ 1 with a concordant positive T-wave in the absence of a conduction defect.

[0496] Myocardial Infarction Subtypes: Several MI subtypes are commonly reported in clinical investigations and each is defined below:

1. Spontaneous MI:

- Detection of rise and/or fall of cardiac biomarkers with at least one value above the URL with at least one of the following:
    - Clinical presentation consistent with ischemia;
    - ECG evidence of acute myocardial ischemia;
    - New pathological Q waves;
    - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; and/or
    - Autopsy evidence of acute MI
- If biomarkers are elevated from a prior infarction, then a spontaneous myocardial infarction is defined as one of the following:
    - Clinical presentation consistent with ischemia;
    - ECG evidence of acute myocardial ischemia;
    - New pathological Q waves;

- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; and/or
- Autopsy evidence of acute MI; and

- Both of the Following:
  - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI (note: If biomarkers are increasing or peak is not reached, then a definite diagnosis of recurrent MI is generally not possible); and
  - ≥ 20% increase (and > URL) in troponin or CK-MB between a measurement made at the time of the initial presentation and a further sample taken 3-6 hours later.

2. Percutaneous Coronary Intervention-Related Myocardial Infarction*:* is defined by any of the following criteria. MI associated with and occurring within 48 hours of PCI, with elevation of cardiac biomarker values to > 5 x 99th percentile of the URL in patients with normal baseline values (≤99th percentile URL), or a rise of [cardiac biomarker] values ≥20% if baseline values are elevated and are stable or falling. This classification also requires at least 1 of the following:

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

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

- Biomarker elevations within 48 hours of CABG:
  - Troponin or CK-MB (preferred) > 10 x 99th percentile of the URL; and

- No evidence that cardiac biomarkers were elevated prior to the procedure; or
- Both of the following are true:
  - ≥ 50% increase in the cardiac biomarker result; and
  - Evidence that cardiac biomarker values were decreasing (e.g., two samples 3-6 hours apart) prior to the suspected MI; and

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

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

[0497] In the case of evanescent Q waves, the last ECG determines whether a silent infarction has occurred.

[0498] Sub-classification of Myocardial Infarction: The universal MI definition includes clinical classification of different types of MI, electrocardiographic features, and by biomarker evaluation, with the definition of each provided below.

[0499] Clinical Classification of Different Types of Myocardial Infarction include the following:

- Type 1: Spontaneous myocardial infarction related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection;
- Type 2: Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension;
- Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood;
- Type 4a: Myocardial infarction associated with Percutaneous Coronary Intervention (PCI);
- Type 4b: Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy;
- Type 4c: Myocardial infarction associated with stent restenosis as detected by angiography or at autopsy; and
- Type 5: Myocardial infarction associated with CABG.

[0500] By Electrocardiographic Features include:

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

[0501] All events adjudicated as MI were classified as STEMI, NSTEMI, or Unknown; however, it is acknowledged that a significant proportion of periprocedural (PCI or CABG) events may have missing, inadequate or uninterpretable ECG documentation.

[0502] By Biomarker Elevation (per Universal MI Definition): The magnitude of cardiac biomarker elevation can be calculated as a ratio of the peak biomarker value divided by the 99th percentile URL. The biomarker elevation can be provided for various MI subtypes.

[0503] Definition of Hospitalize of Unstable Angina: Unstable angina requiring hospitalization is defined as:

- Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥ 10 minutes in duration occurring at rest or in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity;
- Prompting an unscheduled hospitalization within 24 hours of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24-hour stay (or a date change if the time of admission/discharge is not available); and
- At least one of the following:
    - New or worsening ST or T wave changes on resting ECG (in absence of confounders, such as LBBB or LVH);
        - Transient ST elevation (duration <20 minutes): New ST elevation at the J point in two anatomically contiguous leads with the cut-off points: ≥0.2 mV in men (>0.25 mV in men <40 years) or ≥0.15 mV in women in leads V2-V3 and/or ≥0.1 mV in other leads
        - ST depression and T-wave changes: New horizontal or down-sloping ST depression ≥0.05 mV in two contiguous leads; and/or new T inversion ≥0.1 mV in two contiguous leads.
    - Definite evidence of inducible myocardial ischemia as demonstrated by:
        - An early positive exercise stress test, defined as ST elevation or ≥2 mm ST depression prior to 5 mets; or at least one of the

following: stress echocardiography (reversible wall motion abnormality); myocardial scintigraphy (reversible perfusion defect); or MRI (myocardial perfusion deficit under pharmacologic stress.

- Angiographic evidence of new or worse ≥70% lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs; and
- Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge;

- Negative cardiac biomarkers and no evidence of acute MI.

[0504] General Considerations include:

[0505] Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β-blockers, should be considered supportive of the diagnosis of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3, would be insufficient alone to support classification as hospitalization for unstable angina.

[0506] If subjects were admitted with suspected unstable angina, and subsequent testing revealed a noncardiac or non-ischemic etiology, this event should not have been recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for myocardial infarction should not have been adjudicated as unstable angina.

[0507] Planned hospitalization or re-hospitalization for performance of an elective revascularization in patients who did not fulfill the criteria for unstable angina should not have been considered a hospitalization for unstable angina. For example: hospitalization of a patient with stable exertional angina for coronary angiography and PCI that is prompted by a positive outpatient stress test should not be considered hospitalization for unstable angina; or re-hospitalization of a patient meeting the criteria for unstable angina

who was stabilized, discharged, and subsequently readmitted for revascularization, does not constitute a second hospitalization for unstable angina.

[0508] A patient who underwent an elective catheterization where incidental coronary artery disease was found and who subsequently underwent coronary revascularization was not be considered as meeting the hospitalization for unstable angina endpoint.

[0509] Transient Ischemic Attack: Transient ischemic attack (TIA) is defined as a transient episode (< 24 hours) of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

[0510] Stroke: Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

[0511] Ischemic Stroke: Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

[0512] Hemorrhagic Stroke: Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage. However, microhemorrhages seen on T2-weighted MRI imaging, subdural and epidural hemorrhages are not considered hemorrhagic strokes.

[0513] Undetermined Stroke: Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as ischemic or hemorrhagic.

[0514] Stroke Disability: Stroke disability should be measured by a reliable and valid scale in all cases, typically at each visit and 90 days after the event. For example, the modified Rankin Scale show below in Table 13 may be used to address this requirement:

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

Scale	Disability
0	No symptoms at all.

1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability, unable to perform all previous activities but able to look after own affairs without assistance.
3	Moderate disability; requiring some help but able to walk without assistance.
4	Moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability, bedridden, incontinent, and requiring constant nursing and attention.
6	Dead

[0515] Additional Considerations: Evidence of vascular central nervous system injury without recognized neurological dysfunction may be observed. Examples include micro-hemorrhage, silent infarction, and silent hemorrhage. Subdural hematomas are intracranial hemorrhagic events and not strokes. The distinction between a Transient Ischemic Attack and an Ischemic Stroke is the presence of Infarction. Persistence of symptoms is an acceptable indicator of acute infarction.

[0516] Definition of Heart Failure Event: is defined as an event that meets all of the following criteria:

- The patient is admitted to the hospital with a primary diagnosis of HF;
- The patient's length-of-stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable);
- The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least one of the following: dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea), decreased exercise tolerance, fatigue, or other symptoms of worsened end-organ perfusion or volume overload (must be specified and described by the protocol);
- The patient has objective evidence of new or worsening HF, consisting of at least two physical examination findings or one physical examination finding and at least one laboratory criterion), including:
    - Physical examination findings considered to be due to heart failure, including new or worsened: Peripheral edema, increasing abdominal distention or ascites (in the absence of primary hepatic disease), S_3

gallop, clinically significant or rapid weight gain thought to be related to fluid retention; or

- Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including: increased B-type natriuretic peptide (BNP)/ N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of heart failure (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL). In patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline, radiological evidence of pulmonary congestion, or non-invasive or invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic criteria could include: E/e' > 15 or D-dominant pulmonary venous inflow pattern, plethoric inferior vena cava with minimal collapse on inspiration, or decreased left ventricular outflow tract (LVOT) minute stroke distance (time velocity integral [TVI]) OR right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥ 18 mmHg, central venous pressure ≥ 12 mmHg, or a cardiac index < 2.2 L/min/m^2.

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

[0517] New Heart Failure/Heart Failure Not Requiring Hospitalization*:* is defined as an event that meets all of the following: the patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization; all signs and symptoms for HF hospitalization must be met as defined in A Heart Failure Hospitalization above; and the patient receives initiation or intensification of treatment specifically for HF, as detailed in the above section with the exception of oral diuretic therapy, which was not sufficient.

Interventional Cardiology Definitions

[0518] Clinical Definitions:

[0519] Clinically-Driven Target Lesion Revascularization: Revascularization is clinically-driven if the target lesion diameter stenosis is > 50% by quantitative coronary angiography (QCA) and the subject has clinical or functional ischemia which cannot be explained by another native coronary or bypass graft lesion. Clinical or functional ischemia includes any of the following: a history of angina pectoris, presumably related to the target vessel; objective signs of ischemia at rest (electrocardiographic changes) or during exercise test (or equivalent), presumably related to the target vessel; and abnormal results of any invasive functional diagnostic test (e.g., coronary flow reserve [CFR] or fractional flow reserve [FFR]).

[0520] Non-Target Lesion and Non-Target Lesion Revascularization: A lesion for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.

[0521] Non-Target Vessel and Non-Target Vessel Revascularization: A vessel for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.

[0522] Percutaneous Coronary Intervention (PCI) Status includes:

- Elective: The procedure can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of myocardial infarction (MI) or death. For stable in-patients, the procedure is being performed during this hospitalization for convenience and ease of scheduling and NOT because the patient's clinical situation demands the procedure prior to discharge.
- Urgent: The procedure should be performed on an inpatient basis and prior to discharge because of significant concerns that there is risk of myocardial ischemia, MI, and/or death. Patients who are outpatients or in the emergency department at the time that the cardiac catheterization is requested would warrant hospital admission based on their clinical presentation.
- Emergency: The procedure should be performed as soon as possible because of substantial concerns that ongoing myocardial ischemia and/or MI could lead to death. "As soon as possible" refers to a patient who is of sufficient acuity

that one would cancel a scheduled case to perform this procedure immediately in the next available room during business hours, or one would activate the on-call team were this to occur during off-hours.

- Salvage: The procedure is a last resort. The patient is in cardiogenic shock when the PCI begins (i.e., the time at which the first guide wire or intracoronary device is introduced into a coronary artery or bypass graft for the purpose of mechanical revascularization) or within the last ten minutes prior to the start of the case or during the diagnostic portion of the case, the patient has also received chest compressions or has been on unanticipated circulatory support (e.g., intra-aortic balloon pump, extracorporeal mechanical oxygenation, or cardiopulmonary support).

[0523] Percutaneous Coronary Intervention (PCI): Placement of an angioplasty guide wire, balloon, or other device (e.g., stent, atherectomy catheter, brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or coronary artery bypass graft for the purpose of mechanical coronary revascularization. In the assessment of the severity of coronary lesions with the use of intravascular ultrasound, CFR, or FFR, insertion of a guide wire was not considered PCI.

[0524] Peripheral Vascular Intervention Definitions:

[0525] Peripheral Vascular Intervention Definition*:* Peripheral vascular intervention is a catheter-based or open surgical procedure designed to improve peripheral arterial or venous blood flow or otherwise modify or revise vascular conduits. Procedures may include, but are not limited to, balloon angioplasty, stent placement, thrombectomy, embolectomy, atherectomy, dissection repair, aneurysm exclusion, treatment of dialysis conduits, placement of various devices, intravascular thrombolysis or other pharmacotherapies, and open surgical bypass or revision. In general, the intention to perform *percutaneous* peripheral vascular intervention is denoted by the insertion of a guide wire into a peripheral artery or vein. The target vessel(s) and the type of revascularization procedure (e.g., surgical bypass, thrombectomy, endarterectomy, percutaneous angioplasty, stent placement, thromboembolectomy, and thrombolysis) should be specified and recorded. For the sake of simplicity, this definition applies to the extracranial carotid artery and other non-cardiac arteries and veins and excludes the intracranial vessels and lymphatics.

[0526] Procedural Status includes:

- Non-Elective: Non-elective procedures include emergent and urgent procedures. A non-elective procedure is a procedure that is performed without delay, because there is clinical consensus that the procedure should occur imminently. Non-elective procedures imply a degree of instability of the patient, urgency of the medical condition, or instability of the threatening lesion.
    - Emergent: A procedure that is performed immediately because of the acute nature of the medical condition (e.g., acute limb ischemia, acute aortic dissection), and the increased morbidity or mortality associated with a temporal delay in treatment.
    - Urgent: An urgent procedure is one that is not emergent but required to be performed on a timely basis (≤ 24 hrs) (e.g., a patient who has been stabilized following initial treatment of acute limb ischemia, and there is clinical consensus that a definitive procedure should occur within the next 24 hours).
- Elective: An elective procedure is one that is scheduled and is performed on a patient with stable disease, or in whom there is no urgency and/or increased morbidity, or mortality associated with a planned procedure.

[0527] Definition of Any Revascularization Procedure: Any revascularization includes any arterial vascular intervention done to treat ischemia or prevent major ischemic events, including percutaneous or surgical intervention of the coronary, peripheral, or carotid arteries. Aneurysm repairs, dissection repairs, arterial-venous fistula or graft placement or repairs, or renal arterial intervention for hypertension or renal dysfunction are not included.

[0528] Definition of Cardiac Arrhythmia Requiring Hospitalization: An arrhythmia that either results in hospitalization (≥24 hours) during or within 24 hours of the termination of the last episode for treatment or requires continued hospitalization for treatment, including any one of the following:

- Atrial arrhythmia – atrial fibrillation, atrial flutter, supraventricular tachycardia that requires cardio-version, drug therapy, or is sustained for greater than 1 minute;

- Ventricular arrhythmia – Ventricular tachycardia or ventricular fibrillation requiring cardio-version and/or intravenous antiarrhythmics; and/or
- Bradyarrhythmia – High-level AV block (defined as third-degree AV block or second-degree AV block), junctional or ventricular escape rhythm, or severe sinus bradycardia (typically with heart rate < 30 bpm). The bradycardia must require temporary or permanent pacing.

[0529] Definition of Cardiac Arrest (Sudden Cardiac Death): A sudden, unexpected death due to the cessation of cardiac mechanical activity, confirmed by the absence of a detectable pulse, unresponsiveness, and apnea (or agonal, gasping respirations) of presumed cardiac etiology. An arrest is presumed to be cardiac (i.e., related to heart disease) if this is likely, based on the available information, including hospital records and autopsy data. The cardiac arrest is further sub-classified into either: witnessed, occurring within 60 min from the onset of new symptoms, in the absence of a clear cause other than cardiovascular; or unwitnessed, within 24 hours of being observed alive, in the absence of pre-existing other non-cardiovascular causes of death;

[0530] Non-cardiac causes of cardiac arrest, such as drug overdose, suicide, drowning, hypoxia, exsanguination, cerebrovascular accident, subarachnoid hemorrhage, or trauma must not be present.

[0531] Definition of Resuscitated Cardiac Arrest: Resuscitated Cardiac Arrest is present when there is restoration of both: organized electrical activity and organized mechanical activity resulting in restoration of spontaneous circulation (defined as the documented presence of a measurable pulse and blood pressure at any time after initiation of resuscitative efforts).

[0532] Criteria for the Diagnosis of Metabolic Syndrome: The diagnosis of metabolic syndrome requires the presence of three out of the following five specific components using the following criteria with cut points of parameters as defined in Table 1 and listed below, and waist circumference cut points further guided by the Table 14.

- A waist circumference ≥35 inches (88 cm) for all women, and Asian, Hispanic, or Latino men, and waist circumference ≥40 inches (102 cm) for all other men;
- Elevated TG (TG ≥150 mg/dL);
- Reduced HDL-C (HDL-C <40 mg/dL if male; HDL-C <50 mg/dL if female);

- Elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg, or an antihypertensive therapy with medical history of hypertension; and
- Elevated fasting glucose (fasting glucose ≥100 mg/dL, or on drug therapy for elevated glucose.

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

Organization	Population (Reference)	Waist Circumference Threshold	
		Men(cm)	Women (cm)
IDF (4)	Europid	≥94	≥80
WHO (7)	Caucasian	≥94 (increased risk)	≥80
		≥102 (still higher risk)	≥88
AHA/NHLBI (ATP III)*	US	≥102	≥88
Health Canada	Canada	≥102	≥88
European Cardiovascular Societies	European	≥102	≥88
IDF	Asian (including Japanese)	≥90	≥80
WHO	Asian	≥90	≥80
Japanese Obesity Society	Japanese	≥85	≥90
Cooperative Task Force	China	≥85	≥80
IDF	Middle East, Mediterranean	≥94	≥80
IDF	Sub-Saharan African	≥94	≥80
IDF	Ethnic Central & South American	≥90	≥80

IDF=International Diabetes Federation; WHO=World Health Organization; AHA/NHLBI (ATP III)=American Heart Association/National Heart, Lung, and Blood Institute Adult Treatment Panel III; *Recent AHA/NHLBI guidelines for metabolic syndrome recognize an increased risk for cardiovascular disease and diabetes at waist-circumference thresholds of ≥94 cm in men and ≥80 cm in women and identify these as optional cut points for individuals or populations with increased insulin resistance.

[0533] Statistical Analysis

[0534] In this event-driven trial, it was estimated that approximately 1612 adjudicated primary endpoint events would be necessary to provide 90% power to detect a 15% lower risk of the primary composite endpoint in the AMR101 group than in the placebo group. This resulted in an estimated sample size of approximately 7990 patients

to reach the number of primary endpoints. The primary efficacy analysis was based on the time from randomization to the first occurrence of any component of the primary composite endpoint. If the relative risk reduction with administration of AMR101 in the primary endpoint was significant (final two-sided alpha level = 0.0437; determined from O'Brien-Fleming boundaries generated using the Lan-DeMets alpha-spending function after accounting for two protocol pre-specified interim efficacy analyses), in a hierarchical fashion, the key secondary endpoint and other prespecified secondary endpoints were to be tested at the same final alpha level of 0.0437. All primary efficacy analyses followed the intent-to-treat principle. HRs and 95% CI were generated using a Cox proportional hazard model with treatment as covariate, and stratified by cardiovascular risk category, geographic region, and use of ezetimibe. Log-rank P values were reported from a Kaplan–Meier analysis, stratified by the three randomization factors, to evaluate the timing of events in the two treatment groups.

Results

[0535] Subject Disposition*:* The subject disposition by treatment group is depicted in Figure 2. A total of 19,212 patients were screened of whom 8,179 (43%) were randomized. At the time of database lock, vital status was available in 99.8%; 152 (1.9%) patients did not complete final study visits and 578 (7.1%) patients withdrew consent. Demographic and Baseline Disease Characteristics: Among the patients who underwent randomization, 70.7% were enrolled on the basis of secondary prevention (i.e., patients had established cardiovascular disease) and 29.3% for primary prevention (i.e., patients had diabetes mellitus and at least one additional risk factor). The median age was 64 years, 28.8% were female, and 38.5% were from the United States. At baseline, the median LDL-cholesterol was 75.0 mg/dL, HDL-cholesterol was 40.0 mg/dL, and triglycerides were 216.0 mg/dL. The baseline characteristics of the patients are provided below in Table 16.

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

	Icosapent ethyl (N=4089)	Placebo (N=4090)
Age (years), Median (Q1-Q3)	64.0 (57.0 - 69.0)	64.0 (57.0 - 69.0)
Female, (n %)	1162 (28.4%)	1195 (29.2%)
Non-White, (n %)	398 (9.7%)	401 (9.8%)

Age ≥65 years, n (%)	1857 (45.4%)	1906 (46.6%)
Male, n (%)	2927 (71.6%)	2895 (70.8%)
White, n (%)[1]	3691 (90.3%)	3688 (90.2%)
BMI (kg/m^2), Median (Q1-Q3)	30.8 (27.8 - 34.5)	30.8 (27.9 - 34.7)
BMI ≥30 (kg/M^2), n (%)	2331 (57.0%)	2362 (57.8%)
Geographic Region, n (%)		
Westernized [2]	2906 (71.1%)	2905 (71.0%)
Eastern Europe [3]	1053 (25.8%)	1053 (25.7%)
Asia Pacific [4]	130 (3.2%)	132 (3.2%)
CV Risk Category, n (%)		
Secondary Prevention	2892 (70.7%)	2893 (70.7%)
Primary Prevention	1197 (29.3%)	1197 (29.3%)
Ezetimibe Use, n (%)	262 (6.4%)	262 (6.4%)
Statin Intensity, n (%)		
Low	254 (6.2%)	267 (6.5%)
Moderate	2533 (61.9%)	2575 (63.0%)
High	1290 (31.5%)	1226 (30.0%)
Missing	12 (0.3%)	22 (0.5%)
Diabetes, n (%)		
Type I Diabetes	27 (0.7%)	30 (0.7%)
Type II Diabetes	2367 (57.9%)	2363 (57.8%)
No Diabetes at Baseline	1695 (41.5%)	1694 (41.4%)
Data Missing	0	3 (0.1%)
hsCRP (mg/L), Median (Q1-Q3)	2.2 (1.1 - 4.5)	2.1 (1.1 - 4.5)
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5 - 46.0)	40.0 (35.0 - 46.0)
LDL-C (mg/dL), Median (Q1-Q3)	74.0(61.5-88.0)	76.0 (63.0 - 89.0)
Triglycerides Category		
<150 mg/dL	412 (10.1%)	429 (10.5%)

150 to < 200 mg/dL	1193 (29.2%)	1191 (29.1%)
≥ 200 mg/dL	2481 (60.7%)	2469 (60.4%)
Triglycerides ≥ 200 mg/dL and HDL-C ≤ 35 mg/dL	823 (20.1%)	794 (19.4%)
EPA (µg/mL), Median (Q1-Q3)	26.1 (17.1 - 40.1)	26.1 (17.1 - 39.9)

In general, the baseline value is defined as the last non-missing measurement obtained prior to the randomization. The baseline LDL-C value obtained via Preparative Ultracentrifugation was used, unless this value was missing. If the LDL-C Preparative Ultracentrifugation value was missing, then another LDL-C value was be used, with prioritization of values obtained from LDL-C Direct measurements, followed by LDL-C derived by the Friedewald calculation (only for patients with TG < 400 mg/dL), and finally LDL-C derived using the calculation published by Johns Hopkins University investigators.22 At Visit 1 and Visit 1.1 Direct LDL-C was used if at the same visit TG >400 mg/dL At alll remaining visits LDL-C was measured by Direct LDL-C or by Preparative Ultracentrifugation if at the same visit TG >400 mg/dL. For all other lipid and lipoprotein marker parameters, wherever possible, baseline was derived as the arithmetic mean of the Visit 2 (Day 0) value and the preceding Visit 1 (or Visit 1.1) value. If only one of these values was available, the single available value was used as baseline. The only significant baseline between group difference with $p < 0.05$ was LDL-C ($p= 0.03$).
[1] Race as reported by the investigators.
[2] Westernized region includes Australia, Canada, Netherlands, New Zealand, United States, and South Africa.
[3] Eastern European region includes Poland, Romania, Russian Federation, and Ukraine.
[4] Asia Pacific region includes India.

[0536] The median trial follow-up duration was 4.9 years with a maximum of 6.2 years. The median change in triglycerides from baseline to one year was –18.3% (–39.0 mg/dL) in the AMR101 group and +2.2% (4.5 mg/dL) in the placebo group; the median reduction from baseline (as estimated with the use of the Hodges–Lehmann approach) was 19.7% greater in the AMR101 group than in the placebo group (a 44.5 mg/dL [0.50 mmol/L] greater reduction; P<0.001). The median change in LDL cholesterol level from baseline was an increase of 3.1% (2.0 mg/dL [0.05 mmol/L]) in the AMR101 group and an increase of 10.2% (7.0 mg /dL [0.18 mmol/L]) in the placebo group — a 6.6% (5.0 mg/dL [0.13 mmol/L]) lower increase with AMR101 than with placebo (P<0.001).

[0537] Analysis of Primary Composite Endpoint:

[0538] There was a total of 1606 adjudicated primary endpoint first events. Table 17 and Figure 3A shows the Kaplan-Meier event curves for the primary efficacy endpoint of time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in the AMR101 and placebo groups with the inset showing the data on an expanded y axis. All patients were included in the analysis and patients experiencing more than one type of endpoint event were

counted for their first occurrence in each event type. The primary endpoint as shown in Figure 3A occurred in 17.2% of AMR101 patients versus in 22.0% of placebo patients (HR, 0.75; 95% CI, 0.68-0.83; P<0.001) for an absolute risk reduction (AAR) of 4.8% (95% CI, 3.1-6.5%) and number needed to treat (NNT) of 21 (95% CI, 15-33) over median follow up 4.9 years. Similarly, Figure 3B shows the Kaplan-Meier estimates of the cumulative incidence of the primary composition endpoints over time. Significantly, Figure 3B indicates a 25% relative risk reduction for the primary composite endpoint over the course of 5 years.

Table 17. Stratified Analysis of Time to the Primary Composite Endpoint from Date of Randomization (ITT Population)

Endpoint Statistic	AMR101 (N=4089)	Placebo (N=4090)
Primary Composite Endpoint, n (%)[1]	705 (17.2)	901 (22.0)
Treatment Comparison[2]		
P-value from Log-Rank Test	0.00000001	
HR (95% CI) AMR101/Placebo	0.752 (0.682 – 0.830)	
Components Contributing to Primary Endpoint, n (%)[3]		
CV Death[4]	137 (3.4)	149 (3.6)
Nonfatal MI[5]	205 (5.0)	280 (6.8)
Nonfatal Stroke	80 (2.0)	105 (2.6)
Coronary Revascularization	189 (4.6)	244 (6.0)
Hospitalization for Unstable Angina	94 (2.3)	123 (3.0)

Abbreviations: CI = confidence interval; CV = cardiovascular; ECG = electrocardiogram; HR = hazard ratio; ITT = Intent-to-Treat; MI = myocardial infarction.

Note: The number of patients with event (n) is the number of patients in the ITT population within each treatment group (N).

1 Primary composite endpoint includes CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing.

2 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

3 Based on a patient's first post-randomization occurrence of the event contributing to the primary endpoint.

4 CV death includes adjudicated CV deaths and deaths of undetermined causality.

Endpoint Statistic	AMR101 (N=4089)	Placebo (N=4090)

5 Nonfatal MI includes silent MI, which was assumed to occur on the date of the first post-randomization ECG tracing indicative of a silent MI.

[0539] Figure 4 lists the individual components of the primary endpoint analyzed as time to first event of each individual endpoint. Shown first in Figure 4 is the HR and 95% CI for the primary composite endpoint event (time to first occurrence of either cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina). Shown separately beneath Figure 4 are HRs and 95% CIs for time to first occurrence of each type of individual primary endpoint component event, irrespective of whether contributing to the primary composite endpoint event or not.

[0540] Overall, a primary endpoint event occurred in 17.2% (705/4089) of patients in the AMR101 group, as compared with 22.0% (901/4090) of patients in the placebo group (HR of 0.752 [95% CI: 0.682 to 0.830; p=0.00000001]; relative risk reduction [RRR] of 24.8% and number needed to treat [NNT] of 21). Thus, the primary endpoint was met. There was a statistically significantly lower risk of major adverse CV events (i.e., CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina determined to be caused by myocardial ischemia) with AMR101 than with placebo.

[0541] Sensitivity Analysis of the Primary Endpoint

[0542] The sensitivity analyses for the ITT and mITT populations censored patients for death of undetermined cause, study drug discontinuation, study drug discontinuation + 30 days, silent MI at the last normal ECG, and silent MI at mid-point between the date of the last normal ECG and the date of the first indicative ECG. Results were generally consistent with the primary analyses, i.e., there was a significantly lower risk of major adverse CV events with AMR101 than with placebo. Time-to-event analyses, as done for the primary analysis, were carried out at l-year and 2-year landmarks for the ITT population. At the 2-year landmark, there was a significantly lower risk of major adverse CV events with AMR IOI than with placebo (HR of 0.799 [95% CI: 0.693 to 0.920; p=0.0017]).

[0543] Analysis of Key Secondary Endpoints:

[0544] Table 18 and Figure. 5A shows the Kaplan-Meier event curves for the key secondary efficacy endpoint of time to first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the AMR101 and placebo groups with the inset showing the data on an expanded y axis. All patients were included in the analysis and patients experiencing more than one type of endpoint event were counted for their first occurrence in each event type. The key secondary efficacy endpoint as shown in Figure 5A occurred in 11.2% of AMR101 patients versus 14.8% of placebo patients (HR, 0.74, 95% CI 0.65-0.83, P<0.001) for an absolute risk reduction of 3.6% (95% CI, 2.1-5.0%) and a number needed to treat of 28 (95% CI, 20-47) over median follow up 4.9 years. Similarly, Figure 5B shows the Kaplan-Meier estimates of the cumulative incidence of the key secondary composition endpoints over time. Significantly, Figure 5B indicates a 26% relative risk reduction for the key secondary composite endpoint over the course of 5 years.

Table 18. Stratified Analysis of Time to the Primary Composite Endpoint from Date of Randomization (ITT Population).

Endpoint **Statistic**	**AMR101** **(N=4089)**	**Placebo** **(N=4090)**
Key Secondary Composite Endpoint, n (%)[1]	459 (11.2)	606 (14.8)
Treatment Comparison[2]		
P-value from Log-Rank Test	0.0000006	
HR (95% CI) AMR101/Placebo	0.735 (0.651 – 0.830)	
Components Contributing to Key Secondary Endpoint, n (%)[3]		
CV Death[4]	149 (3.6)	167 (4.1)
Nonfatal MI[5]	230 (5.6)	325 (7.9)
Nonfatal Stroke	80 (2.0)	114 (2.8)

Abbreviations: CI = confidence interval; CV = cardiovascular; ECG = electrocardiogram; HR = hazard ratio; ITT = Intent-to-Treat; MACE = major adverse coronary event; MI = myocardial infarction.

Note: The number of patients with event (n) is the number of patients in the ITT population within each treatment group (N).

1 The key secondary composite (i.e., hard MACE) endpoint includes CV death, nonfatal MI, and nonfatal stroke.

2 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

Endpoint Statistic	AMR101 (N=4089)	Placebo (N=4090)
3 Based on a patient's first post-randomization occurrence of the event contributing to the key secondary endpoint.		
4 CV death includes adjudicated CV deaths and deaths of undetermined causality.		
5 Nonfatal MI includes silent MI, which was assumed to occur on the date of the first post-randomization ECG tracing indicative of a silent MI.		

[0545] Overall, a key secondary endpoint event occurred in 11.2% (459/4089) of patients in the AMR101 group, as compared with 14.8% (606/4090) of patients in the placebo group (HR of 0.735 [95% CI: 0.651 to 0.830; p=0.0000006]; RRR of 26.5% and NNT of 28). Thus, the key secondary endpoint was met. There was a statistically significantly lower risk of hard MACE events (CV death, nonfatal MI, and nonfatal stroke) with AMRI0I than with placebo.

[0546] Sensitivity Analysis of the Secondary Endpoint

[0547] As done for the primary analysis, exploratory time-to-event analyses were carried out at 1-year and 2-year landmarks for the key secondary endpoint for the ITT population. At the 2-year landmark, there was a significantly lower risk of major adverse CV events with AMR101 than with placebo (HR of0.831 [95% CI: 0.691 to 0.998; p=0.00469]).

[0548] Individual Components of the Primary and Key Secondary Endpoints

[0549] A forest plot of the analyses of the individual components of the primary and key secondary endpoints, each analyzed as independent endpoints (e.g., time to first occurrence of nonfatal MI, regardless of the time to first occurrence of any other endpoints for the same patient), is presented in Figure 6. Statistically significant differences between AMR101 and placebo in favor of AMR101 were observed in each of the individual components of the primary and key secondary endpoints.

[0550] Composite of Death or Nonfatal: Myocardial Infarction: CV death or nonfatal MI occurred in 9.6% (392/4089) of patients in the AMR101 group, as compared with 12.4% (507/4090) of patients in the placebo group (HR of 0.753 [95% CI: 0.660 to 0.859; p<0.0001]). Thus, there was a statistically significantly lower risk of CV death or nonfatal MI with AMR101 than with placebo.

[0551] Fatal or Nonfatal Myocardial Infarction: Any MI (fatal or nonfatal MI, including silent MI) occurred in 6.1 % (250/4089) of patients in the AMRI0I group, as compared with 8.7% (355/4090) of patients in the placebo group (HR of 0.688 [95% CI: 0.585 to

0.808; p<0.0001]). Thus, there was a statistically significantly lower risk of any MI with AMR IOI than with placebo. A silent MI occurred in 0.7% (27/4089) of patients in the AMR101 group and 0.7% (29/4090) of patients in the placebo group (p=0.7590).

[0552] Emergent or Urgent Coronary Revascularization: Non-elective coronary revascularization (represented as the composite of emergent or urgent coronary revascularization) occurred in 5 .3% (216/4089) of patients in the AMR101 group, as compared with 7.8% (321/4090) of patients in the placebo group (HR of 0.653 [95% CI: 0.550 to 0.776; p<0.0001]). Thus, there was a statistically significantly lower risk of non-elective coronary revascularization with AMR101 than with placebo.

[0553] Cardiovascular Death: CV death occurred in 4.3% (174/4089) of patients in the AMR101 group, as compared with 5.2% (213/4090) of patients in the placebo group (HR of 0.803 [95% CI: 0.657 to 0.981; p=0.0315]). Thus, there was a statistically significantly lower risk of CV death with AMR101 than with placebo. Deaths with an adjudicated undetermined cause and without a preceding primary endpoint event were considered to be included with adjudicated CV deaths.

[0554] Hospitalization for Unstable Angina: Hospitalization for unstable angina occurred in 2.6% (108/4089) of patients in the AMR101 group, as compared with 3.8% (157/4090) of patients in the placebo group (HR of 0.679 [95% CI: 0.531 to 0.868; p=0.0018]). Thus, there was a statistically significantly lower risk of hospitalization for unstable angina with AMR101 than with placebo.

[0555] Fatal or Nonfatal Stroke: Fatal or nonfatal stroke occurred in 2.4% (98/4089) of patients in the AMR101 group, as compared with 3.3% (134/4090) of patients in the placebo group (HR of 0.720 [95% CI: 0.555 to 0.934; p=0.0129]). Thus, there was a statistically significantly lower risk of fatal or nonfatal stroke with AMR101 than with placebo.

[0556] Composite of Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke: Total mortality, nonfatal MI, or nonfatal stroke occurred in 13.4% (549/4089) of patients in the AMR101 group, as compared with 16.9% (690/4090) of patients in the placebo group (HR of 0.772 [95% CI: 0.690 to 0.864; p<0.0001]). Thus, there was a statistically significantly lower risk of total mortality, nonfatal MI, or nonfatal stroke with AMR101 than with placebo.

[0557] Total Mortality: Total mortality, the final secondary endpoint in the pre-specified hierarchy, occurred in 6.7% (274/4089) of patients in the AMR101 group, as compared with 7.6% (310/4090) of patients in the placebo group (HR of 0.870 [95% CI: 0.739 to 1.023; p=0.0915]). Thus, there was not a statistically significantly lower risk of total mortality with AMR101 than with placebo.

[0558] A summary of the overall deaths (including CV death, non-CV death, undetermined death, and total mortality) is presented in Table 19.

Table 19. Summary Overall Deaths for the Safety Population

Summary of Deaths[1], n (%)	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)
Total mortality	274 (6.7)	310 (7.6)	584 (7.1)
CV deaths (excluding deaths with undetermined cause)	138 (3.4)	180 (4.4)	318 (3.9)
Non-CV deaths	100 (2.4)	97 (2.4)	197 (2.4)
Deaths with undetermined cause	36 (0.9)	33 (0.8)	69 (0.8)

Abbreviations: CV = cardiovascular.

Note: CV deaths (excluding deaths with undetermined cause) and deaths with undetermined cause were combined as "CV deaths" for the primary efficacy analysis of CV endpoints.

[0559] Primary Endpoint in Patients with Diabetes Mellitus, Patients with Metabolic Syndrome, and Patients with Impaired Glucose Metabolism at Baseline

[0560] The results of the analysis of the primary endpoint in patients with diabetes mellitus, patients with metabolic syndrome, and patients with impaired glucose metabolism at baseline are summarized in Table 20 for the ITT population.

Table 20. Stratified Analysis of Time to the Primary Endpoint from Date of Randomization: Patients with Diabetes Mellitus, Metabolic Syndrome, or Impaired Glucose Metabolism at Baseline (ITT Population)

			Treatment Comparison[1]	
Baseline Condition Statistic	AMR101 n/N (%)	Placebo n/N (%)	P-value from Log-Rank Test	HR (95% CI) AMR101/Placebo
Diabetes Mellitus				
Primary Endpoint, n (%)[2]	433/2394 (18.1)	536/2393 (22.4)	<0.0001	0.769 (0.677 – 0.873)
Metabolic Syndrome				
Primary Endpoint, n (%)[2]	652/3792 (17.2)	829/3753 (22.1)	<0.0001	0.744 (0.671 – 0.824)

			Treatment Comparison[1]	
			P-value from	
Baseline Condition	AMR101	Placebo	Log-Rank	HR (95% CI)
Statistic	n/N (%)	n/N (%)	Test	AMR101/Placebo
Impaired Glucose Metabolism				
Primary Endpoint, n (%)[2]	257/1454 (17.7)	324/1517 (21.4)	0.0061	0.795 (0.675 – 0.937)

Abbreviations: CI = confidence interval; CV = cardiovascular; ECG = electrocardiogram; HR = hazard ratio; ITT = Intent-to-Treat; MI = myocardial infarction.

Note: The number of patients with event (n) is the number of patients with the event in the ITT population with the baseline condition within each treatment group (N). Patients may be represented in more than one baseline condition category.

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 Based on a patient's first post-randomization occurrence of the event contributing to the primary endpoint. Primary endpoint includes CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing. CV death includes adjudicated CV deaths and deaths of undetermined causality. Nonfatal MI includes silent MI, which was assumed to occur on the date of the first post-randomization ECG tracing indicative of a silent MI.

[0561] Key Secondary Endpoint in Patients with Impaired Glucose Metabolism at Baseline: In patients with impaired glucose metabolism at baseline, a key secondary endpoint event occurred in 11.3% (164/1454) of patients in the AMR101 group, as compared with 13.2% (201/1517) of patients in the placebo group (HR of0.829 [95% CI: 0.675 to 1.020]).

[0562] Tertiary Composite Efficacy Analyses: A summary of the stratified time to event analyses for each of the tertiary composite endpoints is presented in Table 21. For the following tertiary composite endpoints, the HRs and 95% CIs are suggestive of a significantly lower risk of CV events with AMR101 than with placebo:

- Composite of CV death, nonfatal MI (including silent MI), nonfatal stroke, cardiac arrhythmia requiring hospitalization of ≥24 hours, or cardiac arrest
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization
- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive

testing and requiring emergent hospitalization, nonfatal stroke, or PVD requiring intervention, such as angioplasty, bypass surgery, or aneurism repair

- Composite of CV death, nonfatal MI (including silent MI), non-elective coronary revascularizations (defined as emergent or urgent classifications), unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization, PVD requiring intervention, or cardiac arrhythmia requiring hospitalization of ≥24 hours

Table 21. Stratified Analysis of Time to Tertiary Composite Endpoints from Date of Randomization (ITT Population)

			Treatment Comparison[1]	
Composite Endpoint, n (%)[2]	**AMR101 (N=4089)**	**Placebo (N=4090)**	**P-value from Log-Rank Test**	**HR (95% CI) AMR101/Placebo**
CV Death,[3] Nonfatal MI,[4] Nonfatal Stroke, Cardiac Arrhythmia, or Cardiac Arrest	589 (14.4)	701 (17.1)	0.0004	0.82 (0.73 – 0.91)
CV Death[3], Nonfatal MI,[4] Non-Elective Coronary Revascularization,[5] or Unstable Angina[6]	513 (12.5)	656 (16.0)	<0.0001	0.76 (0.68 – 0.85)
CV Death[3], Nonfatal MI,[4] Non-Elective Coronary Revascularization,[5] Unstable Angina,[6] Nonfatal Stroke, or PVD Requiring Intervention	683 (16.7)	852 (20.8)	<0.0001	0.77 (0.70 – 0.86)
CV Death[3], Nonfatal MI,[4] Non-Elective Coronary Revascularization,[5] Unstable Angina,[6] PVD Requiring Intervention, or Cardiac Arrhythmia	741 (18.1)	844 (20.6)	0.0019	0.86 (0.78 – 0.94)
Total Mortality or Newly Emergent CHF	393 (9.6)	431 (10.5)	0.1281	0.90 (0.78 – 1.03)
CV Death[3] or Newly Emergent CHF	306 (7.5)	346 (8.5)	0.0808	0.87 (0.75 – 1.02)

Abbreviations: CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; ECG = electrocardiogram; HR = hazard ratio; ITT = Intent-to-Treat; MI = myocardial infarction; PVD = peripheral vascular disease.

Note: The number of patients with event (n) is the number of patients in the ITT population within each treatment group (N).

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 Based on a patient's first post-randomization occurrence of the event contributing to the composite endpoint.

3 CV death includes adjudicated CV deaths and deaths of undetermined causality.

4 Nonfatal MI includes silent MI, which was assumed to occur on the date of the first post-randomization ECG tracing indicative of a silent MI.

5 Represented as the composite of emergent or urgent classifications.

[0563] Analysis of Prespecified Subgroups

[0564] The primary efficacy outcomes in select prespecified subgroups are shown in Figures 7 and 8 with corresponding HRs and 95% CIs for the primary efficacy endpoint of time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina from select prespecified subgroups in the AMR101 and placebo groups. The key secondary efficacy outcomes in select prespecified subgroups are shown in Figures 9 and 10 with corresponding HRs and 95% CIs for the key secondary efficacy endpoint of time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina from select prespecified subgroups in the AMR101 and placebo groups. Significantly, Figures 7-10 indicate that a subject's baseline triglyceride levels (e.g., ≥150 vs. <150 mg/dL or ≥200 or <200 mg/dL) had no influence on the primary or key secondary efficacy endpoints.

[0565] This conclusion is further substantiated by the combination of Figures 11A and 11B which show that achievement of on-treatment triglyceride levels above or below 150 mg/dL at one year did not influence the efficacy of AMR101 versus placebo. In particular, Figures 11A and 11B show the primary and key secondary endpoints by achieved triglyceride level (e.g., above or below 150 mg/dL) at 1 year (e.g., patients with a triglyceride level above or below 150 mg/dL after 1 year of having received the AMR101). Figure 11A are the Kaplan-Meier curves for the primary endpoint of time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in the AMR101 treatment group for patients with achieved triglycerides, and the placebo group at year 1. Conversely, Figure 11B are the Kaplan-Meier event curves for the key secondary endpoint of time to first occurrence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the AMR101 treatment group for patients with achieved triglycerides, and the placebo group at year 1. Importantly, Figures 11A and 11B indicate that regardless of the subject's triglyceride levels at year 1, the subject experienced a statistically significant reduction in time to first occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The attainment of triglyceride levels of 150 mg/dL or higher or below 150 mg/dL at 1 year after randomization also had no influence on the efficacy of AMR101 as compared with placebo with respect to the primary or key secondary efficacy endpoint. In a *post hoc* analysis, no substantial difference in the benefit of AMR101 as compared with placebo

was observed with respect to the primary endpoint according to whether the patients who received placebo had an increase in LDL cholesterol levels at 1 year or had no change or a decrease in LDL cholesterol levels.

[0566] Figure 12 depicts the prespecified hierarchical testing of the endpoints; except for the last hierarchical secondary endpoint of death from any cause (also referred to as total mortality), all other individual and composite ischemic endpoints were significantly reduced by AMR101, including cardiovascular death (4.3% versus 5.2%; HR, 0.80; 95% CI, 0.66-0.98; P=0.03). Total mortality was 6.7% versus 7.6% (HR, 0.87; 95% CI, 0.74-1.02; P=0.09) in the AMR101 and placebo groups, respectively. For each of the prespecified endpoints in Figure 12, icosapent ethyl 4g per day provide a RRR of 25% for the primary composite endpoint, 26% for the secondary composite endpoint, 25% for the composite of cardiovascular death or nonfatal myocardial infarction, 31% for fatal or nonfatal myocardial infarction, 35% for urgent or emergent revascularization, 20% for cardiovascular death, 32% for hospitalization for unstable angina, 28% for fatal or nonfatal stroke, 23% reduction in the composite of total mortality, nonfatal myocardial infarction, or nonfatal stroke, and lastly, a 13% reduction in total mortality.

[0567] Results for selected tertiary outcomes are shown in Table 22. A tertiary endpoint adjudicated sudden cardiac death was 2.1% versus 1.5% (HR, 0.69; 95% CI, 0.50-0.96).

Table 22. Selected Prespecified Adjudicated Tertiary Endpoints

Tertiary Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)
Primary Endpoint in Patients with Diabetes at Baseline	433/2394 (18.1%)	536/2393 (22.4%)	0.77 (0.68, 0.87)
New Heart Failure	169/4089 (4.1%)	176/4090 (4.3%)	0.95 (0.77, 1.17)
New Heart Failure Requiring Hospitalization	141/4089 (3.4%)	144/4090 (3.5%)	0.97 (0.77, 1.22)
Transient Ischemic Attack	64/4089 (1.6%)	48/4090 (1.2%)	1.32 (0.91, 1.92)
Amputation for PVD	22/4089 (0.5%)	21/4090 (0.5%)	1.04 (0.57, 1.89)

Tertiary Endpoint	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)
Carotid Revascularization	31/4089 (0.8%)	26/4090 (0.6%)	1.18 (0.70, 1.98)
Coronary Revascularization	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58, 0.76)
Emergent Revascularization	41/4089 (1.0%)	65/4090 (1.6%)	0.62 (0.42, 0.92)
Urgent Revascularization	181/4089 (4.4%)	268/4090 (6.6%)	0.66 (0.54, 0.79)
Elective Revascularization	194/4089 (4.7%)	278/4090 (6.8%)	0.68 (0.57, 0.82)
Salvage Revascularization	0/4089 (0.0%)	2/4090 (0.0%)	0.00 (0.00, -)
Cardiac Arrhythmias Requiring Hospitalization of ≥ 24 Hours	188/4089 (4.6%)	154/4090 (3.8%)	1.21 (0.97, 1.49)
Cardiac Arrest	22/4089 (0.5%)	42/4090 (1.0%)	0.52 (0.31, 0.86)
Sudden Cardiac Death	61/4089 (1.5%)	87/4090 (2.1%)	0.69 (0.50, 0.96)
Ischemic Stroke	80/4089 (2.0%)	122/4090 (3.0%)	0.64 (0.49, 0.85)
Hemorrhagic Stroke	13/4089 (0.3%)	10/4090 (0.2%)	1.28 (0.56, 2.93)
New Onset of Diabetes[1]	65/1695 (3.8%)	63/1697 (3.7%)	1.04 (0.73, 1.47)
New Onset Hypertension	13/4089 (0.3)	15/4090 (0.4)	0.86 (0.41-1.80)
Peripheral Artery Disease	156/4089 (3.8)	159/4090 (3.0)	0.97 (0.78-1.21)

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

[0568] Newly Emergent Congestive Heart Failure Events: As shown in Table 22, newly emergent CHF events occurred in 4.1% (169/4089) of patients in the AMR101 group, as compared with 4.3% (176/4090) of patients in the placebo group (HR of 0.95 [95% CI: 0.77 to 1.17]). Newly emergent CHF events requiring hospitalization occurred in 3.4% (141/4089) of patients in the AMR101 group, as compared with 3.5% (144/4090) of patients in the placebo group (HR of 0.97 [95% CI: 0.77 to 1 .22]).

[0569] Transient Ischemic Attack Events: As shown in Table 22, TIA events occurred in 1.6% (64/4089) of patients in the AMR101 group, as compared with 1.2% (48/4090) of patients in the placebo group (HR of 1.32 [95% CI: 0.91 to 1.92]).

[0570] Amputation Events due to Peripheral Vascular Disease: As shown in Table 22, amputation events due to PVD occurred in 0.5% (22/4089) of patients in the AMRI0I group, as compared with 0.5% (21/4090) of patients in the placebo group (HR of 1.04 [95% CI: 0.57 to 1.89]).

[0571] Coronary Revascularization Events: As shown in Table 22, coronary revascularization events occurred in 9.2% (376/4089) of patients in the AMR101 group, as compared with 13.3% (544/4090) of patients in the placebo. Emergent revascularization events occurred in 1.0% (41/4089) of patients in the AMR101 group, as compared with 1.6% (65/4090) of patients in the placebo group (HR of 0.62 [95% CI: 0.42 to 0.92]). Urgent revascularization events occurred in 4.4% (181/4089) of patients in the AMR101 group, as compared with 6.6% (268/4090) of patients in the placebo group (HR of 0.66 [95% CI: 0.54 to 0.79]). Elective revascularization events occurred in 4.7% (194/4089) of patients in the AMR101 group, as compared with 6.8% (278/4090) of patients in the placebo group (HR of 0.68 [95% CI: 0.57 to 0.82]).

[0572] Cardiac Arrhythmia Events Requiring Hospitalization of ≥24 Hours: As shown in Table 22, cardiac arrhythmia events requiring hospitalization of ≥24 hours occurred in 4.6% (188/4089) of patients in the AMR101 group, as compared with 3.8% (154/4090) of patients in the placebo group (HR of 1.21 [95% CI: 0.97 to 1.49]).

[0573] Atrial fibrillation or atrial flutter events requiring hospitalization of ≥:24 hours occurred in 3.1 % (127/4089) of patients in the AMR101 group, as compared with 2.1% (84/4090) of patients in the placebo group (HR of 1.50 [95% CI: 1.14 to 1.98]). The HR and 95% CI are suggestive of a higher risk of atrial fibrillation or atrial flutter events with AMR101 than with placebo.

[0574] Results for selected time to cardiac arrhythmia endpoint events are shown in Table 23.

Table 23. Stratified Analysis of Time to Cardiac Arrhythmia Endpoint Events from Date of Randomization (ITT Population)

Composite Endpoint, n (%)[2]	AMR101 (N=4089)	Placebo (N=4090)	Treatment Comparison[1] P-value from Log-Rank Test	Treatment Comparison[1] HR (95% CI) AMR101/Placebo
CV Death,[3] Nonfatal MI,[4] Nonfatal Stroke, Cardiac Arrhythmia, or Cardiac Arrest	589 (14.4)	701 (17.1)	0.0004	0.82 (0.73 – 0.91)
CV Death[3], Nonfatal MI,[4] Non-Elective Coronary Revascularization,[5] or Unstable Angina[6]	513 (12.5)	656 (16.0)	<0.0001	0.76 (0.68 – 0.85)
CV Death[3], Nonfatal MI,[4] Non-Elective Coronary Revascularization,[5] Unstable Angina,[6] Nonfatal Stroke, or PVD Requiring Intervention	683 (16.7)	852 (20.8)	<0.0001	0.77 (0.70 – 0.86)
CV Death[3], Nonfatal MI,[4] Non-Elective Coronary Revascularization,[5] Unstable Angina,[6] PVD Requiring Intervention, or Cardiac Arrhythmia	741 (18.1)	844 (20.6)	0.0019	0.86 (0.78 – 0.94)
Total Mortality or Newly Emergent CHF	393 (9.6)	431 (10.5)	0.1281	0.90 (0.78 – 1.03)
CV Death[3] or Newly Emergent CHF	306 (7.5)	346 (8.5)	0.0808	0.87 (0.75 – 1.02)

Abbreviations: CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; ECG = electrocardiogram; HR = hazard ratio; ITT = Intent-to-Treat; MI = myocardial infarction; PVD = peripheral vascular disease.

Note: The number of patients with event (n) is the number of patients in the ITT population within each treatment group (N).

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 Based on a patient's first post-randomization occurrence of the event contributing to the composite endpoint.

3 CV death includes adjudicated CV deaths and deaths of undetermined causality.

4 Nonfatal MI includes silent MI, which was assumed to occur on the date of the first post-randomization ECG tracing indicative of a silent MI.

5 Represented as the composite of emergent or urgent classifications.

[0575] Cardiac Arrest Events: As shown in Table 23, cardiac arrest events occurred in 0.5% (22/4089) of patients in the AMR101 group, as compared with 1.0% (42/4090) of patients in the placebo group (HR of 0.52 [95% CI: 0.31 to 0.86]).

[0576] Sudden Cardiac Deaths: As shown in Table 23, sudden cardiac death events occurred in 1.5% (61/4089) of patients in the AMR101 group, as compared with 2.1 % (87 /4090) of patients in the placebo group (HR of 0.69 [95% CI: 0.50 to 0.96]).

[0577] Stroke Events: As shown in Table 23, ischemic stroke events occurred in 2.0% (80/4089) of patients in the AMR101 group, as compared with 3.0% (122/4090) of patients in the placebo group (HR of 0.64 [95% CI: 0.49 to 0.85]). Hemorrhagic stroke

events occurred in 0.3% (13/4089) of patients in the AMR101 group, as compared with 0.2% (10/4090) of patients in the placebo group (HR of 1.28 [95% CI: 0.56 to 2.93]).

[0578] New Onset Type 2 Diabetes Mellitus Events: As shown in Table 23, new onset Type 2 diabetes mellitus events (i.e., newly diagnosed during the treatment/follow-up period) occurred in 3.8% (65/1695) of patients in the AMR101 group, as compared with 3.7% (63/1697) of patients in the placebo group (HR of 1.04 [95% CI: 0.73 to 1.47]).

[0579] New Onset Hypertension Events: As shown in Table 23, programmatically determined (i.e., non-adjudicated) new onset hypertension events (i.e., blood pressure ≥140 mmHg systolic OR ≥ 90 mmHg diastolic newly diagnosed during the treatment/follow-up period and factoring for baseline medical history findings, TEAE findings, and indications for concomitant medications) occurred in 0.3% (13/4089) of patients in the AMR101 group, as compared with 0.4% (15/4090) of patients in the placebo group (HR of 0.86 [95% CI: 0.41 to 1.80]).

[0580] Peripheral Artery Disease: As shown in Table 23, peripheral artery disease occurred in 3.8% (156/4089) of patients in the AMR101 group, as compared with 3.9% (159/4090) of patients in the placebo group (HR of 0.97 [95% CI: 0.78 to 1.21]).

[0581] Analysis of Additional Biomarker from Baseline:

[0582] The effects on additional biomarkers to year 1 are shown in Table 24.

Table 24. Effect on Biomarkers from Baseline to Year 1

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

EPA (µg/mL)	26.1	144.0	26.1	23.3	114.9	358.8	<0.0001

[0583] A plot of median TG over time is presented in Figure 13. In the AMR101 group, median percent decreases from baseline in TG were observed at each time point assessed, with the difference from placebo being significant at each time point. Median percent change in TG from baseline to one year was -18.3% (-39.0 mg/dL) for the AMR101 group and 2.2% (4.5 mg/dL) for the placebo group, for a median difference in percent change from baseline of -19.7% (Hodges-Lehmann estimate; p<0.0001).

[0584] Median percent change in TG from baseline to the last study value was -21.6% (-45.0 mg/dL) for the AMR101 group and -6.5% (-13.0 mg/dL) for the placebo group, for a median difference in percent change from baseline of -14 .1 % (Hodges-Lehmann estimate; p<0.0001), which compares all possible individual cross-patient differences between treatments.

[0585] A plot of median LDL-C (Hopkins approximation) over time is presented in Figure 14. In the AMR101 group, median percent decreases from baseline in approximated LDL-C (Hopkins) were observed at each time point assessed, with the difference from placebo being significant at each time point. Median percent change in approximated LDL-C (Hopkins) from baseline to one year was -1.2% (-1.1 mg/dL) for the AMR101 group and 10.9% (9.3 mg/dL) for the placebo group, for a median difference in percent change from baseline of -11 .4% (Hodges-Lehmann estimate; p<0.0001). Median percent change in approximated LDL-C (Hopkins) from baseline to the last study value was -1.2% (-1.0 mg/dL) for the AMRI0l group and 6.5% (5.7 mg/dL) for the placebo group, for a median difference in percent change from baseline of -7.4% (Hodges-Lehmann estimate; p<0.0001).

[0586] The effects on lipid, lipoprotein, and inflammatory marker overtime for the ITT population are shown in Table 25.

Table 25. Lipid, Lipoprotein, and Inflammatory Marker Data Over Time for the ITT Population

		Icosapent Ethyl (N=4089)				Placebo (N=4090)				Between Group Difference		
Biomarker	Visit	Median Observed Value	Median Absolute Change from Baseline	Median % Change from Baseline	Median % Change P-value[1]	Median Observed Value	Median Absolute Change from Baseline	Median % Change from Baseline	Median % Change P-value[1]	Median Absolute Change from Baseline[2]	Median % Change from Baseline[2]	Median % Change P value[3]
Triglycerides (mg/dL)	Baseline	216.5				216.0						
	Month 4	177.0	-37.5	-18.6	<0.001	221.0	5.5	2.7	<0.001	-45.5	-20.1	<0.001

	Year 1	175.0	-39.0	-18.3	<0.001	221.0	4.5	2.2	<0.001	-44.5	-19.7	<0.001
	Year 2	173.0	-38.5	-18.9	<0.001	220.0	4.3	2.1	<0.001	-43.8	-19.7	<0.001
	Year 3	167.0	-44.0	-21.7	<0.001	212.0	1.0	0.4	<0.001	-45.5	-20.3	<0.001
	Year 4	163.0	-42.5	-21.7	<0.001	200.0	-7.0	-3.7	>0.99	-38.0	-17.4	<0.001
	Year 5	158.0	-38.0	-20.0	<0.001	193.0	-3.0	-1.5	0.23	-33.5	-16.7	<0.001
	Last Visit	170.0	-45.0	-21.6	<0.001	202.0	-13.0	-6.5	<0.001	-32.0	-14.1	<0.001
Non-HDL-C (mg/dL)	Baseline	118.0				118.5						
	Month 4	113.0	-4.5	-4.0	<0.001	128.0	9.5	8.2	<0.001	-14.3	-12.2	<0.001
	Year 1	113.0	-4.0	-3.6	<0.001	130.0	12.0	10.4	<0.001	-15.5	-13.1	<0.001
	Year 2	113.0	-3.5	-3.1	0.002	129.0	11.5	9.8	<0.001	-14.5	-12.5	<0.001
	Year 3	112.0	-4.8	-4.2	<0.001	128.0	10.5	9.2	<0.001	-14.5	-12.4	<0.001
	Year 4	110.5	-5.0	-4.2	<0.001	126.0	9.5	8.1	<0.001	-14.0	-12.0	<0.001
	Year 5	109.0	-5.0	-4.4	0.004	123.0	7.0	6.1	<0.001	-11.0	-9.9	<0.001
	Last Visit	112.0	-5.0	-4.4	<0.001	124.0	6.0	5.1	<0.001	-10.0	-8.6	<0.001
LDL-C derived (mg/dL)[4]	Baseline	74.0				76.0						
	Year 1	77.0	2.0	3.1	<0.001	84.0	7.0	10.2	<0.001	-5.0	-6.6	<0.001
	Last Visit	77.0	2.0	3.1	<0.001	84.0	7.0	10.2	<0.001	-5.0	-6.6	<0.001
LDL-C Hopkins (mg/dL)	Baseline	85.8				86.7						
	Month 4	83.6	-1.6	-2.0	0.01	93.7	7.3	8.7	<0.001	-8.7	-10.3	<0.001
	Year 1	85.3	-1.1	-1.2	0.06	95.8	9.3	10.9	<0.001	-9.6	-11.4	<0.001
	Year 2	85.5	-0.1	-0.2	<0.001	96.1	9.5	11.4	<0.001	-9.4	-11.1	<0.001
	Year 3	84.6	-1.0	-1.2	0.01	95.7	9.0	10.5	<0.001	-8.7	-10.4	<0.001
	Year 4	83.6	-0.5	-0.6	0.07	94.7	8.8	10.1	<0.001	-8.9	-10.6	<0.001
	Year 5	82.2	-0.8	-0.7	0.23	91.6	6.2	6.9	<0.001	-6.6	-8.0	<0.001
	Last Visit	84.0	-1.0	-1.2	0.14	92.1	5.7	6.5	<0.001	-6.2	-7.4	<0.001
HDL-C (mg/dL)	Baseline	40.0				40.0						
	Month 4	39.0	-1.0	-2.8	<0.001	42.0	2.0	4.7	<0.001	-3.0	-7.2	<0.001
	Year 1	39.0	-1.0	-2.6	<0.001	42.0	1.5	3.8	<0.001	-2.5	-6.3	<0.001
	Year 2	40.0	0.0	0.0	0.21	42.0	1.5	4.2	<0.001	-2.0	-4.6	<0.001
	Year 3	40.0	0.0	0.0	0.006	42.0	1.5	4.0	<0.001	-1.5	-3.8	<0.001
	Year 4	40.5	0.5	1.0	<0.001	43.0	2.0	4.8	<0.001	-1.5	-3.9	<0.001
	Year 5	41.0	0.0	0.0	0.02	43.0	1.5	3.0	<0.001	-1.5	-3.0	<0.001
	Last Visit	41.0	1.0	2.5	<0.001	42.0	2.0	5.7	<0.001	-1.0	-3.0	<0.001
Apo B (mg/dL)	Baseline	82.0				83.0						
	Year 2	80.0	-2.0	-2.5	0.05	89.0	6.0	7.8	<0.001	-8.0	-9.7	<0.001
	Last Visit	80.0	-2.0	-2.5	0.06	86.0	4.0	4.5	<0.001	-5.0	-6.7	<0.001
hsCRP (mg/L)	Baseline	2.2				2.1						
	Year 2	1.8	-0.2	-13.9	0.04	2.8	0.5	32.3	<0.001	-0.9	-39.9	<0.001
	Last Visit	1.8	-0.2	-12.6	0.75	2.8	0.4	29.9	<0.001	-0.8	-37.6	<0.001
Log hsCRP (mg/L)	Baseline	0.8				0.8						
	Year 2	0.6	-0.1	-21.8	<.0001	1.0	0.3	0.0	0.9203	-0.4	-22.5	<.0001
	Last Visit	0.6	-0.1	-23.1	<.0001	1.0	0.3	-4.0	0.0481	-0.4	-21.2	<.0001
EPA (µg/mL)[5]	Baseline	26.1				26.1						
	Year 1	144.0	112.6	393.5	<0.001	23.3	-2.9	-12.8	<0.001	114.9	358.8	<0.001

Safety Results

[0587] The results from this study showed no new or unexpected important adverse effects were observed in the safety population for this study as shown below in Tables 26 and 27. These conclusions are consistent with the independent DMC review conclusions and with quarterly safety review conclusions.

Table 26. Overview of Treatment-Emergent Adverse Events of the Safety Population

	AMR101 (N=4089)	Placebo (N=4090)	p-value[1]
Subjects with at Least One TEAE [2], n(%)	3343 (81.8%)	3326 (81.3%)	0.63

	AMR101 (N=4089)	Placebo (N=4090)	p-value[1]
Serious TEAE	1252 (30.6%)	1254 (30.7%)	0.98
TEAE Leading to Withdrawal of Study Drug [3]	321 (7.9%)	335 (8.2%)	0.60
Serious TEAE Leading to Withdrawal of Study Drug [3]	88 (2.2%)	88 (2.2%)	1.00
Serious TEAE Leading to Death[4]	94 (2.3%)	102 (2.5%)	0.61

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

Table 27. Serious Bleeding Treatment-Emergent Adverse Events by Preferred term.

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

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

[0588] Adverse events occurring in ≥5% are reported in Table 28. Compared with placebo, AMR101 was associated with a significantly higher rate of atrial fibrillation (5.3% versus 3.9%), and peripheral edema (6.5% vs 5%), but a lower rate of diarrhea (9% vs 11.1 %), anemia (4.7% vs 5.8%), and gastrointestinal adverse events (33.0% to 35.1%). There was no significant difference in the prespecified adjudicated tertiary endpoint of heart failure (4.1% vs 4.3%). The prespecified adjudicated tertiary endpoint of atrial fibrillation or flutter requiring hospitalization was more common with the AMR101 group than the placebo group (3.1% vs 2.1%; P=0.004).

Table 28. Number (%) Patients with Most Frequent Treatment-Emergent Adverse Events (≥5%) in Either Treatment Group By Preferred Term for the Safety Population

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

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

[0589] Serious treatment-emergent events occurring in ≥2% are reported in Table 29.

Table 29. Number (%) Patients with Serious Treatment-Emergent Adverse Events (≥2%) in Either Treatment Group) By Preferred Term

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

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

[0590] Adjudicated events from hospitalization for arterial fibrillation or atrial flutter are reported in Table 30.

Table 30. Number (%) Patients with Serious Treatment-Emergent Adverse Events (≥2%) in Either Treatment Group) By Preferred Term

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

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

[0591] Tolerability of gastrointestinal TEAS in either treatment group are reported are reported in Table 31.

Table 31. Tolerability of gastrointestinal TEAS

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

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

[0592] When grouping treatment-emergent serious adverse events for bleeding, the rate was 2.7% in the AMR101 group versus 2.1% in the placebo group (P=0.06), although there were no fatal bleeding events in either group, and no significant increases in adjudicated hemorrhagic stroke (0.3% vs 0.2 %; P=0.55), serious central nervous system bleeding (0.3% versus 0.2%; P=0.42), or gastrointestinal bleeding (1.5% versus 1.1%; P=0.15). Table 32 enumerates the serious bleeding treatment-emergent adverse events by preferred term.

Table 32. Assessment of Serious Bleeding Treatment-Emergent Adverse Events by Category and by Preferred Term.

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

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

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

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

[0593] Among the 8,179 patients (70.7% secondary prevention) followed for a median 4.9 years, the primary endpoint occurred in 17.2% of AMR101 patients versus 22.0% of placebo (HR, 0.75; 95% CI, 0.68-0.83; P<0.001) and the key secondary endpoint in 11.2% versus 14.8% (HR, 0.74; 95% CI, 0.65-0.83; P<0.001). Additional ischemic endpoints, assessed according to a prespecified hierarchical schema, were significantly reduced, including cardiovascular death (4.3% versus 5.2%; HR, 0.80; 95% CI, 0.66-0.98; P=0.03). Atrial fibrillation or flutter hospitalization was more common with the AMR101 patients than the placebo patients (3.1% versus 2.1%; P=0.004); serious bleeding occurred in 2.7% of the AMR101 patients versus 2.1% in the placebo patients (P=0.06). There were no significant differences between treatments in the overall rate of treatment emergent adverse events or serious adverse events leading to withdrawal of study drug. The only serious adverse event occurring at a frequency ≥2% was pneumonia at 2.6% in the AMR101 group versus 2.9% in the placebo group (P=0.42).

Analysis of Patient Disposition

[0594] Of the 8179 randomized patients, 89.4% (7314/8179) completed the study: 90.1% (3684/4089) and 88.8% (3630/4090) in the AMR101 and placebo groups, respectively. Of patients who completed the study, 82.6% (6754/8179) completed the final visit within the 2018 final visit window (83.6% [3419/4089] and 81.5% [3335/4090] in the AMRI0I and placebo groups, respectively), and 6.8% (560/8179) died before the final visit within the 2018 final visit window (6.5% [265/4089] and 7.2% [295/4090] in the AMR101 and placebo groups, respectively).

[0595] Thus, 10.6% (865/8179) of patients, 9.9% (405/4089) and 11.2% (460/4090) in the AMRI0I and placebo groups, respectively, terminated the study early. Of patients who terminated the study early, 9.6% (788/8179) terminated prior to having a confirmed primary event: 9.3% (380/4089) and 10.0% (408/4090) in the AMR101 and placebo groups, respectively. Among patients who terminated the study early, the most common reasons overall were:

- Withdrawal of consent: 6.9% (281/4089) and 7.3% (297/4090) in the AMR101 and placebo groups, respectively.
- Incomplete final visit (lost to follow-up): 1.5% (63/4089) and 2.2% (89/4090) in the AMR101 and placebo groups, respectively.
- Investigator judgment: 0.3% (12/4089) and 0.3% (12/4090) in the AMR101 and placebo groups, respectively

[0596] The most common reasons overall for early study drug discontinuation were:

- Patient preference: 15.4% (629/4089) and 17.4% (713/4090) in the AMR101 and placebo groups, respectively
- Adverse event: 9.2% (375/4089) and 10.1 % (413/4090) in the AMR101 and placebo groups, respectively
- Physician decision: 1.1% (47/4089) and 1.7% (68/4090) in the AMRI0I and placebo groups, respectively

[0597] Overall, 29.0% (2368/8179) of patients, 26.8% (1096/4089) and 31.1% (1272/4090) in the AMR101 and placebo groups, respectively, had a study drug interruption for >30 days during the study. Overall, 24.3% (1989/8179) of patients, 22.4% (916/4089) and 26.2% (1073/4090) in the AMR101 and placebo groups, respectively,

were ODIS at the final visit. At the time of database lock, vital status was known for 99.8% (8160/8179) of patients: 99.9% (4083/4089) and 99.7% (4077/4090) in the AMR101 and placebo groups, respectively.

[0598] A Kaplan-Meier analysis of time to early termination from the study is summarized in Table 33, and the Kaplan-Meier curve is displayed in Figure 15. As shown, there is a statistically significant difference between groups with regard to the estimated time from randomization to early termination from the study, suggesting a lower rate of early termination in the AMR101 group.

Table 33. Kaplan Kaplan-Meier Analysis of Time to Early Termination from Study from Date of Randomization (ITT Population).

	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)
Total Number of Patients with Event, n (%)[1]	670 (16.4)	755 (18.5)	1425 (17.4)
Total Censored Patients, n (%)	3419 (83.6)	3335 (81.5)	6754 (82.6)
Mean (SE) of the Follow-Up Time (Day)[2]	NE	NE	NE
P-value[3]			0.0114
Cumulative Incidence Rate (95% CI) at:			
0.5 years (Day 180)	1.7 (1.3, 2.1)	2.4 (2.0, 2.9)	2.1 (1.8, 2.4)
1 year (Day 360)	3.6 (3.1, 4.2)	4.2 (3.6, 4.9)	3.9 (3.5, 4.3)
1.5 years (Day 540)	5.9 (5.2, 6.7)	5.9 (5.2, 6.7)	5.9 (5.4, 6.5)
2 years (Day 720)	7.3 (6.5, 8.1)	7.8 (7.0, 8.7)	7.6 (7.0, 8.1)
2.5 years (Day 900)	8.7 (7.8, 9.6)	10.0 (9.1, 11.0)	9.4 (8.7, 10.0)
3 years (Day 1080)	10.5 (9.6, 11.5)	11.7 (10.7, 12.7)	11.1 (10.4, 11.8)
3.5 years (Day 1260)	11.8 (10.8, 12.8)	13.6 (12.5, 14.7)	12.7 (11.9, 13.4)
4 years (Day 1440)	13.3 (12.2, 14.4)	15.3 (14.2, 16.4)	14.3 (13.5, 15.1)

	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)
4.5 years (Day 1620)	15.0 (13.9, 16.2)	17.6 (16.4, 18.8)	16.3 (15.5, 17.1)
5 years (Day 1800)	16.6 (15.4, 17.9)	19.1 (17.8, 20.4)	17.9 (17.0, 18.7)
5.5 years (Day 1980)	19.1 (17.7, 20.5)	21.1 (19.7, 22.5)	20.1 (19.1, 21.1)
6 years (Day 2160)	22.8 (19.6, 26.1)	25.2 (21.5, 29.0)	24.0 (21.5, 26.5)
6.5 years (Day 2340)	22.8 (19.6, 26.1)	31.4 (19.4, 44.2)	26.5 (21.2, 32.1)
7 years (Day 2520)	22.8 (19.6, 26.1)	31.4 (19.4, 44.2)	26.5 (21.2, 32.1)

Abbreviations: CI = confidence interval; ITT = Intent-to-Treat; NE = non estimable; SE = standard error.

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N).

1 Includes events from the study. Deaths were censored in this analysis.

2 Not estimable.

3 P-value was based on a log-rank test comparing treatment groups.

Concomitant Medications

[0599] Concomitant Statin Use: At randomization (Visit 2), and at each post-randomization time point assessed, over 93% of statin-treated patients were receiving moderate or high intensity statins.

[0600] Other Concomitant Medications of Interest: An overview of baseline medications of special interest is summarized in Table 34, overall and by treatment group. The proportions of patients taking each type of medication of special interest at baseline were similar between the AMR101 and placebo groups. The high proportion of patients taking anti diabetic, antihypertensive, anti-platelet, and anti-thrombotic medications is indicative of appropriate treatment of this at-risk patient population. The proportions of patients taking each type of medication of special interest throughout the study were similar between the AMR101 and placebo groups.

Table 34. Overview of Medications of Special Interest (ITT Population)

Medication Taken at Baseline, n (%)	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)
Antidiabetic	2190 (53.6)	2196 (53.7)	4386 (53.6)
Antihypertensive	3895 (95.3)	3895 (95.2)	7790 (95.2)
Antiplatelet	3257 (79.7)	3236 (79.1)	6493 (79.4)
ACE Inhibitors	2112 (51.7)	2131 (52.1)	4243 (51.9)
ARBs	1108 (27.1)	1096 (26.8)	2204 (26.9)
ACE Inhibitors or ARBs	3164 (77.4)	3176 (77.7)	6340 (77.5)
Beta Blockers	2902 (71.0)	2880 (70.4)	5782 (70.7)

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; ITT = Intent-to-Treat.

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N).

Analysis of the Demographic and Other Baseline Characteristics

[0601] Patient demographics and baseline characteristics are summarized in Table 35, overall and by treatment group. Overall, the majority of patients were male (71.2% [5822/8179]) and white (90.2% [7379/8179]). The mean age of patients was 63.4 years (range 44 to 92 years), with 46.0% (3763/8179) of patients aged :::65 years. Mean height, weight, and BMI were 171.3 cm, 93 .0 kg, and 31.6 kg/m2, respectively. Overall, 22.2% (1816/8179) of patients were renally impaired at baseline (eGFR <60 mL/min/l.73m2).

Table 35. Demographic and Baseline Characteristics, Overall, and by Treatment Group (ITT Population).

Parameter Statistic	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)	P-value[1]
Age (years)[2]				0.7524
n	4089	4090	8179	
Mean (SD)	63.4 (8.37)	63.4 (8.43)	63.4 (8.40)	
Median	64.0	64.0	64.0	
Min, Max	45.0, 92.0	44.0, 91.0	44.0, 92.0	
Age Group, n (%)				0.2815
<65 Years	2232 (54.6)	2184 (53.4)	4416 (54.0)	
≥65 Years	1857 (45.4)	1906 (46.6)	3763 (46.0)	
Sex, n (%)				0.4245

Parameter Statistic	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)	P-value[1]
Male	2927 (71.6)	2895 (70.8)	5822 (71.2)	
Female	1162 (28.4)	1195 (29.2)	2357 (28.8)	
Ethnicity, n (%)				0.0877
Hispanic or Latino	188 (4.6)	157 (3.8)	345 (4.2)	
Not Hispanic or Latino	3901 (95.4)	3933 (96.2)	7834 (95.8)	
Race, n (%)				0.3415
White	3691 (90.3)	3688 (90.2)	7379 (90.2)	
Black or African American	69 (1.7)	89 (2.2)	158 (1.9)	
Asian	225 (5.5)	221 (5.4)	446 (5.5)	
American Indian or Alaska Native	18 (0.4)	11 (0.3)	29 (0.4)	
Native Hawaiian or Other Pacific Islander	7 (0.2)	3 (0.1)	10 (0.1)	
Multiple	49 (1.2)	42 (1.0)	91 (1.1)	
Other	30 (0.7)	35 (0.9)	65 (0.8)	
Missing	0 (0.0)	1 (0.0)	1 (0.0)	
Weight (kg)				0.1347
n	4082	4076	8158	
Mean (SD)	92.7 (18.32)	93.3 (18.46)	93.0 (18.39)	
Median	91.0	91.2	91.1	
Min, Max	46.0, 197.3	40.8, 189.4	40.8, 197.3	
Height (cm)				0.3441
n	4078	4072	8150	
Mean (SD)	171.2 (9.76)	171.4 (9.62)	171.3 (9.69)	
Median	172.0	172.0	172.0	
Min, Max	137.2, 208.0	137.2, 203.2	137.2, 208.0	
BMI (kg/m^2)				0.2803
n	4078	4071	8149	
Mean (SD)	31.5 (5.41)	31.7 (5.47)	31.6 (5.44)	
Median	30.8	30.8	30.8	
Min, Max	18.3, 65.0	16.4, 64.0	16.4, 65.0	
BMI Group, n (%)				0.5287
<25 kg/m^2	320 (7.8)	295 (7.2)	615 (7.5)	
≥25 to <30 kg/m^2	1427 (34.9)	1414 (34.6)	2841 (34.7)	
≥30 kg/m^2	2331 (57.0)	2362 (57.8)	4693 (57.4)	
Missing	11 (0.3)	19 (0.5)	30 (0.4)	
Waist Circumference (cm)				0.4730
n	4025	4031	8056	

Parameter Statistic	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)	P-value[1]
Mean (SD)	106.6 (13.39)	106.8 (13.40)	106.7 (13.40)	
Median	105.0	105.5	105.4	
Min, Max	46.5, 182.9	44.0, 170.2	44.0, 182.9	
Renal Impairment[3], n (%)				0.8872
Yes	905 (22.1)	911 (22.3)	1816 (22.2)	
No	3180 (77.8)	3177 (77.7)	6357 (77.7)	
Missing	4 (0.1)	2 (0.0)	6 (0.1)	
Baseline eGFR, n (%)				0.8104
<60 mL/min/1.73m^2	905 (22.1)	911 (22.3)	1816 (22.2)	
≥60 and <90 mL/min/1.73m^2	2217 (54.2)	2238 (54.7)	4455 (54.5)	
≥90 mL/min/1.73m^2	963 (23.6)	939 (23.0)	1902 (23.3)	
Missing	4 (0.1)	2 (0.0)	6 (0.1)	
Diabetes, n (%)				0.7627
No diabetes at baseline	1695 (41.5)	1694 (41.4)	3389 (41.4)	
Type 1 diabetes	27 (0.7)	30 (0.7)	57 (0.7)	
Type 2 diabetes	2366 (57.9)	2363 (57.8)	4729 (57.8)	
Both Type 1 and Type 2 diabetes	1 (0.0)	0 (0.0)	1 (0.0)	
Missing	0 (0.0)	3 (0.1)	3 (0.0)	
Type 1 or 2[4]	2394 (58.5)	2393 (58.5)	4787 (58.5)	0.9622
BMI <25 kg/m^2	134 (5.6)	138 (5.8)	272 (5.7)	
BMI ≥25 to <30 kg/m^2	681 (28.4)	676 (28.2)	1357 (28.3)	
BMI ≥30 kg/m^2	1571 (65.6)	1567 (65.5)	3138 (65.6)	
BMI missing	8 (0.3)	12 (0.5)	20 (0.4)	
Hypertension[5], n (%)				0.9706
Yes	3541 (86.6)	3543 (86.6)	7084 (86.6)	
No	548 (13.4)	547 (13.4)	1095 (13.4)	
Metabolic Syndrome[6], n (%)				0.0988
Yes	3792 (92.7)	3753 (91.8)	7545 (92.2)	
No	297 (7.3)	337 (8.2)	634 (7.8)	
Impaired Glucose Metabolism[7], n (%)				0.1570
Yes	1454 (35.6)	1517 (37.1)	2971 (36.3)	
No	2630 (64.3)	2571 (62.9)	5201 (63.6)	
Missing	5 (0.1)	2 (0.0)	7 (0.1)	

Abbreviations: BMI = body mass index; CRF = case report form; eGFR = estimated glomerular filtration rate; ITT = Intent-to-Treat; Max = maximum; Min = minimum; SD = standard deviation.

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N) except as noted below.

Parameter Statistic	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)	P-value[1]

1 To assess balance between treatment groups, p-values were reported from a chi-square test for categorical variables and a t-test for continuous variables. Missing categories were excluded from any comparisons.

2 Age (years) was at randomization.

3 eGFR <60 mL/min/1.73m^2.

4 Percentages were based on the number of patients with Type 1 or Type 2 diabetes.

5 Hypertension as identified on the CRF "Cardiovascular History."

6 For the diagnosis of metabolic syndrome, refer to Appendix D of Protocol Amendment 2 (Appendix 16.1.1).

7 Impaired glucose metabolism was based on Visit 2 fasting blood glucose of 100 to 125 mg/dL.

[0602] Patients were analyzed for the history for cardiovascular disease as enumerated in Tables 36-38.

[0603] Reported CV disease history and risk factors are summarized in Table 36, overall and by treatment group, for the ITT population. For this table, data are limited to pre-populated terms on the CV history CRF. Overall, the most common incidences of reported CV disease history or other prior conditions influencing CV risk were hypertension (86.6% [7084/8179]), Type 2 diabetes (57.8% [4730/8179]), and MI (46.7% [3819/8179]). The individual incidences of reported CV disease history or other prior conditions influencing CV risk were comparable between the AMR101 and placebo groups.

[0604] The most common incidences of reported CV disease history or other prior conditions influencing CV risk were the same as those for the ITT population and included hypertension (86.6% [7067/8160]), Type 2 diabetes (57.8% [4717/8160]), and MI (46.7% [3812/8160]) (Table 36). A similar trend was observed in each component of reported CV disease history and other conditions influencing CV risk, indicating comparability across the ITT and mITT populations.

Table 36. Reported Cardiovascular Disease History and Risk Factors, Overall and by Treatment Group (ITT Population).

Category Term	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Prior Atherosclerotic Cardiovascular Disease	2816 (68.9)	2835 (69.3)	5651 (69.1)

Category Term	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Prior Atherosclerotic Coronary Artery Disease and Related Morbidities	2387 (58.4)	2393 (58.5)	4780 (58.4)
Ischemic dilated cardiomyopathy	137 (3.4)	109 (2.7)	246 (3.0)
Myocardial infarction	1938 (47.4)	1881 (46.0)	3819 (46.7)
Unstable angina	1017 (24.9)	1015 (24.8)	2032 (24.8)
Prior Atherosclerotic Cerebrovascular Disease and Related Morbidities	641 (15.7)	662 (16.2)	1303 (15.9)
Carotid disease	343 (8.4)	372 (9.1)	715 (8.7)
Ischemic stroke	267 (6.5)	242 (5.9)	509 (6.2)
Transient ischemic attack	194 (4.7)	181 (4.4)	375 (4.6)
Prior Atherosclerotic Peripheral Arterial Disease	387 (9.5)	388 (9.5)	775 (9.5)
Ankle brachial index <0.9 without symptoms of intermittent claudication	97 (2.4)	76 (1.9)	173 (2.1)
Peripheral arterial disease	377 (9.2)	377 (9.2)	754 (9.2)
Prior Non-Atherosclerotic Cardiovascular Disease	3649 (89.2)	3645 (89.1)	7294 (89.2)
Prior Structural Cardiac Disorders	827 (20.2)	866 (21.2)	1693 (20.7)
Congestive heart failure	703 (17.2)	743 (18.2)	1446 (17.7)
Hypertrophic cardiomyopathy	23 (0.6)	20 (0.5)	43 (0.5)
Non-ischemic dilated cardiomyopathy	35 (0.9)	29 (0.7)	64 (0.8)
Non-rheumatic valvular heart disease	150 (3.7)	163 (4.0)	313 (3.8)
Rheumatic valvular heart disease	17 (0.4)	9 (0.2)	26 (0.3)
Prior Cardiac Arrhythmias	229 (5.6)	243 (5.9)	472 (5.8)
Atrio-ventricular block above first degree	51 (1.2)	54 (1.3)	105 (1.3)
Sick sinus syndrome	30 (0.7)	32 (0.8)	62 (0.8)
Supra-ventricular tachycardia other than atrial fibrillation/atrial flutter	74 (1.8)	77 (1.9)	151 (1.8)
Sustained ventricular tachycardia	34 (0.8)	34 (0.8)	68 (0.8)
Torsades de pointes	1 (0.0)	3 (0.1)	4 (0.0)
Ventricular fibrillation	61 (1.5)	65 (1.6)	126 (1.5)
Prior Non-Cardiac/Non-Atherosclerotic Vascular Disorders	3568 (87.3)	3566 (87.2)	7134 (87.2)
Arterial embolism	12 (0.3)	9 (0.2)	21 (0.3)
Deep vein thrombosis	70 (1.7)	60 (1.5)	130 (1.6)
Hypertension	3541 (86.6)	3543 (86.6)	7084 (86.6)

Category Term	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Hypotension	45 (1.1)	33 (0.8)	78 (1.0)
Pulmonary embolism	31 (0.8)	42 (1.0)	73 (0.9)
Non-ischemic stroke	79 (1.9)	84 (2.1)	163 (2.0)
Hemorrhagic stroke	18 (0.4)	22 (0.5)	40 (0.5)
Stroke of unknown origin	63 (1.5)	62 (1.5)	125 (1.5)
Other Prior Conditions or Investigations Influencing Cardiovascular Risk	3044 (74.4)	3055 (74.7)	6099 (74.6)
Prior Metabolic Disorders	2480 (60.7)	2515 (61.5)	4995 (61.1)
Diabetes type 1	28 (0.7)	30 (0.7)	58 (0.7)
Diabetes type 2	2367 (57.9)	2363 (57.8)	4730 (57.8)
Metabolic syndrome	507 (12.4)	540 (13.2)	1047 (12.8)
Baseline Investigations	1783 (43.6)	1707 (41.7)	3490 (42.7)
Renal Disorders	470 (11.5)	429 (10.5)	899 (11.0)
Creatinine clearance >30 and <60 mL/min	309 (7.6)	286 (7.0)	595 (7.3)
Macroalbuminuria	34 (0.8)	24 (0.6)	58 (0.7)
Microalbuminuria	146 (3.6)	134 (3.3)	280 (3.4)
Proteinuria	75 (1.8)	63 (1.5)	138 (1.7)
Abnormal Lipids	1496 (36.6)	1419 (34.7)	2915 (35.6)
High HDL-C (≥60 mg/dL)	187 (4.6)	187 (4.6)	374 (4.6)
Low HDL-C (<40 mg/dL)	1327 (32.5)	1259 (30.8)	2586 (31.6)
Triglycerides >1000 mg/dL	76 (1.9)	72 (1.8)	148 (1.8)
hsCRP >3 mg/L	236 (5.8)	252 (6.2)	488 (6.0)
Other Morbidities	173 (4.2)	173 (4.2)	346 (4.2)
Pancreatitis	14 (0.3)	9 (0.2)	23 (0.3)
Retinopathy	161 (3.9)	167 (4.1)	328 (4.0)
Carotid Stenosis (%)			
n	316	346	662
Mean (SD)	59.0 (21.04)	56.9 (22.99)	57.9 (22.09)
Median	60.0	59.0	59.5
Min, Max	0.0, 100.0	0.0, 100.0	0.0, 100.0

Abbreviations: HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; ITT = Intent-to-Treat; Max = maximum; Min = minimum; SD = standard deviation.

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N). This summary was based on data collected from the "Cardiovascular History" case report form. Two outliers of carotid stenosis (%) with a value over 100% were excluded from the

Category Term	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
analysis. Carotid stenosis (%) data reported in categorical format of >x% and <y% were analyzed as x% and y%, respectively, and reported as x% to y% was analyzed as an average of x% and y%.			

[0605] The most frequently reported CV history findings were coronary artery disease (12.8% [1045/8179]), angina pectoris (11.6% [94 7 /8179]), and atrial fibrillation (8. 7% [713/8179]). A summary of reported history of CV procedures is presented in Table 37, overall and by treatment group. The most common prior CV procedures overall included:

- PTCA/stenting in 41.7% (3408/8179) of patients, with a median time from the procedure to randomization of 35.4 months.
- Coronary artery bypass graft in 22.5% (1837/8179) of patients, with a median time from the procedure to randomization of 60.7 months.

[0606] Overall, <5% of patients had previously undergone other types of CV procedures, including aorto-iliac or peripheral arterial intervention (4.5% [365/8179]); carotid revascularization (2.6% [212/8179]); permanent pacemaker placement (2.9% [237/8179]); and implantable cardioverter defibrillator placement (2.0% [166/8179]) (Table 37).

Table 37. Reported History of Cardiovascular Procedures, Overall and by Treatment Group (ITT Population).

