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(54) Titre : METHODES DE TRAITEMENT DE PATIENTS PRESENTANT UN RISQUE CARDIOVASCULAIRE ELEVE AVEC HYPERCHOLESTEROLEMIE

(54) Title: METHODS FOR TREATING HIGH CARDIOVASCULAR RISK PATIENTS WITH HYPERCHOLESTEROLEMIA

(57) Abrégé/Abstract:
The present invention provides methods for treating hypercholesterolemia. The methods of the present invention comprise administering to a high cardiovascular risk patient a pharmaceutical composition comprising a PCSK9 inhibitor. In certain embodiments, the PCSK9 inhibitor is an anti-PCSK9 antibody such as the exemplary antibody referred to herein as mAb316P. The methods of the present invention are useful for treating high cardiovascular risk patients with hypercholesterolemia and established CHD or CHD risk equivalents that are not adequately controlled by maximum tolerated dose statin therapy.

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(54) **Title**: METHODS FOR TREATING HIGH CARDIOVASCULAR RISK PATIENTS WITH HYPERCHOLESTEROLEMIA

(57) **Abstract**: The present invention provides methods for treating hypercholesterolemia. The methods of the present invention comprise administering to a high cardiovascular risk patient a pharmaceutical composition comprising a PCSK9 inhibitor. In certain embodiments, the PCSK9 inhibitor is an anti-PCSK9 antibody such as the exemplary antibody referred to herein as mAb316P. The methods of the present invention are useful for treating high cardiovascular risk patients with hypercholesterolemia and established CHD or CHD risk equivalents that are not adequately controlled by maximum tolerated dose statin therapy.

METHODS FOR TREATING HIGH CARDIOVASCULAR RISK PATIENTS WITH HYPERCHOLESTEROLEMIA

FIELD OF THE INVENTION

[0001] The present invention relates to the field of therapeutic treatments of diseases and disorders that are associated with elevated levels of lipids and lipoproteins. More specifically, the invention relates to the use of PCSK9 inhibitors to treat high cardiovascular risk patients with hypercholesterolemia and established coronary heart disease (CHD) or CHD risk equivalents that are not adequately controlled by maximum tolerated dose statin therapy.

BACKGROUND

[0002] Hypercholesterolemia, particularly an increase in low-density lipoprotein (LDL) cholesterol (LDL-C) levels, constitutes a major risk for the development of atherosclerosis and coronary heart disease (CHD) (Sharrett et al., 2001, Circulation 104:1108-1113). Low-density lipoprotein cholesterol is identified as the primary target of cholesterol lowering therapy and is accepted as a valid surrogate therapeutic endpoint. Numerous studies have demonstrated that reducing LDL-C levels reduces the risk of CHD with a strong direct relationship between LDL-C levels and CHD events; for each 1 mmol/L (~40 mg/dL) reduction in LDL-C, cardiovascular disease (CVD) mortality and morbidity is lowered by 22%. Greater reductions in LDL-C produce greater reduction in events, and comparative data of intensive versus standard statin treatment suggest that the lower the LDL-C level, the greater the benefit in patients at very high cardiovascular (CV) risk.

[0003] Current LDL-C lowering medications include statins, cholesterol absorption inhibitors (e.g., ezetimibe [EZE]), fibrates, niacin, and bile acid sequestrants. Statins are the most commonly prescribed, as they have shown a greater ability to lower LDL-C and reduce CHD events. However, many patients at risk of cardiovascular disease (CVD) have poorly controlled low-density lipoprotein cholesterol (LDL-C) despite statin therapy.

BRIEF SUMMARY OF THE INVENTION

[0004] The present invention provides methods for treating hypercholesterolemia. In particular, the methods of the present invention are useful for treating high cardiovascular risk patients with hypercholesterolemia and established coronary heart disease (CHD) or CHD risk equivalents that are not adequately controlled by maximum tolerated dose statin therapy.

[0005] According to one aspect, the methods of the present invention comprise administering one or more doses of a PCSK9 inhibitor to a high cardiovascular risk patient with hypercholesterolemia and established coronary heart disease or CHD risk equivalents that are

not adequately controlled by maximum tolerated dose statin therapy (*i.e.*, hypercholesterolemia that is not adequately controlled by maximum tolerated dose statin therapy in the absence of a PCSK9 inhibitor, with or without other lipid modifying therapy). According to certain embodiments of the present invention, the PCSK9 inhibitor is administered to the high cardiovascular risk patient as an add-on therapy to the patient's existing statin therapy.

[0006] According to another aspect, the methods of the present invention comprise selecting a high cardiovascular risk patient who is on a therapeutic regimen comprising a daily dose of a statin (*e.g.*, a maximum tolerated dose statin therapy), and administering to the patient one or more doses of a PCSK9 inhibitor in combination with (*i.e.*, "on top of") the statin therapy.

[0007] An aspect of the invention includes a method for treating a high cardiovascular risk patient with hypercholesterolemia and established coronary heart disease (CHD) or CHD risk equivalents that are not adequately controlled by maximum tolerated dose statin therapy with or without other lipid lowering therapy comprising administering one or more doses of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to the patient, wherein the patient exhibits inadequate control of the hypercholesterolemia despite treatment with the maximum tolerated dose statin therapy with or without other lipid lowering therapy in the absence of the PCSK9 inhibitor.

[0008] Another aspect of the invention includes a method for reducing low-density lipoprotein cholesterol (LDL-C) in a high cardiovascular risk patient with hypercholesterolemia and established coronary heart disease (CHD) or CHD risk equivalents that is not adequately controlled by maximum tolerated dose statin therapy with or without other lipid lowering therapy comprising administering one or more doses of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to the patient, wherein the patient exhibits inadequate control of LDL-C despite treatment with a maximum tolerated dose statin therapy with or without other lipid lowering therapy in the absence of the PCSK9 inhibitor.

[0009] Another aspect of the invention includes a method for treating hypercholesterolemia in a high cardiovascular risk patient with hypercholesterolemia and established coronary heart disease (CHD) or CHD risk equivalents that are not adequately controlled by maximum tolerated dose statin therapy with or without other lipid lowering therapy comprising administering one or more doses of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to the patient, wherein the patient exhibits inadequate control of the hypercholesterolemia despite treatment with the maximum tolerated dose statin therapy with or without other lipid lowering therapy in the absence of the PCSK9 inhibitor.

[0010] Another aspect of the invention includes a method for improving the serum level of one or more lipid components in a high cardiovascular risk patient with hypercholesterolemia and established coronary heart disease (CHD) or CHD risk equivalents that are not adequately

controlled by maximum tolerated dose statin therapy with or without other lipid lowering therapy comprising administering one or more doses of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to the patient, wherein the patient exhibits inadequate control of the lipid component despite treatment with the maximum tolerated dose statin therapy with or without other lipid lowering therapy in the absence of the PCSK9 inhibitor. In certain aspects, the invention provides a decrease in the serum level of a lipid component selected from the group consisting of LDL-C, Apo B, non-HDL-C, total cholesterol, Lp(a), and triglycerides. In certain aspects, the invention provides an increase in the serum level of a lipid component selected from the group consisting of HDL-C and ApoA-1.

[0011] In certain aspects, established CHD is defined by a history of CHD, including one or more of the following: acute myocardial infarction (MI), silent MI, unstable angina, coronary revascularization procedure, and clinically significant CHD diagnosed by invasive or non-invasive testing.

[0012] In certain aspects, the CHD risk equivalents include one or more of the following four criteria: 1) peripheral arterial disease (PAD); 2) ischemic stroke; 3) chronic kidney disease (CKD); and/or 4) known history of diabetes mellitus and 2 or more additional risk factors, including: a) history of hypertension, b) history of ankle-brachial index ≤0.90, c) history of microalbuminuria or macroalbuminuria or dipstick urinalysis at screening visit with >2+ protein, d) history of preproliferative or proliferative retinopathy or laser treatment for retinopathy, and e) known family history of premature CHD.

[0013] In certain aspects, the PCSK9 inhibitor is an antibody or an antigen-binding fragment thereof that specifically binds PCSK9. In some aspects, the antibody or antigen-binding fragment thereof comprises the heavy and light chain complementarity determining regions (CDRs) of a heavy chain variable region/light chain variable region (HCVR/LCVR) amino acid sequence pair selected from the group consisting of SEQ ID NOs: 1/6 and 11/15. In some aspects, the antibody or antigen-binding fragment thereof comprises heavy and light chain CDR amino acid sequences having SEQ ID NOs: 12, 13, 14, 16, 17, and 18. In some aspects, the antibody or antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:11 and an LCVR having the amino acid sequence of SEQ ID NO:15. In some aspects, the antibody or antigen-binding fragment thereof comprises heavy and light chain CDR amino acid sequences having SEQ ID NOs:2, 3, 4, 7, 8, and 10. In some aspects, the antibody or antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:1 and an LCVR having the amino acid sequence of SEQ ID NO:6. In some aspects, the antibody or antigen-binding fragment thereof binds to the same epitope on PCSK9 as an antibody comprising heavy and light chain CDR amino acid sequences having SEQ ID NOs: 12, 13, 14, 16, 17, and 18; or SEQ ID NOs: 2, 3, 4, 7, 8, and 10. In some aspects,

the antibody or antigen-binding fragment thereof competes for binding to PCSK9 with an antibody comprising heavy and light chain CDR amino acid sequences having SEQ ID NOs: 12, 13, 14, 16, 17, and 18; or SEQ ID NOs: 2, 3, 4, 7, 8, and 10.