Procedure, n (%)	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)
PTCA/Stenting	1737 (42.5)	1671 (40.9)	3408 (41.7)
Time from Procedure to Randomization (months)			
n	1303	1256	2559
Mean (SD)	51.6 (51.34)	50.4 (53.52)	51.0 (52.41)
Median	36.5	33.8	35.4
Min, Max	0.4, 354.3	0.4, 367.8	0.4, 367.8
Emergent[1]	842 (48.5)	843 (50.4)	1685 (49.4)
Non-emergent	895 (51.5)	828 (49.6)	1723 (50.6)
Successful[1]	1695 (97.6)	1625 (97.2)	3320 (97.4)
Unsuccessful	42 (2.4)	46 (2.8)	88 (2.6)

Procedure, n (%)	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)
Coronary Artery Bypass Graft	897 (21.9)	940 (23.0)	1837 (22.5)
Time from Procedure to Randomization (months)			
n	619	644	1263
Mean (SD)	72.2 (65.66)	82.5 (69.92)	77.5 (68.04)
Median	55.1	67.0	60.7
Min, Max	1.3, 367.6	0.7, 399.6	0.7, 399.6
Emergent[2]	310 (34.6)	327 (34.8)	637 (34.7)
Non-emergent	587 (65.4)	613 (65.2)	1200 (65.3)
Successful[2]	893 (99.6)	935 (99.5)	1828 (99.5)
Unsuccessful	4 (0.4)	5 (0.5)	9 (0.5)
Implantable Cardioverter Defibrillator	78 (1.9)	88 (2.2)	166 (2.0)
Time from Procedure to Randomization (months)			
n	51	56	107
Mean (SD)	52.2 (41.96)	41.1 (31.23)	46.4 (36.98)
Median	42.8	34.7	38.2
Min, Max	1.4, 191.6	1.9, 113.9	1.4, 191.6
Permanent Pacemaker	105 (2.6)	132 (3.2)	237 (2.9)
Time from Procedure to Randomization (months)			
n	65	78	143
Mean (SD)	44.7 (36.66)	44.2 (49.22)	44.4 (43.81)
Median	37.8	32.4	34.2
Min, Max	2.0, 211.5	1.0, 325.8	1.0, 325.8
Carotid Revascularization	90 (2.2)	122 (3.0)	212 (2.6)
Catheter-based[3]	30 (33.3)	28 (23.0)	58 (27.4)
Surgical	60 (66.7)	94 (77.0)	154 (72.6)
Aorto-Iliac or Peripheral Arterial Intervention	191 (4.7)	174 (4.3)	365 (4.5)
Catheter-based[4]	108 (56.5)	72 (41.4)	180 (49.3)
Surgical	83 (43.5)	102 (58.6)	185 (50.7)

Abbreviations: ITT = Intent-to-Treat; Max = maximum; Min = minimum; PTCA = percutaneous transluminal coronary angioplasty; SD = standard deviation.

Note: Percentages were based on the number of patients randomized to each treatment group in the ITT population (N) except where otherwise stated.

1 Percentages were based on the number of patients with a history of PTCA/stenting.

Procedure, n (%)	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)

2 Percentages were based on the number of patients with a history of coronary artery bypass graft.

3 Percentages were based on the number of patients with a history of implantable cardioverter defibrillator. For 1 patient, the treatment was selected "No," but treatment method was specified as "surgical."

4 Percentages were based on the number of patients with a history of aorto-iliac peripheral arterial intervention.

[0607] Family history of premature CHD is summarized in Table 38, overall and by treatment group. As shown, approximately one-third (30.4% [2483/8179]) of patients had a family history of premature CHD, most commonly in a male first degree relative <55 years of age.

Table 38. Family History of Premature Coronary Heart Disease, Overall and by Treatment Group (ITT Population).

Category	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Patients with a Family History of Premature CHD	1245 (30.4)	1238 (30.3)	2483 (30.4)
Male first degree relative <55 years	660 (16.1)	653 (16.0)	1313 (16.1)
Female first degree relative <65 years	358 (8.8)	364 (8.9)	722 (8.8)
Both first degree male <55 years and female <65 years	226 (5.5)	220 (5.4)	446 (5.5)

Abbreviations: CHD = coronary heart disease; ITT = Intent-to-Treat.

Note: Percentages were based on the number of patients randomized to each treatment group (N). There were 5 patients with family history of "Yes" who had missing categories; 3 patients with family history of "No" had non-missing categories.

[0608] Patients were further analyzed for the history of medical conditions other than cardiovascular disease. Patients most commonly had a history of metabolism and nutrition system disorders (76.8% [6281/8179]), primarily lipid abnormalities, including hyperlipidemia (28.2% [2303/8179]), hypercholesterolemia (22.2% [1815/8179]), and dyslipidemia (20.5% [1673/8179]). Other conditions reported for> 10% of patients overall were typical of an older population of adults and included gastroesophageal reflux

disease (18.9% [1545/8179]), osteoarthritis (16.2% [1323/8179]), obesity (16.4% [1339/8179]), and depression (11.9% [977/8179]).

Conclusion

[0609] In this study, the risk of the primary composite endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, assessed in a time-to-event analysis, was significantly lower, by 25%, among the patients who received 2 g of icosapent ethyl twice daily than among those who received placebo, corresponding to an absolute between-group difference of 4.8 percentage points in the rate of the endpoint and a number needed to treat of 21. The risk of the key secondary composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in a time-to-event analysis was also significantly lower, by 26%, in patients who received 2 g of icosapent ethyl twice daily than among those who received placebo, corresponding to an absolute between-group difference of 3.6 percentage points in the rate of the endpoint and a number needed to treat of 28. Prespecified hierarchical testing of other secondary endpoints revealed that the risks of a variety of fatal and nonfatal ischemic events were lower in the AMR101 group than in the placebo group, including a 20% lower risk of cardiovascular death. The benefits were observed against a background of appropriate statin use among patients who had a median LDL cholesterol level of 75.0 mg/dL at baseline.

[0610] Overall adverse event rates were similar across treatment groups. There were numerically more serious adverse events related to bleeding, though overall rates were low, with no fatal bleeding observed in either group and no significant increase in adjudicated hemorrhagic stroke or serious central nervous system or gastrointestinal bleeding. There was a significantly higher rate of hospitalization for atrial fibrillation or flutter, though rates were low in those patients who received 2 g of icosapent ethyl twice daily. Adverse event and serious adverse event rates leading to study drug discontinuation were similar to placebo. The rates of adverse events and serious adverse events leading to discontinuation of trial drug were similar in the two groups.

[0611] The results from this study stand apart from the negative findings of several recent trials of other agents that also lower triglyceride levels, such as other omega-3 fatty acids, extended-release niacin, fenofibrate, and cholesteryl ester transfer protein-inhibitors. It is not known whether the lack of benefit of omega-3 fatty acids in previous

trials might be attributable to the low dose or the low ratio of EPA to DHA. Both the formulation (a highly purified and stable EPA acid ethyl ester) and dose (4 grams daily) used in this study are different from all prior omega-3 outcome trials. Despite utilizing a standard PROBE design limitation of those previous trials included an open label design without placebo, use of a low-intensity statin, and conducted in a single country; in contrast to the present report, patients in those trials had higher baseline LDL-C levels (182 mg/dL prior to statin initiation) and lower triglyceride values (151 mg/dL). In contrast, the present study provides robust, multinational data showing significant reductions in ischemic events with administration of icosapent ethyl in patients with well-controlled LDL-C. Metabolic data support that icosapent ethyl does not raise LDL cholesterol levels, which DHA containing formulations do.

[0612] A triglyceride level ≥150 mg/dL was required for inclusion in this study however, owing to initial allowance for variability in these levels and differences between qualifying and randomization measurements, 10.3% of enrolled patients had triglycerides less than 150 mg/dL on study entry. Cardiovascular benefits appeared similar across baseline levels of triglycerides (e.g., 135-149, 150 to 199, and 200 mg/dL or greater). Additionally, the robust reduction in major adverse cardiovascular events with administration of icosapent ethyl appeared to occur irrespective of an achieved triglyceride level above or below 150 mg/dL at one year, suggesting that the cardiovascular risk reduction was not tied to achieving a more normal (i.e., <150 mg/dL) triglyceride level. These observations suggest that at least some of the impact of icosapent ethyl on the reduction in ischemic events may be explained by metabolic effects other than triglyceride lowering.

[0613] Mechanisms responsible for the benefit in the present study are currently not known. The timing of divergence of the Kaplan-Meier event curves suggests a delayed onset to benefit, which may reflect the time to benefit from triglyceride reduction or other mechanisms. The modestly higher rate of bleeding suggests that there might be an anti-thrombotic mechanism of action. However, it is unlikely that an anti-thrombotic effect would reduce elective revascularization. Also, if the full explanation were an antiplatelet or anticoagulant effect, one might expect a large increase in major bleeding, which was not seen. Potentially, membrane-stabilizing effects could explain part of the benefit. Stabilization and/or regression of coronary plaque may also play a part. The observation in the present study of a lower rate of sudden cardiac death might support that

mechanism, though this finding should be viewed as exploratory. It is also possible that the 40% reduction in hsCRP observed in patients from this trial may contribute to benefit. Samples (e.g., serum and plasma) from patients who participated in this trial have been banked for biomarker and genetic analyses, which may provide more information regarding mechanisms of action.

[0614] Regarding higher rates of diarrhea in the mineral oil placebo group, a *post hoc* analysis excluding patients with diarrhea still resulted in a significant risk reduction of 25% in the primary endpoint. Also, there were no differences in the primary or key secondary endpoints for placebo patients with an increase in LDL-C compared to those with no change or a decrease in LDL-C.

[0615] In conclusion, AMR101 4 grams daily demonstrated similar overall adverse event rates as placebo, and reduced important ischemic events, including cardiovascular death, in statin-treated patients with elevated triglycerides. Compared with placebo, icosapent ethyl 4 g per day significantly reduced cardiovascular events by 25% including: a 31% reduction in heart attack, 28% reduction in stroke, 31% reduction in myocardial infarction, and a 20% reduction in death due to cardiovascular events.

[0616] The following are key conclusions obtained from this trial that indicate a very favorable risk-benefit profile (1) significant reduction in primary endpoint with a RRR of 24.8%, ARR of 4.8%, NNT of 21, and a p-value of 0.00000001, (2) significant reduction in key secondary endpoint with a RRR of 26.5%, ARR of 3.6%, NNT of 28, and a p-value of 0.0000062, (3) consistent results across subgroups to include triglycerides and secondary and primary prevention, (4) consistent results across hierarchical secondary endpoints to include cardiovascular death, (5) consistent results across recurrent events, and (6) safety with a small but insignificant increase in atrial fibrillation/flutter with low event rates and non-significant increase in serious bleeding with low event rates.

EXAMPLE 2: The Impact of Icosapent Ethyl on Recurrent Events and Total Ischemic Events in Statin-Treated Patients

[0617] Despite statin therapy, patients with established cardiovascular disease or diabetes remain at high risk for, not only first but also, recurrent ischemic events. The study results described in Example 1 demonstrated that icosapent ethyl reduces the first occurrence of the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina, with a 25% relative risk

reduction and a 4.8% absolute risk reduction. The time to first occurrence of the composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke was also reduced with icosapent ethyl, with a 26% relative risk reduction and a 3.6% absolute risk reduction.

[0618] The objective of the following study was to assess the impact of icosapent ethyl on recurrent events and total ischemic events. With a greater number of events, it was contemplated that there might be sufficient statistical power to examine the effect of icosapent ethyl in the two separate cardiovascular risk strata in the trial: patients with established atherosclerosis or patients with diabetes plus at least one other cardiovascular risk factor. Accordingly, the goal of the following study was to determine if icosapent ethyl administered at 4 g per day (e.g., 2 g twice daily) reduces total major adverse cardiovascular events in patients with fasting triglycerides ≥150 and <500 mg/dL and LDL-cholesterol >40 and ≤100 mg/dL who are at increased cardiovascular risk despite statin therapy.

Study Design

[0619] The following study was a multi-center, placebo-controlled clinical trial the details of which are described above in Example 1, the REDUCE-IT design. As shown in Figure 16, patients were randomized in a double-blind manner to icosapent ethyl 4 g/day (2 grams twice daily with food) versus placebo. Randomization was stratified by cardiovascular risk cohort (i.e., secondary or primary prevention), use of ezetimibe, and by geographic region.

Study Population

[0620] The study participants included patients with a history of atherosclerosis or diabetes who were on statins and had fasting triglycerides ≥150 and <500 mg/dL and LDL-cholesterol >40 and ≤100 mg/dL. Of the study participants, 71% of the patients had a history of atherosclerosis and 29% had a history of diabetes. In order to be eligible for the trial, patients had to be ≥45 years of age with either established cardiovascular disease (i.e., secondary prevention stratum) or ≥50 years old with type 2 or type 1 diabetes mellitus requiring treatment with medication and at least one additional risk factor (i.e., primary prevention stratum).

[0621] The secondary prevention stratum consisted of patients with documented coronary artery disease (≥50% stenosis in at least two major epicardial coronary arteries with or without prior revascularization; prior MI; hospitalization for non-ST-segment elevation acute coronary syndrome with ST-segment deviation or positive biomarkers); documented cerebrovascular disease (prior ischemic stroke; symptomatic ≥50% carotid stenosis; asymptomatic carotid disease with ≥70% stenosis; history of carotid revascularization); or documented peripheral artery disease (ankle-brachial index <0.9 with symptoms of intermittent claudication; history of aorto-iliac or peripheral surgery or intervention).

[0622] The primary prevention stratum consisted of patients with no documented cardiovascular disease as defined above, with diabetes, and with at least one of the following cardiovascular risk factors: men ≥55 years of age or women ≥65 years of age; cigarette smoker or stopped smoking within 3 months before first visit; blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic or on antihypertensive medication; HDL-cholesterol ≤40 mg/dL for men or ≤50 mg/dL for women; hsCRP >3 mg/L; creatinine clearance >30 and <60 mL/min; non-proliferative retinopathy, pre-proliferative retinopathy, proliferative retinopathy, maculopathy, advanced diabetic eye disease or a history of photocoagulation; micro- or macro-albuminuria; or asymptomatic ankle-brachial index <0.9.

[0623] The participants were required to have fasting triglycerides between ≥150 mg/dL and <500 mg/dL and LDL-cholesterol >40 mg/dL and ≤100 mg/dL. In the initial version of the clinical trial protocol, a 10% allowance in qualifying triglyceride levels was allowed, and therefore patients with triglycerides ≥135 mg/dL were randomized. The study included 841 (10.3%) patients with baseline triglyceride levels <150 mg/dL. After approximately 60% of the patients were enrolled, an amendment changed the lower limit of allowed triglyceride levels to 200 mg/dL with no variability allowance. Patients were required to be on stable statin therapy for at least four weeks.

[0624] Exclusion criteria for the study participants included severe heart failure or liver disease, hemoglobin A1c levels >10.0%, planned coronary intervention, familial lipoprotein lipase deficiency, intolerance or hypersensitivity to statins, history of acute or chronic pancreatitis, and hypersensitivity to fish, shellfish, or ingredients of icosapent ethyl or placebo.

Main outcomes and Measures

[0625] The primary outcome for the study was total recurrent events consisting of the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. Recurrent event analyses were also performed for the key secondary endpoint, a composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. For each of these composite endpoints, the effects of icosapent ethyl in the secondary and primary prevention strata were examined separately.

Statistical Considerations

[0626] Demographic and baseline disease characteristics are presented using frequencies and percentages for categorical variables and medians with interquartile ranges for continuous variables. Between treatment group comparisons were derived using the chi-square test for categorical variables and Wilcoxon rank test for continuous variables. All clinical endpoint events used in the efficacy analyses were adjudicated by an independent Clinical Endpoint Committee (CEC) who were blinded to the treatment assignment. Since the primary efficacy endpoint was the time from randomization to the first occurrence of any component of the composite endpoint, and recurrence of such events within each patient is possible, a pre-specified analysis using a Cox proportional-hazard with the counting-process formulation of Andersen and Gill was performed to model the first and all recurrent cardiovascular events. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) are reported from this model. In addition, as a marginal model and an extension of survival models based on the Cox proportional hazard model, the modified Wei-Lin-Weissfeld (WLW) method for analysis of recurrent events in the presence of deaths was carried out as a supportive analysis. In addition, as pre-specified, a recurrent event analysis using the Andersen-Gill and Wei-Lin-Weissfeld methods were carried out for the individual primary event components other than CV death. Though not pre-specified, additional recurrent event analyses were performed for the key secondary endpoint, which is a composite of CV death, non-fatal MI, or non-fatal stroke, and for the primary endpoint and the key secondary endpoint in the primary and secondary prevention strata to explore further the consistency of clinical benefit of icosapent ethyl. In subgroup analyses of the two cardiovascular risk strata (i.e., primary and secondary prevention), site-level discrepancies in cardiovascular risk group

assignment occurring at entry and detected during the study (1.8%) were adjusted to conform with documented medical history data prior to randomization. All efficacy analyses were performed according to the intention-to-treat principle. All tests were based on a 2-sided nominal significance level of 5% with no adjustments for multiple comparisons.

Results

Baseline Characteristics

[0627] A total of 8,179 patients were randomized and followed for a median of 4.9 years. The patients were well matched in the icosapent ethyl and placebo groups as shown in Table 16 (See Example 1). The secondary and primary prevention according to the adjusted stratification for this study are shown in Table 38.

Table 38. Secondary and Primary Prevent Per Adjusted Stratification for Patients Randomized to Placebo or Icosapent Ethyl.

	Icosapent ethyl (N=4089)	Placebo (N=4090)	p-value [1]
Stratification Factors			
			0.7367
Secondary Prevention per Adjusted Stratification	2933 (71.7%)	2920 (71.4%)	
Primary Prevention per Adjusted Stratification	1156 (28.3%)	1170 (28.6%)	
[1] P-value is from a Wilcoxon rank-sum test for continuous variables and a chi-square test for categorical variables.			

[0628] At baseline, the patient's median triglyceride levels were 216 mg/dL and median LDL-C levels were 75 mg/dL. Additional baseline characteristics of the patients with no events, a single event, and multiple recurrent events are shown in Table 39.

Table 39. Baseline Characteristics of Patients with No Events, a Single Event, or Multiple Events.

Baseline Characteristics in Patients with No Events, a Single Event, or Multiple Events				
	No Events (N=6573)	**1 Event (N=844)**	**Multiple Events (N=762)**	**p-value [1]**
Demographics				
Age (years), Median (Q1-Q3)	63.0 (57.0 - 69.0)	65.0 (59.0 - 71.0)	64.0 (58.0 - 70.0)	<.0001
Age ≥65 years, n(%)	2939 (44.7%)	456 (54.0%)	368 (48.3%)	<.0001

Male, n(%)	4556 (69.3%)	661 (78.3%)	605 (79.4%)	<.0001
White, n(%)[2]	5921 (90.1%)	765 (90.6%)	693 (90.9%)	0.6908
BMI (kg/m^2), Median (Q1-Q3)	30.8 (27.8 - 34.6)	31.1 (27.8 - 34.7)	30.8 (28.0 - 34.2)	0.5124
BMI ≥30, n(%)[3]	3762 (57.2%)	499 (59.1%)	432 (56.7%)	0.7771
Stratification Factors				
Geographic Region, n(%)				<.0001
Westernized [4]	4547 (69.2%)	639 (75.7%)	625 (82.0%)	
Eastern Europe [5]	1796 (27.3%)	185 (21.9%)	125 (16.4%)	
Asia Pacific [6]	230 (3.5%)	20 (2.4%)	12 (1.6%)	
CV Risk Category as Randomized, n(%)				<.0001
Secondary Prevention per Randomization	4488 (68.3%)	640 (75.8%)	657 (86.2%)	
Primary Prevention per Randomization	2085 (31.7%)	204 (24.2%)	105 (13.8%)	
CV Risk Category Actual, n(%)				<.0001
Secondary Prevention per Adjusted Stratification	4537 (69.0%)	652 (77.3%)	664 (87.1%)	
Primary Prevention per Adjusted Stratification	2036 (31.0%)	192 (22.7%)	98 (12.9%)	
Ezetimibe Use, n(%)	401 (6.1%)	59 (7.0%)	64 (8.4%)	0.0378
Statin Intensity and Diabetes Status				
Statin Intensity, n(%)				0.0819
Low	428 (6.5%)	49 (5.8%)	44 (5.8%)	
Moderate	4141 (63.0%)	519 (61.5%)	448 (58.8%)	
High	1974 (30.0%)	274 (32.5%)	268 (35.2%)	
Missing	30 (0.5%)	2 (0.2%)	2 (0.3%)	
Diabetes, n(%)				0.5535
Type I Diabetes	44 (0.7%)	5 (0.6%)	8 (1.0%)	
Type II Diabetes	3773 (57.4%)	511 (60.5%)	445 (58.4%)	
Both Type I and Type II Diabetes	1 (0.0%)	0	0	

No Diabetes at Baseline	2752 (41.9%)	328 (38.9%)	309 (40.6%)	
Missing	3 (0.0%)	0	0	
Laboratory Measurements				
hsCRP (mg/L), Median (Q1-Q3)	2.1 (1.1 - 4.4)	2.4 (1.2 - 5.3)	2.4 (1.2 - 4.6)	0.0004
Triglycerides (mg/dL), Median (Q1-Q3)	215.5 (176.0 - 272.0)	215.5 (175.0 - 270.3)	223.0 (178.5 - 285.5)	0.0539
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (35.0 - 46.0)	39.5 (34.4 - 45.5)	38.8 (33.5 - 44.5)	<.0001
LDL-C (mg/dL), Median (Q1-Q3)	75.0 (62.0 - 89.0)	75.0 (63.0 - 88.0)	75.0 (63.0 - 89.0)	0.9903
Triglycerides Category				0.3523
<150 mg/dL	686 (10.4%)	79 (9.4%)	76 (10.0%)	
150 to < 200 mg/dL	1922 (29.2%)	259 (30.7%)	203 (26.6%)	
≥ 200 mg/dL	3961 (60.3%)	506 (60.0%)	483 (63.4%)	
Triglycerides ≥ 200 mg/dL and HDL-C ≤ 35 mg/dL	1254 (19.1%)	173 (20.5%)	190 (24.9%)	0.0005
EPA (µg/mL), Median (Q1-Q3)	26.2 (17.2 - 40.3)	24.6 (15.9 - 36.7)	26.9 (17.7 - 40.2)	0.0141

In general, the baseline value is defined as the last non-missing measurement obtained prior to the randomization.
The baseline LDL-C value obtained via preparative ultracentrifugation was used, unless this value was missing. If the LDL-C preparative ultracentrifugation value was missing, then another LDL-C value was be used, with prioritization of values obtained from LDL-C Direct measurements, followed by LDL-C derived by the Friedewald calculation (only for subjects with TG < 400 mg/dL), and finally LDL-C derived using the calculation published by Johns Hopkins University investigators.
For all other lipid and lipoprotein marker parameters, wherever possible, baseline was derived as the arithmetic mean of the Visit 2 (Day 0) value and the preceding Visit 1 (or Visit 1.1) value. If only one of these values was available, the single available value was used as baseline.
[1] P-value is from a Wilcoxon rank-sum test for continuous variables and a chi-square test for categorical variables.
[2] Race as reported by the investigators.
[3] Percentages are based on the number of randomized subjects.
[4] Westernized region includes Australia, Canada, Netherlands, New Zealand, United States, and South Africa.
[5] Eastern European region includes Poland, Romania, Russian Federation, and Ukraine.
[6] Asia Pacific region includes India.

[0629] Total Events for Primary Efficacy Endpoint: The total events for the primary efficacy endpoint showed that of 8,179 patients, there were 1,606 (i.e., 55.2% of the endpoints) first primary endpoints and 1,303 (i.e., 44.8% of the endpoints) additional primary endpoints, for a total of 2,909 endpoint events among the 1,606 patients. There were 762 second events, 272 third events, and 269 fourth or more events. Figure 17 shows a distribution of first and recurrent events in the patients randomized to icosapent ethyl or placebo before and after the trial. In the overall trial, total primary endpoints were reduced from 1,724 to 1,185 (HR 0.68, 95% CI 0.63-0.74, P<0.0001) with icosapent ethyl

as shown in Figure 17. Within the primary endpoint reductions, first events were reduced from 901 to 705 (i.e., a total reduction of 196), second events were reduced from 463 to 299 (i.e., a total reduction of 164), and additional endpoints were reduced from 360 to 131 (i.e., a total reduction of 179) with icosapent ethyl (See Figure 17). Using the Wei-Lin-Weissfeld model, the first occurrence of a primary composite endpoint was reduced with icosapent ethyl versus placebo (HR 0.75, 95% CI 0.68-0.83, P <0.0001) as was the second occurrence (HR 0.72, 95% CI 0.62-0.83, P <0.0001). Figures 18-20 depict the overall cumulative event curves from the primary endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina. The overall cumulative events are shown in Figure 18, the secondary prevention stratum events are shown in Figure 19, and the primary prevention stratum events are shown in Figure 20.

[0630] The total events for each occurrence of the primary endpoint, inclusive of the first and all subsequent occurrences of primary endpoints components (i.e., cardiovascular death, nonfatal myocardial in fraction, nonfatal stroke, coronary revascularization, and unstable angina) are shown in Figure 21. Importantly, Figure 21 shows that the times to first occurrence, second occurrence, third occurrence or fourth occurrence of the primary composite endpoint were consistently reduced in the icosapent ethyl group as compared to the placebo control group. The proportions of first and subsequent primary endpoint events, overall and by component, are depicted in Figure 22. The risk differences for every 100 patients treated for five years with icosapent ethyl vs placebo control for the components of the composite primary endpoint are shown in Figure 23.

[0631] The total events for each component of the primary and key secondary efficacy endpoints inclusive of the first and all subsequent occurrences of the primary and key secondary endpoints components (i.e., cardiovascular death, nonfatal myocardial in fraction, nonfatal stroke, coronary revascularization, and unstable angina) and key secondary endpoint components (i.e., nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death) are shown in Figure 24. Importantly, Figure 24 shows that total events for each component of the primary endpoint were also significantly reduced. In the secondary prevention stratum, total primary endpoint events were reduced from 1,468 to 988 (HR 0.66, 95% CI 0.61-0.72, P<0.0001), and in the primary prevention stratum, from 256 to 197 (HR 0.79, 95% CI 0.65-0.96, P=0.018;

$P_{interaction}$=0.098). Without adjusting for stratification differences, total primary endpoint events in the secondary prevention stratum were reduced from 1,461 to 964 (HR 0.65, 95% CI 0.60-0.71, P<0.0001) and from 263 to 221 (HR 0.86, 95% CI 0.71-1.03, P=0.105) in the primary prevention stratum; $P_{interaction}$=0.009.

[0632] Total Events for the Key Secondary Efficacy Endpoint: Figures 25-27 depict the cumulative event curves from the key secondary endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The overall cumulative events are shown in Figure 25, the secondary prevention stratum events are shown in Figure 26, and the primary prevention stratum events are shown in Figure 27. Total key secondary endpoints were significantly reduced from 861 to 590 (HR 0.71, 95% CI 0.63-0.79, P<0.0001) with icosapent ethyl versus placebo as shown in Figure 25. Similar patterns were seen for the key secondary endpoint, both in the secondary prevention (HR 0.70, 95% CI 0.63-0.79, P<0.0001) and primary prevention (HR 0.71, 95% CI 0.55-0.93, P=0.011) strata as shown in Figures 26 and 27, respectively, $P_{interaction}$=0.90. Without adjustment for stratification differences, total key secondary endpoint events in the secondary prevention stratum were reduced from 671 to 478 (HR 0.69, 95% CI 0.61-0.78, P<0.0001) and from 142 to 112 (HR 0.78, 95% CI 0.60-1.00, P=0.047) in primary prevention; $P_{interaction}$=0.39.

[0633] Similarly, the total events for the primary and key secondary efficacy endpoints are further depicted in Figures 28-33 as a function of the total cumulative incidence vs years since randomization. This contrasts Figures 18-20 and Figures 25-27 which report the total events for the primary and key secondary efficacy endpoints as a function of the mean cumulative function vs follow up time in days from randomization. Figures 28 and 29 show the overall mean cumulative recurrent events of the primary composite endpoint and key secondary endpoint, respectively. Figures 30 and 31 depict the recurrent events of primary and key secondary endpoints for the secondary prevention stratum, respectively. Lastly, Figures 32 and 33 further depict the recurrent events of primary and key secondary endpoints for the primary prevention stratum, respectively.

[0634] Overall, the results of this study indicated that the use icosapent ethyl was superior as compared to a placebo in reducing total ischemic events, with a consistent benefit in secondary as well as primary prevention.

Conclusion

[0635] This study, an analysis of the total events in the REDUCE-IT trial as outlined above in Example 1, indicated a significant reduction in ischemic events with icosapent ethyl versus placebo. More specifically, the results from this study show that there was a 32% relative risk reduction and in total events for the primary composite efficacy outcome. In addition, first events were reduced by 25%, second events were reduced by 28%, and third or more events were reduced by 50%. For every 100 patients treated with icosapent ethyl for five years, approximately 16 total primary endpoint events could be prevented: 1 cardiovascular death, 4 myocardial infarctions, 1 stroke, 8 coronary revascularizations, and 2 episodes of unstable angina. An examination of total events for the key secondary endpoint corroborated the significant reduction in important ischemic events seen with the primary endpoint. There was a consistent benefit in both the secondary prevention and primary prevention strata.

[0636] There were significant reductions in the number of total events for each individual component of the composite primary endpoint. This benefit of icosapent ethyl across a variety of different endpoints (i.e., coronary, cerebral, fatal, non-fatal, ischemic events, revascularizations) suggests that the drug benefit is not likely to be explained by triglyceride lowering alone but rather, strongly suggests that there are multiple mechanisms of action of the drug beyond triglyceride lowering that work together to achieve the observed benefits. Basic investigations support this contention. Icosapent ethyl was well tolerated with no significant difference in rates of serious adverse events versus placebo. Although overall rates were low in both treatment groups, and none of the events were fatal, there was a trend towards increased serious bleeding with no significant increases in adjudicated hemorrhagic stroke, serious central nervous system bleeding, or gastrointestinal bleeding. There was a small, but statistically significant increase in hospitalization for atrial fibrillation or flutter noted in the REDUCE-IT study as described in Example 1. Nevertheless, the large number of important ischemic events averted, including a significant reduction in cardiovascular death, provides a very favorable risk-benefit profile. Given the broad inclusion criteria and relatively few exclusion criteria, these results are likely generalizable to a large proportion of statin-treated patients with atherosclerosis or diabetes.

[0637] In conclusion, icosapent ethyl 4 g per day (i.e., 2 g per day) significantly reduces total ischemic events in patients with established atherosclerosis or with diabetes and additional cardiovascular risk factors already being treated with statin therapy, with consistent benefits across a variety of individual ischemic endpoints. In patients with elevated triglycerides with cardiovascular disease or diabetes, icosapent ethyl reduces total ischemic events in both secondary and primary prevention. In such patients with fasting triglycerides 135 mg/dL and above, icosapent ethyl should be considered in order to reduce the total burden of atherosclerotic events.

EXAMPLE 3: The Impact of Icosapent Ethyl on Total Ischemic Events in Statin-Treated Patients

[0638] As described above in Example 1, in time-to-first-event analyses, icosapent ethyl significantly reduced the risk of ischemic events, including cardiovascular death, among patients with elevated triglycerides receiving statins. However, these patients remain at risk for first and subsequent ischemic events. Results from Example 2 indicated that the use icosapent ethyl was superior as compared to a placebo in reducing total ischemic events, with a consistent benefit in secondary as well as primary prevention. The objective of the study described in this example was to use pre-specified analyses to determine the extent to which icosapent ethyl reduced total ischemic events in patients from the REDUCE-IT trial.

Methods

[0639] The following study was a multi-center, placebo-controlled clinical trial the details of which are described above in Example 1, the REDUCE-IT design. Briefly, the REDUCE-IT trial randomized 8,179 statin-treated patients with triglycerides ≥135 and <500 mg/dL (median baseline of 216 mg/dL) and LDL-cholesterol >40 and ≤100 mg/dL (median baseline of 75 mg/dL), and a history of atherosclerosis (i.e., 71% patients) or diabetes (i.e., 29% patients) to icosapent ethyl 4g per day or placebo. The main outcomes were total primary composite endpoint events defined as cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina and total key secondary composite endpoint events defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. In the context of this study, total events refer to any first event as well as any subsequent event. Differences in total events were determined using other statistical models, including

Andersen-Gill, Wei-Lin-Weisfeld (Li and Lagakos), both pre-specified, and a *post hoc* and joint-frailty analysis.

[0640] For the present prespecified analysis, the primary outcome was the total of first plus subsequent ischemic events consisting of the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina. The composite of hard major adverse cardiovascular events (i.e., cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) are designated as the "key secondary endpoint" per suggestions from the Food and Drug Administration. Exploratory analyses of the total of first and subsequent events were also performed for the key secondary composite endpoint.

[0641] Baseline characteristics were compared between treatment groups using the chi-squared test for categorical variables and the Wilcoxon rank sum test for continuous variables. There are several methods for analyzing first and subsequent (recurrent) event data. As a pre-specified statistical method, a negative binomial regression was used to calculate rates and rate ratios for total cardiovascular events, which accounts for the variability in each patient's risk of events. As pre-specified supportive analyses, the modified Wei-Lin-Weissfeld method (Li and Lagakos modification) was used to calculate hazard ratios (HRs) for the time to the first event, second event, or third event. An additional pre-specified analysis, the Andersen-Gill model using a Cox proportional-hazard with the counting-process formulation was performed to model the total events. In addition, in order to account for informative censoring due to cardiovascular death, the HR for total non-fatal events was calculated using a joint frailty model (*See* Rondeau V. Joint frailty models for recurring events and death using maximum penalized likelihood estimation: application on cancer events. Biostatistics. 2007; 8:708-21). The joint frailty model simultaneously estimates hazard functions for non-fatal and fatal CV events and takes into account the fact that patients who are prone to have nonfatal events have an elevated risk of a cardiovascular death. The application of the joint frailty model used a gamma distribution for the frailty term.

[0642] To improve the performance and validity of the statistical models, a bundling approach was employed, whereby non-fatal events occurring on the same day as a CV death were excluded, and at most, one non-fatal event was counted on any given day (e.g., for coronary revascularization occurring after a myocardial infarction which

eventually resulted in the patient's death, only the death would be included). Statistical analyses using the full adjudicated endpoint events dataset without exclusions using this bundling approach were also determined.

[0643] All efficacy analyses were conducted in accordance with the intention-to-treat principle. All tests were based on a 2-sided nominal significance level of 5% with no adjustments for multiple comparisons, consistent with prespecified plans for such endpoints.

Results

[0644] A total of 8,179 patients were randomized and followed for a median of 4.9 years. The baseline characteristics were well matched across the icosapent ethyl and placebo groups as shown in Table 40. At baseline, the median triglyceride levels were 216 mg/dL with median LDL-C levels of 75 mg/dL. Additional baseline characteristics across treatment groups and for patients with no events, a single event, and multiple subsequent events are shown in Tables 39 and 40, respectively.

Table 39. Baseline Characteristics of Patients in Icosapent Ethyl and Placebo Treatment Groups

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	*P* Value [1]
Demographics			
Age (years), Median (Q1-Q3)	64.0 (57.0 - 69.0)	64.0 (57.0 - 69.0)	0.7446
Age ≥65 years, n (%)	1857 (45.4%)	1906 (46.6%)	0.2815
Male, n (%)	2927 (71.6%)	2895 (70.8%)	0.4245
White, n (%)[2]	3691 (90.3%)	3688 (90.2%)	0.9110
BMI (kg/m^2), Median (Q1-Q3)	30.8 (27.8 - 34.5)	30.8 (27.9 - 34.7)	0.3247
BMI ≥30, n (%)[3]	2331 (57.0%)	2362 (57.8%)	0.5287
Stratification Factors			
Geographic Region, n (%)			0.9924
Westernized [4]	2906 (71.1%)	2905 (71.0%)	
Eastern Europe [5]	1053 (25.8%)	1053 (25.7%)	
Asia Pacific [6]	130 (3.2%)	132 (3.2%)	
CV Risk Category, n (%)			0.9943
Secondary Prevention	2892 (70.7%)	2893 (70.7%)	

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	*P* Value [1]
Primary Prevention	1197 (29.3%)	1197 (29.3%)	
Ezetimibe Use, n (%)	262 (6.4%)	262 (6.4%)	0.9977
Statin Intensity and Diabetes Status			
Statin Intensity, n (%)			0.1551
Low	254 (6.2%)	267 (6.5%)	
Moderate	2533 (61.9%)	2575 (63.0%)	
High	1290 (31.5%)	1226 (30.0%)	
Missing	12 (0.3%)	22 (0.5%)	
Diabetes, n (%)			0.9926
Type I Diabetes	27 (0.7%)	30 (0.7%)	
Type II Diabetes	2367 (57.9%)	2363 (57.8%)	
No Diabetes at Baseline	1695 (41.5%)	1694 (41.4%)	
Missing	0	3 (0.1%)	
Laboratory Measurements			
hsCRP (mg/L), Median (Q1-Q3)	2.2 (1.1 - 4.5)	2.1 (1.1 - 4.5)	0.7197
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)	0.9120
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (34.5 - 46.0)	40.0 (35.0 - 46.0)	0.1370
LDL-C (mg/dL), Median (Q1-Q3)	74.5 (62.0 - 88.0)	76.0 (63.0 - 89.0)	0.0284
LDL-C Tertiles, n(%)			0.0556
Lowest (≤67 mg/dL)	14831 (36.2%)	1386 (33.9%)	
Middle (>67 - ≤84 mg/dL)	1347 (32.9%)	1364 (33.3%)	
Upper (>84 mg/dL)	1258 (30.8%)	1339 (32.7%)	
Missing	3 (0.1%)	1	
Triglycerides Category, n (%)			0.8297
<150 mg/dL	412 (10.1%)	429 (10.5%)	
150 to < 200 mg/dL	1193 (29.2%)	1191 (29.1%)	
≥ 200 mg/dL	2481 (60.7%)	2469 (60.4%)	
Triglyceride Tertiles, n (%)			0.4887
Lowest (≤190 mg/dL)	1378 (33.7%)	1381 (33.8%)	
Middle (>190 - ≤250 mg/dL)	1370 (33.5%)	1326 (32.4%)	
Upper (>250 mg/dL)	1338 (32.7%)	1382 (33.8%)	

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	*P* Value [1]
Missing	3 (0.1%)	1	
Triglycerides ≥ 200 mg/dL and HDL-C ≤ 35 mg/dL, n (%)	823 (20.1%)	794 (19.4%)	0.4019
EPA (µg/mL), Median (Q1-Q3)	26.1 (17.1 - 40.1)	26.1 (17.1 - 39.9)	0.8867
Cardiovascular Disease History[7]			
Prior Atherosclerotic Cardiovascular Disease (ASCVD), n (%)	2816 (68.9%)	2835 (69.3%)	0.6667
Prior Atherosclerotic Coronary Artery Disease and Related Morbidities	2387 (58.4%)	2393 (58.5%)	0.9107
Ischemic Dilated Cardiomyopathy	137 (3.4%)	109 (2.7%)	0.0702
Myocardial Infarction	1938 (47.4%)	1881 (46.0%)	0.2065
Unstable Angina	1017 (24.9%)	1015 (24.8%)	0.9592
Prior Atherosclerotic Cerebrovascular Disease and Related Morbidities, n (%)	641 (15.7%)	662 (16.2%)	0.5457
Carotid Disease	343 (8.4%)	372 (9.1%)	0.2730
Ischemic Stroke	267 (6.5%)	242 (5.9%)	0.2529
Transient Ischemic Attack	194 (4.7%)	181 (4.4%)	0.4925
Prior Atherosclerotic Peripheral Arterial Disease, n (%)	387 (9.5%)	388 (9.5%)	1.0000
ABI <0.9 Without Symptoms of Intermittent Claudication	97 (2.4%)	76 (1.9%)	0.1073
Peripheral Artery Disease	377 (9.2%)	377 (9.2%)	1.0000
Prior Non-Atherosclerotic Cardiovascular Disease, n (%)	3649 (89.2%)	3645 (89.1%)	0.8868
Prior Structural Cardiac Disorders	827 (20.2%)	866 (21.2%)	0.2997
Congestive Heart Failure	703 (17.2%)	743 (18.2%)	0.2583
Hypertrophic Cardiomyopathy	23 (0.6%)	20 (0.5%)	0.6507
Non-Ischemic Dilated Cardiomyopathy	35 (0.9%)	29 (0.7%)	0.4552
Non-Rheumatic Valvular Heart Disease	150 (3.7%)	163 (4.0%)	0.4892
Rheumatic Valvular Heart Disease	17 (0.4%)	9 (0.2%)	0.1215

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	*P* Value [1]
Prior Cardiac Arrhythmias	229 (5.6%)	243 (5.9%)	0.5377
Atrio-Ventricular Block Above First Degree	51 (1.2%)	54 (1.3%)	0.8444
Sick Sinus Syndrome	30 (0.7%)	32 (0.8%)	0.8987
Supra-Ventricular Tachycardia Other Than Atrial Fibrillation /Atrial flutter	74 (1.8%)	77 (1.9%)	0.8696
Sustained Ventricular Tachycardia	34 (0.8%)	34 (0.8%)	1.0000
Torsades De Pointes	1 (0.0%)	3 (0.1%)	0.6249
Ventricular Fibrillation	61 (1.5%)	65 (1.6%)	0.7877
Prior Non-Cardiac/Non-Atherosclerotic Vascular Disorders, n (%)	3568 (87.3%)	3566 (87.2%)	0.9472
Arterial Embolism	12 (0.3%)	9 (0.2%)	0.5229
Deep Vein Thrombosis	70 (1.7%)	60 (1.5%)	0.3785
Hypertension	3541 (86.6%)	3543 (86.6%)	0.9741
Hypotension	45 (1.1%)	33 (0.8%)	0.1745
Pulmonary Embolism	31 (0.8%)	42 (1.0%)	0.2396
Non-Ischemic Stroke	79 (1.9%)	84 (2.1%)	0.7518
Hemorrhagic Stroke	18 (0.4%)	22 (0.5%)	0.6350
Stroke of Unknown Origin	63 (1.5%)	62 (1.5%)	0.9285
Other Prior Conditions			
Metabolic Syndrome	507 (12.4%)	540 (13.2%)	0.2896
Baseline Laboratory Abnormalities, n (%)	1783 (43.6%)	1707 (41.7%)	0.0893
Renal Disorders	470 (11.5%)	429 (10.5%)	0.1474
Creatinine Clearance (CRCL) >30 and <60 ML/Min	309 (7.6%)	286 (7.0%)	0.3279
Macroalbuminuria	34 (0.8%)	24 (0.6%)	0.1909
Microalbuminuria	146 (3.6%)	134 (3.3%)	0.4664
Proteinuria	75 (1.8%)	63 (1.5%)	0.3046
Other Morbidities	173 (4.2%)	173 (4.2%)	1.0000
Pancreatitis	14 (0.3%)	9 (0.2%)	0.3067

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	*P* Value [1]
Retinopathy	161 (3.9%)	167 (4.1%)	0.7782
Carotid Stenosis [8]			
n	316	346	
Mean (%) (SD)	59.0 (21.04)	56.9 (22.99)	0.4101
Medication Taken at Baseline			
Anti-Diabetic, n (%)	2190 (53.6%)	2196 (53.7%)	0.9036
Anti-Hypertensive	3895 (95.3%)	3895 (95.2%)	0.9605
Anti-Platelet[9]	3257 (79.7%)	3236 (79.1%)	0.5514
One Anti-platelet	2416 (59.09%)	2408 (58.88%)	0.8469
Two or more Anti-platelets	841 (20.57%)	828 (20.4%)	0.7171
Anticoagulant	385 (9.4%)	390 (9.5%)	0.8531
Anticoagulant plus Anti-platelet	137 (3.4%)	137 (3.4%)	0.9984
No Antithrombotic	584 (14.3%)	601 (14.7%)	0.5965
ACE	2112 (51.7%)	2131 (52.1%)	0.6825
ARB	1108 (27.1%)	1096 (26.8%)	0.7598
ACE or ARB	3164 (77.4%)	3176 (77.7%)	0.7662
Beta Blockers	2902 (71.0%)	2880 (70.4%)	0.5812

Abbreviations: ABI = ankle brachial index; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers.
Percentages are based on the number of subjects randomized to each treatment group in the ITT population (N).
In general, the baseline value is defined as the last non-missing measurement obtained prior to the randomization.
The baseline LDL-C value obtained via Preparative Ultracentrifugation was used, unless this value was missing. If the LDL-C Preparative Ultracentrifugation value was missing, then another LDL-C value was be used, with prioritization of values obtained from LDL-C Direct measurements, followed by LDL-C derived by the Friedewald calculation (only for subjects with TG < 400 mg/dL), and finally LDL-C derived using the calculation published by Johns Hopkins University investigators.[1]
For all other lipid and lipoprotein marker parameters, wherever possible, baseline was derived as the arithmetic mean of the Visit 2 (Day 0) value and the preceding Visit 1 (or Visit 1.1) value. If only one of these values was available, the single available value was used as baseline.
[1] *P* Values from Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables.
[2] Race as reported by the investigators.
[3] Body-mass index is the weight in kilograms divided by the square of the height in meters.
[4] Westernized region includes Australia, Canada, Netherlands, New Zealand, United States, and South Africa.
[5] Eastern European region includes Poland, Romania, Russian Federation, and Ukraine.
[6] Asia Pacific region includes India.
[7] The summary is based on the data collected from CV history Case Report Form (CRF).
[8] Two outliers of Carotid Stenosis (%) with a value over 100% are excluded from the analysis. Carotid Stenosis (%) data reported in categorical format of >x% and <y% is analysed as x% and y%, respectively; and data reported as x% to y% is analysed as an average of x% and y%.
[9] Dual anti-platelets were classified as such if both components have a robust history of regulatory approval affirming anti-platelet effects, thus excluding combinations where one element lacks robust regulatory approval (e.g. Aspirin + Magnesium Oxide is classified as a single agent because the latter component lacks robust regulatory support as an anti-platelet agent).

Table 40. Baseline Characteristics of Patients with No Primary Endpoint Events, a Single Event, or Multiple Events

	No Events (N=6573)	1 Event (N=844)	Multiple Events (N=762)	*P* Value [1]
Demographics				
Age (years), Median (Q1-Q3)	63.0 (57.0 - 69.0)	65.0 (59.0 - 71.0)	64.0 (58.0 - 70.0)	0.0400
Age ≥ 65 years, n (%)	2939 (44.7%)	456 (54.0%)	368 (48.3%)	0.0217
Male, n (%)	4556 (69.3%)	661 (78.3%)	605 (79.4%)	0.5972
White, n (%)[2]	5921 (90.1%)	765 (90.6%)	693 (90.9%)	0.8328
BMI (kg/m^2), Median (Q1-Q3)	30.8 (27.8 - 34.6)	31.1 (27.8 - 34.7)	30.8 (28.0 - 34.2)	0.2609
BMI ≥ 30, n (%)[3]	3762 (57.2%)	499 (59.1%)	432 (56.7%)	0.4656
Stratification Factors				
Geographic Region				0.0082
Westernized [4]	4547 (69.2%)	639 (75.7%)	625 (82.0%)	
Eastern Europe [5]	1796 (27.3%)	185 (21.9%)	125 (16.4%)	
Asia Pacific [6]	230 (3.5%)	20 (2.4%)	12 (1.6%)	
CV Risk Category as Randomized, n (%)				<.0001
Secondary Prevention	4488 (68.3%)	640 (75.8%)	657 (86.2%)	
Primary Prevention	2085 (31.7%)	204 (24.2%)	105 (13.8%)	
Ezetimibe Use, n (%)	401 (6.1%)	59 (7.0%)	64 (8.4%)	0.2892
Statin Intensity and Diabetes Status				
Statin Intensity, n (%)				0.7138
Low	436 (6.6%)	52 (6.2%)	44 (5.8%)	
Moderate	4153 (63.2%)	520 (61.6%)	451 (59.2%)	
High	1953 (29.7%)	270 (32.0%)	265 (34.8%)	
Missing	31 (0.5%)	2 (0.2%)	2 (0.3%)	
Diabetes, n (%)				0.4420
Type I	44 (0.7%)	5 (0.6%)	8 (1.0%)	
Type II	3773 (57.4%)	511 (60.5%)	445 (58.4%)	
No Diabetes at Baseline	2752 (41.9%)	328 (38.9%)	309 (40.6%)	

	No Events (N=6573)	1 Event (N=844)	Multiple Events (N=762)	*P* Value [1]
Missing	3 (0.0%)	0	0	
Laboratory Measurements				
hsCRP (mg/L), Median (Q1-Q3)	2.1 (1.1 - 4.4)	2.4 (1.2 - 5.3)	2.4 (1.2 - 4.6)	0.3325
Triglycerides (mg/dL), Median (Q1-Q3)	215.5 (176.0 - 272.0)	215.5 (175.0 - 270.3)	223.0 (178.5 - 285.5)	0.0701
HDL-C (mg/dL), Median (Q1-Q3)	40.0 (35.0 - 46.0)	39.5 (34.4 - 45.5)	38.8 (33.5 - 44.5)	0.0631
LDL-C (mg/dL), Median (Q1-Q3)	75.0 (62.0 - 89.0)	75.0 (63.0 - 88.0)	75.0 (63.0 - 89.0)	0.7384
LDL-C Tertiles, n (%)				0.5416
Lowest (≤67 mg/dL)	2321 (35.3%)	283 (33.5%)	263 (34.5%)	
Middle (>67 - ≤84 mg/dL)	2156 (32.8%)	302 (35.8%)	253 (33.2%)	
Upper (>84 mg/dL)	2092 (31.8%)	259 (30.7%)	246 (32.3%)	
Triglyceride Category				
<150 mg/dL	686 (10.4%)	79 (9.4%)	76 (10.0%)	
150 to ≤200 mg/dL	1922 (29.2%)	259 (30.7%)	203 (26.6%)	
≥ 200 mg/dL	3961 (60.3%)	506 (60.0%)	483 (63.4%)	
Triglyceride Tertiles, n (%)				0.1993
Lowest (≤190 mg/dL)	2235 (34.0%)	287 (34.0%)	237 (31.1%)	
Middle (>190 - ≤250 mg/dL)	2167 (33.0%)	283 (33.5%)	246 (32.3%)	
Upper (>250 mg/dL)	2167 (33.0%)	274 (32.5%)	279 (36.6%)	
Lowest				
Triglycerides ≥ 200 mg/dL and HDL-C ≤ 35 mg/dL	1254 (19.1%)	173 (20.5%)	190 (24.9%)	0.0336
EPA (µg/mL), Median (Q1-Q3)	26.2 (17.2 - 40.4)	24.6 (15.9 - 36.7)	26.9 (17.7 - 40.2)	0.0120
Cardiovascular Disease History [7]				
Prior Atherosclerotic Cardiovascular Disease	4370 (66.5%)	633 (75.0%)	648 (85.0%)	<.0001
Prior Atherosclerotic Coronary Artery Disease and Related Morbidities	3662 (55.7%)	542 (64.2%)	576 (75.6%)	<.0001
Myocardial Infarction	2931 (44.6%)	430 (50.9%)	458 (60.1%)	<.0002
Unstable Angina	1497 (22.8%)	236 (28.0%)	299 (39.2%)	<.0001

	No Events (N=6573)	1 Event (N=844)	Multiple Events (N=762)	*P* Value [1]
Ischemic Dilated Cardiomyopathy	164 (2.5%)	46 (5.5%)	36 (4.7%)	0.5707
Prior Atherosclerotic Cerebrovascular Disease and	965 (14.7%)	173 (20.5%)	165 (21.7%)	0.5816
Carotid Disease	543 (8.3%)	90 (10.7%)	82 (10.8%)	1.0000
Ischemic Stroke	380 (5.8%)	64 (7.6%)	65 (8.5%)	0.5203
Transient Ischemic Attack	254 (3.9%)	61 (7.2%)	60 (7.9%)	0.6371
Prior Atherosclerotic Peripheral Arterial Disease	548 (8.3%)	109 (12.9%)	118 (15.5%)	0.115
Peripheral Artery Disease	534 (8.1%)	106 (12.6%)	114 (15.0%)	0.1679
ABI <0.9 Without Symptoms of Intermittent Claudication	132 (2.0%)	24 (2.8%)	17 (2.2%)	0.5269
Prior Non-Atherosclerotic Cardiovascular Disease	5836 (88.8%)	775 (91.8%)	683 (89.6%)	0.1420
Prior Structural Cardiac Disorders	1289 (19.6%)	234 (27.7%)	170 (22.3%)	0.0133
Congestive Heart Failure	1099 (16.7%)	200 (23.7%)	147 (19.3%)	0.0337
Hypertrophic Cardiomyopathy	32 (0.5%)	6 (0.7%)	5 (0.7%)	1.0000
Non-Ischemic Dilated Cardiomyopathy	49 (0.7%)	11 (1.3%)	4 (0.5%)	0.1239
Non-Rheumatic Valvular Heart Disease	225 (3.4%)	54 (6.4%)	34 (4.5%)	0.0996
Rheumatic Valvular Heart Disease	22 (0.3%)	3 (0.4%)	1 (0.1%)	0.6265
Prior Cardiac Arrhythmias	354 (5.4%)	65 (7.7%)	53 (7.0%)	0.6323
Atrio-Ventricular Block Above First Degree	77 (1.2%)	15 (1.8%)	13 (1.7%)	1.0000
Sick Sinus Syndrome	49 (0.7%)	5 (0.6%)	8 (1.0%)	0.4056
Supra-Ventricular Tachycardia Other Than Atrial fibrillation/Atrial flutter	115 (1.7%)	24 (2.8%)	12 (1.6%)	0.0934

	No Events (N=6573)	1 Event (N=844)	Multiple Events (N=762)	*P* Value [1]
Sustained Ventricular Tachycardia	50 (0.8%)	10 (1.2%)	8 (1.0%)	0.8179
Torsades De Pointes	3 (0.0%)	0 (0.0%)	1 (0.1%)	0.4744
Ventricular Fibrillation	95 (1.4%)	16 (1.9%)	15 (2.0%)	1.0000
Prior Non-Cardiac/Non-Atherosclerotic Vascular Disorders	5716 (87.0%)	752 (89.1%)	666 (87.4%)	0.3125
Hypotension	52 (0.8%)	9 (1.1%)	17 (2.2%)	0.0754
Hypertension	5669 (86.2%)	750 (88.9%)	665 (87.3%)	0.3544
Non-Ischemic Stroke	123 (1.9%)	24 (2.8%)	16 (2.1%)	0.4231
Hemorrhagic Stroke	32 (0.5%)	4 (0.5%)	4 (0.5%)	1.0000
Stroke of Unknown Origin	92 (1.4%)	20 (2.4%)	13 (1.7%)	0.3826
Arterial Embolism	9 (0.1%)	11 (1.3%)	1 (0.1%)	0.0069
Deep Vein Thrombosis	90 (1.4%)	20 (2.4%)	20 (2.6%)	0.7514
Pulmonary Embolism	49 (0.7%)	12 (1.4%)	12 (1.6%)	0.8391
Other Prior Conditions or Investigations Influencing Cardiovascular Risk	4870 (74.1%)	642 (76.1%)	587 (77.0%)	0.6799
Prior Metabolic Disorders	3988 (60.7%)	530 (62.8%)	477 (62.6%)	0.9588
Diabetes Type I	45 (0.7%)	5 (0.6%)	8 (1.0%)	0.4056
Diabetes Type II	3774 (57.4%)	511 (60.5%)	445 (58.4%)	0.3872
Metabolic Syndrome	843 (12.8%)	108 (12.8%)	96 (12.6%)	0.9402
Baseline Laboratory Abnormalities	2725 (41.5%)	395 (46.8%)	370 (48.6%)	0.4842
Renal Disorders	660 (10.0%)	129 (15.3%)	110 (14.4%)	0.6737
Creatinine Clearance >30 And <60 mL/Min	430 (6.5%)	83 (9.8%)	82 (10.8%)	0.5651
Proteinuria	100 (1.5%)	20 (2.4%)	18 (2.4%)	1.0000
Macroalbuminuria	43 (0.7%)	7 (0.8%)	8 (1.0%)	0.7964
Microalbuminuria	217 (3.3%)	38 (4.5%)	25 (3.3%)	0.2468
Other Morbidities	275 (4.2%)	42 (5.0%)	29 (3.8%)	0.2754

	No Events (N=6573)	1 Event (N=844)	Multiple Events (N=762)	*P* Value [1]
Pancreatitis	19 (0.3%)	2 (0.2%)	2 (0.3%)	1.0000
Retinopathy	259 (3.9%)	42 (5.0%)	27 (3.5%)	0.1758
Carotid Stenosis[8]				
n	503	86	73	
Mean (%) (SD)	57.0(21.94)	58.2(22.85)	63.5(21.67)	0.1582
Medication Taken at Baseline				
Anti-Diabetic	3498 (53.2%)	478 (56.6%)	410 (53.8%)	0.2548
Anti-Hypertensive	6239 (94.9%)	817 (96.8%)	734 (96.3%)	0.6008
Anti-Platelet	5138 (78.2%)	691 (81.9%)	664 (87.1%)	0.0037
One Anti-platelet	3912 (59.52%)	486 (57.58%)	426 (55.91%)	0.4980
Two or more Anti-platelets	1226 (18.65%)	205 (24.29%)	238 (31.23%)	0.0019
Anticoagulant	560 (8.5%)	125 (14.8%)	90 (11.8%)	0.0780
Anticoagulant plus Anti-platelet	185 (2.8%)	46 (5.5%)	43 (5.6%)	0.8661
No Antithrombotic	1060 (16.1%)	74 (8.8%)	51 (6.7%)	0.1212
ACE	3424 (52.1%)	429 (50.8%)	390 (51.2%)	0.8880
ARB	1743 (26.5%)	235 (27.8%)	226 (29.7%)	0.4220
ACE or ARB	5090 (77.4%)	645 (76.4%)	605 (79.4%)	0.1518
Beta Blockers	4541 (69.1%)	655 (77.6%)	586 (76.9%)	0.7368

Abbreviations: ABI = ankle brachial index; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers.
In general, the baseline value is defined as the last non-missing measurement obtained prior to the randomization.
The baseline LDL-C value obtained via Preparative Ultracentrifugation was used, unless this value was missing. If the LDL-C preparative ultracentrifugation value was missing, then another LDL-C value was used, with prioritization of values obtained from LDL-C Direct measurements, followed by LDL-C derived by the Friedewald calculation (only for subjects with TG < 400 mg/dL), and finally LDL-C derived using the calculation published by Johns Hopkins University investigators.
For all other lipid and lipoprotein marker parameters, wherever possible, baseline was derived as the arithmetic mean of the Visit 2 (Day 0) value and the preceding Visit 1 (or Visit 1.1) value. If only one of these values was available, the single available value was used as baseline.
[1] P-value comparing Single Event group with Multiple Events group is from a Wilcoxon test for continuous variables and a Fishers Exact test for categorical variables.
[2] Race as reported by the investigators.
[3] Body-mass index is the weight in kilograms divided by the square of the height in meters.
[4] Westernized region includes Australia, Canada, Netherlands, New Zealand, United States, and South Africa.
[5] Eastern European region includes Poland, Romania, Russian Federation, and Ukraine.
[6] Asia Pacific region includes India.
[7] The summary is based on the data collected from CV history Case Report Form (CRF).
[8] Two outliers of Carotid Stenosis (%) with a value over 100% are excluded from the analysis. Carotid Stenosis (%) data reported in categorical format of >x% and <y% is analysed as x% and y%, respectively; and data reported as x% to y% is analysed as an average of x% and y%.
[9] Dual anti-platelets were classified as such if both components have a robust history of regulatory approval affirming anti-platelet effects, thus excluding combinations where one element lacks robust regulatory approval (e.g. Aspirin + Magnesium Oxide is classified as a single agent because the latter component lacks robust regulatory support as an anti-platelet agent).

[0645] At baseline the percentage of patients taking at least one other cardiovascular medication including antiplatelet agents was (79.7 and 79.1%), beta

blockers (71.0% and 70.4%), angiotensin converting enzyme (ACE) inhibitors (51.7% and 52.1%), or angiotensin receptor blockers (27.1% and 26.8%) in the icosapent ethyl and placebo treatment arms, respectively.

[0646] Total Events for the Primary Efficacy Endpoint: Across 8,179 randomized patients, there were 1,606 (i.e., 55.2%) first primary endpoint events and 1,303 (i.e., 44.8%) additional primary endpoint events, for a total of 2,909 endpoint events as shown in Table 41 and Figures 34, 35A and 35B. There were 762 second primary endpoint events, 272 third primary endpoint events, 129 fourth primary endpoint events, and 140 more primary endpoint events. The numbers(%) of patients with one or more primary endpoint event were 705 (17.2%) in the AMR101 group and 901 (22.0%) in the placebo group.

Table 41. Total Primary and Key Secondary Composite Endpoints Accounting for Statistical Handling of Multiple Endpoints Occurring in a Single Calendar Day as a Single Event

n (%)	Primary endpoint			Key secondary endpoint		
	Icosapent ethyl (N=4089)	Placebo (N=4090)	Overall (N=8179)	Icosapent ethyl (N=4089)	Placebo (N=4090)	Overall (N=8179)
Total events before reduction	1185 (40.7)	1724 (59.3)	2909* (100)	590 (42.0)	816 (58.0)	1406 (100)
Total events after reduction	1076 (41.0)	1546 (59.0)	2622 (100)	558 (42.1)	767 (57.9)	1325 (100)
Fatal events	174 (45.0)	213 (55.0)	387 (100)	174 (45.0)	213 (55.0)	387 (100)
Non-fatal events	902 (40.4)	1333 (59.6)	2235 (100)	384 (40.9)	554 (59.1)	938 (100)

Percentages are based on the total number of randomized patients within each category.
*A single event was experienced by 844 patients (844 events) and 2 or more events were experienced by 762 patients (2065) events, for a total of 1606 patients experiencing a total of 2909 events.
ł Reduction means 1) any nonfatal events on the same day as death are removed and 2) if 2 nonfatal events occur on the same day only the first one is counted.

[0647] A summary of total events in the primary and key secondary endpoints, including recurrent events on the same day, is presented in Table 42. There were 1065 (75.7%) first key secondary endpoint events and 341 (24.3%) additional key secondary endpoint events, for a total of 1406 key secondary endpoint events. There were 253 second key secondary endpoint events, 57 third key secondary endpoint events, 14 fourth key secondary endpoint events, and 17 more key secondary endpoint events. The

numbers(%) of patients with one or more key secondary endpoint event were 459 (11.2%) in the AMR101 group and 606 (14.8%) in the placebo group.

Table 42. Summary of Total Events in the Primary and Key Secondary Endpoints Including Recurrent Events on the Same Day (ITT Population)

Event, n (%)	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)
Primary Endpoint Events	1185 (40.7)	1724 (59.3)	2909
≥1 event	705 (43.9)	901 (56.1)	1606
≥2 events	299 (39.2)	463 (60.8)	762
≥3 events	96 (35.3)	176 (64.7)	272
≥4 events	36 (27.9)	93 (72.1)	129
Others	49 (35.0)	91 (65.0)	140
Key Secondary Endpoint Events	590 (42.0)	816 (58.0)	1406
≥1 event	459 (43.1)	606 (56.9)	1065
≥2 events	96 (37.9)	157 (62.1)	253
≥3 events	20 (35.1)	37 (64.9)	57
≥4 events	6 (42.9)	8 (57.1)	14
Others	9 (52.9)	8 (47.1)	17

Abbreviations: ITT = Intent-to-Treat.

Note: Percentages of events in each category were calculated using the total number of events as the denominator.

[0648] The proportions of first and subsequent primary endpoint events, overall and by component type, are depicted in Figure 36. There were 762 second events, 272 third events, and 269 fourth or more events. Overall, total (i.e., first and subsequent) primary endpoint event rates were reduced to 61 from 89 to per 1000 patient years (i.e., rate ratio (RR) 0.70, 95% CI 0.62-0.78, P<0.0001) with icosapent ethyl as shown in the central illustration in Figure 37A. Using the Wei-Lin-Weissfeld model, the first occurrence of a primary composite endpoint was reduced with icosapent ethyl versus placebo (i.e., HR 0.75, 95% CI 0.68-0.83, P <0.0001) as was the second occurrence (i.e., HR 0.68, 95% CI 0.60-0.78, P <0.0001). There was a 30% relative risk reduction in the total (first and subsequent) ischemic events for the primary composite endpoint with icosapent ethyl. First events were reduced by 25%, second events by 32%, third events by 31%, and fourth or more events by 48%. Figure 37B similarly shows the primary and key secondary endpoints, including recurrent events on the same day.

[0649] The cumulative events over time are shown in Figures 38A and 38B. Specifically, Figure 38A depicts the total (i.e., first and subsequent) and time to first primary composition endpoint events and Figure 38B shows the key secondary endpoint events. Total key secondary endpoint event rates were significantly reduced to 32 from 44 per 1000 patient years for icosapent ethyl versus placebo, respectively (i.e., RR 0.72, 95% CI 0.63-0.82, P<0.0001) with icosapent ethyl versus placebo as shown in Figure 38B. The times to first occurrence, second occurrence, third occurrence or fourth occurrence of the primary composite endpoint were consistently reduced as shown Figure 39 with icosapent ethyl. There were similar results for the models irrespective of whether bundling and/or single accounting was employed as shown in Tables 43-45.

Table 43. HRs for Pre-Specified Analyses of Total for Primary and Key Secondary Composite Endpoint Events Using the Reduced Dataset

		Primary composite endpoint				Key secondary composite endpoint			
		Unadjusted RR/HR (95% CI)	Unadjusted p-value	Adjusted RR/HR (95% CI)	Adjusted p-value	Unadjusted RR/HR (95% CI)	Unadjusted p-value	Adjusted RR/HR (95% CI)	Adjusted p-value
Negative binomial	.	0.68 (0.61, 0.77)	1.5×10^{-10}	0.70 (0.62, 0.78)	3.6×10^{-10}	0.71 (0.62, 0.82)	8.9×10^{-7}	0.72 (0.63, 0.82)	7.1×10^{-7}
Andersen-Gill (I)		0.69 (0.64, 0.74)	3.5×10^{-21}	0.69 (0.64, 0.74)	3.3×10^{-21}	0.72 (0.64, 0.80)	2.4×10^{-9}	0.72 (0.64, 0.80)	2.4×10^{-9}
Andersen-Gill (II)	.	0.69 (0.61, 0.77)	9.1×10^{-11}	0.69 (0.61, 0.77)	5.2×10^{-11}	0.72 (0.63, 0.82)	1.2×10^{-6}	0.72 (0.63, 0.82)	1.0×10^{-6}
Modified WLW	First event	0.76 (0.69, 0.83)	2.7×10^{-8}	0.75 (0.68, 0.83)	1.6×10^{-8}	0.74 (0.65, 0.83)	7.4×10^{-7}	0.74 (0.65, 0.83)	7.0×10^{-7}
	Second event	0.69 (0.60, 0.79)	2.7×10^{-8}	0.68 (0.60, 0.78)	1.8×10^{-8}	0.75 (0.63, 0.89)	1.1×10^{-3}	0.75 (0.63, 0.89)	1.1×10^{-3}
	Third event	0.69 (0.59, 0.82)	2.1×10^{-5}	0.69 (0.59, 0.82)	2.0×10^{-5}	0.79 (0.65, 0.96)	.0170	0.79 (0.65, 0.96)	.0171

Rate ratios (RR) are presented for results from negative binomial model; Hazard ratios (HR) are presented for results from Andersen Gill (I) model, Andersen Gill (II) model, and modified Wei-Lin-Weisfeld model.
Unadjusted analyses only included treatment group in the model; Adjusted analyses also included stratification factors (cardiovascular risk category, geographic region, and use of ezetimibe) as covariate, in addition to treatment group in the model.
Andersen Gill (I) model is based on an intensity model with model-based variance estimate and was a pre-specified methodology.

Andersen Gill (II) model is based on a proportional means model with cluster-robust standard errors, with the cluster set to the patient ID. This is a an updated methodology than the prespecified method. Wei-Lin-Weisfeld model is based on Li-Lagarkos modification. Analyses are based on reduced dataset accounting for statistical handling of multiple endpoints occurring in a single calendar day as a single event.

Table 44. Results from Joint Frailty Model for Primary and Key Secondary Endpoints Using the Reduced Dataset

		Non-fatal Cardiovascular Event		Cardiovascular Death	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Primary endpoint	Unadjusted	0.66 (0.60, 0.73)	7.40×10^{-17}	0.80 (0.65, 0.98)	0.0282
	Adjusted	0.67 (0.61, 0.74)	7.20×10^{-16}	0.80 (0.65, 0.98)	0.0306
Key secondary endpoint	Unadjusted	0.68 (0.59, 0.78)	3.30×10^{-8}	0.79 (0.63, 0.99)	0.0366
	Adjusted	0.68 (0.59, 0.78)	4.30×10^{-8}	0.79 (0.63, 0.99)	0.0380

Joint frailty model is based on Rondeau (See Rondeau V. Joint frailty models for recurring events and death using maximum penalized likelihood estimation: application on cancer events. Biostatistics. 2007; 8:708-21) implemented in the frailty pack R package. Default settings were used, except that 3 knots were used to model the baseline hazard function (to improve speed given that we know from the mean cumulative plots that the shape of the baseline hazard function is unlikely to be complex) and recurrent AG==TRUE (i.e., thereby assuming independence between events conditional on the frailty term).
Unadjusted analyses only included treatment group in the model; Adjusted analyses also included stratification factors (cardiovascular risk category, geographic region, and use of ezetimibe) as covariate, in addition to treatment group in the model.
Analyses are based on reduced dataset accounting for statistical handling of multiple endpoints occurring in a single calendar day as a single event.

Table 45. Hazard and Rate Ratios for Pre-Specified Analyses for Primary and Key Secondary Endpoints Using the Full Dataset

	Primary Composite Endpoint				Key Secondary Composite Endpoint			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	RR/HR (95% CI)	p-value	RR/HR (95% CI)	p-value	RR/HR (95% CI)	p-value	HR (95% CI)	p-value
Negative binomial	0.67 (0.60, 0.76)	1.6×10^{-10}	0.69 (0.61, 0.77)	4.4×10^{-10}	0.71 (0.62, 0.81)	1.4e-06	0.71 (0.62, 0.82)	1.2×10^{-06}
Andersen-Gill (I)	0.68 (0.63, 0.74)	3.4e-22	0.68 (0.63, 0.74)	3.0e-22	0.71 (0.64, 0.79)	1.8×10^{-10}	0.71 (0.63, 0.79)	1.7×10^{-10}
Andersen-Gill (II)	0.68 (0.61, 0.77)	4.5×10^{-11}	0.68 (0.61, 0.76)	3.4×10^{-11}	0.71 (0.62, 0.81)	4.1×10^{-7}	0.71 (0.62, 0.81)	3.4×10^{-07}
Modified WLW								
First event	0.76 (0.69, 0.83)	2.7×10^{-8}	0.75 (0.68, 0.83)	1.7×10^{-8}	0.74 (0.65, 0.83)	7.4×10^{-7}	0.74 (0.65, 0.83)	7.1×10^{-07}
Second event	0.69 (0.61, 0.78)	4.6×10^{-9}	0.68 (0.60, 0.78)	3.1×10^{-9}	0.75 (0.63, 0.89)	0.0011	0.75 (0.63, 0.89)	0.0011
Third event	0.70 (0.60, 0.83)	2.2×10^{-5}	0.70 (0.60, 0.83)	2.1×10^{-5}	0.79 (0.65, 0.96)	0.0170	0.79 (0.65, 0.96)	0.0171

Rate ratios (RR) are presented for results from negative binomial model; Hazard ratios (HR) are presented for results from Andersen Gill (I) model, Andersen Gill (II) model, and modified Wei-Lin-Weisfeld model.

Unadjusted analyses only included treatment group in the model; Adjusted analyses also included stratification factors (cardiovascular risk category, geographic region, and use of ezetimibe) as covariate, in addition to treatment group in the model.
Negative Binomial model. (add references)
Andersen Gill (I) model is based on an intensity model with model-based variance estimate and was a pre-specified methodology.
Andersen Gill (II) model is based on a proportional means model with cluster-robust standard errors, with the cluster set to the patient ID. This is a more standard methodology than the prespecified method.

[0650] Total events for each component of the primary endpoint were also significantly reduced as shown in Figure 40, Figure 34, and Table 47.

[0651] Figures 41A and 41B show the total primary and key secondary composite endpoints in selected subgroup analyses by the negative binomial model. The risk differences for every 1000 patients treated for five years with icosapent ethyl for the five components of the composite primary endpoint are shown in Figure 42; approximately 159 total primary endpoint events could be prevented within that time frame: 12 cardiovascular deaths, 42 myocardial infarctions, 14 strokes, 76 coronary revascularizations, and 16 episodes of hospitalization for unstable angina. Figures 43 and 44 show the forest plot for total primary and key secondary composite endpoint events and first second, and third occurrences for the reduced dataset with unadjusted and adjusted values, respectively. Figures 45 and 46 show the forest plots for the total primary composite endpoint events and total key secondary composite endpoint events and first, second, and third occurrences for the reduced data with unadjusted values, respectively. Figures 47 and 48 show the total primary composite endpoint events and key secondary composite endpoint events and first, second, and third occurrences for the reduced data set with adjusted values, respectively. Figures 49 and 50 show the total primary and key secondary composite endpoint events and first, second, and third occurrences for the full data set for the unadjusted and adjusted values, respectively.

[0652] The risk differences for every 1000 patients treated for five years with AMR101 for the five components of the composite primary endpoint are shown in Figure 51; approximately 159 total primary endpoint events could be prevented within that timeframe: 12 cardiovascular deaths, 42 myocardial infarctions, 14 strokes, 76 coronary revascularizations, and 16 episodes of hospitalization for unstable angina.

[0653] The study drug adherence in patients with recurrent events was also explored. At the time of a first primary endpoint event (fatal or nonfatal), 81.3% (573/705) of icosapent ethyl and 81.8% (737/901) of placebo patients with a first primary endpoint event were receiving randomized study drug. At the time of subsequent primary endpoint events (fatal or nonfatal), 79.7% (188/236) and 79.5% (299/376) of patients with a second

event, 68.1% (49/72) and 74.1% (106/143) of patients with a third event, and 68.0% (17/25) and 71.6% (48/67) of patients with a fourth event were receiving randomized study drug in the icosapent ethyl and placebo groups, respectively. Therefore, the majority of the first, second, third, and fourth events occurred while patients were on randomized study treatment. Numerical differences in study drug adherence among patients with recurrent events were not statistically significant between treatment groups.

Conclusion

[0654] In these total event analyses of the REDUCE-IT clinical trial as described in Example 1, large and significant reductions in total ischemic events with icosapent ethyl versus placebo were found in the total event analyses. Three prespecified and one post hoc analyses with various statistical methodologies demonstrated consistent effects on total ischemic events, with substantial relative and absolute risk reductions. There was a 30% relative risk reduction in the total (i.e., first and subsequent) ischemic events for the primary composite endpoint with icosapent ethyl. For every 1000 patients treated with icosapent ethyl for five years, approximately 159 total primary endpoint events could be prevented. Total events for the hard MACE key secondary endpoint also demonstrated large and clinically meaningful reductions, which further corroborated the significant reduction in important ischemic events seen with the primary endpoint.

[0655] There were significant reductions in the first, subsequent and total ischemic events for each individual component of the composite primary endpoint. This benefit of icosapent ethyl across a variety of different ischemic endpoints (e.g., coronary, cerebral, fatal and non-fatal events, and revascularizations) suggests that the drug benefit is not likely to be explained by triglyceride lowering alone and suggests strongly that there are multiple mechanisms of action of the drug beyond triglyceride lowering that may work together to achieve the observed benefits.

[0656] Icosapent ethyl was well tolerated with no significant differences in rates of serious adverse events versus placebo. Although overall rates were low in both treatment groups, and none of the events were fatal, with icosapent ethyl there was a trend towards increased serious bleeding albeit with no significant increases in adjudicated hemorrhagic stroke, serious central nervous system bleeding, or gastrointestinal bleeding. There was a small, but statistically significant increase in hospitalization for atrial fibrillation or flutter endpoints observed in patients from the

clinical trial. Nevertheless, the large number of important ischemic events averted with the drug, including a significant reduction in fatal and nonfatal stroke (28%), cardiac arrest (48%), sudden death (31%) and cardiovascular death (20%), in indicative of a very favorable risk-benefit profile.

[0657] The patients for the REDUCE-IT clinical trial represent a population at high risk for ischemic events, as suggested by the annualized placebo event rate (5.74%), which was expected per study design and is consistent with historical data for similar high-risk statin-treated patient populations. It is therefore not surprising that the total atherosclerotic event burden was also high for REDUCE-IT patients. Substantial and consistent risk reduction with icosapent ethyl was observed in total event analyses for the primary endpoint, each contributing component, and the key secondary endpoint. Time-to-first-event results provide low number needed to treat (NNT) values (i.e., 21 for the primary endpoint; 28 for the key secondary endpoint); the total event analyses results provide incremental evidence of substantial reduction of the total atherosclerotic burden with icosapent ethyl in these patients, with 16 total primary events prevented for every 100 patients treated with icosapent ethyl for 5 years. Without intending to be bound by any particular theory, given the broad inclusion criteria and relatively few exclusion criteria, these results may be generalizable to a large proportion of at-risk statin-treated patients with atherosclerosis or diabetes.

[0658] Study drug adherence in patients with recurrent events was strong in both treatment groups at the time of their first primary endpoint event, decreasing somewhat across both treatment groups from the occurrence of the first to the fourth event. For example, at the time of a first occurrence of a fatal or nonfatal primary endpoint event, 81.3% of icosapent ethyl and 81.8% of placebo patients with a first primary endpoint event were on study drug; these rates decreased to 68.0% and 71.6% for patients with a fourth primary endpoint event.

[0659] The primary study results for the REDUCE-IT trial and the recurrent and total endpoint event findings discussed herein stand in stark contrast to cardiovascular outcome studies with other agents that lower triglyceride levels and with low-dose omega-3 fatty acid mixtures, where cardiovascular outcome benefit has not been consistently observed in statin-treated patients. EPA has unique lipid and lipoprotein, anti-inflammatory, anti-platelet, anti-thrombotic, and cellular modifying effects, all of

which may contribute to benefits in atherosclerotic processes such as reduced development, slowed progression, and increased stabilization of atherosclerotic plaque. The aggregate contribution of these EPA-related effects may contribute to the large observed reductions in total ischemic events with icosapent ethyl.

[0660] Each total event analysis model employed in this study provides statistical handling of subsequent events, with some distinct and some overlapping strengths. Despite differences in statistical methodologies, the consistency of findings across the models speaks to the robustness of the study conclusions and the underlying outcomes data.

[0661] In conclusion, icosapent ethyl four grams daily (i.e., administered two grams twice daily) significantly reduces total ischemic events in statin-treated patients with well-controlled LDL-C and cardiovascular risk factors including elevated triglycerides with consistent benefits observed across a variety of individual ischemic endpoints. In such patients, icosapent ethyl presents an important treatment option to further reduce the total burden of atherosclerotic events beyond that provided by statin therapy alone.

EXAMPLE 4: The Impact of Icosapent Ethyl on Ischemic Events in Statin-Treated Patients as a Function of Baseline Triglyceride and LDL-C Tertile

[0662] The objective of the following example was to determine the extent to which icosapent ethyl reduced ischemic events in patients from the REDUCE-IT trial, as described in Example 1 as a function of triglyceride level and LDL-C level.

[0663] In the REDUCE-IT trial as described in Example 1, patients underwent a screening visit to determine eligibility, including testing of statin-stabilized triglyceride levels. If patients met inclusion and exclusion criteria, including triglyceride levels and LDL-C levels, they could then be entered into the study at a subsequent randomization visit. Triglyceride levels and LDL-C levels were also measured from blood drawn at the randomization visit, but randomization values were not utilized for study qualification. Randomization values did not always fall within the inclusion criteria that were previously met within qualifying visits.

Analysis of Triglyceride Levels

[0664] In total, the baseline triglyceride levels of the patients ranged from 81 mg/dL to 1401 mg/dL. The patients were then categorized into three tertiles based on their

triglyceride levels. The lowest tertile range included those patients with triglyceride levels of ≥ 81 to ≤ 190 mg/dL with a median triglyceride level of 163 mg/dL, the middle tertile range included those patients with triglycerides of >190 to ≤250 mg/dL with a median triglyceride level of 217 mg/dL, and the uppermost tertile range included patients with triglyceride levels of >250 to ≤1401 mg/dL with a median triglyceride level 304 mg/dL. The baseline characteristics of the patients to include the triglyceride category by tertile are shown below in Table 46.

Table 46. Baseline Characteristics of Patients

	Icosapent Ethyl (N=4089)	**Placebo (N=4090)**
Age (Years)	64	64
Female, %	28.4%	29.2%
CV Risk Category, %		
Secondary Prevention Cohort	70.7%	70.7%
Primary Prevention Cohort	29.3%	29.3%
Prior Atherosclerotic Cardiovascular Disease, %	68.9%	69.3%
Prior Atherosclerotic Cerebrovascular Disease, %	15.7%	662 (16.2%)
Prior Atherosclerotic Peripheral Artery Disease, %	9.5%	388 (9.5%)
LDL-C (mg/dL), Median (Q1-Q3)	74.0 (61.5 - 88.0)	76.0 (63.0 - 89.0)
Triglycerides (mg/dL), Median (Q1-Q3)	216.5 (176.5 - 272.0)	216.0 (175.5 - 274.0)
Triglycerides Category (by Tertiles)*		
≥81 to ≤190 mg/dL	Median 163 mg/dL	
>190 to ≤250 mg/dL	Median 217 mg/dL	
>250 to ≤1401 mg/dL	Median 304 mg/dL	

[0665] Figure 52 is a forest plot demonstrating that the total events (i.e., first and subsequent) for the primary composite endpoint of CV death, non-fatal stroke, non-fatal myocardial infarction, coronary revascularizations, or unstable angina requiring hospitalization was reduced in all patients across the entire triglyceride range and within each of the defined triglyceride tertiles. Similarly, Figure 53 demonstrates that the time to first event of the primary composition endpoint was reduced across the entire triglyceride range.

Analysis of LDL-C Levels

[0666] In total, the LDL-C levels of the patients ranged from patients having less than 1 mg/dL to less than 208 mg/dL. The patients were then categorized into three tertiles based on their LDL-C levels. The lowest tertile range included those patients with LDL-C levels of ≥1 mg/dL to ≤67 mg/dL, the middle tertile range included those patients with LDL-C levels of >67 to ≤84 mg/dL, and the uppermost tertile range included patients with LDL-C levels of >84 to ≤208. Figure 54 is a forest plot showing the effects of administering icosapent ethyl on the primary composite endpoint of CV death, non-fatal stroke, non-fatal myocardial infarction, coronary revascularizations, or unstable angina in all patients across the entire LDL-C range and within each of the defined LDL-C tertiles at year 1. The study demonstrated that the key primary composite endpoint was reduced regardless of the patient's LDL-C levels.

Conclusion

[0667] In conclusion, patients from the REDUCE-IT clinical trial with baseline triglyceride levels across all tertiles (e.g., between 81 mg/dl to 1410 mg/dl) and/or LDL-C levels across all tertiles (e.g., between 1 mg/dl to 208 mg/dl), regardless of their specific triglyceride baseline level and/or LDL-C level, benefited from the administration of 4 g of icosapent ethyl per day and experienced statistically significant reductions in not only the time to first cardiovascular event, but also, total cardiovascular events in both the primary and key secondary composite endpoints.

[0668] The results from the REDUCE-IT clinical trial showed a significant cardiovascular benefit associated with the administration of icosapent ethyl. It is contemplated that a number of factors contribute to the significant reduction in the cardiovascular risk. Without intending to be bound by any particular theory, one of the contributing factors might relate to the dose and formulation of the icosapent ethyl administered to the patients, in marked contrast to previous studies of omega-3 fatty acid studies. An additional contributing factor could relate to the patients' blood pressure. For example, prespecified exploratory analyses of icosapent ethyl with no adjustment for multiple comparisons showed average placebo-corrected reductions from baseline in systolic blood pressure of 1.3 mm Hg (95% CI, 0.9 to 1.6) and in diastolic blood pressure of 0.5 mm Hg (95% CI, 0.3 to 0.7) as shown in Figure 55. Figure 55 shows repeated-measurements analysis of change from baseline blood pressure over time by a mixed effects model for the ITT population (icosapent ethyl: n = 4089, placebo: n = 4091,

maximum number of observations per patient = 6). These differences appear to be modest, but it is contemplated, that they might contribute to the benefits of icosapent ethyl. It is further contemplated that biomarkers (e.g., the ratio of EPA to arachidonic acid) and blood pressure, may also provide an understanding of the effects of icosapent ethyl and potential mechanistic insight for the observed reduction in cardiovascular risk. Further, as common in long-term clinical trials, study drug adherence waned overtime. However, despite the waning there was a long-sustained treatment effect on total events as shown in Figure 56.

EXAMPLE 5: Control Group Response Analyses for the REDUCE-IT Trial

[0669] The objective of the following example was to perform a control group analysis of the ischemic events in patients from the REDUCE-IT trial, as described in Example 1. The study focused on exploring if outcomes were affected by possible malabsorption. If mineral oil in the placebo might have negatively affected statin absorption in some patients, this could have contributed to differences in outcomes between the groups.

[0670] To explore this possibility, post hoc analyses were conducted to compare the effects of AMR101 to placebo with respect to the primary and key secondary endpoints according to whether placebo-treated patients had an increase in derived LDL-C levels at one year or had no change/a decrease in LDL-C levels, along with direct comparisons of these two placebo groups.

Results

[0671] A Kaplan-Meier curve of time to the primary endpoint from date of randomization for AMR101 versus placebo by an LDL-C increase or no change/a decrease at one year in the placebo group is presented in Figure 57A. For the comparison of the AMR101 group versus the group of placebo patients with an increase in LDL-C, the HR was 0.79 (95% CI: 0.70 to 0.88); for the comparison of the AMR101 group versus the group of placebo patients with no change or a decrease in LDL-C, the HR was also 0.79 (95% CI: 0.70 to 0.91); and for the comparison of the group of placebo patients with an increase in LDL-C versus the group of placebo patients with no change or a decrease in LDL-C, the HR was 1.01 (95% CI: 0.87 to 1.17). Thus, there was no apparent difference in the primary endpoint event rates between patients in the placebo group who had an increase in LDL-C as compared to those with no change or a decrease in LDL-C.

[0672] A Kaplan-Meier curve of time to the key secondary endpoint from date of randomization for AMR101 versus placebo by an LDL-C increase or no change/a decrease at one year in the placebo group is presented in Figure 57B. For the comparison of the AMR101 group versus the group of placebo patients with an increase in LDL-C, the HR was 0.80 (95% CI: 0.70 to 0.93); for the comparison of the AMR101 group versus the group of placebo patients with no change or a decrease in LDL-C, the HR was 0.74 (95% CI: 0.63 to 0.88); and for the comparison of the group of placebo patients with an increase in LDL-C versus the group of placebo patients with no change or a decrease in LDL-C, the HR was 0.92 (95% CI: 0.77 to 1.10).

[0673] Thus, similar to the findings for the primary endpoint event rates, there was no apparent difference in the key secondary endpoint event rates between patients in the placebo group who had an increase in LDL-C as compared to those with no change or a decrease in LDL-C.

[0674] Similar post hoc analyses were conducted to compare the effects of AMR101 to placebo with respect to the primary and key secondary endpoints according to whether placebo-treated patients had an increase or had no change/a decrease in non-HDL-C, TG, and HDL-C (each at one year), as well as apo Band hsCRP levels (each at two years).

[0675] A Kaplan-Meier curve of time to the primary endpoint from date of randomization for AMR101 versus placebo by an hsCRP increase or no change/a decrease at two years in the placebo group is presented in Figure 58A. For the comparison of the AMRI0I group versus the group of placebo patients with an increase in hsCRP, the HR was 0.79 (95% CI: 0.71 to 0.89); for the comparison of the AJ\tIRI0I group versus the group of placebo patients with no change or a decrease in hsCRP, the HR was 0.83 (95% CI: 0.72 to 0.96); and for the comparison of the group of placebo patients with an increase in hsCRP versus the group of placebo patients with no change or a decrease in hsCRP, the HR was 1.05 (95% CI: 0.90 to 1.22).

[0676] Thus, there was no apparent difference in the primary endpoint event rates between patients in the placebo group who had an increase in hsCRP as compared to those with no change or a decrease in hsCRP.

[0677] A Kaplan-Meier curve of time to the key secondary endpoint from date of randomization for AMR101 versus placebo by an hsCRP increase or no change/a decrease at two years in the placebo group is presented in Figure 58B. For the

comparison of the AMR101 group versus the group of placebo patients with an increase in hsCRP, the HR was 0.83 (95% CI: 0.71 to 0.95); for the comparison of the AMR101 group versus the group of placebo patients with no change or a decrease in hsCRP, the HR was 0.85 (95% CI: 0. 71 to 1.02); and for the comparison of the group of placebo patients with an increase in hsCRP versus the group of placebo patients with no change or a decrease in hsCRP, the HR was 1.03 (95% CI: 0.85 to 1.24).

[0678] Thus, there was no apparent difference in the key secondary endpoint event rates between patients in the placebo group who had an increase in hsCRP as compared to those with no change or a decrease in hsCRP.

Conclusion

[0679] In these post hoc analyses, there were no apparent differences in primary endpoint or key secondary endpoint event rates between patients in the placebo group who had an increase in lipid and inflammatory biomarkers as compared to those with no change or a decrease in lipid and inflammatory biomarkers.

[0680] If mineral oil in the placebo were causing significant malabsorption of statins or other critical medications, then patients with diarrhea (as a potential marker in a theoretical scenario of malabsorption) might be expected to have higher event rates related to decreased absorption and rates from potentially decreased absorption and efficacy of other administered therapies. Analyses of the primary and key secondary endpoints by censoring patients at the onset date of diarrhea (as a potential marker in a theoretical scenario of malabsorption) suggest no differences in primary analyses using the overall ITT population.