[0014] In certain aspects, the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is administered to the patient at a dose of about 75 mg at a frequency of once every two weeks. In some aspects, the about 75 mg dose is maintained if the patient's LDL-C measured after five or more doses is <70 mg/dL. In some aspects, the about 75 mg dose is discontinued if the patient's LDL-C measured after five or more doses remains ≥70 mg/dL, and the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is subsequently administered to the patient at a dose of about 150 mg at a frequency of once every two weeks. In some aspects, the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is administered to the patient at a dose of about 150 mg at a frequency of once every two weeks.

[0015] In certain aspects, the PCSK9 inhibitor is administered to the patient in combination with the maximum tolerated dose statin therapy. In some aspects, the maximum tolerated dose statin therapy comprises a daily dose of about 40 mg to about 80 mg of atorvastatin. In some aspects, the maximum tolerated dose statin therapy comprises a daily dose of about 20 mg to about 40 mg of rosuvastatin. In some aspects, the maximum tolerated dose statin therapy comprises a daily dose of about 80 mg of simvastatin. In some aspects, the PCSK9 inhibitor is administered to the patient in combination with the other lipid lowering therapy, wherein the other lipid lowering therapy comprises a therapeutic agent selected from the group consisting of ezetimibe, a fibrate, niacin, an omega-3 fatty acid, and a bile acid resin.

[0016] In certain aspects, the method improves at least one hypercholesterolemia-associated parameter selected from the group consisting of: (a) reduction of the patient's low density lipoprotein cholesterol (LDL-C) by at least 40%; (b) reduction of the patient's apolipoprotein B100 (ApoB) by at least 35%; (c) reduction of the patient's non-high density lipoproprotein cholesterol (non-HDL-C) by at least 35%; (d) reduction of the patient's total cholesterol by at least 20%; (e) increase of the patient's high density lipoprotein cholesterol (HDL-C) by at least 1%; (f) reduction of the patient's triglycerides by at least 1%; (g) reduction of the patient's lipoprotein a (Lp(a)) by at least 10%; and (h) increase of the patient's apolipoprotein A-1 by at least 1%.

[0017] Other embodiments of the present invention will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

[0018] **Figure 1A** is a graphic representation of the study design for ODYSSEY COMBO I. **Figure 1B** is a graphic representation of the study design for ODYSSEY COMBO II. LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; PO, *per os*; Q2W, every 2 weeks; R, randomization; SC, subcutaneous; TLC, therapeutic lifestyle changes.

[0019] **Figure 2** is a graph that shows the calculated LDL-C LS mean (+/- SE) percent change from baseline for placebo and alirocumab over time for the ITT analysis – ITT population in the ODYSSEY COMBO I study. Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C-by-time point interaction.

[0020] **Figure 3** is a graph that shows the calculated LDL-C LS mean (+/- SE) percent change from baseline for placebo and alirocumab over time for the on treatment analysis – mITT population in the ODYSSEY COMBO I study. The efficacy treatment period ends at last injection date + 21 days. Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C-by-time point interaction.

[0021] **Figure 4** is a graph of LDL-C levels over time for alirocumab-treated patients with/without dose increase at week 12 in the ODYSSEY COMBO I study.

[0022] **Figure 5** is a graph of the percentage LDL-C reduction from baseline at week 24 for various alirocumab and placebo demographic subgroups in the ODYSSEY COMBO I study.

[0023] **Figure 6** is a graph that shows the calculated LDL-C LS mean (+/- SE) percent change from baseline over time for the ITT population in the ODYSSEY COMBO II study. Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C-by-time point interaction.

[0024] **Figure 7** is a graph of achieved LDL-C concentrations at 24 weeks by decile of baseline LDL-C in patients for the alirocumab and ezetimibe groups in the ODYSSEY COMBO II study.

[0025] **Figure 8** is a graph of LDL-C concentrations versus study time point by dose-increase status (intention-to-treat analysis) for the alirocumab and ezetimibe groups in the ODYSSEY COMBO II study. LS = least squares; SD = standard deviation; SE = standard error.

[0026] **Figure 9** is chart of the percent change from baseline to week 24 in LDL-C in various subgroups (ITT analysis) of the alirocumab and ezetimibe groups in the ODYSSEY COMBO II study. BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease; LS = least squares; MI = myocardial infarction; SC = subcutaneous; TG = triglyceride.

[0027] **Figure 10** is a graphic representation of the study design for ODYSSEY LONG TERM. Phone call visits are indicated in italics, and continue every 4 weeks between on-site visits until the end of the double-blind treatment period visit. Labels in the study design are defined as follows: HeFH: heterozygous familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy; Q2W: every two weeks; and SC: subcutaneous.

[0028] **Figure 11** is a graph that shows the calculated LDL-C LS mean (+/- SE) percent change from baseline for placebo and alirocumab over time for the ITT population in the ODYSSEY LONG TERM study at the time of the pre-specified analysis. Note: Least-squares (LS) means and standard errors (SE) taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C-by-time point interaction.

[0029] **Figure 12** is a set of graphs showing the LS mean (SE) percent change from baseline to Week 24 for LDL-C in the non-HeFH and HeFH populations of the ODYSSEY LONG TERM study (A), as well as the same population of HeFH patients separated by baseline LDL-C levels (< 160 mg/dL and ≥160 mg/dL (B); and < 190 mg/dL and ≥190 mg/dL. (C)). All patients were on a background statin (at the maximum tolerated level). A subset of patients also received a further lipid lowering therapy.

[0030] **Figure 13** is a graph demonstrating the difference in LS mean (SE) percent change from baseline to Week 24 in different subgroups of the ODYSSEY LONG TERM study. Labels in the graph are defined as follows: CKD: chronic kidney disease; TGs: triglycerides. All patients were on a background statin (at the maximum tolerated level). A subset of patients also received a further lipid lowering therapy.

[0031] **Figure 14** is a graph demonstrating the difference in LS mean (SE) percent change from baseline to Week 24 in specific statin and LLT use subgroups of the ODYSSEY LONG TERM study. All patients were on a background statin (at the maximum tolerated level). A subset of patients also received a further lipid lowering therapy.

[0032] **Figure 15** is a graph that shows the calculated LDL-C LS mean (+/- SE) percent change from baseline for placebo and alirocumab over time for the ITT population in the ODYSSEY LONG TERM study. Values above data points indicate LS mean absolute LDL cholesterol levels, values below data points indicate LS mean % change from baseline. Values below chart indicate number of patients with LDL cholesterol values available for ITT analysis at each time point, i.e., LDL cholesterol measurements taken both on-treatment and post-treatment (for patients who had discontinued study treatment but had returned to the clinic for assessments). Missing data were accounted for using a mixed effects model with repeated measures.

DETAILED DESCRIPTION

[0033] Before the present invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

[0034] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.*, 99.1, 99.2, 99.3, 99.4, etc.).

[0035] Although any methods and materials similar or equivalent to those described herein can be used in the practice of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to describe in their entirety.

Hypercholesterolemia and Established Coronary Heart Disease or CHD Risk Equivalents Not Adequately Controlled by Maximum Tolerated Dose Statin Therapy

[0036] The present invention relates generally to methods and compositions for treating high cardiovascular risk patients who have hypercholesterolemia and established CHD or CHD risk equivalents that are not adequately controlled by statins, *i.e.*, hypercholesterolemia not adequately controlled by a therapeutic regimen comprising a daily maximum tolerated dose of a statin. As used herein, the expression "not adequately controlled," in reference to hypercholesterolemia, means that the patient's serum low-density lipoprotein cholesterol (LDL-C) concentration, total cholesterol concentration, and/or triglyceride concentration is not reduced

to a recognized, medically-acceptable level (taking into account the patient's relative risk of coronary heart disease) after at least 4 weeks on a therapeutic regimen comprising a stable daily dose of a statin. For example, "a patient with hypercholesterolemia that is not adequately controlled by a statin" includes patients with a serum LDL-C concentration of greater than about 70 mg/dL, 100 mg/dL, 130 mg/dL, 140 mg/dL, or more (depending on the patient's underlying risk of heart disease) after the patient has been on a stable daily statin regimen for at least 4 weeks.

[0037] According to certain embodiments, the high cardiovascular risk patient who is treatable by the methods of the present invention has hypercholesterolemia (*e.g.*, a serum LDL-C concentration of greater than or equal to 70 mg/dL) despite taking a stable daily dose of a statin (with or without other lipid modifying therapy) for at least 4 weeks, 5 weeks, 6 weeks, or more. In certain embodiments, the high cardiovascular risk patient's hypercholesterolemia is inadequately controlled by a maximum tolerated dose statin therapy (also referred to herein as "a daily maximum tolerated dose therapeutic statin regimen").