EXAMPLE 6: Statistical and Analytical Considerations and Analyses from the REDUCE-IT Trial

[0681] The objective of the following example was to perform an exploratory and supportive analysis of the REDUCE-IT trial, as described in Example 1.

Adjustment of Covariates

[0682] In the main analysis of the primary endpoint for the REDUCE-IT trial, treatment was the only covariate employed in the stratified Cox proportional hazards model. Stratification variables included CV risk category at baseline (primary prevention

cohort and secondary prevention cohort), use of ezetimibe at baseline (yes/no), and geographical region (Westernized, Eastern European, and Asia Pacific).

[0683] The model included treatment and any of the following variables, identified by a stepwise selection procedure: (1) sex; (2) age at baseline (<65 or ≥65 years); (3) race (white and non-white); (4) presence/absence of diabetes at baseline; (5) baseline LDL-C (by tertile); (6) baseline HDL-C (by tertile); (7) baseline non-HDL-C (by tertile); (8) baseline TG (by tertile); (9) baseline hsCRP (≤3 mg/Land >3 mg/L); (10) baseline apo B (by tertile); (11) baseline RLP-C (by tertile); (12) Hopkins calculated LDL-C at baseline (by tertile); (13) waist/height ratio at baseline; (14) waist circumference at baseline.

[0684] The SAS proportional hazard regression procedure was used to automatically conduct the stepwise selection of the important baseline covariates. The minimum p-value for the inclusion of the baseline covariate into the proportional hazard model was 0.05, and these selected baseline covariates with p<0.10 would remain in the final model as important baseline covariates after all baseline covariates were evaluated by the model. The HR, 95% CI, and p-value comparing the two treatment groups, and the HR, 95% CI, and p-value for adjusting each selected important baseline covariate in the final model were presented.

[0685] The results of the analysis of the primary endpoint adjusting for baseline covariates identified by a stepwise selection procedure are summarized in Table 47. The HRs and 95% CIs are suggestive of a significantly lower risk of major CV events with AMR101 than with placebo, consistent with the findings for the analysis of the primary endpoint.

Table 47. Stratified Analysis of Time to the Primary Endpoint from Date of Randomization by Adjusting Baseline Covariates Identified by Stepwise Selection Procedure (ITT Population)

Covariate	Significance P-value	HR (95% CI) AMR101/Placebo
Adjusting Identified Significant Covariates[1]		
Sex	<0.0001	0.751 (0.680 – 0.829)
Age at baseline (<65 or ≥65 years)	0.0006	0.755 (0.684 – 0.833)
Presence/absence of diabetes at baseline	<0.0001	0.750 (0.679 – 0.827)
Baseline hsCRP (≤3 mg/L or >3 mg/L)	<0.0001	0.750 (0.679 – 0.828)
Baseline non-HDL-C (by tertile)	0.0003	0.755 (0.684 – 0.833)
Overall (with all selected covariates)		0.750 (0.680 – 0.828)

Covariate	Significance P-value	HR (95% CI) AMR101/Placebo

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; ITT= Intent-to-Treat; non-HDL-C = non-high-density lipoprotein cholesterol.

1 Hazard ratio and 95% CI are from a Cox proportional hazard model with treatment as factor and the identified significant baseline variable as covariate, and stratified by geographic region, CV risk category, and use of ezetimibe. P-value for significance of the covariate is from the final model per a stepwise selection process using the Cox proportional hazard model with p-value of 0.05 and 0.1 for a covariate to enter and remain in the model, respectively.

[0686] The results of the analysis of the key secondary endpoint adjusting for baseline covariates identified by a stepwise selection procedure are summarized in Table 48. The HRs and 95% CIs are suggestive of a significantly lower risk of hard MACE events with AMR101 than with placebo, consistent with the findings for the analysis of the key secondary endpoint.

Table 48. Stratified Analysis of Time to the Key Secondary Endpoint from Date of Randomization by Adjusting Baseline Covariates Identified by Stepwise Selection Procedure (ITT Population)

Covariate	Significance P-value	HR (95% CI) AMR101/Placebo
Adjusting Identified Significant Covariates[1]		
Sex	<0.0001	0.734 (0.650 – 0.829)
Age at baseline (<65 or ≥65 years)	<0.0001	0.739 (0.654 – 0.834)
Presence/absence of diabetes at baseline	<0.0001	0.731 (0.647 – 0.825)
Baseline hsCRP (≤3 mg/L or >3 mg/L)	<0.0001	0.731 (0.648 – 0.826)
Baseline non-HDL-C (by tertile)	0.0015	0.738 (0.654 – 0.833)
Overall (with all selected covariates)		0.730 (0.647 – 0.825)

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; ITT= Intent-to-Treat; non-HDL-C = non-high-density lipoprotein cholesterol.

1 Hazard ratio and 95% CI are from a Cox proportional hazard model with treatment as factor and the identified significant baseline variable as covariate, and stratified by geographic region, CV risk category, and use of ezetimibe. P-value for significance of the covariate is from the final model per a stepwise selection process using the Cox proportional hazard model with p-value of 0.05 and 0.1 for a covariate to enter and remain in the model, respectively.

[0687] As an additional exploratory analysis, the relationships between post-baseline lipid values and treatment effects with the primary and key secondary endpoints were assessed by adding lipid values (at 4 months, 1 year, etc.) as time varying covariates in the Cox proportional hazards model. Diagnostic plots for the proportional hazard's assumption was evaluated.

[0688] The results of the analysis of the primary endpoint adjusting for time varying covariates of post-baseline lipids are summarized in Table 49. The HRs and 95% Cis are suggestive of a significantly lower risk of major CV events with AMR101 than with placebo, consistent with the findings for the analysis of the primary endpoint.

Table 49: Stratified Analysis of Time to the Primary Endpoint from Date of Randomization by Adjusting Time Varying Covariates of Post-Baseline Lipids (ITT Population)

	Treatment (AMR101 vs Placebo)	Lipid Covariate	
Lipid Covariate[1]	HR (95% CI) for Treatment (Adjusting Covariate[2])	HR (95% CI) for One Unit Covariate Change[3]	Significance P-value[4]
TG (mg/dL)	0.772 (0.700 – 0.853)	1.001 (1.000 – 1.001)	<0.0001
LDL-C derived (mg/dL)	0.752 (0.681 – 0.830)	1.000 (0.998 – 1.002)	0.8043
LDL-C (ultracentrifugation) (mg/dL)	0.759 (0.687 – 0.839)	1.000 (0.998 – 1.002)	0.9774
LDL-C (Friedewald) (mg/dL)	0.760 (0.688 – 0.839)	1.002 (1.000 – 1.003)	0.0521
LDL-C (Hopkins) (mg/dL)	0.772 (0.699 – 0.852)	1.004 (1.002 – 1.006)	<0.0001
HDL-C (mg/dL)	0.730 (0.661 – 0.806)	0.978 (0.973 – 0.983)	<0.0001
non-HDL-C (mg/dL)	0.784 (0.710 – 0.866)	1.004 (1.003 – 1.005)	<0.0001
apo B (mg/dL)	0.762 (0.690 – 0.842)	1.002 (1.000 – 1.005)	0.0309
hsCRP (mg/dL)	0.758 (0.686 – 0.836)	1.068 (1.021 – 1.117)	0.0043
RLP-C (mg/dL)	0.784 (0.709 – 0.866)	1.008 (1.006 – 1.011)	<0.0001

Abbreviations: apo B = apolipoprotein B; CI = confidence interval; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; ITT= Intent-to-Treat; LDL-C = low-density lipoprotein cholesterol; RLP-C = remnant lipoprotein cholesterol; TG = triglycerides.

1 Time varying lipid covariate was derived as the last non-missing lipid data collected prior to the onset of the efficacy endpoint.

2 Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as factor and time varying lipids as covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

3 Hazard ratio for one unit increase of lipid covariate, based on estimated time varying covariate from the Cox proportional hazard model.

Lipid Covariate[1]	Treatment (AMR101 vs Placebo) HR (95% CI) for Treatment (Adjusting Covariate[2])	Lipid Covariate HR (95% CI) for One Unit Covariate Change[3]	Lipid Covariate Significance P-value[4]

4 P-value for testing significance of including time varying covariate in the proportional hazard model.

[0689] The results of the analysis of the key secondary endpoint adjusting for time varying covariates of post-baseline lipids are summarized in Table 50. The HRs and 95% Cis are suggestive of a significantly lower risk of hard MACE events with AMR101 than with placebo, consistent with the findings for the analysis of the key secondary endpoint.

Table 50. Stratified Analysis of Time to the Key Secondary Endpoint from Date of Randomization by Adjusting Time Varying Covariates of Post-Baseline Lipids (ITT Population)

Lipid Covariate[1]	Treatment (AMR101 vs Placebo) HR (95% CI) for Treatment (Adjusting Covariate[2])	Lipid Covariate HR (95% CI) for One Unit Covariate Change[3]	Lipid Covariate Significance P-value[4]
TG (mg/dL)	0.754 (0.668 – 0.851)	1.001 (1.000 – 1.001)	<0.0001
LDL-C derived (mg/dL)	0.740 (0.655 – 0.836)	1.001 (0.999 – 1.003)	0.3818
LDL-C (ultracentrifugation) (mg/dL)	0.737 (0.652 – 0.834)	1.001 (0.999 – 1.003)	0.3873
LDL-C (Friedewald) (mg/dL)	0.747 (0.662 – 0.844)	1.003 (1.001 – 1.005)	0.0014
LDL-C (Hopkins) (mg/dL)	0.761 (0.674 – 0.860)	1.006 (1.004 – 1.008)	<0.0001
HDL-C (mg/dL)	0.710 (0.629 – 0.802)	0.975 (0.969 – 0.981)	<0.0001
non-HDL-C (mg/dL)	0.773 (0.684 – 0.874)	1.005 (1.004 – 1.006)	<0.0001
apo B (mg/dL)	0.752 (0.665 – 0.850)	1.005 (1.002 – 1.007)	0.0004
hsCRP (mg/dL)	0.745 (0.660 – 0.841)	1.120 (1.070 – 1.171)	<0.0001
RLP-C (mg/dL)	0.768 (0.679 – 0.867)	1.009 (1.006 – 1.012)	<0.0001

Abbreviations: apo B = apolipoprotein B; CI = confidence interval; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; ITT= Intent-to-Treat; LDL-C = low-density lipoprotein cholesterol; RLP-C = remnant lipoprotein cholesterol; TG = triglycerides.

1 Time varying lipid covariate was derived as the last non-missing lipid data collected prior to the onset of the efficacy endpoint.

2 Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as factor and time varying lipids as covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

Lipid Covariate[1]	Treatment (AMR101 vs Placebo) HR (95% CI) for Treatment (Adjusting Covariate[2])	Lipid Covariate HR (95% CI) for One Unit Covariate Change[3]	Lipid Covariate Significance P-value[4]

3 Hazard ratio for one unit increase of lipid covariate, based on estimated time varying covariate from the Cox proportional hazard model.

4 P-value for testing significance of including time varying covariate in the proportional hazard model.

Examination of Subgroups

[0690] Subgroup analyses of the primary endpoint.

[0691] Analyses of the primary endpoint were performed for the following key subgroups of interest: (1) sex (males and females); (2) Age group (<65 years and ≥65 years); (3) race (white and non-white); (4) geographic region (Westernized, Eastern European, and Asia Pacific); (5) US and non-US; (6) baseline ezetimibe use (yes and no); (7) CV risk category (CV risk category 1 = secondary prevention cohort; CV risk category 2 = primary prevention cohort); (8) baseline diabetes (yes and no); (9) baseline statin intensity (high, moderate, and low); (10) Baseline TG ≥200 mg/dL and <200 mg/dL; (11) Baseline TG ≥150 mg/dL and <150 mg/dL; (12) baseline TG ≥ median and TG <median; (13) Baseline TG ≥200 mg/dL and HDL-C ≤35 mg/dL (yes and no); (14) Baseline TG levels ≥150 mg/dL with HDL-C levels ≤40 mg/dL for males and ≤50 mg/dL for females; (15) baseline HbA1c value (<6.5% or ≥6.5%); (16) baseline peripheral artery disease (yes and no); (17) baseline RLP-C by tertile; (18) Baseline hsCRP (≤2 mg/L and >2 mg/L) and by sex; (19) baseline hsCRP (≤3 mg/Land >3 mg/L) and by sex; (20) baseline eGFR (<60 mL/min/1.73m^2, 60 to <90 mL/min/1.73m^2, and ≥90 mL/min/1.73m^2); (21) baseline LDL-C by tertiles (≥1 to ≤67 mg/dL, >67 to ≤84 mg/dL, and >84 to ≤208 mg/dL); (22) baseline HDL-C by tertiles (≥17 to >36.5 mg/dL, >36.5 to ≤43.5 mg/dL, and >43.5 to ≤107.5 mg/dL) and tertile by sex; (23) baseline apo B by tertiles (≥17.5 to ≤76 mg/dL, >76 to ≤89 mg/dL, and >89 to ≤207 mg/dL); (24) Baseline non-HDL-C by tertiles (≥60.5 to ≤109 mg/dL, >109 to ≤127.5 mg/dL, and >127.5 to ≤244 mg/dL); (25) baseline TG by tertiles (≥81.25 to ≤190 mg/dL, >190 to >250 mg/dL, and >250 to ≤1401 mg/dL) and tertile by sex; (25) combined highest tertile for baseline TG and lowest tertile for baseline HDL-C; and (26) sex-specific highest tertile for baseline TG and lowest tertile for baseline HDL-C.

[0692] For the interaction terms, a p-value <0.15 was considered significant, indicating that the subgroup interaction may have impacted treatment benefit. Of note regarding the following subgroup analyses, per study design, subgroup analyses are underpowered to detect statistically significant results within each individual subgroup, particularly when a subgroup represents less than 50% of the enrolled population, and when a subgroup has low event rates. For example, if an individual subgroup has statistics that approach significance and non-significant interaction p-values for the subgroup comparison, these results suggest that if more patients from a particular subgroup had been enrolled, or if enrolled patients were followed longer, then more events would have accrued, and the trending of individual analyses could flip from nearly significant to actually significant. Even when subgroup interaction p-values are significant, this does not necessarily denote a lack of effect in one subgroup, but instead, simply differential effects across subgroups.

[0693] A forest plot of the analyses of the primary endpoint by the subgroups of geographic region, CV risk category, baseline ezetimibe use, sex, and age group are presented in Figure 59. As indicated by point estimates of the HRs sitting to the left of the unity line (HR= 1), results were generally consistent with the primary analyses, i.e., the treatment benefit of AMR101 (a significantly lower risk of major adverse CV events) was generally consistent across these subgroups, and non-significant interaction p-values were observed for subgroup analyses by region, ezetimibe use, and sex.

[0694] For the secondary prevention subgroup (CV risk category l), a primary endpoint event occurred in 19.3% (559/2892) of patients in the AMR101 group, as compared with 25.5% (738/2893) of patients in the placebo group (HR of 0.726 [95% CI: 0.650 to 0.810]). For the primary prevention subgroup (CV risk category 2), a primary endpoint event occurred in 12.2% (146/1197) of patients in the AMR101 group, as compared with 13.6% (163/1197) of patients in the placebo group (HR of 0.876 [95% CI: 0. 700 to 1.095]). The interaction p-value was significant (p=0.1388).

[0695] Consistent with the study design, 29.3% of the patients randomized in the ITT population were in the primary prevention subgroup (CV risk category 2), and the event rates were low compared to those of the secondary prevention subgroup (CV risk category 1).

[0696] For the <65 years subgroup, a primary endpoint event occurred in 14.4% (322/2232) of patients in the AMR101 group, as compared with 21.1% (460/2184) of

patients in the placebo group (HR of 0.650 [95% CI: 0.564 to 0.750]). For the ≥65 years subgroup, a primary endpoint event occurred in 20.6% (383/1857) of patients in the AMR101 group, as compared with 23.1% (441/1906) of patients in the placebo group (HR of 0.873 [95% CI: 0.761 to 1.001]). The interaction p-value was significant (p=0.003 7). Less than half of randomized patients (46%) were ≥65 years old at baseline, and the upper bound of the 95% CI just surpassed unity (1.001), suggesting a trend toward benefit.

[0697] A forest plot of the analyses of the primary endpoint by the subgroups of white vs non-white, baseline diabetes, baseline statin intensity, baseline TG ≥200 vs <200 mg/dL, baseline TG ≥150, and baseline TG ≥200 mg/dL and HDL-C ≤35 mg/dL is presented in Figure 60.

[0698] Of note, the interaction p-values for isolated TG were not significant for patients with baseline TG ≥150 mg/dL vs TG <150 mg/dL, or for patients with baseline TG ≥200 mg/dL vs TG <200 mg/dL. AMR101 effects in patients with baseline TG <150 mg/dL did not independently reach significance, as denoted by the upper-bound of the 95% CI crossing unity (1.087), but this subgroup was small (10.3% of randomized patients). Combined with the non-significant interaction p-values for baseline TG cuts at 150 and 200 mg/dL, there is a suggestion of AMR101 benefit in the primary endpoint regardless of baseline TG level within the study population.

[0699] Patients with baseline TG ≥200 mg/dL and HDL-C ≤35 mg/dL likely represent the subset of mixed dyslipidemia with the atherogenic lipoprotein phenotype (i.e., atherogenic dyslipidemia), which is suggested to increase CHD risk (NCEP 2002). For patients with atherogenic dyslipidemia, a primary endpoint event occurred in 18.1 % (149/823) of patients in the AMR101 group, as compared with 27.0% (214/794) of patients in the placebo group (HR of 0.623 [95% CI: 0.505 to 0.769]). For patients without atherogenic dyslipidemia, a primary endpoint event occurred in 17.0% (554/3258) of patients in the AMR101 group, as compared with 20.9% (687/3293) of patients in the placebo group (HR of 0.791 [95% CI: 0.707 to 0.885]). The interaction p-value was significant (p=0.0408). Taken together, these data suggest that, while both subsets derive benefit regardless of the presence or absence of atherogenic dyslipidemia, patients with atherogenic dyslipidemia may experience greater treatment benefit with AMR101.

[0700] A forest plot of the analyses of the primary endpoint by the subgroups of US vs non-US, baseline hsCRP ≤2 vs >2 mg/L, baseline hsCRP ≤3 vs >3 mg/L, baseline eGFR, baseline LDL-C (derived) by tertiles, and baseline HDL-C by tertiles is presented in Figure 61. As indicated by point estimates of the HRs sitting to the left of the unity line (HR= 1), results were generally consistent with the primary analyses, i.e., the treatment benefit of AMR101 (a significantly lower risk of major adverse CV events) was generally consistent across these subgroups, and all individual subgroups reached significance.

[0701] For US patients, a primary endpoint event occurred in 18.2% (281/1548) of patients in the AMR101 group, as compared with 24.7% (394/1598) of patients in the placebo group (HR of 0.687 [95% CI: 0.590 to 0.801]). For non-US patients, a primary endpoint event occurred in 16.7% (424/2541) of patients in the AMR101 group, as compared with 20.3% (507/2492) of patients in the placebo group (HR of 0.803 [95% CI: 0.706 to 0.913]). The interaction p-value was significant (p=0.1383), suggesting that, while both subsets derive benefit regardless of residence in the US or outside the US, patients within the US may experience greater treatment benefit with AMR101.

[0702] For patients with baseline hsCRP ≤2 mg/L, a primary endpoint event occurred in 15.0% (288/1919) of patients in the AMR101 group, as compared with 21.0% (407/1942) of patients in the placebo group (HR of 0.680 [95% CI: 0.585 to 0.791]). For patients with baseline hsCRP >2 mg/L, a primary endpoint event occurred in 19.2% (417/2167) of patients in the AMR101 group, as compared with 23.0% (494/2147) of patients in the placebo group (HR of 0.813 [95% CI: 0.713 to 0.926]). The interaction p-value was significant (p=0.0716), suggesting that, while both subsets derive benefit regardless of baseline hsCRP levels above or below 2 mg/L, patients with hsCRP ≤2 mg/L may experience greater treatment benefit with AMR101.

[0703] A forest plot of the analyses of the primary endpoint by the subgroups of baseline apo B by tertiles, non-HDL-C by tertiles, and TG by tertiles is presented in Figure 62. As indicated by point estimates of the HRs sitting to the left of the unity line (HR= l), results were generally consistent with the primary analyses, i.e., the treatment benefit of AMR101 (a significantly lower risk of major adverse CV events) was generally consistent across these subgroups. All individual subgroups reached significance, and no interaction p-values reached significance.

[0704] An analysis of the primary endpoint by baseline TG <median and TG ≥median is summarized in Table 51.

[0705] For patients below the median baseline TG (≥81.25 and ≤216 mg/dL), a primary endpoint event occurred in 17.3% (353/2041) of patients in the AMR101 group, as compared with 21.0% (432/2057) of patients in the placebo group (HR of 0.803 [95% CI: 0.698 to 0.924; p=0.0022]). For patients above or at the median baseline TG (>216 and s1401 mg/dL), a primary endpoint event occurred in 17.2% (352/2045) of patients in the AMR101 group, as compared with 23.1% (469/2032) of patients in the placebo group (HR of 0.709 [95% CI: 0.618 to 0.815; p<0.0001]).

[0706] Results were generally consistent with the primary analyses, i.e., the treatment benefit of AMR101 (a significantly lower risk of major adverse CV events) was generally consistent across these subgroups; each subgroup reached significance, and there was a non-significant interaction p-value.

Table 51. Analysis of Time to the Primary Endpoint from Date of Randomization by Baseline TG <Median and ≥Median (ITT Population)

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
TG Lower Half (≥81.25 and ≤216 mg/dL)	353/2041 (17.3)	432/2057 (21.0)	0.2243
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0022	
HR (95% CI) AMR101/Placebo		0.803 (0.698 – 0.924)	
TG Upper Half (>216 and ≤1401 mg/dL)	352/2045 (17.2)	469/2032 (23.1)	
Treatment Comparison[1]			
P-value from Log-Rank Test		<0.0001	
HR (95% CI) AMR101/Placebo		0.709 (0.618 – 0.815)	

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT= Intent-to-Treat; TG = triglycerides.

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 P-value for treatment by the subgroup interaction is reported from a Cox proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

[0707] An analysis of the primary endpoint by baseline TG levels ≥150 mg/dL with HDL-C levels ≤40 mg/dL for males and ≤50 mg/dL for females is summarized in Table 52.

[0708] For patients with baseline TG levels ≥150 mg/dL and HDL-C levels ≤40 mg/dL (males) or ≤50 mg/dL (females), a primary endpoint event occurred in 16.5% (399/2414) of patients in the AMR101 group, as compared with 22.3% (533/2386) of patients in the placebo group (HR of 0.691 [95% CI: 0.607 to 0.787; p<0.0001]). For patients with baseline TG levels <150 mg/dL and HDL-C levels >40 mg/dL (males) or >50 mg/dL (females), a primary endpoint event occurred in 18.2% (303/1665) of patients in the AMR101 group, as compared with 21.5% (365/1695) of patients in the placebo group (HR of 0.842 [95% CI: 0.723 to 0.980; p=0.0263]).

[0709] Each subgroup reached significance. The interaction p-value was significant (p=0.0506), suggesting that, while both subsets derive benefit regardless of baseline TG levels above or below 150 mg/dL and HDL-C levels above and below 40 mg/dL (males) or 50 mg/dL (females), patients with baseline TG levels ≥150 mg/dL and HDL-C levels ≤40 mg/dL (males) or ≤50 mg/dL (females) may experience greater treatment benefit with AMR101.

Table 52. Stratified Analysis of Time to the Primary Endpoint from Date of Randomization by Baseline TG ≥150 mg/dL and HDL-C ≤40 mg/dL (Males) or ≤50 mg/dL (Females) (ITT Population)

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
Baseline TG ≥150 mg/dL and HDL-C ≤40 mg/dL (Males) or ≤50 mg/dL (Females)	399/2414 (16.5)	533/2386 (22.3)	0.0506
Treatment Comparison[1]			
P-value from Log-Rank Test		<0.0001	
HR (95% CI) AMR101/Placebo		0.691 (0.607 – 0.787)	
Baseline TG <150 mg/dL or HDL-C >40 mg/dL (Males) or >50 mg/dL (Females)	303/1665 (18.2)	365/1695 (21.5)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0263	
HR (95% CI) AMR101/Placebo		0.842 (0.723 – 0.980)	

Abbreviations: CI = confidence interval; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; ITT= Intent-to-Treat; TG = triglycerides.

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]

2 P-value for treatment by the subgroup interaction is reported from a Cox proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

[0710] An analysis of the primary endpoint by baseline RLP-C tertile (derived by TC -HDL-C - LDL-C [Varbo 2014]) is summarized in Table 53.

[0711] For patients in the lowest tertile for baseline RLP-C (≥11.89 to ≤28.09 mg/dL), a primary endpoint event occurred in 17.1 % (230/1347) of patients in the AMR101 group, as compared with 20.6% (283/1372) of patients in the placebo group (HR of0.806 [95% CI: 0.677 to 0.959; p=0.0 150]).

[0712] For patients in the middle tertile for baseline RLP-C (>28.09 to ≤34.30 mg/dL), a primary endpoint event occurred in 16.8% (234/1391) of patients in the AMR101 group, as compared with 21.7% (288/1329) of patients in the placebo group (HR of 0.750 [95% CI: 0.631 to 0.891; p=0.0010]).

[0713] For patients in the highest tertile for baseline RLP-C (>34.30 to ≤105.86 mg/dL), a primary endpoint event occurred in 17.8% (238/1339) of patients in the AMR101 group, as compared with 23.6% (326/1379) of patients in the placebo group (HR of 0.715 [95% CI: 0.605 to 0.846; p<0.0001]).

[0714] Results were generally consistent with the primary analyses, i.e., the treatment benefit of AMR101 (a significantly lower risk of major adverse CV events) was generally consistent across these subgroups; each subgroup reached significance, and there was a non-significant interaction p-value.

Table 53. Stratified Analysis of Time to the Primary Endpoint from Date of Randomization by Baseline RLP-C Tertiles (ITT Population)

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
RLP-C (Derived) Lowest Tertile (≥11.89 to ≤28.09 mg/dL)	230/1347 (17.1)	283/1372 (20.6)	0.6349
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0150	
HR (95% CI) AMR101/Placebo		0.806 (0.677 – 0.959)	

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
RLP-C (Derived) Middle Tertile (>28.09 to ≤34.30 mg/dL)	234/1391 (16.8)	288/1329 (21.7)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0010	
HR (95% CI) AMR101/Placebo		0.750 (0.631 – 0.891)	
RLP-C (Derived) Highest Tertile (>34.30 to ≤105.86 mg/dL)	238/1339 (17.8)	326/1379 (23.6)	
Treatment Comparison[1]			
P-value from Log-Rank Test		<0.0001	
HR (95% CI) AMR101/Placebo		0.715 (0.605 – 0.846)	

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT= Intent-to-Treat; RLP-C = remnant lipoprotein cholesterol.

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 P-value for treatment by the subgroup interaction is reported from a Cox proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

[0715] An analysis of the primary endpoint by baseline HbA1c <6.5% and ≥6.5% is summarized in Table 54.

[0716] For patients with baseline HbA1c <6.5%, a primary endpoint event occurred in 16.5% (378/2289) of patients in the AMR101 group, as compared with 20.1 % (466/2314) of patients in the placebo group (HR of 0.793 [95% CI: 0.692 to 0.908; p=0.0008]).

[0717] For patients with baseline HbA1c ≥6.5%, a primary endpoint event occurred in 18.1 % (325/1791) of patients in the AMR101 group, as compared with 24.6% (434/1765) of patients in the placebo group (HR of 0.701 [95% CI: 0.607 to 0.809; p<0.0001]).

[0718] Results were generally consistent with the primary analyses, i.e., the treatment benefit of AMR101 (a significantly lower risk of major adverse CV events) was generally consistent across these subgroups; each subgroup reached significance, and there was a non-significant interaction p-value.

Table 54. Stratified Analysis of Time to the Primary Endpoint from Date of Randomization by Baseline HbA1c <6.5% and ≥6.5% (ITT Population)

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
Baseline HbA1c <6.5%	378/2289 (16.5)	466/2314 (20.1)	0.2089
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0008	
HR (95% CI) AMR101/Placebo		0.793 (0.692 – 0.908)	
Baseline HbA1c ≥6.5%	325/1791 (18.1)	434/1765 (24.6)	
Treatment Comparison[1]			
P-value from Log-Rank Test		<0.0001	
HR (95% CI) AMR101/Placebo		0.701 (0.607 – 0.809)	

Abbreviations: CI = confidence interval; CV = cardiovascular; HbA1c = glycated hemoglobin; HR = hazard ratio; ITT= Intent-to-Treat.

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 P-value for treatment by the subgroup interaction is reported from a Cox proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

[0719] An analysis of the primary endpoint by baseline peripheral artery disease status is summarized in Table 55.

[0720] For patients with history of peripheral artery disease, a primary endpoint event occurred in 26.6% (103/387) of patients in the AMR101 group, as compared with 32.0% (124/388) of patients in the placebo group (HR of 0.803 [95% CI: 0.617 to 1.046; p=0.1024]). This subgroup did not reach significance, but the sample size was small (9. 5% of randomized patients). For patients without history of peripheral artery disease, a primary endpoint event occurred in 16.3% (602/3702) of patients in the AMR101 group, as compared with 21.0% (777/3702) of patients in the placebo group (HR of 0.744 [95% CI: 0.669 to 0.828; p<0.0001]). There was a non-significant interaction p-value, suggesting consistent AMR101 benefit in the primary endpoint regardless of history of peripheral artery disease.

Table 55. Stratified Analysis of Time to the Primary Endpoint from Date of Randomization by Baseline Peripheral Artery Disease Status (ITT Population)

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
PAD History – Yes	103/387 (26.6)	124/388 (32.0)	0.5811
Treatment Comparison[1]			
P-value from Log-Rank Test		0.1024	
HR (95% CI) AMR101/Placebo		0.803 (0.617 – 1.046)	
PAD History – No	602/3702 (16.3)	777/3702 (21.0)	
Treatment Comparison[1]			
P-value from Log-Rank Test		<0.0001	
HR (95% CI) AMR101/Placebo		0.744 (0.669 – 0.828)	

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT= Intent-to-Treat; PAD = peripheral artery disease.

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 P-value for treatment by the subgroup interaction is reported from a Cox proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

[0721] An analysis of the primary endpoint by baseline hsCRP ≤2 and >2 mg/L (overall and sex-specific) is summarized in Table 56.

[0722] Overall (males and females), for patients with baseline hsCRP ≤2 mg/L, a primary endpoint event occurred in 15.0% (288/1919) of patients in the AMR101 group, as compared with 21.0% (407/1942) of patients in the placebo group (HR of 0.680 [95% CI: 0.585 to 0.791; p<0.0001]). For patients with baseline hsCRP >2 mg/L, a primary endpoint event occurred in 19.2% (417/2167) of patients in the AMR101 group, as compared with 23.0% (494/2147) of patients in the placebo group (HR of 0.813 [95% CI: 0.713 to 0.926; p=0.0018]). The interaction p-value was significant (p=0.0716), suggesting that while both subsets derive benefit regardless of baseline hsCRP levels above or below 2 mg/L, patients with hsCRP ≤2 mg/L may experience greater treatment benefit with AMR101.

[0723] Results were generally consistent with the primary analyses, i.e., the treatment benefit of AMR101 (a significantly lower risk of major adverse CV events) was generally consistent across these subgroups.

[0724] In both the male and female subgroups, a primary endpoint event occurred in a lower percentage of patients in the AMR101 group than in the placebo group. The

differences between the AMR101 and placebo group were significant for each subgroup, with the exception of females with hsCRP >2 mg/L. As noted previously, the number of female patients was substantially lower than the number of male patients across the study (28.8% of randomized patients) and subsequently within each subgroup, which is common in CV outcome trials enrolling Westernized patients. In addition, event rates were substantially lower in females compared to males.

[0725] The interaction p-value (0.0851) was significant for females, suggesting that female patients with hsCRP ≤2 mg/L may experience greater treatment benefit with AlvIR101 than female patients with hsCRP >2 mg/L.

[0726] Results were generally consistent with the primary analyses of the primary endpoint by baseline hsCRP ≤3 and >3 mg/L by sex, i.e., the treatment benefit of AMR101 (a significantly lower risk of major adverse CV events) was generally consistent across these subgroups. In both the male and female subgroups, a primary endpoint event occurred in a lower percentage of patients in the AlvIRI0I group than in the placebo group. The differences between the AMR101 and placebo group were significant for the male subgroups but not the female subgroups. Again, the number of female patients was substantially lower than the number of male patients across the study (28.8% of randomized patients) and subsequently within each subgroup and lower event rates were observed in females.

Table 56. Stratified Analysis of Time to the Primary Endpoint from Date of Randomization by Baseline hsCRP ≤2 and >2 mg/L, Overall and Sex-Specific (ITT Population)

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
Overall (Males and Females)			
Baseline hsCRP ≤2 mg/L	288/1919 (15.0)	407/1942 (21.0)	0.0716
Treatment Comparison[1]			
P-value from Log-Rank Test		<0.0001	
HR (95% CI) AMR101/Placebo		0.680 (0.585 – 0.791)	
Baseline hsCRP >2 mg/L	417/2167 (19.2)	494/2147 (23.0)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0018	
HR (95% CI) AMR101/Placebo		0.813 (0.713 – 0.926)	

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
Males			
Baseline hsCRP ≤2 mg/L	247/1510 (16.4)	337/1493 (22.6)	0.3244
Treatment Comparison[1]			
P-value from Log-Rank Test		<0.0001	
HR (95% CI) AMR101/Placebo		0.691 (0.587 – 0.815)	
Baseline hsCRP >2 mg/L	304/1415 (21.5)	378/1401 (27.0)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0008	
HR (95% CI) AMR101/Placebo		0.772 (0.663 – 0.898)	
Females			
Baseline hsCRP ≤2 mg/L	41/409 (10.0)	70/449 (15.6)	0.0851
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0149	
HR (95% CI) AMR101/Placebo		0.621 (0.422 – 0.915)	
Baseline hsCRP >2 mg/L	113/752 (15.0)	116/746 (15.5)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.5836	
HR (95% CI) AMR101/Placebo		0.930 (0.717 – 1.206)	

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; hsCRP = high-sensitivity C-reactive protein; ITT= Intent-to-Treat.

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 P-value for treatment by the subgroup interaction is reported from a Cox proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

[0727] Triglycerides and HDL-C by Tertile and Sex

[0728] An analysis of the primary endpoint by baseline TG tertile (overall and sex-specific) is summarized in Table 57 and Table 58, respectively.

[0729] Overall (males and females), for patients in the lowest tertile for baseline TG (≥81.25 to ≤190 mg/dL), a primary endpoint event occurred in 16.9% (233/1378) of patients in the AMR101 group, as compared with 21.1 % (291/1381) of patients in the placebo group (HR of0.789 [95% CI: 0.664 to 0.938; p=0.0069]).

[0730] For patients in the middle tertile for baseline TG (> 190 to ≤250 mg/dL), a primary endpoint event occurred in 18.0% (246/1370) of patients in the AMR101 group,

as compared with 21.3% 283/1326) of patients in the placebo group (HR of 0.804 [95% CI: 0.677 to 0.954; p=0.0121]).

[0731] For patients in the highest tertile for baseline TG (>250 to ≤401 mg/dL), a primary endpoint event occurred in 16.9% (226/1338) of patients in the AMR101 group, as compared with 23.7% (327/1382) of patients in the placebo group (HR of 0.675 [95% CI: 0.570 to 0.800; p<0.0001]).

[0732] Results were generally consistent with the primary analyses, i.e., the treatment benefit of AMR101 (a significantly lower risk of major adverse CV events) was generally consistent across these subgroups; each subgroup reached significance, and there was a non-significant interaction p-value.

[0733] In both the male and female subgroups, a primary endpoint event occurred in a lower percentage of patients in the AMR101 group than in the placebo group, with the exception of females in the middle tertile for baseline TG (>186 to ≤241.5 mg/dL) (15.1 % in the AMR101 group vs 13.4% in the placebo group) (HR of 1.077 [95% CI: 0.739 to 1.568; p=0.7001]), but the interaction p-value was not significant, suggesting consistent effects across TG tertiles in females. The differences between the AMRI0l and placebo group were significant for males but not for females, but the interaction p-value was not significant, suggesting consistent effects across tertiles in males. As noted previously, the number of female patients was substantially lower than the number of male patients across the study (28.8% of randomized patients) and subsequently within each tertile, and lower event rates were observed in females.

[0734] Similarly, the differences between the AMR101 and placebo group were significant for the lowest and middle tertiles of baseline HDL-C for males, and for the middle tertile of baseline HDL-C for females, but not for the highest tertile of baseline HDL-C for males or the lowest and highest tertiles of baseline HDL-C for females. The interaction p-value for females was not significant, suggesting similar AMR101 effects across HDL-C tertiles in females.

Table 57. Stratified Analysis of Time to the Primary Endpoint from Date of Randomization by Baseline TG Tertiles (ITT Population)

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
Overall (Males and Females)			
TG Lowest Tertile (≥81.25 to ≤190 mg/dL)	233/1378 (16.9)	291/1381 (21.1)	0.3311

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0069	
HR (95% CI) AMR101/Placebo		0.789 (0.664 – 0.938)	
TG Middle Tertile (>190 to ≤250 mg/dL)	246/1370 (18.0)	283/1326 (21.3)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0121	
HR (95% CI) AMR101/Placebo		0.804 (0.677 – 0.954)	
TG Highest Tertile (>250 to ≤1401 mg/dL)	226/1338 (16.9)	327/1382 (23.7)	
Treatment Comparison[1]			
P-value from Log-Rank Test		<0.0001	
HR (95% CI) AMR101/Placebo		0.675 (0.570 – 0.800)	

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT= Intent-to-Treat; TG = triglycerides.

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 P-value for treatment by the subgroup interaction is reported from a Cox proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

Table 58. Stratified Analysis of Time to the Primary Endpoint from Date of Randomization by Baseline TG Tertiles and Sex (ITT Population)

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
Males			
TG Lowest Tertile (≥81.25 to ≤191.5 mg/dL)	185/972 (19.0)	225/971 (23.2)	0.4887
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0233	
HR (95% CI) AMR101/Placebo		0.799 (0.657 – 0.970)	
TG Middle Tertile (>191.5 to ≤253.5 mg/dL)	185/993 (18.6)	232/950 (24.4)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0023	
HR (95% CI) AMR101/Placebo		0.741 (0.611 – 0.900)	
TG Highest Tertile (>253.5 to ≤830 mg/dL)	181/960 (18.9)	258/973 (26.5)	

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
Treatment Comparison[1]			
P-value from Log-Rank Test		<0.0001	
HR (95% CI) AMR101/Placebo		0.671 (0.554 – 0.812)	
Females			
TG Lowest Tertile (≥92.5 to ≤186 mg/dL)	49/396 (12.4)	68/394 (17.3)	0.2965
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0903	
HR (95% CI) AMR101/Placebo		0.728 (0.503 – 1.053)	
TG Middle Tertile (>186 to ≤241.5 mg/dL)	59/390 (15.1)	53/395 (13.4)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.7001	
HR (95% CI) AMR101/Placebo		1.077 (0.739 – 1.568)	
TG Highest Tertile (>241.5 to ≤1401 mg/dL)	46/375 (12.3)	65/406 (16.0)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.1082	
HR (95% CI) AMR101/Placebo		0.734 (0.502 – 1.072)	

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT= Intent-to-Treat; TG = triglycerides.

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 P-value for treatment by the subgroup interaction is reported from a Cox proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

[0735] An analysis of the primary endpoint by baseline HDL-C tertile (overall and sex-specific) is summarized in Table 59 and Table 60, respectively.

[0736] Overall (males and females), for patients in the lowest tertile for baseline HDL-C (≥17 to ≤36.5 mg/dL), a primary endpoint event occurred in 18.1 % (257/1416) of patients in the AMR101 group, as compared with 25.3% (346/1368) of patients in the placebo group (HR of 0.667 [95% CI: 0.567 to 0.784; p<0.0001]).

[0737] For patients in the middle tertile for baseline HDL-C (>36.5 to ≤43.5 mg/dL), a primary endpoint event occurred in 17.6% (233/1324) of patients in the AMRI0I group, as compared with 21.6% (292/1353) of patients in the placebo group (HR of 0.800 [95% CI: 0.674 to 0.951; p=0.0112]).

[0738] For patients in the highest tertile for baseline HDL-C (>43.5 to ≤107.5 mg/dL), a primary endpoint event occurred in 15.9% (212/1337) of patients in the AMR101 group, as compared with 19.1 % (259/1359) of patients in the placebo group (HR of 0.812 [95% CI: 0.677 to 0.974; p=0.0242]).

[0739] Results were generally consistent with the primary analyses, i.e., the treatment benefit of AMR101 (a significantly lower risk of major adverse CV events) was generally consistent across these subgroups; each subgroup reached significance, and there was a non-significant interaction p-value.

[0740] In both the male and female subgroups, a primary endpoint event occurred in a lower percentage of patients in the AMR101 group than in the placebo group. The differences between the AMR101 and placebo group were significant for males in the lowest and middle tertiles for baseline HDL-C and for females in the middle tertile for baseline HDL-C. As noted previously, the number of female patients was substantially lower than the number of male patients across the study (28.8% of randomized patients) and subsequently within each tertile, and lower event rates were observed in females. In addition, the interaction p-value for females was not significant, suggesting similar AMR101 effects across HDL-C tertiles in females.

[0741] The interaction p-value was significant (0.1417) for males, suggesting that while each subset may derive benefit at various baseline HDL-C levels, these benefits may vary across tertiles, with male patients in the lowest HDL-C tertile (≥17 to ≤35.5 mg/dL) potentially experiencing the greatest benefit.

Table 59. Stratified Analysis of Time to the Primary Endpoint from Date of Randomization by Baseline HDL-C Tertiles (ITT Population)

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
Overall (Males and Females)			
HDL-C Lowest Tertile (≥17 to ≤36.5 mg/dL)	257/1416 (18.1)	346/1368 (25.3)	0.1686
Treatment Comparison[1]			
P-value from Log-Rank Test		<0.0001	
HR (95% CI) AMR101/Placebo		0.667 (0.567 – 0.784)	
HDL-C Middle Tertile (>36.5 to ≤43.5 mg/dL)	233/1324 (17.6)	292/1353 (21.6)	
Treatment Comparison[1]			

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
P-value from Log-Rank Test		0.0112	
HR (95% CI) AMR101/Placebo		0.800 (0.674 – 0.951)	
HDL-C Highest Tertile (>43.5 to ≤107.5 mg/dL)	212/1337 (15.9)	259/1359 (19.1)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0242	
HR (95% CI) AMR101/Placebo		0.812 (0.677 – 0.974)	

Abbreviations: CI = confidence interval; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; ITT= Intent-to-Treat.

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 P-value for treatment by the subgroup interaction is reported from a Cox proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

Table 60: Stratified Analysis of Time to the Primary Endpoint from Date of Randomization by Baseline HDL-C Tertiles and Sex (ITT Population)

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
Males			
HDL-C Lowest Tertile (≥17 to ≤35.5 mg/dL)	201/1060 (19.0)	271/1018 (26.6)	0.1417
Treatment Comparison[1]			
P-value from Log-Rank Test		<0.0001	
HR (95% CI) AMR101/Placebo		0.652 (0.543 – 0.783)	
HDL-C Middle Tertile (>35.5 to ≤42 mg/dL)	160/945 (16.9)	230/968 (23.8)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0012	
HR (95% CI) AMR101/Placebo		0.717 (0.586 – 0.877)	
HDL-C Highest Tertile (>42 to ≤107.5 mg/dL)	187/913 (20.5)	210/903 (23.3)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.1252	
HR (95% CI) AMR101/Placebo		0.857 (0.703 – 1.044)	

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
Females			
HDL-C Lowest Tertile (≥21 to ≤41 mg/dL)	71/426 (16.7)	70/402 (17.4)	0.2723
Treatment Comparison[1]			
P-value from Log-Rank Test		0.5059	
HR (95% CI) AMR101/Placebo		0.894 (0.642 – 1.246)	
HDL-C Middle Tertile (>41 to ≤48 mg/dL)	33/374 (8.8)	50/376 (13.3)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0258	
HR (95% CI) AMR101/Placebo		0.609 (0.392 – 0.946)	
HDL-C Highest Tertile (>48 to ≤96.5 mg/dL)	50/359 (13.9)	66/413 (16.0)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.7257	
HR (95% CI) AMR101/Placebo		0.936 (0.645 – 1.357)	

Abbreviations: CI = confidence interval; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; ITT= Intent-to-Treat.

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 P-value for treatment by the subgroup interaction is reported from a Cox proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

[0742] An analysis of the primary endpoint by combined highest tertile for baseline TG and lowest tertile for baseline HDL-C (overall and sex-specific) is summarized in Table 61.

[0743] Overall (males and females), for patients in the highest tertile for baseline TG and lowest tertile for baseline HDL-C, a primary endpoint event occurred in 19.1 % (118/619) of patients in the AMR101 group, as compared with 26.7% (165/618) of patients in the placebo group (HR of 0.670 [95% CI: 0.528 to 0.849; p=0.0009]). For patients not in the highest tertile for baseline TG and lowest tertile for baseline HDL-C, a primary endpoint event occurred in 16.3% (247/1516) of patients in the AMR101 group, as compared with 22.7% (343/1514) of patients in the placebo group (HR of 0.679 [95% CI: 0.577 to 0.800; p<0.0001]).

[0744] Results were generally consistent with the primary analyses, i.e., the treatment benefit of AMR101 (a significantly lower risk of major adverse CV events) was generally consistent across these subgroups; each subgroup reached significance, with the exception of females, and no interaction p-values reached significance.

[0745] In both the male and female subgroups, a primary endpoint event occurred in a lower percentage of patients in the AMR101 group than in the placebo group. The differences between the AMR101 and placebo group were significant for males but not for females. Of note, the number of female patients was substantially lower than the number of male patients across the study (28.8% of randomized patients) and subsequently within each tertile, which is common in CV outcome trials enrolling Westernized patients. In addition, event rates were substantially lower in females compared to males.

Table 61: Stratified Analysis of Time to the Primary Endpoint from Date of Randomization by Combined Highest Tertile for Baseline TG and Lowest Tertile for Baseline HDL-C, Overall and Sex-Specific (ITT Population)

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
Overall (Males and Females)			
Highest tertile for baseline TG and lowest tertile for baseline HDL-C (Yes)	118/619 (19.1)	165/618 (26.7)	0.8085
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0009	
HR (95% CI) AMR101/Placebo		0.670 (0.528 – 0.849)	
Highest tertile for baseline TG and lowest tertile for baseline HDL-C (No)	247/1516 (16.3)	343/1514 (22.7)	
Treatment Comparison[1]			
P-value from Log-Rank Test		<0.0001	
HR (95% CI) AMR101/Placebo		0.679 (0.577 – 0.800)	
Males			
Highest tertile for baseline TG and lowest tertile for baseline HDL-C (Yes)	90/453 (19.9)	130/451 (28.8)	0.5049
Treatment Comparison[1]			
P-value from Log-Rank Test		0.0008	
HR (95% CI) AMR101/Placebo		0.632 (0.482 – 0.829)	
Highest tertile for baseline TG and lowest tertile for baseline HDL-C (No)	202/1114 (18.1)	269/1089 (24.7)	

Primary Endpoint Statistic	AMR101 n/N (%)	Placebo n/N (%)	Interaction P-value[2]
Treatment Comparison[1]			
P-value from Log-Rank Test		<0.0001	
HR (95% CI) AMR101/Placebo		0.693 (0.577 – 0.832)	
Females			
Highest tertile for baseline TG and lowest tertile for baseline HDL-C (Yes)	29/185 (15.7)	33/198 (16.7)	0.5823
Treatment Comparison[1]			
P-value from Log-Rank Test		0.7906	
HR (95% CI) AMR101/Placebo		0.934 (0.564 – 1.547)	
Highest tertile for baseline TG and lowest tertile for baseline HDL-C (No)	59/431 (13.7)	69/412 (16.7)	
Treatment Comparison[1]			
P-value from Log-Rank Test		0.1132	
HR (95% CI) AMR101/Placebo		0.755 (0.533 – 1.070)	

Abbreviations: CI = confidence interval; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; ITT= Intent-to-Treat; TG = triglycerides.

1 Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

2 P-value for treatment by the subgroup interaction is reported from a Cox proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

[0746] Other Subgroup Analyses:

[0747] The same subgroup analyses were performed for the key secondary endpoint as for the primary endpoint. For the interaction terms, as for the primary endpoint, a p-value <0.15 was considered significant, indicating that the subgroup interaction may have impacted treatment benefit. As noted for the primary endpoint subgroup analyses, per study design, subgroup analyses are underpowered to detect statistically significant results within each individual subgroup, particularly when a subgroup represents less than 50% of the enrolled population, and when a subgroup has low event rates. In addition, a significant subgroup interaction p-value does not necessarily denote a lack of effect in one subgroup, but instead, simply differential effects across subgroups.

[0748] A forest plot of the analyses of the key secondary endpoint by the subgroups of geographic region, CV risk category, baseline ezetimibe use, sex, and age group is presented in Figure 63. As indicated by point estimates of the HRs sitting to the left of the unity line (HR= 1), results were generally consistent with the key secondary endpoint analyses, i.e., the treatment benefit of AMR101 (a significantly lower risk of hard MACE events [CV death, nonfatal MI, and nonfatal stroke]) was generally consistent across these subgroups, and non-significant interaction p-values were observed for subgroup analyses by region, CV risk category, ezetimibe use, and sex.

[0749] For the <65 years subgroup, a key secondary endpoint event occurred in 9.0% (200/2232) of patients in the AMR101 group, as compared with 13.3% (290/2184) of patients in the placebo group (HR of0.652 [95% CI: 0.544 to 0.781]). For the ≥65 years subgroup, a key secondary endpoint event occurred in 13.9% (259/1857) of patients in the AMR101 group, as compared with 16.6% (316/1906) of patients in the placebo group (HR of 0.824 [95% CI: 0.699 to 0.972]). The interaction p-value was significant (p=0.0589), suggesting that while both subsets derive benefit regardless of age above or below 65 years, patients <65 years of age may experience greater treatment benefit with AMR101.

[0750] A forest plot of the analyses of the key secondary endpoint by the subgroups of white vs non-white, baseline diabetes, baseline statin intensity, baseline TG :2:200 vs <200 mg/dL, baseline TG ≥150 vs <150 mg/dL, and baseline TG ≥200 mg/dL and HDL-C ≤35 mg/dL is presented in Figure 64. As indicated by point estimates of the HRs sitting to the left of the unity line (HR= 1), results were generally consistent with the key secondary endpoint analyses, i.e., the treatment benefit of AMR101 (a significantly lower risk of hard MACE events [CV death, nonfatal MI, and nonfatal stroke]) was generally consistent across these subgroups. As with the subgroup analyses of the primary endpoint, the exception was for patients on statins of low intensity at baseline, for which the point estimate of the HR crossed to the right of the unity line (1.200), but this subgroup had a small sample size (6.4% of randomized patients) and a low event rate (69 events across the subgroup). All other individual subgroups reached significance.

[0751] For subgroup analyses of the key secondary endpoint, the interaction p-value for white vs non-white was significant. For white patients, a key secondary endpoint event occurred in 11.3% (418/3691) of patients in the AMR101 group, as compared with 14.6% (538/3688) of patients in the placebo group (HR of 0.758 [95% CI: 0.667 to 0.861]).

For non-white patients, a key secondary endpoint event occurred in 10.3% (41/398) of patients in the AMR101 group, as compared with 17.0% (68/401) of patients in the placebo group (HR of 0.554 [95% CI: 0.376 to 0.818]). The interaction p-value was significant (p=0.1327), suggesting that while both white and non-white patients derive benefit, non-white patients may experience greater treatment benefit with AMR101. However, the sample size for non-white patients was disproportionately small (9.8% of 8179 randomized patients), which may have impacted the interaction p-value.

[0752] For subgroup analyses of the key secondary endpoint, the interaction p-value was not significant for patients with/without baseline TG ≥200 mg/dL and HDL-C ≤35 mg/dL. Of note, the interaction p-values for isolated TG were not significant for patients with baseline TG ≥150 mg/dL vs TG <150 mg/dL, or for patients with baseline TG ≥200 mg/dL vs TG <200 mg/dL, suggesting consistent benefit with AMR101 in the key secondary endpoint regardless of baseline TG level within the study population.

[0753] A forest plot of the analyses of the key secondary endpoint by the subgroups of US vs non-US, baseline hsCRP ≤2 vs >2 mg/L, baseline hsCRP ≤3 vs >3 mg/L, baseline eGFR, baseline LDL-C (derived) by tertiles, and baseline HDL-C by tertiles is presented in Figure 65. As indicated by point estimates of the HRs sitting to the left of the unity line (HR= 1), results were generally consistent with the key secondary endpoint analyses, i.e., the treatment benefit of AMR101 (a significantly lower risk of hard MACE events [CV death, nonfatal MI, and nonfatal stroke]) was generally consistent across these subgroups. All individual subgroups reached significance, and no interaction p-values reached significance.

[0754] For subgroup analyses of the primary endpoint, the interaction p-value was not significant for patients with baseline hsCRP ≤2 mg/L vs patients with baseline hsCRP >2 mg/L or for US vs non-US patients.

[0755] A forest plot of the analyses of the key secondary endpoint by the subgroups of baseline apo B by tertiles, non-HDL-C by tertiles, and TG by tertiles is presented in Figure 66. As indicated by point estimates of the HRs sitting to the left of the unity line (HR= 1), results were generally consistent with the key secondary endpoint analyses, i.e., the treatment benefit of AMR101 (a significantly lower risk of hard MACE events [CV death, nonfatal MI, and nonfatal stroke]) was generally consistent across these subgroups. All individual subgroups reached significance, with the exception of the TG middle tertile (>190 to ≤250 mg/dL).

Conclusion

[0756] In this study of statin-treated patients with elevated TG levels and CVD or diabetes in combination with at least one additional risk factor for CVD, the primary endpoint was the time from randomization to the first occurrence of any component of the composite of the following clinical events: CV death, nonfatal MI (including silent MI; ECGs were performed annually for the detection of silent Mis), nonfatal stroke, coronary revascularization, or unstable angina determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization. A primary endpoint event occurred in 17.2% of patients in the AMR101 group, as compared with 22.0% of patients in the placebo group (HR of 0.752 [95% CI: 0.682 to 0.830; p=0.00000001]; RRR of 24.8% and NNT of 21). Thus, the primary endpoint was met, demonstrating a substantial and statistically significantly lower risk of major adverse CV events with AMR101 than with placebo. The AMR101 and placebo Kaplan-Meier curves begin to separate at approximately one year after randomization.

[0757] The key secondary endpoint was the time from randomization to the first occurrence of the composite of CV death, nonfatal MI (including silent MI), or nonfatal stroke (i.e., hard MACE endpoint). A key secondary endpoint event occurred in 11.2% of patients in the AMRI0I group as compared with 14.8% of patients in the placebo group (HR of 0.735 [95% CI: 0.651 to 0.830; p=0.0000006]; RRR of 26.5% and NNT of 28). Thus, the key secondary endpoint was also met, demonstrating a substantial and statistically significantly lower risk of hard MACE events with AMR101 than with placebo. The AMR101 and placebo Kaplan-Meier curves begin to separate at approximately 1.75 years after randomization.

[0758] In addition, substantial and statistically significant differences between AMR101 and placebo in favor of AMR101 were observed in each of the individual components of the primary and key secondary endpoints, including a 20% RRR in CV death (HR of 0.803 [95% CI: 0.657 to 0.981; p=0.0315]).

[0759] Subgroup analyses of the primary and key secondary endpoints suggest generally consistent benefit of AMR101 treatment across many pre-specified subgroups.

[0760] The effects of AMR101 were also generally consistent across other secondary endpoints. All other secondary endpoints following the pre-specified hierarchical testing procedures demonstrated statistically significantly lower incidences of fatal and nonfatal ischemic events in the AMR101 group than in the placebo group,

with the exception of the final pre-specified secondary endpoint of total mortality. Statistically significant reductions in select secondary endpoints for AMR101 versus placebo included:

- Composite of CV death or nonfatal MI (9.6% vs 12.4%; HR of 0.753 [95% CI: 0.660 to 0.859; p<0.0001])
- CV death (4.3% vs 5.2%; HR of 0.803 [95% CI: 0.657 to 0.981; p=0.0315])
- Fatal or nonfatal MI (6.1 % vs 8.7%; HR of 0.688 [95% CI: 0.585 to 0.808; p<0.0001])
- Fatal or nonfatal stroke (2.4% vs 3.3%; HR of 0.720 [95% CI: 0.555 to 0.934; p=0.0129])

[0761] Total mortality, the final secondary endpoint in the pre-specified hierarchy, was the only endpoint that did not reach statistical significance, although it trended toward reduction (HR of 0.870 [95% CI: 0.739 to I.023; p=0.0915]).

[0762] Also consistent with the primary and key secondary endpoint findings, clinically meaningful reductions were observed in the tertiary endpoints of total primary endpoint events (HR of 0.68 or rate ratio of 0.69) and total key secondary endpoint events (HR or rate ratio of 0.71). A clinically meaningful lower risk in the AMR101 group versus the placebo group was observed across other tertiary endpoints, including four composite endpoints; all coronary revascularizations (HR of 0.66 [95% CI: 0.58 to 0.76]; p<0.0001) and individually for emergent, urgent, and elective revascularizations; cardiac arrests (HR of 0.52 [95% CI: 0.31 to 0.86]; p=0.0105); sudden cardiac deaths (HR of 0.69 [95% CI: 0.50 to 0.96]; p=0.0259); and ischemic strokes (HR of 0.64 [95% CI: 0.49 to 0.85]; p=0.002).

[0763] The REDUCE-IT study was not designed to distinguish the relative contribution of changes in biomarkers on CV outcomes. Nonetheless, clinically meaningful reductions in lipid and inflammatory biomarkers were observed with AMR101 compared to placebo, including TG, LDL-C, non-HDL-C, apo B, and hsCRP.

[0764] As indicated in subgroup analyses of the primary and key secondary endpoints, treatment with AMR101 appeared to provide consistent benefit compared to placebo regardless of baseline TG above or below 150 mg/dL or 200 mg/dL, respectively. Although patients with higher TG levels might still define a higher risk population versus those with normal TG levels, treatment with AMR101 was consistently beneficial across tested baseline TG subgroups. Patients with or without atherogenic dyslipidemia at

baseline (TG ≥200 mg/dL and HDL-C ≤35 mg/dL) both had significant reductions in the primary and key secondary endpoints, and the interaction p-value for the primary endpoint also reached significance, suggesting patients with atherogenic dyslipidemia may experience additional benefit of AMR101 treatment.

[0765] REDUCE-IT patients represent a population at significant risk for CV events, as suggested by the annualized placebo event rate (5.74%), which was expected per study design and is consistent with historical data for similar at-risk statin-treated patient populations. REDUCE-IT patients had well-controlled LDL-C (75 mg/dL median baseline) and observed substantial and consistent risk reduction in the primary and key secondary endpoints across patient subgroups, suggesting benefit to a broad patient population. Overall, treatment with AMR101 in this population of statin-treated patients with elevated TG levels and other CVD risk factors resulted in a significantly and consistently reduced risk of major adverse CV events compared to placebo.

EXAMPLE 7: The Impact of Icosapent Ethyl on Atrial Fibrillation and Flutter

[0766] The objective of the following study was to determine how icosapent ethyl affected the incidence of atrial fibrillation and/or flutter in patients from the REDUCE-IT trial, as described in Example 1.

[0767] The term “on-therapy” patients refers to all patients who have an active prescription for a AMR101 during any day within a specified time period. On therapy patients include both patients who have a prescription dispensed during the specified time period and patients who filled a prescription in a prior period whose days’ supply takes them into the specified period.

[0768] The REDUCE-IT clinical trial did not exclude patients having a history of atrial arrhythmias. Rather, 9.2% of the enrolled patients had a history of atrial fibrillation and/or flutter. The on-treatment incidence of atrial fibrillation and/or flutter was relatively low. For example, the absolute risk difference in positively adjudicated events treatment groups was 0.3% at 6 months in the icosapent ethyl and placebo group. In addition, the cumulative absolute risk difference over the course of the study remained less than 1% through 3 years and less than or equal to 2% across the fully study population (i.e., <1% to ≤2%). The adverse events were 5.8% TEAEs in the icosapent ethyl group as compared to 4.5% in the placebo group and both groups had 0.5% SEAs. A summary of data from this study is provided in Tables 62-75 and Figures 67-78 as described below.

[0769] Table 62 shows the treatment comparison for additional tertiary endpoints in the intent-to-treat (ITT) population for the icosapent ethyl and placebo groups.

Table 62. Treatment comparison for additional tertiary endpoints in the intent-to-treat (ITT) population for the icosapent ethyl and placebo groups

Additional Tertiary Endpoint Events (ITT).				
			Treatment Comparison[1]	
Endpoint Event, n (%)[2]	Icosapent ethyl n/N (%)	Placebo n/N (%)	HR (95% CI) Icosapent Ethyl / Placebo	P-value from Log-Rank Test
Newly Emergent CHF	169/4089 (4.1)	176/4090 (4.3)	0.95 (0.77 - 1.17)	0.6260
Newly Emergent CHF Requiring Hospitalization	141/4089 (3.4)	144/4090 (3.5)	0.97 (0.77 - 1.22)	0.7810
Transient Ischemic Attack	64/4089 (1.6)	48/4090 (1.2)	1.32 (0.91 - 1.92)	0.1459
Amputation for PVD	22/4089 (0.5)	21/4090 (0.5)	1.04 (0.57 - 1.89)	0.9053
Carotid Revascularization	31/4089 (0.8)	26/4090 (0.6)	1.18 (0.70 - 1.98)	0.5399
Coronary Revascularization[3]	376/4089 (9.2)	544/4090 (13.3)	0.66 (0.58 - 0.76)	<0.0001
Emergent Revascularization	41/4089 (1.0)	65/4090 (1.6)	0.62 (0.42 - 0.92)	0.0158
Urgent Revascularization	181/4089 (4.4)	268/4090 (6.6)	0.66 (0.54 - 0.79)	<0.0001
Elective Revascularization	194/4089 (4.7)	278/4090 (6.8)	0.68 (0.57 - 0.82)	<0.0001
Salvage Revascularization	0/4089 (0.0)	2/4090 (0.0)	0.00 (0.00 - 0.00)	0.1563
Cardiac Arrhythmia Requiring Hospitalization of ≥24 Hours	188/4089 (4.6)	154/4090 (3.8)	1.21 (0.97 - 1.49)	0.0856
Cardiac Arrest	22/4089 (0.5)	42/4090 (1.0)	0.52 (0.31 - 0.86)	0.0105
Sudden Cardiac Death	61/4089 (1.5)	87/4090 (2.1)	0.69 (0.50 - 0.96)	0.0259
Ischemic Stroke	80/4089 (2.0)	122/4090 (3.0)	0.64 (0.49 - 0.85)	0.0020
Hemorrhagic Stroke	13/4089 (0.3)	10/4090 (0.2)	1.28 (0.56 - 2.93)	0.5507
New Onset Type 2 Diabetes[4]	65/1695 (3.8)	63/1697 (3.7)	1.04 (0.73 - 1.47)	0.8361
New Onset Hypertension[5]	13/4089 (0.3)	15/4090 (0.4)	0.86 (0.41 - 1.80)	0.6847
Peripheral Artery Disease	156/4089 (3.8)	159/4090 (3.9)	0.97 (0.78 - 1.21)	0.7604

Abbreviations: AE = adverse event; CHF = congestive heart failure; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; PVD = peripheral vascular disease.

Note: The number of patients with event (n) is the number of patients with the event in the ITT population within each treatment group (N).

[1] Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox Proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

[2] Based on a patient's first post-randomization occurrence of the specified endpoint event.

[3] Coronary revascularization was defined as the composite of emergent, urgent, elective, and salvage revascularization.
[4] Excludes patients with Type 1 or Type 2 diabetes at baseline.
[5] As per the Clinical Endpoint Committee Charter, new onset of hypertension was determined programmatically. To identify new onset of hypertension cases, the hypertension standardized MedDRA query was used to search all AEs and negatively adjudicated endpoints. All patients who had hypertension reported on the Cardiovascular History page are excluded.

[0770] Figure 67 shows the pre-specified hierarchical endpoint testing. The data show the clinical sequelae related to atrial fibrillation and/or flutter, emphasizing the relative risk reductions (RRR) for each of the endpoints. For example, the RRR for primary compositive endpoints was 25%; key secondary endpoints was 26%; cardiovascular death or nonfatal myocardial infarction was 25%; fatal or nonfatal myocardial infarction was 31%; urgent or emergent revascularization was 35%; cardiovascular death was 29%; hospitalization for unstable angina was 32%; fatal or nonfatal stroke was 28%; and total mortality, nonfatal myocardial infarction, or nonfatal stroke was 23%.

[0771] Figure 68 is a forest plot showing patients from both the icosapent ethyl and placebo group who, at baseline, had a history of atrial fibrillation and/or flutter that required ≥ 24 h hospitalization for the ITT population.

[0772] Figures 69A-69C are plots showing the atrial fibrillation and/or flutter and bleeding overlap between the placebo and icosapent ethyl groups. Figure 69A shows the atrial fibrillation and/or flutter and bleeding overlap between the placebo and the icosapent ethyl groups as well as the risk difference between the two groups for the ITT population. Figure 69B and 69C are plots showing the atrial fibrillation and/or flutter and bleeding overlap between the placebo and icosapent ethyl groups for the secondary prevention cohort and high-risk primary prevention cohort, respectively. As demonstrated in Figures 69A-69C, the additional events that occurred beyond the placebo occurred at low rates. The data include all bleeding events (e.g., TEAEs and hemorrhagic stroke) and positively adjudicated atrial fibrillation and/or flutter endpoints.

[0773] Post hoc analyses were performed on the primary risk and key secondary risk composite endpoints as shown in Table 63. Table 63 shows the impact of atrial fibrillation and/or flutter and bleeding risks for each of the endpoints for the ITT population.

Table 63. Impact of atrial fibrillation and/or flutter and bleeding risks for each of the endpoints for the ITT population.

Summary of Post Hoc Analyses of the Primary+ Risk and Key Secondary+ Risk Composite Endpoints						
					Rate/1000 pt yrs	
Endpoint	Icosapent Ethyl (N=4089)	Placebo (N=4090)	HR (95% CI)	P-value	Icosapent Ethyl	Placebo
Primary + AFib/AFlutter	785 (19.2%)	946 (23.1%)	0.803 (0.731, 0.883)	<0.0001	49.0	60.7
Key Secondary + AFib/AFlutter	552 (13.5%)	660 (16.1%)	0.818 (0.731, 0.916)	0.0005	33.1	40.3
Primary + Serious Bleeding	775 (19.0%)	950 (23.2%)	0.785 (0.714, 0.863)	<0.0001	48.2	61.0
Key Secondary + Serious Bleeding	539 (13.2%)	664 (16.2%)	0.789 (0.704, 0.884)	<0.0001	32.1	40.6
Primary + AFib/AFlutter + Serious Bleeding	850 (20.8%)	992 (24.3%)	0.830 (0.757, 0.910)	<0.0001	53.5	64.2
Key Secondary + AFib/AFlutter + Serious Bleeding	625 (15.3%)	715 (17.5%)	0.855 (0.768, 0.952)	0.0042	37.8	44.1
AFib/AFlutter + MI + Stroke + Cardiac Arrest + Sudden Cardiac Death	491 (12.0%)	609 (14.9%)	0.789 (0.701, 0.889)	<0.0001	29.4	37.2
Note: All components presented on the table except serious bleeding are adjudicated by CEC. Note: The number of subjects with event (n) is the number of subjects with the event in the ITT Population within each treatment group (N). Rate per 1000 patient years (pt-yrs) is 1000 x n/pt-yrs subjects at-risk. Log-Rank test statistic and p-value are reported from a Kalpan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.						

[0774] One of the adjudicated endpoints for this study included atrial fibrillation that required hospitalization of greater than 24 hours in patients with baseline characteristics shown in Table 64. The clinical trial showed that stroke, myocardial infarction, cardiac arrest, and sudden cardiac death were reduced with consistent results in those with a history of atrial fibrillation at baseline. Figures 70A and 70B are Kaplan-Meier curves from time to endpoint of atrial fibrillation and/or flutter requiring hospitalization of greater than 24 hours by treatment arm for the ITT population that corroborates the findings that cardiovascular risks were reduced in patients having a history of atrial fibrillation at baseline as compared to placebo control. This data provides a significant *p* value of 0.0037 and a HR of 1.5000 (1.138, 1.976).

Table 64. Data showing the adjudicated endpoint for atrial fibrillation requiring hospitalization ≥24 hours

	Icosapent ethyl (N=4089) n (%)	Placebo (N=4090) n (%)	P-Value
Atrial fibrillation/flutter AEs	236 5.8)	183 (4.5)	0.008
Serious Afib/Aflutter AEs	22 (0.5)	20 (0.5)	0.76
Positively adjudicated Afib/Aflutter requiring ≥24 hours hospitalization	127 (3.1)	84 (2.1)	0.004

[0775] Table 65 shows the multivariate cox regression of the positively adjudicated endpoint of atrial fibrillation and/or flutter to identify significant baseline covariants by stepwise selection for the ITT population. Table 66 shows the multivariate cox regression on atrial fibrillation and/or atrial flutter TEAEs (excluding endpoints). Some of the differences in the baseline characteristics associated in patients with or without atrial fibrillation and/or flutter were significant; however, the differences did not affect the overall conclusions of the trial.

Table 65. Multivariate cox regression of the positively adjudicated endpoint of atrial fibrillation and/or flutter

	Stepwise Selected Covariate		
	Covariates[1]	Significance P-value[2]	HR (95% CI) (Icosapent Ethyl/Placebo)
Stratified by geographic region, CV risk category, and use of ezetimibe	Age (yr) at Baseline (<65, ≥65)	<0.0001	1.516 (1.151, 1.997)
	hsCRP at Baseline by 2*std deviation (≤1.27, >1.27)	0.0011	1.505 (1.143, 1.983)
	Overall (with all selected covariates)		1.520 (1.154, 2.003)
Non-Stratified	Age (yr) at Baseline (<65, ≥65)	<0.0001	1.518 (1.152, 1.999)
	Race (White, Non-White)	0.0404	1.503 (1.141, 1.980)
	hsCRP at Baseline by 2*std deviation (≤1.27, >1.27)	0.0013	1.507 (1.144, 1.985)
	US vs. Non-US	0.0084	1.505 (1.143, 1.983)
	Overall (with all selected covariates)		1.526 (1.158, 2.010)

Abbreviations: CI = confidence interval; CV = cardiovascular; hsCRP = high-sensitivity C-reactive protein; HR = hazard ratio; ITT = Intention-to-Treat; std = standard; US = United States; yr = year.
Baseline variables considered: Age, Sex, Race, Cardiovascular risk stratum, Triglycerides (150, 150-200, ≥200), Triglycerides by median (≤216, >216), LDL-C (≤70, >70), LDL-C by mean (<76.21, ≥76.21), hs-CRP by 2*std deviation (≤1.27, >1.27), Ezetimibe use, Location (Westernized, Eastern Europe, Asia Pacific), Western region vs. other regions, US vs. Non-US, Baseline statin intensity.
[1] Covariates are from a Cox proportional hazard model with treatment as factor and the identified significant baseline variable as covariate.
[2] P-value for significance of the covariate is from the final model per a stepwise selection process using the Cox proportional hazard model with p-value of 0.05 and 0.1 for a covariate to enter and stay in the model, respectively.

Table 66. Multivariate cox regression on atrial fibrillation and/or atrial flutter TEAEs

	Stepwise Selected Covariate		
	Covariates[1]	**Significance P-value[2]**	**HR (95% CI) (Icosapent Ethyl/Placebo)**
Stratified by geographic region, CV risk category, and use of ezetimibe	Age (yr) at Baseline (<65, ≥65)	<0.0001	1.295 (1.068, 1.571)
	Sex	0.0231	1.281 (1.056, 1.553)
	Race (White, Non-White)	0.0073	1.284 (1.058, 1.557)
	Overall (with all selected covariates)		1.292 (1.065, 1.567)
Non-Stratified	Age (yr) at Baseline (<65, ≥65)	<0.0001	1.296 (1.069, 1.573)
	Sex	0.0051	1.281 (1.056, 1.554)
	Race (White, Non-White)	0.0002	1.285 (1.059, 1.558)
	CV Risk Stratum	0.0466	1.283 (1.058, 1.556)
	Region (Western, Other)	<0.0001	1.284 (1.059, 1.558)
	Overall (with all selected covariates)		1.293 (1.066, 1.569)

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = Intention-to-Treat; TEAE = treatment emergent adverse event; yr = year.
Baseline variables considered: Age, Sex, Race, Cardiovascular risk stratum, Triglycerides (150, 150-200, ≥200), Triglycerides by median (≤216, >216), LDL-C (≤70, >70), LDL-C by mean (<76.21, ≥76.21), hs-CRP by 2*std deviation (≤1.27, >1.27), Ezetimibe use, Location (Westernized, Eastern Europe, Asia Pacific), Western region vs. other regions, US vs. Non-US, Baseline statin intensity.
[1] Covariates are from a Cox proportional hazard model with treatment as factor and the identified significant baseline variable as covariate.
[2] P-value for significance of the covariate is from the final model per a stepwise selection process using the Cox proportional hazard model with p-value of 0.05 and 0.1 for a covariate to enter and stay in the model, respectively.

[0776] Table 67 shows the time to first onset of atrial fibrillation and/or flutter by 6 month intervals for the ITT population. The 6 month incidence was 0.3% in each treatment group and the cumulative incidence overtime remained less than 2%.

Table 67. Time to first onset of atrial fibrillation and/or flutter by 6 month intervals for the ITT population

	Cumulative Incidence Rate[1], % (SE)		
Time (Days)	**Icosapent Ethyl (N=4089)**	**Placebo (N=4090)**	**Icosapent Ethyl-Placebo Risk Diff., % (95% CI)**
At 0.5 years (Day 180)	0.3 (0.08)	0.3 (0.08)	-0.00 (-0.23, 0.23)
At 1 year (Day 360)	0.6 (0.12)	0.4 (0.10)	0.20 (-0.12, 0.51)
At 1.5 years (Day 540)	1.1 (0.16)	0.6 (0.12)	0.51 (0.11, 0.91)
At 2 years (Day 720)	1.4 (0.19)	0.8 (0.15)	0.59 (0.12, 1.06)
At 2.5 years (Day 900)	1.9 (0.22)	1.1 (0.17)	0.78 (0.24, 1.32)
At 3 years (Day 1080)	2.3 (0.24)	1.4 (0.20)	0.83 (0.22, 1.44)
At 3.5 years (Day 1260)	2.6 (0.26)	1.4 (0.20)	1.17 (0.52, 1.81)
At 4 years (Day 1440)	2.9 (0.28)	1.7 (0.22)	1.23 (0.53, 1.93)
At 4.5 years (Day 1620)	3.1 (0.29)	2.1 (0.25)	1.00 (0.25, 1.74)
At 5 years (Day 1800)	3.4 (0.31)	2.4 (0.27)	1.08 (0.27, 1.89)
At 5.5 years (Day 1980)	3.7 (0.35)	2.7 (0.31)	1.00 (0.09, 1.92)
At 6 years (Day 2160)	5.4 (1.03)	3.3 (0.56)	2.07 (-0.23, 4.37)
Note: SE = Standard Error [1] Cumulative incidence rate was estimated based on a Kaplan-Meier analysis.			

[0777] Figure 71 shows the endpoints by emergent atrial fibrillation and/or flutter. The endpoints are by patients with or without on-study atrial fibrillation and/or flutter. As shown in Figure 71, the emergent atrial fibrillation and/or flutter did not substantially alter the primary and key secondary composite analyses. Figure 72 also shows the endpoints by on-study atrial fibrillation and/or flutter and similarly indicates that regardless of whether the patient had atrial fibrillation and/or flutter, the patient exhibited a decrease in a incidence of a primary composite endpoint, secondary composite endpoint, as well as the individual cardiovascular risks of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina.

[0778] Figure 73 shows the summary of endpoints for patients having a history of atrial fibrillation and/or flutter from that ITT population. As shown in Figure 73, a history of atrial fibrillation/flutter also did not substantially alter the primary and key secondary

composite analyses nor the individual risk reductions of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, and unstable angina.

[0779] Table 68A-68B show the bleeding prevalence of risk for patients in the icosapent ethyl and placebo groups. The data indicate that there is an increased prevalence of the risk in the patient population but that the risk is similar for those patients with atrial fibrillation and/or flutter as compared to patients without atrial fibrillation and/or flutter. Most bleeding events associated with emergent atrial fibrillation and/or flutter involved non-serious bleeding, irrespective of prior history of atrial fibrillation and/or flutter. Table 68A shows the bleeding TEAEs (including hemorrhagic stroke) in patients with baseline or post-baseline atrial fibrillation and/or flutter and Table 68B shows bleeding TEAEs (including hemorrhagic stroke) in patients without baseline or post-baseline atrial fibrillation and/or flutter.

Table 68A. The bleeding prevalence of risk for patients in the icosapent ethyl and placebo groups

	Icosapent Ethyl (N=449)	Placebo (N=443)	p-value[2]
Bleeding related disorders[1]	113 (25.2%)	77 (17.4%)	0.0054
Gastrointestinal bleeding	25 (5.6%)	31 (7.0%)	0.4095
Central nervous system bleeding	5 (1.1%	5 (1.1%)	1.0000
Hemorrhagic stroke	3 (0.7%)	1 (0.2%)	0.6242
Other bleeding	91 (20.3%)	49 (11.1%)	0.0002

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
[1] Bleeding-related disorders are identified by the standardized MedDRA queries of "Gastrointestinal haemorrhage," "Central Nervous System haemorrhages and cerebrovascular conditions," and "Haemorrhage terms (excl laboratory terms)."
[2] Fishers Exact test.
Baseline: Atrial Fibrillation/Atrial Flutter history/AE (prerandomization)
Post-Baseline: Atrial Fibrillation or Flutter Requiring Hospitalization of ≥24 hours

Table 68B. The bleeding prevalence of risk for patients in the icosapent ethyl and placebo groups

	Icosapent Ethyl (N=3640)	Placebo (N=3647)	p-value[2]
Bleeding related disorders[1]	381 (10.5%)	335 (9.2%)	0.0702
Gastrointestinal bleeding	102 (2.8%)	85 (2.3%)	0.2086

Central nervous system bleeding	15 (0.4%)	7 (0.2%)	0.0924
Hemorrhagic stroke	10 (0.3%)	9 (0.2%)	0.8234
Other bleeding	285 (7.8%)	263 (7.2%)	0.3286

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

[1] Bleeding-related disorders are identified by the standardized MedDRA queries of "Gastrointestinal haemorrhage," "Central Nervous System haemorrhages and cerebrovascular conditions," and "Haemorrhage terms (excl laboratory terms)."

[2] Fishers Exact test.

Baseline: Atrial Fibrillation/Atrial Flutter history/AE (prerandomization)

Post-Baseline: Atrial Fibrillation or Flutter Requiring Hospitalization of ≥24 hours

[0780] Tables 69-73A-73C include the adjudicated data from the safety population from this study. Specifically, Tables 69-73A-73C show data from the clinically adjudicated arrhythmia sequelae (Table 69), treatment-emergent arrhythmias (Table 70), . incidence of treatment-emergent atrial flutter (Table 71), and the incidence of treatment-emergent atrial fibrillation (Table 72) for the safety population. A summary of the positively and negatively adjudicated cardiac arrhythmia in patients having a history of atrial fibrillation and/or flutter at baseline for the safety population is provided inTables 73A-73C.

Table 69. Clinically adjudicated arrhythmia sequelae for the safety population

Event	Icosapent Ethyl Events n/N (%)	Placebo Events n/N (%)	HR (95% CI)	Log-Rank p-value[1]
Any Stroke	98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55 to 0.93)	0.0129
Transient Ischemic Attack	64/4089 (1.6%)	48/4090 (1.2%)	1.32 (0.91 to 1.92)	0.1459
Any Myocardial Infarction	250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58 to 0.81)	<0.0001
Carotid Revascularization	31/4089 (0.8%)	26/4090 (0.6%)	1.18 (0.70 to 1.98)	0.5399
Coronary Revascularization[2]	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58 to 0.76)	<0.0001
Cardiac Arrest	22/4089 (0.5%)	42/4090 (1.0%)	0.52 (0.31 to 0.86)	0.0105
Sudden Cardiac Death	61/4089 (1.5%)	87/4090 (2.1%)	0.69 (0.50 to 0.96)	0.0259

[1] Log-Rank test statistic and p-value are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

[2] Composite of emergent, urgent, elective, and salvage revascularization.

Table 70. Treatment-emergent arrhythmias for the safety population

	Icosapent Ethyl		Placebo	
Preferred Term[1]	Number of Subjects (N=4089)	Event Rate	Number of Subjects (N=4089)	Event Rate

Atrial fibrillation	215	5.3%	159	3.9%
Ventricular extrasystoles	27	0.7%	48	1.2%
Ventricular tachycardia	12	0.3%	24	0.6%
Ventricular fibrillation	0	0.0%	6	0.1%

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

[1] All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).

Table 71. Incidence of treatment-emergent atrial flutter for the safety population

	Icosapent Ethyl		Placebo	
Preferred Term[1]	**Number of Subjects (N=4089)**	**Event Rate**	**Number of Subjects (N=4089)**	**Event Rate**
Atrial flutter	32	0.8%	26	0.6%
Atrial flutter (Serious)	1	0.0%	3	0.1%

Table 72. Incidence of treatment-emergent atrial fibrillation for the safety population

	Icosapent Ethyl		Placebo	
Preferred Term[1]	**Number of Subjects (N=4089)**	**Event Rate**	**Number of Subjects (N=4089)**	**Event Rate**
Atrial fibrillation	215	5.3%	159	3.9%
Atrial fibrillation (Serious)	21	0.5%	17	0.4%

Table 73A. Positively and negatively adjudicated cardiac arrhythmia in patients having a history of atrial fibrillation and/or flutter at baseline for the safety population

	Event Level		Patient Level	
Category	**Icosapent Ethyl m**	**Placebo m**	**Icosapent Ethyl (N=4089) n (%)**	**Placebo (N=4090) n (%)**
Reported Potential Cardiac Arrythmias[1] [2]	315	292	239 (5.8)	223 (5.5)

Patients with AF History	102	76	72 (1.8)	52 (1.3)
Patients without AF History	213	216	167 (4.1)	171 (4.2)
Adjudicated as AF (with or without Hosp. ≥24 hrs)	179	134	142 (3.5)	109 (2.7)
Patients with AF History	63	42	47 (1.1)	30 (0.7)
Patients without AF History	116	92	95 (2.3)	79 (1.9)
Adjudicated as VT/VF (with or without Hosp. ≥24 hrs)	43	51	36 (0.9)	41 (1.0)
Patients with AF History	11	9	9 (0.2)	5 (0.1)
Patients without AF History	32	42	27 (0.7)	36 (0.9)
Adjudicated as Bradycardia/Heart Block (with or without Hosp. ≥24 hrs)	31	44	29 (0.7)	41 (1.0)
Patients with AF History	7	8	7 (0.2)	8 (0.2)
Patients without AF History	24	36	22 (0.5)	33 (0.8)
Adjudicated as Other Tachycardia (with or without Hosp. ≥24 hrs)	11	13	11 (0.3)	11 (0.3)
Patients with AF History	3	3	3 (0.1)	3 (0.1)
Patients without AF History	8	10	8 (0.2)	8 (0.2)

AF = Atrial Fibrillation/Atrial Flutter; VT/VF = Ventricular Tachycardia/Ventricular Fibrillation; Hosp = Hospitalization.

[1] Includes 2 events (2 in Icosapent Ethyl group) positively adjudicated as cardiac arrhythmia for hospitalization ≥24 hrs with missing type.

[2] Includes 99 events (49 in Icosapent Ethyl and 50 in Placebo groups) negatively adjudicated for cardiac arrhythmia.

Note: n is the number of subjects with event in the ITT Population within each category for each treatment group.

Note: m is the number of events for patients with event in the ITT Population within each category for each treatment group.

Table 73B. Positively and negatively adjudicated cardiac arrhythmia in patients having a history of atrial fibrillation and/or flutter at baseline for the safety population

	Event Level		Patient Level	
Category	**Icosapent Ethyl m**	**Placebo m**	**Icosapent Ethyl (N=4089) n (%)**	**Placebo (N=4090) n (%)**
Positively Adjudicated Cardiac Arrythmias for Hosp. ≥24 hrs[1] [2]	239	200	188 (4.6)	154 (3.8)
Patients with AF History	80	52	61 (1.5)	35 (0.9)
Patients without AF History	159	148	127 (3.1)	119 (2.9)
Positively Adjudicated as AF for Hosp. ≥24 hrs	159	104	127 (3.1)	84 (2.1)

Patients with AF History	59	32	46 (1.1)	24 (0.6)
Patients without AF History	100	72	81 (2.0)	60 (1.5)
Positively Adjudicated as VT/VF for Hosp. ≥24 hrs	41	46	35 (0.9)	37 (0.9)
Patients with AF History	10	9	8 (0.2)	5 (0.1)
Patients without AF History	31	37	27 (0.7)	32 (0.8)
Positively Adjudicated as Bradycardia/Heart Block for Hosp. ≥24 hrs	30	42	28 (0.7)	40 (1.0)
Patients with AF History	7	8	7 (0.2)	8 (0.2)
Patients without AF History	23	34	21 (0.5)	32 (0.8)
Positively Adjudicated as Other Tachycardia for Hosp. ≥24 hrs	7	8	7 (0.2)	7 (0.2)
Patients with AF History	3	3	3 (0.1)	3 (0.1)
Patients without AF History	4	5	4 (0.1)	4 (0.1)

AF = Atrial Fibrillation/Atrial Flutter; VT/VF = Ventricular Tachycardia/Ventricular Fibrillation; Hosp = Hospitalization.
[1] Includes 2 events (2 in Icosapent Ethyl group) positively adjudicated as cardiac arrhythmia for hospitalization ≥24 hrs with missing type.
[2] Includes 99 events (49 in Icosapent Ethyl and 50 in Placebo groups) negatively adjudicated for cardiac arrhythmia.
Note: n is the number of subjects with event in the ITT Population within each category for each treatment group.
Note: m is the number of events for patients with event in the ITT Population within each category for each treatment group.

Table 73C. Positively and negatively adjudicated cardiac arrhythmia in patients having a history of atrial fibrillation and/or flutter at baseline for the safety population

	Event Level		**Patient Level**	
Category	**Icosapent Ethyl m**	**Placebo m**	**Icosapent Ethyl (N=4089) n (%)**	**Placebo (N=4090) n (%)**
Negatively Adjudicated Cardiac Arrythmias for Hosp. ≥24 hrs[1] [2]	76	92	70 (1.7)	85 (2.1)
Patients with AF History	22	24	21 (0.5)	20 (0.5)
Patients without AF History	54	68	49 (1.2)	65 (1.6)
Adjudicated as AF (without Hosp. ≥24 hrs)	20	30	19 (0.5)	29 (0.7)
Patients with AF History	4	10	4 (0.1)	9 (0.2)
Patients without AF History	16	20	15 (0.5)	20 (0.5)
Adjudicated as VT/VF (without Hosp. ≥24 hrs)	2	5	2 (0.0)	5 (0.1)
Patients with AF History	1	0	1 (0.0)	0 (0.0)

Patients without AF History	1	5	1 (0.0)	5 (0.1)
Adjudicated as Bradycardia/Heart Block (without Hosp. ≥24 hrs)	1	3	1 (0.0)	1 (0.0)
Patients with AF History	0	0	0 (0.0)	0 (0.0)
Patients without AF History	1	2	1 (0.0)	1 (0.0)
Adjudicated as Other Tachycardia (without Hosp. ≥24 hrs)	4	5	4 (0.1)	4 (0.1)
Patients with AF History	0	0	0 (0.0)	0 (0.0)
Patients without AF History	4	5	4 (0.1)	4 (0.1)

AF = Atrial Fibrillation/Atrial Flutter; VT/VF = Ventricular Tachycardia/Ventricular Fibrillation; Hosp = Hospitalization.
[1] Includes 2 events (2 in Icosapent Ethyl group) positively adjudicated as cardiac arrhythmia for hospitalization ≥24 hrs with missing type.
[2] Includes 99 events (49 in Icosapent Ethyl and 50 in Placebo groups) negatively adjudicated for cardiac arrhythmia.
Note: n is the number of subjects with event in the ITT Population within each category for each treatment group.
Note: m is the number of events for patients with event in the ITT Population within each category for each treatment group.

[0781] Figures 74-76 summarize the data shown in Tables 73A-73C and include a forest plot showing positively adjudicated atrial fibrillation or flutter by baseline history of atrial fibrillation or flutter for the high-risk primary prevention cohort (Figure 74), a forest plot showing positively adjudicated atrial fibrillation or flutter by baseline history of atrial fibrillation or flutter (Figure 75), and a forest plot showing atrial fibrillation an/d or flutter requiring hospitalization of greater than 24 hours by baseline for the ITT (Figure 76).

[0782] Table 74 shows the baseline or on-study medication use by type in patients with on-study atrial fibrillation/atrial flutter events for the ITT population. Table 75 shows the baseline or on-study medication use by type in subjects was a history of atrial fibrillation and/or flutter for the ITT population.

Table 74. Baseline or on-study medication use by type in patients with on-study atrial fibrillation/atrial flutter events for the ITT population

Medication Category	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Fisher's Exact P-value
Subjects with at least one Atrial Fibrillation/Atrial Flutter event	321	248	
Anticoagulant	276/321 (86.0%)	211/248 (85.1%)	0.8101
No Anticoagulant	45/321 (14.0%)	37/248 (14.9%)	
Antiplatelet	277/321 (86.3%)	209/248 (84.3%)	0.5497
One antiplatelet	152/321 (47.4%)	118/248 (47.6%)	1.0000

Two or more antiplatelets	125/321 (38.9%)	91/248 (36.7%)	0.6020
No Antiplatelet	44/321 (13.7%)	39/248 (15.7%)	
Anticoagulant plus antiplatelet	233/321 (72.6%)	179/248 (72.2%)	0.9249
No (Anticoagulant plus Anti-platelet)	88/321 (27.4%)	69/248 (27.8%)	
Antithrombotic	32/321 (99.7%)	241/248 (97.2%)	0.0241
No Antithrombotic	1/321 (0.3%)	7/248 (2.8%)	
Note: Percentages are based on the number of ITT subjects with Atrial Fibrillation/Atrial Flutter events per treatment group.			

Table 75. Baseline or on-study medication use by type in subjects was a history of atrial fibrillation and/or flutter for the ITT population

Medication Category	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Fisher's Exact P-value
Subjects with Baseline History of Atrial Fibrillation/Atrial Flutter	368	383	
Anticoagulant	286/328 (77.7%)	298/383 (77.8%)	1.0000
No Anticoagulant	82/328 (22.3%)	85/383 (22.2%)	
Antiplatelet	239/328 (64.9%)	243/383 (63.4%)	0.7036
One antiplatelet	157/328 (42.7%)	173/383 (45.2%)	1.5085
Two or more antiplatelets	82/328 (22.3%)	70/383 (18.3%)	0.1745
No Antiplatelet	129/328 (35.1%)	140/383 (36.6%)	
Anticoagulant plus antiplatelet	163/328 (44.3%)	166/383 (43.3%)	0.8254
No (Anticoagulant plus Anti-platelet)	205/328 (55.7%)	217/383 (56.7%)	
Antithrombotic	362/328 (98.4%)	375/383 (97.9%)	0.7891
No Antithrombotic	6/328 (1.6%)	8/383 (2.1%)	
Note: Percentages are based on the number of ITT subjects with Atrial Fibrillation/Atrial Flutter events per treatment group.			

[0783] Figures 77-78 show the risk and benefits correlations of the administration of AMR101 based on the patient's age and indicate that risks for atrial fibrillation and bleeding are greater in patients who are 65 years or older relative (Figure 77) to patients who are less than 65 years (Figure 78). However, as shown in Figures 77-78 regardless of the patient's age and associated increase in atrial fibrillation or bleeding events, the patient nevertheless exhibited a reduction in cardiovascular events.

[0784] In conclusion, this study showed that there were no increases in associated adjudicated events with RRR in stroke, myocardial infarction, cardiac arrest, and sudden cardiac death in patients with on-treatment atrial fibrillation or flutter and/or patients with a history of atrial fibrillation or flutter. There were similarly no changes in new CHF or hospitalization for new CHF. Patients with atrial fibrillation and/or flutter history may experience more bleeding and positively-adjudicated atrial fibrillation with icosapent ethyl. However, trends were consistent with or without atrial fibrillation and/or flutter and most bleeding events were non-serious. Having history or on-treatment atrial fibrillation and/or flutter do not appear to affect cardiovascular benefit as observed in the primary and key secondary endpoints. Furthermore, including adjudicated atrial fibrillation and/or flutter and/or bleeding in primary and key secondary analyses did not alter the study conclusion. Therefore, while atrial fibrillation and/or flutter (and bleeding SAEs) are clinically important, they may not be as consequential as the primary endpoint events.

EXAMPLE 8: Safety Analysis of the REDUCE-IT Trial

[0785] The objective of the following example was to do an in-depth safety evaluation of the REDUCE-IT trial, as described in Example 1.

Adverse Events:

[0786] An overview of TEAEs is presented in Table 76, overall and by treatment group. Overall, 81.8% (3343/4089) and 81.3% (3326/4090) of patients in the AMR101 and placebo groups, respectively, experienced at least one TEAE. The proportions of patients who experienced the categories of TEAEs listed in Table 64 were similar between the AMR101 and placebo groups.

Table 76. Overview of Treatment-Emergent Adverse Events, Overall and by Treatment Group (Safety Population)

	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Patients with at least 1 TEAE, n (%)	3343 (81.8)	3326 (81.3)	6669 (81.5)
Severe TEAE	805 (19.7)	816 (20.0)	1621 (19.8)
Study Drug-Related TEAE[1]	514 (12.6)	499 (12.2)	1013 (12.4)
Serious TEAE	1252 (30.6)	1254 (30.7)	2506 (30.6)
Study Drug-Related Serious TEAE[1]	8 (0.2)	5 (0.1)	13 (0.2)
TEAE Leading to Withdrawal of Study Drug[2]	321 (7.9)	335 (8.2)	656 (8.0)

	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Study Drug-Related TEAE Leading to Withdrawal of Study Drug[1,2]	139 (3.4)	164 (4.0)	303 (3.7)
Serious TEAE Leading to Withdrawal of Study Drug[2]	88 (2.2)	88 (2.2)	176 (2.2)
Serious TEAE Leading to Death	94 (2.3)	102 (2.5)	196 (2.4)
Study Drug-Related Serious TEAE Leading to Withdrawal of Study Drug[1,2]	2 (0.0)	4 (0.1)	6 (0.1)

Abbreviations: ODIS = off drug in study; TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study.

Percentages were based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

1 Study drug-related TEAEs include those characterized as related, probably related, or possibly related.

2 Withdrawal of study drug excludes patients who were ODIS for 30 days or more and restarted study drug.

Most Frequent TEAEs

[0787] Overall, 81.8% (3343/4089) and 81.3% (3326/4090) of patients in the AMR101 and placebo groups, respectively, experienced at least one TEAE, with the most common class of TEAEs being infections and infestations (44.6% [1822/4089] and 43.4% [1774/4090], respectively).

[0788] In addition to infections and infestations, the most common classes of TEAEs in the AMR101 group, with the corresponding incidence in the placebo group, were:

- Musculoskeletal and connective tissue disorders (35.9% [1466/4089] and 34.4% [1406/4090], respectively)
- Gastrointestinal (GI) disorders (33.0% [1350/4089] and 35.1 % [1437/4090], respectively)
- General disorders and administration site conditions (25.2% [1030/4089] and 23.9% [979/4090], respectively)
- Nervous system disorders (24.6% [1004/4089] and 23.8% [972/4090], respectively)

[0789] The incidence of GI disorders was 2.1% higher in the placebo group than in the AMR101 group.

[0790] A summary of TEAEs occurring at an incidence of ≥3% in either treatment group is presented in Table 77, by MedDRA SOC and PT, overall and by treatment group.

[0791] The most frequent individual TEAEs that occurred in ≥5% in either treatment group and were statistically different across groups were:

- Diarrhea (9.0% [367/4089] and 11.1% [453/4090] in the AMR101 and placebo groups, respectively)
- Peripheral edema (6.5% [267/4089] and 5.0% [203/4090] in the AMR101 and placebo groups, respectively)
- Constipation (5.4% [221/4089] and 3.6% [149/4090] in the AMR101 and placebo groups, respectively)
- Atrial fibrillation (5.3% [215/4089] and 3.9% [159/4090] in the AMR101 and placebo groups, respectively)
- Anemia (4.7% [191/4089] and 5.8% [236/4090] in the AMR101 and placebo groups, respectively)

Table 77: Treatment-Emergent Adverse Events Occurring at an Incidence of ≥3% in Either Treatment Group, by MedDRA System Organ Class and Preferred Term, Overall and by Treatment Group (Safety Population)

System Organ Class Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Infections and infestations	1822 (44.6)	1774 (43.4)	3596 (44.0)
Nasopharyngitis	314 (7.7)	300 (7.3)	614 (7.5)
Upper respiratory tract infection	312 (7.6)	320 (7.8)	632 (7.7)
Bronchitis	306 (7.5)	300 (7.3)	606 (7.4)
Pneumonia	263 (6.4)	277 (6.8)	540 (6.6)
Influenza	263 (6.4)	271 (6.6)	534 (6.5)
Urinary tract infection	253 (6.2)	261 (6.4)	514 (6.3)
Sinusitis	169 (4.1)	166 (4.1)	335 (4.1)
Musculoskeletal and connective tissue disorders	1466 (35.9)	1406 (34.4)	2872 (35.1)
Back pain	335 (8.2)	309 (7.6)	644 (7.9)
Arthralgia	313 (7.7)	310 (7.6)	623 (7.6)
Osteoarthritis	241 (5.9)	218 (5.3)	459 (5.6)
Pain in extremity	235 (5.7)	241 (5.9)	476 (5.8)

System Organ Class Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Musculoskeletal pain	176 (4.3)	130 (3.2)	306 (3.7)
Myalgia	135 (3.3)	147 (3.6)	282 (3.4)
Muscle spasms	101 (2.5)	136 (3.3)	237 (2.9)
Gastrointestinal disorders	1350 (33.0)	1437 (35.1)	2787 (34.1)
Diarrhea	367 (9.0)	453 (11.1)	820 (10.0)
Constipation	221 (5.4)	149 (3.6)	370 (4.5)
Nausea	190 (4.6)	197 (4.8)	387 (4.7)
Gastroesophageal reflux disease	124 (3.0)	118 (2.9)	242 (3.0)
General disorders and administration site conditions	1030 (25.2)	979 (23.9)	2009 (24.6)
Chest pain	273 (6.7)	290 (7.1)	563 (6.9)
Edema peripheral	267 (6.5)	203 (5.0)	470 (5.7)
Fatigue	228 (5.6)	196 (4.8)	424 (5.2)
Non-cardiac chest pain	161 (3.9)	173 (4.2)	334 (4.1)
Nervous system disorders	1004 (24.6)	972 (23.8)	1976 (24.2)
Dizziness	235 (5.7)	246 (6.0)	481 (5.9)
Headache	171 (4.2)	180 (4.4)	351 (4.3)
Respiratory, thoracic, and mediastinal disorders	989 (24.2)	946 (23.1)	1935 (23.7)
Dyspnea	254 (6.2)	240 (5.9)	494 (6.0)
Cough	241 (5.9)	241 (5.9)	482 (5.9)
Metabolism and nutrition disorders	953 (23.3)	877 (21.4)	1830 (22.4)
Gout	171 (4.2)	127 (3.1)	298 (3.6)
Diabetes mellitus	169 (4.1)	173 (4.2)	342 (4.2)
Type 2 diabetes mellitus	147 (3.6)	133 (3.3)	280 (3.4)
Cardiac disorders	910 (22.3)	855 (20.9)	1765 (21.6)
Atrial fibrillation	215 (5.3)	159 (3.9)	374 (4.6)
Angina pectoris	200 (4.9)	205 (5.0)	405 (5.0)
Injury, poisoning, and procedural complications	748 (18.3)	697 (17.0)	1445 (17.7)
Fall	149 (3.6)	138 (3.4)	287 (3.5)
Vascular disorders	709 (17.3)	717 (17.5)	1426 (17.4)
Hypertension	320 (7.8)	344 (8.4)	664 (8.1)
Eye disorders	478 (11.7)	429 (10.5)	907 (11.1)
Cataract	233 (5.7)	208 (5.1)	441 (5.4)
Psychiatric disorders	372 (9.1)	362 (8.9)	734 (9.0)
Insomnia	124 (3.0)	111 (2.7)	235 (2.9)

System Organ Class Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Blood and lymphatic system disorders	321 (7.9)	372 (9.1)	693 (8.5)
Anemia	191 (4.7)	236 (5.8)	427 (5.2)

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

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term. TEAEs are listed in descending order of AMR101 frequency. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

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

Study Drug-Related TEAEs

[0792] Overall, 12.6% (514/4089) and 12.2% (499/4090) of patients in the AMR101 and placebo groups, respectively, experienced at least one TEAE that was characterized by the as at least possibly related to study drug (i.e., study drug-related), with the most common class of study drug-related TEAEs being GI disorders (7.4% [302/4089] and 7.5% [305/4090], respectively)

[0793] A summary of study drug-related TEAEs occurring at an incidence of ≥0.5% in either treatment group is presented in Table 78, by MedDRA SOC and PT, overall and by treatment group. Individual study drug-related TEAEs in the AMR101 group occurred at a low incidence. The most frequent study drug-related TEAE in both treatment groups was diarrhea, with a lower incidence in the AMR101 group than in the placebo group (2.7% [110/4089] versus 3.9% [161/4090], respectively).

Table 78. Study Drug-Related Treatment-Emergent Adverse Events Occurring at an Incidence of ≥0.5% in Either Treatment Group, by MedDRA System Organ Class and Preferred Term, Overall and by Treatment Group (Safety Population)

System Organ Class Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Patients with at least 1 study drug-related TEAE	514 (12.6)	499 (12.2)	1013 (12.4)

System Organ Class Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Gastrointestinal disorders	302 (7.4)	305 (7.5)	607 (7.4)
Diarrhea	110 (2.7)	161 (3.9)	271 (3.3)
Eructation	35 (0.9)	12 (0.3)	47 (0.6)
Flatulence	34 (0.8)	34 (0.8)	68 (0.8)
Nausea	34 (0.8)	30 (0.7)	64 (0.8)
Dyspepsia	18 (0.4)	20 (0.5)	38 (0.5)
Musculoskeletal and connective tissue disorders	58 (1.4)	33 (0.8)	91 (1.1)
Arthralgia	23 (0.6)	10 (0.2)	33 (0.4)

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

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term. TEAEs are listed in descending order of AMR101 frequency. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

Study drug-related TEAEs include those characterized as related, probably related, or possibly related.

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

Treatment-Emergent Adverse Events by Severity

[0794] Most TEAEs were mild or moderate in intensity. Overall, 19.7% (805/4089) and 20.0% (816/4090) of patients in the AMR101 and placebo groups, respectively, experienced at least one severe TEAE, with the most common class of severe TEAEs being infections and infestations (5.1 % [210/4089] and 4.8% [198/4090], respectively).

[0795] A summary of severe TEAEs occurring at an incidence of ≥ 0.5% in either treatment group is presented in Table 79, by MedDRA SOC and PT, overall and by treatment group. The most frequent severe TEAE in both treatment groups was pneumonia, with similar incidences in the AMR101 and placebo groups (1.5% [62/4089] and 1.5% [61/4090], respectively).

[0796] In addition to pneumonia, the most frequent individual severe TEAEs in the AMR101 group, with the corresponding incidence in the placebo group, were:

- Osteoarthritis (0.8% [34/4089] and 0.7% [29/4090], respectively)
- Acute kidney injury (0.7% [29/4089] and 0.6% [24/4090], respectively)

- Chest pain (0.7% [29/4089] and 0.6% [25/4090], respectively)

Table 79. Severe Treatment-Emergent Adverse Events Occurring at an Incidence of ≥0.5% in Either Treatment Group, by MedDRA System Organ Class and Preferred Term, Overall and by Treatment Group (Safety Population)

System Organ Class Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Patients with at least 1 severe TEAE	805 (19.7)	816 (20.0)	1621 (19.8)
Infections and infestations	210 (5.1)	198 (4.8)	408 (5.0)
Pneumonia	62 (1.5)	61 (1.5)	123 (1.5)
Sepsis	22 (0.5)	29 (0.7)	51 (0.6)
Urinary tract infection	13 (0.3)	20 (0.5)	33 (0.4)
Musculoskeletal and connective tissue disorders	117 (2.9)	100 (2.4)	217 (2.7)
Osteoarthritis	34 (0.8)	29 (0.7)	63 (0.8)
Back pain	21 (0.5)	16 (0.4)	37 (0.5)
Respiratory, thoracic, and mediastinal disorders	104 (2.5)	102 (2.5)	206 (2.5)
Acute respiratory failure	20 (0.5)	20 (0.5)	40 (0.5)
Chronic obstructive pulmonary disease	18 (0.4)	21 (0.5)	39 (0.5)
Cardiac disorders	98 (2.4)	143 (3.5)	241 (2.9)
Angina unstable	12 (0.3)	24 (0.6)	36 (0.4)
Angina pectoris	7 (0.2)	20 (0.5)	27 (0.3)
Nervous system disorders	78 (1.9)	77 (1.9)	155 (1.9)
Syncope	12 (0.3)	19 (0.5)	31 (0.4)
Renal and urinary disorders	77 (1.9)	58 (1.4)	135 (1.7)
Acute kidney injury	29 (0.7)	24 (0.6)	53 (0.6)
General disorders and administration site conditions	76 (1.9)	71 (1.7)	147 (1.8)
Chest pain	29 (0.7)	25 (0.6)	54 (0.7)

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

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term. TEAEs are listed in descending order of AMR101 frequency. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

System Organ Class Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)

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

Adverse Events of Special Interest

[0797] An overview of pre-specified TEAEs of special interest is presented in Table 80, overall and by treatment group. Abnormal glucose control occurred in 15.2% (621/4089) of patients in the AMR101 group and 15.4% (630/4090) of patients in the placebo group. Bleeding-related disorders occurred in 11.8% (482/4089) of patients in the AMR101 group and 9.9% (404/4090) of patients in the placebo group. Hepatic disorders occurred in 5.4% (221/4089) of patients in the AMR101 group and 4.9% (201/4090) of patients in the placebo group.

Table 80. Overview of Pre-Specified Treatment-Emergent Adverse Events of Special Interest, Overall and by Treatment Group (Safety Population)

	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	P-value[4]
Hepatic disorders[1]	221 (5.4)	201 (4.9)	0.3180
Bleeding-related disorders[2]	482 (11.8)	404 (9.9)	0.0055
Gastrointestinal bleeding	127 (3.1)	116 (2.8)	0.4747
Central nervous system bleeding	20 (0.5)	12 (0.3)	0.1619
Other bleeding	376 (9.2)	312 (7.6)	0.0108
Abnormal glucose control[3]	621 (15.2)	630 (15.4)	0.8059

Abbreviations: AE = adverse event; excl = excluding; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event.

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

1 Hepatic disorders were identified by the Hepatic Disorder SMQ (MedDRA v20.0).

2 Bleeding-related disorders were identified by the SMQs of "Gastrointestinal haemorrhage," "Central Nervous System haemorrhages and cerebrovascular conditions," and "Haemorrhage terms (excl laboratory terms)."

3 Glucose control AEs were identified based on the risk of impaired glucose control as defined in the Investigator's Brochure.

4 The p-value was based on Fisher's exact test.

[0798] A summary of bleeding TEAEs is presented in Table 81. A statistically significantly higher incidence of bleeding TEAEs occurred in the AMR101 group than in the placebo group (11.8% [482/4089] versus 9.9% [404/4090], respectively; p=0.0055). Serious bleeding TEAEs trended toward significance in the AMR101 group versus the placebo group (2.7% [111/4089] versus 2.1 % [85/4090], respectively; p=0.0605).

[0799] Of note, the rates of adjudicated hemorrhagic stroke were not significantly higher in the AMR101 group than in the placebo group.

Table 81. Summary of Bleeding Treatment-Emergent Adverse Events (Safety Population)

Incidence of Bleeding AE	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	P-value[1]
Bleeding TEAEs	482 (11.8)	404 (9.9)	0.0055
Serious bleeding TEAEs	111 (2.7)	85 (2.1)	0.0605

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study.

Percentages were based on the number of patients in the Safety population within each treatment group (N). All AEs were coded using the MedDRA, Version 20.1.

1 The p-value was based on Fisher's exact test.

[0800] Due to the convergence of clinical events shortly before a patient's death, direct causality of an individual bleeding event with death cannot always be determined. Bleeding-related clinical events (i.e., TEAEs, SAEs, or positively adjudicated endpoints) that occurred proximal to death (per site Investigator, CEC, or Sponsor medical assessment) are presented in Table 82 and occurred in 23 (0.6%) patients in the AMR101 group and 34 (0.8%) patients in the placebo group, with no statistically significant difference between treatment groups (p=0.18). Sponsor medical assessment classified 20 (0.5%) patients in the AMR101 group and 23 (0.6%) patients in the placebo group as having a bleeding event that likely contributed to death, with no statistically significant difference between treatment groups (p=0.76). Sponsor medical assessment also classified 3 (0.1 %) patients in the AMR101 group and 11 (0.3%) patients in the placebo group as having a bleeding event that did not likely contribute to death (p=0.06). None of these 57 deaths were associated with study drug per Investigator assessment;

one bleeding event in each treatment group was considered possibly related to study drug per Investigator assessment.

Table 82. Summary of Bleeding Events with Possible Fatal Association (Safety Population)

	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	P-value[1]
Any Bleeding with a Possible Fatal Association	23 (0.6)	34 (0.8)	0.18
Bleeding Likely Contributing to a Fatal Event	20 (0.5)	23 (0.6)	0.76
Bleeding Not Likely Contributing to a Fatal Event	3 (0.1)	11 (0.3)	0.06

Note: Identification of patients with a fatal event possibly associated with a bleeding event was conducted through exhaustive search of the clinical adverse events dataset and the Clinical Endpoint Committee (CEC) endpoint database, as well as through comprehensive Sponsor medical review of the relevant data/source documents.

1 The p-value was based on Fisher's exact test.

[0801] Although not pre-specified as TEAEs of special interest, atrial fibrillation and atrial flutter were also explored post hoc as potential safety signals as discussed above in Example 7. A summary of TEAEs and SAEs of atrial fibrillation/flutter is presented in Table 83, along with positively adjudicated atrial fibrillation/flutter requiring hospitalization of ≥24 hours as a comprehensive compilation of all documented post-randomization occurrences of these atrial arrhythmias. Occurrences of atrial fibrillation or flutter not meeting endpoint criteria (i.e., not positively adjudicated as endpoints) were counted as TEAEs or SAEs, per seriousness criteria.

[0802] The incidences of atrial fibrillation/flutter TEAEs reported in the AE dataset within the clinical database (i.e., not positively adjudicated as endpoints) were statistically significantly higher in the AMR101 group than in the placebo group (7.7% [315/4089] versus 5.9% [243/4090], respectively; p=0.0016), while the incidences of atrial fibrillation/flutter SAEs reported in the safety database (i.e., not positively adjudicated as endpoints and meeting seriousness criteria) were similar between the AMR101 and placebo groups (0.6% [23/4089] and 0.5% [22/4090], respectively). The incidences of positively adjudicated atrial fibrillation/flutter requiring hospitalization of ≥24 hours were also statistically significantly higher in the AMR101 group than in the placebo group (3.1% [127/4089] versus 2.1% [84/4090], respectively; p=0.0037).

Table 83. Summary of Atrial Fibrillation and Atrial Flutter (ITT Population)

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

Abbreviations: AE = adverse event; ITT = Intent-to-Treat; MedDRA = Medical Dictionary for Regulatory Activities.

Note: Percentages were based on the number of patients in the ITT population within each treatment group (N). All AEs were coded using the MedDRA, Version 20.1. Counts of atrial fibrillation/flutter AEs and counts of positively adjudicated atrial fibrillation/flutter events are mutually exclusive.

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

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

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

Most Common Classes of Adverse Events by Subgroups of Interest

[0803] The incidences of TEAEs by subgroups of interest (race, sex, age, BMI, baseline ezetimibe use, CV risk category, and geographic region) for the most common classes (i.e., top 6 SOCs in the overall Safety population) of TEAEs are summarized in Table 84. Across all subgroups, the overall incidences of TEAEs were similar between the AMR101 and placebo groups, with the exception of the Asia Pacific region subgroup, in which the incidence of TEAEs in the AMR101 group was >5% higher than that in the placebo group (76.9% [100/130] versus 70.5% [93/132], respectively). However, this subgroup was small (3.2% of randomized patients), which may be insufficient from which to draw conclusions for these differences.

[0804] Among patients taking ezetimibe at baseline, the incidences of TEAEs were lower in the AMR101 group than in the placebo group for the following classes of TEAEs:

- Musculoskeletal and connective tissue disorders (41.2% [108/262] versus 47.3% [124/262], respectively)
- GI disorders (37.4% [98/262] versus 46.2% [121/262], respectively)
- General disorders and administration site conditions (26.3% [69/262] versus 34.4% [90/262], respectively)

- Nervous system disorders (23.7% [62/262] versus 31.3% [82/262], respectively)
- Respiratory, thoracic, and mediastinal disorders (27.5% [72/262] versus 34.4% [90/262], respectively)

[0805] In the BMI ≥25 to <30 kg/m^2 subgroup, the incidences of TEAEs were lower in the AMR101 group than in the placebo group for GI disorders (30.8% [440/1427] versus 36.1 % [511/1414], respectively). In the Asian Pacific region subgroup, the incidences of TEAEs were higher in the AMR101 group than in the placebo group for nervous system disorders (20.8% [27/130] versus 15.2% [20/132], respectively). Across all subgroups, there were no other classes of TEAEs with a >5% difference between treatment groups in the most common classes (i.e., top 6 SOCs in the overall Safety population) of TEAEs.

Table 84. Incidence of Most Common Classes (Top 6 Overall) of Treatment-Emergent Adverse Events by Subgroups, by Treatment Group (Safety Population)

Treatment Group	Subgroup (N)	Class of TEAE, n (%)						
		Patients with at least 1 TEAE	Infections and infestations	Musculo-skeletal and connective tissue disorders	GI disorders	General disorders and administration site conditions	Nervous system disorders	Respiratory, thoracic, and mediastinal disorders
Race								
AMR101	White (N=3691)	3019 (81.8)	1670 (45.2)	1343 (36.4)	1235 (33.5)	929 (25.2)	911 (24.7)	894 (24.2)
	Non-white (N=398)	324 (81.4)	152 (38.2)	123 (30.9)	115 (28.9)	101 (25.4)	93 (23.4)	95 (23.9)
Placebo	White (N=3688)	3006 (81.5)	1624 (44.0)	1282 (34.8)	1307 (35.4)	891 (24.2)	891 (24.2)	863 (23.4)
	Non-white (N=401)	320 (79.8)	150 (37.4)	124 (30.9)	130 (32.4)	88 (21.9)	81 (20.2)	83 (20.7)
Sex								
AMR101	Male (N=2927)	2414 (82.5)	1254 (42.8)	1029 (35.2)	905 (30.9)	734 (25.1)	683 (23.3)	717 (24.5)
	Female (N=1162)	929 (79.9)	568 (48.9)	437 (37.6)	445 (38.3)	296 (25.5)	321 (27.6)	272 (23.4)
Placebo	Male (N=2895)	2359 (81.5)	1192 (41.2)	947 (32.7)	973 (33.6)	674 (23.3)	676 (23.4)	641 (22.1)
	Female (N=1195)	967 (80.9)	582 (48.7)	459 (38.4)	464 (38.8)	305 (25.5)	296 (24.8)	305 (25.5)
Age								
AMR101	<65 years (N=2232)	1725 (77.3)	883 (39.6)	700 (31.4)	622 (27.9)	483 (21.6)	453 (20.3)	422 (18.9)
	≥65 years (N=1857)	1618 (87.1)	939 (50.6)	766 (41.2)	728 (39.2)	547 (29.5)	551 (29.7)	567 (30.5)
Placebo	<65 years (N=2184)	1686 (77.2)	865 (39.6)	671 (30.7)	668 (30.6)	468 (21.4)	453 (20.7)	426 (19.5)
	≥65 years (N=1906)	1640 (86.0)	909 (47.7)	735 (38.6)	769 (40.3)	511 (26.8)	519 (27.2)	520 (27.3)
BMI								
AMR101	<25 kg/m^2 (N=320)	258 (80.6)	124 (38.8)	86 (26.9)	108 (33.8)	74 (23.1)	73 (22.8)	68 (21.3)
	≥25 to <30 kg/m^2 (N=1427)	1163 (81.5)	579 (40.6)	477 (33.4)	440 (30.8)	343 (24.0)	337 (23.6)	324 (22.7)
	≥30 kg/m^2 (N=2331)	1918 (82.3)	1119 (48.0)	903 (38.7)	800 (34.3)	613 (26.3)	594 (25.5)	597 (25.6)
Placebo	<25 kg/m^2 (N=295)	228 (77.3)	114 (38.6)	82 (27.8)	109 (36.9)	69 (23.4)	67 (22.7)	53 (18.0)
	≥25 to <30 kg/m^2 (N=1414)	1150 (81.3)	581 (41.1)	461 (32.6)	511 (36.1)	334 (23.6)	325 (23.0)	315 (22.3)

Treatment Group	Subgroup (N)	Class of TEAE, n (%)						
		Patients with at least 1 TEAE	Infections and infestations	Musculo-skeletal and connective tissue disorders	GI disorders	General disorders and administration site conditions	Nervous system disorders	Respiratory, thoracic, and mediastinal disorders
	≥30 kg/m^2 (N=2362)	1945 (82.3)	1077 (45.6)	861 (36.5)	817 (34.6)	574 (24.3)	579 (24.5)	577 (24.4)
Baseline Ezetimibe Use								
AMR101	Ezetimibe (N=262)	241 (92.0)	134 (51.1)	108 (41.2)	98 (37.4)	69 (26.3)	62 (23.7)	72 (27.5)
	No Ezetimibe (N=3827)	3102 (81.1)	1688 (44.1)	1358 (35.5)	1252 (32.7)	961 (25.1)	942 (24.6)	917 (24.0)
Placebo	Ezetimibe (N=262)	236 (90.1)	137 (52.3)	124 (47.3)	121 (46.2)	90 (34.4)	82 (31.3)	90 (34.4)
	No Ezetimibe (N=3828)	3090 (80.7)	1637 (42.8)	1282 (33.5)	1316 (34.4)	889 (23.2)	890 (23.2)	856 (22.4)
CV Risk Category								
AMR101	Risk Category 1 (N=2892)	2360 (81.6)	1210 (41.8)	972 (33.6)	905 (31.3)	732 (25.3)	676 (23.4)	676 (23.4)
	Risk Category 2 (N=1197)	983 (82.1)	612 (51.1)	494 (41.3)	445 (37.2)	298 (24.9)	328 (27.4)	313 (26.1)
Placebo	Risk Category 1 (N=2893)	2350 (81.2)	1193 (41.2)	936 (32.4)	968 (33.5)	713 (24.6)	634 (21.9)	659 (22.8)
	Risk Category 2 (N=1197)	976 (81.5)	581 (48.5)	470 (39.3)	469 (39.2)	266 (22.2)	338 (28.2)	287 (24.0)
Region								
AMR101	Westernized (N=2906)	2631 (90.5)	1573 (54.1)	1348 (46.4)	1201 (41.3)	936 (32.2)	871 (30.0)	898 (30.9)
	Eastern Europe (N=1053)	612 (58.1)	217 (20.6)	NA	125 (11.9)	NA	NA	NA
	Asia Pacific (N=130)	100 (76.9)	32 (24.6)	23 (17.7)	24 (18.5)	29 (22.3)	27 (20.8)	23 (17.7)

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Treatment Group	Subgroup (N)	Class of TEAE, n (%)						
		Patients with at least 1 TEAE	Infections and infestations	Musculo-skeletal and connective tissue disorders	GI disorders	General disorders and administration site conditions	Nervous system disorders	Respiratory, thoracic, and mediastinal disorders
Placebo	Westernized (N=2905)	2619 (90.2)	1540 (53.0)	1287 (44.3)	1273 (43.8)	885 (30.5)	852 (29.3)	854 (29.4)
	Eastern Europe (N=1053)	614 (58.3)	205 (19.5)	NA	137 (13.0)	NA	NA	NA
	Asia Pacific (N=132)	93 (70.5)	29 (22.0)	24 (18.2)	27 (20.5)	27 (20.5)	20 (15.2)	18 (13.6)

Abbreviations: BMI = body mass index; CV = cardiovascular; GI = gastrointestinal; NA = not applicable (i.e., the incidences of TEAEs [preferred terms] for this class of TEAE are less than 3%); TEAE = treatment-emergent adverse advent.

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

[0806] Deaths: Serious TEAEs led to death at similar incidences in the AMR101 and placebo groups (2.3% [94/4089] and 2.5% [102/4090], respectively). Note that serious TEAEs leading to death and death itself were to be recorded as separate events.

[0807] A summary of CEC-adjudicated deaths (including CV death, non-CV death, undetermined death, and total mortality) is presented in Table 85. There were a total of 584/8179 (7.1 %) CEC-adjudicated deaths during the study: 274/4089 (6.7%) in the AMR101 group and 310/4090 (7.6%) in the placebo group. Of these, there were a total of 318/8179 (3. 9%) CV deaths (excluding deaths with undetermined cause): 138/4089 (3.4%) in the AMR101 group and 180/4090 (4.4%) in the placebo group; and there were a total of 197/8179 (2.4%) non-CV deaths: 100/4089 (2.4%) in the AMR101 group and 97/4090 (2.4%) in the placebo group.

Table 85. Summary of CEC-Adjudicated Deaths (Including CV Death, Non-CV Death, Undetermined Death, and Total Mortality) (Safety Population)

Summary of Deaths[1], n (%)	AMR101 (N=4089)	Placebo (N=4090)	Overall (N=8179)
Total mortality	274 (6.7)	310 (7.6)	584 (7.1)
CV deaths (excluding deaths with undetermined cause)	138 (3.4)	180 (4.4)	318 (3.9)
Non-CV deaths	100 (2.4)	97 (2.4)	197 (2.4)
Deaths with undetermined cause	36 (0.9)	33 (0.8)	69 (0.8)

Abbreviations: CV = cardiovascular.

Note: CV deaths (excluding deaths with undetermined cause) and deaths with undetermined cause were combined as "CV deaths" for the primary efficacy analysis of CV endpoints.

[0808] Utilizing known vital status data through 31 May 2018 (study end date) and assessed as of 06 September 2018 (database lock), total mortality was 7.3% (298/4089) and 8.3% (339/4090 in the AMR101 group and the placebo group, respectively.

Other Serious Adverse Events

[0809] A summary of SAEs occurring at an incidence of ≥0.5% in either treatment group is presented in Table 86, by MedDRA SOC and PT, overall and by treatment group. Note that positively adjudicated endpoint events were not to be reported in the safety database as SAEs. Overall, 30.6% (1252/4089) and 30.7% (1254/4090) of patients in the

AMR101 and placebo groups, respectively, experienced at least one SAE, with the most common class of SAEs being infections and infestations (8.1 % [332/4089] and 7.6% [309/4090], respectively).

[0810] In addition to infections and infestations, the most common classes of SAEs in the AMR101 group, with the corresponding incidence in the placebo group, were:

- Neoplasms benign, malignant, and unspecified (including cysts and polyps) (5.4% [222/4089] and 5.1 % [208/4090], respectively)
- Cardiac disorders (4.7% [192/4089] and 5.5% [224/4090], respectively)
- GI disorders (4.7% [191/4089] and 4.3% [176/4090], respectively)
- Musculoskeletal and connective tissue disorders (4.6% [188/4089] and 4.0% [165/4090], respectively)

[0811] The incidences of classes of SAEs and individual SAEs were similar between the AMR101 and placebo groups. The most frequent SAE in both treatment groups was pneumonia, with similar incidences in the AMR101 and placebo groups (2.6% [105/4089] and 2.9% [118/4090], respectively). In addition to pneumonia, the most frequent individual SAEs in the AMR101 group, with the corresponding incidence in the placebo group, were:

- Osteoarthritis (2.0% [81/4089] and 1.8% [73/4090], respectively)
- Chest pain (1.6% [66/4089] and 1.6% [66/4090], respectively)
- Non-cardiac chest pain (1.2% [49/4089] and 1.3% [52/4090], respectively)
- Angina pectoris (1.2% [48/4089] and 1.2% [48/4090], respectively)
- Acute kidney injury (1.1% [47/4089] and 0.8% [34/4090], respectively)

[0812] No other individual SAEs occurred in >1% of patients in the AMR101 group. Of note, the incidences of serious GI hemorrhage were similar between the AMR101 and placebo groups (0.6% [26/4089] and 0.5% [20/4090], respectively), as were the incidences of serious anemia (0.5% [22/4089] and 0.5% [20/4090], respectively).

Table 86. Serious Adverse Events Occurring at an Incidence of ≥0.5% in Either Treatment Group, by MedDRA System Organ Class and Pref erred Term, Overall and by Treatment Group (Safety Population)

System Organ Class Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Patients with at least 1 serious TEAE	1252 (30.6)	1254 (30.7)	2506 (30.6)
Infections and infestations	332 (8.1)	309 (7.6)	641 (7.8)
Pneumonia	105 (2.6)	118 (2.9)	223 (2.7)
Cellulitis	36 (0.9)	28 (0.7)	64 (0.8)
Sepsis	25 (0.6)	31 (0.8)	56 (0.7)
Urinary tract infection	25 (0.6)	22 (0.5)	47 (0.6)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	222 (5.4)	208 (5.1)	430 (5.3)
Prostate cancer	26 (0.6)	26 (0.6)	52 (0.6)
Cardiac disorders	192 (4.7)	224 (5.5)	416 (5.1)
Angina pectoris	48 (1.2)	48 (1.2)	96 (1.2)
Angina unstable	41 (1.0)	53 (1.3)	94 (1.1)
Atrial fibrillation	21 (0.5)	17 (0.4)	38 (0.5)
Cardiac failure congestive	19 (0.5)	13 (0.3)	32 (0.4)
Gastrointestinal disorders	191 (4.7)	176 (4.3)	367 (4.5)
Gastrointestinal hemorrhage	26 (0.6)	20 (0.5)	46 (0.6)
Musculoskeletal and connective tissue disorders	188 (4.6)	165 (4.0)	353 (4.3)
Osteoarthritis	81 (2.0)	73 (1.8)	154 (1.9)
Respiratory, thoracic, and mediastinal disorders	143 (3.5)	141 (3.4)	284 (3.5)
Chronic obstructive pulmonary disease	33 (0.8)	34 (0.8)	67 (0.8)
Acute respiratory failure	19 (0.5)	18 (0.4)	37 (0.5)
Pulmonary embolism	14 (0.3)	22 (0.5)	36 (0.4)
General disorders and administration site conditions	139 (3.4)	153 (3.7)	292 (3.6)
Chest pain	66 (1.6)	66 (1.6)	132 (1.6)
Non-cardiac chest pain	49 (1.2)	52 (1.3)	101 (1.2)
Renal and urinary disorders	120 (2.9)	100 (2.4)	220 (2.7)
Acute kidney injury	47 (1.1)	34 (0.8)	81 (1.0)
Nervous system disorders	104 (2.5)	100 (2.4)	204 (2.5)
Syncope	28 (0.7)	31 (0.8)	59 (0.7)
Blood and lymphatic system disorders	39 (1.0)	35 (0.9)	74 (0.9)
Anemia	22 (0.5)	20 (0.5)	42 (0.5)

System Organ Class Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)

Abbreviations: incl = including; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term. TEAEs are listed in descending order of AMR101 frequency. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

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

[0813] A summary of serious bleeding TEAEs occurring at an incidence of >0.1 % in either treatment group is presented in Table 87, by category and PT, overall and by treatment group. The incidences of serious central nervous system (CNS) bleeding and serious GI bleeding were similar between the AMR101 and placebo groups.

Table 87. Serious Bleeding Adverse Events Occurring at an Incidence of >0.1 % in Either Treatment Group, by Category and Preferred Term, Overall and by Treatment Group (Safety Population)

Category Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Patients with any serious bleeding TEAE	111 (2.7)	85 (2.1)	196 (2.4)
Patients with serious CNS bleeding	14 (0.3)	10 (0.2)	24 (0.3)
Subdural hematoma	9 (0.2)	5 (0.1)	14 (0.2)
Patients with serious GI bleeding	62 (1.5)	47 (1.1)	109 (1.3)
GI hemorrhage	26 (0.6)	20 (0.5)	46 (0.6)
Rectal hemorrhage	10 (0.2)	6 (0.1)	16 (0.2)
Patients with serious other bleeding	41 (1.0)	30 (0.7)	71 (0.9)
Hematuria	8 (0.2)	4 (0.1)	12 (0.1)
Epistaxis	7 (0.2)	4 (0.1)	11 (0.1)

Abbreviations: CNS = central nervous system; GI = gastrointestinal; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Category Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term. TEAEs are listed in descending order of AMR101 frequency. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

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

[0814] Overall, 0.2% (8/4089) and 0.1 % (5/4090) of patients in the AMR101 and placebo groups, respectively, experienced at least one SAE that was characterized by the Investigator as at least possibly related to study drug (i.e., study drug-related).

Adverse Events Leading to Study Drug Withdrawal

[0815] Overall, 7.9% (321/4089) and 8.2% (335/4090) of patients in the AMR101 and placebo groups, respectively, experienced at least one TEAE that led to study drug withdrawal, with the most common class of TEAEs leading to study drug withdrawal being GI disorders (3.6% [146/4089] and 3.9% [160/4090], respectively).

[0816] The only TEAEs leading to study drug withdrawal for >0.5% of patients in the AMR101 group were diarrhea (1. 1 % [47/4089] versus 1.9% [76/4090] in the placebo group) and nausea (0.6% [23/4089] versus 0.4% [18/4090] in the placebo group). All other TEAEs leading to study drug withdrawal were experienced by <0.5% of patients in either treatment group.

[0817] A summary of all study drug-related TEAEs leading to study drug withdrawal, occurring at an incidence of ≥0.1 % in either treatment group is presented in Table 88, by MedDRA SOC and PT, overall and by treatment group. Overall, 3.4% (139/4089) and 4.0% (164/4090) of patients in the AMR101 and placebo groups, respectively, experienced at least one TEAE that led to study drug withdrawal that was characterized by the Investigator as at least possibly related to study drug (i.e., study drug-related). The only study drug-related TEAE leading to study drug withdrawal in >0.5% of patients in either treatment group was diarrhea, with a lower incidence in the AMR101 group than in the placebo group (1.0% [41/4089] and 1.6% [66/4090], respectively).

Table 88. Study Drug-Related Treatment-Emergent Adverse Events Leading to Study Drug Withdrawal Occurring at an Incidence of ≥0.1 % in Either Treatment Group, by MedDRA System Organ Class and Preferred Term, Overall and by Treatment Group (Safety Population)

System Organ Class Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)
Patients with at least 1 study drug-related TEAE leading to study drug withdrawal	139 (3.4)	164 (4.0)	303 (3.7)
Gastrointestinal disorders	97 (2.4)	121 (3.0)	218 (2.7)
Diarrhea	41 (1.0)	66 (1.6)	107 (1.3)
Nausea	16 (0.4)	11 (0.3)	27 (0.3)
Abdominal discomfort	6 (0.1)	6 (0.1)	12 (0.1)
Flatulence	6 (0.1)	6 (0.1)	12 (0.1)
Gastroesophageal reflux disease	5 (0.1)	3 (0.1)	8 (0.1)
Abdominal pain upper	4 (0.1)	5 (0.1)	9 (0.1)
Dyspepsia	4 (0.1)	5 (0.1)	9 (0.1)
Constipation	4 (0.1)	2 (0.0)	6 (0.1)
Gastric disorder	4 (0.1)	0 (0.0)	4 (0.0)
Eructation	3 (0.1)	4 (0.1)	7 (0.1)
Vomiting	3 (0.1)	4 (0.1)	7 (0.1)
Abdominal distension	3 (0.1)	3 (0.1)	6 (0.1)
Abdominal pain	1 (0.0)	3 (0.1)	4 (0.0)
Abnormal feces	0 (0.0)	3 (0.1)	3 (0.0)
Skin and subcutaneous disorders	16 (0.4)	15 (0.4)	31 (0.4)
Rash	3 (0.1)	8 (0.2)	11 (0.1)
Pruritus generalized	3 (0.1)	0 (0.0)	3 (0.0)
Skin odor abnormal	3 (0.1)	0 (0.0)	3 (0.0)
Pruritus	1 (0.0)	3 (0.1)	4 (0.0)
Musculoskeletal and connective tissue disorders	13 (0.3)	10 (0.2)	23 (0.3)
Arthralgia	7 (0.2)	2 (0.0)	9 (0.1)
Arthritis	3 (0.1)	0 (0.0)	3 (0.0)
Muscle spasms	0 (0.0)	3 (0.1)	3 (0.0)
Immune system disorders	4 (0.1)	0 (0.0)	4 (0.0)
Hypersensitivity	3 (0.1)	0 (0.0)	3 (0.0)

System Organ Class Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)	Overall (N=8179) n (%)

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

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term. TEAEs are listed in descending order of AMR101 frequency. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

Study drug-related TEAEs include those characterized as related, probably related, or possibly related.

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

Clinical Laboratory Evaluation

[0818] Hematology: Bleeding and anemia have been previously reported by patients taking omega-3 fatty acids. A summary of mean (SD) baseline values and changes from baseline over time in hemoglobin and platelet count is presented in Table 89, by treatment group. Plots of median hemoglobin and platelet count over time are presented in Figures 79-80, respectively.

[0819] Small mean changes from baseline in hemoglobin were observed at each post-baseline time point in the AMR101 and placebo groups, with no notable differences seen between groups. In the AMR101 group, the greatest mean change from baseline of-4.1 g/L was observed at Visit 9, at which time only 8 patients had data; excluding Visit 9, the greatest mean change from baseline was -1.1 g/L at the final visit.

[0820] With regard to platelet count, successive mean decreases from baseline to each post-baseline time point were observed in both the AMR101 and placebo groups, with the mean decrease being slightly less in the AMR101 group than in the placebo group at each time point, with the exception of Visit 9. In the AMR101 group, the greatest mean decrease from baseline of 32.9 x 10^9/L was observed at Visit 9, again, with only 8 patients having data available; excluding Visit 9, the greatest mean decrease from baseline was 18.5 x 10^9 /Lat Visit 8.

Table 89. Mean (SD) Baseline Values and Change from Baseline in Hemoglobin and Platelet Count Over Time on Study, by Treatment Group (Safety Population)

Parameter	AMR101 (N=4089)		Placebo (N=4090)	
Time Point	n	Mean (SD)	n	Mean (SD)
Hemoglobin (g/L)				
Baseline (Visit 2)	4080	141.16 (14.270)	4085	141.73 (14.219)
Change from Baseline to:				
Visit 3	3812	0.17 (8.170)	3838	-0.61 (8.346)
Visit 4	3609	0.85 (9.507)	3549	-0.55 (9.614)
Visit 5	3264	1.39 (10.609)	3190	-0.74 (10.463)
Visit 6	2820	0.92 (10.775)	2740	-1.97 (11.366)
Visit 7	2405	0.64 (11.161)	2311	-2.69 (11.887)
Visit 8	1355	-0.33 (12.309)	1274	-3.45 (12.591)
Visit 9	8	-4.13 (16.522)	3	-5.67 (8.622)
Last Visit	3960	-1.12 (12.326)	3963	-3.88 (12.727)
Platelet Count ($\times 10^9$/L)				
Baseline (Visit 2)	4075	243.01 (66.094)	4075	241.51 (64.636)
Change from Baseline to:				
Visit 3	3780	-2.36 (42.661)	3807	-5.69 (44.001)
Visit 4	3578	-4.85 (41.965)	3512	-6.62 (43.820)
Visit 5	3240	-10.50 (45.440)	3164	-13.73 (45.157)
Visit 6	2802	-13.68 (44.121)	2718	-17.29 (46.312)
Visit 7	2390	-17.30 (45.665)	2288	-21.94 (46.669)
Visit 8	1347	-18.54 (47.493)	1264	-22.21 (50.418)
Visit 9	8	-32.88 (42.273)	3	-16.67 (24.214)
Last Visit	3951	-5.52 (51.553)	3952	-10.84 (52.235)

Abbreviations: SD = standard deviation.

[0821] Liver Function Tests: A summary of mean (SD) baseline values and changes from baseline over time in ALT and AST is presented in Table 90, by treatment group. Plots of median ALT and AST over time are presented in Figures 81-82, respectively.

Table 90. Mean (SD) Baseline Values and Change from Baseline in AST and ALT Over Time on Study, by Treatment Group (Safety Population)

Parameter	AMR101 (N=4089)		Placebo (N=4090)	
Time Point	n	Mean (SD)	n	Mean (SD)
ALT (U/L)				
Baseline (Visit 2)	4085	27.72 (13.730)	4088	28.64 (21.080)
Change from Baseline to:				
Visit 3	3853	0.39 (11.963)	3861	-1.27 (19.833)
Visit 4	3665	-0.28 (13.371)	3607	-1.69 (21.558)
Visit 5	3330	-1.27 (19.522)	3240	-3.37 (23.165)
Visit 6	2869	-1.66 (18.890)	2775	-2.77 (22.577)
Visit 7	2444	-2.80 (15.272)	2345	-4.29 (17.995)
Visit 8	1368	-3.42 (15.494)	1290	-4.18 (16.217)
Visit 9	8	-1.25 (10.938)	3	-8.33 (13.577)
Last Visit	3968	-2.33 (17.416)	3970	-3.47 (24.834)
AST (U/L)				
Baseline (Visit 2)	4084	24.47 (9.564)	4086	24.76 (11.641)
Change from Baseline to:				
Visit 3	3819	0.24 (8.895)	3809	-0.59 (11.179)
Visit 4	3639	0.03 (9.940)	3574	-0.46 (13.161)
Visit 5	3296	-0.83 (11.518)	3202	-1.38 (21.361)
Visit 6	2842	-1.10 (13.081)	2746	-1.26 (23.793)
Visit 7	2416	-1.56 (11.888)	2328	-2.16 (11.374)
Visit 8	1357	-1.66 (11.164)	1278	-1.32 (15.565)
Visit 9	8	0.25 (8.812)	3	-3.00 (3.606)
Last Visit	3965	-1.25 (12.925)	3965	-1.01 (22.231)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; SD = standard deviation.

[0822] Other Clinical Chemistries: Review of other clinical chemistry parameters, including albumin, alkaline phosphatase, bilirubin, BUN, chloride, creatine kinase, creatinine, glucose, calcium, potassium, protein, sodium, or urate (uric acid), revealed no notable changes from baseline in the AMR101 group or differences from placebo in any parameter. Note that only 11 patients had clinical chemistry data available at Visit 9; thus, mean changes at this time point are not comparable to those at other time points at which notably larger numbers of patients had data. Of note, no notable increases in HbA1c were observed over the study period.

Individual Patient Changes

[0823] Hematology: The proportions of patients with PCS hematology values in the AMR101 group were lower than or similar to those in the placebo group, with the exception of basophils PCS high >1% (47.0% versus 41.4%, respectively).

[0824] Liver Function Tests: A summary of treatment-emergent liver function test elevations is presented in Table 91, by treatment group. As shown, the proportions of patients with treatment-emergent increases in liver function tests in the AMR101 group were lower than or similar to those in the placebo group, with the exception of total bilirubin >ULN (7.5% versus 2.7%, respectively). The increases in ALT and AST were generally not associated with increases in total bilirubin.

[0825] A plot of distribution of peak values of ALT or AST versus peak values of total bilirubin is presented in Figure 83. The upper right quadrant (>3 x ULN for ALT or AST and >2 x ULN for total bilirubin) contains patients who potentially met Hy's Law or were potentially drug-induced liver injury cases.

[0826] An increase of 3 x ULN in ALT or AST and an increase of 2 x ULN in total bilirubin was reported in one patient in each treatment group. An increase of 3 x ULN in ALT or AST, an increase of 2 x ULN in total bilirubin, and a decrease of ≤2 x ULN in alkaline phosphatase was reported in one patient in the AMR101 group.

Table 91. Treatment-Emergent Liver Function Test Elevations, by Treatment Group (Safety Population)

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

Statistic at Any Post-Baseline Visit, n (%)	AMR101 (N=4089)	Placebo (N=4090)
>2 × ULN	18 (0.5)	30 (0.8)
>ULN	308 (7.7)	494 (12.4)
ALT + Total Bilirubin	3977	3978
PCS High >3 × ULN (ALT) and >2 × ULN (Total Bilirubin)[1]	1 (0.0)	1 (0.0)
AST + Total Bilirubin	3975	3975
PCS High >3 × ULN (AST) and >2 × ULN (Total Bilirubin)[1]	1 (0.0)	1 (0.0)
ALT and AST	3975	3975
ALT or AST >3 × ULN	61 (1.5)	71 (1.8)
ALT, AST, and Total Bilirubin	3975	3975
ALT or AST >3 × ULN and Total Bilirubin >2 × ULN[1]	1 (0.0)	1 (0.0)
ALT, AST, Total Bilirubin, and ALP	3975	3975
ALT or AST >3 × ULN, Total Bilirubin >2 × ULN, and ALP ≤2 × ULN[1]	1 (0.0)	0 (0.0)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; PCS = potentially clinically significant; ULN = upper limit of normal.

Note: Potential drug-induced liver injuries were investigated through the above analysis of liver toxicity. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N) at any post-baseline visit (or last visit) for the referenced laboratory tests (n). Categories are not mutually exclusive.

1 The same patient per treatment group is represented in each of these rows.

[0827] Individual Clinically Significant Abnormalities: Treatment-emergent laboratory abnormalities that were considered by the Investigator to be clinically significant were to be reported as TEAEs. No individual hematology or clinical chemistry TEAEs occurred at an incidence :2:3% among AMR101-treated patients. All individual hematology abnormalities reported as TEAEs occurred at a low (<1%) incidence.

[0828] As might be expected in the patient population, the most frequently reported clinical chemistry TEAEs overall were glucose abnormalities, with similar or lower incidences in the AMR101 versus placebo groups, most commonly including:

- Blood glucose increased (2.6% [105/4089] and 2.9% [120/4090], respectively)
- Hyperglycemia (1.7% [71/4089] and 2.3% [93/4090], respectively)
- Hypoglycemia (1.5% [60/4089] and 1.4% [58/4090], respectively)

[0829] Other clinical chemistry abnormalities reported as TEAEs occurring at a> 1 % but <3% incidence among AMR101-treated patients included blood creatine phosphokinase increased, HbA1c increased, and hypokalemia.

[0830] Most clinical laboratory abnormalities reported as TEAEs were assessed by the Investigator as unrelated to study drug. All individual study drug-related hematology and clinical chemistry TEAEs occurred at an incidence <0.2% in the AMR101 group.

Electrocardiograms, Vital Signs, Physical Findings, and Other Observations Related to Safety

[0831] A summary of mean (SD) baseline values and changes from baseline over time in selected ECG parameters is presented in Table 92, by treatment group. All ECGs were also reviewed by the CEC for detection of silent Mis at any time point of the study. Silent Mis were detected in 0.7% (27/4089) of patients in the AMR101 group and 0.7% (29/4090) of patients in the placebo group (p=0.7590).

Table 92. Mean (SD) Baseline Values and Change from Baseline in Selected ECG Parameters Over Time on Study, by Treatment Group (Safety Population)

Parameter	AMR101 (N=4089)		Placebo (N=4090)	
Time Point	n	Mean (SD)	n	Mean (SD)
Heart Rate (beats/minute)				
Baseline (Visit 2)	4085	66.6 (10.97)	4084	66.7 (11.58)
Change from Baseline to:				
Visit 4	3679	1.2 (9.33)	3628	1.2 (9.41)
Visit 5	3363	1.7 (10.15)	3268	1.7 (10.41)
Visit 6	2892	1.6 (10.76)	2791	1.6 (10.76)
Visit 7	2461	1.8 (11.36)	2357	1.5 (10.89)
Visit 8	1387	1.4 (10.80)	1308	1.5 (11.49)
Visit 9	7	7.6 (8.00)	3	2.0 (5.00)
Last Visit	3825	2.1 (11.55)	3791	2.0 (11.75)
PR Interval (msec)				
Baseline (Visit 2)	3925	172.2 (30.85)	3906	173.0 (30.95)
Change from Baseline to:				
Visit 4	3465	-0.3 (24.37)	3404	0.0 (21.10)
Visit 5	3149	0.4 (21.77)	3060	1.9 (26.41)

Parameter Time Point	AMR101 (N=4089) n	 Mean (SD)	Placebo (N=4090) n	 Mean (SD)
Visit 6	2667	0.8 (25.09)	2599	0.8 (25.14)
Visit 7	2246	1.4 (22.54)	2178	2.0 (25.29)
Visit 8	1253	2.2 (31.33)	1200	4.5 (35.35)
Visit 9	5	-21.2 (27.66)	1	-7.0 (NA)
Last Visit	3636	1.7 (26.03)	3600	2.4 (29.88)
QTc Interval (msec)				
Baseline (Visit 2)	4085	422.4 (30.79)	4082	422.7 (32.45)
Change from Baseline to:				
Visit 4	3675	1.8 (27.56)	3627	3.1 (28.83)
Visit 5	3364	2.8 (29.61)	3262	5.5 (29.35)
Visit 6	2892	3.7 (29.96)	2788	6.1 (30.78)
Visit 7	2457	5.0 (32.01)	2354	7.0 (32.34)
Visit 8	1380	6.6 (32.43)	1298	8.2 (34.77)
Last Visit	3812	5.0 (32.97)	3773	6.6 (33.90)

Abbreviations: ECG = electrocardiogram; NA = not applicable; SD = standard deviation.

[0832] The proportions of patients with PCS ECG findings at any time on study is summarized in Table 93, by treatment group.

Table 93. Proportion of Patients with Potentially Clinically Significant ECG Findings at Any Time on Study, by Treatment Group (Safety Population)

12-lead ECG Result at Any Post-Baseline Visit, n (%)	AMR101 (N=4089)	Placebo (N=4090)
PR Interval (msec)	3683	3661
<120 msec	261 (7.1)	224 (6.1)
>120 msec and increase >20 msec from baseline	913 (24.8)	938 (25.6)
QRS Interval (msec)	3834	3802
>110 msec	1124 (29.3)	1034 (27.2)
QTc Interval (msec)	3823	3785
>500 msec	208 (5.4)	245 (6.5)

Abbreviations: ECG = electrocardiogram; PCS = potentially clinically significant.

Note: Treatment-emergent PCS values were any post-baseline values that met the specified criteria. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N) at any post-baseline visit (or last visit) for the referenced ECG test (n)

[0833] Electrocardiogram abnormalities that were considered by the Investigator to be clinically significant were reported as TEAEs, as summarized in Table 94 (excluding events [or clinically significant ECG abnormalities] that were positively adjudicated as CV events). As shown, the incidence of individual ECG TEAEs was low (<0.5%) in each treatment group, with the incidence of individual ECG TEAEs in the AMR101 group being lower than or similar to that in the placebo group. All ECG TEAEs were non-serious, with the exception of 1 patient in the placebo group (ECG T wave abnormal).

Table 94. ECG Abnormalities Reported as Treatment-Emergent Adverse Events, by Treatment Group (Safety Population)

Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)
Electrocardiogram QT prolonged	10 (0.2)	15 (0.4)
Electrocardiogram abnormal	10 (0.2)	7 (0.2)
Electrocardiogram T wave inversion	7 (0.2)	6 (0.1)
Electrocardiogram T wave abnormal	6 (0.1)	10 (0.2)
Electrocardiogram ST segment abnormal	6 (0.1)	4 (0.1)
Electrocardiogram ST segment depression	4 (0.1)	1 (0.0)
Electrocardiogram change	3 (0.1)	2 (0.0)
Electrocardiogram ST-T segment abnormal	2 (0.0)	1 (0.0)
ECG signs of myocardial ischemia	2 (0.0)	2 (0.0)
Electrocardiogram QRS complex abnormal	2 (0.0)	0 (0.0)
Electrocardiogram ST-T change	1 (0.0)	3 (0.1)
Electrocardiogram Q wave abnormal	1 (0.0)	1 (0.0)
Exercise electrocardiogram abnormal	1 (0.0)	0 (0.0)
Electrocardiogram T wave amplitude decreased	0 (0.0)	2 (0.0)
Electrocardiogram PR prolongation	0 (0.0)	1 (0.0)
Electrocardiogram T wave normal	0 (0.0)	1 (0.0)

Abbreviations: ECG = electrocardiogram; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: A TEAE was defined as an event that first occurred or worsened in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each patient, multiple TEAEs of the same preferred term were counted only once within each preferred term. TEAEs are listed in descending order of AMR101 frequency. Percentages were based on the number of patients

Preferred Term[1]	AMR101 (N=4089) n (%)	Placebo (N=4090) n (%)

randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints were not included.

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

[0834] Vital Signs: Mean (SD) baseline values and changes from baseline in selected vital signs parameters are summarized in Table 95, by treatment group.

Table 95: Mean (SD) Change from Baseline in Selected Vital Signs Parameters, by Treatment Group (Safety Population)

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

Parameter	AMR101 (N=4089)		Placebo (N=4090)	
Time Point	n	Mean (SD)	n	Mean (SD)
Heart Rate (beats/minute)				
Baseline (Visit 2)	4082	68.1 (10.31)	4076	68.0 (10.55)
Change from Baseline to:				
Visit 3	3912	1.2 (9.03)	3901	1.5 (8.63)
Visit 4	3716	0.9 (9.23)	3661	1.4 (9.38)
Visit 5	3376	1.3 (9.93)	3281	1.3 (9.82)
Visit 6	2920	1.4 (10.35)	2811	1.4 (10.42)
Visit 7	2485	1.5 (11.05)	2378	1.3 (10.81)
Visit 8	1393	0.9 (10.96)	1320	1.4 (10.91)
Visit 9	8	2.8 (11.84)	3	-3.7 (6.03)
Last Visit	3980	1.7 (11.23)	3981	1.9 (10.98)

Abbreviations: SD = standard deviation.

[0835] The proportion of patients with PCS vital sign values at any time on study is summarized in Table 96, by treatment group. As shown, no meaningful differences were observed between the proportions of patients with PCS vital sign values in the AMR101 and placebo groups.

Table 96. Proportion of Patients with Potentially Clinically Significant Vital Sign Values at Any Time on Study, by Treatment Group (Safety Population)

Vital Sign Values at Any Post-Baseline Visit, n (%)	AMR101 (N=4089)	Placebo (N=4090)
Systolic Blood Pressure	3983	3985
PCS Low ≤90 mmHg	40 (1.0)	22 (0.6)
Decrease of ≥20 mmHg	1009 (25.3)	904 (22.7)
PCS Low ≤90 mmHg and decrease of ≥20 mmHg	27 (0.7)	19 (0.5)
PCS High ≥160 mmHg	715 (18.0)	784 (19.7)
Increase of ≥20 mmHg	1163 (29.2)	1192 (29.9)
PCS High ≥160 mmHg and increase of ≥20 mmHg	450 (11.3)	496 (12.4)
Diastolic Blood Pressure	3983	3985
PCS Low ≤50 mmHg	42 (1.1)	37 (0.9)
Decrease of ≥10 mmHg	1569 (39.4)	1444 (36.2)

Vital Sign Values at Any Post-Baseline Visit, n (%)	AMR101 (N=4089)	Placebo (N=4090)
PCS Low ≤50 mmHg and decrease of ≥10 mmHg	35 (0.9)	34 (0.9)
PCS High ≥100 mmHg	223 (5.6)	199 (5.0)
Increase of ≥10 mmHg	1442 (36.2)	1468 (36.8)
PCS High ≥100 mmHg and increase of ≥10 mmHg	179 (4.5)	164 (4.1)
Pulse	3983	3985
PCS Low ≤50 beats/min	293 (7.4)	284 (7.1)
Decrease of ≥15 beats/min	562 (14.1)	501 (12.6)
PCS Low ≤50 beats/min and decrease of ≥15 beats/min	68 (1.7)	74 (1.9)
PCS High ≥90 beats/min	551 (13.8)	531 (13.3)
Increase of ≥15 beats/min	1092 (27.4)	1055 (26.5)
PCS High ≥90 beats/min and increase of ≥15 beats/min	370 (9.3)	328 (8.2)

Abbreviations: PCS = potentially clinically significant.

Note: Treatment-emergent PCS vital signs were any post-baseline values that met the specified criteria. Percentages were based on the number of patients randomized to each treatment group in the Safety population (N) at any post-baseline visit (or last visit) for the referenced vital sign (n).

Serious Bleeding Events by On-Treatment Anti-Thrombic Medication

[0836] A summary of baseline or on-treatment anti-thrombic medication use by type in patients with serious bleeding events for the ITT population is provided in Tables 97A-97D.

Table 97A: Summary of Patients with Serious Bleeding Events by On-Treatment Antithrombotic Medication (ITT Population)

	Patients with bleeding / at risk (%)		
Antithrombotic therapy (on treatment)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Fisher's Exact P Value
All randomized patients	111/4089 (2.7)	85/4090 (2.1)	0.0605
No Antithrombotics	1/449 (0.2)	1/455 (0.2)	1.0000
Antithrombotics	110/3640 (3.0)	84/3635 (2.3)	0.0686
Antiplatelet	96/3407 (2.8)	72/3417 (2.1)	0.0610
One antiplatelet	41/2166 (1.9)	32/2098 (1.5)	0.4088
Two or More antiplatelets	55/1241 (4.4)	40/1319 (3.0)	0.0749

Antithrombotic therapy (on treatment)	Patients with bleeding / at risk (%) Icosapent Ethyl n/N (%)	Placebo n/N (%)	Fisher's Exact P Value
Aspirin	62/2832 (2.2)	38/2800 (1.4)	0.0201
Aspirin only (Aspirin as monotherapy)	19/1699 (1.1)	13/1631 (0.8)	0.3780
Clopidogrel	34/951 (3.6)	16/971 (1.6)	0.0094
Clopidogrel only (Clopidogrel as monotherapy)	3/103 (2.9)	0/91 (0.0)	0.2490
Anticoagulant	63/989 (6.4)	58/1009 (5.7)	0.5748
Warfarin	23/345 (6.7)	18/339 (5.3)	0.5205
Warfarin only (Warfarin as monotherapy)	8/143 (5.6)	5/140 (3.6)	0.5722
Single antiplatelet plus anticoagulant	20/401 (5.0)	19/396 (4.8)	1.0000
Two or more antiplatelets plus anticoagulant	29/355 (8.2)	27/395 (6.8)	0.4910

Note: n is the number of patients with treatment emergent adverse events of bleeding; N is the total number subjects within each medication category.

Table 97B: Summary of Patients with Serious Bleeding Events by Baseline Antithrombotic Medication (ITT Population)

Antithrombotic therapy (at baseline)	Patients with bleeding / at risk (%) Icosapent Ethyl n/N (%)	Placebo n/N (%)	Fisher's Exact P Value
All randomized patients	111/4089 (2.7)	85/4090 (2.1)	0.0605
No Antithrombotics	8/584 (1.4)	6/601 (1.0)	0.6004
Antithrombotics	103/3505 (2.9)	79/3489 (2.3)	0.0840
Antiplatelet	89/3257 (2.7)	62/3236 (1.9)	0.0321
One antiplatelet	58/2416 (2.4)	43/2408 (1.8)	0.1589

	Patients with bleeding / at risk (%)		
Antithrombotic therapy (at baseline)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Fisher's Exact P Value
Two or More antiplatelets	31/841 (3.7)	19/828 (2.3)	0.1139
Aspirin	83/3095 (2.7)	57/3084 (1.8)	0.0323
Aspirin only (Aspirin as monotherapy)	44/2174 (2.0)	34/2168 (1.6)	0.3038
Clopidogrel	35/847 (4.1)	17/817 (2.1)	0.0167
Clopidogrel only (Clopidogrel as monotherapy)	6/134 (4.5)	0/119 (0.0)	0.0310
Anticoagulant	27/385 (7.0)	27/390 (6.9)	1.0000
Warfarin	24/327 (7.3)	25/332 (7.5)	1.0000
Warfarin only (Warfarin as monotherapy)	13/217 (6.0)	15/220 (6.8)	0.8456
Single antiplatelet plus anticoagulant	8/114 (7.0)	8/123 (6.5)	1.0000
Two or more antiplatelets plus anticoagulant	5/23 (21.7)	2/14 (14.3)	0.6869

Note: n is the number of patients with treatment emergent adverse events of bleeding; N is the total number subjects within each medication category.

Table 97C. Summary of Patients with Any Bleeding Events by On-Treatment Antithrombotic Medication (ITT Population)

	Patients with bleeding / at risk (%)		
Antithrombotic therapy (on treatment)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Fisher's Exact P Value
All randomized patients	482/4089 (11.8)	404/4090 (9.9)	0.0055
No Antithrombotics	22/449 (4.9)	22/455 (4.8)	1.0000

	Patients with bleeding / at risk (%)		
Antithrombotic therapy (on treatment)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Fisher's Exact P Value
Antithrombotics	460/3640 (12.6)	382/3635 (10.5)	0.0048
Antiplatelet	415/3407 (12.2)	349/3417 (10.2)	0.0101
One antiplatelet	216/2166 (10.0)	174/2098 (8.3)	0.0628
Two or More antiplatelets	199/1241 (16.0)	175/1319 (13.3)	0.0501
Aspirin	290/2832 (10.2)	219/2800 (7.8)	0.0016
Aspirin only (Aspirin as monotherapy)	125/1699 (7.4)	93/1631 (5.7)	0.0584
Clopidogrel	124/951 (13.0)	91/971 (9.4)	0.0113
Clopidogrel only (Clopidogrel as monotherapy)	7/103 (6.8)	6/91 (6.6)	1.0000
Anticoagulant	230/989 (23.3)	195/1009 (19.3)	0.0331
Warfarin	70/345 (20.3)	50/339 (14.7)	0.0701
Warfarin only (Warfarin as monotherapy)	26/143 (18.2)	16/140 (11.4)	0.1327
Single antiplatelet plus anticoagulant	89/401 (22.2)	76/396 (19.2)	0.3362
Two or more antiplatelets plus anticoagulant	96/355 (27.0)	86/395 (21.8)	0.1050

Note: n is the number of patients with treatment emergent adverse events of bleeding; N is the total number subjects within each medication category.

Table 97D. Summary of Patients with Any Bleeding Events by Baseline Antithrombotic Medication (ITT Population)

	Patients with bleeding / at risk (%)		
Antithrombotic therapy (at baseline)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Fisher's Exact P Value
All randomized patients	482/4089 (11.8)	404/4090 (9.9)	0.0055
No Antithrombotics	45/584 (7.7)	42/601 (7.0)	0.6572
Antithrombotics	437/3505 (12.5)	362/3489 (10.4)	0.0061
Antiplatelet	389/3257 (11.9)	321/3236 (9.9)	0.0097
One antiplatelet	269/2416 (11.1)	234/2408 (9.7)	0.1094
Two or More antiplatelets	120/841 (14.3)	87/828 (10.5)	0.0213
Aspirin	369/3095 (11.9)	302/3084 (9.8)	0.0078
Aspirin only (Aspirin as monotherapy)	228/2174 (10.5)	201/2168 (9.3)	0.1862
Clopidogrel	122/847 (14.4)	80/817 (9.8)	0.0043
Clopidogrel only (Clopidogrel as monotherapy)	15/134 (11.2)	11/119 (9.2)	0.6812
Anticoagulant	81/385 (21.0)	64/390 (16.4)	0.1172
Warfarin	69/327 (21.1)	57/332 (17.2)	0.2345
Warfarin only (Warfarin as monotherapy)	42/217 (19.4)	38/220 (17.3)	0.6215
Single antiplatelet plus anticoagulant	26/114 (22.8)	21/123 (17.1)	0.3283
Two or more antiplatelets plus anticoagulant	7/23 (30.4)	2/14 (14.3)	0.4339

Note: n is the number of patients with treatment emergent adverse events of bleeding; N is the total number subjects within each medication category.

Conclusion

[0837] Treatment with AMR101 was generally well tolerated compared to placebo. Across all subgroups, the overall incidences of TEAEs were generally similar between the AMR101 and placebo groups.

[0838] Overall, 81.8% (3343/4089) and 81.3% (3326/4090) of patients in the AMR101 and placebo groups, respectively, experienced at least one TEAE. The proportions of patients who experienced any SAE (30.6% versus 30.7%), severe TEAE (19.7% versus 20.0%), study drug related TEAE (12.6% versus 12.2%), study drug-related SAE (0.2% versus 0.1 %), TEAE leading to study drug withdrawal (7.9% versus 8.2%), SAE leading to study drug withdrawal (2.2% versus 2.2%), or SAE leading to death (2.3% versus 2.5%) were similar between the AMR101 and placebo groups, respectively.

[0839] The most frequent individual TEAE in both treatment groups was diarrhea, with a lower incidence in the AMR101 group than in the placebo group (9.0% [367/4089] versus 11.1% [453/4090], respectively). Individual study drug-related TEAEs in the AMR101 group occurred at a low incidence, with the most frequent being diarrhea (2.7% [l 10/4089]); diarrhea was reported as a study drug-related TEAE with a marginally higher incidence in the placebo group (3.9% [161/4090]). Most TEAEs were mild or moderate in intensity, with similar incidences of severe TEAEs in the AMR101 and placebo groups (19.7% [805/4089] and 20.0% [816/4090], respectively).

[0840] The incidence of peripheral edema TEAEs was higher in the AMR101 group than in the placebo group (6.5% [267/4089] versus 5.0% [203/4090], respectively). Heart failure can be associated with peripheral edema, but no significant differences were observed between the AMR101 and placebo groups for the tertiary endpoints of newly emergent CHF events (HR of 0.95 [95% CI: 0.77 to 1.17]) or newly emergent CHF events requiring hospitalization (HR of 0.97 [95% CI: 0.77 to 1.22]).

[0841] A statistically significantly higher incidence of bleeding events occurred in the AMR101 group than in the placebo group (11.8% [482/4089] versus 9.9% [404/4090], respectively; p=0.0055). Serious bleeding events trended toward significance in the AMR101 group versus the placebo group (2.7% [111/4089] versus 2.1 % [85/4090], respectively; p=0.0605), while the rates of adjudicated hemorrhagic stroke were not significantly higher in the AMR101 group than in the placebo group. The incidences of serious GI bleeding, serious CNS bleeding, and serious anemia were low overall and similar between the AMR101 and placebo groups. The most frequent SAE in both treatment groups was pneumonia, occurring in 2.6% (105/4089) of patients in the AMR101 group and 2.9% (118/4090]) of patients in the placebo group.

[0842] Atrial fibrillation or flutter requiring hospitalization of ≥24 hours was an endpoint adjudicated by the CEC; occurrences of atrial fibrillation or flutter not meeting endpoint criteria (i.e., not positively adjudicated as endpoints) were counted as TEAEs or SAEs. The incidences of positively adjudicated atrial fibrillation/flutter endpoint events were significantly higher in the AMR101 group than in the placebo group (3.1 % versus 2.1 %, respectively; p=0.0037). The incidences of atrial fibrillation/flutter TEAEs reported in the AE dataset within the clinical database (i.e., not positively adjudicated as endpoints) were also significantly higher in the AMR101 group than in the placebo group (7.7% versus 5.9%, respectively; p=0.0016); the incidences of atrial fibrillation/flutter SAEs reported in the safety database (i.e., not positively adjudicated as endpoints and meeting seriousness criteria) were similar between the AMR101 and placebo groups (0.6% versus 0.5%, respectively; p=0.8827). Stroke, myocardial infarction, cardiac arrest, and sudden cardiac death can be associated with atrial fibrillation or atrial flutter, but significantly lower risk was observed in the AMR101 group versus the placebo group for the endpoints of fatal or nonfatal stroke (HR of 0.720 [95% CI: 0.555 to 0.934; p=0.0129]), fatal or nonfatal myocardial infarction (HR of 0.688 [95% CI: 0.585 to 0.808; p<0.0001]), cardiac arrest (HR of 0.52 [95% CI: 0.31 to 0.86]), and sudden cardiac death (HR of 0.69 [95% CI: 0.50 to 0.96]).

[0843] The only study drug-related TEAE leading to study drug withdrawal in >0.5% of patients in either treatment group was diarrhea, with a lower incidence in the AMR101 group than in the placebo group (1.0% [41/4089] and 1.6% [66/4090], respectively). Findings related to clinical laboratory, ECG, vital signs, or physical examination parameters were generally consistent across treatment groups.

EXAMPLE 6: SAFETY ANALYSIS FOR ICOSAPENT ETHYL (VASCEPA®)

[0844] Over 320,000 patients are currently receiving icosapent ethyl (referenced interchangeably with AMR101 or VASCEPA®) therapy. With over 7 years of postmarket experience, there have been no signals necessitating a label change and no actions taken for safety reasons. Of the patients undergoing treatment with icosapent ethyl, a total of 1,204 unique adverse events (AEs) have been reported. However, there have been no signals of atrial fibrillation and flutter identified in the postmarket reports.

[0845] Adverse Events: Of the total 1,204 unique AEs reported, the most frequent include: arthralgia, product taste abnormal, blood triglycerides increased, diarrhea, nausea, and eructation. Periodic comprehensive reviews have not revealed any new significant safety information and no action has been take for any safety reasons. There has been no change to the benefit risk assessment on post-market reports received to date.

[0846] Serious Adverse Events: There have been 48 serious and unexpected AE reports, totaling 69 individual serious AEs. Four reports have shown fatal outcomes to include: one report by suicide, one report on accidently death by fire, and two reports of unknown cause while taking icosapent ethyl. However, there are only three serious AEs that could possibly be related to icosapent ethyl including: coronary artery occlusion, neonatal respiratory distress disorder, and elevated liver enzymes. Of the three serious adverse events, only neonatal and elevated liver enzymes were assessed as possibly related to icosapent ethyl use. The postmarket safety analysis showed 13 additional serious AEs that could possibly be related to icosapent ethyl and include: two reports of chocking/choking sensation, two reports of epistaxis, atrial fibrillation, diarrhea, dyspnea, hypersensitivity, loss of consciousness, nausea, pre-syncope, prostate cancer, and syncope.

[0847] Nonserious Adverse Events: The postmarket safety analysis showed a total of 1,156 unique nonserious AEs. The most common nonserious AEs report were gastrointestinal (GI) disorders to include: diarrhea, nausea, eructation, abdominal pain, abdominal pain upper, abdominal discomfort, dyspepsia, dysphagia, abdominal distention, retching, flatulence, and vomiting.

[0848] In conclusion, the FDA reviews the safety of new products no later than 18 months after approval. The FDA has reported that there are no significant safety issues for icosapent ethyl that would necessitate a label change. All hepatic reports are under continuous surveillance.

[0849] Various embodiments of the present disclosure are set forth herein below.

[0850] Para. A. A method for treating a patient comprising: determining or having determined whether the patient has a triglyceride level of at least 150 mg/dl and a history of

atrial fibrillation and/or atrial flutter by: obtaining or having obtained information which indicates that the patient has the triglyceride level of at least 150 mg/dl and has previously had symptoms of atrial fibrillation and/or atrial flutter and/or was previously diagnosed with atrial fibrillation and/or atrial flutter; and/or monitoring or having monitored the subject for the triglyceride level of at least 150 mg/dl and for symptoms of atrial fibrillation and/or atrial flutter; and (a) if the patient has previously had symptoms of atrial fibrillation and/or atrial flutter, was previously diagnosed with atrial fibrillation and/or atrial flutter, and/or had symptoms of atrial fibrillation and/or atrial flutter when monitored, then (i) determining whether a risk that the patient will experience symptoms of atrial fibrillation and/or atrial flutter if the patient were administered about 4 g of eicosapentaenoic acid (EPA) per day is greater than reducing a risk of one or more cardiovascular events in the patient; or (ii) determining whether reducing a risk of one or more cardiovascular events if the patient were administered about 4 g of EPA per day is greater than a risk that the patient will experience symptoms of atrial fibrillation and/or atrial flutter; and (b) if the risk is greater that the patient in (i) will experience symptoms of atrial fibrillation and/or atrial flutter, administering an atrial fibrillation flutter and/or atrial flutter therapeutic agent to the patient instead of about 4 g of EPA per day; and (c) if the risk is greater that the patient in (ii) will have a reduced risk of one or more cardiovascular events, administering about 4 g of EPA per day to the patient.

[0851] Para B. The method of Para. A., wherein the subject in (c) is likely to experience both (1) increased frequency of atrial fibrillation and/or atrial flutter symptoms, and (2) decreased frequency of cardiovascular events if administered about 4 g of EPA per day.

[0852] Para. C. The method of Para. A or B, wherein the subject is being treated with a statin and regardless if the subject is in (a) or (b), continuing to treat the subject with the statin.

[0853] Para. D. A method for treating a subject comprising: determining or having determined whether the subject has a triglyceride level of at least 150 mg/dl and a history of atrial fibrillation and/or atrial flutter by: (i) obtaining or having obtained information which indicates that the subject has the triglyceride level of at least 150 mg/dl and has previously had symptoms of atrial fibrillation and/or atrial flutter and/or was previously diagnosed with atrial fibrillation and/or atrial flutter; and/or (ii) monitoring or having monitored the subject for

the triglyceride level of at least 150 mg/dl and symptoms of atrial fibrillation and/or atrial flutter; and (a) if the subject has previously had symptoms of atrial fibrillation and/or atrial flutter, was previously diagnosed with atrial fibrillation and/or atrial flutter, and/or symptoms of atrial fibrillation and/or atrial flutter were determined during the monitoring, then administering atrial fibrillation and/or atrial flutter therapeutic agent to the subject, and (b) if the subject has not previously had symptoms of atrial fibrillation and/or atrial flutter, was not previously diagnosed with atrial fibrillation and/or atrial flutter, and/or symptoms of atrial fibrillation and/or atrial flutter were not determined during the monitoring, then administering about 4 g of eicosapentaenoic acid (EPA) per day to the subject to reduce a risk for a cardiovascular event, wherein a risk of atrial fibrillation and/or atrial flutter for the subject in (a) is lower following administration of an atrial fibrillation flutter and/or atrial flutter therapeutic agent than it would be if the subject in (a) were administered about 4 g of EPA per day.

[0854] Para. E. The method of Para. D, wherein the subject in (a) is likely to experience both (1) increased frequency of atrial fibrillation and/or atrial flutter symptoms, and (2) decreased frequency of cardiovascular events if administered about 4 g of EPA per day.

[0855] Para. F. The method of Para. E or D, wherein the subject is being treated with a statin and regardless if the subject is in (a) or (b), continuing to treat the subject with the statin.

[0856] Para. G. The method of any one of Paras. A to F, wherein the atrial fibrillation flutter and/or atrial flutter therapeutic agent is one or more of warfarin, beta blocker, calcium channel blocker.

[0857] Para. H. The method of Para. G., wherein the warfarin is administered at a dose of about 25 mg per day.

[0858] Para. I. The method of any one of Paras. A to H, wherein reducing the risk for the cardiovascular event for the subject further comprises determining that one or more cardiovascular benefits are expected to occur.

[0859] Para. J. The method of any one of Paras. A to I, wherein the cardiovascular event does not include atrial fibrillation and/or atrial flutter.

[0860] Para. K. A method of treatment comprising: identifying a subject whose measured triglyceride level is above 150 mg/dl and who has previously experienced symptoms of atrial fibrillation or atrial flutter; determining that individuals who have triglyceride levels above 150 mg/dl and who have previously experienced atrial fibrillation or atrial flutter episodes are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) decreased frequency of cardiovascular events other than atrial fibrillation or atrial flutter; and selecting a treatment according to either (a) or (b) below: (a) determining that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so treating the subject with 4 g EPA per day; or (b) determining that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead treating the subject with a statin.

[0861] Para. L. A method of treatment comprising: identifying a subject whose measured triglyceride level is above 150 mg/dl, who is being treated with a statin, and who has previously experienced symptoms of atrial fibrillation or atrial flutter; determining that individuals who have triglyceride levels above 150 mg/dl, who are being treated with a statin, and who have previously experienced atrial fibrillation or atrial flutter episodes are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) decreased frequency of cardiovascular events other than atrial fibrillation or atrial flutter; and selecting a treatment according to either (a) or (b) below: (a) determining that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so treating the subject with 4 g EPA per day and a statin; or (b) determining that decreasing a subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead continuing to treat the subject with a statin.

[0862] Para. M. A method of treatment comprising: identifying a subject whose measured triglyceride level is above 150 mg/dl who is being treated with a statin, and who has a previous history of atrial fibrillation or atrial flutter; determining that individuals who have triglyceride levels above 150 mg/dl, who are being treated with a statin, and who have a previous history of atrial fibrillation or atrial flutter are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) cardiovascular benefits expected to result from the EPA treatment; and selecting a treatment according to either (a) or (b) below:(a) determining that the expected cardiovascular benefits are worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so treating the subject with 4 g EPA per day; or (b) determining that the expected cardiovascular benefits are not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead treating the subject with a statin.

[0863] Para. N. A method of reducing a risk of a cardiovascular event in a subject having triglyceride levels of at least about 150 mg/dl, the method comprising administering to the subject at least about 4 g of eicosapentaenoic acid (EPA) per day for a period of time effective to reduce the cardiovascular event, wherein the subject develops atrial fibrillation and/or atrial flutter during the period of time effective to reduce the risk of the cardiovascular event.

[0864] Para. O. The method of Para. N, wherein the subject did not have a history of atrial fibrillation and/or flutter prior to administration of the 4 g of EPA.

[0865] Para. P. A method of reducing a risk of a cardiovascular event in a subject having triglyceride levels of at least about 150 mg/dl and less than 65 years of age, the method comprising administering to the subject at least about 4 g of eicosapentaenoic acid (EPA) per day for a period of time effective to reduce the cardiovascular event, wherein the subject does not exhibit an increase in symptoms atrial fibrillation and/or atrial flutter.

[0866] Para Q. The method of any one of Paras. A to P, wherein the subject has established cardiovascular disease.

[0867] Para. R. The method of Para. Q, 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.

[0868] Para. S. The method of any one of Paras. A to P, wherein the subject does not have an established cardiovascular disease but at least two risk factors for cardiovascular disease.

[0869] Para. T. The method of any one of Paras. A to S, wherein the EPA is administered to the subject in 1 to 4 dosage units per day.

[0870] Para. U. The method of any one of Paras. A to T, 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.

[0871] Para. V. The method of any one of Paras. A to U, the subject is administered the EPA for at least about 4 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, or at least about 5 years.

CLAIMS

1. A method for treating a patient comprising:

determining or having determined whether the patient has a triglyceride level of at least 150 mg/dl and a history of atrial fibrillation and/or atrial flutter by:

obtaining or having obtained information which indicates that the patient has the triglyceride level of at least 150 mg/dl and has previously had symptoms of atrial fibrillation and/or atrial flutter and/or was previously diagnosed with atrial fibrillation and/or atrial flutter; and/or

monitoring or having monitored the subject for the triglyceride level of at least 150 mg/dl and for symptoms of atrial fibrillation and/or atrial flutter; and

(a) if the patient has previously had symptoms of atrial fibrillation and/or atrial flutter, was previously diagnosed with atrial fibrillation and/or atrial flutter, and/or had symptoms of atrial fibrillation and/or atrial flutter when monitored, then

(i) determining whether a risk that the patient will experience symptoms of atrial fibrillation and/or atrial flutter if the patient were administered about 4 g of eicosapentaenoic acid (EPA) per day is greater than reducing a risk of one or more cardiovascular events in the patient; or

(ii) determining whether reducing a risk of one or more cardiovascular events if the patient were administered about 4 g of EPA per day is greater than a risk that the patient will experience symptoms of atrial fibrillation and/or atrial flutter; and

(b) if the risk is greater that the patient in (i) will experience symptoms of atrial fibrillation and/or atrial flutter, administering an atrial fibrillation flutter and/or atrial flutter therapeutic agent to the patient instead of about 4 g of EPA per day; and

(c) if the risk is greater that the patient in (ii) will have a reduced risk of one or more cardiovascular events, administering about 4 g of EPA per day to the patient.

2. The method of claim 1, wherein the subject in (c) is likely to experience both (1) increased frequency of atrial fibrillation and/or atrial flutter symptoms, and (2) decreased frequency of cardiovascular events if administered about 4 g of EPA per day.

3. The method of claim 1, wherein the subject is being treated with a statin and regardless if the subject is in (a) or (b), continuing to treat the subject with the statin.

4. A method for treating a subject comprising:

determining or having determined whether the subject has a triglyceride level of at least 150 mg/dl and a history of atrial fibrillation and/or atrial flutter by:

(i) obtaining or having obtained information which indicates that the subject has the triglyceride level of at least 150 mg/dl and has previously had symptoms of atrial fibrillation and/or atrial flutter and/or was previously diagnosed with atrial fibrillation and/or atrial flutter; and/or

(ii) monitoring or having monitored the subject for the triglyceride level of at least 150 mg/dl and symptoms of atrial fibrillation and/or atrial flutter; and

(a) if the subject has previously had symptoms of atrial fibrillation and/or atrial flutter, was previously diagnosed with atrial fibrillation and/or atrial flutter, and/or symptoms of atrial fibrillation and/or atrial flutter were determined during the monitoring, then administering atrial fibrillation and/or atrial flutter therapeutic agent to the subject, and

(b) if the subject has not previously had symptoms of atrial fibrillation and/or atrial flutter, was not previously diagnosed with atrial fibrillation and/or atrial flutter, and/or symptoms of atrial fibrillation and/or atrial flutter were not determined during the monitoring,

then administering about 4 g of eicosapentaenoic acid (EPA) per day to the subject to reduce a risk for a cardiovascular event,

wherein a risk of atrial fibrillation and/or atrial flutter for the subject in (a) is lower following administration of an atrial fibrillation flutter and/or atrial flutter therapeutic agent than it would be if the subject in (a) were administered about 4 g of EPA per day.

5. The method of claim 4, wherein the subject in (a) is likely to experience both (1) increased frequency of atrial fibrillation and/or atrial flutter symptoms, and (2) decreased frequency of cardiovascular events if administered about 4 g of EPA per day.