[0038] As used herein, “maximum tolerated dose statin therapy” means a therapeutic regimen comprising the administration of daily dose of a statin that is the maximally tolerated dose for a particular patient. Maximally tolerated dose means the highest dose of statin that can be administered to a patient without causing unacceptable adverse side effects in the patient. Maximum tolerated dose statin therapy includes, but is not limited to, e.g., 40-80 mg of atorvastatin daily, 20-40 mg of rosuvastatin daily, or 80 mg of simvastatin (if already on this dose for >1 year). However, patients not able to tolerate the above statin doses could take a lower dose of daily atorvastatin, rosuvastatin, or simvastatin provided there was an acceptable reason for not using the higher dose. Some examples of acceptable reasons for a patient taking a lower statin dose include: adverse effects on higher doses, advanced age, low body mass index (BMI), regional practices, local prescribing information, concomitant medications, concern about cognitive adverse events, and comorbid conditions such as impaired glucose tolerance/impaired fasting glucose, increased blood glucose, glycated hemoglobin, liver disease or elevated liver enzymes, and muscle symptoms and/or raised creatine phosphokinase.

[0039] The present invention also includes methods for treating high cardiovascular risk patients with hypercholesterolemia and established CHD or CHD risk equivalents that are not adequately controlled by maximum tolerated dose statin therapy comprising daily administration of other statins such as cerivastatin, pitavastatin, fluvastatin, lovastatin, and pravastatin.

Patient Selection

[0040] The present invention includes methods and compositions useful for treating high cardiovascular risk patients who have hypercholesterolemia and established CHD or CHD risk

equivalents that are not adequately controlled by a daily maximum tolerated dose therapeutic statin regimen.

[0041] Established CHD is defined as a documented history of CHD, including one or more of the following: acute myocardial infarction (MI), silent MI, unstable angina, coronary revascularization procedure (e.g., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery), and clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging).

[0042] CHD risk equivalents includes one or more of the following 4 criteria: 1) peripheral arterial disease (PAD); 2) ischemic stroke; 3) chronic kidney disease; and/or 4) known history of diabetes mellitus and 2 or more additional risk factors, including: a) history of hypertension (established on antihypertensive medication), b) history of ankle-brachial index ≤0.90, c) history of microalbuminuria or macroalbuminuria or dipstick urinalysis at screening visit (Week -2) with >2+ protein, d) history of preproliferative or proliferative retinopathy or laser treatment for retinopathy, e) known family history of premature CHD (CHD in father or brother before 55 years of age; CHD in mother or sister before 65 years of age).

[0043] As used herein, in peripheral arterial disease (PAD), one of the following criteria [a, b, or c] must be satisfied): a) current intermittent claudication (muscle discomfort in the lower limb produced by exercise that is both reproducible and relieved by rest within 10 minutes) of presumed atherosclerotic origin together with ankle-brachial index equal to or less than 0.90 in either leg at rest, or b) history of intermittent claudication together with endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease, or c) history of critical limb ischemia together with thrombolysis, endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease.

[0044] As used herein, documented ischemic stroke includes ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. Computed tomography (CT) or magnetic resonance imaging (MRI) can be performed to rule out hemorrhage and non-ischemic neurological disease.

[0045] As used herein, chronic kidney disease (CKD) is defined by an estimated glomerular filtration rate (eGFR) of ≥30–<60 ml/min/1.73 m2 for 3 months or more.

[0046] According to certain embodiments, the high cardiovascular risk patient may be selected on the basis of having one or more additional risk factors selected from the group consisting of age (*e.g.*, older than 40, 45, 50, 55, 60, 65, 70, 75, or 80 years), race, national origin, gender (male or female), exercise habits (*e.g.*, regular exerciser, non-exerciser), other preexisting medical conditions (*e.g.*, type-II diabetes, high blood pressure, etc.), and current medication

status (*e.g.*, currently taking beta blockers, niacin, ezetimibe, fibrates, omega-3 fatty acids, bile acid resins, etc.).

[0047] According to the present invention, high cardiovascular risk patients may be selected on the basis of a combination of one or more of the foregoing selection criteria or therapeutic characteristics.

Administration of a PCSK9 Inhibitor as Add-On Therapy to Maximum Tolerated Dose Statin Therapy

[0048] The present invention includes methods wherein a high cardiovascular risk patient with hypercholesterolemia and established CHD or CHD risk equivalents that are not adequately controlled by a stable daily maximum tolerated dose therapeutic statin regimen in the absence of a PCSK9 inhibitor is administered a PCSK9 inhibitor according to a particular dosing amount and frequency, and wherein the PCSK9 inhibitor is administered as an add-on to the patient's therapeutic statin regimen. For example, according to certain embodiments, if a high cardiovascular risk patient has hypercholesterolemia and established CHD or CHD risk equivalents that are not adequately controlled despite being on a stable daily maximum tolerated dose therapeutic statin regimen comprising, *e.g.*, 40-80 mg of atorvastatin, the high cardiovascular risk patient may be administered a PCSK9 inhibitor at a particular amount and dosing interval while the patient continues his or her stable daily therapeutic statin regimen.