6. The method of claim 4, wherein the subject is being treated with a statin and regardless if the subject is in (a) or (b), continuing to treat the subject with the statin.

7. The method of any one of claims 1 to 6, wherein the atrial fibrillation flutter and/or atrial flutter therapeutic agent is one or more of warfarin, beta blocker, calcium channel blocker.

8. The method of claim 7, wherein the warfarin is administered at a dose of about 25 mg per day.

9. The method of any one of claims 1 to 8, wherein reducing the risk for the cardiovascular event for the subject further comprises determining that one or more cardiovascular benefits are expected to occur.

10. The method of any one of claims 1 to 9, wherein the cardiovascular event does not include atrial fibrillation and/or atrial flutter.

11. A method of treatment comprising:

identifying a subject whose measured triglyceride level is above 150 mg/dl and who has previously experienced symptoms of atrial fibrillation or atrial flutter;

determining that individuals who have triglyceride levels above 150 mg/dl and who have previously experienced atrial fibrillation or atrial flutter episodes are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) decreased frequency of cardiovascular events other than atrial fibrillation or atrial flutter; and

selecting a treatment according to either (a) or (b) below:

(a) determining that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so treating the subject with 4 g EPA per day; or

(b) determining that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead treating the subject with a statin.

12. A method of treatment comprising:

identifying a subject whose measured triglyceride level is above 150 mg/dl, who is being treated with a statin, and who has previously experienced symptoms of atrial fibrillation or atrial flutter;

determining that individuals who have triglyceride levels above 150 mg/dl, who are being treated with a statin, and who have previously experienced atrial fibrillation or atrial flutter episodes are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) decreased frequency of cardiovascular events other than atrial fibrillation or atrial flutter; and

selecting a treatment according to either (a) or (b) below:

(a) determining that decreasing the subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so treating the subject with 4 g EPA per day and a statin; or

(b) determining that decreasing a subject's frequency of cardiovascular events other than atrial fibrillation or atrial flutter is not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead continuing to treat the subject with a statin.

13. A method of treatment comprising:

identifying a subject whose measured triglyceride level is above 150 mg/dl who is being treated with a statin, and who has a previous history of atrial fibrillation or atrial flutter;

determining that individuals who have triglyceride levels above 150 mg/dl, who are being treated with a statin, and who have a previous history of atrial fibrillation or atrial flutter are, upon treatment with 4 g eicosapentaenoic acid (EPA) per day, likely to experience both (1) increased frequency of atrial fibrillation or atrial flutter episodes, and (2) cardiovascular benefits expected to result from the EPA treatment; and

selecting a treatment according to either (a) or (b) below:

(a) determining that the expected cardiovascular benefits are worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so treating the subject with 4 g EPA per day; or

(b) determining that the expected cardiovascular benefits are not worth a risk of increased frequency of atrial fibrillation or atrial flutter in the subject, and so excluding the subject from treatment with EPA, and instead treating the subject with a statin.

14. A method of reducing a risk of a cardiovascular event in a subject having triglyceride levels of at least about 150 mg/dl, the method comprising administering to the subject at least about 4 g of eicosapentaenoic acid (EPA) per day for a period of time effective to reduce the cardiovascular event, wherein the subject develops atrial fibrillation and/or atrial flutter during the period of time effective to reduce the risk of the cardiovascular event.

15. The method of claim 14, wherein the subject does not have a history of atrial fibrillation and/or flutter prior to administration of the 4 g of EPA.

16. A method of reducing a risk of a cardiovascular event in a subject having triglyceride levels of at least about 150 mg/dl and less than 65 years of age, the method comprising administering to the subject at least about 4 g of eicosapentaenoic acid (EPA) per day for a period of time effective to reduce the cardiovascular event, wherein the subject does not exhibit an increase in symptoms atrial fibrillation and/or atrial flutter.

17. The method of any one of claims 1 to 16, wherein the subject has established cardiovascular disease.

18. The method of claim 17, 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.

19. The method of any one of claims 1 to 16, wherein the subject does not have an established cardiovascular disease but at least two risk factors for cardiovascular disease.

20. The method of any one of claims 1 to 19, wherein the EPA is administered to the subject in 1 to 4 dosage units per day.

21. The method of any one of claims 1 to 20, 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.

22. The method of any one of claims 1 to 21, wherein the subject is administered the EPA for at least about 4 months, at least about 1 year, at least about 2 years, at least about 3 years, at least about 4 years, or at least about 5 years.

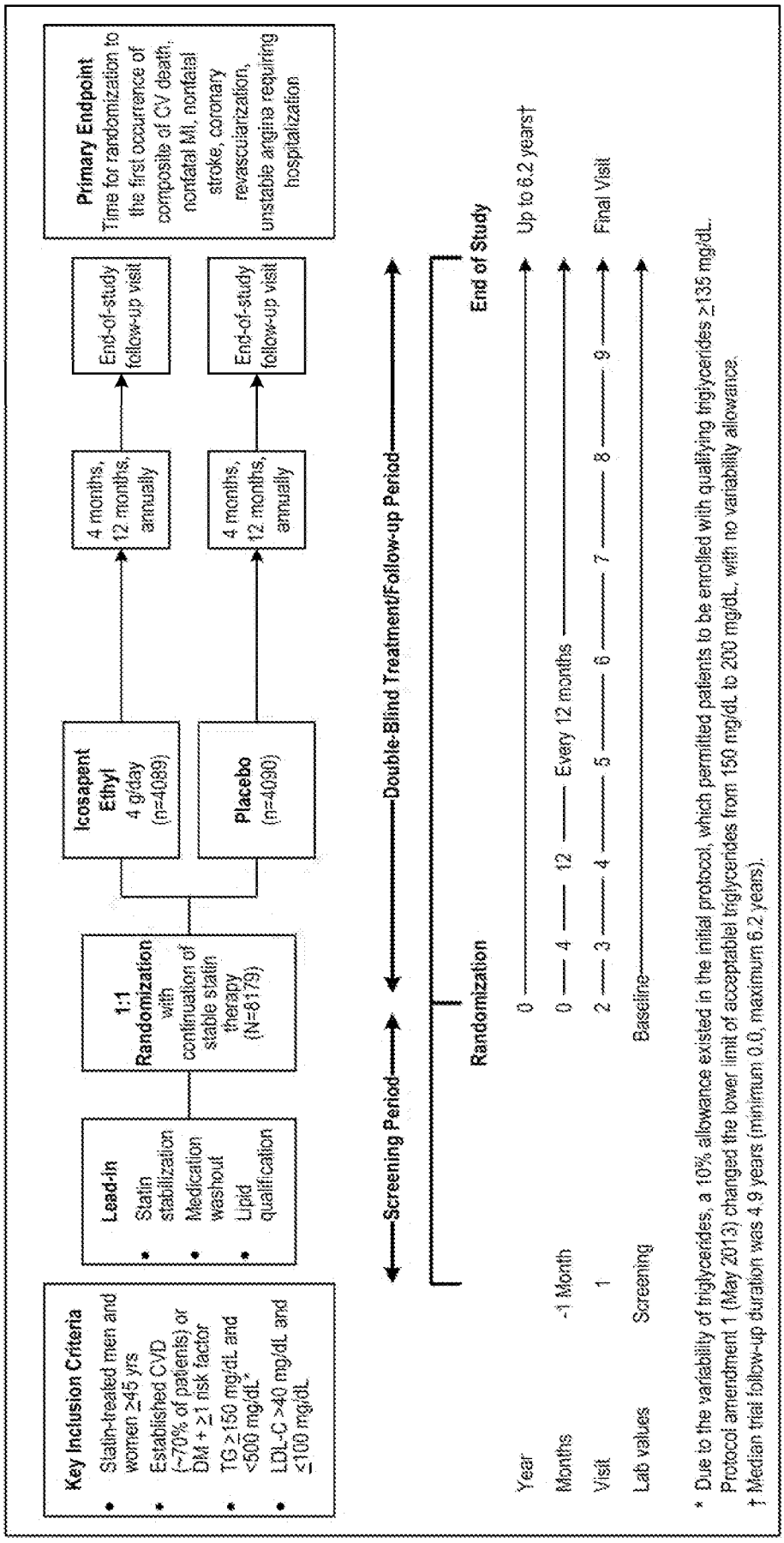

Key Inclusion Criteria
Statin-treated men and women ≥45 yrs
Established CVD (~70% of patients) or DM + ≥1 risk factor
TG ≥150 mg/dL and <500 mg/dL*
LDL-C >40 mg/dL and ≤100 mg/dL
Lead-in
Statin stabilization
Medication washout
Lipid qualification
1:1 Randomization with continuation of stable statin therapy (N=8179)
Icosapent Ethyl 4 g/day (n=4089)
Placebo (n=4090)
4 months, 12 months, annually
4 months, 12 months, annually
End-of-study follow-up visit
End-of-study follow-up visit
Primary Endpoint
Time for randomization to the first occurrence of composite of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina requiring hospitalization
Screening Period
Randomization
Double-Blind Treatment/Follow-up Period
End of Study
Year 0 Up to 6.2 years†
Months -1 Month 0 4 12 Every 12 months
Visit 1 2 3 4 5 6 7 8 9 Final Visit
Lab values Screening Baseline
* Due to the variability of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL. Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.
† Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).

FIG. 1

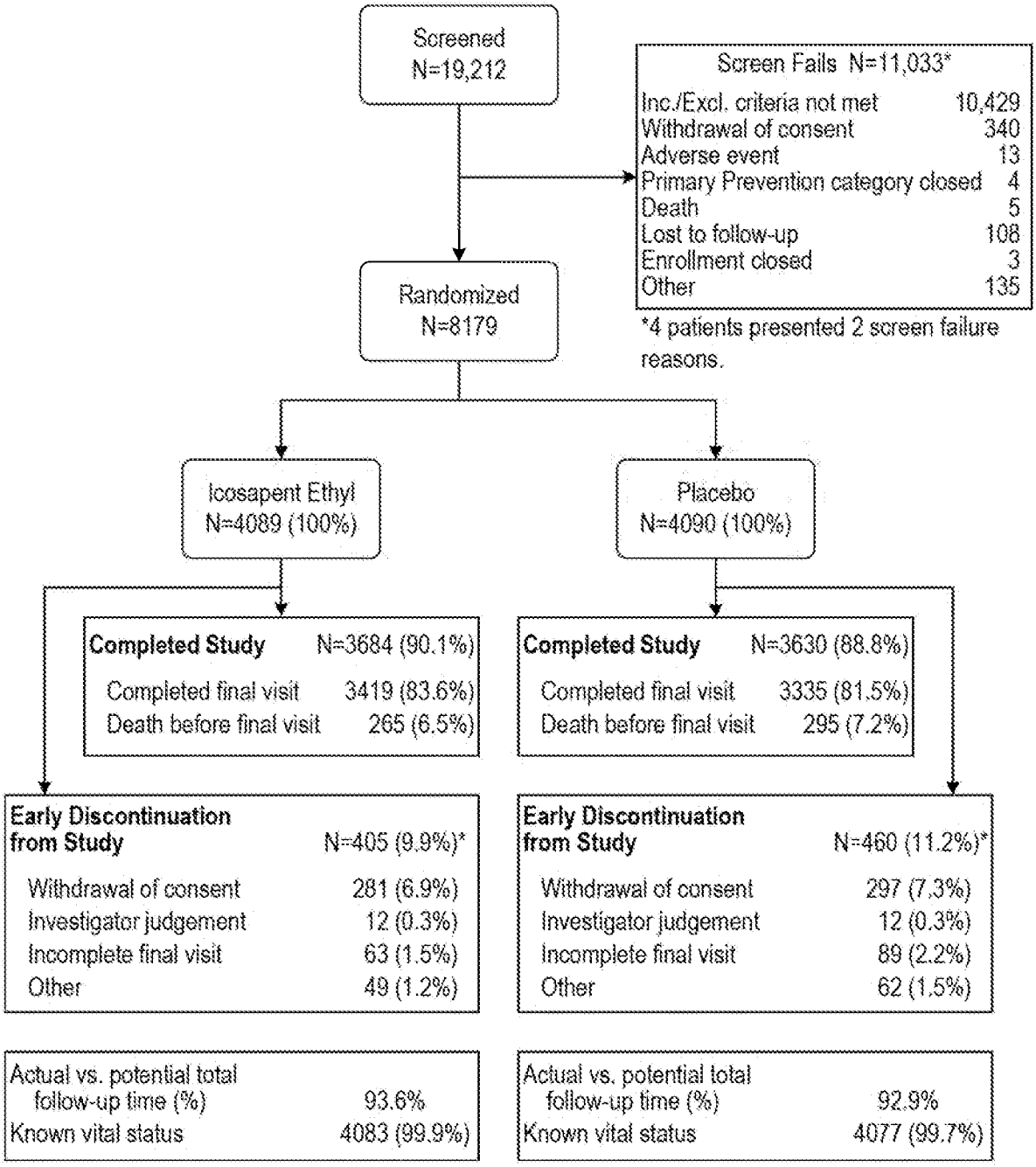

Screened
N=19,212
Screen Fails N=11,033*
Inc./Excl. criteria not met 10,429
Withdrawal of consent 340
Adverse event 13
Primary Prevention category closed 4
Death 5
Lost to follow-up 108
Enrollment closed 3
Other 135
*4 patients presented 2 screen failure reasons.
Randomized
N=8179
Icosapent Ethyl
N=4089 (100%)
Placebo
N=4090 (100%)
Completed Study N=3684 (90.1%)
Completed final visit 3419 (83.6%)
Death before final visit 265 (6.5%)
Completed Study N=3630 (88.8%)
Completed final visit 3335 (81.5%)
Death before final visit 295 (7.2%)
Early Discontinuation from Study N=405 (9.9%)*
Withdrawal of consent 281 (6.9%)
Investigator judgement 12 (0.3%)
Incomplete final visit 63 (1.5%)
Other 49 (1.2%)
Early Discontinuation from Study N=460 (11.2%)*
Withdrawal of consent 297 (7.3%)
Investigator judgement 12 (0.3%)
Incomplete final visit 89 (2.2%)
Other 62 (1.5%)
Actual vs. potential total follow-up time (%) 93.6%
Known vital status 4083 (99.9%)
Actual vs. potential total follow-up time (%) 92.9%
Known vital status 4077 (99.7%)

FIG. 2

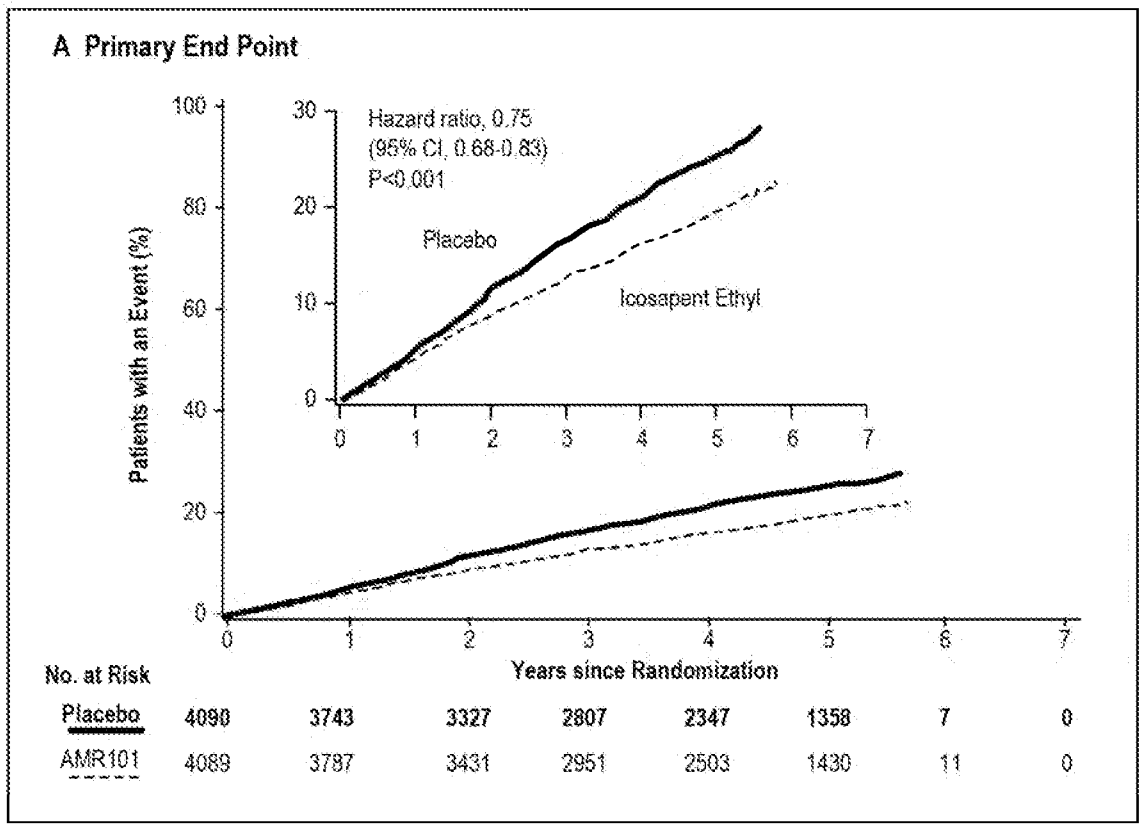

A Primary End Point
Patients with an Event (%)
Hazard ratio, 0.75
(95% CI, 0.68-0.83)
P<0.001
Placebo
Icosapent Ethyl
Years since Randomization
No. at Risk
Placebo 4090 3743 3327 2807 2347 1358 7 0
AMR101 4089 3787 3431 2951 2503 1430 11 0

FIG. 3A

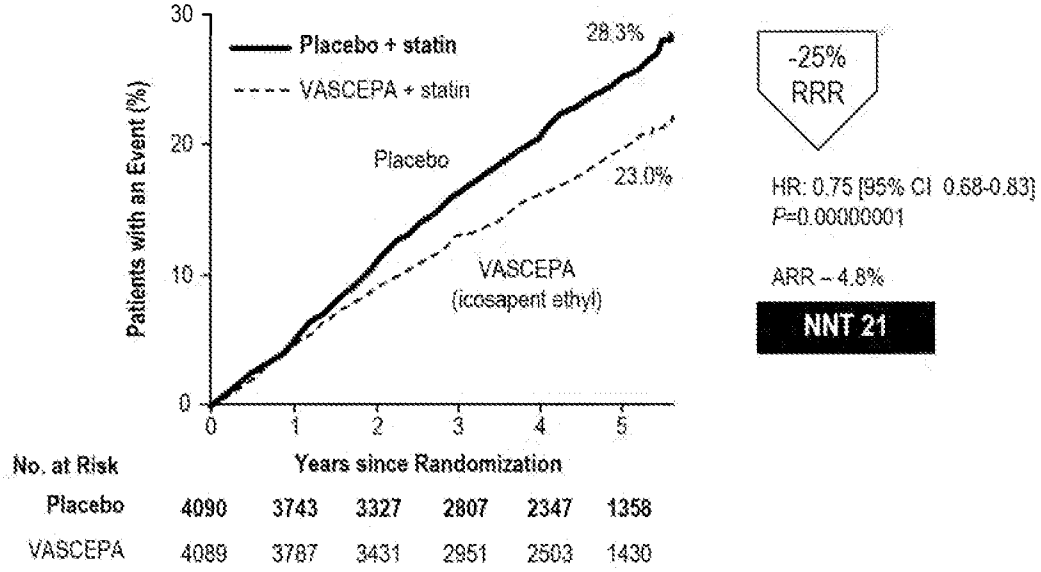

30
20
10
0
Patients with an Event (%)
Placebo + statin
VASCEPA + statin
28.3%
Placebo
23.0%
VASCEPA
(icosapent ethyl)
0
1
2
3
4
5
Years since Randomization
-25%
RRR
HR: 0.75 [95% CI 0.68-0.83]
P=0.00000001
ARR – 4.8%
NNT 21
No. at Risk
Placebo 4090 3743 3327 2807 2347 1358
VASCEPA 4089 3787 3431 2951 2503 1430

FIG. 3B

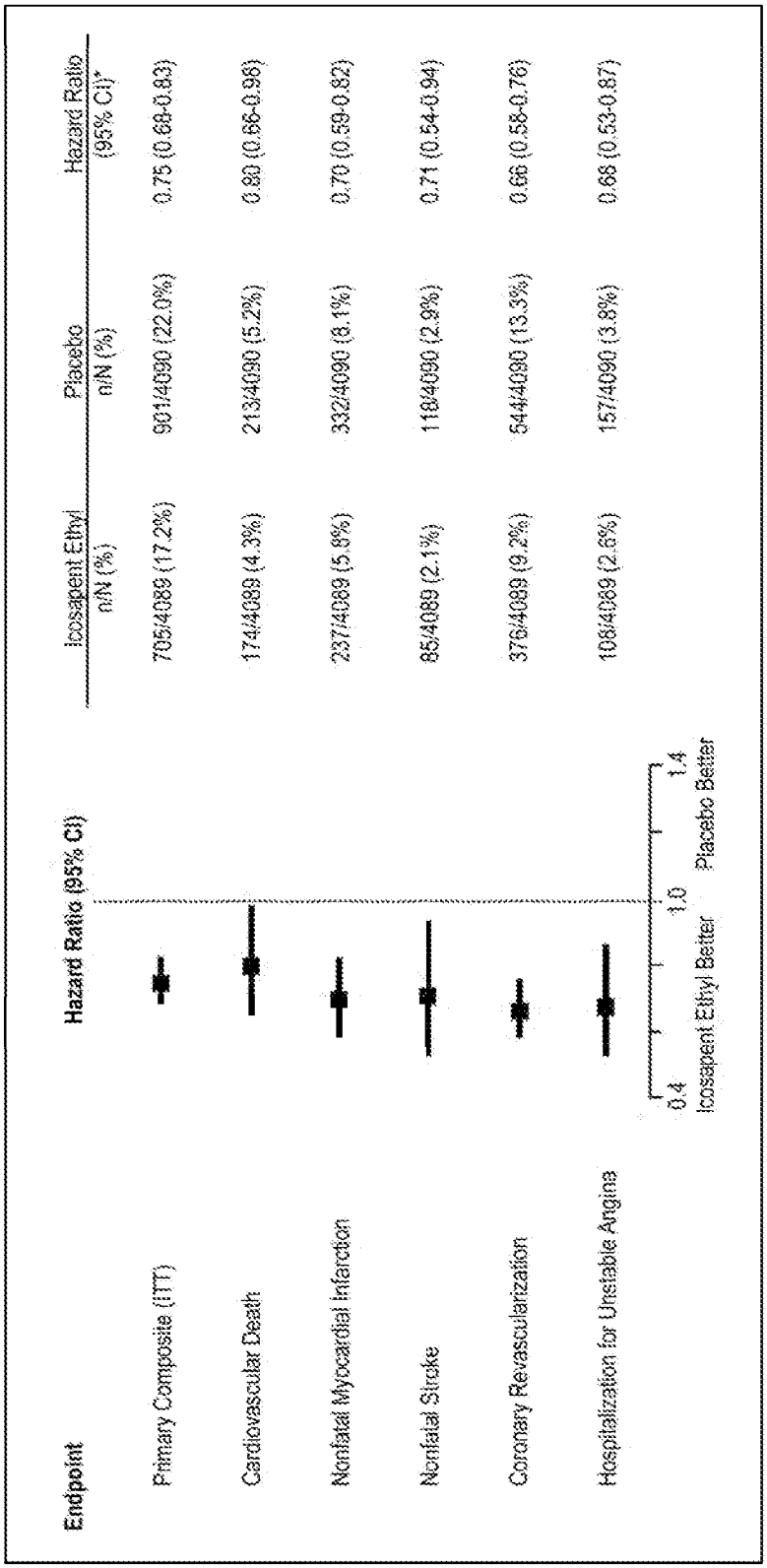

Endpoint
Hazard Ratio (95% CI)
Icosapent Ethyl n/N (%)
Placebo n/N (%)
Hazard Ratio (95% CI)*
Primary Composite (ITT) 705/4089 (17.2%) 901/4090 (22.0%) 0.75 (0.68-0.83)
Cardiovascular Death 174/4089 (4.3%) 213/4090 (5.2%) 0.80 (0.66-0.96)
Nonfatal Myocardial Infarction 237/4089 (5.8%) 332/4090 (8.1%) 0.70 (0.59-0.82)
Nonfatal Stroke 85/4089 (2.1%) 118/4090 (2.9%) 0.71 (0.54-0.94)
Coronary Revascularization 376/4089 (9.2%) 544/4090 (13.3%) 0.66 (0.58-0.76)
Hospitalization for Unstable Angina 108/4089 (2.6%) 157/4090 (3.8%) 0.68 (0.53-0.87)
0.4
1.0
1.4
Icosapent Ethyl Better
Placebo Better

FIG. 4

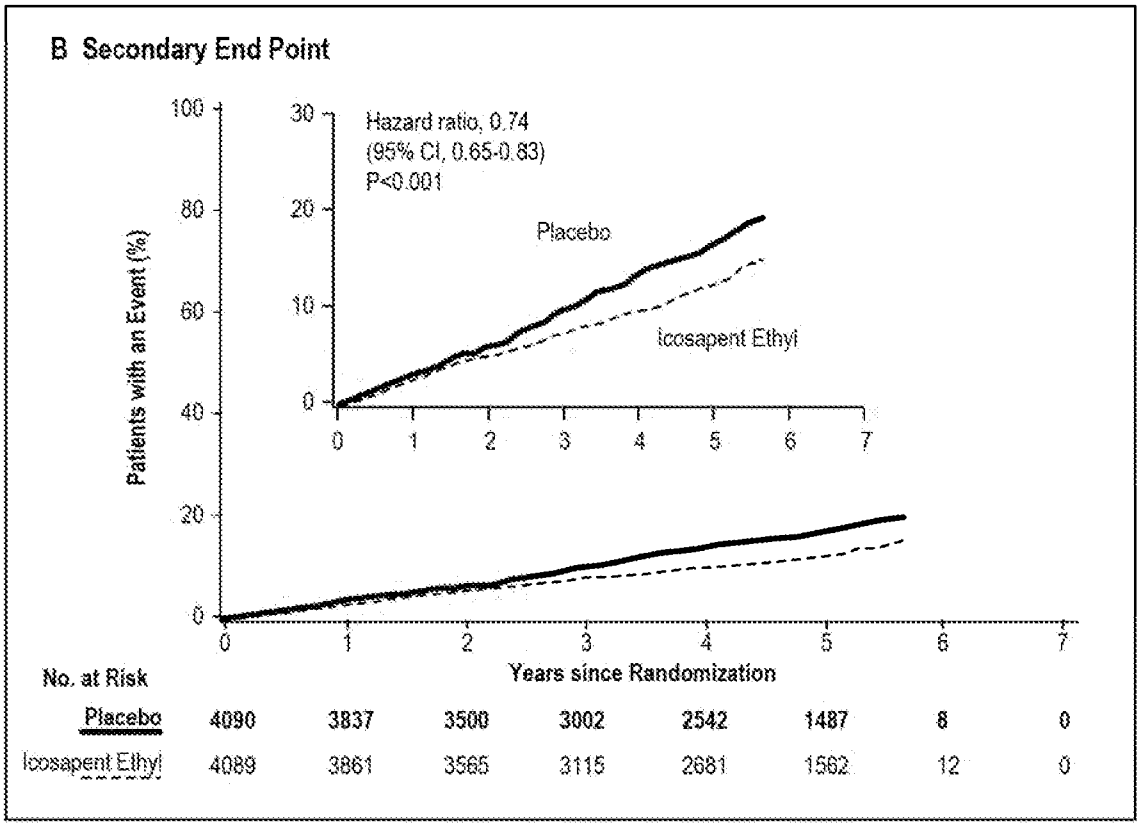

B Secondary End Point
Hazard ratio, 0.74
(95% CI, 0.65-0.83)
P<0.001
Placebo
Icosapent Ethyl
Patients with an Event (%)
Years since Randomization
No. at Risk
Placebo 4090 3837 3500 3002 2542 1487 8 0
Icosapent Ethyl 4089 3861 3565 3115 2681 1562 12 0

FIG. 5A

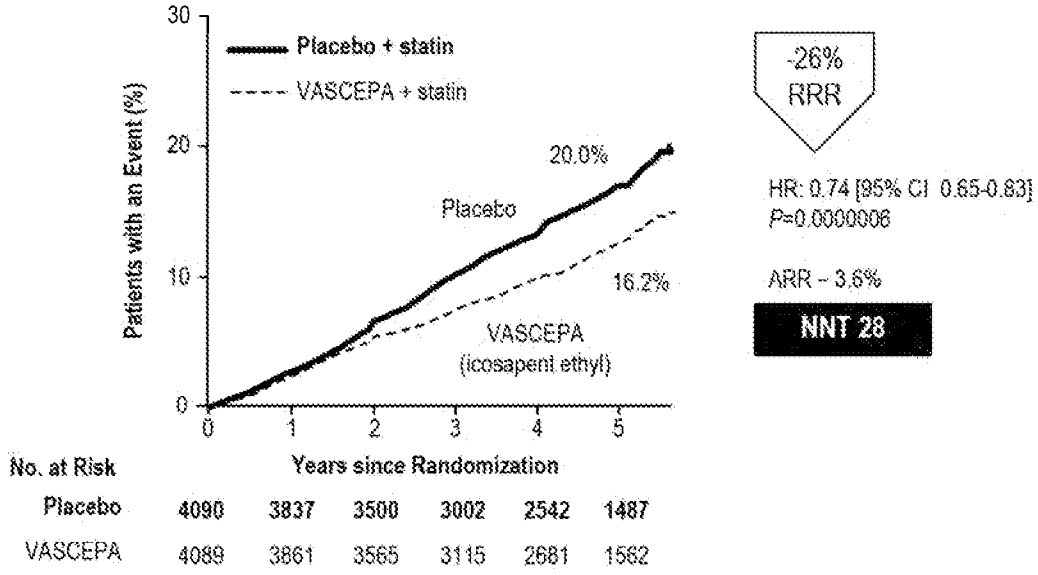

30
20
10
0
Patients with an Event (%)
Placebo + statin
VASCEPA + statin
20.0%
Placebo
16.2%
VASCEPA
(icosapent ethyl)
0
1
2
3
4
5
Years since Randomization
-26%
RRR
HR: 0.74 [95% CI 0.65-0.83]
P=0.0000006
ARR – 3.6%
NNT 28
No. at Risk
Placebo 4090 3837 3500 3002 2542 1487
VASCEPA 4089 3861 3565 3115 2681 1562

FIG. 5B

Figure 11-3: Forest Plot of Analyses of Individual Components of the Primary and Key Secondary Endpoints (ITT Population)

Endpoint	Hazard Ratio (95% CI)	AMR101 n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	p-Value
Primary Composite (ITT)		705/4089 (17.2)	901/4090 (22.0)	0.752 (0.682, 0.830)	<0.0001
Key Secondary Composite		463/4089 (11.2)	606/4090 (14.8)	0.735 (0.651, 0.830)	<0.0001
Cardiovascular Death		174/4089 (4.3)	219/4090 (5.2)	0.803 (0.657, 0.981)	0.03
Nonfatal Myocardial Infarction		237/4089 (5.8)	332/4090 (8.1)	0.697 (0.590, 0.823)	<0.0001
Nonfatal Stroke		85/4089 (2.1)	118/4090 (2.9)	0.708 (0.536, 0.936)	0.01
Coronary Revascularization		378/4089 (9.2)	544/4090 (13.3)	0.664 (0.583, 0.758)	<0.0001
Hospitalization for Unstable Angina		109/4089 (2.6)	157/4090 (3.8)	0.679 (0.531, 0.868)	0.002

0.4 1.0 1.4

AMR101 Better — Placebo Better

Abbreviations: CI = confidence interval, MI = myocardial infarction, ITT = Intent-to-Treat.

FIG. 6

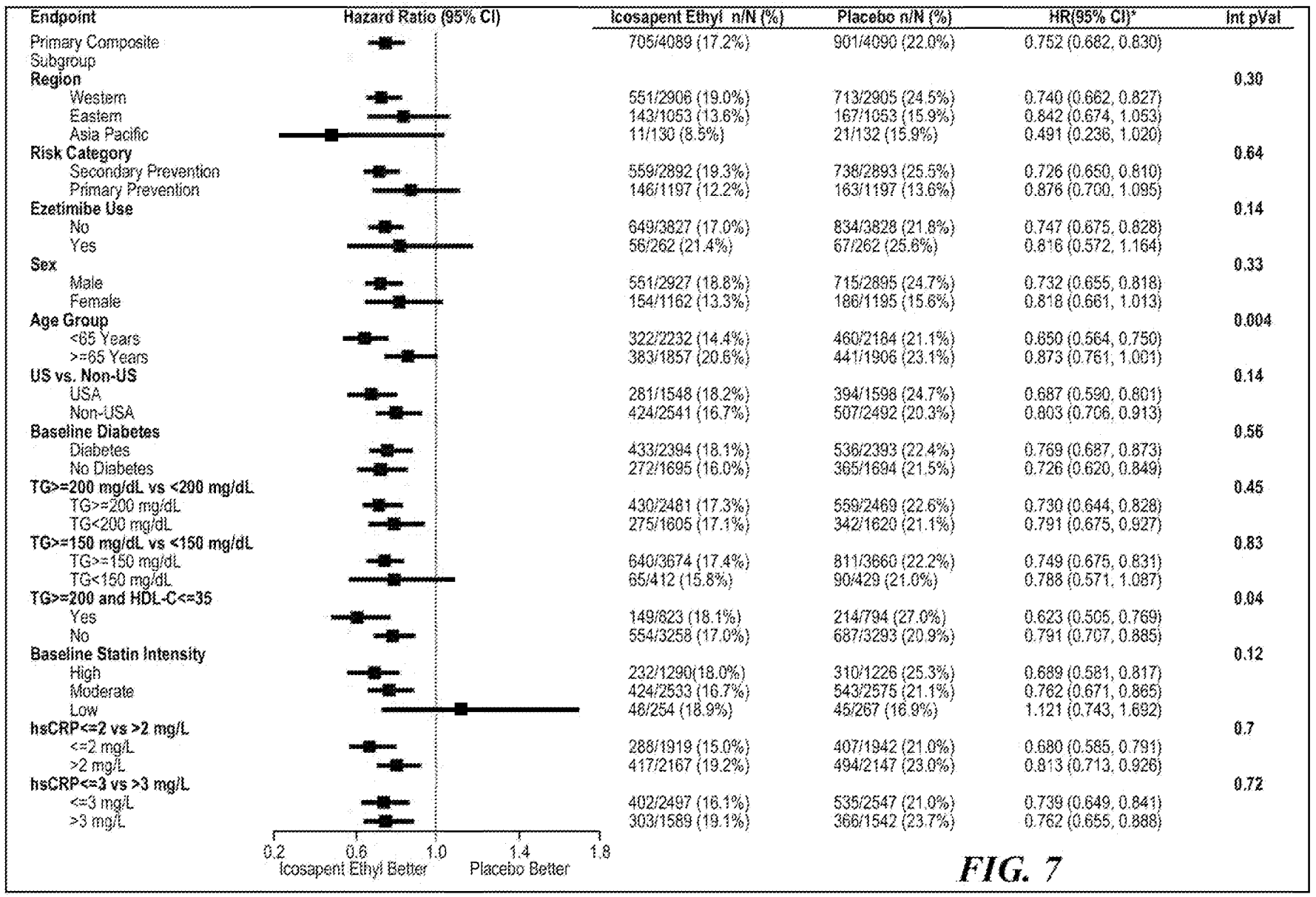

Endpoint
Hazard Ratio (95% CI)
Icosapent Ethyl n/N (%)
Placebo n/N (%)
HR(95% CI)*
Int pVal
Primary Composite 705/4089 (17.2%) 901/4090 (22.0%) 0.752 (0.682, 0.830)
Subgroup
Region 0.30
Western 551/2906 (19.0%) 713/2905 (24.5%) 0.740 (0.662, 0.827)
Eastern 143/1053 (13.6%) 167/1053 (15.9%) 0.842 (0.674, 1.053)
Asia Pacific 11/130 (8.5%) 21/132 (15.9%) 0.491 (0.236, 1.020)
Risk Category 0.64
Secondary Prevention 559/2892 (19.3%) 738/2893 (25.5%) 0.726 (0.650, 0.810)
Primary Prevention 146/1197 (12.2%) 163/1197 (13.6%) 0.876 (0.700, 1.095)
Ezetimibe Use 0.14
No 649/3827 (17.0%) 834/3828 (21.8%) 0.747 (0.675, 0.828)
Yes 56/262 (21.4%) 67/262 (25.6%) 0.816 (0.572, 1.164)
Sex 0.33
Male 551/2927 (18.8%) 715/2895 (24.7%) 0.732 (0.655, 0.818)
Female 154/1162 (13.3%) 186/1195 (15.6%) 0.818 (0.661, 1.013)
Age Group 0.004
<65 Years 322/2232 (14.4%) 460/2184 (21.1%) 0.650 (0.564, 0.750)
>=65 Years 383/1857 (20.6%) 441/1906 (23.1%) 0.873 (0.761, 1.001)
US vs. Non-US 0.14
USA 281/1548 (18.2%) 394/1598 (24.7%) 0.687 (0.590, 0.801)
Non-USA 424/2541 (16.7%) 507/2492 (20.3%) 0.803 (0.706, 0.913)
Baseline Diabetes 0.56
Diabetes 433/2394 (18.1%) 536/2393 (22.4%) 0.769 (0.687, 0.873)
No Diabetes 272/1695 (16.0%) 365/1694 (21.5%) 0.726 (0.620, 0.849)
TG>=200 mg/dL vs <200 mg/dL 0.45
TG>=200 mg/dL 430/2481 (17.3%) 559/2469 (22.6%) 0.730 (0.644, 0.828)
TG<200 mg/dL 275/1605 (17.1%) 342/1620 (21.1%) 0.791 (0.675, 0.927)
TG>=150 mg/dL vs <150 mg/dL 0.83
TG>=150 mg/dL 640/3674 (17.4%) 811/3660 (22.2%) 0.749 (0.675, 0.831)
TG<150 mg/dL 65/412 (15.8%) 90/429 (21.0%) 0.788 (0.571, 1.087)
TG>=200 and HDL-C<=35 0.04
Yes 149/823 (18.1%) 214/794 (27.0%) 0.623 (0.505, 0.769)
No 554/3258 (17.0%) 687/3293 (20.9%) 0.791 (0.707, 0.885)
Baseline Statin Intensity 0.12
High 232/1290(18.0%) 310/1226 (25.3%) 0.689 (0.581, 0.817)
Moderate 424/2533 (16.7%) 543/2575 (21.1%) 0.762 (0.671, 0.865)
Low 48/254 (18.9%) 45/267 (16.9%) 1.121 (0.743, 1.692)
hsCRP<=2 vs >2 mg/L 0.7
<=2 mg/L 288/1919 (15.0%) 407/1942 (21.0%) 0.680 (0.585, 0.791)
>2 mg/L 417/2167 (19.2%) 494/2147 (23.0%) 0.813 (0.713, 0.926)
hsCRP<=3 vs >3 mg/L 0.72
<=3 mg/L 402/2497 (16.1%) 535/2547 (21.0%) 0.739 (0.649, 0.841)
>3 mg/L 303/1589 (19.1%) 366/1542 (23.7%) 0.762 (0.655, 0.888)
0.2
0.6
1.0
1.4
1.8
Icosapent Ethyl Better
Placebo Better

FIG. 7

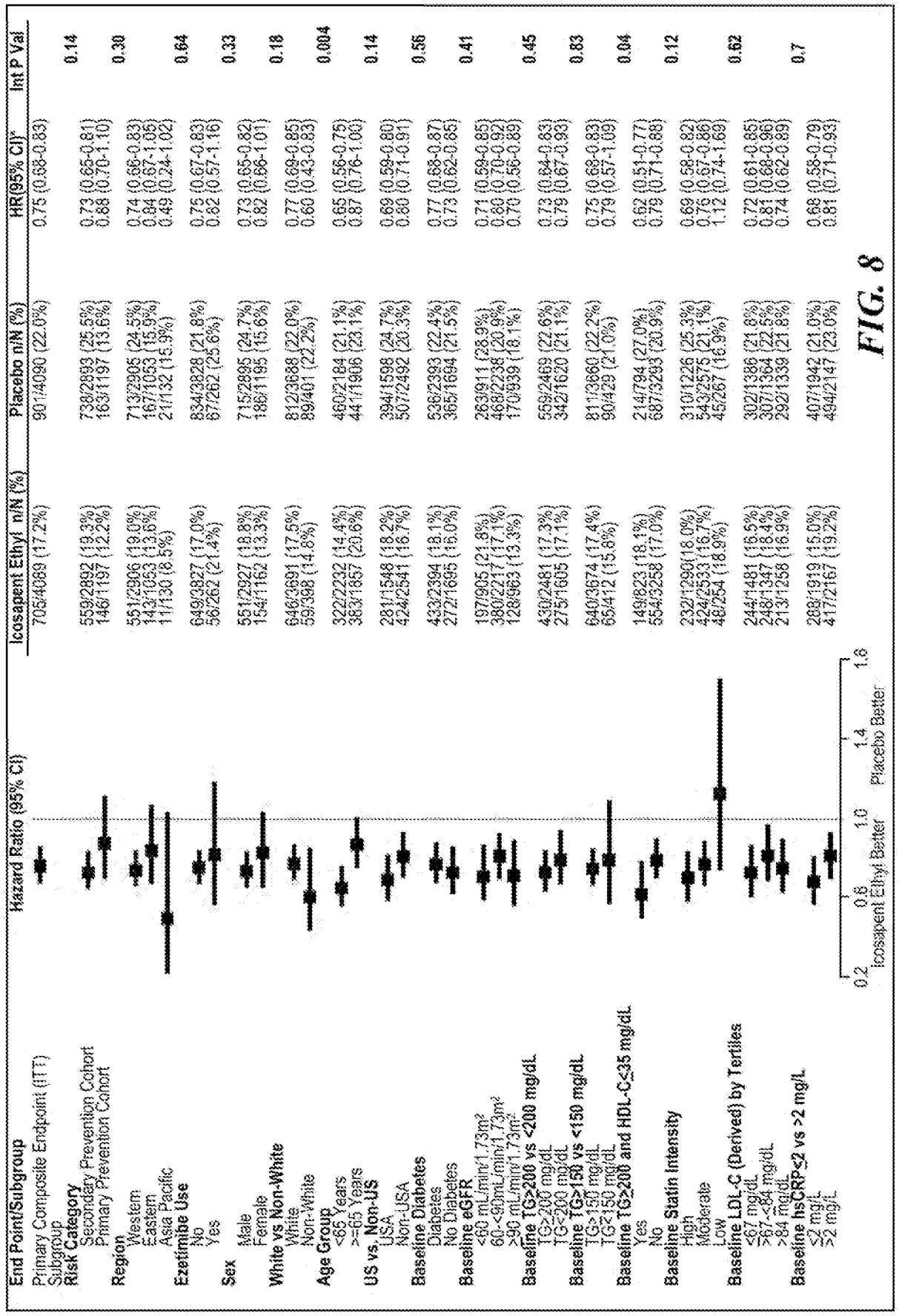

End Point/Subgroup
Hazard Ratio (95% CI)
Icosapent Ethyl n/N (%)
Placebo n/N (%)
HR(95% CI)*
Int P Val
Primary Composite Endpoint (ITT)
705/4089 (17.2%)
901/4090 (22.0%)
0.75 (0.68-0.83)
Subgroup
Risk Category 0.14
Secondary Prevention Cohort 559/2892 (19.3%) 738/2893 (25.5%) 0.73 (0.65-0.81)
Primary Prevention Cohort 146/1197 (12.2%) 163/1197 (13.6%) 0.88 (0.70-1.10)
Region 0.38
Western 551/2906 (19.0%) 713/2905 (24.5%) 0.74 (0.66-0.83)
Eastern 143/1053 (13.6%) 167/1053 (15.9%) 0.84 (0.67-1.05)
Asia Pacific 11/130 (8.5%) 21/132 (15.9%) 0.49 (0.24-1.02)
Ezetimibe Use 0.64
No 649/3827 (17.0%) 834/3828 (21.8%) 0.76 (0.67-0.83)
Yes 56/262 (21.4%) 67/262 (25.6%) 0.82 (0.57-1.16)
Sex 0.33
Male 551/2927 (18.8%) 715/2895 (24.7%) 0.73 (0.65-0.82)
Female 154/1162 (13.3%) 186/1195 (15.6%) 0.82 (0.66-1.01)
White vs Non-White 0.18
White 646/3691 (17.5%) 812/3688 (22.0%) 0.77 (0.69-0.85)
Non-White 59/398 (14.8%) 89/401 (22.2%) 0.60 (0.43-0.83)
Age Group 0.004
<65 Years 322/2232 (14.4%) 460/2184 (21.1%) 0.65 (0.56-0.75)
>=65 Years 383/1857 (20.6%) 441/1906 (23.1%) 0.87 (0.76-1.00)
US vs. Non-US 0.14
USA 281/1548 (18.2%) 394/1598 (24.7%) 0.69 (0.59-0.80)
Non-USA 424/2541 (16.7%) 507/2492 (20.3%) 0.80 (0.71-0.91)
Baseline Diabetes 0.56
Diabetes 433/2394 (18.1%) 536/2393 (22.4%) 0.77 (0.68-0.87)
No Diabetes 272/1695 (16.0%) 365/1694 (21.5%) 0.73 (0.62-0.85)
Baseline eGFR 0.41
<60 mL/min/1.73m² 197/905 (21.8%) 263/911 (28.9%) 0.71 (0.59-0.85)
60-<90mL/min/1.73m² 380/2217 (17.1%) 468/2238 (20.9%) 0.80 (0.70-0.92)
>90 mL/min/1.73m² 128/963 (13.3%) 170/939 (18.1%) 0.70 (0.56-0.89)
Baseline TG≥200 vs <200 mg/dL 0.45
TG≥200 mg/dL 430/2481 (17.3%) 559/2469 (22.6%) 0.73 (0.64-0.83)
TG<200 mg/dL 275/1605 (17.1%) 342/1620 (21.1%) 0.79 (0.67-0.93)
Baseline TG≥150 vs <150 mg/dL 0.83
TG≥150 mg/dL 640/3674 (17.4%) 811/3660 (22.2%) 0.75 (0.68-0.83)
TG<150 mg/dL 65/412 (15.8%) 90/429 (21.0%) 0.79 (0.57-1.09)
Baseline TG≥200 and HDL-C≤35 mg/dL 0.04
Yes 149/823 (18.1%) 214/794 (27.0%) 0.62 (0.51-0.77)
No 554/3258 (17.0%) 687/3293 (20.9%) 0.79 (0.71-0.88)
Baseline Statin Intensity 0.12
High 232/1290 (18.0%) 310/1226 (25.3%) 0.69 (0.58-0.82)
Moderate 424/2533 (16.7%) 543/2575 (21.1%) 0.76 (0.67-0.86)
Low 48/254 (18.9%) 45/267 (16.9%) 1.12 (0.74-1.69)
Baseline LDL-C (Derived) by Tertiles 0.62
<67 mg/dL 244/1481 (16.5%) 302/1386 (21.8%) 0.72 (0.61-0.85)
>67-<84 mg/dL 248/1347 (18.4%) 307/1364 (22.5%) 0.81 (0.68-0.96)
>84 mg/dL 213/1258 (16.9%) 292/1339 (21.8%) 0.74 (0.62-0.89)
Baseline hsCRP≤2 vs >2 mg/L 0.7
≤2 mg/L 288/1919 (15.0%) 407/1942 (21.0%) 0.68 (0.58-0.79)
>2 mg/L 417/2167 (19.2%) 494/2147 (23.0%) 0.81 (0.71-0.93)
0.2
0.6
1.0
1.4
1.8
Icosapent Ethyl Better
Placebo Better

FIG. 8

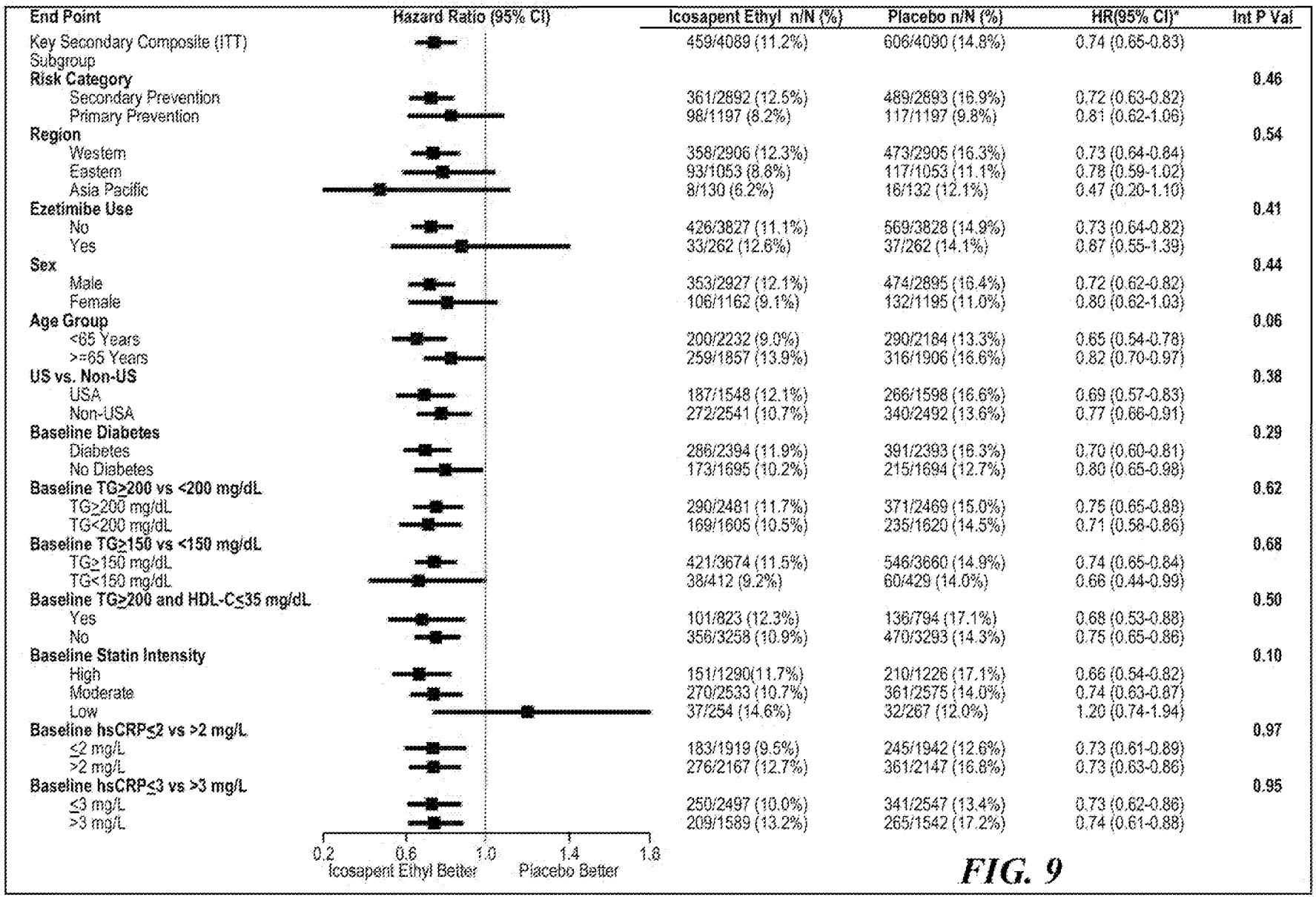

End Point
Hazard Ratio (95% CI)
Icosapent Ethyl n/N (%)
Placebo n/N (%)
HR(95% CI)*
Int P Val
Key Secondary Composite (ITT)
459/4089 (11.2%)
606/4090 (14.8%)
0.74 (0.65-0.83)
Subgroup
Risk Category
0.46
Secondary Prevention
361/2892 (12.5%)
489/2893 (16.9%)
0.72 (0.63-0.82)
Primary Prevention
98/1197 (8.2%)
117/1197 (9.8%)
0.81 (0.62-1.06)
Region
0.54
Western
358/2906 (12.3%)
473/2905 (16.3%)
0.73 (0.64-0.84)
Eastern
93/1053 (8.8%)
117/1053 (11.1%)
0.78 (0.59-1.02)
Asia Pacific
8/130 (6.2%)
16/132 (12.1%)
0.47 (0.20-1.10)
Ezetimibe Use
0.41
No
426/3827 (11.1%)
569/3828 (14.9%)
0.73 (0.64-0.82)
Yes
33/262 (12.6%)
37/262 (14.1%)
0.87 (0.55-1.39)
Sex
0.44
Male
353/2927 (12.1%)
474/2895 (16.4%)
0.72 (0.62-0.82)
Female
106/1162 (9.1%)
132/1195 (11.0%)
0.80 (0.62-1.03)
Age Group
0.06
<65 Years
200/2232 (9.0%)
290/2184 (13.3%)
0.65 (0.54-0.78)
>=65 Years
259/1857 (13.9%)
316/1906 (16.6%)
0.82 (0.70-0.97)
US vs. Non-US
0.38
USA
187/1548 (12.1%)
266/1598 (16.6%)
0.69 (0.57-0.83)
Non-USA
272/2541 (10.7%)
340/2492 (13.6%)
0.77 (0.66-0.91)
Baseline Diabetes
0.29
Diabetes
286/2394 (11.9%)
391/2393 (16.3%)
0.70 (0.60-0.81)
No Diabetes
173/1695 (10.2%)
215/1694 (12.7%)
0.80 (0.65-0.98)
Baseline TG≥200 vs <200 mg/dL
0.62
TG≥200 mg/dL
290/2481 (11.7%)
371/2469 (15.0%)
0.75 (0.65-0.88)
TG<200 mg/dL
169/1605 (10.5%)
235/1620 (14.5%)
0.71 (0.58-0.86)
Baseline TG≥150 vs <150 mg/dL
0.68
TG≥150 mg/dL
421/3674 (11.5%)
546/3660 (14.9%)
0.74 (0.65-0.84)
TG<150 mg/dL
38/412 (9.2%)
60/429 (14.0%)
0.66 (0.44-0.99)
Baseline TG≥200 and HDL-C≤35 mg/dL
0.50
Yes
101/823 (12.3%)
136/794 (17.1%)
0.68 (0.53-0.88)
No
356/3258 (10.9%)
470/3293 (14.3%)
0.75 (0.65-0.86)
Baseline Statin Intensity
0.10
High
151/1290(11.7%)
210/1226 (17.1%)
0.66 (0.54-0.82)
Moderate
270/2533 (10.7%)
361/2575 (14.0%)
0.74 (0.63-0.87)
Low
37/254 (14.6%)
32/267 (12.0%)
1.20 (0.74-1.94)
Baseline hsCRP≤2 vs >2 mg/L
0.97
≤2 mg/L
183/1919 (9.5%)
245/1942 (12.6%)
0.73 (0.61-0.89)
>2 mg/L
276/2167 (12.7%)
361/2147 (16.8%)
0.73 (0.63-0.86)
Baseline hsCRP≤3 vs >3 mg/L
0.95
≤3 mg/L
250/2497 (10.0%)
341/2547 (13.4%)
0.73 (0.62-0.86)
>3 mg/L
209/1589 (13.2%)
265/1542 (17.2%)
0.74 (0.61-0.88)
0.2
0.6
1.0
1.4
1.8
Icosapent Ethyl Better
Placebo Better

FIG. 9

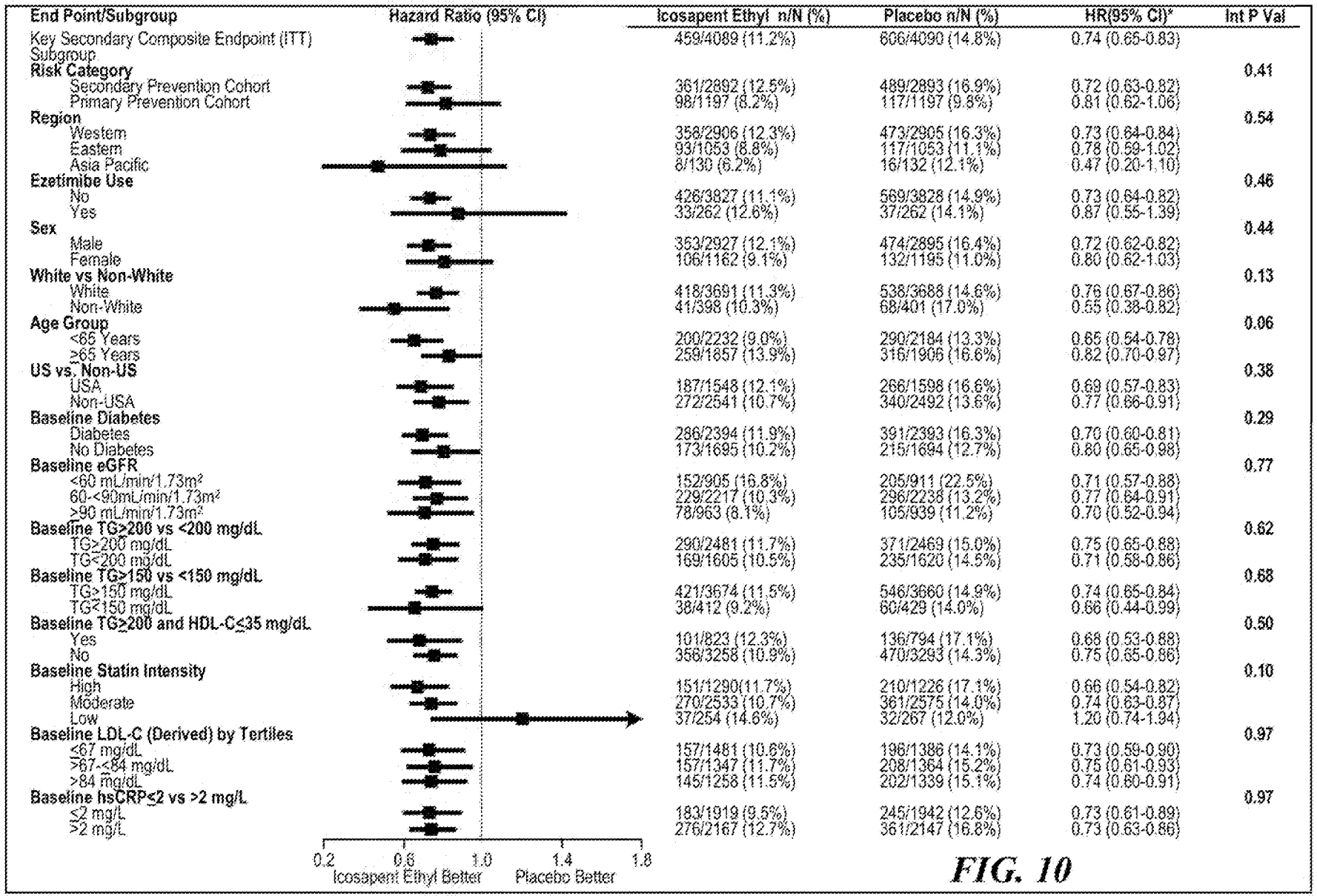

End Point/Subgroup
Hazard Ratio (95% CI)
Icosapent Ethyl n/N (%)
Placebo n/N (%)
HR(95% CI)*
Int P Val
Key Secondary Composite Endpoint (ITT) 459/4089 (11.2%) 606/4090 (14.8%) 0.74 (0.65-0.83)
Subgroup
Risk Category 0.41
Secondary Prevention Cohort 361/2892 (12.5%) 489/2893 (16.9%) 0.72 (0.63-0.82)
Primary Prevention Cohort 98/1197 (8.2%) 117/1197 (9.8%) 0.81 (0.62-1.06)
Region 0.54
Western 358/2906 (12.3%) 473/2905 (16.3%) 0.73 (0.64-0.84)
Eastern 93/1053 (8.8%) 117/1053 (11.1%) 0.78 (0.59-1.02)
Asia Pacific 8/130 (6.2%) 16/132 (12.1%) 0.47 (0.20-1.10)
Ezetimibe Use 0.46
No 426/3827 (11.1%) 569/3828 (14.9%) 0.73 (0.64-0.82)
Yes 33/262 (12.6%) 37/262 (14.1%) 0.87 (0.55-1.39)
Sex 0.44
Male 353/2927 (12.1%) 474/2895 (16.4%) 0.72 (0.62-0.82)
Female 106/1162 (9.1%) 132/1195 (11.0%) 0.80 (0.62-1.03)
White vs Non-White 0.13
White 418/3691 (11.3%) 538/3688 (14.6%) 0.76 (0.67-0.86)
Non-White 41/398 (10.3%) 68/401 (17.0%) 0.55 (0.38-0.82)
Age Group 0.06
<65 Years 200/2232 (9.0%) 290/2184 (13.3%) 0.65 (0.54-0.78)
≥65 Years 259/1857 (13.9%) 316/1906 (16.6%) 0.82 (0.70-0.97)
US vs. Non-US 0.38
USA 187/1548 (12.1%) 266/1598 (16.6%) 0.69 (0.57-0.83)
Non-USA 272/2541 (10.7%) 340/2492 (13.6%) 0.77 (0.66-0.91)
Baseline Diabetes 0.29
Diabetes 286/2394 (11.9%) 391/2393 (16.3%) 0.70 (0.60-0.81)
No Diabetes 173/1695 (10.2%) 215/1694 (12.7%) 0.80 (0.65-0.98)
Baseline eGFR 0.77
<60 mL/min/1.73m² 152/905 (16.8%) 205/911 (22.5%) 0.71 (0.57-0.88)
60-<90mL/min/1.73m² 229/2217 (10.3%) 296/2238 (13.2%) 0.77 (0.64-0.91)
≥90 mL/min/1.73m² 78/963 (8.1%) 105/939 (11.2%) 0.70 (0.52-0.94)
Baseline TG≥200 vs <200 mg/dL 0.62
TG≥200 mg/dL 290/2481 (11.7%) 371/2469 (15.0%) 0.75 (0.65-0.88)
TG<200 mg/dL 169/1605 (10.5%) 235/1620 (14.5%) 0.71 (0.58-0.86)
Baseline TG≥150 vs <150 mg/dL 0.68
TG≥150 mg/dL 421/3674 (11.5%) 546/3660 (14.9%) 0.74 (0.65-0.84)
TG<150 mg/dL 38/412 (9.2%) 60/429 (14.0%) 0.66 (0.44-0.99)
Baseline TG≥200 and HDL-C≤35 mg/dL 0.50
Yes 101/823 (12.3%) 136/794 (17.1%) 0.68 (0.53-0.88)
No 358/3258 (10.9%) 470/3293 (14.3%) 0.75 (0.65-0.86)
Baseline Statin Intensity 0.10
High 151/1290(11.7%) 210/1226 (17.1%) 0.66 (0.54-0.82)
Moderate 270/2533 (10.7%) 361/2575 (14.0%) 0.74 (0.63-0.87)
Low 37/254 (14.6%) 32/267 (12.0%) 1.20 (0.74-1.94)
Baseline LDL-C (Derived) by Tertiles 0.97
≤67 mg/dL 157/1481 (10.6%) 196/1386 (14.1%) 0.73 (0.59-0.90)
>67-≤84 mg/dL 157/1347 (11.7%) 208/1364 (15.2%) 0.75 (0.61-0.93)
>84 mg/dL 145/1258 (11.5%) 202/1339 (15.1%) 0.74 (0.60-0.91)
Baseline hsCRP≤2 vs >2 mg/L 0.97
≤2 mg/L 183/1919 (9.5%) 245/1942 (12.6%) 0.73 (0.61-0.89)
>2 mg/L 276/2167 (12.7%) 361/2147 (16.8%) 0.73 (0.63-0.86)
0.2
0.6
1.0
1.4
1.8
Icosapent Ethyl Better
Placebo Better

FIG. 10

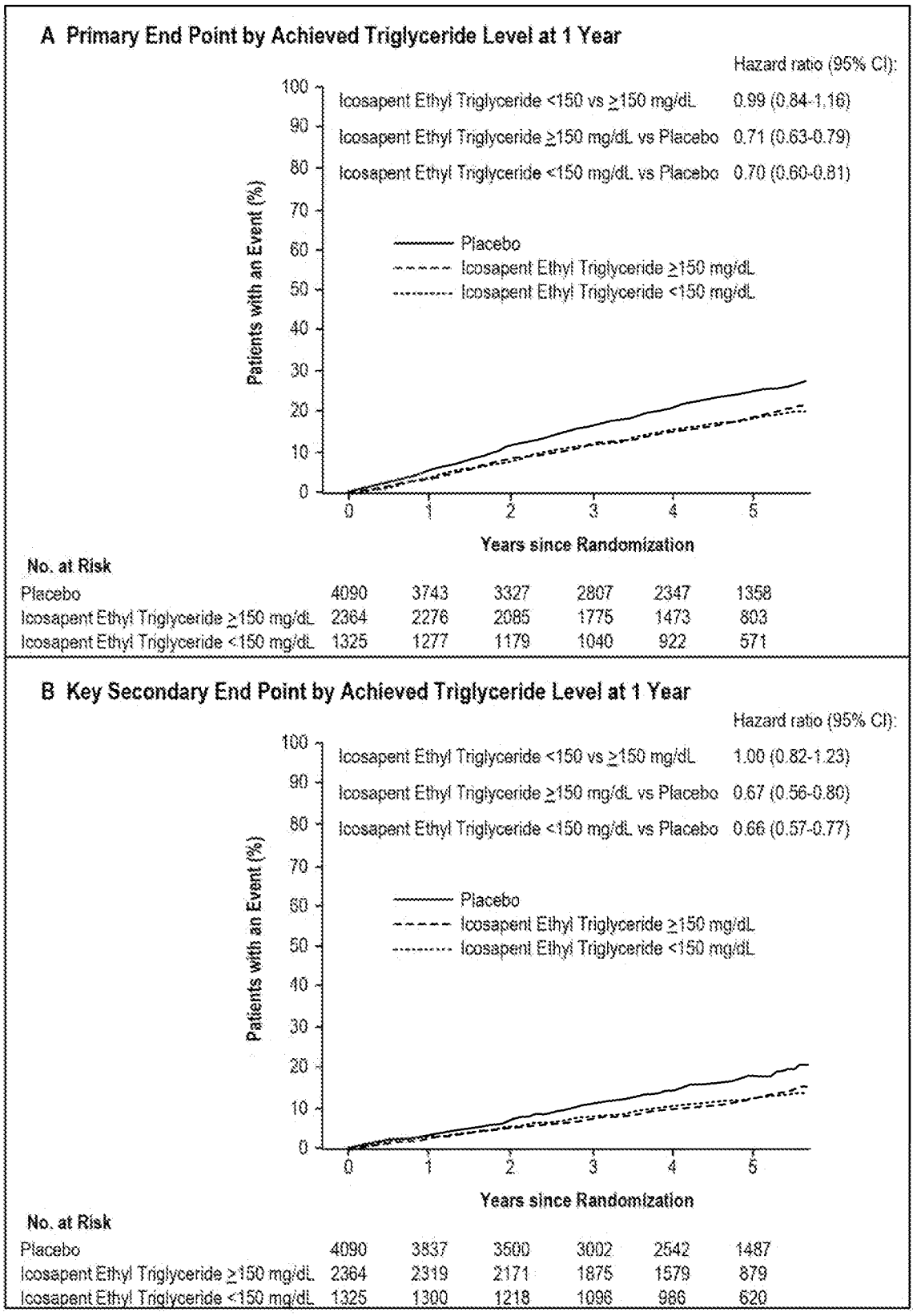

A Primary End Point by Achieved Triglyceride Level at 1 Year
Hazard ratio (95% CI):
Icosapent Ethyl Triglyceride <150 vs ≥150 mg/dL 0.99 (0.84-1.16)
Icosapent Ethyl Triglyceride ≥150 mg/dL vs Placebo 0.71 (0.63-0.79)
Icosapent Ethyl Triglyceride <150 mg/dL vs Placebo 0.70 (0.60-0.81)
Placebo
Icosapent Ethyl Triglyceride ≥150 mg/dL
Icosapent Ethyl Triglyceride <150 mg/dL
Patients with an Event (%)
Years since Randomization
No. at Risk
Placebo 4090 3743 3327 2807 2347 1358
Icosapent Ethyl Triglyceride ≥150 mg/dL 2364 2276 2085 1775 1473 803
Icosapent Ethyl Triglyceride <150 mg/dL 1325 1277 1179 1040 922 571
B Key Secondary End Point by Achieved Triglyceride Level at 1 Year
Hazard ratio (95% CI):
Icosapent Ethyl Triglyceride <150 vs ≥150 mg/dL 1.00 (0.82-1.23)
Icosapent Ethyl Triglyceride ≥150 mg/dL vs Placebo 0.67 (0.56-0.80)
Icosapent Ethyl Triglyceride <150 mg/dL vs Placebo 0.66 (0.57-0.77)
Placebo
Icosapent Ethyl Triglyceride ≥150 mg/dL
Icosapent Ethyl Triglyceride <150 mg/dL
Patients with an Event (%)
Years since Randomization
No. at Risk
Placebo 4090 3837 3500 3002 2542 1487
Icosapent Ethyl Triglyceride ≥150 mg/dL 2364 2319 2171 1875 1579 879
Icosapent Ethyl Triglyceride <150 mg/dL 1325 1300 1218 1096 986 620

FIG. 11

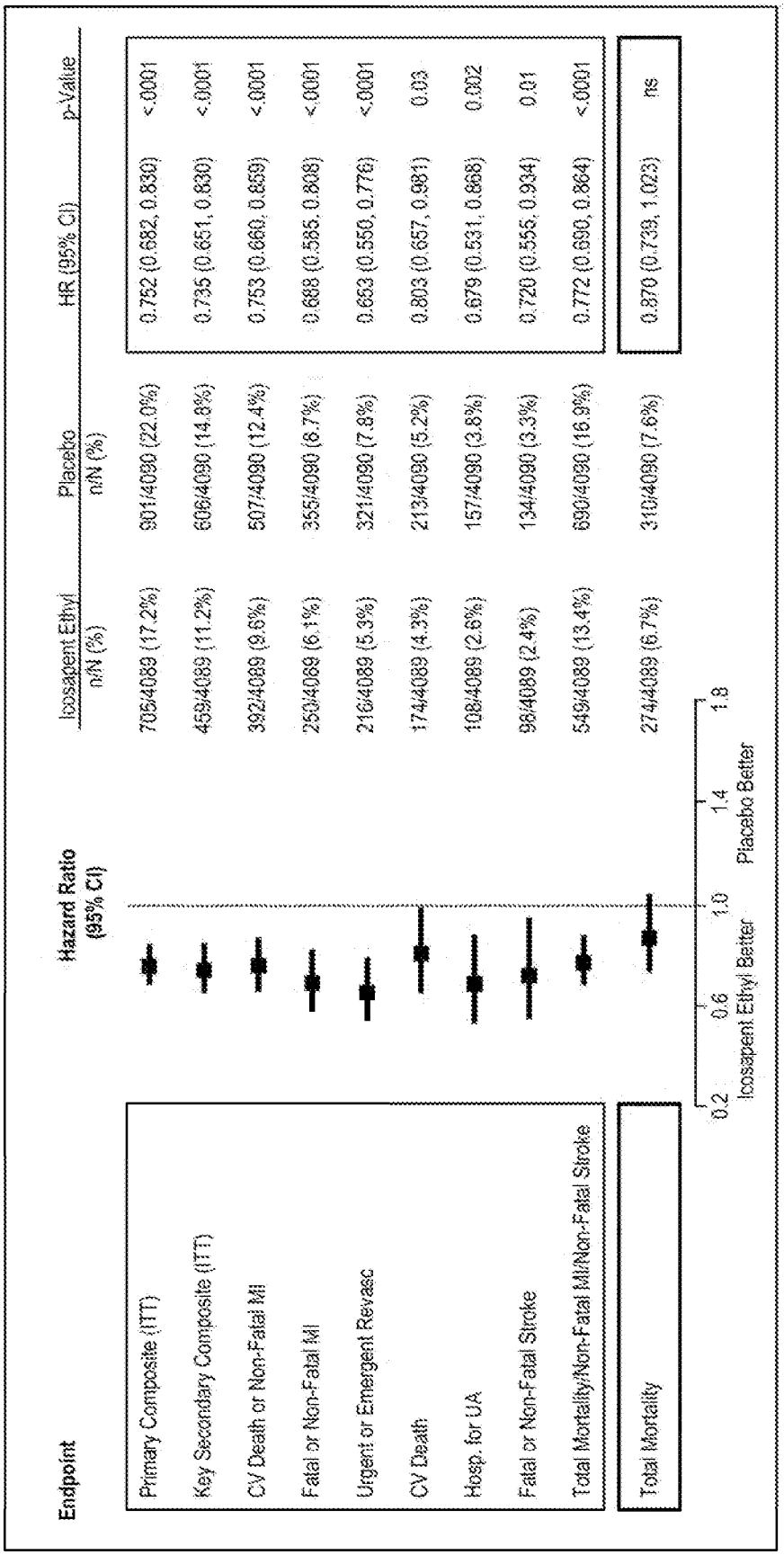

Endpoint
Hazard Ratio (95% CI)
Icosapent Ethyl n/N (%)
Placebo n/N (%)
HR (95% CI)
p-Value
Primary Composite (ITT)
705/4089 (17.2%)
901/4090 (22.0%)
0.752 (0.682, 0.830)
<.0001
Key Secondary Composite (ITT)
458/4089 (11.2%)
606/4090 (14.8%)
0.735 (0.651, 0.830)
<.0001
CV Death or Non-Fatal MI
392/4089 (9.6%)
507/4090 (12.4%)
0.753 (0.660, 0.859)
<.0001
Fatal or Non-Fatal MI
259/4089 (6.1%)
355/4090 (8.7%)
0.688 (0.585, 0.808)
<.0001
Urgent or Emergent Revasc
216/4089 (5.3%)
321/4090 (7.8%)
0.653 (0.550, 0.776)
<.0001
CV Death
174/4089 (4.3%)
213/4090 (5.2%)
0.803 (0.657, 0.981)
0.03
Hosp. for UA
108/4089 (2.6%)
157/4090 (3.8%)
0.679 (0.531, 0.868)
0.002
Fatal or Non-Fatal Stroke
98/4089 (2.4%)
134/4090 (3.3%)
0.720 (0.555, 0.934)
0.01
Total Mortality/Non-Fatal MI/Non-Fatal Stroke
549/4089 (13.4%)
690/4090 (16.9%)
0.772 (0.690, 0.864)
<.0001
Total Mortality
274/4089 (6.7%)
310/4090 (7.6%)
0.870 (0.739, 1.023)
ns
0.2
0.6
1.0
1.4
1.8
Icosapent Ethyl Better
Placebo Better

FIG. 12

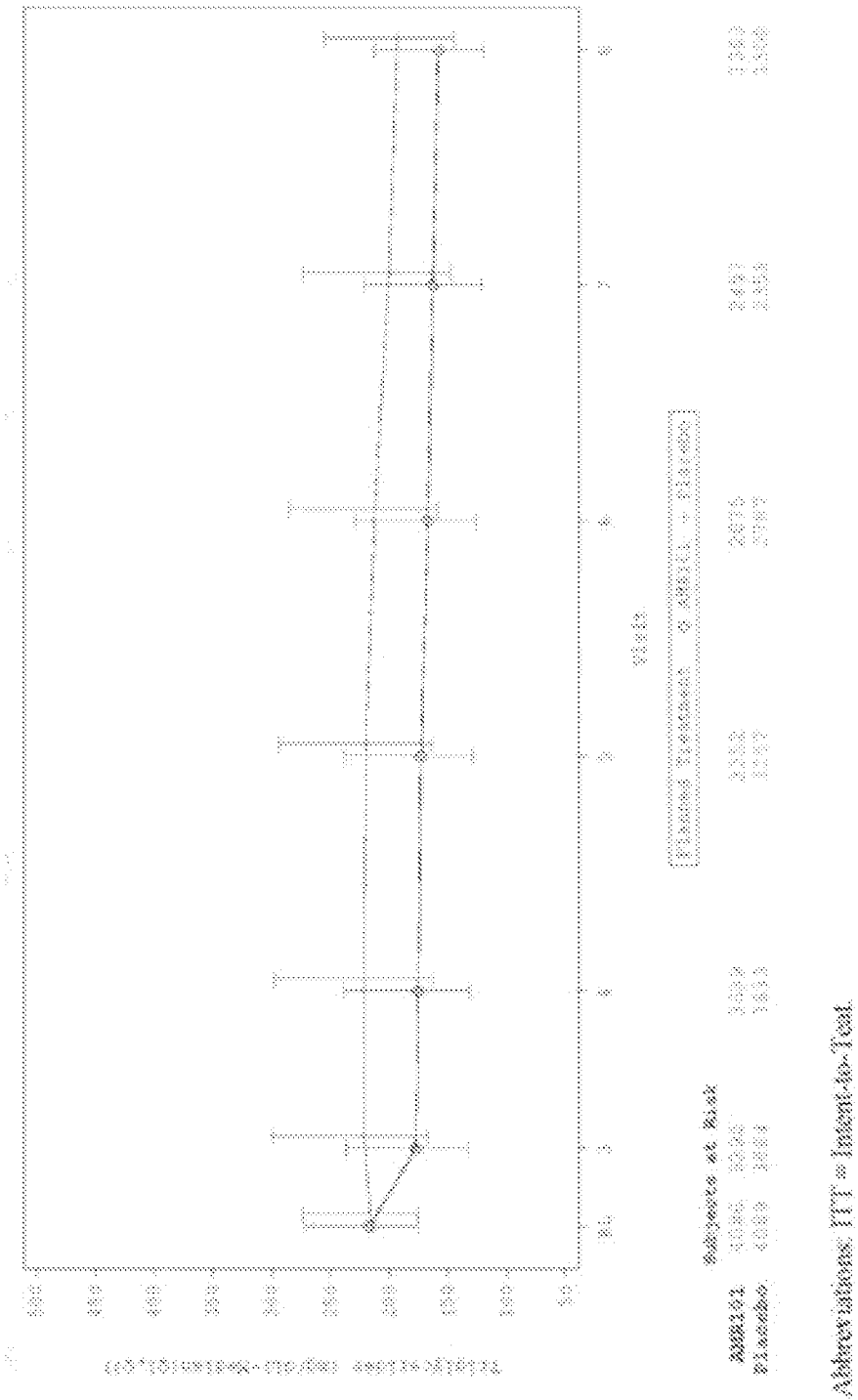
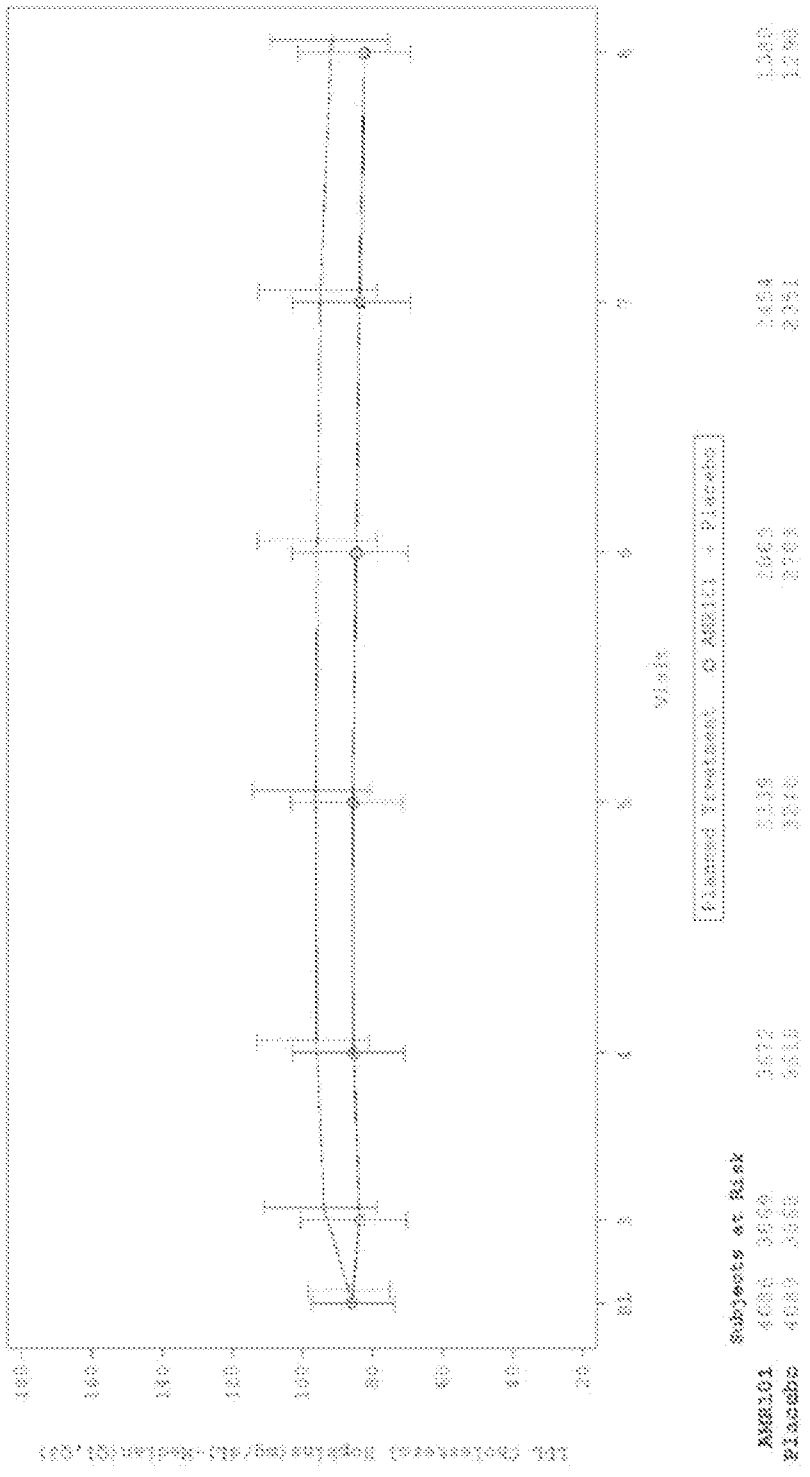
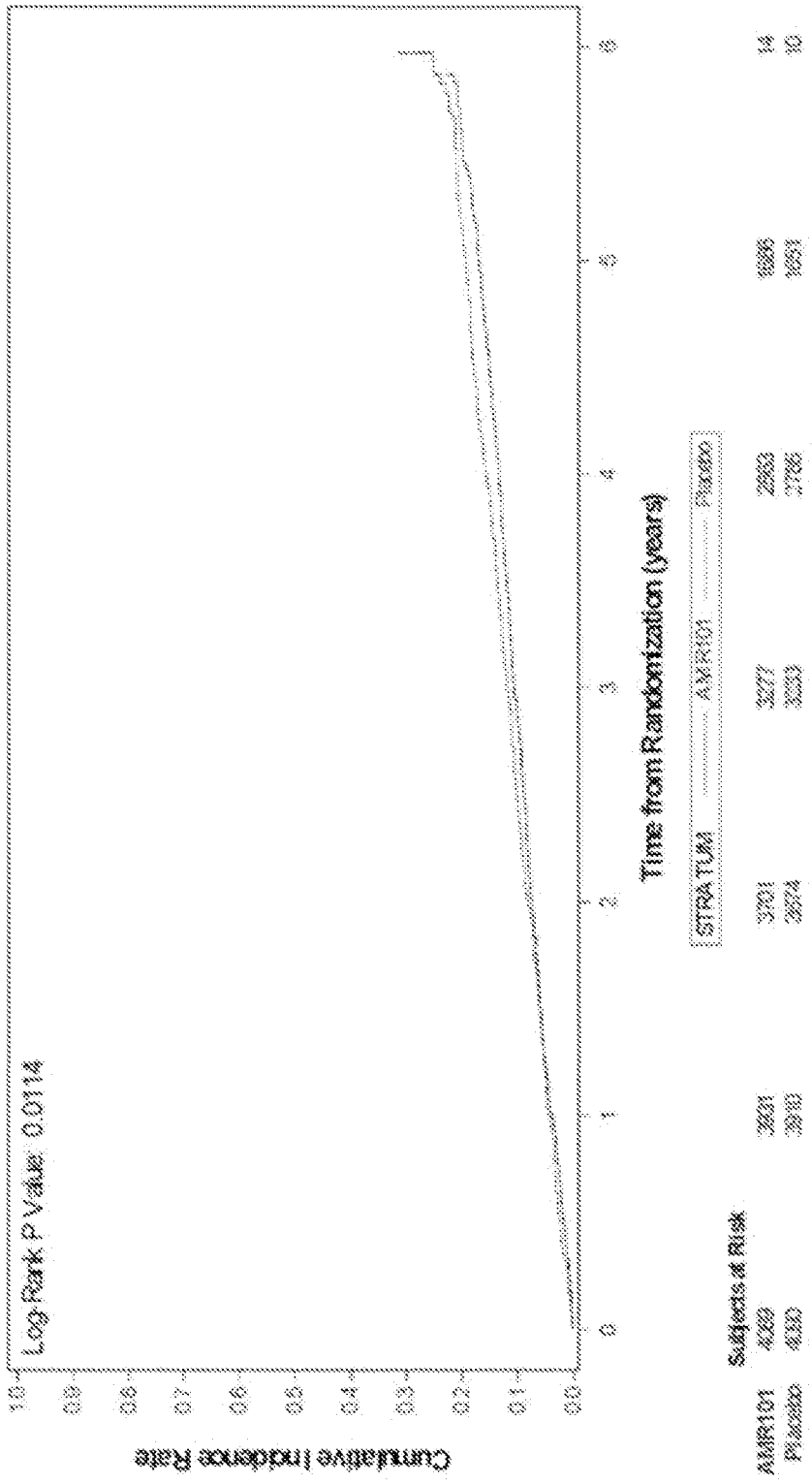


FIG. 13



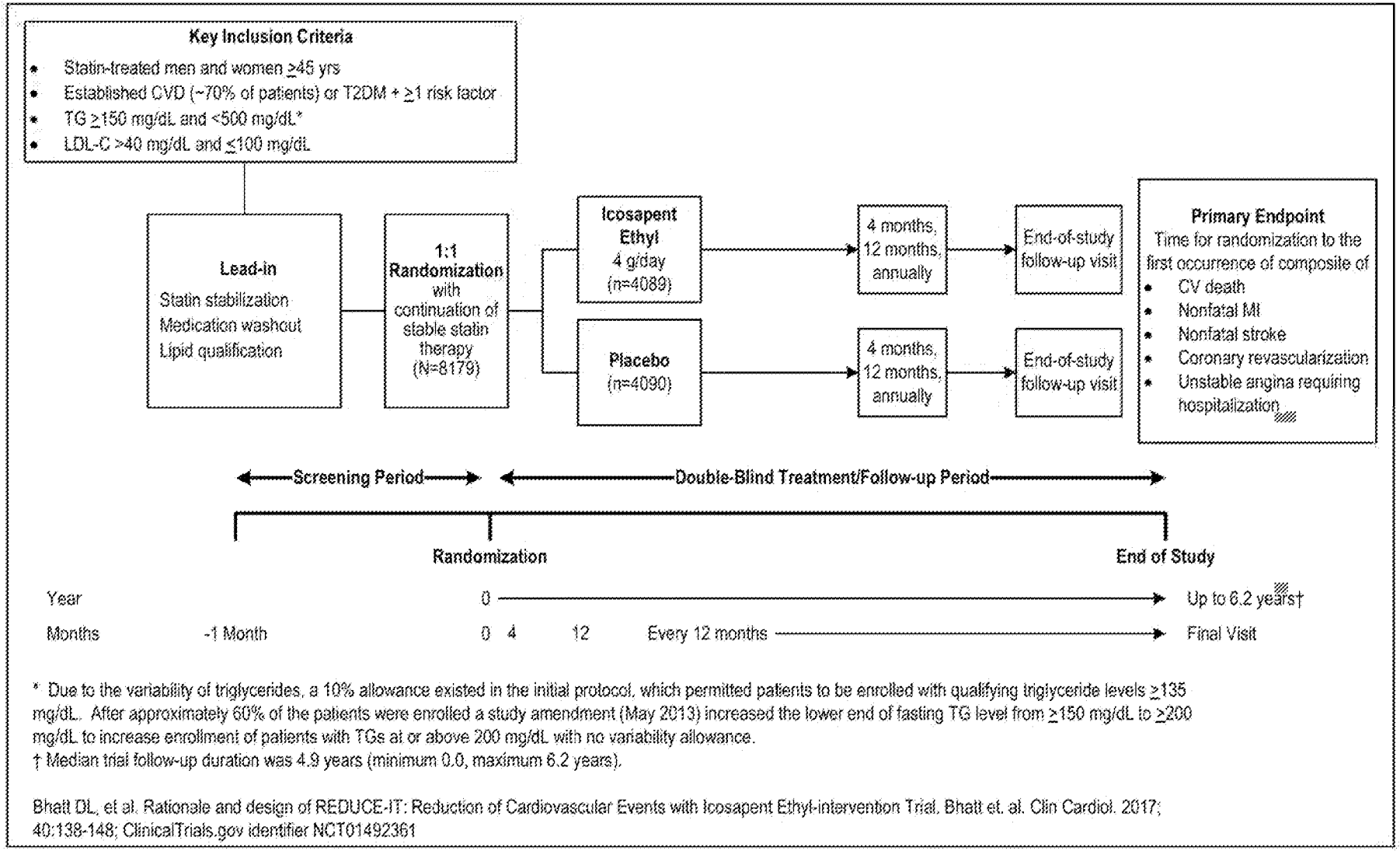
Abbreviations: ITT = intent-to-treat; LDL-C = low-density lipoprotein cholesterol.

FIG. 14



Abbreviations: ITT = Intent-to-Treat.

FIG. 15



* Due to the variability of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglyceride levels ≥135 mg/dL. After approximately 60% of the patients were enrolled a study amendment (May 2013) increased the lower end of fasting TG level from ≥150 mg/dL to ≥200 mg/dL to increase enrollment of patients with TGs at or above 200 mg/dL with no variability allowance.
† Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).

Bhatt DL, et al. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl-intervention Trial. Bhatt et. al. Clin Cardiol. 2017; 40:138-148; ClinicalTrials.gov identifier NCT01492361

FIG. 16

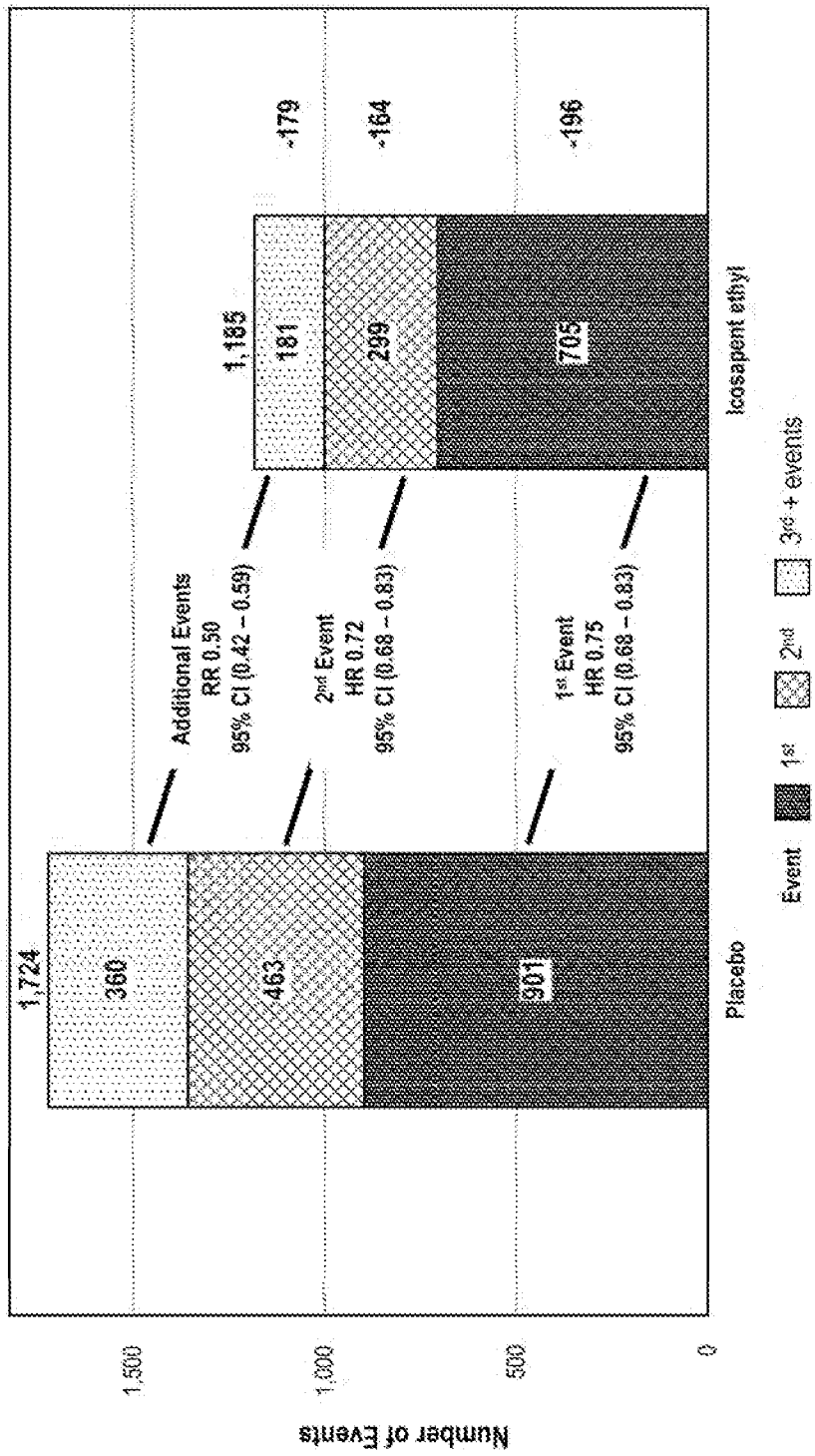

Number of Events
1,500
1,000
500
0
1,724
360
463
901
Placebo
1,185
181
299
705
Icosapent ethyl
-179
-164
-196
Additional Events
RR 0.50
95% CI (0.42 – 0.59)
2nd Event
HR 0.72
95% CI (0.68 – 0.83)
1st Event
HR 0.75
95% CI (0.68 – 0.83)
Event
1st
2nd
3rd + events

FIG. 17

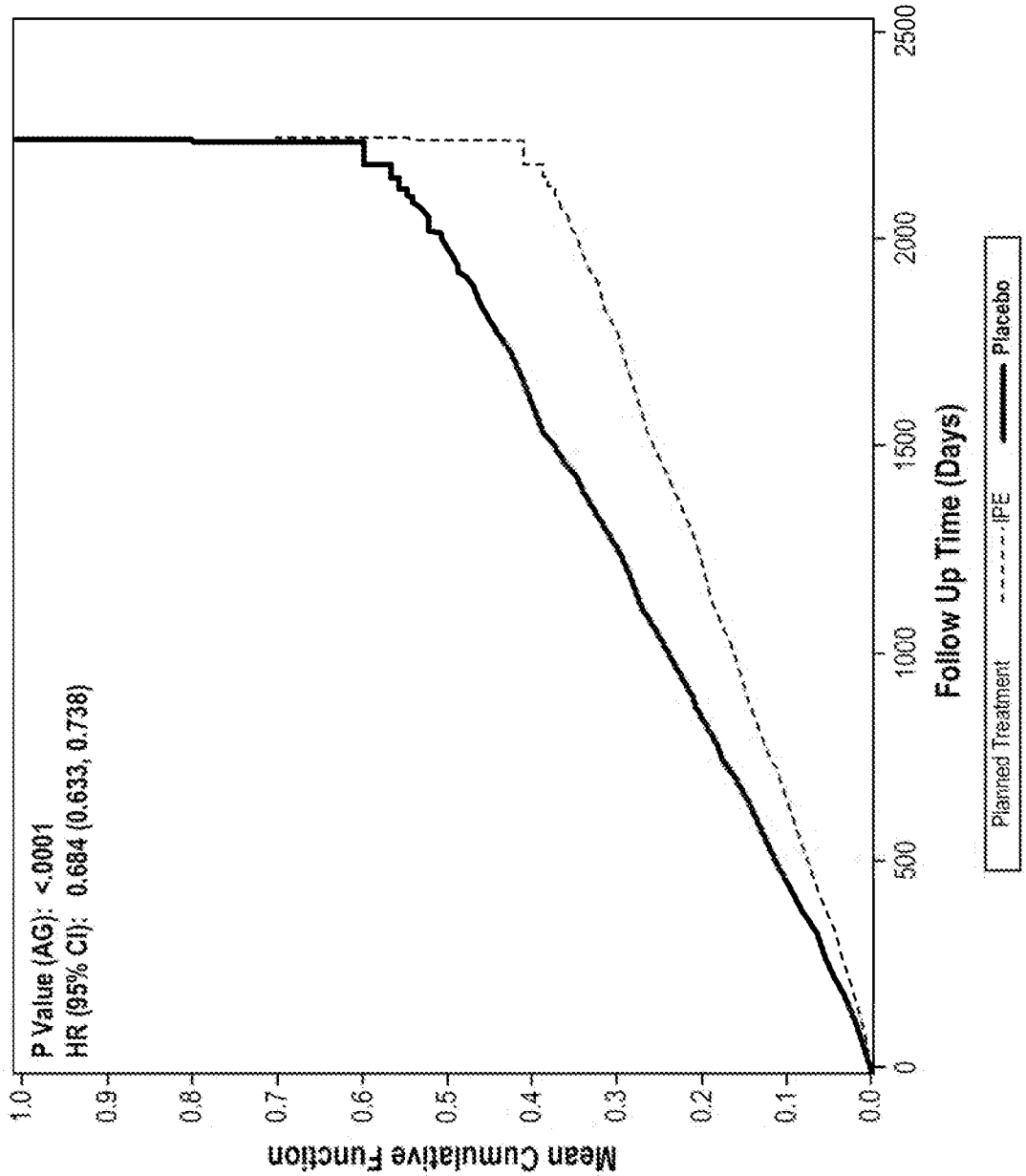

P Value (AG): <.0001
HR (95% CI): 0.684 (0.633, 0.738)
Mean Cumulative Function
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
500
1000
1500
2000
2500
Follow Up Time (Days)
Planned Treatment
IPE
Placebo

FIG. 18

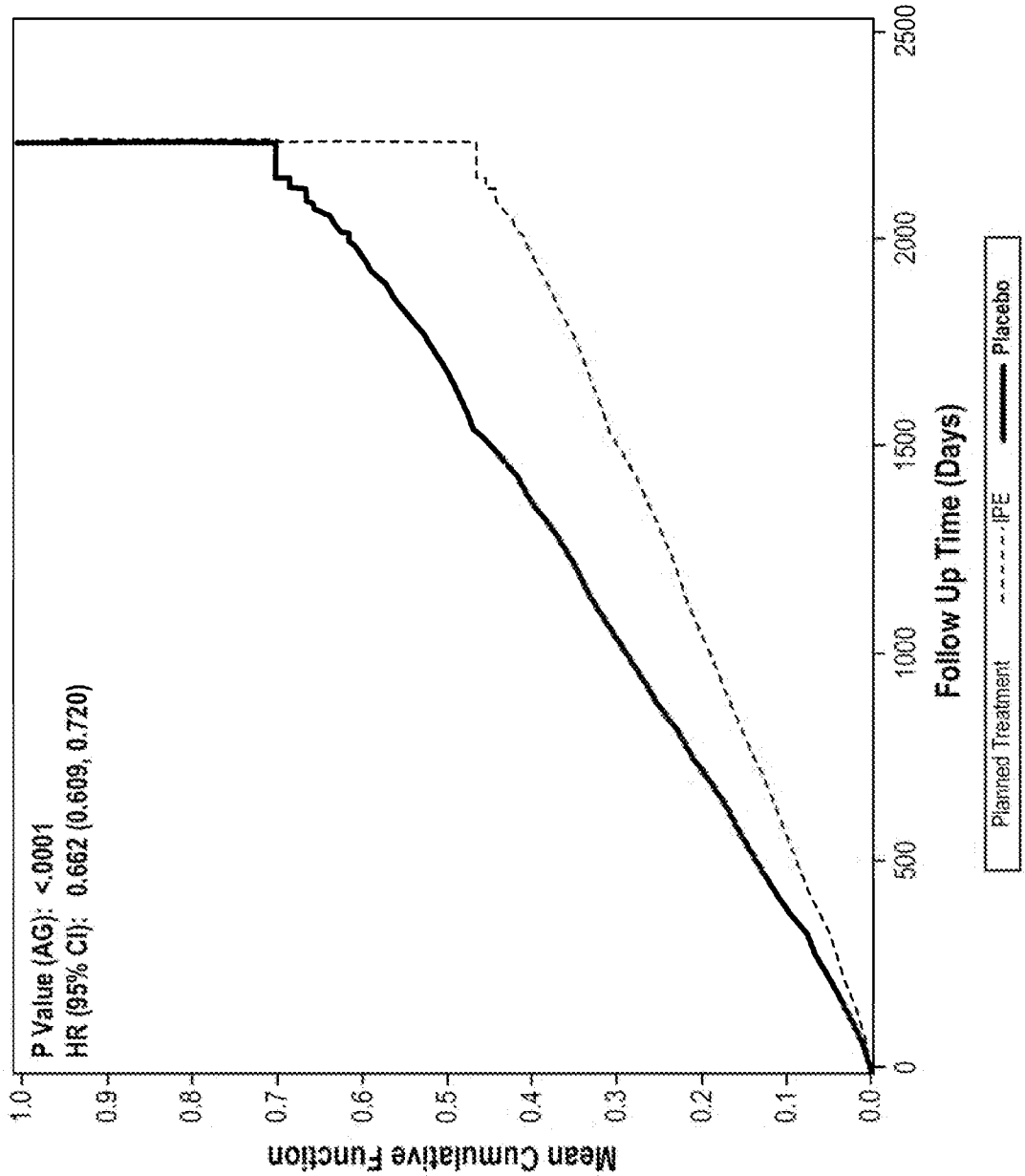

P Value (AG): <.0001
HR (95% CI): 0.662 (0.609, 0.720)
Mean Cumulative Function
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
500
1000
1500
2000
2500
Follow Up Time (Days)
Planned Treatment
IPE
Placebo

FIG. 19

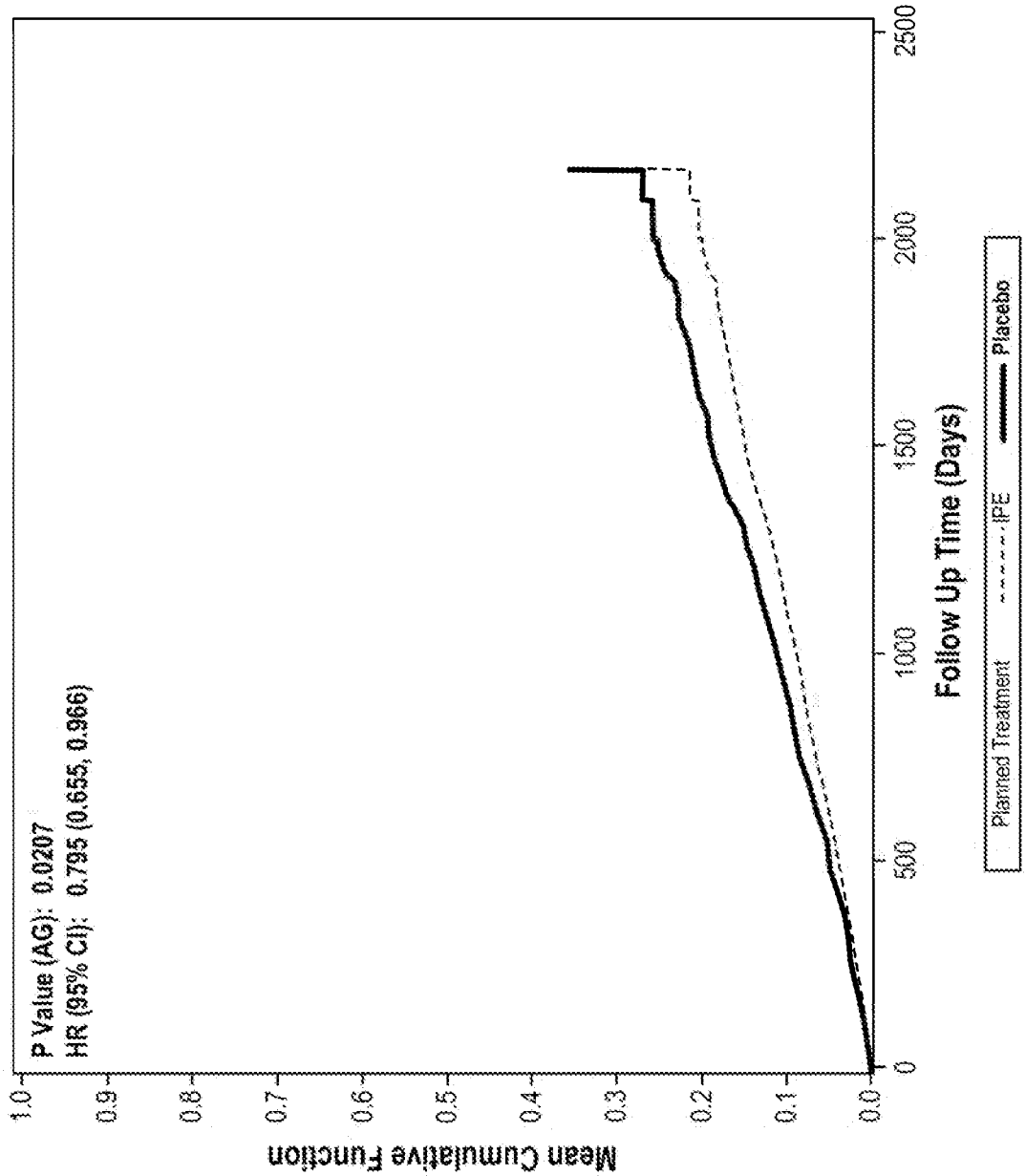

P Value (AG): 0.0207
HR (95% CI): 0.795 (0.655, 0.966)
Mean Cumulative Function
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
500
1000
1500
2000
2500
Follow Up Time (Days)
Planned Treatment
IPE
Placebo

FIG. 20

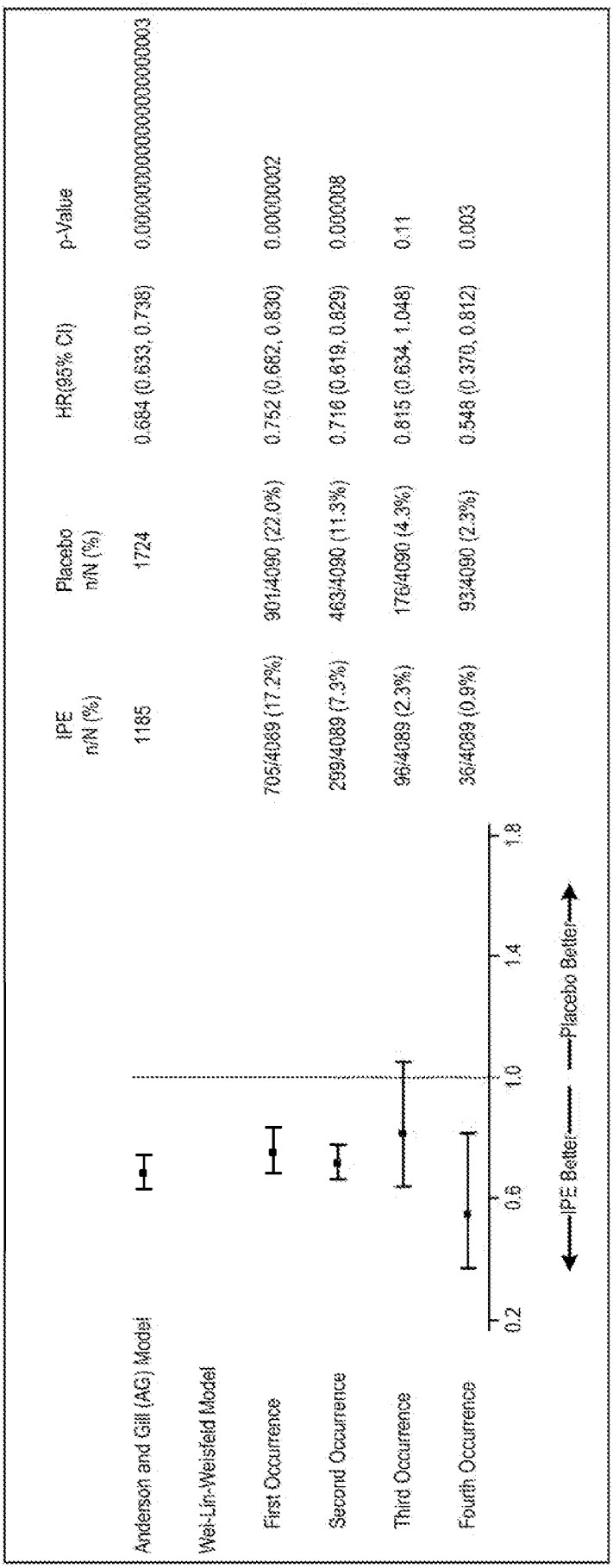

IPE n/N (%)
Placebo n/N (%)
HR(95% CI)
p-Value
Anderson and Gill (AG) Model
1185
1724
0.684 (0.633, 0.738)
0.000000000000000000003
Wei-Lin-Weisfeld Model
First Occurrence
705/4089 (17.2%)
901/4090 (22.0%)
0.752 (0.682, 0.830)
0.00000002
Second Occurrence
299/4089 (7.3%)
463/4090 (11.3%)
0.716 (0.619, 0.829)
0.000008
Third Occurrence
96/4089 (2.3%)
176/4090 (4.3%)
0.815 (0.634, 1.048)
0.11
Fourth Occurrence
36/4089 (0.9%)
93/4090 (2.3%)
0.548 (0.370, 0.812)
0.003
0.2
0.6
1.0
1.4
1.8
IPE Better
Placebo Better

FIG. 21

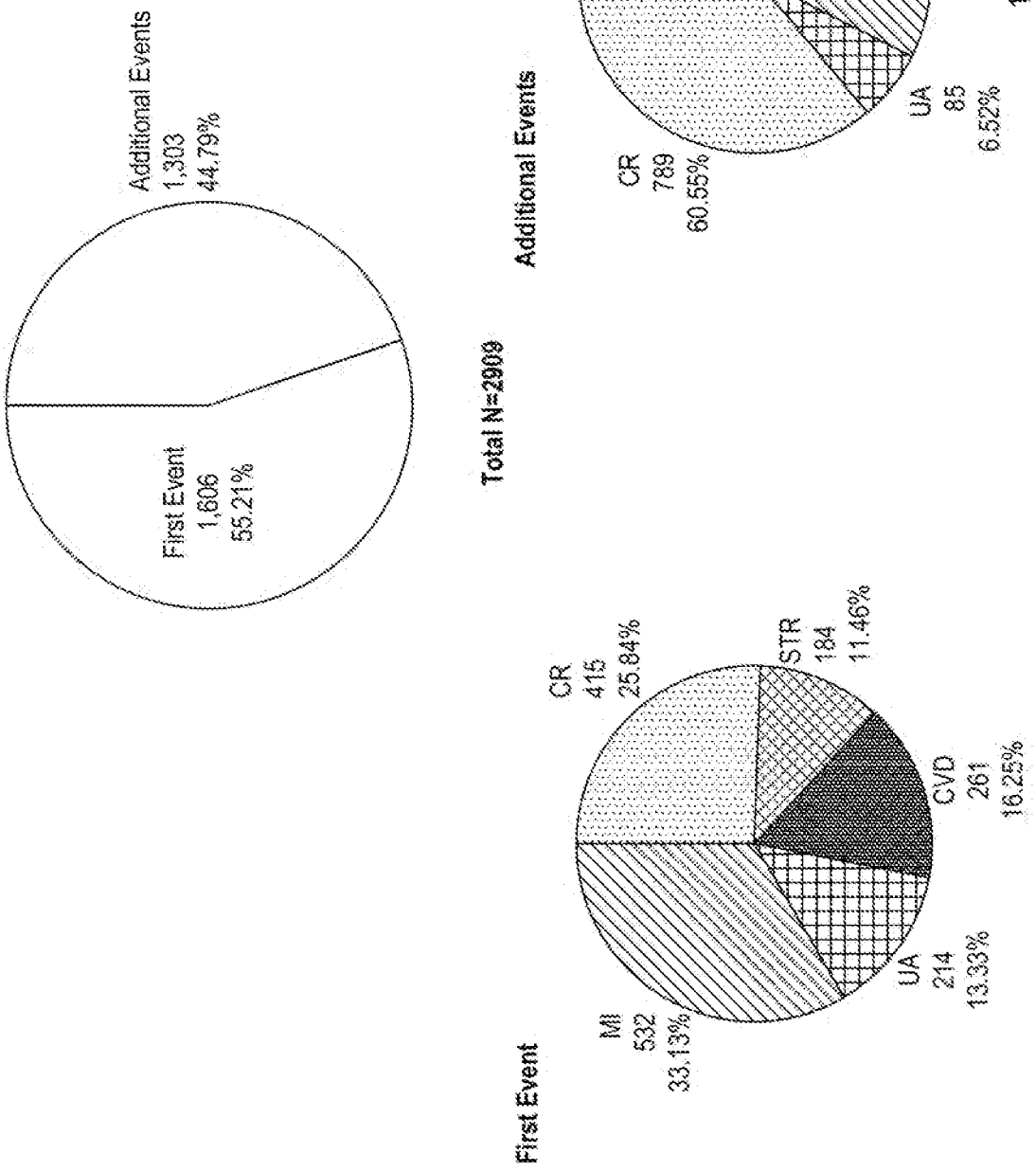

Additional Events
1,303
44.79%
First Event
1,606
55.21%
Total N=2909
Additional Events
CR
789
60.55%
STR
78
5.99%
CVD
126
9.67%
MI
225
17.27%
UA
85
6.52%
First Event
MI
532
33.13%
CR
415
25.84%
STR
184
11.46%
CVD
261
16.25%
UA
214
13.33%

FIG. 22

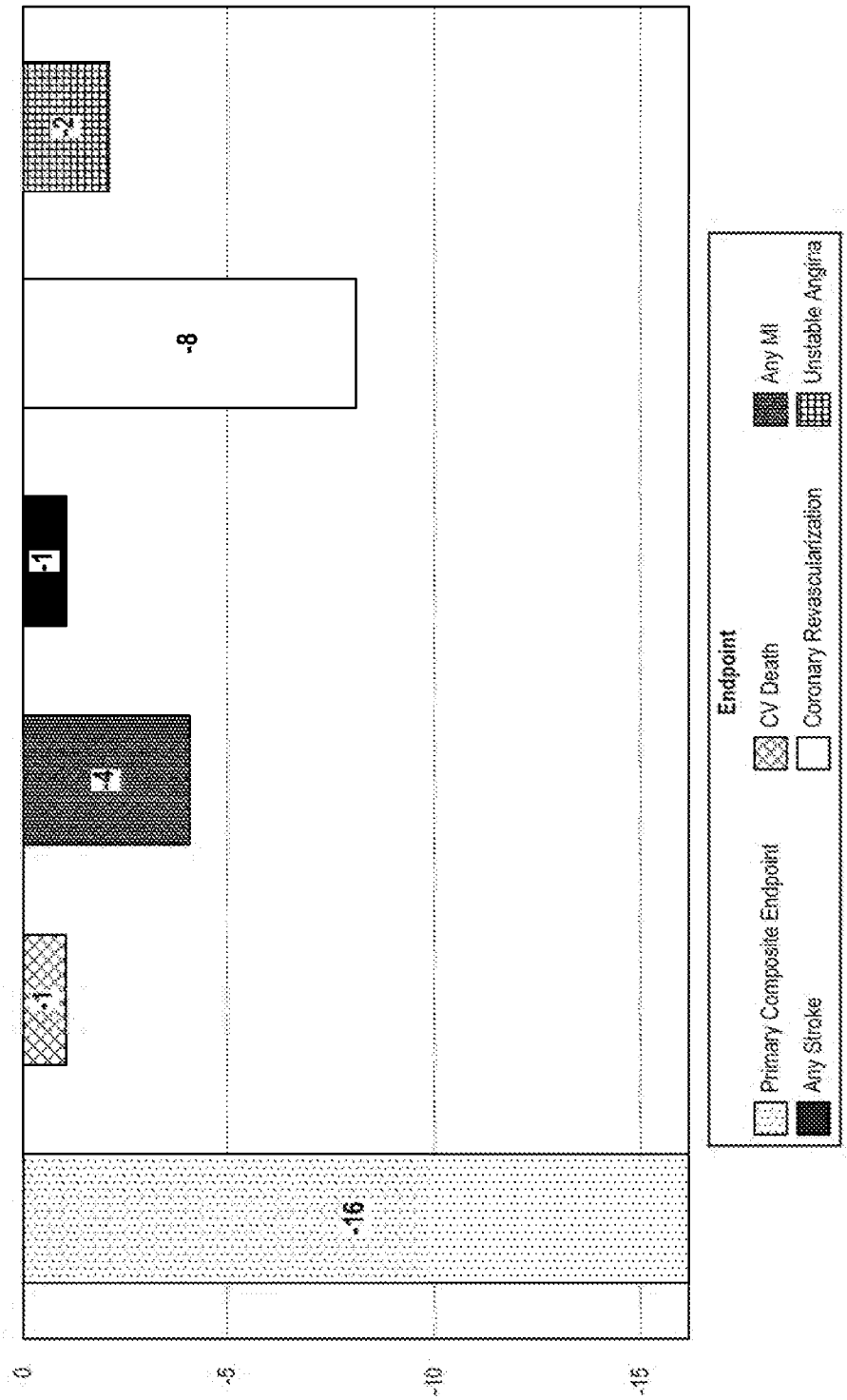

-2
-8
-1
-4
-1
-16
0
-5
-10
-15
Endpoint
Primary Composite Endpoint
CV Death
Any MI
Any Stroke
Coronary Revascularization
Unstable Angina

FIG. 23

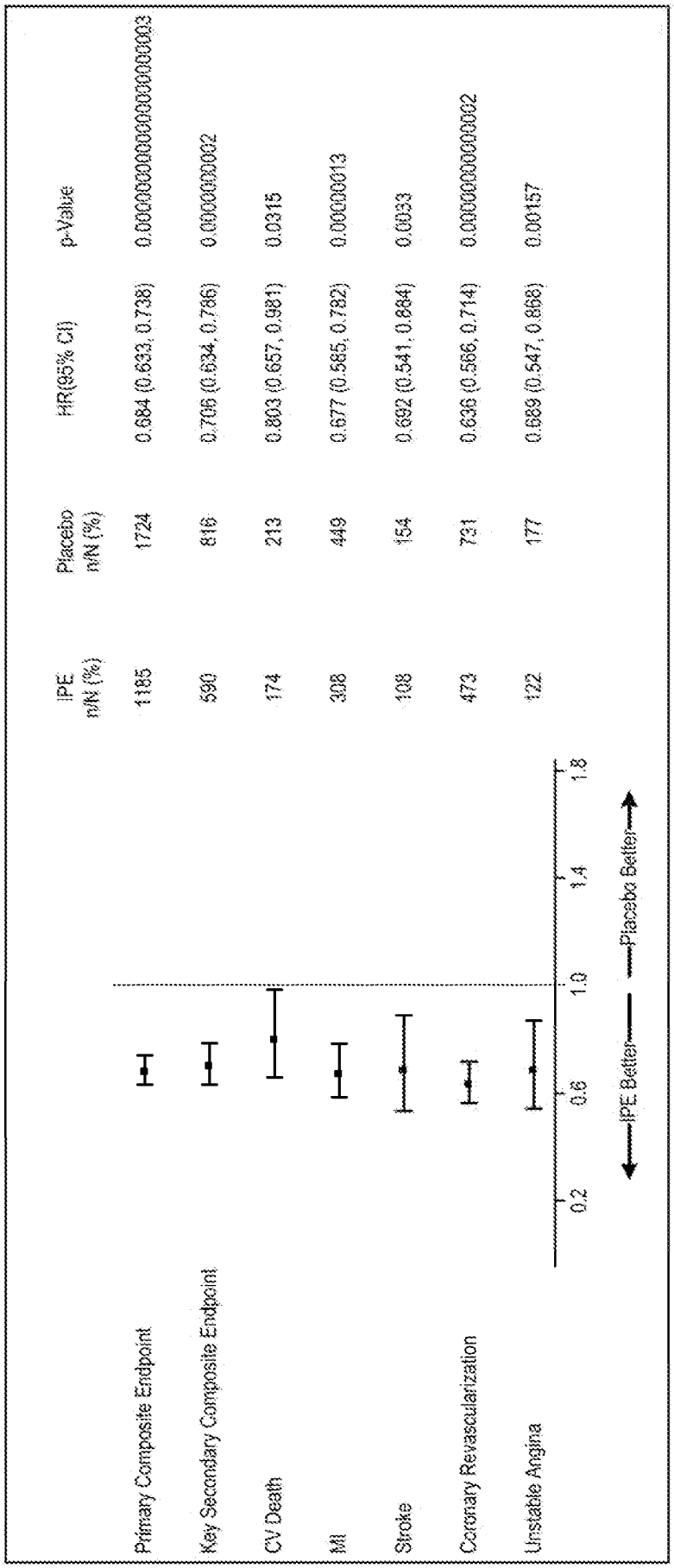

IPE n/N (%)
Placebo n/N (%)
HR(95% CI)
p-Value
Primary Composite Endpoint
1185
1724
0.684 (0.633, 0.738)
0.000000000000000000003
Key Secondary Composite Endpoint
590
816
0.706 (0.634, 0.786)
0.0000000002
CV Death
174
213
0.803 (0.657, 0.981)
0.0315
MI
308
449
0.677 (0.585, 0.782)
0.00000013
Stroke
108
154
0.692 (0.541, 0.884)
0.0033
Coronary Revascularization
473
731
0.636 (0.566, 0.714)
0.00000000000002
Unstable Angina
122
177
0.689 (0.547, 0.868)
0.00157
0.2
0.6
1.0
1.4
1.8
IPE Better
Placebo Better

FIG. 24

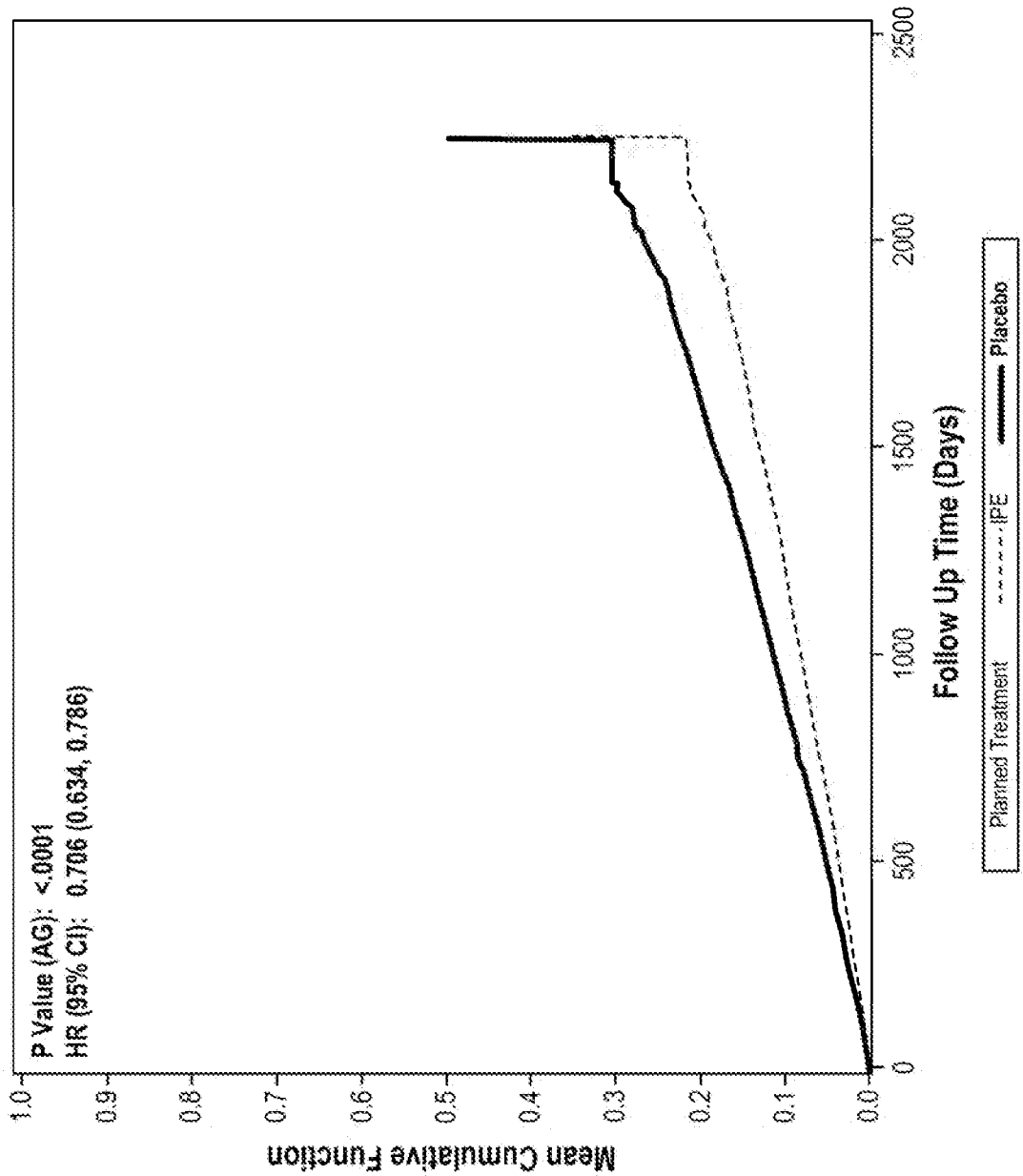

P Value (AG): <.0001
HR (95% CI): 0.706 (0.634, 0.786)
Mean Cumulative Function
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
500
1000
1500
2000
2500
Follow Up Time (Days)
Planned Treatment
IPE
Placebo

FIG. 25

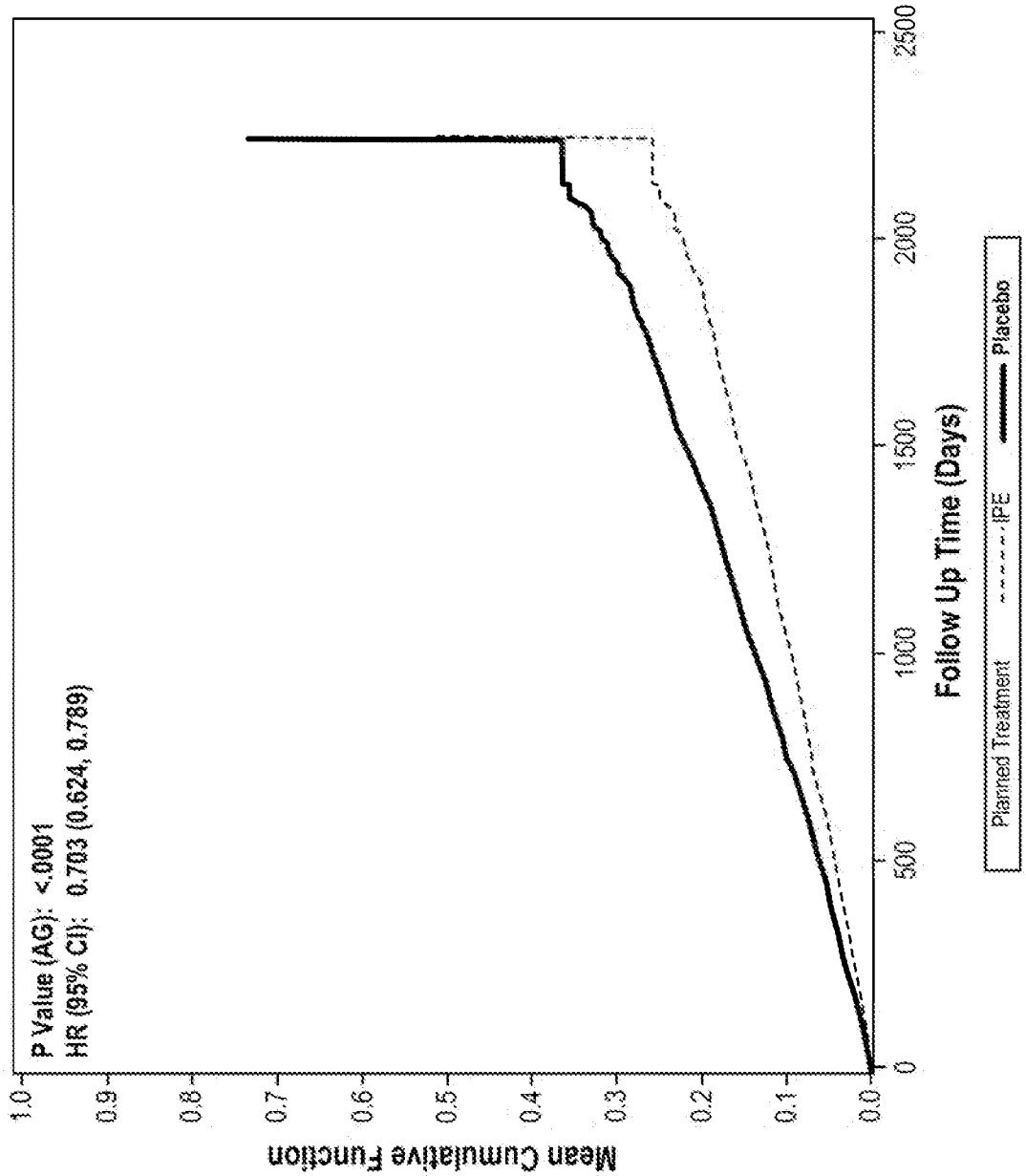

P Value (AG): <.0001
HR (95% CI): 0.703 (0.624, 0.789)
Mean Cumulative Function
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
500
1000
1500
2000
2500
Follow Up Time (Days)
Planned Treatment
IPE
Placebo

FIG. 26

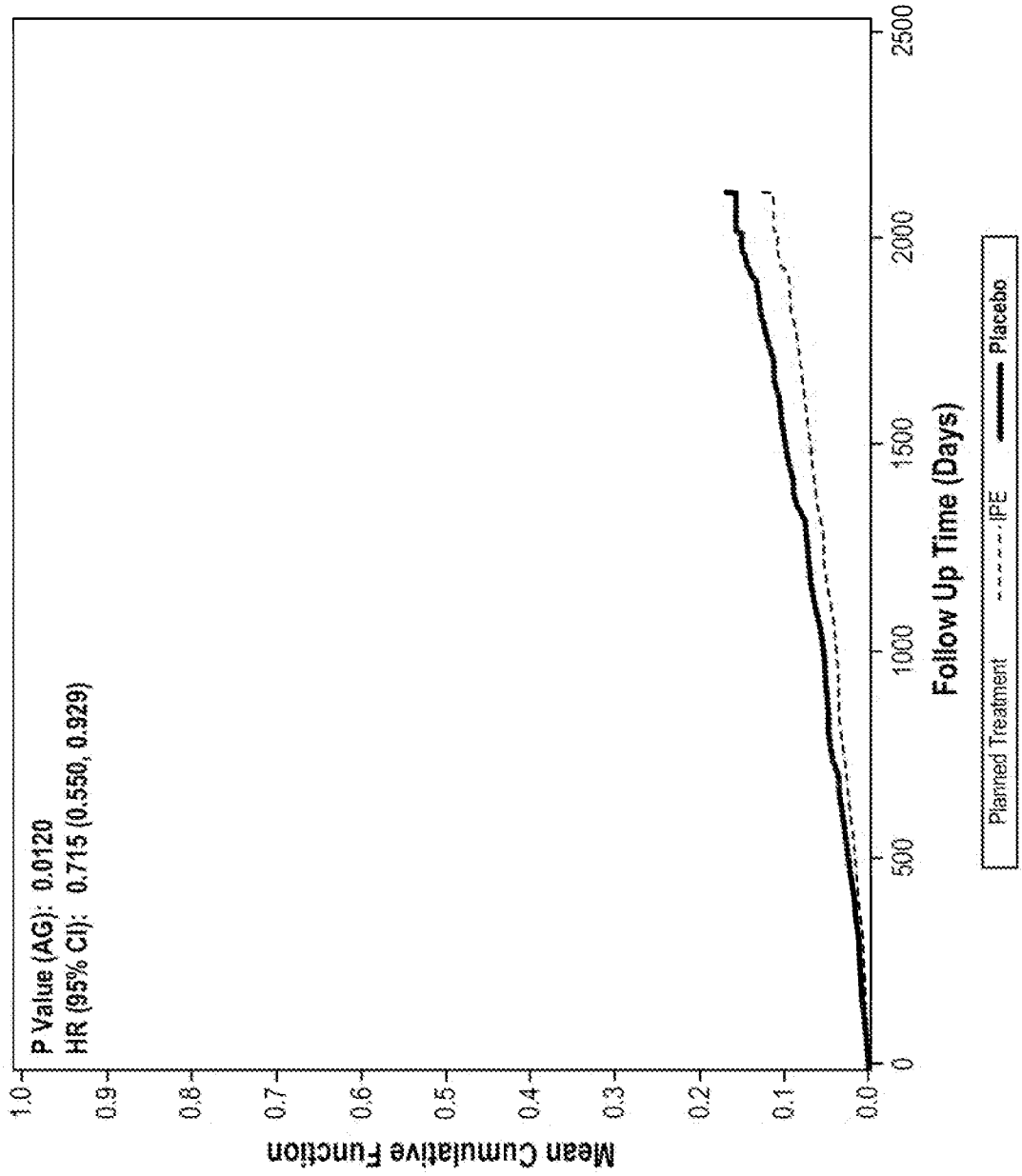

P Value (AG): 0.0120
HR (95% CI): 0.715 (0.550, 0.929)
Mean Cumulative Function
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0
0
500
1000
1500
2000
2500
Follow Up Time (Days)
Planned Treatment
IPE
Placebo

FIG. 27

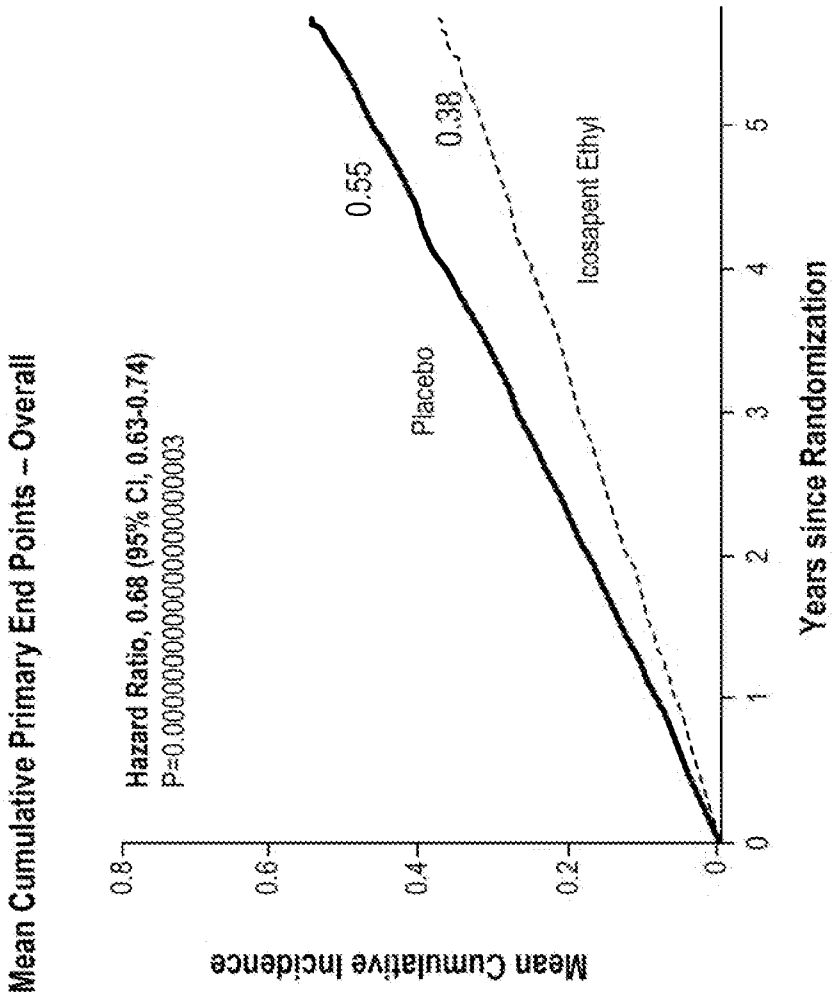

Mean Cumulative Primary End Points – Overall
Hazard Ratio, 0.68 (95% CI, 0.63-0.74)
P=0.0000000000000000003
Mean Cumulative Incidence
0.8
0.6
0.4
0.2
0
0.55
0.38
Placebo
Icosapent Ethyl
0
1
2
3
4
5
Years since Randomization

FIG. 28

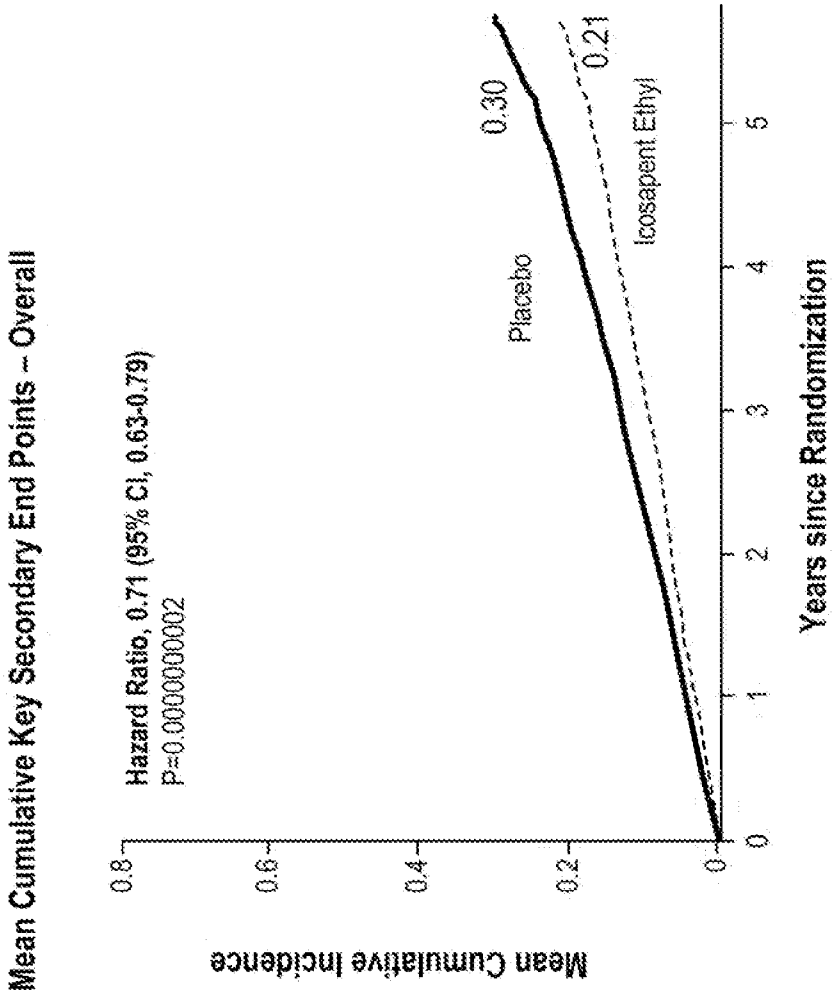

Mean Cumulative Key Secondary End Points – Overall
Hazard Ratio, 0.71 (95% CI, 0.63-0.79)
P=0.0000000002
Mean Cumulative Incidence
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
Years since Randomization
Placebo
0.30
Icosapent Ethyl
0.21

FIG. 29

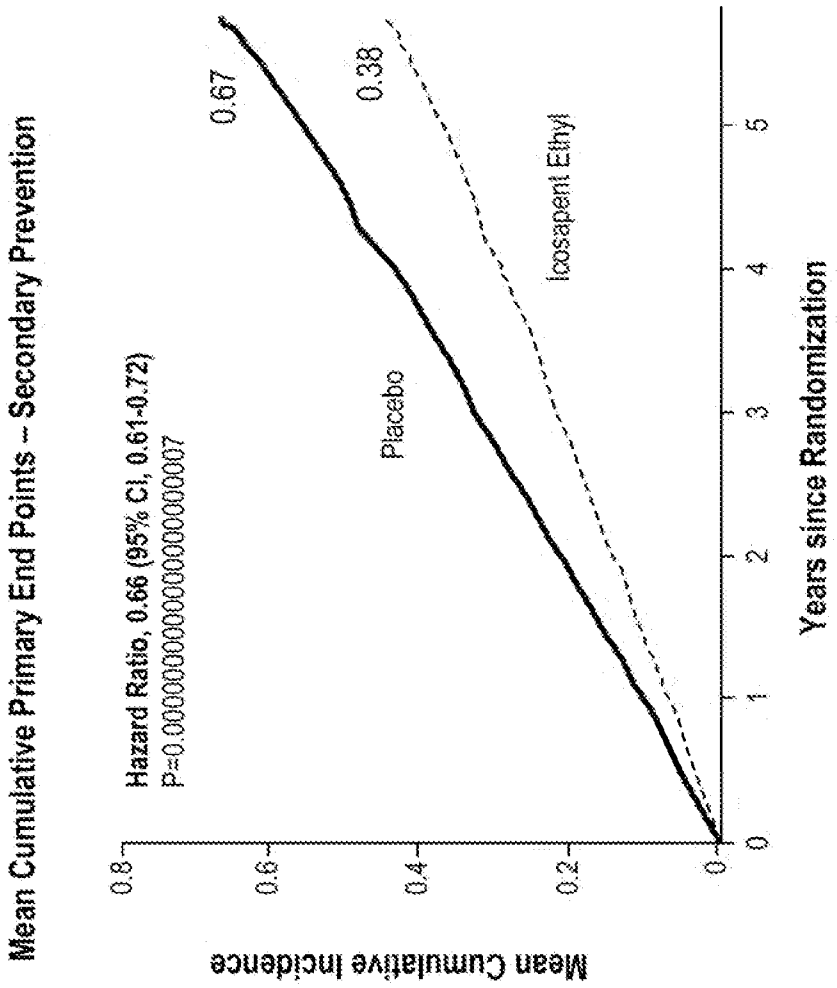

Mean Cumulative Primary End Points – Secondary Prevention
Hazard Ratio, 0.66 (95% CI, 0.61-0.72)
P=0.00000000000000000007
0.67
0.38
Placebo
Icosapent Ethyl
Mean Cumulative Incidence
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
Years since Randomization

FIG. 30

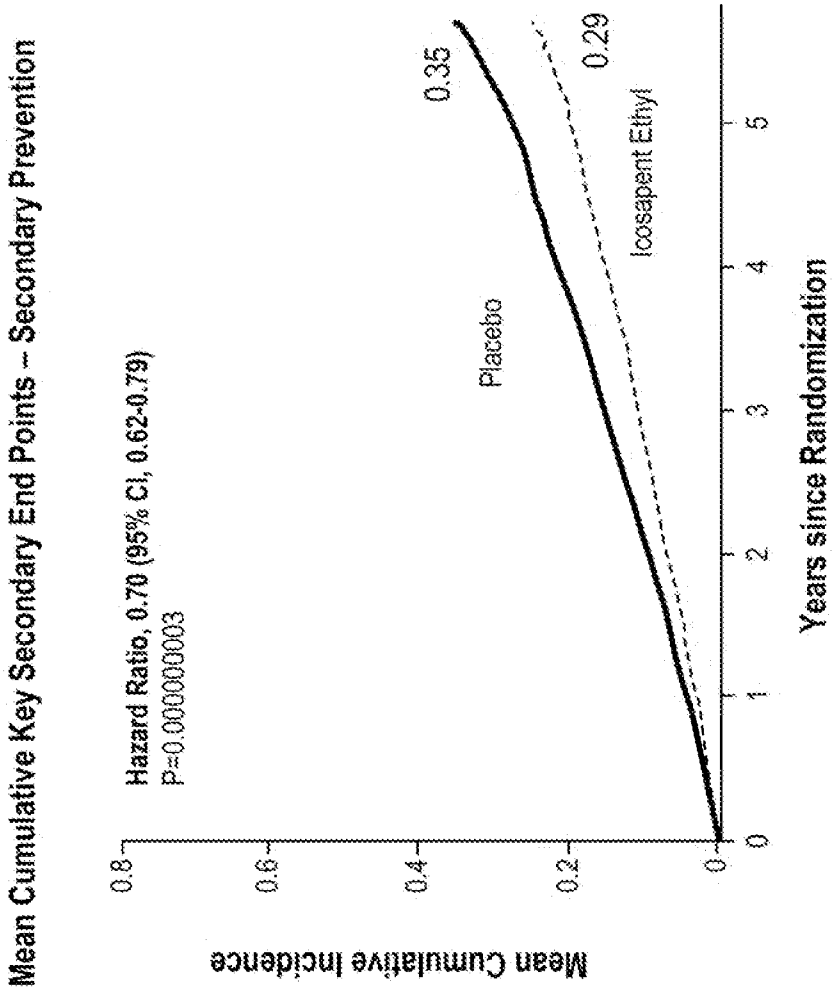

Mean Cumulative Key Secondary End Points – Secondary Prevention
Hazard Ratio, 0.70 (95% CI, 0.62-0.79)
P=0.000000003
Mean Cumulative Incidence
0.8
0.6
0.4
0.2
0
0.35
0.29
Placebo
Icosapent Ethyl
0
1
2
3
4
5
Years since Randomization

FIG. 31

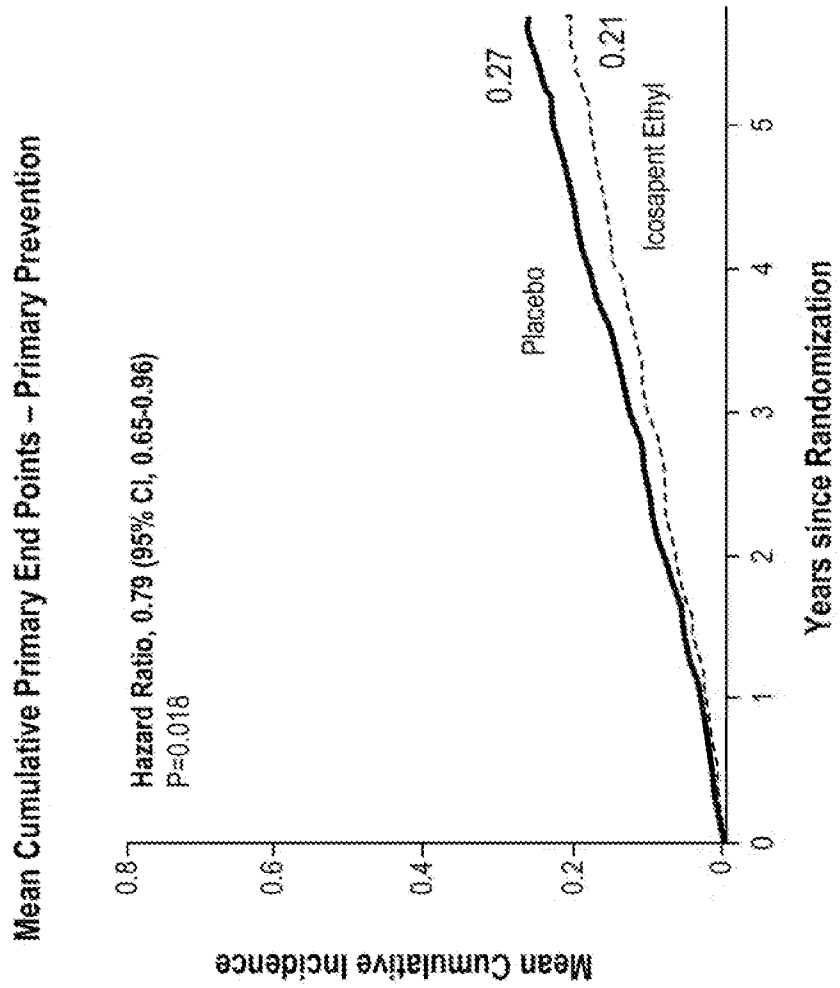

Mean Cumulative Primary End Points – Primary Prevention
Hazard Ratio, 0.79 (95% CI, 0.65-0.96)
P=0.018
Mean Cumulative Incidence
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
Years since Randomization
Placebo
0.27
Icosapent Ethyl
0.21

FIG. 32

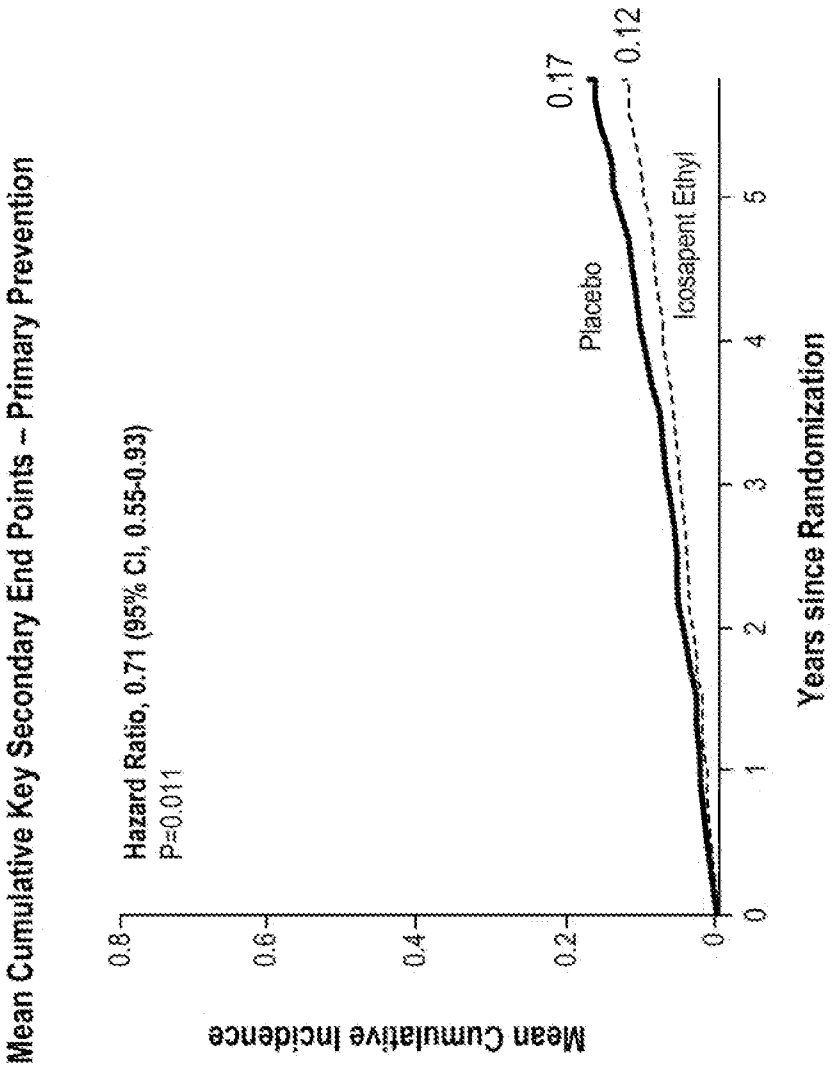

Mean Cumulative Key Secondary End Points – Primary Prevention
Hazard Ratio, 0.71 (95% CI, 0.55-0.93)
P=0.011
Mean Cumulative Incidence
0.8
0.6
0.4
0.2
0
0.17
0.12
Placebo
Icosapent Ethyl
0
1
2
3
4
5
Years since Randomization

FIG. 33

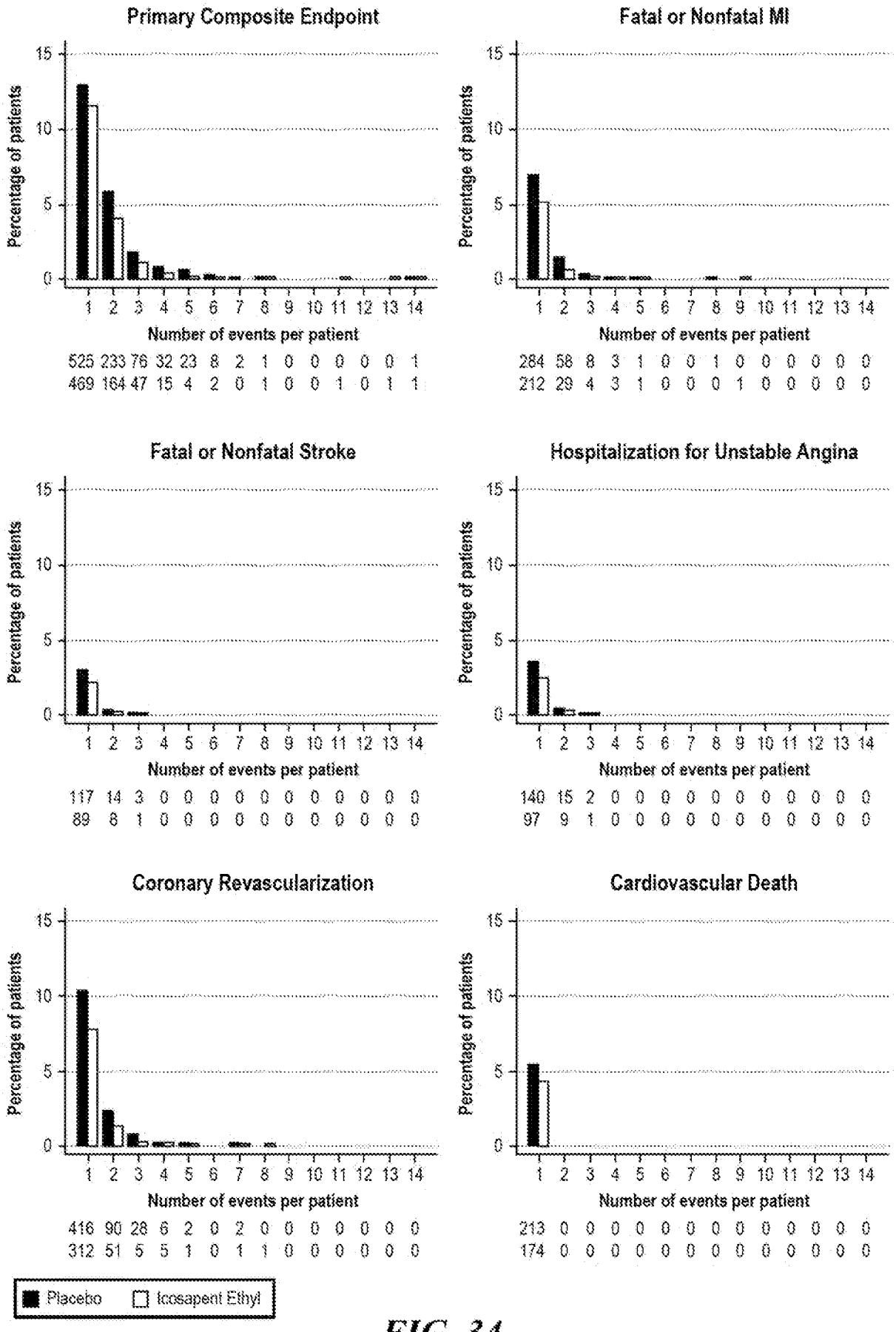

Primary Composite Endpoint
Percentage of patients
15
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14
Number of events per patient
525 233 76 32 23 8 2 1 0 0 0 0 0 1
469 164 47 15 4 2 0 1 0 0 1 0 1 1
Fatal or Nonfatal MI
Percentage of patients
15
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14
Number of events per patient
284 58 8 3 1 0 0 1 0 0 0 0 0 0
212 29 4 3 1 0 0 0 1 0 0 0 0 0
Fatal or Nonfatal Stroke
Percentage of patients
15
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14
Number of events per patient
117 14 3 0 0 0 0 0 0 0 0 0 0 0
89 8 1 0 0 0 0 0 0 0 0 0 0 0
Hospitalization for Unstable Angina
Percentage of patients
15
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14
Number of events per patient
140 15 2 0 0 0 0 0 0 0 0 0 0 0
97 9 1 0 0 0 0 0 0 0 0 0 0 0
Coronary Revascularization
Percentage of patients
15
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14
Number of events per patient
416 90 28 6 2 0 2 0 0 0 0 0 0 0
312 51 5 5 1 0 1 1 0 0 0 0 0 0
Cardiovascular Death
Percentage of patients
15
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14
Number of events per patient
213 0 0 0 0 0 0 0 0 0 0 0 0 0
174 0 0 0 0 0 0 0 0 0 0 0 0 0
Placebo
Icosapent Ethyl

FIG. 34

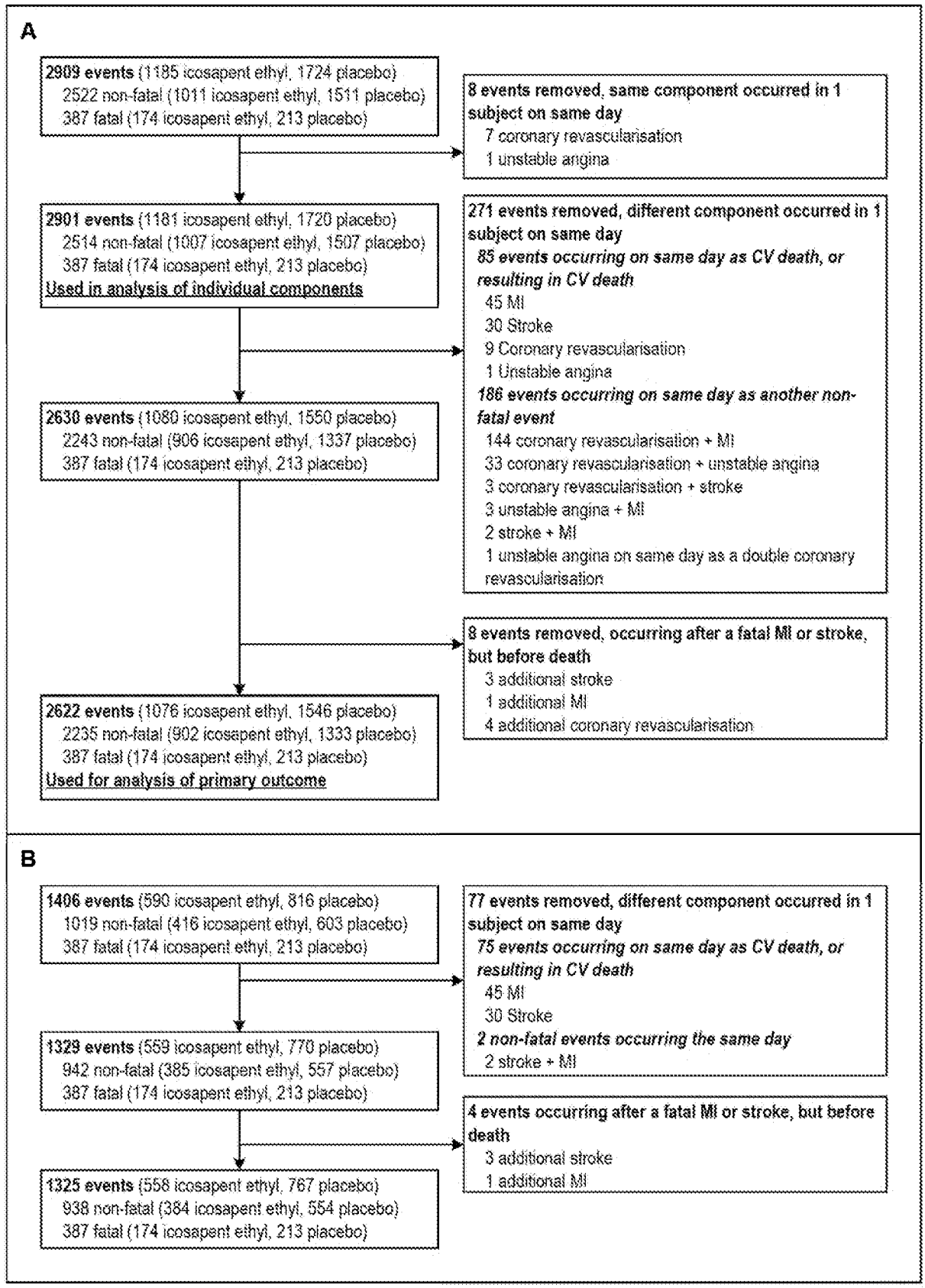

A
2909 events (1185 icosapent ethyl, 1724 placebo)
2522 non-fatal (1011 icosapent ethyl, 1511 placebo)
387 fatal (174 icosapent ethyl, 213 placebo)
8 events removed, same component occurred in 1 subject on same day
7 coronary revascularisation
1 unstable angina
2901 events (1181 icosapent ethyl, 1720 placebo)
2514 non-fatal (1007 icosapent ethyl, 1507 placebo)
387 fatal (174 icosapent ethyl, 213 placebo)
Used in analysis of individual components
271 events removed, different component occurred in 1 subject on same day
85 events occurring on same day as CV death, or resulting in CV death
45 MI
30 Stroke
9 Coronary revascularisation
1 Unstable angina
186 events occurring on same day as another non-fatal event
144 coronary revascularisation + MI
33 coronary revascularisation + unstable angina
3 coronary revascularisation + stroke
3 unstable angina + MI
2 stroke + MI
1 unstable angina on same day as a double coronary revascularisation
2630 events (1080 icosapent ethyl, 1550 placebo)
2243 non-fatal (906 icosapent ethyl, 1337 placebo)
387 fatal (174 icosapent ethyl, 213 placebo)
8 events removed, occurring after a fatal MI or stroke, but before death
3 additional stroke
1 additional MI
4 additional coronary revascularisation
2622 events (1076 icosapent ethyl, 1546 placebo)
2235 non-fatal (902 icosapent ethyl, 1333 placebo)
387 fatal (174 icosapent ethyl, 213 placebo)
Used for analysis of primary outcome
B
1406 events (590 icosapent ethyl, 816 placebo)
1019 non-fatal (416 icosapent ethyl, 603 placebo)
387 fatal (174 icosapent ethyl, 213 placebo)
77 events removed, different component occurred in 1 subject on same day
75 events occurring on same day as CV death, or resulting in CV death
45 MI
30 Stroke
2 non-fatal events occurring the same day
2 stroke + MI
1329 events (559 icosapent ethyl, 770 placebo)
942 non-fatal (385 icosapent ethyl, 557 placebo)
387 fatal (174 icosapent ethyl, 213 placebo)
4 events occurring after a fatal MI or stroke, but before death
3 additional stroke
1 additional MI
1325 events (558 icosapent ethyl, 767 placebo)
938 non-fatal (384 icosapent ethyl, 554 placebo)
387 fatal (174 icosapent ethyl, 213 placebo)

FIG. 35

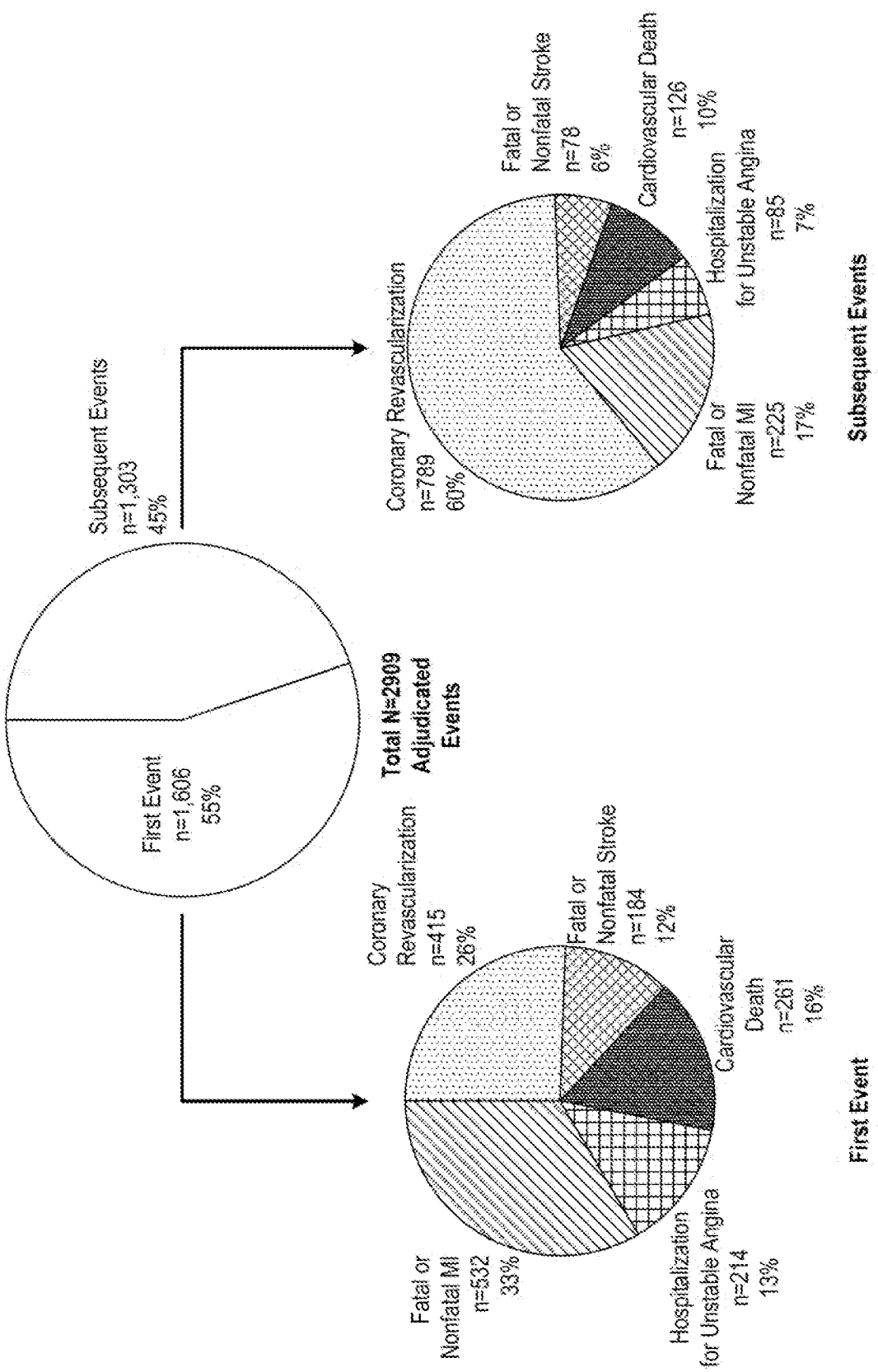

Subsequent Events
n=1,303
45%
First Event
n=1,606
55%
Total N=2909
Adjudicated
Events
Coronary Revascularization
n=789
60%
Fatal or
Nonfatal Stroke
n=78
6%
Cardiovascular Death
n=126
10%
Hospitalization
for Unstable Angina
n=85
7%
Fatal or
Nonfatal MI
n=225
17%
Subsequent Events
Coronary
Revascularization
n=415
26%
Fatal or
Nonfatal Stroke
n=184
12%
Cardiovascular
Death
n=261
16%
Hospitalization
for Unstable Angina
n=214
13%
Fatal or
Nonfatal MI
n=532
33%
First Event

FIG. 36

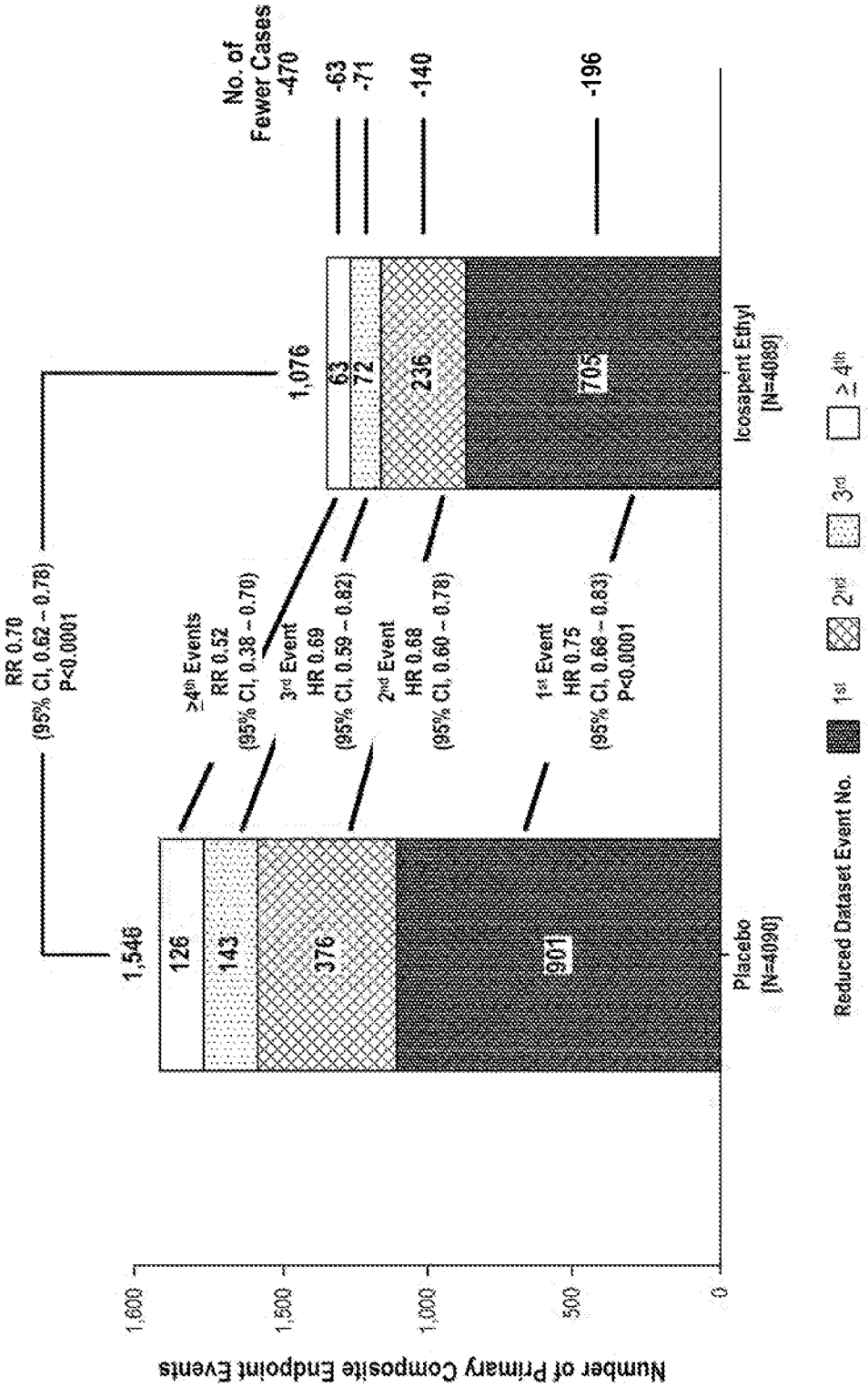
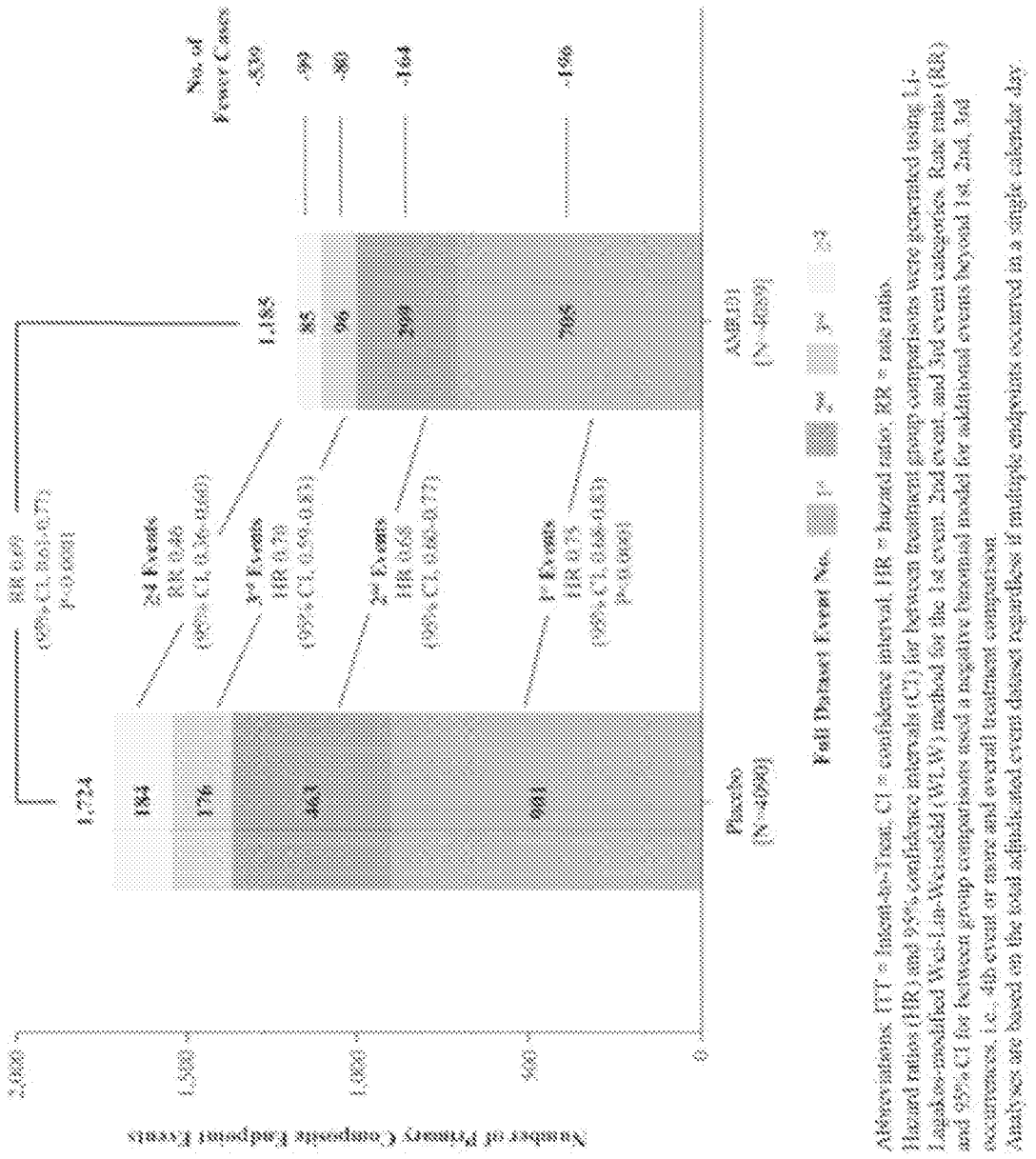

Number of Primary Composite Endpoint Events
1,600
1,500
1,000
500
0
Placebo
(N=4090)
Icosapent Ethyl
(N=4089)
1,546
126
143
376
901
1,076
63
72
236
705
RR 0.70
(95% CI, 0.62 – 0.78)
P<0.0001
≥4th Events
RR 0.52
(95% CI, 0.38 – 0.70)
3rd Event
HR 0.69
(95% CI, 0.59 – 0.82)
2nd Event
HR 0.68
(95% CI, 0.60 – 0.78)
1st Event
HR 0.75
(95% CI, 0.68 – 0.83)
P<0.0001
No. of
Fewer Cases
-470
-63
-71
-140
-196
Reduced Dataset Event No.
1st
2nd
3rd
≥ 4th

FIG. 37A



Abbreviations: ITT = Intent-to-Treat, CI = confidence interval, HR = hazard ratio, RR = rate ratio.
Hazard ratios (HR) and 95% confidence intervals (CI) for between treatment group comparisons were generated using Lin-Lachin-modified Wei-Lin-Weissfeld (WLW) method for the 1st event, 2nd event, and 3rd event categories. Rate ratio (RR) and 95% CI for between group comparisons used a negative binomial model for additional events beyond 1st, 2nd, 3rd occurrences, i.e., 4th event or more and overall treatment comparison.
Analyses are based on the total adjudicated event dataset regardless if multiple endpoints occurred in a single calendar day

FIG. 37B

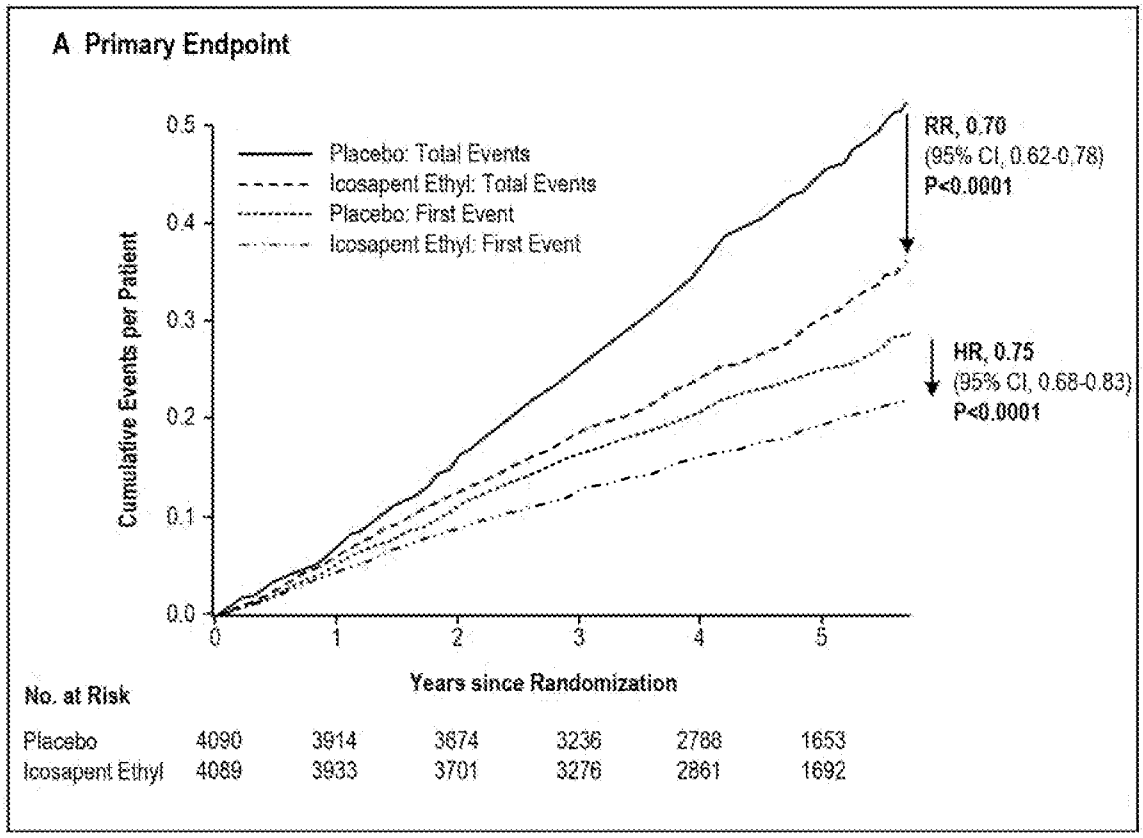

A Primary Endpoint
Placebo: Total Events
Icosapent Ethyl: Total Events
Placebo: First Event
Icosapent Ethyl: First Event
RR, 0.70
(95% CI, 0.62-0.78)
P<0.0001
HR, 0.75
(95% CI, 0.68-0.83)
P<0.0001
Cumulative Events per Patient
0.0
0.1
0.2
0.3
0.4
0.5
0
1
2
3
4
5
Years since Randomization
No. at Risk
Placebo 4090 3914 3674 3236 2788 1653
Icosapent Ethyl 4089 3933 3701 3276 2861 1692