[0049] The methods of the present invention include add-on therapeutic regimens wherein the PCSK9 inhibitor is administered as add-on therapy to the same stable daily maximum tolerated dose therapeutic statin regimen (*i.e.*, same dosing amount of statin) that the high cardiovascular risk patient was on prior to receiving the PCSK9 inhibitor. In other embodiments, the PCSK9 inhibitor is administered as add-on therapy to a daily maximum tolerated dose therapeutic statin regimen comprising a statin in an amount that is more than or less than the dose of statin the patient was on prior to receiving the PCSK9 inhibitor. For example, after starting a therapeutic regimen comprising a PCSK9 inhibitor administered at a particular dosing frequency and amount, the daily dose of statin administered or prescribed to the patient may (a) stay the same, (b) increase, or (c) decrease (*e.g.*, up-titrate or down-titrate) in comparison to the daily statin dose the high cardiovascular risk patient was taking before starting the PCSK9 inhibitor therapeutic regimen, depending on the therapeutic needs of the patient.

Therapeutic Efficacy

[0050] The methods of the present invention will result in the improvement in the serum level of one or more lipid components selected from the group consisting of LDL-C, ApoB, non-HDL-C, total cholesterol, HDL-C, ApoA-1, triglycerides, and Lp(a). For example, according to certain

embodiments of the present invention, administration of a pharmaceutical composition comprising a PCSK9 inhibitor to a high cardiovascular risk patient with hypercholesterolemia and established CHD or CHD risk equivalents that are not adequately controlled by a stable daily maximum tolerated dose therapeutic statin regimen (*e.g.*, administration of the PCSK9 inhibitor on top of the patient's maximum tolerated dose statin therapy) will result in a mean percent reduction from baseline in serum low density lipoprotein cholesterol (LDL-C) of at least about 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, or greater; a mean percent reduction from baseline in ApoB of at least about 35%, 36%, 37%, 38%, 39%, 40%, or greater; a mean percent reduction from baseline in non-HDL-C of at least about 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, or greater; a mean percent reduction from baseline in total cholesterol of at least about 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, or greater; a mean percent increase from baseline in HDL-C of at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, or greater; a mean percent increase from baseline in ApoA-1 of at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, or greater; a mean percent reduction from baseline in triglycerides of at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, or greater; and/or a mean percent reduction from baseline in Lp(a) of at least about 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, or greater.

PCSK9 Inhibitors

[0051] The methods of the present invention comprise administering to a high cardiovascular risk patient a therapeutic composition comprising a PCSK9 inhibitor. As used herein, a "PCSK9 inhibitor" is any agent which binds to or interacts with human PCSK9 and inhibits the normal biological function of PCSK9 *in vitro* or *in vivo*. Non-limiting examples of categories of PCSK9 inhibitors include small molecule PCSK9 antagonists, peptide-based PCSK9 antagonists (*e.g.*, "peptibody" molecules), and antibodies or antigen-binding fragments of antibodies that specifically bind human PCSK9.

[0052] The term “human proprotein convertase subtilisin/kexin type 9” or "human PCSK9" or "hPCSK9", as used herein, refers to PCSK9 having the nucleic acid sequence shown in SEQ ID NO:197 and the amino acid sequence of SEQ ID NO:198, or a biologically active fragment thereof.

[0053] The term "antibody", as used herein, is intended to refer to immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (*e.g.*, IgM). Each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or V_H) and a heavy chain

constant region. The heavy chain constant region comprises three domains, C_H1, C_H2 and C_H3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or V_L) and a light chain constant region. The light chain constant region comprises one domain (C_L1). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In different embodiments of the invention, the FRs of the anti-PCSK9 antibody (or antigen-binding portion thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

[0054] The term "antibody," as used herein, also includes antigen-binding fragments of full antibody molecules. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. Antigen-binding fragments of an antibody may be derived, *e.g.*, from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and optionally constant domains. Such DNA is known and/or is readily available from, *e.g.*, commercial sources, DNA libraries (including, *e.g.*, phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

[0055] Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (*e.g.*, an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (*e.g.* monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein.