FIG. 38A

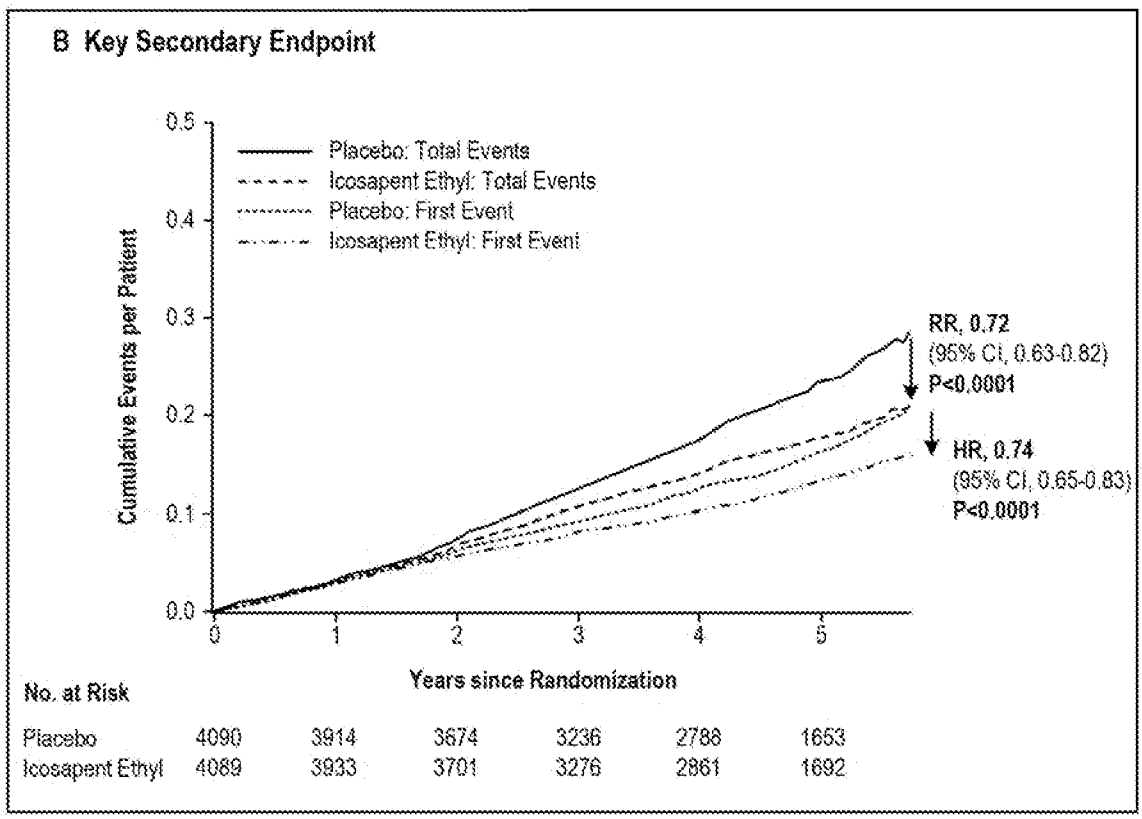

B Key Secondary Endpoint
Placebo: Total Events
Icosapent Ethyl: Total Events
Placebo: First Event
Icosapent Ethyl: First Event
Cumulative Events per Patient
0.0
0.1
0.2
0.3
0.4
0.5
0
1
2
3
4
5
Years since Randomization
RR, 0.72
(95% CI, 0.63-0.82)
P<0.0001
HR, 0.74
(95% CI, 0.65-0.83)
P<0.0001
No. at Risk
Placebo 4090 3914 3674 3236 2788 1653
Icosapent Ethyl 4089 3933 3701 3276 2861 1692

FIG. 38B

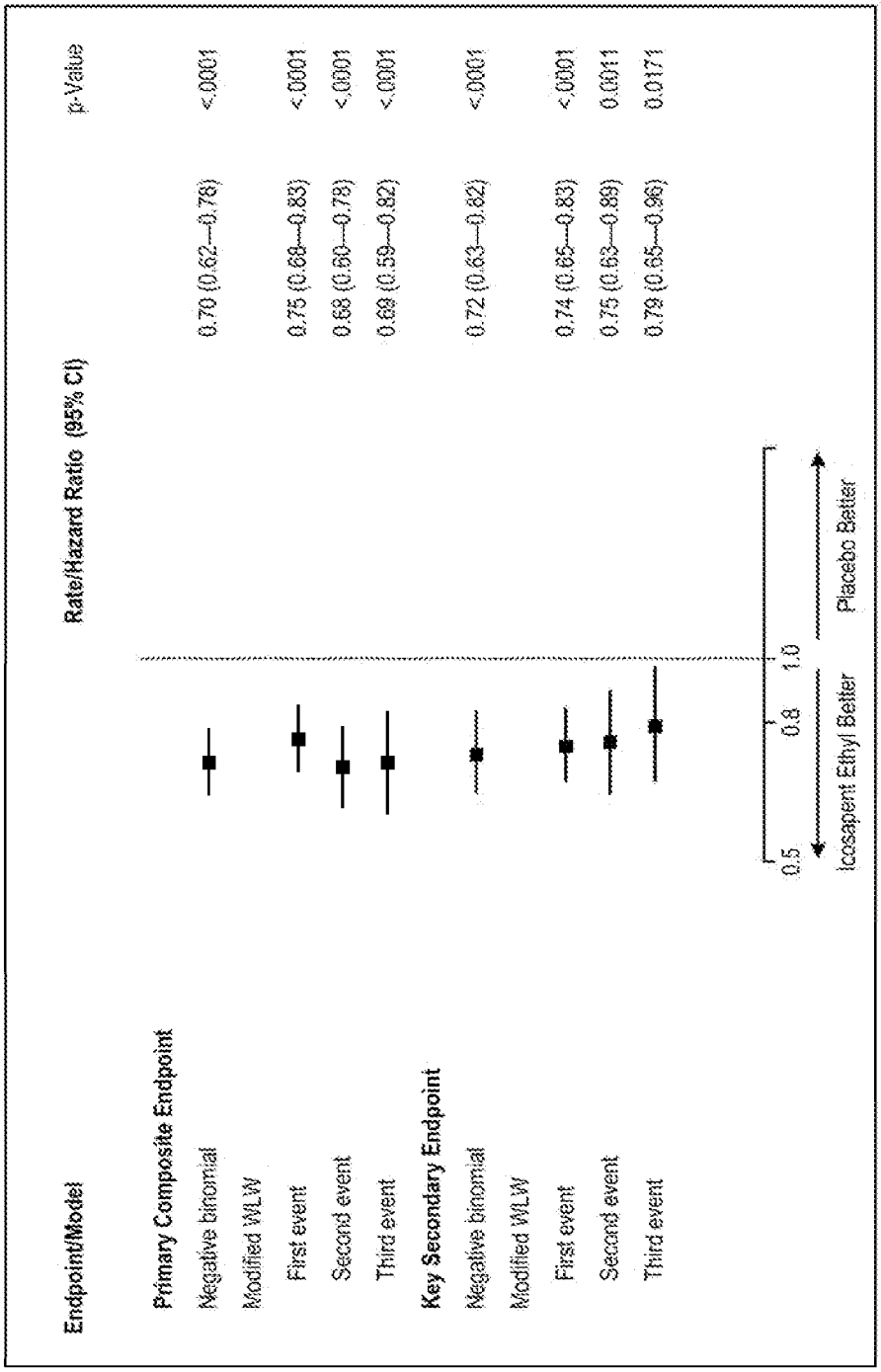

Endpoint/Model
Rate/Hazard Ratio (95% CI)
p-Value
Primary Composite Endpoint
Negative binomial
0.70 (0.62—0.78)
<.0001
Modified WLW
First event
0.75 (0.68—0.83)
<.0001
Second event
0.68 (0.60—0.78)
<.0001
Third event
0.69 (0.59—0.82)
<.0001
Key Secondary Endpoint
Negative binomial
0.72 (0.63—0.82)
<.0001
Modified WLW
First event
0.74 (0.65—0.83)
<.0001
Second event
0.75 (0.63—0.89)
0.0011
Third event
0.79 (0.65—0.96)
0.0171
0.5
0.8
1.0
Icosapent Ethyl Better
Placebo Better

FIG. 39

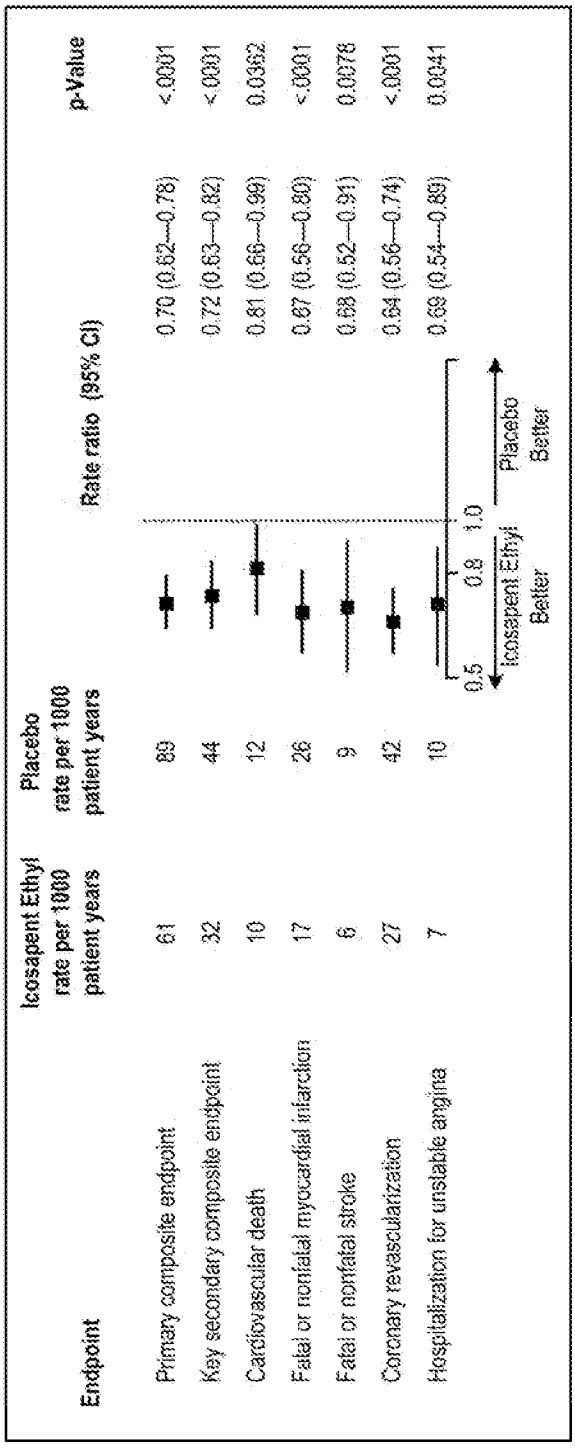

Endpoint
Icosapent Ethyl rate per 1000 patient years
Placebo rate per 1000 patient years
Rate ratio (95% CI)
p-Value
Primary composite endpoint
61
89
0.70 (0.62–0.78)
<.0001
Key secondary composite endpoint
32
44
0.72 (0.63–0.82)
<.0001
Cardiovascular death
10
12
0.81 (0.66–0.99)
0.0362
Fatal or nonfatal myocardial infarction
17
26
0.67 (0.56–0.80)
<.0001
Fatal or nonfatal stroke
6
9
0.68 (0.52–0.91)
0.0078
Coronary revascularization
27
42
0.64 (0.56–0.74)
<.0001
Hospitalization for unstable angina
7
10
0.69 (0.54–0.89)
0.0041
0.5
0.8
1.0
Icosapent Ethyl Better
Placebo Better

FIG. 40

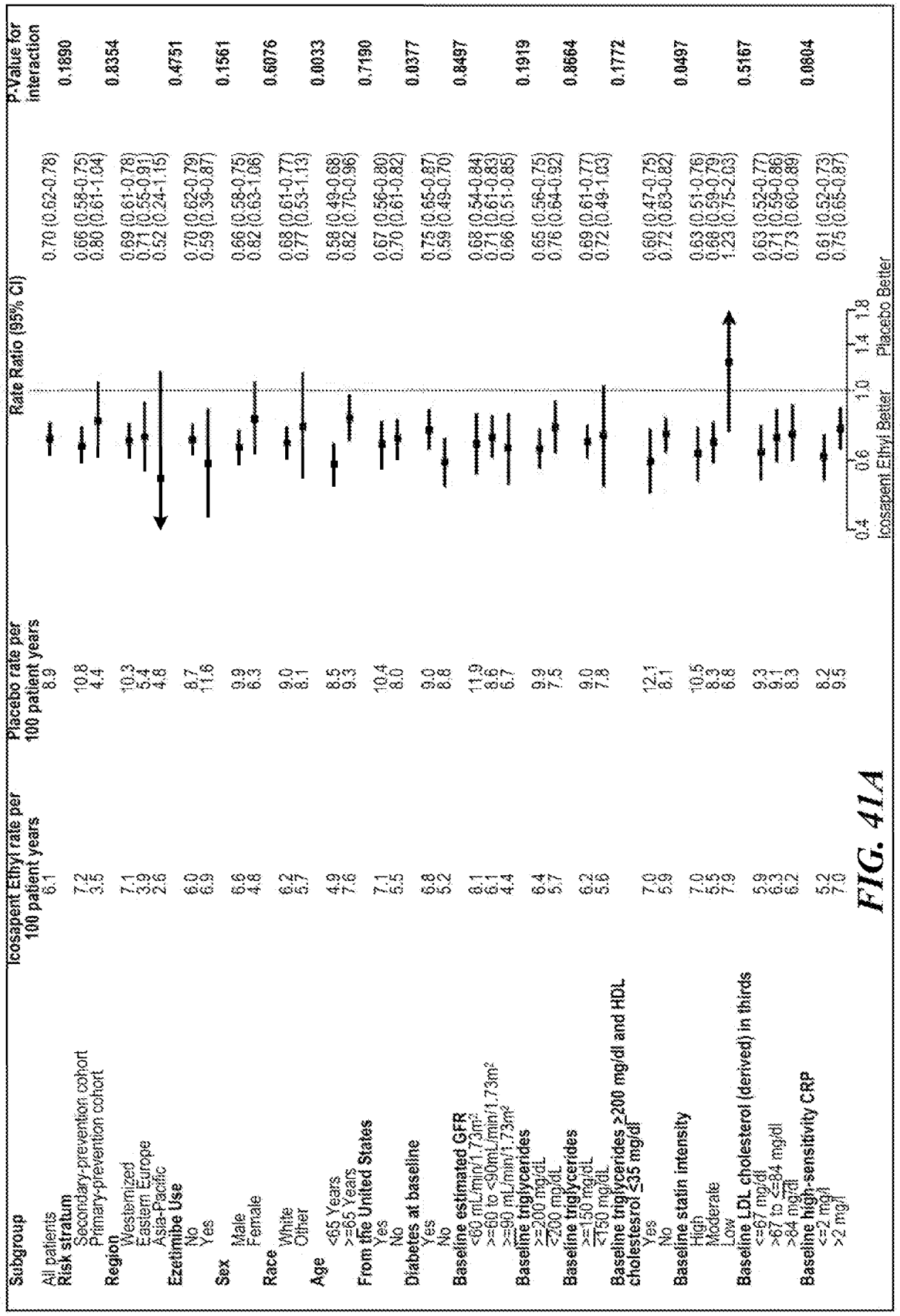

Subgroup
Icosapent Ethyl rate per 100 patient years
Placebo rate per 100 patient years
Rate Ratio (95% CI)
P-Value for interaction
All patients 6.1 8.9 0.70 (0.62-0.78) 0.1890
Risk stratum
Secondary-prevention cohort 7.2 10.8 0.68 (0.58-0.75)
Primary-prevention cohort 3.5 4.4 0.80 (0.61-1.04) 0.8354
Region
Westernized 7.1 10.3 0.69 (0.61-0.78)
Eastern Europe 3.9 5.4 0.71 (0.55-0.91)
Asia-Pacific 2.6 4.8 0.52 (0.24-1.15) 0.4751
Ezetimibe Use
No 6.0 8.7 0.70 (0.62-0.79)
Yes 6.9 11.6 0.59 (0.39-0.87) 0.1561
Sex
Male 6.6 9.9 0.66 (0.58-0.75)
Female 4.8 6.3 0.82 (0.63-1.06) 0.6076
Race
White 6.2 9.0 0.68 (0.61-0.77)
Other 5.7 8.1 0.77 (0.53-1.13) 0.0033
Age
<65 Years 4.9 8.5 0.58 (0.49-0.68)
>=65 Years 7.6 9.3 0.82 (0.70-0.96) 0.7190
From the United States
Yes 7.1 10.4 0.67 (0.56-0.80)
No 5.5 8.0 0.70 (0.61-0.82) 0.0377
Diabetes at baseline
Yes 5.8 9.0 0.75 (0.65-0.87)
No 5.2 8.8 0.59 (0.49-0.70) 0.8497
Baseline estimated GFR
<60 mL/min/1.73m2 8.1 11.9 0.68 (0.54-0.84)
>=60 to <90mL/min/1.73m2 6.1 8.6 0.71 (0.61-0.83)
>=90 mL/min/1.73m2 4.4 6.7 0.66 (0.51-0.85) 0.1919
Baseline triglycerides
>=200 mg/dL 6.4 9.9 0.65 (0.56-0.75)
<200 mg/dL 5.7 7.5 0.76 (0.64-0.92) 0.8664
Baseline triglycerides
>=150 mg/dL 6.2 9.0 0.69 (0.61-0.77)
<150 mg/dL 5.6 7.8 0.72 (0.49-1.03) 0.1772
Baseline triglycerides ≥200 mg/dl and HDL cholesterol ≤35 mg/dl
Yes 7.0 12.1 0.60 (0.47-0.75)
No 5.9 8.1 0.72 (0.63-0.82) 0.0497
Baseline statin intensity
High 7.0 10.5 0.63 (0.51-0.76)
Moderate 5.5 8.3 0.68 (0.59-0.79)
Low 7.9 6.8 1.23 (0.75-2.03) 0.5167
Baseline LDL cholesterol (derived) in thirds
<=67 mg/dl 5.9 9.3 0.63 (0.52-0.77)
>67 to <=84 mg/dl 6.3 9.1 0.71 (0.59-0.86)
>84 mg/dl 6.2 8.3 0.73 (0.60-0.89) 0.0804
Baseline high-sensitivity CRP
<=2 mg/l 5.2 8.2 0.61 (0.52-0.73)
>2 mg/l 7.0 9.5 0.75 (0.65-0.87)
0.4 0.6 1.0 1.4 1.8
Icosapent Ethyl Better
Placebo Better

FIG. 41A

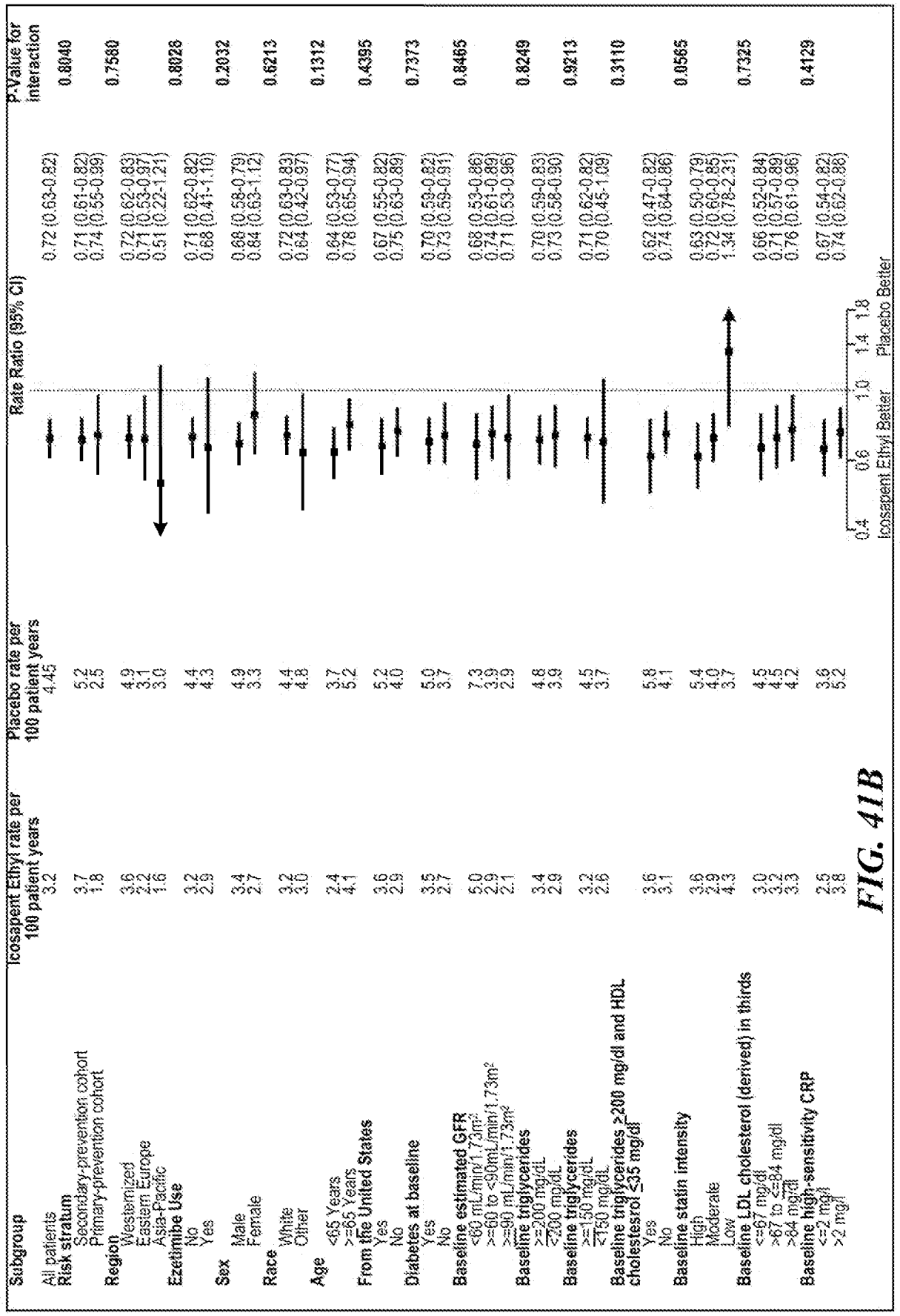

Subgroup
Icosapent Ethyl rate per 100 patient years
Placebo rate per 100 patient years
Rate Ratio (95% CI)
P-Value for interaction
All patients 3.2 4.45 0.72 (0.63-0.82) 0.8040
Risk stratum
Secondary-prevention cohort 3.7 5.2 0.71 (0.61-0.82)
Primary-prevention cohort 1.8 2.5 0.74 (0.55-0.99) 0.7560
Region
Westernized 3.6 4.9 0.72 (0.62-0.83)
Eastern Europe 2.2 3.1 0.71 (0.53-0.97)
Asia-Pacific 1.6 3.0 0.51 (0.22-1.21) 0.8026
Ezetimibe Use
No 3.2 4.4 0.71 (0.62-0.82)
Yes 2.9 4.3 0.68 (0.41-1.10) 0.2032
Sex
Male 3.4 4.9 0.68 (0.58-0.79)
Female 2.7 3.3 0.84 (0.63-1.12) 0.6213
Race
White 3.2 4.4 0.72 (0.63-0.83)
Other 3.0 4.8 0.64 (0.42-0.97) 0.1312
Age
<65 Years 2.4 3.7 0.64 (0.53-0.77)
>=65 Years 4.1 5.2 0.78 (0.65-0.94) 0.4395
From the United States
Yes 3.6 5.2 0.67 (0.55-0.82)
No 2.9 4.0 0.75 (0.63-0.89) 0.7373
Diabetes at baseline
Yes 3.5 5.0 0.70 (0.59-0.82)
No 2.7 3.7 0.73 (0.59-0.91) 0.8465
Baseline estimated GFR
<60 mL/min/1.73m2 5.0 7.3 0.68 (0.53-0.86)
>=60 to <90mL/min/1.73m2 2.9 3.9 0.74 (0.61-0.89)
>=90 mL/min/1.73m2 2.1 2.9 0.71 (0.53-0.96) 0.8249
Baseline triglycerides
>=200 mg/dL 3.4 4.8 0.70 (0.59-0.83)
<200 mg/dL 2.9 3.9 0.73 (0.58-0.90) 0.9213
Baseline triglycerides
>=150 mg/dL 3.2 4.5 0.71 (0.62-0.82)
<150 mg/dL 2.6 3.7 0.70 (0.45-1.09) 0.3110
Baseline triglycerides ≥200 mg/dl and HDL cholesterol ≤35 mg/dl
Yes 3.6 5.8 0.62 (0.47-0.82)
No 3.1 4.1 0.74 (0.64-0.86) 0.0565
Baseline statin intensity
High 3.6 5.4 0.63 (0.50-0.79)
Moderate 2.9 4.0 0.72 (0.60-0.85)
Low 4.3 3.7 1.34 (0.78-2.31) 0.7325
Baseline LDL cholesterol (derived) in thirds
<=67 mg/dl 3.0 4.5 0.66 (0.52-0.84)
>67 to <=84 mg/dl 3.2 4.5 0.71 (0.57-0.89)
>84 mg/dl 3.3 4.2 0.76 (0.61-0.96) 0.4129
Baseline high-sensitivity CRP
<=2 mg/l 2.5 3.6 0.67 (0.54-0.82)
>2 mg/l 3.8 5.2 0.74 (0.62-0.88)
0.4
0.6
1.0
1.4
1.8
Icosapent Ethyl Better
Placebo Better

FIG. 41B

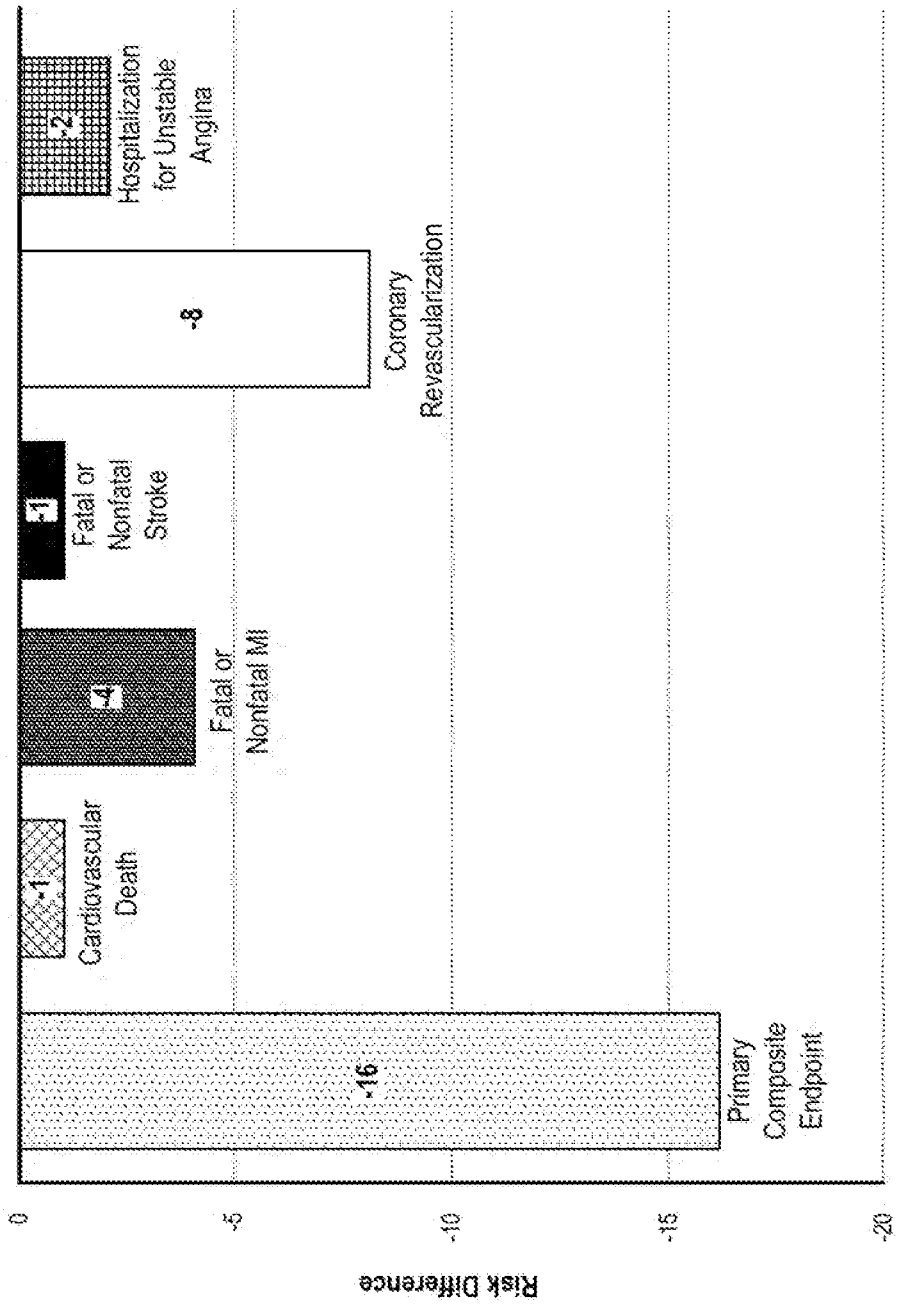

Risk Difference
0
-5
-10
-15
-20
-16
Primary Composite Endpoint
-1
Cardiovascular Death
-4
Fatal or Nonfatal MI
-1
Fatal or Nonfatal Stroke
-8
Coronary Revascularization
-2
Hospitalization for Unstable Angina

FIG. 42

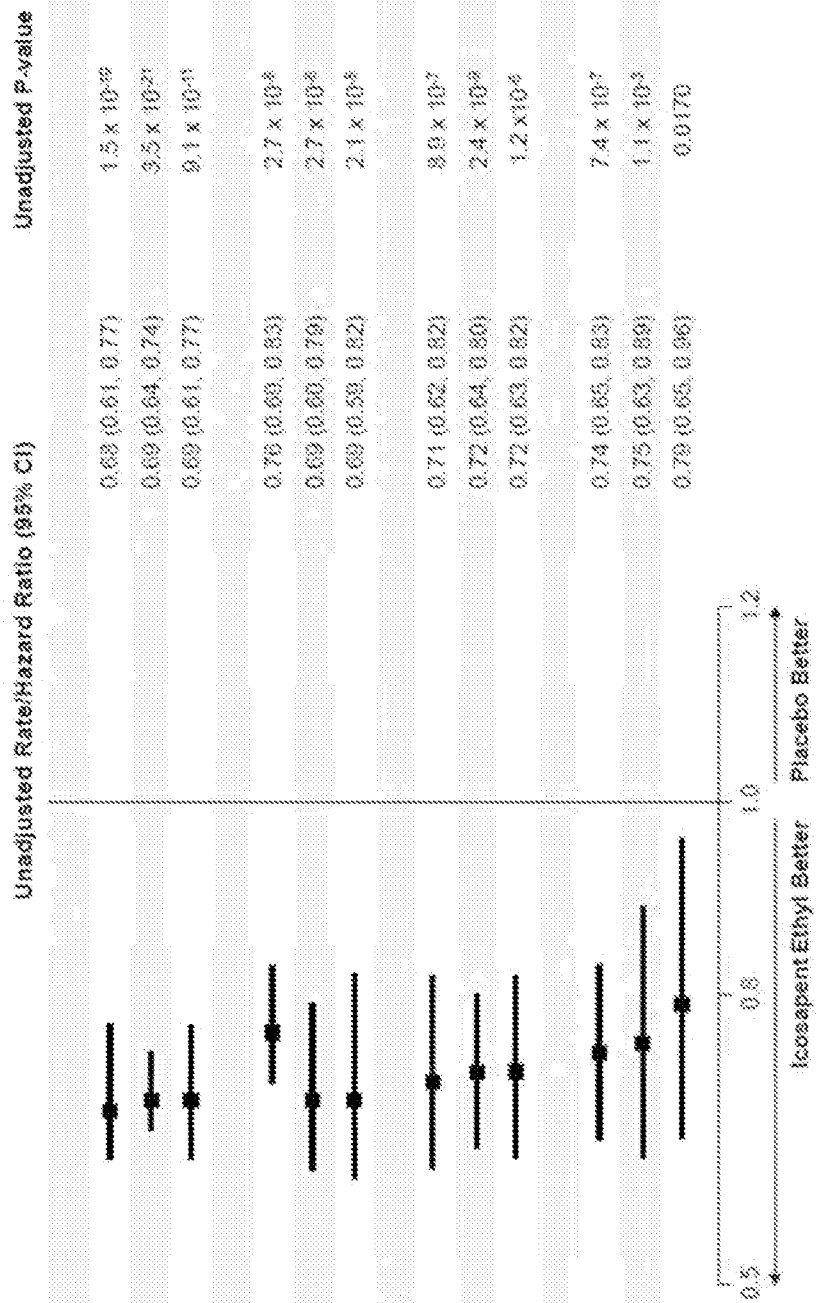

Endpoint/Model
Unadjusted Rate/Hazard Ratio (95% CI)
Unadjusted P-value
Primary Composite Endpoint
Negative binomial
0.69 (0.61, 0.77)
1.5 x 10⁻⁹
Anderson-Gill (I)
0.69 (0.64, 0.74)
3.5 x 10⁻²¹
Anderson-Gill (II)
0.69 (0.61, 0.77)
9.1 x 10⁻¹⁰
Modified WLW
First event
0.76 (0.69, 0.83)
2.7 x 10⁻⁸
Second event
0.69 (0.60, 0.79)
2.7 x 10⁻⁸
Third event
0.69 (0.59, 0.82)
2.1 x 10⁻⁵
Key Secondary Composite Endpoint
Negative binomial
0.71 (0.62, 0.82)
8.9 x 10⁻⁷
Anderson-Gill (I)
0.72 (0.64, 0.80)
2.4 x 10⁻⁸
Anderson-Gill (II)
0.72 (0.63, 0.82)
1.2 x 10⁻⁶
Modified WLW
First event
0.74 (0.65, 0.83)
7.4 x 10⁻⁷
Second event
0.75 (0.63, 0.89)
1.1 x 10⁻³
Third event
0.79 (0.65, 0.96)
0.0170
0.5
0.8
1.0
1.2
Icosapent Ethyl Better
Placebo Better

FIG. 43

Endpoint/Model
Adjusted Rate/Hazard Ratio (95% CI)
Adjusted P-value
Primary Composite Endpoint
Negative binomial
0.70 (0.62, 0.78)
3.6 x 10-9
Andersen-Gill (i)
0.69 (0.64, 0.74)
3.3 x 10-21
Andersen-Gill (ii)
0.69 (0.61, 0.77)
5.2 x 10-11
Modified WLW
First event
0.75 (0.68, 0.83)
1.6 x 10-8
Second event
0.69 (0.60, 0.79)
1.8 x 10-8
Third event
0.60 (0.50, 0.82)
2.0 x 10-5
Key Secondary Composite Endpoint
Negative binomial
0.72 (0.63, 0.82)
7.1 x 10-7
Andersen-Gill (i)
0.72 (0.64, 0.80)
2.4 x 10-9
Andersen-Gill (ii)
0.72 (0.63, 0.82)
1.0 x 10-6
Modified WLW
First event
0.74 (0.65, 0.83)
7.0 x 10-7
Second event
0.75 (0.63, 0.89)
1.1 x 10-3
Third event
0.79 (0.65, 0.96)
0.0171
0.5
0.8
1.0
1.2
Icosapent Ethyl Better
Placebo Better

FIG. 44

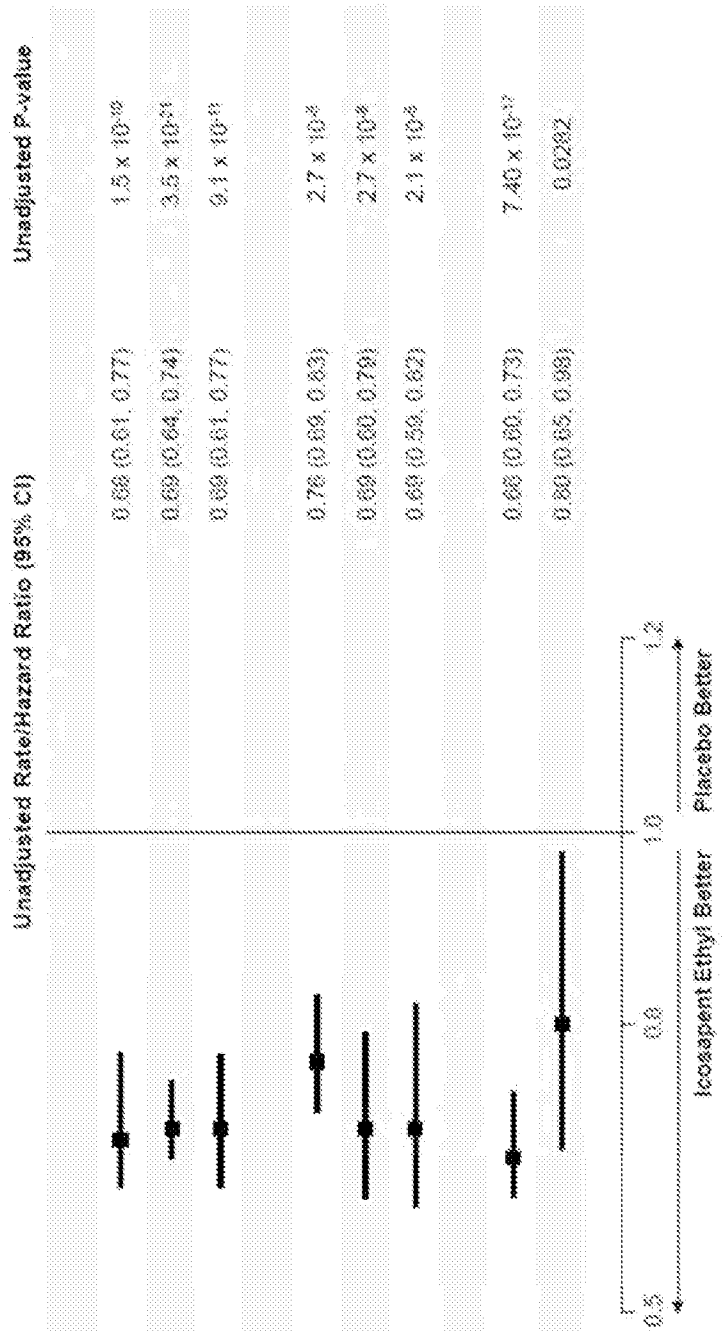

Endpoint/Model
Unadjusted Rate/Hazard Ratio (95% CI)
Unadjusted P-value
Primary Composite Endpoint
Negative binomial
0.69 (0.61, 0.77)
1.5 x 10-10
Andersen-Gill (I)
0.69 (0.64, 0.74)
3.6 x 10-31
Andersen-Gill (II)
0.69 (0.61, 0.77)
9.1 x 10-10
Modified WLW
First event
0.76 (0.69, 0.83)
2.7 x 10-8
Second event
0.69 (0.60, 0.79)
2.7 x 10-8
Third event
0.68 (0.59, 0.82)
2.1 x 10-5
Joint Frailty
Non-fatal cardiovascular event
0.68 (0.60, 0.73)
7.40 x 10-17
Cardiovascular death
0.80 (0.65, 0.98)
0.0282
0.5
0.8
1.0
1.2
Icosapent Ethyl Better
Placebo Better

FIG. 45

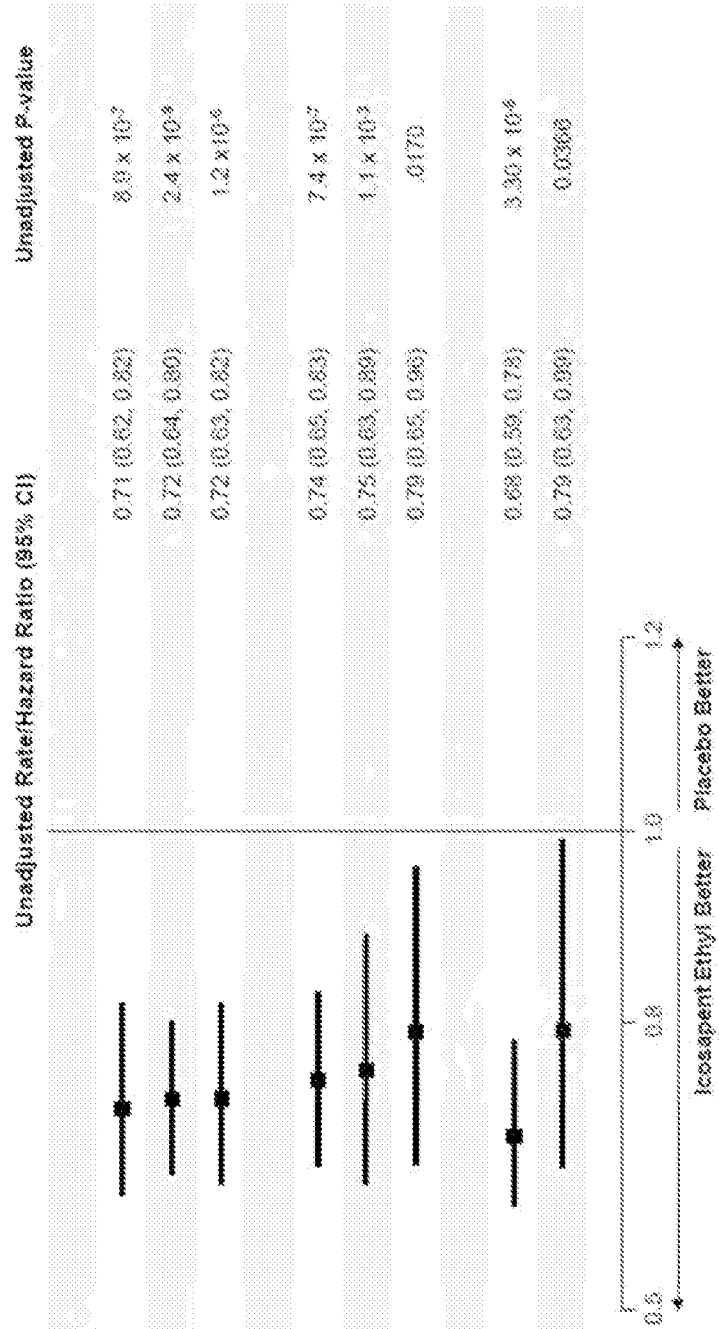

Endpoint/Model
Unadjusted Rate/Hazard Ratio (95% CI)
Unadjusted P-value
Key Secondary Composite Endpoint
Negative binomial
0.71 (0.62, 0.82)
8.9 x 10⁻⁷
Andersen-Gill (I)
0.72 (0.64, 0.80)
2.4 x 10⁻⁸
Andersen-Gill (II)
0.72 (0.63, 0.82)
1.2 x 10⁻⁶
Modified WLW
First event
0.74 (0.66, 0.83)
7.4 x 10⁻⁷
Second event
0.75 (0.63, 0.89)
1.1 x 10⁻³
Third event
0.79 (0.65, 0.96)
.0170
Joint Frailty
Non-fatal cardiovascular event
0.69 (0.59, 0.79)
3.30 x 10⁻⁸
Cardiovascular death
0.79 (0.63, 0.99)
0.0368
0.6
0.8
1.0
1.2
Icosapent Ethyl Better
Placebo Better

FIG. 46

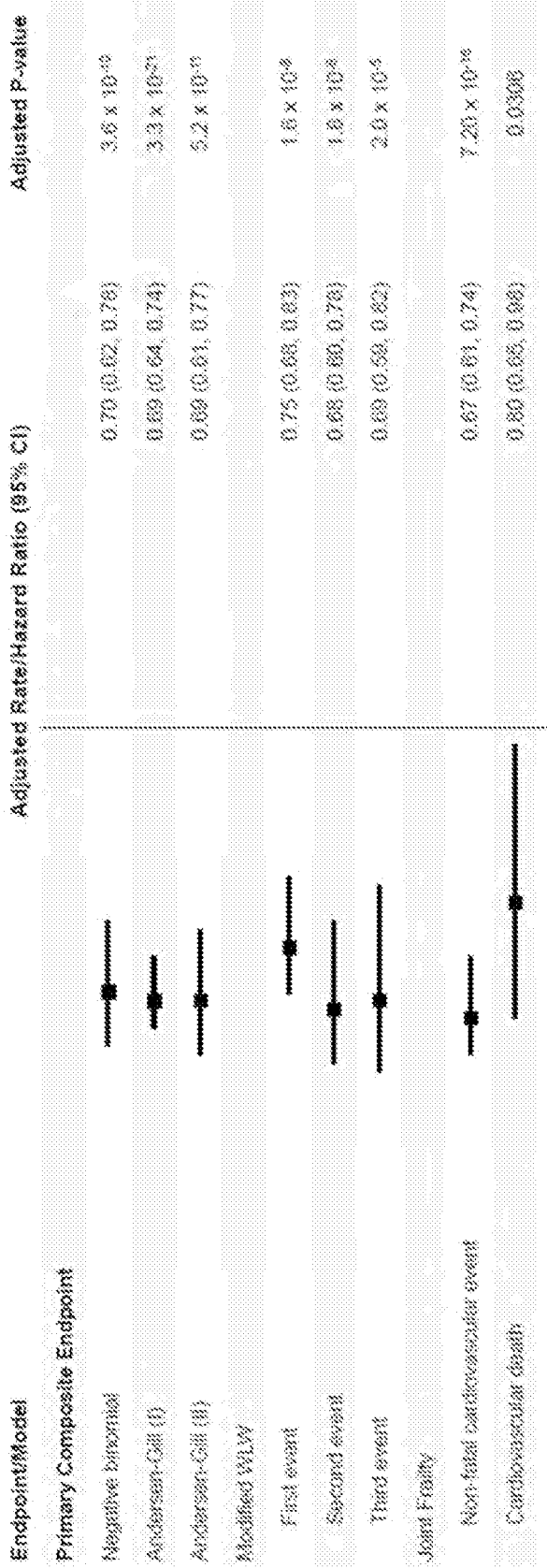

Endpoint/Model
Adjusted Rate/Hazard Ratio (95% CI)
Adjusted P-value
Primary Composite Endpoint
Negative binomial
0.70 (0.62, 0.79)
3.6 x 10⁻⁹
Andersen-Gill (I)
0.69 (0.64, 0.74)
3.3 x 10⁻²¹
Andersen-Gill (II)
0.69 (0.61, 0.77)
5.2 x 10⁻⁹
Modified WLW
First event
0.75 (0.68, 0.83)
1.6 x 10⁻⁸
Second event
0.68 (0.60, 0.76)
1.6 x 10⁻⁸
Third event
0.69 (0.58, 0.82)
2.0 x 10⁻⁵
Joint Frailty
Non-fatal cardiovascular event
0.67 (0.61, 0.74)
7.20 x 10⁻²⁶
Cardiovascular death
0.80 (0.68, 0.96)
0.0308
0.5
0.8
1.0
1.2
Icosapent Ethyl Better
Placebo Better

FIG. 47

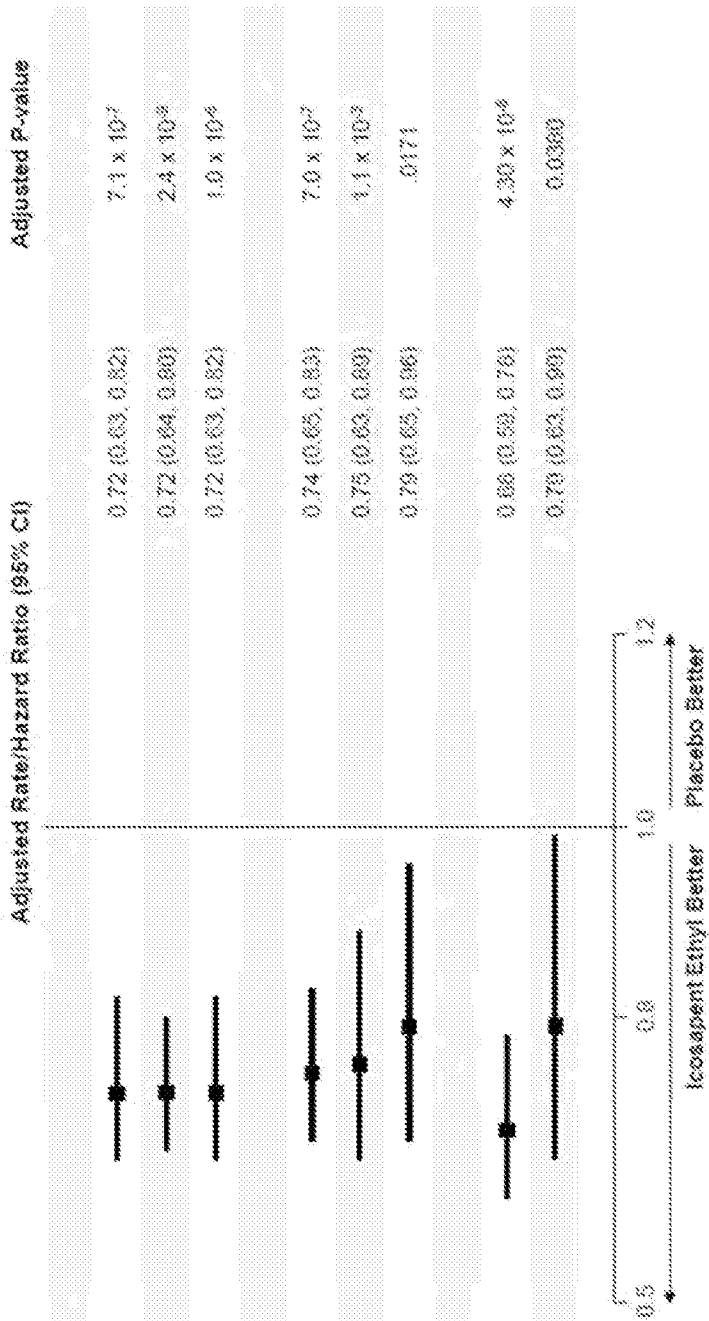

Endpoint/Model
Adjusted Rate/Hazard Ratio (95% CI)
Adjusted P-value
Key Secondary Composite Endpoint
Negative binomial
0.72 (0.63, 0.82)
7.1 x 10-7
Andersen-Gill (I)
0.72 (0.64, 0.80)
2.4 x 10-8
Andersen-Gill (II)
0.72 (0.63, 0.82)
1.0 x 10-6
Modified WLW
First event
0.74 (0.65, 0.83)
7.0 x 10-7
Second event
0.75 (0.63, 0.89)
1.1 x 10-3
Third event
0.78 (0.65, 0.96)
.0171
Joint Frailty
Non-fatal cardiovascular event
0.68 (0.59, 0.78)
4.30 x 10-8
Cardiovascular death
0.79 (0.63, 0.99)
0.0300
0.5
0.8
1.0
1.2
Icosapent Ethyl Better
Placebo Better

FIG. 48

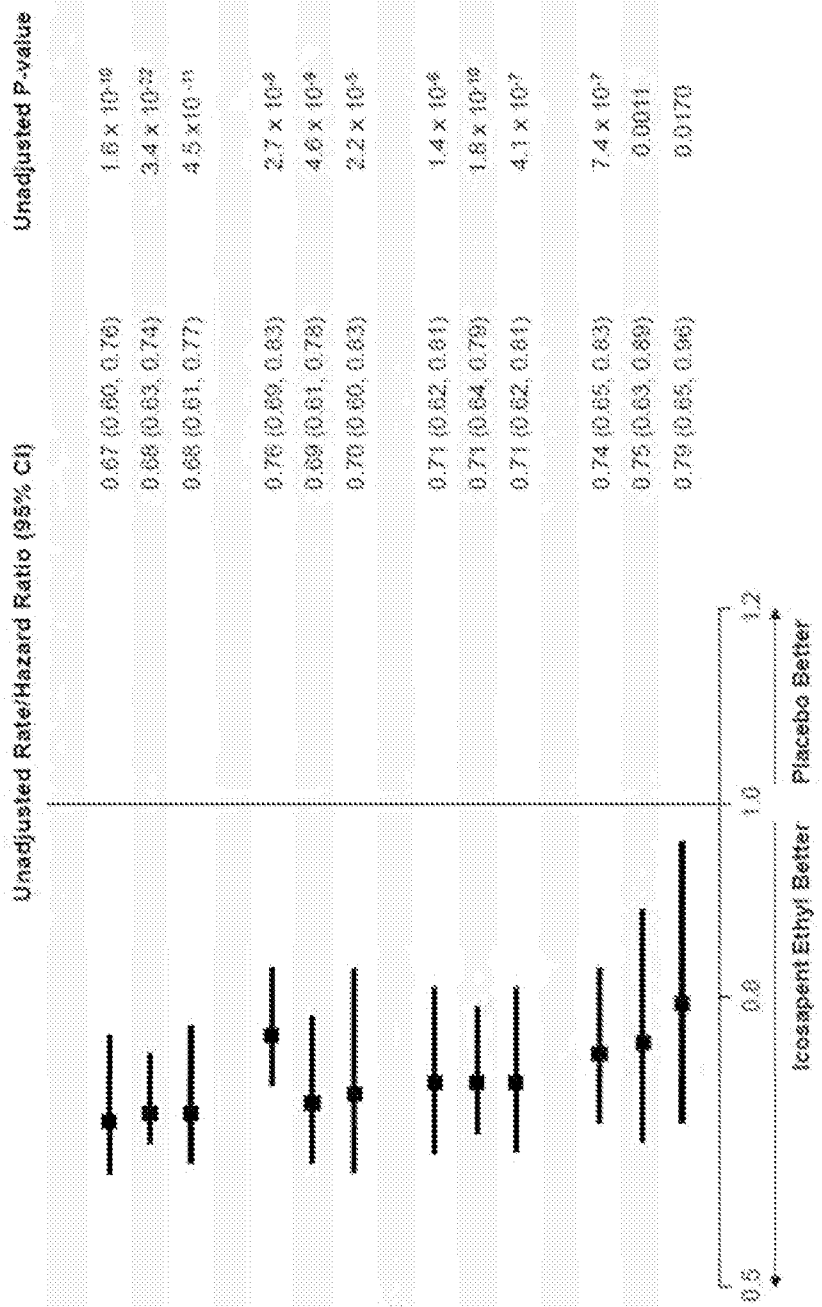

Endpoint/Model
Unadjusted Rate/Hazard Ratio (95% CI)
Unadjusted P-value
Primary Composite Endpoint
Negative binomial
0.67 (0.60, 0.76)
1.6 x 10-10
Andersen-Gill (I)
0.69 (0.63, 0.74)
3.4 x 10-22
Andersen-Gill (II)
0.68 (0.61, 0.77)
4.5 x10-11
Modified WLW
First event
0.76 (0.69, 0.83)
2.7 x 10-8
Second event
0.69 (0.61, 0.78)
4.6 x 10-8
Third event
0.70 (0.60, 0.83)
2.2 x 10-5
Key Secondary Composite Endpoint
Negative binomial
0.71 (0.62, 0.81)
1.4 x 10-6
Andersen-Gill (I)
0.71 (0.64, 0.79)
1.8 x 10-10
Andersen-Gill (II)
0.71 (0.62, 0.81)
4.1 x 10-7
Modified WLW
First event
0.74 (0.65, 0.83)
7.4 x 10-7
Second event
0.75 (0.63, 0.89)
0.0011
Third event
0.79 (0.65, 0.96)
0.0170
0.5
0.8
1.0
1.2
Icosapent Ethyl Better
Placebo Better

FIG. 49

Endpoint/Model
Adjusted Rate/Hazard Ratio (95% CI)
Adjusted P-value
Primary Composite Endpoint
Negative binomial
0.69 (0.61, 0.77)
4.4 x 10-16
Anderson-Gill (I)
0.68 (0.63, 0.74)
3.0 x 10-22
Anderson-Gill (II)
0.68 (0.61, 0.76)
3.4 x 10-11
Modified WLW
First event
0.75 (0.68, 0.83)
1.7 x 10-8
Second event
0.68 (0.60, 0.78)
3.1 x 10-8
Third event
0.70 (0.60, 0.83)
2.1 x 10-5
Key Secondary Composite Endpoint
Negative binomial
0.71 (0.62, 0.82)
1.2 x 10-6
Anderson-Gill (I)
0.71 (0.63, 0.79)
1.7 x 10-10
Anderson-Gill (II)
0.71 (0.62, 0.81)
3.4 x 10-7
Modified WLW
First event
0.74 (0.65, 0.83)
7.1 x 10-7
Second event
0.75 (0.63, 0.89)
0.0011
Third event
0.79 (0.65, 0.96)
0.0171
0.6
0.8
1.0
1.2
Icosapent Ethyl Better
Placebo Better

FIG. 50

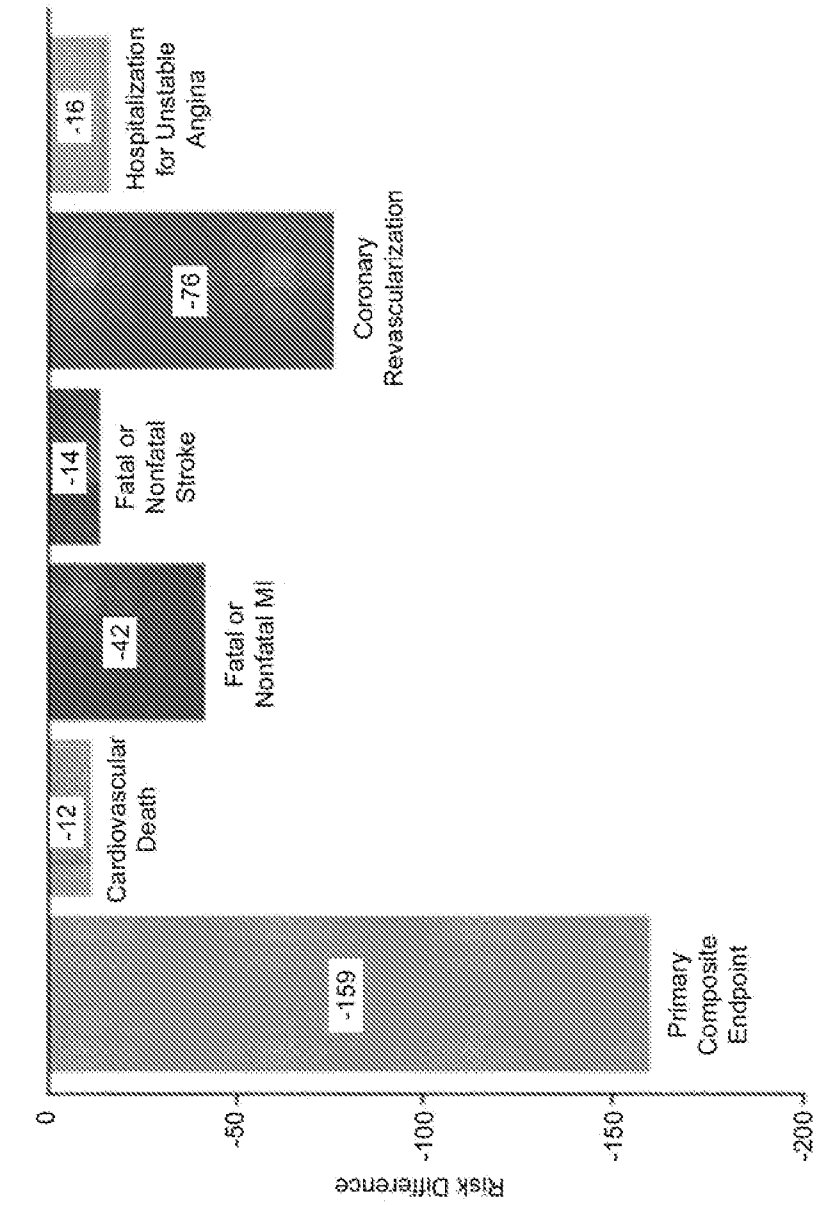


FIG. 51

Abbreviations: ITT = Intent-to-Treat; MI = myocardial infarction.
Analyses are based on the total adjudicated event dataset regardless if multiple endpoints occurred in a single calendar day.

TOTAL EVENTS – Primary Composite Endpoint/Subgroup
Icosapent Ethyl
Placebo
RR (95% CI)
P-value
Rate per 1000 Patient Years
Rate per 1000 Patient Years
Primary Composite Endpoint (ITT)
61.1
88.8
0.70 (0.82–0.78)
<0.0001
Baseline Triglycerides by Tertiles*
≥81 to ≤190 mg/dL
56.4
74.5
0.74 (0.61–0.90)
0.0025
>190 to ≤250 mg/dL
63.2
86.8
0.77 (0.63–0.95)
0.0120
>250 to ≤1401 mg/dL
64.4
107.4
0.60 (0.50–0.73)
<0.0001
*P (interaction) = 0.17
0.2
0.6
1.0
1.4
1.8
Icosapent Ethyl Better
Placebo Better

FIG. 52

TIME TO FIRST EVENT – Primary Composite Endpoint/Subgroup
Icosapent Ethyl
Placebo
HR (95% CI)
P-value
n/N (%)
n/N (%)
Primary Composite Endpoint (ITT)
705/4089 (17.2)
901/4090 (22.0)
0.75 (0.68–0.83)
<0.0001
Baseline Triglycerides by Tertiles*
≥81 to ≤190 mg/dL
233/1378 (16.9)
291/1381 (21.1)
0.79 (0.66–0.94)
0.0069
>190 to ≤250 mg/dL
246/1370 (18.0)
283/1328 (21.3)
0.80 (0.68–0.95)
0.0121
>250 to ≤1401 mg/dL
226/1339 (16.9)
327/1392 (23.7)
0.68 (0.57–0.80)
<0.0001
0.2
0.6
1.0
1.4
1.8
Icosapent Ethyl Better
Placebo Better
*P (interaction) = 0.33

FIG. 53

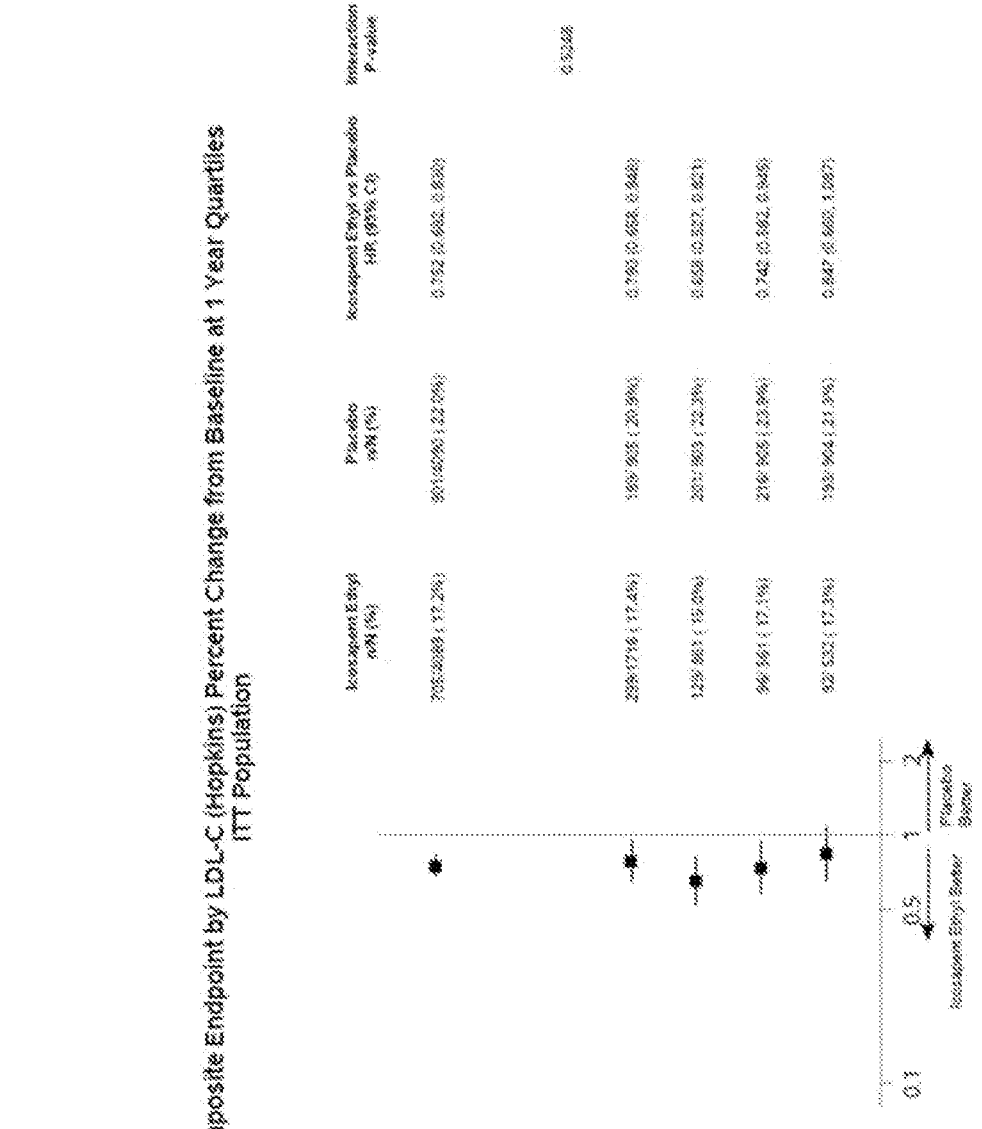
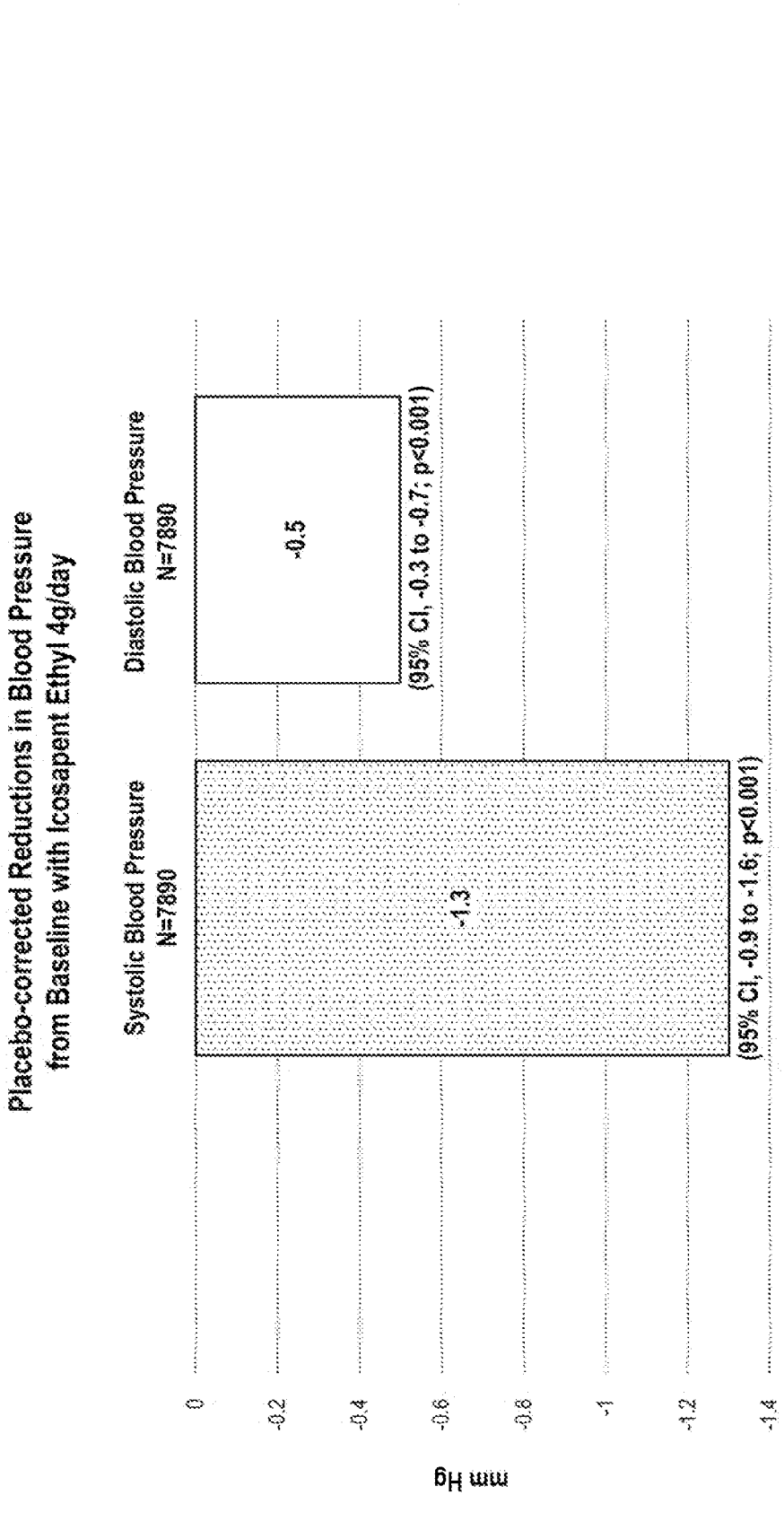

Forest Plot of Primary Composite Endpoint by LDL-C (Hopkins) Percent Change from Baseline at 1 Year Quartiles
ITT Population
Inclisiran Better
Placebo Better
0.1
0.5
1
2

FIG. 54



Prespecified exploratory analysis with no adjustment for multiple comparisons. Repeated-measurements analysis of change from baseline blood pressure over time by mixed-effects model. ITT population. Icosapent ethyl n=4089, Placebo n=4091. Maximum number of observations per patient = 6.

FIG. 55

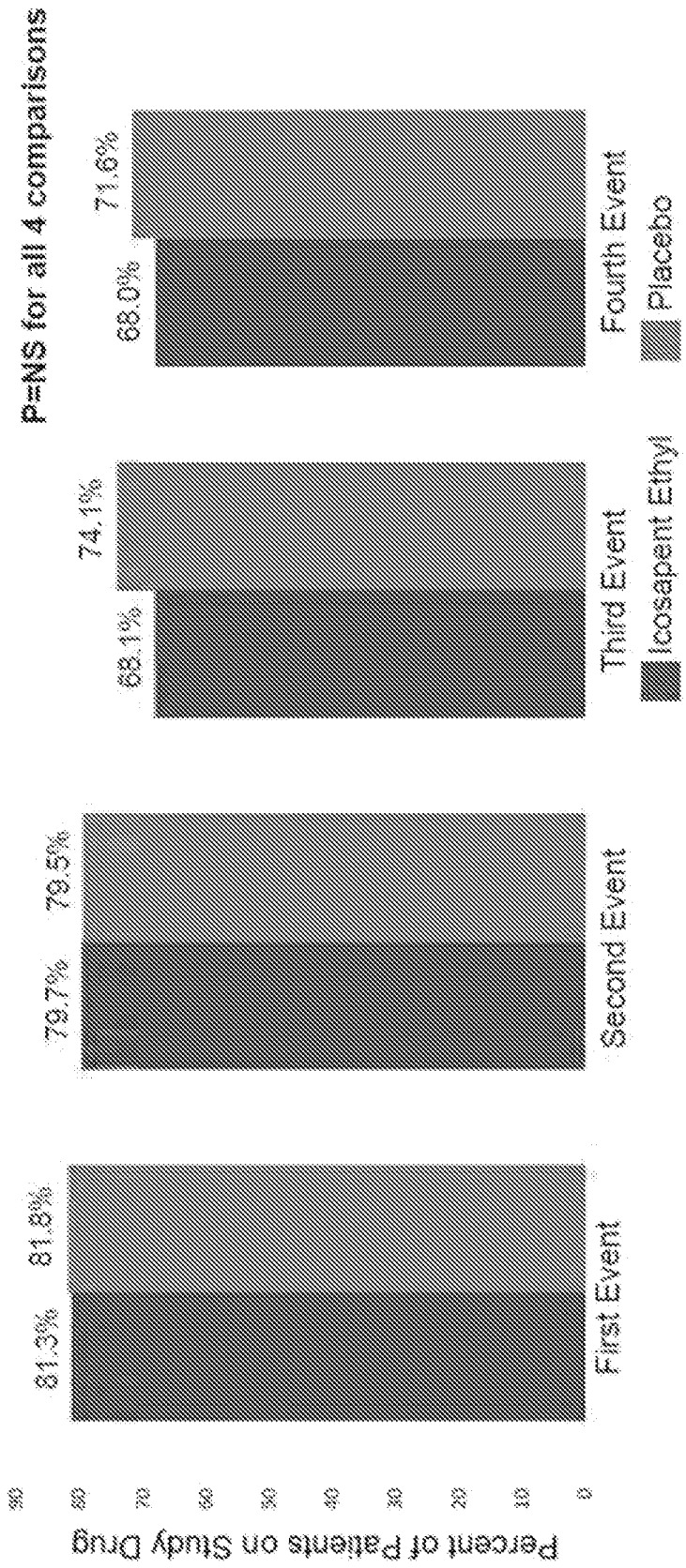
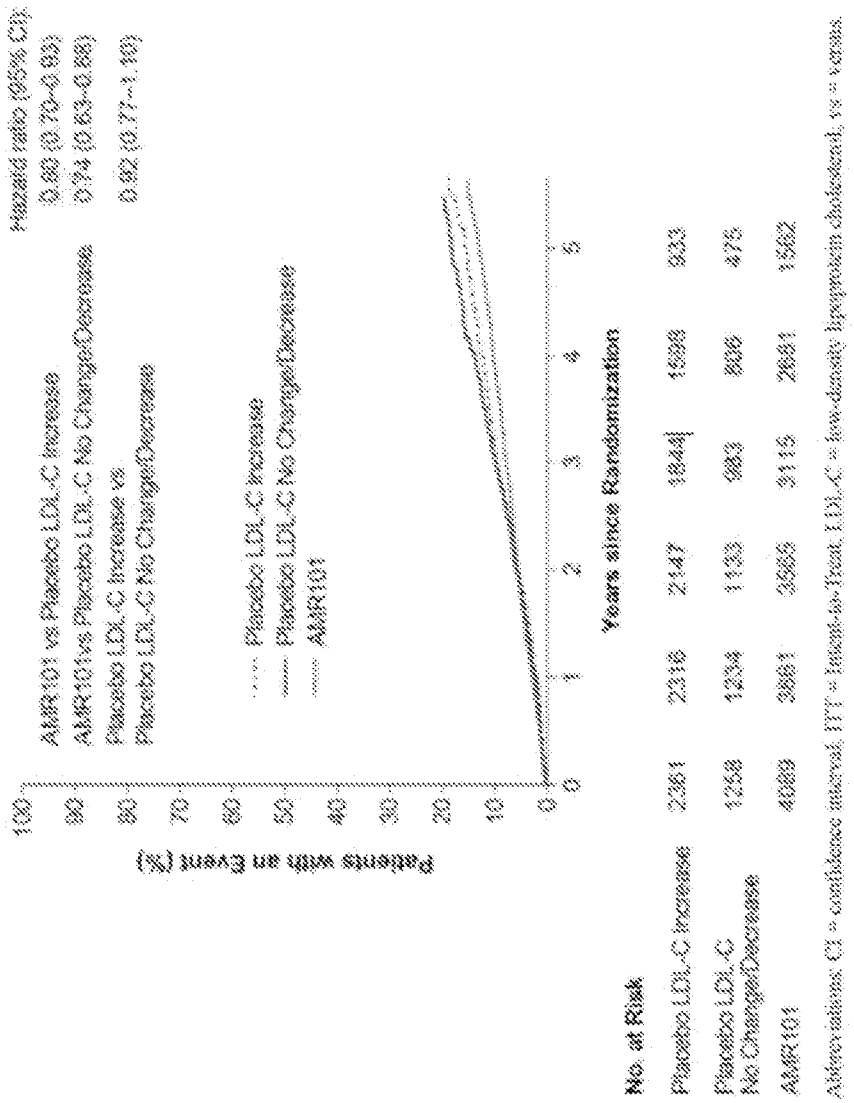

P=NS for all 4 comparisons
Percent of Patients on Study Drug
90
80
70
60
50
40
30
20
10
0
81.3%
81.8%
79.7%
79.5%
68.1%
74.1%
68.0%
71.6%
First Event
Second Event
Third Event
Fourth Event
Icosapent Ethyl
Placebo

FIG. 56

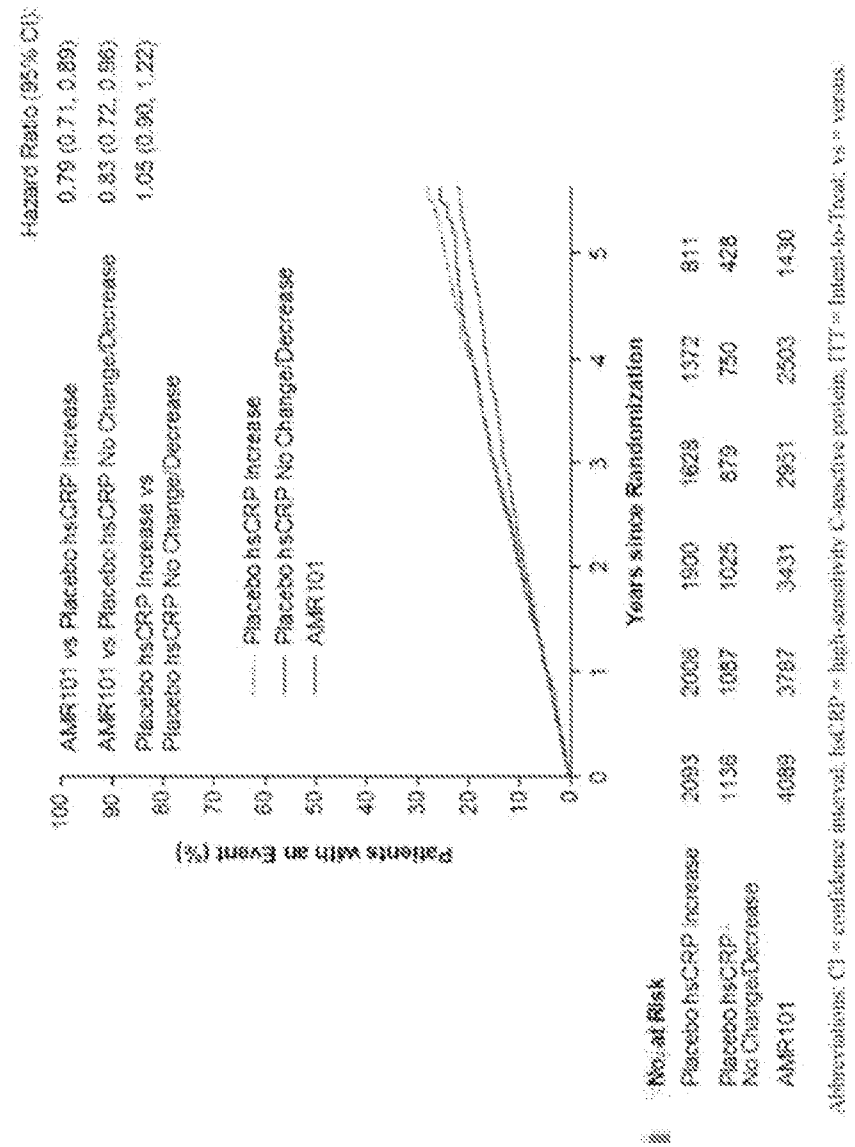
Abbreviations: CI = confidence interval; ITT = Intent-to-Treat; LDL-C = low-density lipoprotein cholesterol; vs = versus

FIG. 57A



Abbreviations: CI = confidence interval; ITT = Intent-to-Treat; LDL-C = low-density lipoprotein cholesterol; vs = versus.

FIG. 57B



Abbreviations: CI = confidence interval; hsCRP = high-sensitivity C-reactive protein; ITT = Intent-to-Treat; vs = versus

FIG. 58A

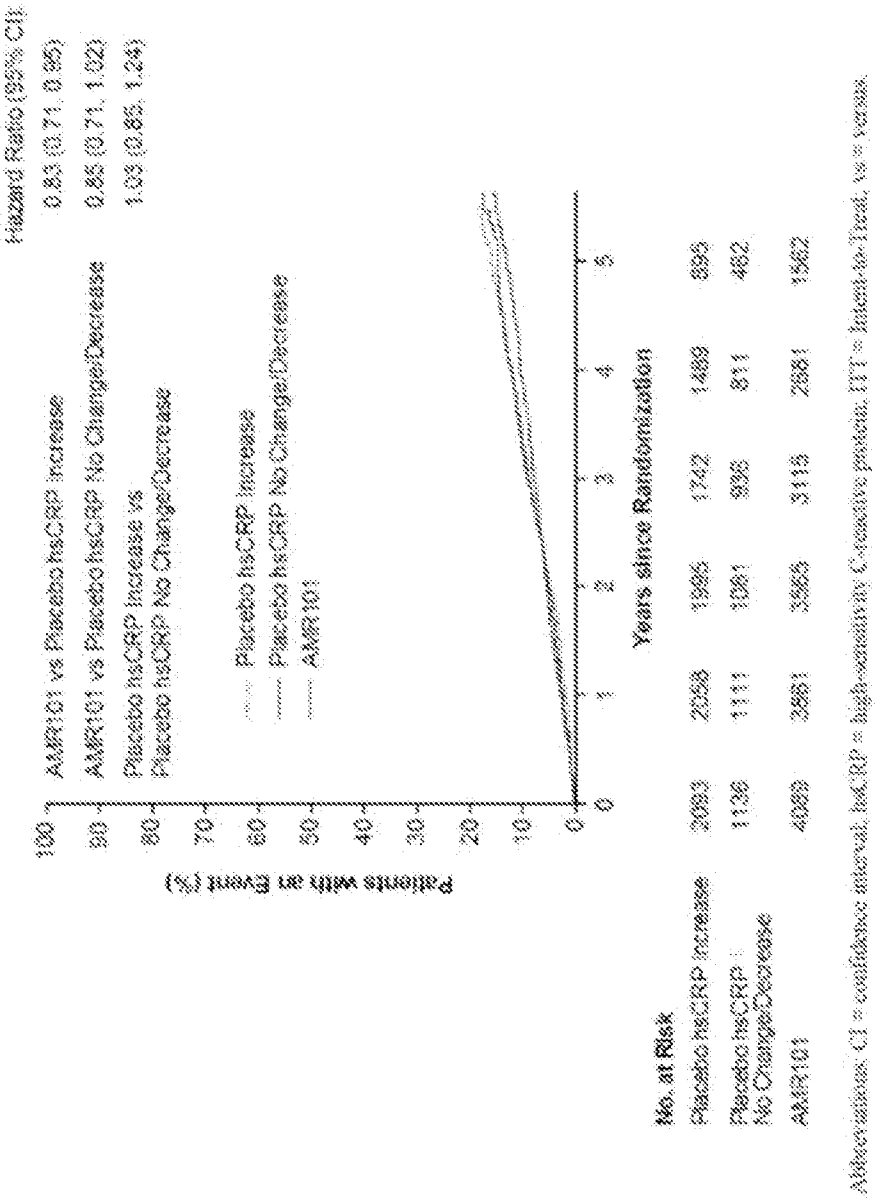


FIG. 58B

Abbreviations: CI = confidence interval, hsCRP = high-sensitivity C-reactive protein, ITT = Intent-to-Treat, vs = versus.

Abbreviations: CI = confidence interval, HR = hazard ratio, Int = interaction, ITT = Intent-to-Treat, pVal = p-value.

FIG. 59

Abbreviations: CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; Int = interaction; ITT = intent-to-Treat; pVal = p-value; TG = triglycerides; vs = versus.

FIG. 60

Abbreviations: CI = confidence interval, eGFR = estimated glomerular filtration rate, HDL-C = high-density lipoprotein cholesterol, HR = hazard ratio, hsCRP = high-sensitivity C-reactive protein, Int = interaction, ITT = Intent-to-Treat, LDL-C = low-density lipoprotein cholesterol, pVal = p-value, US = United States, vs = versus.