[0056] An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally

comprise at least one CDR which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H-V_H, V_H-V_L or V_L-V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

[0057] In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) V_H-C_H1; (ii) V_H-C_H2; (iii) V_H-C_H3; (iv) V_H-C_H1-C_H2; (v) V_H-C_H1-C_H2-C_H3; (vi) V_H-C_H2-C_H3; (vii) V_H-C_L; (viii) V_L-C_H1; (ix) V_L-C_H2; (x) V_L-C_H3; (xi) V_L-C_H1-C_H2; (xii) V_L-C_H1-C_H2-C_H3; (xiii) V_L-C_H2-C_H3; and (xiv) V_L-C_L. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (*e.g.*, 5, 10, 15, 20, 40, 60 or more) amino acids which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (*e.g.*, by disulfide bond(s)).

[0058] As with full antibody molecules, antigen-binding fragments may be monospecific or multispecific (*e.g.*, bispecific). A multispecific antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multispecific antibody format, including the exemplary bispecific antibody formats disclosed herein, may be adapted for use in the context of an antigen-binding fragment of an antibody of the present invention using routine techniques available in the art.

[0059] The constant region of an antibody is important in the ability of an antibody to fix complement and mediate cell-dependent cytotoxicity. Thus, the isotype of an antibody may be selected on the basis of whether it is desirable for the antibody to mediate cytotoxicity.

[0060] The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the invention may nonetheless include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis *in vitro* or by somatic mutation *in vivo*), for example in the CDRs and in

particular CDR3. However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

[0061] The term "recombinant human antibody", as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor et al. (1992) Nucl. Acids Res. 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to *in vitro* mutagenesis (or, when an animal transgenic for human Ig sequences is used, *in vivo* somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire *in vivo*.

[0062] Human antibodies can exist in two forms that are associated with hinge heterogeneity. In one form, an immunoglobulin molecule comprises a stable four chain construct of approximately 150-160 kDa in which the dimers are held together by an interchain heavy chain disulfide bond. In a second form, the dimers are not linked via inter-chain disulfide bonds and a molecule of about 75-80 kDa is formed composed of a covalently coupled light and heavy chain (half-antibody). These forms have been extremely difficult to separate, even after affinity purification.

[0063] The frequency of appearance of the second form in various intact IgG isotypes is due to, but not limited to, structural differences associated with the hinge region isotype of the antibody. A single amino acid substitution in the hinge region of the human IgG4 hinge can significantly reduce the appearance of the second form (Angal et al. (1993) Molecular Immunology 30:105) to levels typically observed using a human IgG1 hinge. The instant invention encompasses antibodies having one or more mutations in the hinge, C_H2 or C_H3 region which may be desirable, for example, in production, to improve the yield of the desired antibody form.

[0064] An "isolated antibody," as used herein, means an antibody that has been identified and separated and/or recovered from at least one component of its natural environment. For example, an antibody that has been separated or removed from at least one component of an

organism, or from a tissue or cell in which the antibody naturally exists or is naturally produced, is an "isolated antibody" for purposes of the present invention. An isolated antibody also includes an antibody *in situ* within a recombinant cell. Isolated antibodies are antibodies that have been subjected to at least one purification or isolation step. According to certain embodiments, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0065] The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Methods for determining whether an antibody specifically binds to an antigen are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. For example, an antibody that "specifically binds" PCSK9, as used in the context of the present invention, includes antibodies that bind PCSK9 or portion thereof with a K_D of less than about 1000 nM, less than about 500 nM, less than about 300 nM, less than about 200 nM, less than about 100 nM, less than about 90 nM, less than about 80 nM, less than about 70 nM, less than about 60 nM, less than about 50 nM, less than about 40 nM, less than about 30 nM, less than about 20 nM, less than about 10 nM, less than about 5 nM, less than about 4 nM, less than about 3 nM, less than about 2 nM, less than about 1 nM or less than about 0.5 nM, as measured in a surface plasmon resonance assay. An isolated antibody that specifically binds human PCSK9, however, have cross-reactivity to other antigens, such as PCSK9 molecules from other (non-human) species.

[0066] The anti-PCSK9 antibodies useful for the methods of the present invention may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences from which the antibodies were derived. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The present invention includes methods involving the use of antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as "germline mutations"). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework

and/or CDR residues within the V_H and/or V_L domains are mutated back to the residues found in the original germline sequence from which the antibody was derived. In other embodiments, only certain residues are mutated back to the original germline sequence, *e.g.*, only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence (*i.e.*, a germline sequence that is different from the germline sequence from which the antibody was originally derived). Furthermore, the antibodies of the present invention may contain any combination of two or more germline mutations within the framework and/or CDR regions, *e.g.*, wherein certain individual residues are mutated to the corresponding residue of a particular germline sequence while certain other residues that differ from the original germline sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antibodies and antigen-binding fragments that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. The use of antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present invention.