FIG. 61

FIG. 62

Abbreviations: apo B = apolipoprotein B; CI = confidence interval; non-HDL-C = non-high-density lipoprotein cholesterol; HR = hazard ratio; Int = interaction; ITT = Intent-to-Treat; pVal = p-value; TG = triglycerides

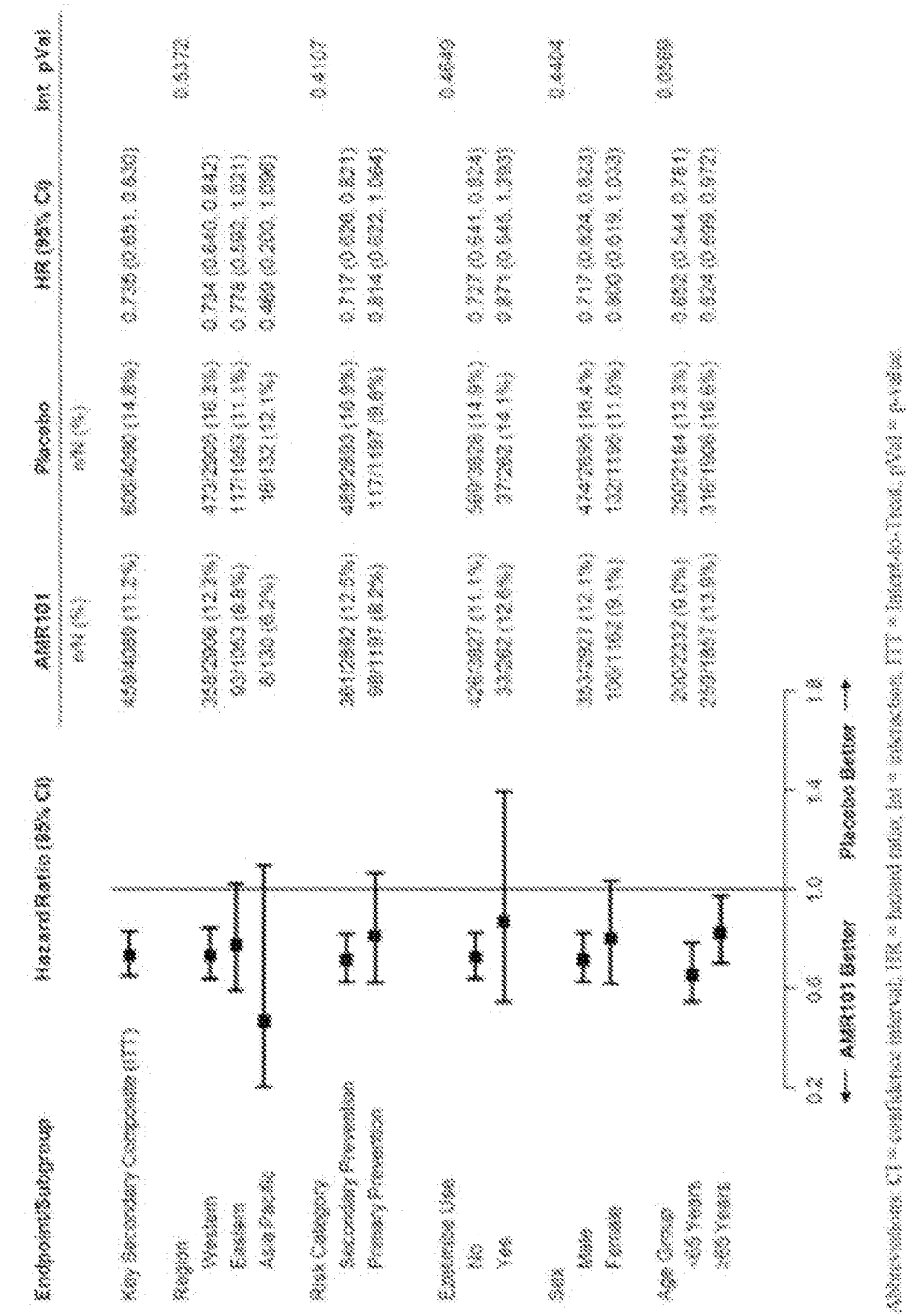

Endpoint/Subgroup
AMR101
Placebo
HR (95% CI)
Int. pVal
n/N (%)
n/N (%)
Key Secondary Composite (ITT)
456/4099 (11.2%)
606/4088 (14.8%)
0.735 (0.651, 0.830)
Region
0.6372
Western
253/2008 (12.6%)
473/2009 (16.3%)
0.734 (0.640, 0.842)
Eastern
97/1053 (9.2%)
117/1053 (11.1%)
0.778 (0.592, 1.021)
Asia Pacific
8/130 (6.2%)
16/132 (12.1%)
0.466 (0.200, 1.086)
Risk Category
0.4107
Secondary Prevention
281/2882 (12.5%)
485/2883 (16.8%)
0.717 (0.626, 0.821)
Primary Prevention
88/1187 (8.2%)
117/1187 (9.6%)
0.814 (0.622, 1.064)
Exercise Use
0.4049
No
426/3827 (11.1%)
569/3838 (14.8%)
0.727 (0.641, 0.824)
Yes
33/362 (12.8%)
37/362 (14.1%)
0.871 (0.546, 1.393)
Sex
0.4404
Male
253/2827 (10.1%)
414/2808 (18.4%)
0.717 (0.624, 0.823)
Female
106/1165 (9.1%)
132/1186 (11.6%)
0.806 (0.619, 1.050)
Age Group
0.0589
<65 Years
202/2323 (8.7%)
295/2324 (13.3%)
0.653 (0.544, 0.781)
≥65 Years
257/1667 (15.4%)
316/1650 (19.6%)
0.824 (0.699, 0.972)
0.2
0.6
1.0
1.4
1.8
AMR101 Better
Placebo Better
Abbreviations: CI = confidence interval, HR = hazard ratio, Int = interaction, ITT = Intent-to-Treat, pVal = p-value

FIG. 63

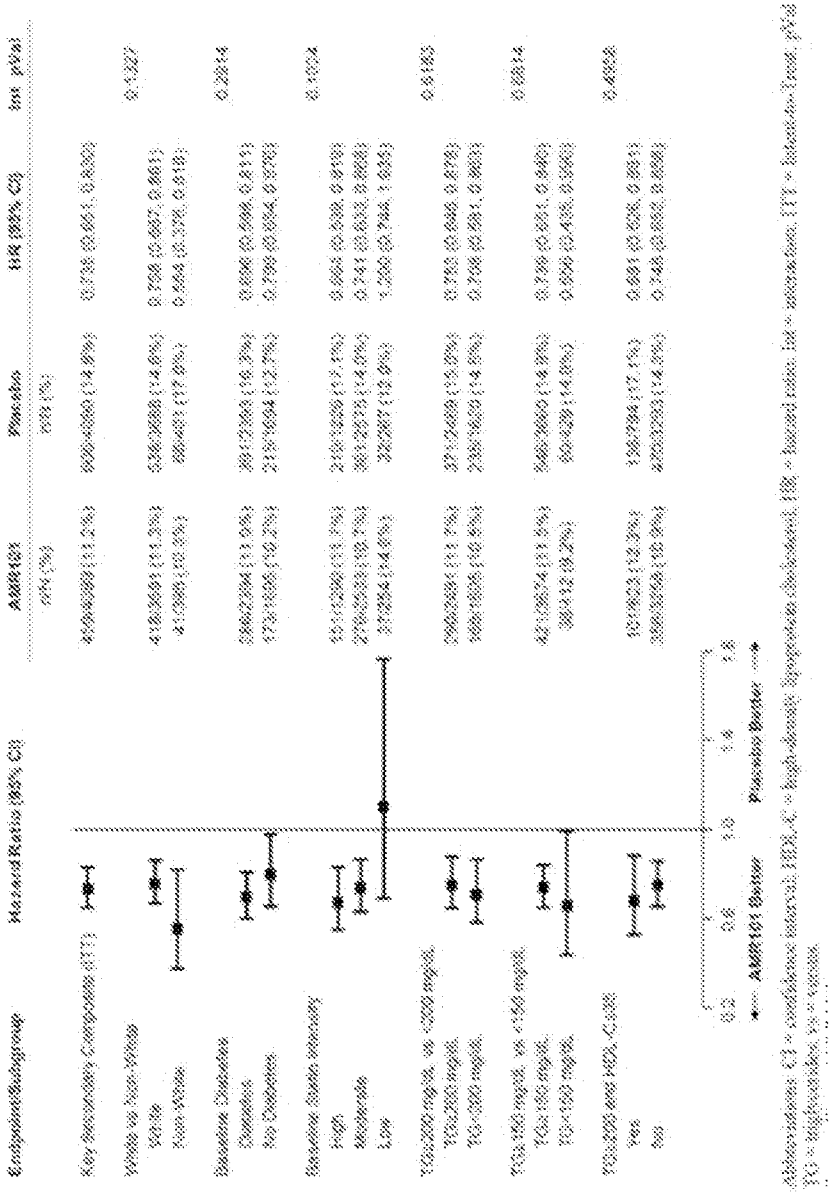
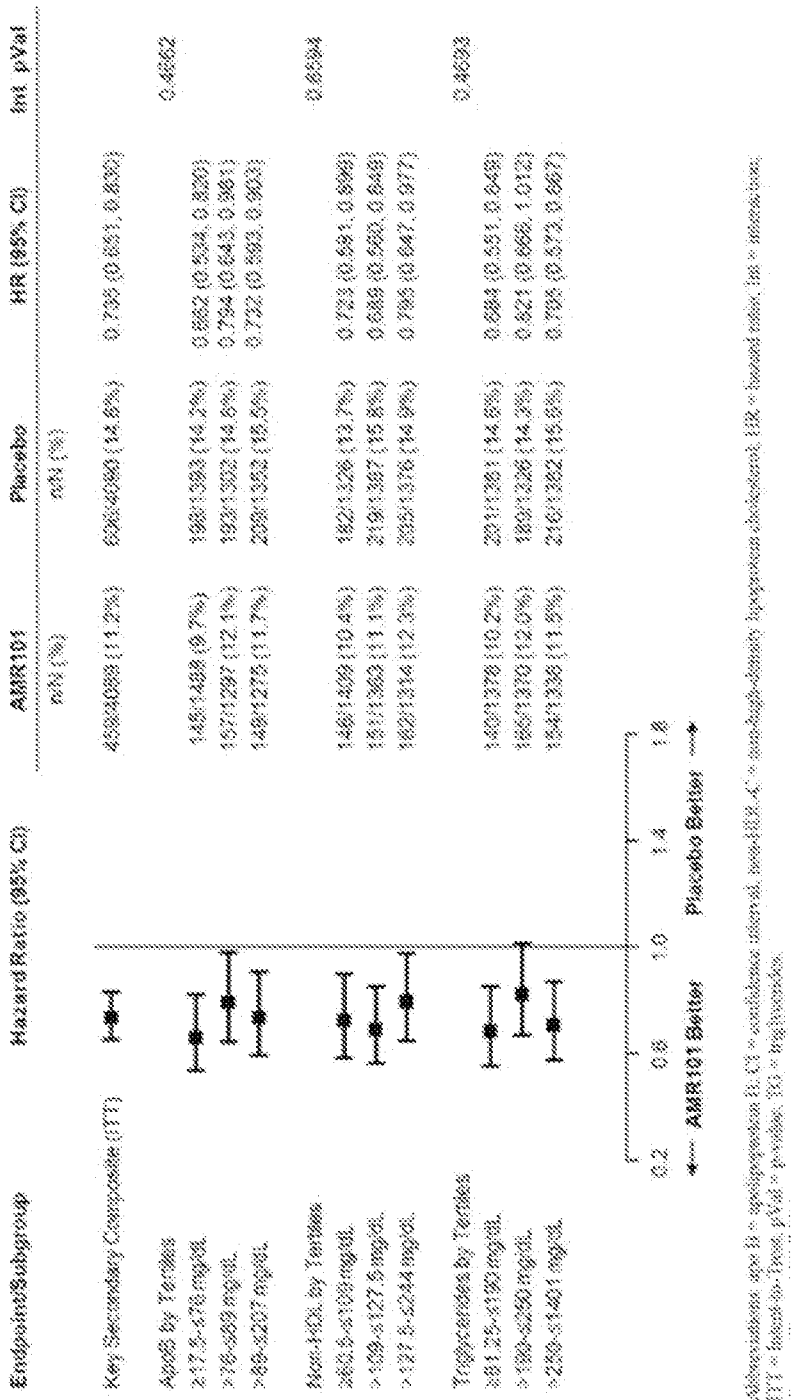

Subgroup
Hazard Ratio (95% CI)
AMG193
Placebo
HR (95% CI)
Int. p-val
n/N (%)
n/N (%)
All
0.706 (0.564, 0.885)
Age (continuous) (FU)
0.327
Male
0.758 (0.587, 0.981)
Female
0.644 (0.378, 0.918)
Region
0.2814
Europe
0.696 (0.496, 0.977)
Asia
0.799 (0.564, 0.978)
Rest of World
Tumor Histology
0.1024
PDA
0.664 (0.488, 0.903)
Ampulla
0.741 (0.533, 0.988)
CBD
1.200 (0.734, 1.960)
Tumor Stage at Diagnosis
0.6183
Stage III
0.750 (0.496, 0.979)
Stage IV
0.706 (0.551, 0.905)
Tumor Stage at Study Entry
0.8814
Stage III
0.749 (0.551, 0.949)
Stage IV
0.690 (0.478, 0.995)
ECOG PS at Study Entry
0.4958
0
0.681 (0.505, 0.951)
1
0.748 (0.552, 0.998)
0.2
0.6
1.0
1.8
AMG193 Better
Placebo Better
Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; FU = follow-up; HR = hazard ratio; Int. = interaction; ITT = intent-to-treat; p-val = p-value; PDA = pancreatic ductal adenocarcinoma; vs. = versus.

FIG. 64

FIG. 65



Abbreviations: apo B = apolipoprotein B; CI = confidence interval; non-HDL-C = non-high-density lipoprotein cholesterol; HR = hazard ratio; Int = interaction; ITT = intent-to-treat; pVal = p-value; TG = triglyceride.

FIG. 66

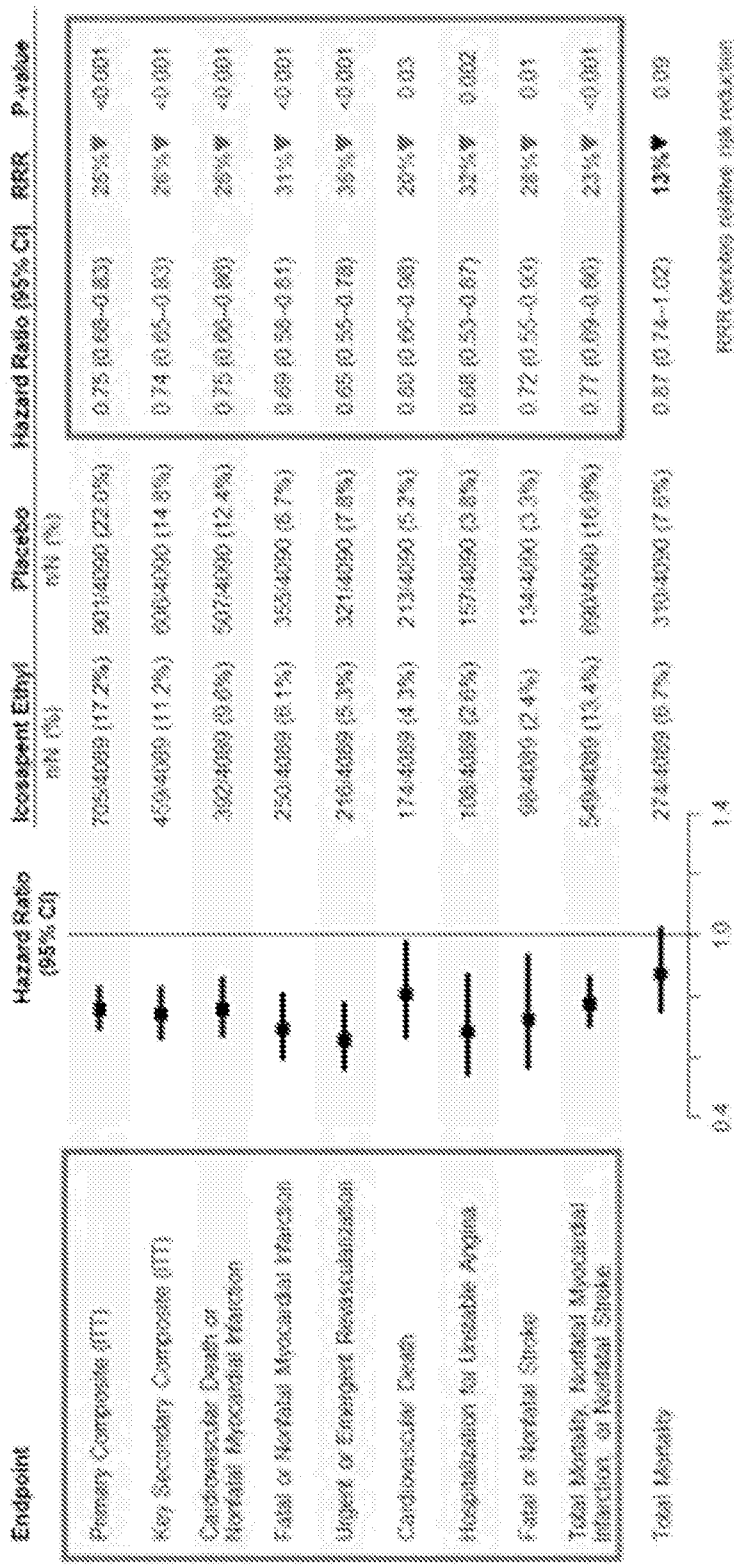

Endpoint
Hazard Ratio (95% CI)
Icosapent Ethyl n/N (%)
Placebo n/N (%)
Hazard Ratio (95% CI)
RRR
P-value
Primary Composite (ITT)
705/4089 (17.2%)
901/4090 (22.0%)
0.75 (0.68–0.83)
25%
<0.001
Key Secondary Composite (ITT)
459/4089 (11.2%)
606/4090 (14.8%)
0.74 (0.65–0.83)
26%
<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction
302/4089 (7.4%)
507/4090 (12.4%)
0.75 (0.66–0.86)
26%
<0.001
Fatal or Nonfatal Myocardial Infarction
252/4089 (6.1%)
353/4090 (8.7%)
0.69 (0.59–0.81)
31%
<0.001
Urgent or Emergent Revascularization
216/4089 (5.3%)
321/4090 (7.8%)
0.65 (0.55–0.78)
35%
<0.001
Cardiovascular Death
174/4089 (4.3%)
213/4090 (5.2%)
0.80 (0.66–0.98)
20%
0.03
Hospitalization for Unstable Angina
168/4089 (3.6%)
157/4090 (3.8%)
0.68 (0.53–0.87)
32%
0.002
Fatal or Nonfatal Stroke
66/4089 (2.4%)
124/4090 (3.2%)
0.72 (0.55–0.93)
28%
0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke
540/4089 (13.4%)
680/4090 (16.6%)
0.77 (0.69–0.87)
23%
<0.001
Total Mortality
278/4089 (6.7%)
310/4090 (7.6%)
0.87 (0.74–1.02)
12%
0.09
0.4
1.0
1.4
Icosapent Ethyl Better
Placebo Better
RRR denotes relative risk reduction

FIG. 67

HR(95% CI)
Icosapent Ethyl
Placebo
HR (95% CI)
Int P-value
n/N (%)
n/N (%)
Atrial Fibrillation/Atrial Flutter history/AE (pre-randomization)
Yes
No
0.2
0.8
1.0
2.0
4.0
Icosapent Ethyl Better
Placebo Better

FIG. 68

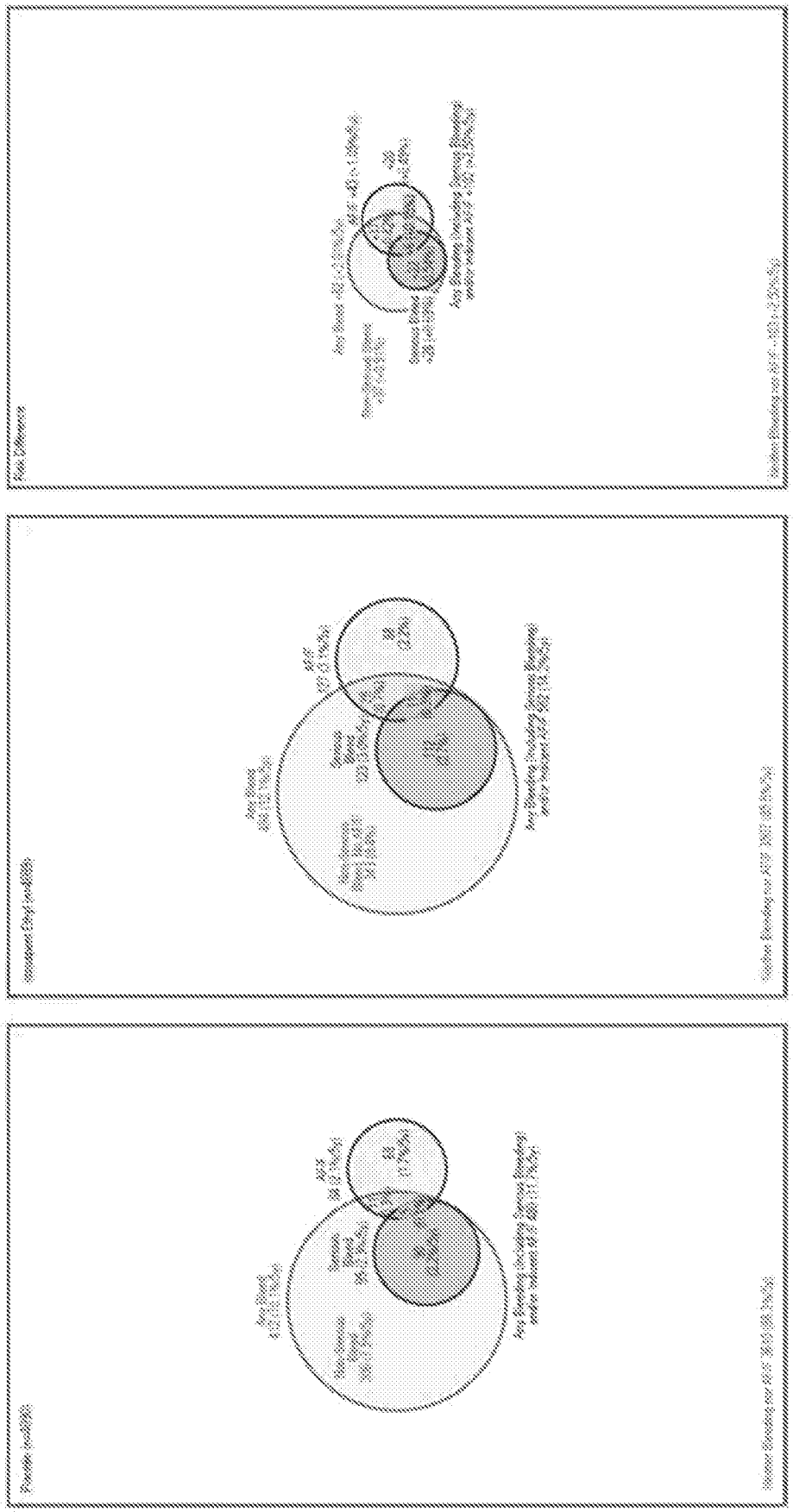


FIG. 69A

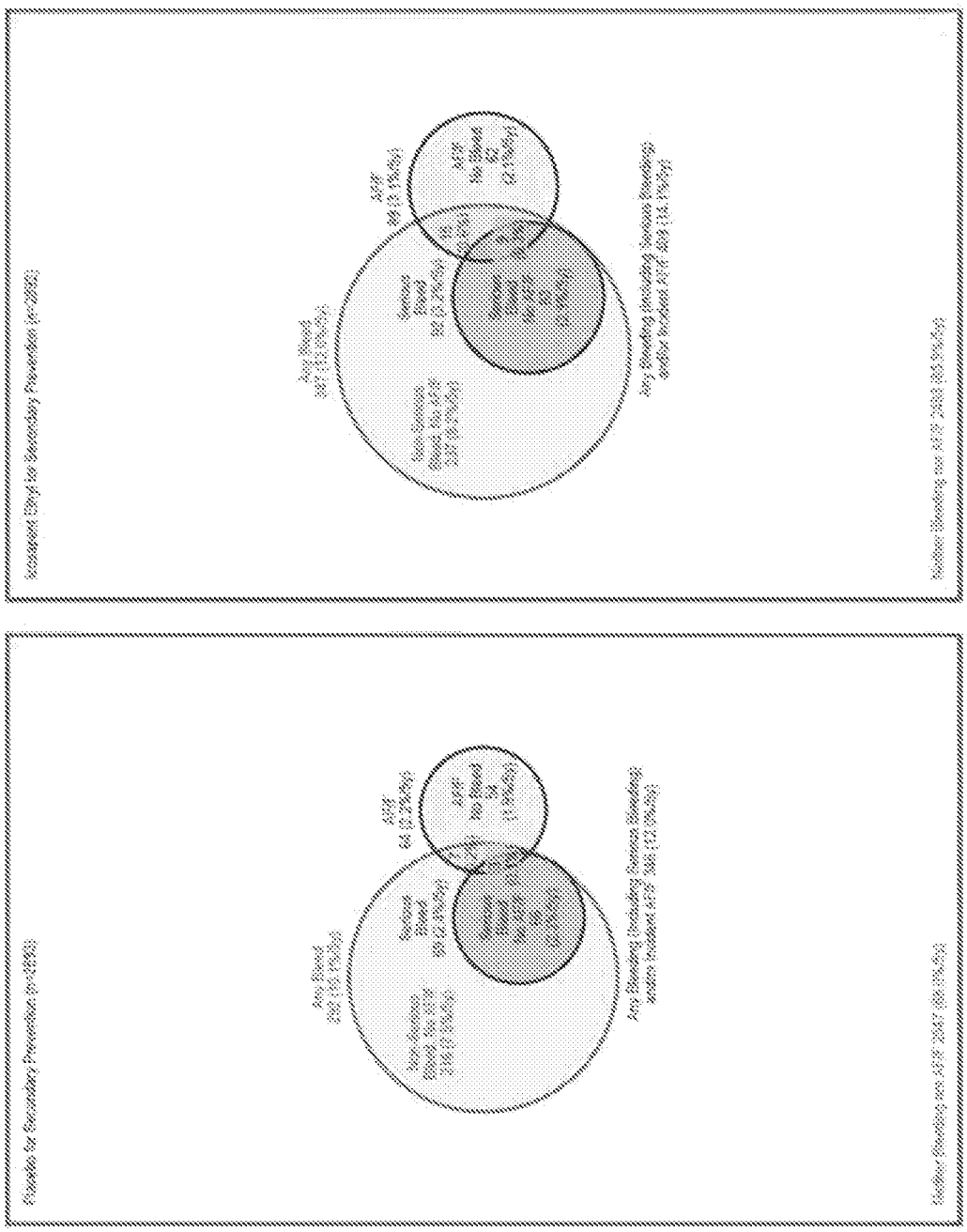


FIG. 69B

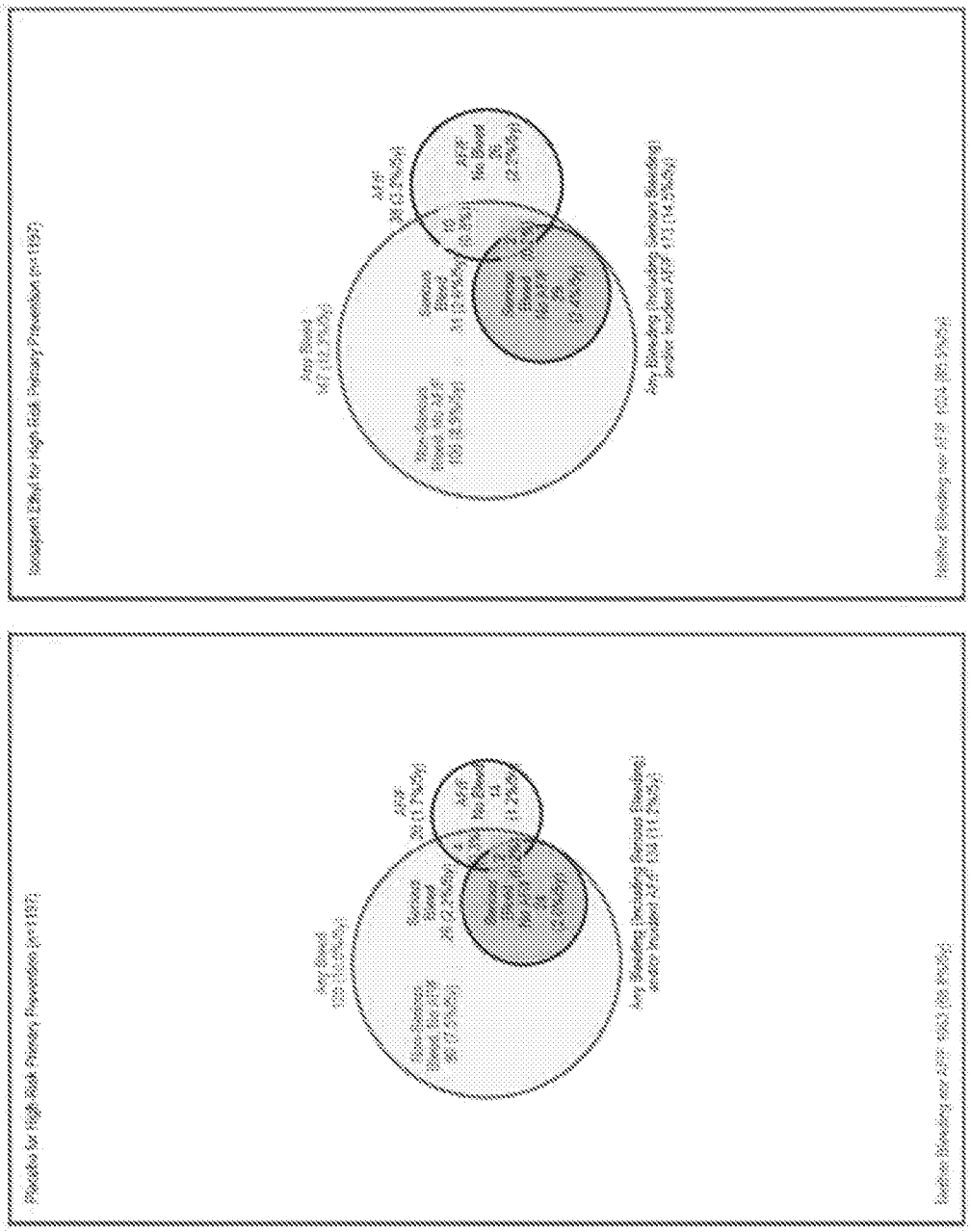


FIG. 69C

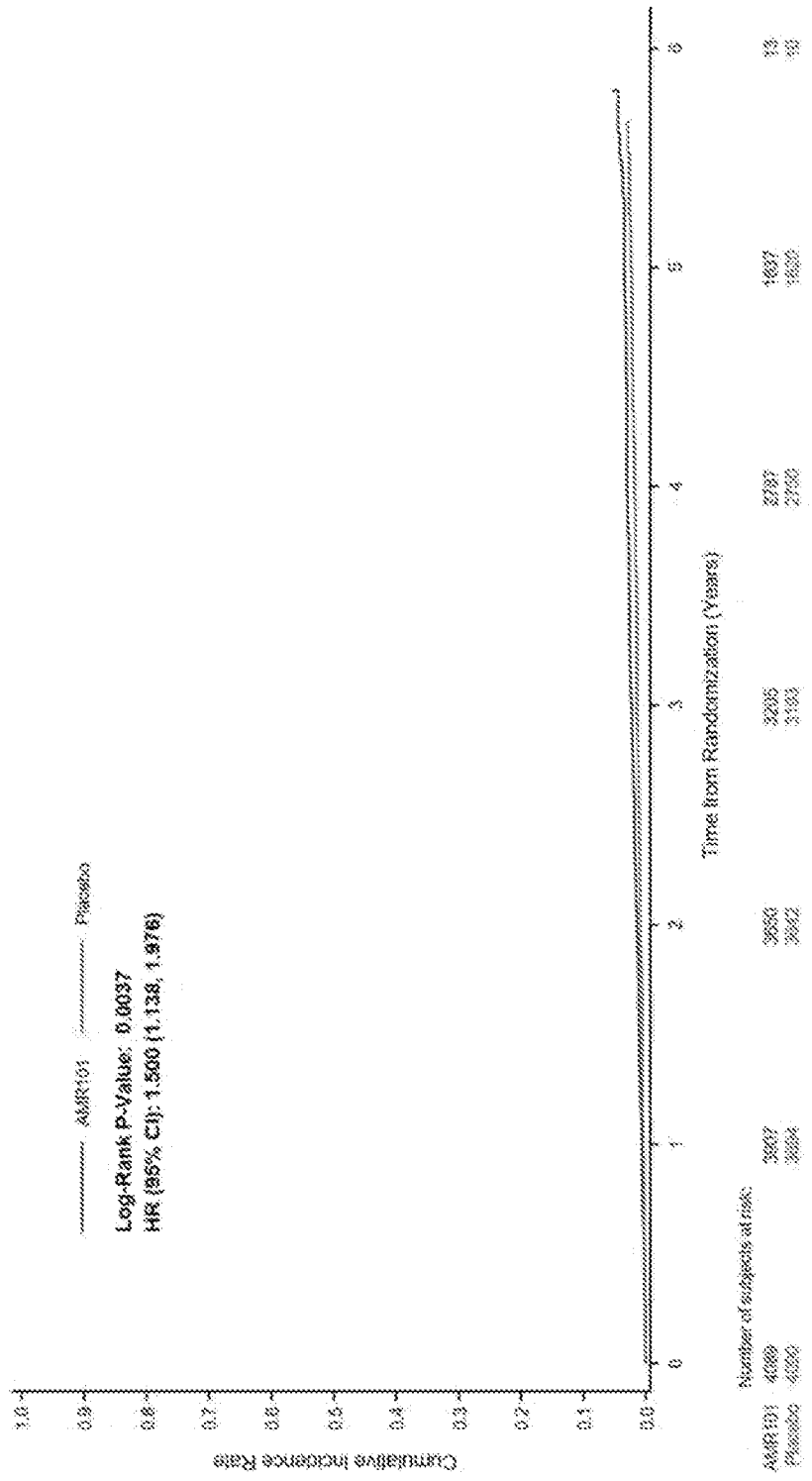

Kaplan-Meier Curve for Time to Endpoint of Atrial Fibrillation and/or Flutter Requiring Hospitalization of ≥ 24 Hours by Treatment Arm
AMR101
Placebo
Log-Rank P-Value: 0.0037
HR (95% CI): 1.500 (1.138, 1.976)
Cumulative Incidence Rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
1
2
3
4
5
6
Time from Randomization (Years)
Number of subjects at risk:
AMR101 4089 3907 3650 3205 2787 1687 13
Placebo 4090 3884 3662 3103 2709 1620 10
AMR101 = icosapent ethyl

FIG. 70A

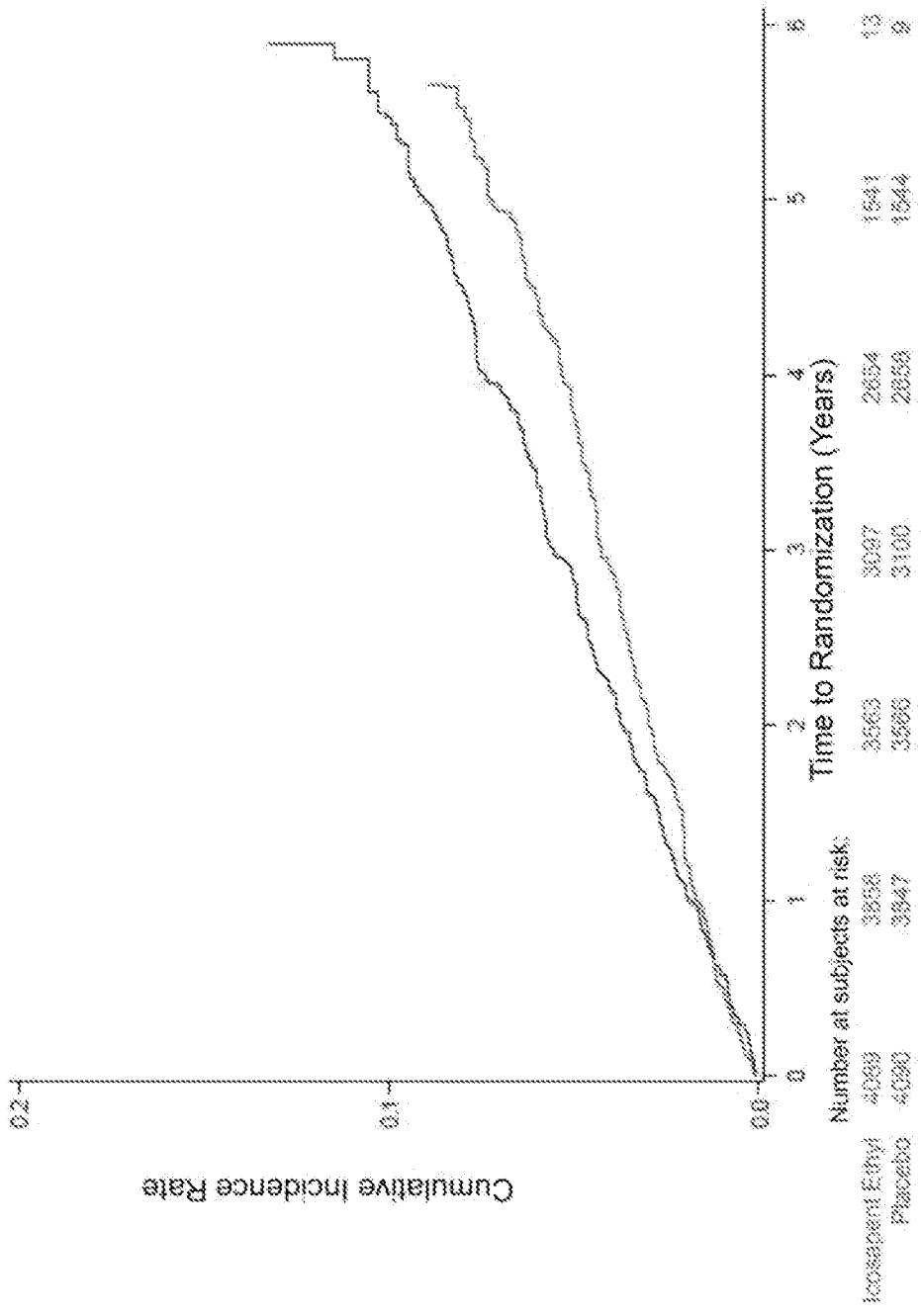

Cumulative Incidence Rate
0.2
0.1
0.0
0
1
2
3
4
5
6
Time to Randomization (Years)
Number at subjects at risk
Icosapent Ethyl 4089 3858 3563 3097 2654 1941 13
Placebo 4090 3847 3586 3100 2659 1944 9

FIG. 70B

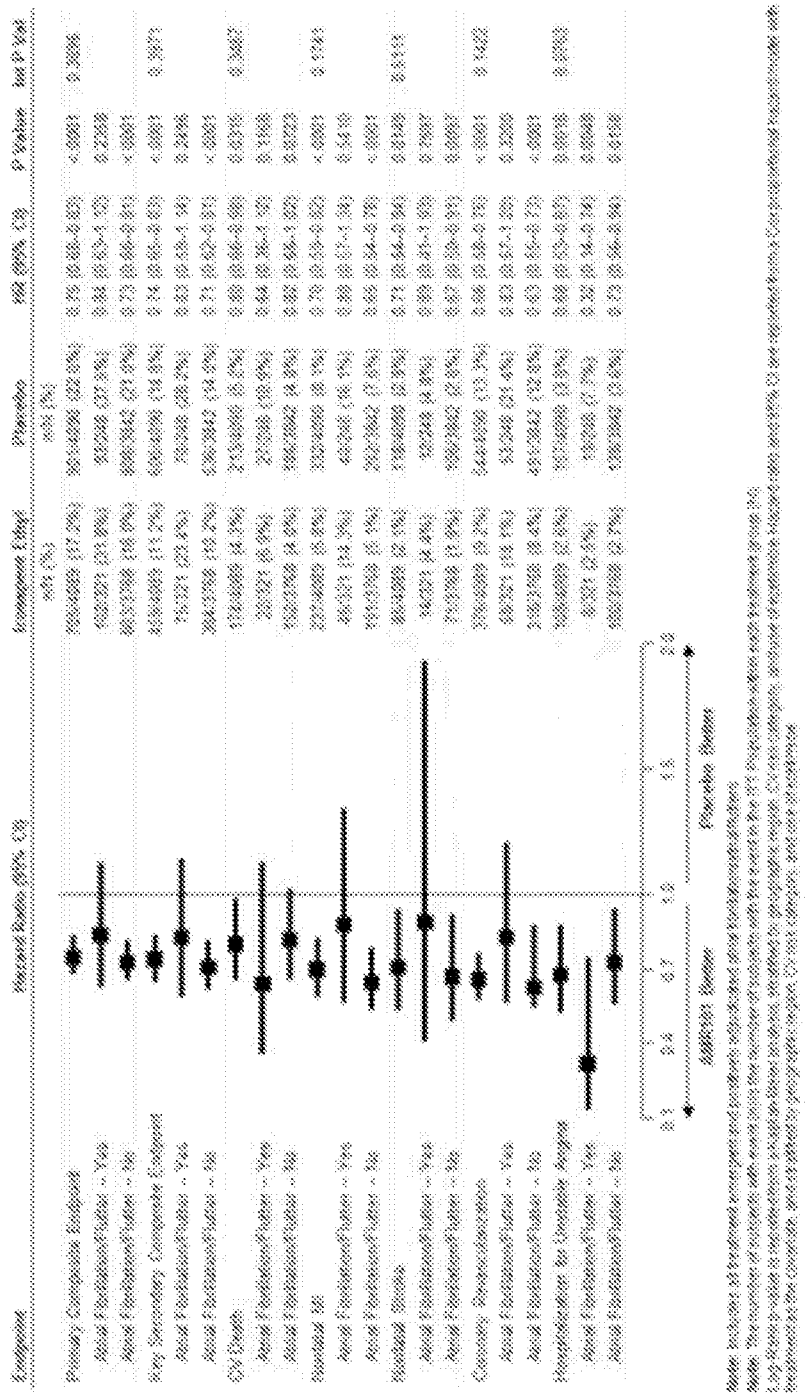
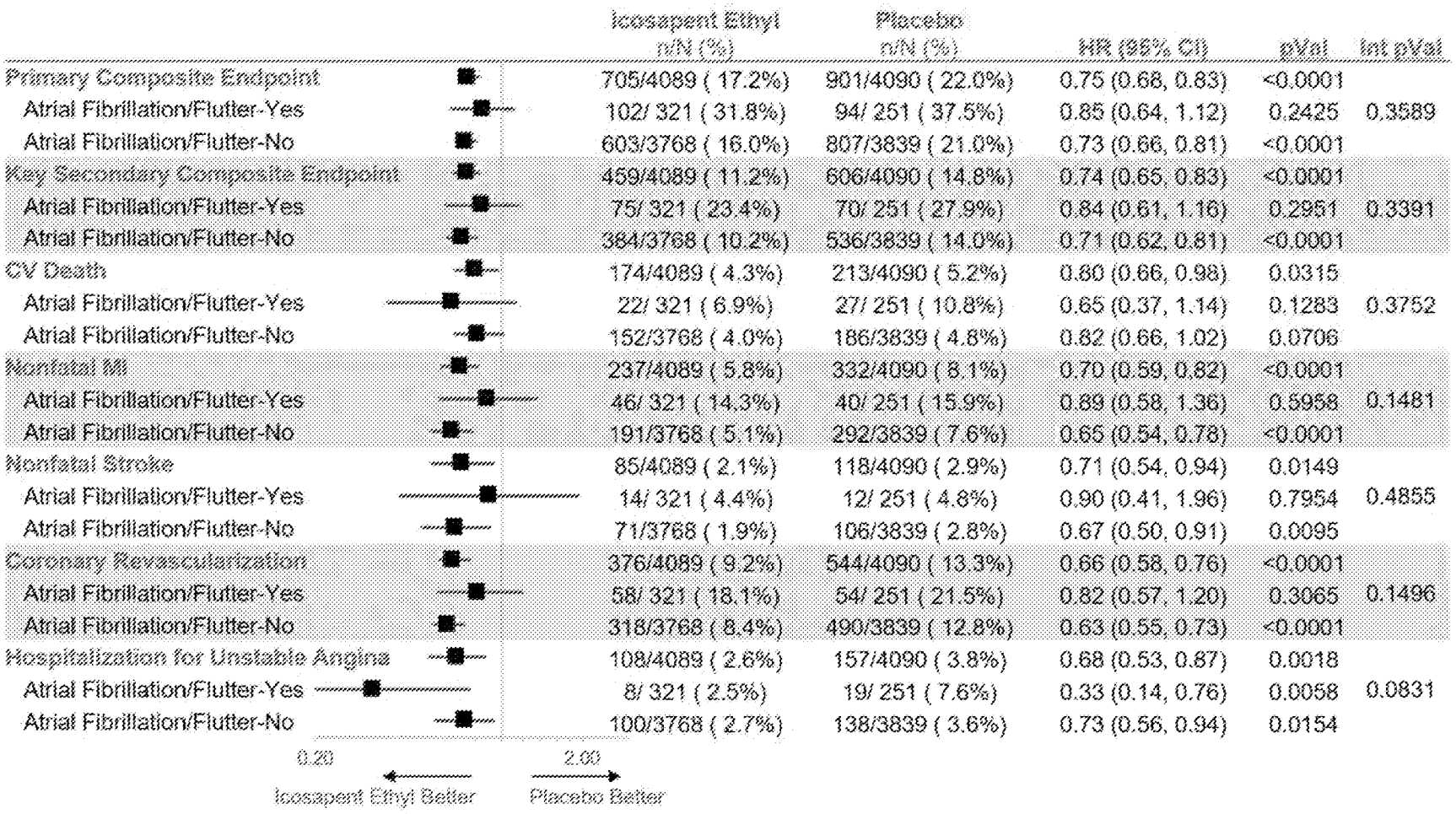


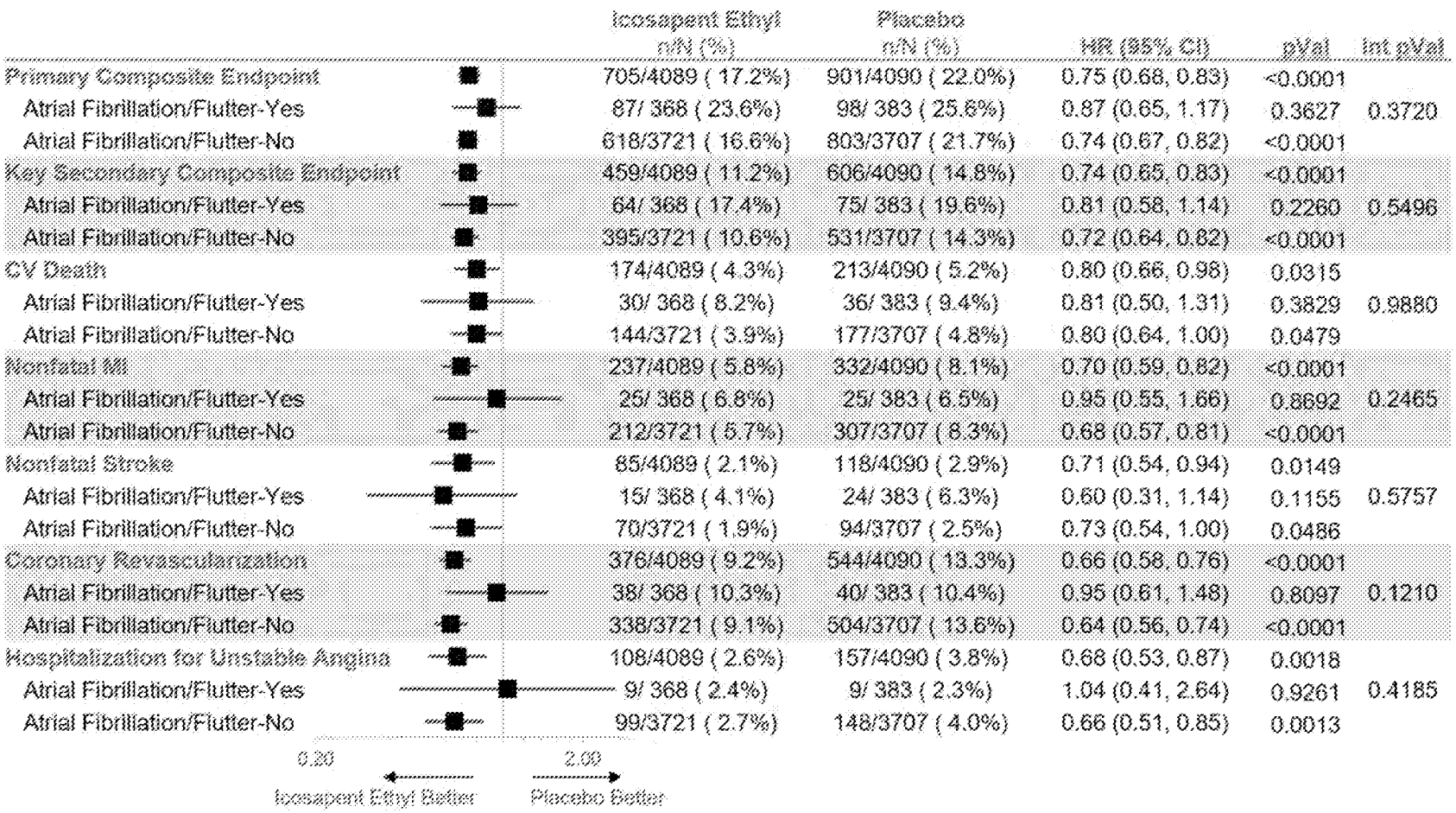
FIG. 71



	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	pVal	Int pVal
Primary Composite Endpoint	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68, 0.83)	<0.0001	
Atrial Fibrillation/Flutter-Yes	102/ 321 (31.8%)	94/ 251 (37.5%)	0.85 (0.64, 1.12)	0.2425	0.3589
Atrial Fibrillation/Flutter-No	603/3768 (16.0%)	807/3839 (21.0%)	0.73 (0.66, 0.81)	<0.0001	
Key Secondary Composite Endpoint	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65, 0.83)	<0.0001	
Atrial Fibrillation/Flutter-Yes	75/ 321 (23.4%)	70/ 251 (27.9%)	0.84 (0.61, 1.16)	0.2951	0.3391
Atrial Fibrillation/Flutter-No	384/3768 (10.2%)	536/3839 (14.0%)	0.71 (0.62, 0.81)	<0.0001	
CV Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66, 0.98)	0.0315	
Atrial Fibrillation/Flutter-Yes	22/ 321 (6.9%)	27/ 251 (10.8%)	0.65 (0.37, 1.14)	0.1283	0.3752
Atrial Fibrillation/Flutter-No	152/3768 (4.0%)	186/3839 (4.8%)	0.82 (0.66, 1.02)	0.0706	
Nonfatal MI	237/4089 (5.8%)	332/4090 (8.1%)	0.70 (0.59, 0.82)	<0.0001	
Atrial Fibrillation/Flutter-Yes	46/ 321 (14.3%)	40/ 251 (15.9%)	0.89 (0.58, 1.36)	0.5958	0.1481
Atrial Fibrillation/Flutter-No	191/3768 (5.1%)	292/3839 (7.6%)	0.65 (0.54, 0.78)	<0.0001	
Nonfatal Stroke	85/4089 (2.1%)	118/4090 (2.9%)	0.71 (0.54, 0.94)	0.0149	
Atrial Fibrillation/Flutter-Yes	14/ 321 (4.4%)	12/ 251 (4.8%)	0.90 (0.41, 1.96)	0.7954	0.4855
Atrial Fibrillation/Flutter-No	71/3768 (1.9%)	106/3839 (2.8%)	0.67 (0.50, 0.91)	0.0095	
Coronary Revascularization	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58, 0.76)	<0.0001	
Atrial Fibrillation/Flutter-Yes	58/ 321 (18.1%)	54/ 251 (21.5%)	0.82 (0.57, 1.20)	0.3065	0.1496
Atrial Fibrillation/Flutter-No	318/3768 (8.4%)	490/3839 (12.8%)	0.63 (0.55, 0.73)	<0.0001	
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53, 0.87)	0.0018	
Atrial Fibrillation/Flutter-Yes	8/ 321 (2.5%)	19/ 251 (7.6%)	0.33 (0.14, 0.76)	0.0058	0.0831
Atrial Fibrillation/Flutter-No	100/3768 (2.7%)	138/3839 (3.6%)	0.73 (0.56, 0.94)	0.0154	

Abbreviations: CI = confidence interval; HR = hazard ratio; Int = interaction; ITT = Intent-to-Treat; pVal = p-value.

FIG. 72



	Icosapent Ethyl n/N (%)	Placebo n/N (%)	HR (95% CI)	pVal	Int pVal
Primary Composite Endpoint	705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68, 0.83)	<0.0001	
Atrial Fibrillation/Flutter-Yes	87/ 368 (23.6%)	98/ 383 (25.6%)	0.87 (0.65, 1.17)	0.3627	0.3720
Atrial Fibrillation/Flutter-No	618/3721 (16.6%)	803/3707 (21.7%)	0.74 (0.67, 0.82)	<0.0001	
Key Secondary Composite Endpoint	459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65, 0.83)	<0.0001	
Atrial Fibrillation/Flutter-Yes	64/ 368 (17.4%)	75/ 383 (19.6%)	0.81 (0.58, 1.14)	0.2260	0.5496
Atrial Fibrillation/Flutter-No	395/3721 (10.6%)	531/3707 (14.3%)	0.72 (0.64, 0.82)	<0.0001	
CV Death	174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66, 0.98)	0.0315	
Atrial Fibrillation/Flutter-Yes	30/ 368 (8.2%)	36/ 383 (9.4%)	0.81 (0.50, 1.31)	0.3829	0.9880
Atrial Fibrillation/Flutter-No	144/3721 (3.9%)	177/3707 (4.8%)	0.80 (0.64, 1.00)	0.0479	
Nonfatal MI	237/4089 (5.8%)	332/4090 (8.1%)	0.70 (0.59, 0.82)	<0.0001	
Atrial Fibrillation/Flutter-Yes	25/ 368 (6.8%)	25/ 383 (6.5%)	0.95 (0.55, 1.66)	0.8692	0.2465
Atrial Fibrillation/Flutter-No	212/3721 (5.7%)	307/3707 (8.3%)	0.68 (0.57, 0.81)	<0.0001	
Nonfatal Stroke	85/4089 (2.1%)	118/4090 (2.9%)	0.71 (0.54, 0.94)	0.0149	
Atrial Fibrillation/Flutter-Yes	15/ 368 (4.1%)	24/ 383 (6.3%)	0.60 (0.31, 1.14)	0.1155	0.5757
Atrial Fibrillation/Flutter-No	70/3721 (1.9%)	94/3707 (2.5%)	0.73 (0.54, 1.00)	0.0486	
Coronary Revascularization	376/4089 (9.2%)	544/4090 (13.3%)	0.66 (0.58, 0.76)	<0.0001	
Atrial Fibrillation/Flutter-Yes	38/ 368 (10.3%)	40/ 383 (10.4%)	0.95 (0.61, 1.48)	0.8097	0.1210
Atrial Fibrillation/Flutter-No	338/3721 (9.1%)	504/3707 (13.6%)	0.64 (0.56, 0.74)	<0.0001	
Hospitalization for Unstable Angina	108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53, 0.87)	0.0018	
Atrial Fibrillation/Flutter-Yes	9/ 368 (2.4%)	9/ 383 (2.3%)	1.04 (0.41, 2.64)	0.9261	0.4185
Atrial Fibrillation/Flutter-No	99/3721 (2.7%)	148/3707 (4.0%)	0.66 (0.51, 0.85)	0.0013	

Abbreviations: CI = confidence interval; HR = hazard ratio; Int = interaction; ITT = Intent-to-Treat; pVal = p-value.

FIG. 73

Atrial Fibrillation Requiring
>=24 hrs Hospitalization
Atrial Fibrillation/Flutter-Yes
Atrial Fibrillation/Flutter-No
Icosapent Ethyl n/N (%)
Placebo n/N (%)
Icosapent Ethyl - Placebo RD (95% CI)
p-value
331/197 (3.2%)
207/197 (1.7%)
1.59 (0.28, 2.91)
0.0166
15/ 96 (15.6%)
8/ 103 (7.8%)
8.01 (-0.86, 17.34)
0.0766
331/161 (2.1%)
12/1082 (1.1%)
0.99 (-0.06, 2.13)
0.0638
-5
0
5
10
Icosapent Ethyl Better
Placebo Better

FIG. 74

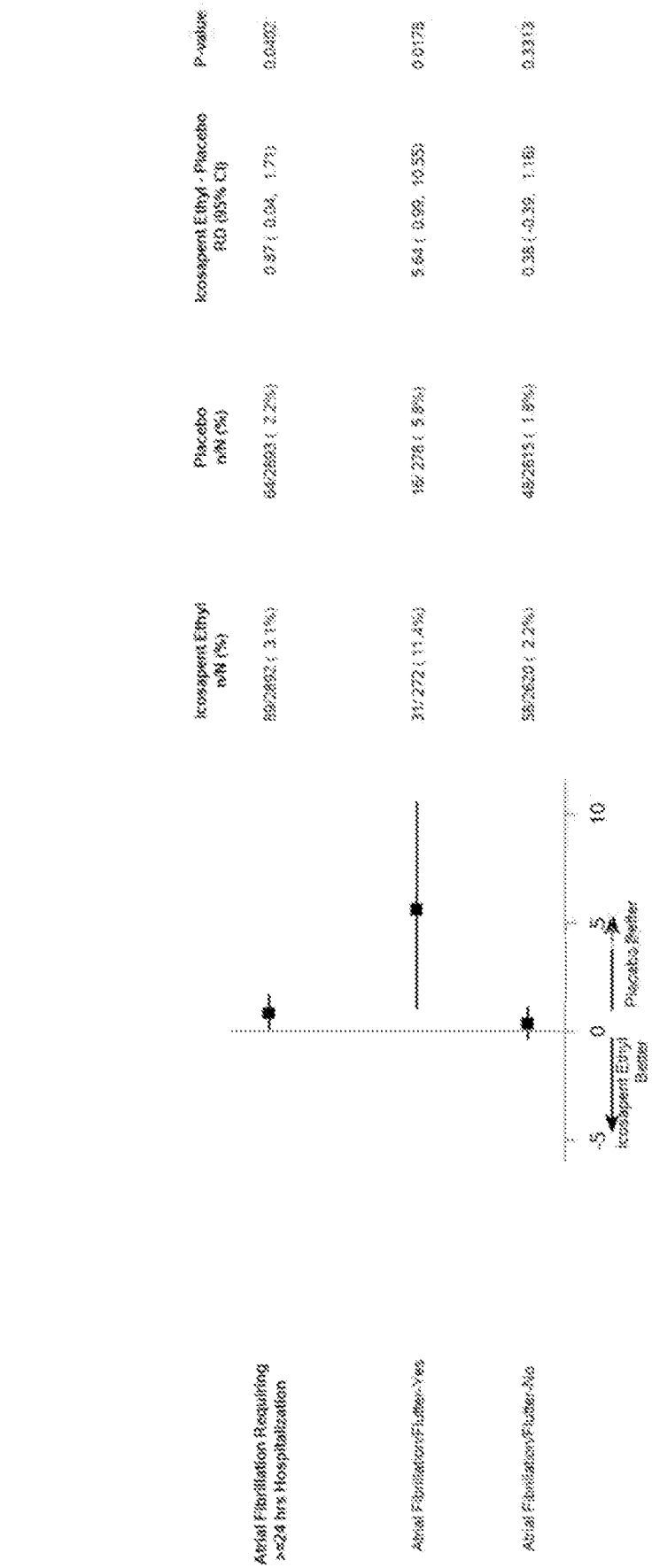
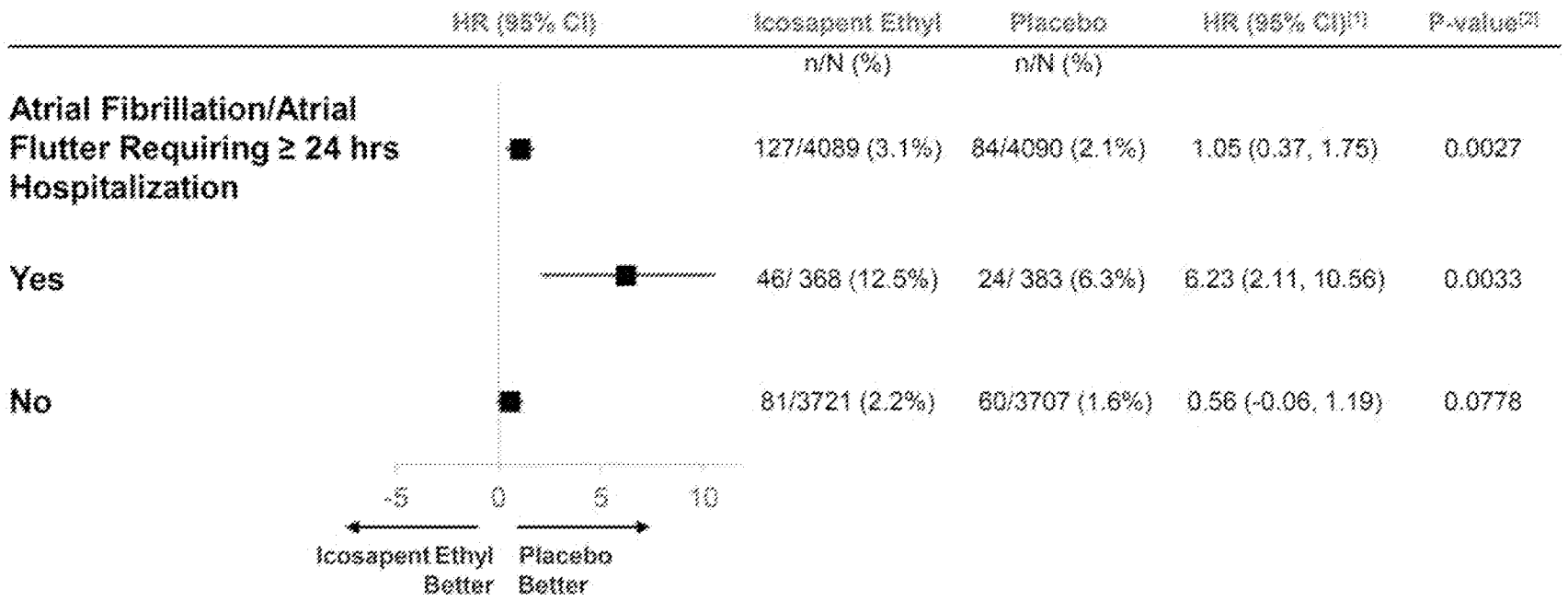

Atrial Fibrillation Requiring >=24 hrs Hospitalization
Atrial Fibrillation/Flutter-Yes
Atrial Fibrillation/Flutter-No
Icosapent Ethyl n/N (%)
Placebo n/N (%)
Icosapent Ethyl - Placebo RD (95% CI)
P-value
89/2892 (3.1%)
64/2883 (2.2%)
0.87 (0.24, 1.71)
0.0402
311/272 (11.4%)
182/278 (6.6%)
5.64 (0.99, 10.55)
0.0178
58/2620 (2.2%)
48/2611 (1.8%)
0.38 (-0.39, 1.16)
0.3313
-5
0
5
10
Icosapent Ethyl Better
Placebo Better

FIG. 75



[1] Log-Rank test statistic and p-value for each subgroup are reported from a Kaplan-Meier analysis, stratified by geographic region, CV risk category, and use of ezetimibe. Hazard ratio and 95% CI for each subgroup are reported from a Cox proportional hazard model with treatment as the covariate, and stratified by geographic region, CV risk category, and use of ezetimibe.

[2] P-value for treatment by the subgroup interaction is reported from a Cox proportional hazard model with treatment, subgroup, and treatment by subgroup interaction as the covariates, and stratified by geographic region, CV risk category, and use of ezetimibe.

FIG. 76

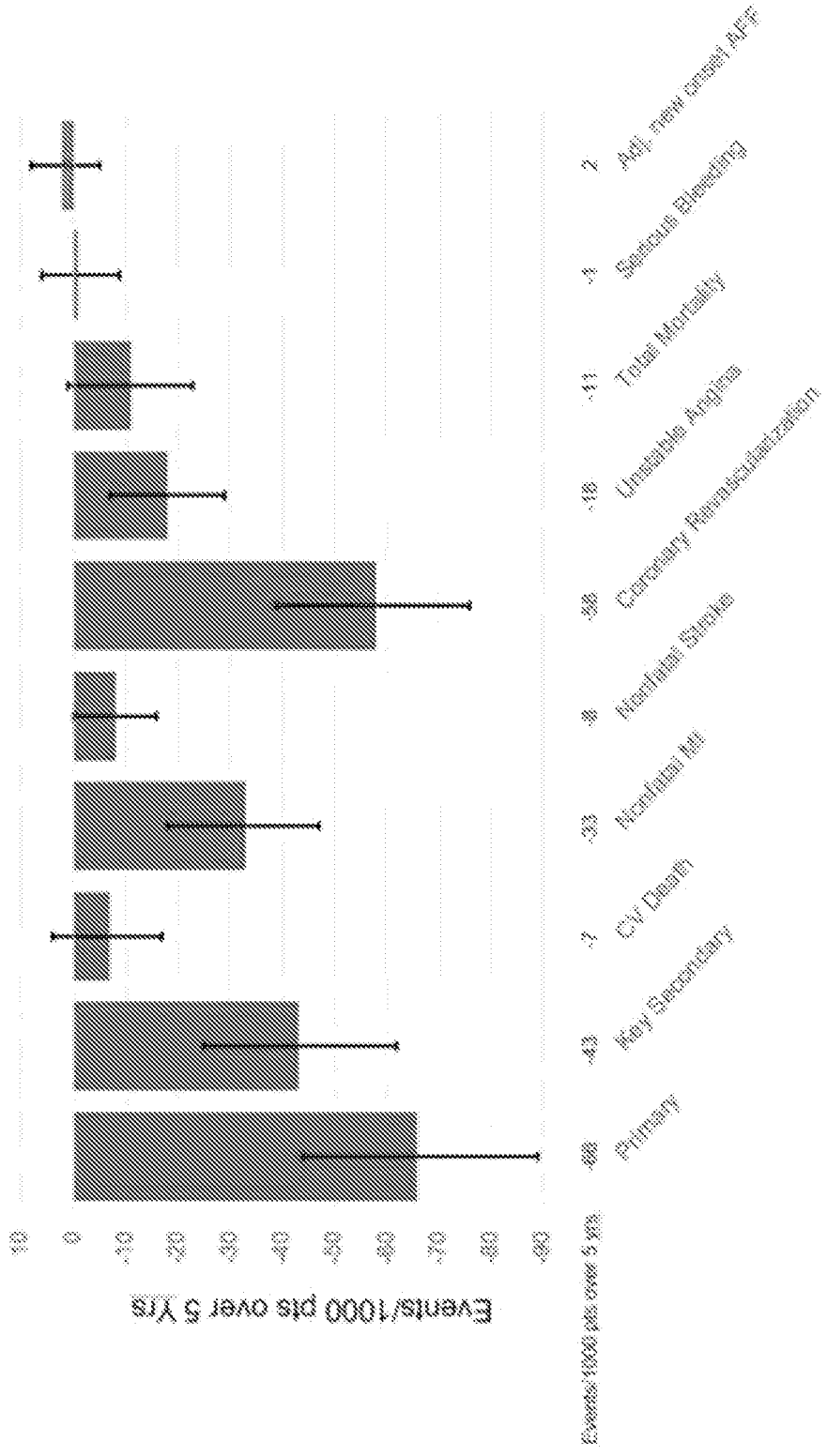

Events/1000 pts over 5 Yrs
Events/1000 pts over 5 yrs
Primary
Key Secondary
CV Death
Nonfatal MI
Nonfatal Stroke
Coronary Revascularization
Unstable Angina
Total Mortality
Spontaneous Bleeding
Adj. new onset AFF

FIG. 77

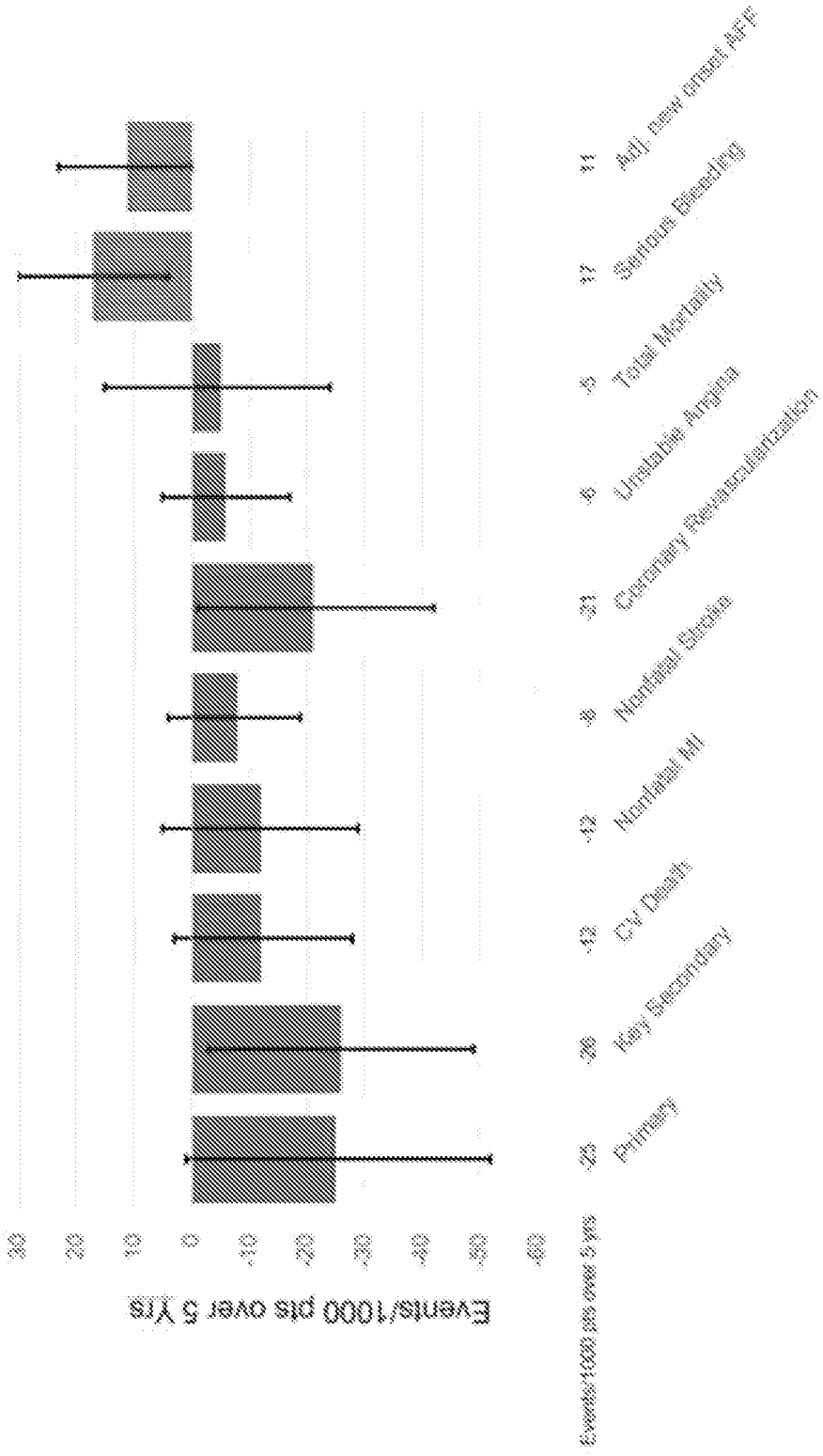

Events/1000 pts over 5 yrs
-20
-10
0
10
20
30
40
50
60
Events/1000 pts over 5 yrs
.05 Primary
.06 Key Secondary
.07 CV Death
.08 Nonfatal MI
.09 Nonfatal Stroke
.01 Coronary Revascularization
.06 Unstable Angina
.05 Total Mortality
.12 Serious Bleeding
.11 Adj. new onset AFF

FIG. 78

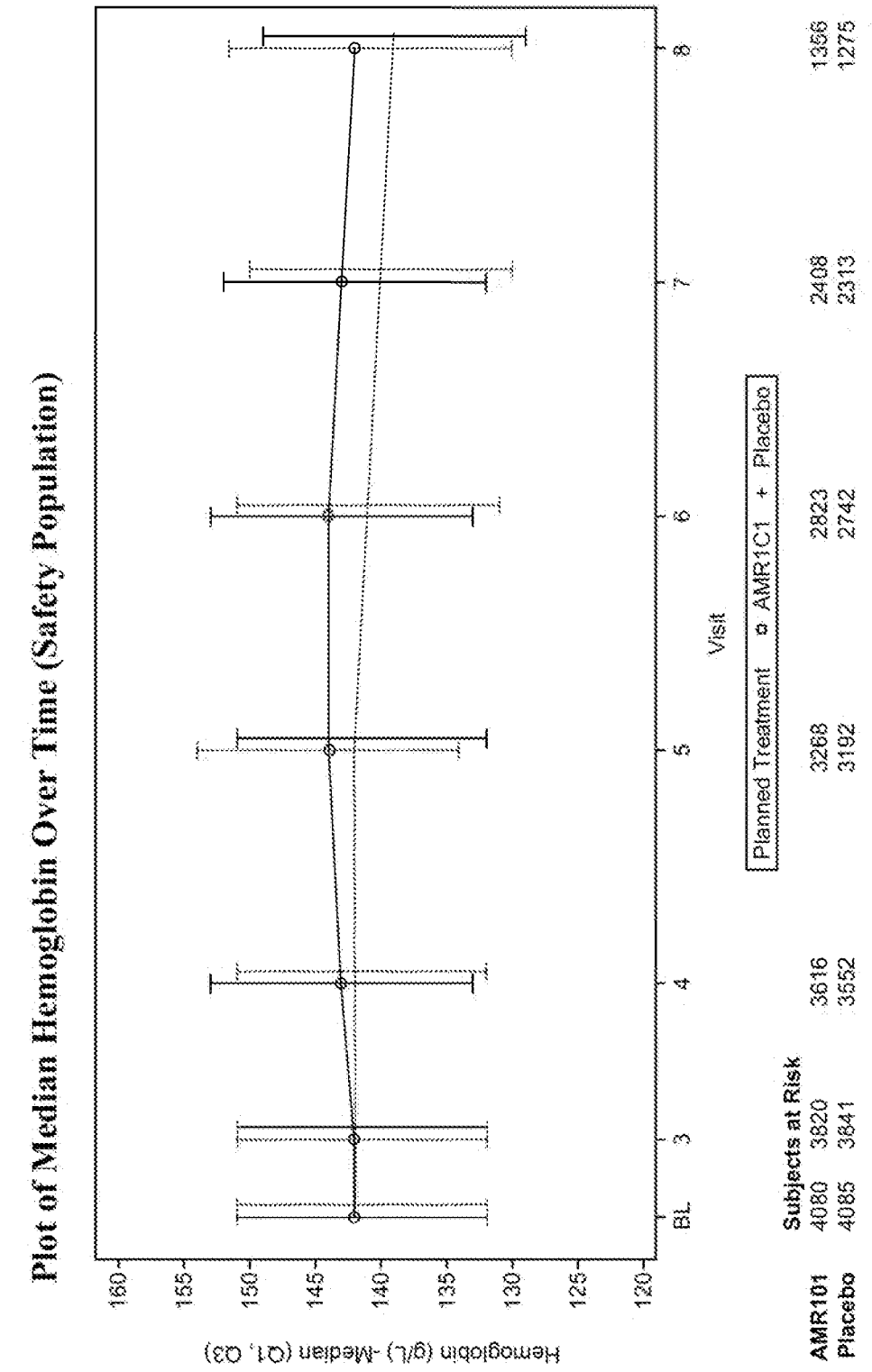

Plot of Median Hemoglobin Over Time (Safety Population)
Hemoglobin (g/L) -Median (Q1, Q3)
160
155
150
145
140
135
130
125
120
BL
3
4
5
6
7
8
Visit
Planned Treatment ¤ AMR1C1 + Placebo
Subjects at Risk
AMR101 4080 3820 3616 3268 2823 2408 1366
Placebo 4085 3841 3552 3192 2742 2313 1275

FIG. 79

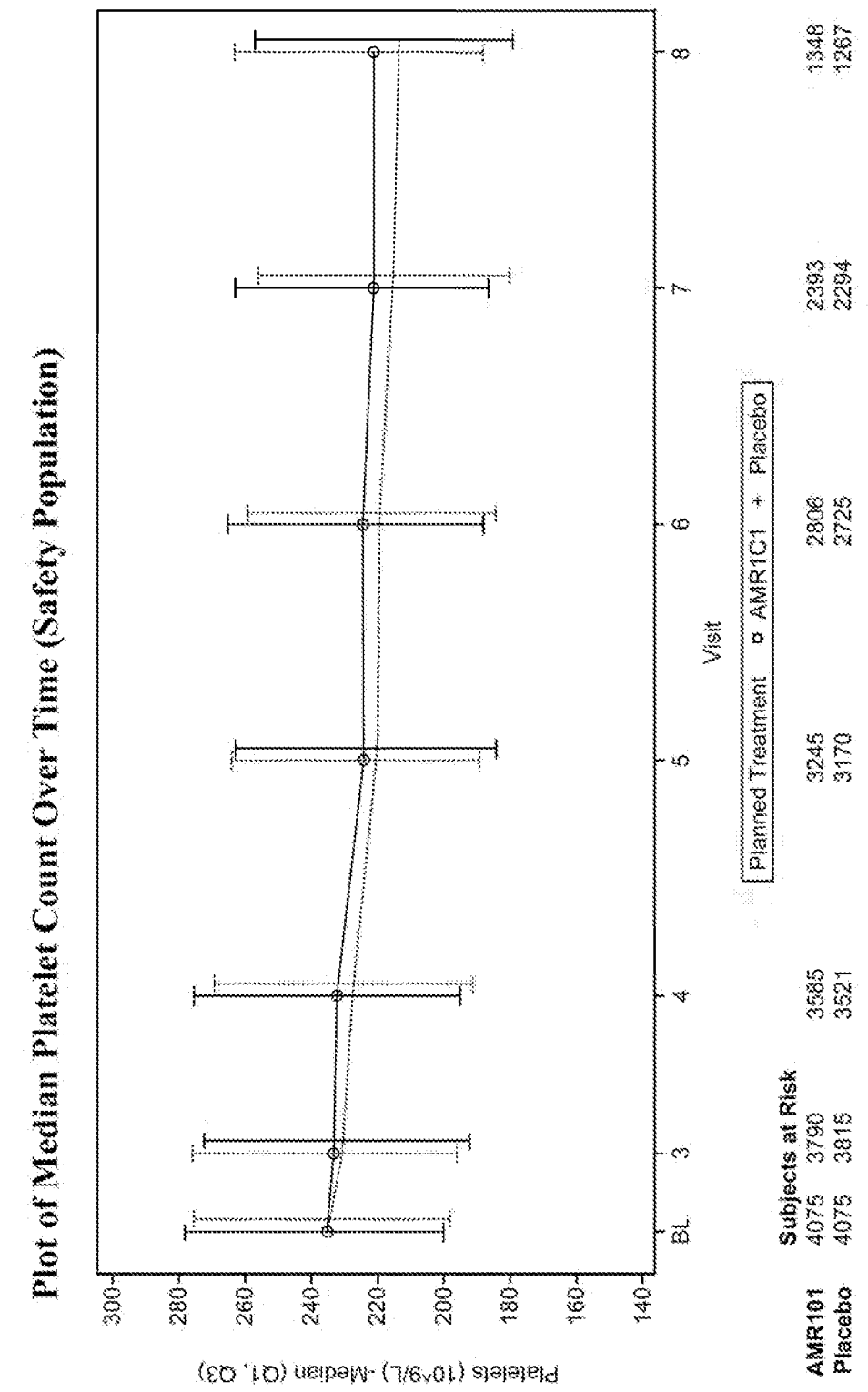

Plot of Median Platelet Count Over Time (Safety Population)
Platelets (10^9/L) -Median (Q1, Q3)
300
280
260
240
220
200
180
160
140
BL
3
4
5
6
7
8
Visit
Planned Treatment ¤ AMR1C1 + Placebo
Subjects at Risk
AMR101 4075 3790 3585 3245 2806 2393 1348
Placebo 4075 3815 3521 3170 2725 2294 1267

FIG. 80

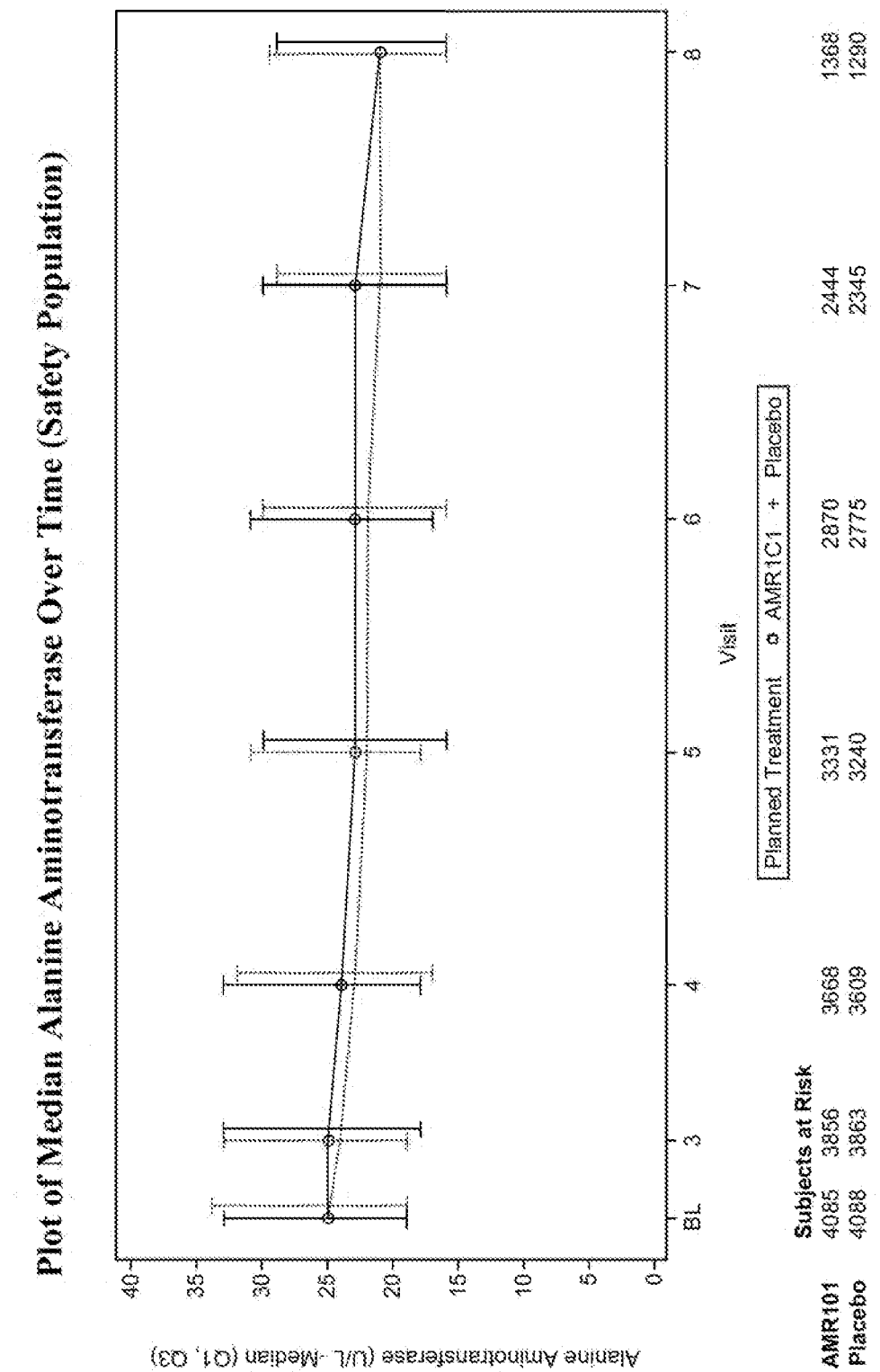

Plot of Median Alanine Aminotransferase Over Time (Safety Population)
Alanine Aminotransferase (U/L - Median (Q1, Q3))
40
35
30
25
20
15
10
5
0
BL
3
4
5
6
7
8
Visit
Planned Treatment AMR1C1 + Placebo
Subjects at Risk
AMR101 4085 3856 3668 3331 2870 2444 1368
Placebo 4088 3863 3609 3240 2775 2345 1280

FIG. 81

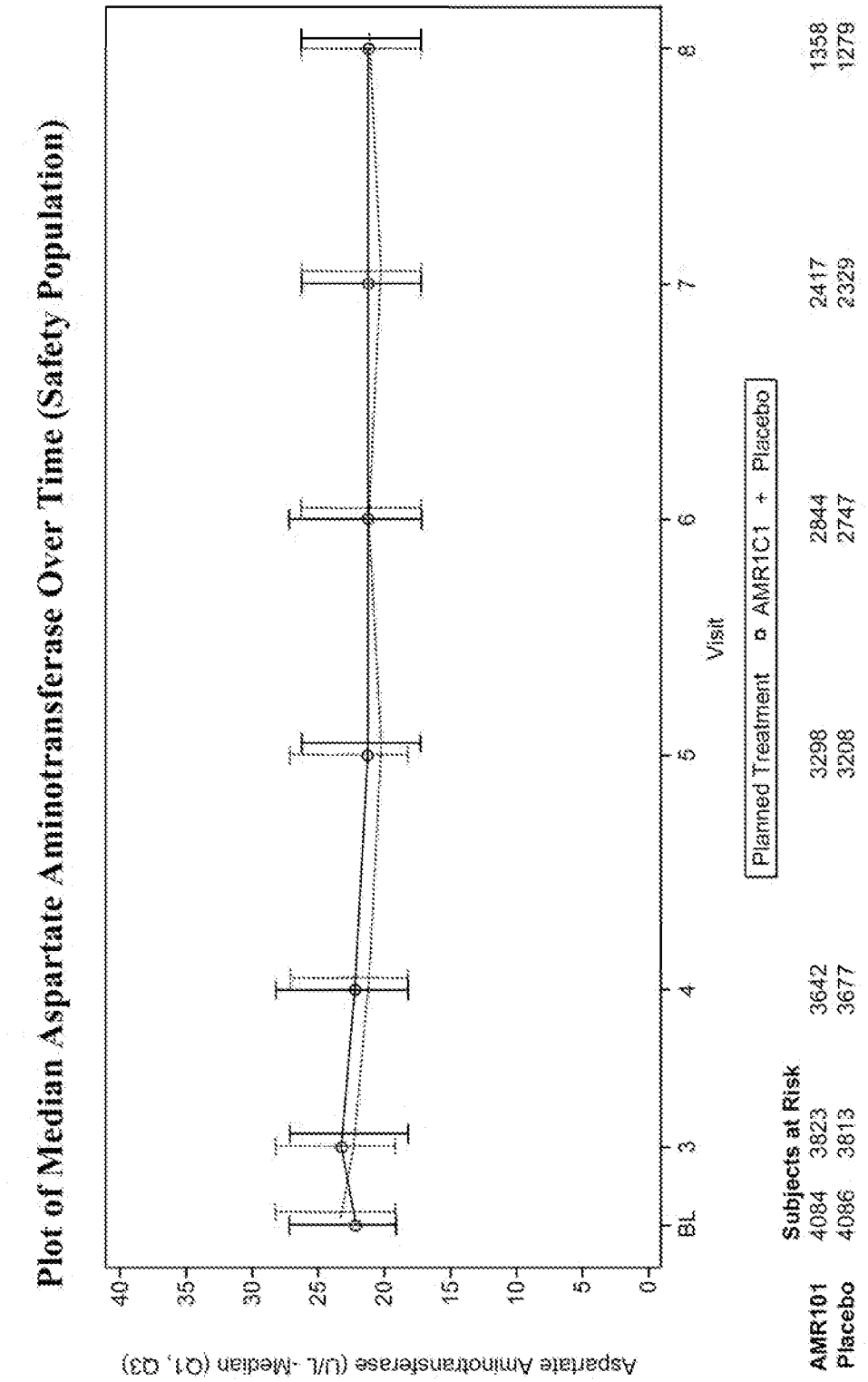
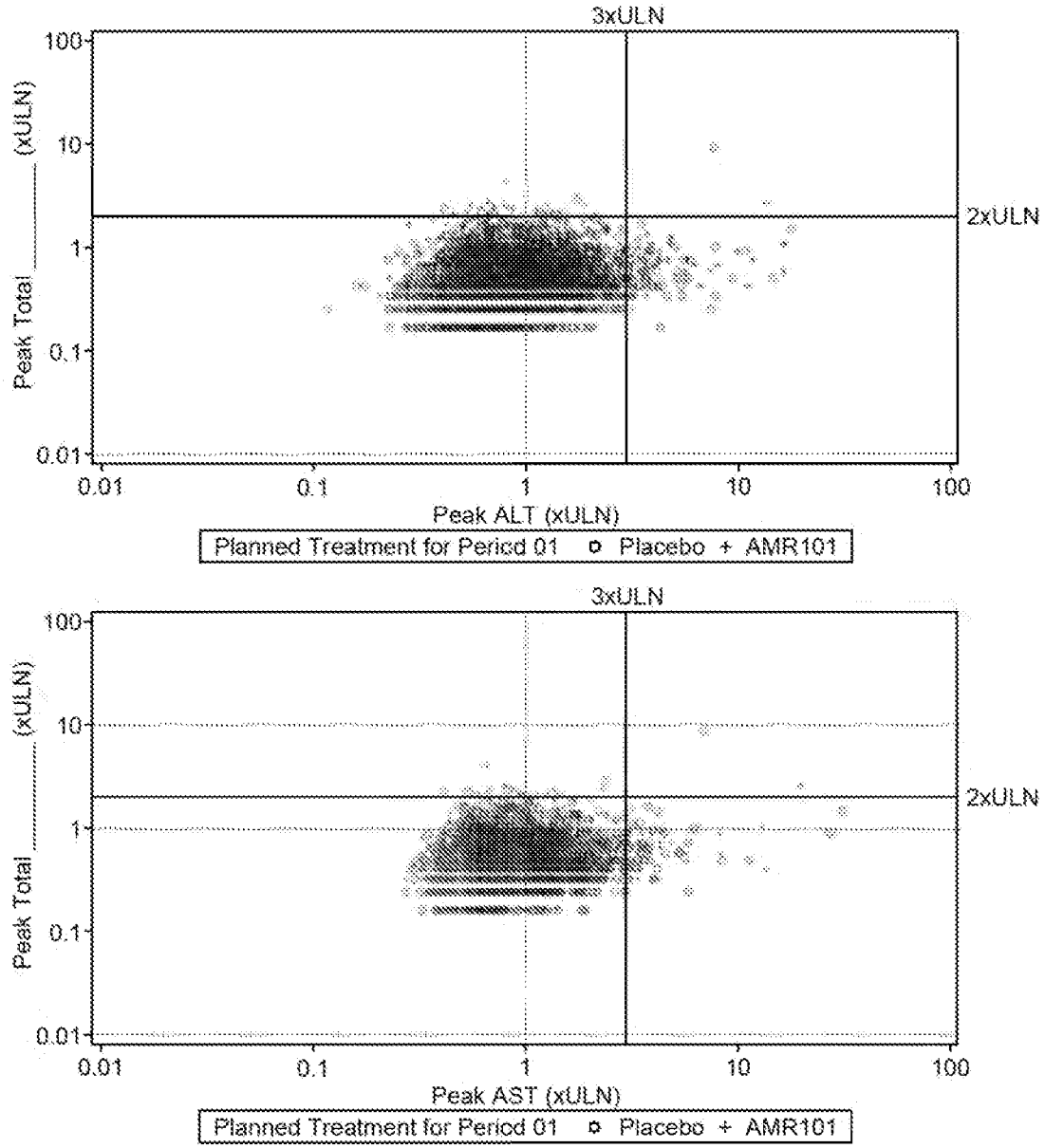

Plot of Median Aspartate Aminotransferase Over Time (Safety Population)
Aspartate Aminotransferase (U/L - Median (Q1, Q3))
40
35
30
25
20
15
10
5
0
BL
3
4
5
6
7
8
Visit
Planned Treatment AMR101 + Placebo
Subjects at Risk
AMR101 4084 3823 3642 3298 2844 2417 1358
Placebo 4086 3813 3677 3208 2747 2329 1279

FIG. 82

Plot of Distribution of Peak Values of ALT or AST vs Peak Values of Total Bilirubin – Evaluation of Drug-Induced Serious Hepatotoxicity (ITT Population)



Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ITT = Intent-to-Treat; ULN = upper limit of normal; vs = versus.

FIG. 83