[0067] The present invention also includes methods involving the use of anti-PCSK9 antibodies comprising variants of any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present invention includes the use of anti-PCSK9 antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, *e.g.*, 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein.

[0068] The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore™ system (Biacore Life Sciences division of GE Healthcare, Piscataway, NJ).

[0069] The term "K_D ", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

[0070] The term "epitope" refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. Epitopes may be either conformational or linear. A conformational epitope is produced by spatially juxtaposed amino

acids from different segments of the linear polypeptide chain. A linear epitope is one produced by adjacent amino acid residues in a polypeptide chain. In certain circumstances, an epitope may include moieties of saccharides, phosphoryl groups, or sulfonyl groups on the antigen.

[0071] According to certain embodiments, the anti-PCSK9 antibody used in the methods of the present invention is an antibody with pH-dependent binding characteristics. As used herein, the expression "pH-dependent binding" means that the antibody or antigen-binding fragment thereof exhibits "reduced binding to PCSK9 at acidic pH as compared to neutral pH" (for purposes of the present disclosure, both expressions may be used interchangeably). For example, antibodies "with pH-dependent binding characteristics" includes antibodies and antigen-binding fragments thereof that bind PCSK9 with higher affinity at neutral pH than at acidic pH. In certain embodiments, the antibodies and antigen-binding fragments of the present invention bind PCSK9 with at least 3, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, or more times higher affinity at neutral pH than at acidic pH.

[0072] According to this aspect of the invention, the anti-PCSK9 antibodies with pH-dependent binding characteristics may possess one or more amino acid variations relative to the parental anti-PCSK9 antibody. For example, an anti-PCSK9 antibody with pH-dependent binding characteristics may contain one or more histidine substitutions or insertions, *e.g.*, in one or more CDRs of a parental anti-PCSK9 antibody. Thus, according to certain embodiments of the present invention, methods are provided comprising administering an anti-PCSK9 antibody which comprises CDR amino acid sequences (*e.g.*, heavy and light chain CDRs) which are identical to the CDR amino acid sequences of a parental anti-PCSK9 antibody, except for the substitution of one or more amino acids of one or more CDRs of the parental antibody with a histidine residue. The anti-PCSK9 antibodies with pH-dependent binding may possess, *e.g.*, 1, 2, 3, 4, 5, 6, 7, 8, 9, or more histidine substitutions, either within a single CDR of a parental antibody or distributed throughout multiple (*e.g.*, 2, 3, 4, 5, or 6) CDRs of a parental anti-PCSK9 antibody. For example, the present invention includes the use of anti-PCSK9 antibodies with pH-dependent binding comprising one or more histidine substitutions in HCDR1, one or more histidine substitutions in HCDR2, one or more histidine substitutions in HCDR3, one or more histidine substitutions in LCDR1, one or more histidine substitutions in LCDR2, and/or one or more histidine substitutions in LCDR3, of a parental anti-PCSK9 antibody.

[0073] As used herein, the expression "acidic pH" means a pH of 6.0 or less (*e.g.*, less than about 6.0, less than about 5.5, less than about 5.0, etc.). The expression "acidic pH" includes pH values of about 6.0, 5.95, 5.90, 5.85, 5.8, 5.75, 5.7, 5.65, 5.6, 5.55, 5.5, 5.45, 5.4, 5.35, 5.3, 5.25, 5.2, 5.15, 5.1, 5.05, 5.0, or less. As used herein, the expression "neutral pH" means a pH of about 7.0 to about 7.4. The expression "neutral pH" includes pH values of about 7.0, 7.05, 7.1, 7.15, 7.2, 7.25, 7.3, 7.35, and 7.4.

Preparation of Human Antibodies

[0074] Methods for generating human antibodies in transgenic mice are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to human PCSK9.

[0075] Using VELOCIMMUNE® technology (see, for example, US 6,596,541, Regeneron Pharmaceuticals) or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to PCSK9 are initially isolated having a human variable region and a mouse constant region. The VELOCIMMUNE® technology involves generation of a transgenic mouse having a genome comprising human heavy and light chain variable regions operably linked to endogenous mouse constant region loci such that the mouse produces an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation. The DNA encoding the variable regions of the heavy and light chains of the antibody are isolated and operably linked to DNA encoding the human heavy and light chain constant regions. The DNA is then expressed in a cell capable of expressing the fully human antibody.

[0076] Generally, a VELOCIMMUNE® mouse is challenged with the antigen of interest, and lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. The lymphatic cells may be fused with a myeloma cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. DNA encoding the variable regions of the heavy chain and light chain may be isolated and linked to desirable isotypic constant regions of the heavy chain and light chain. Such an antibody protein may be produced in a cell, such as a CHO cell. Alternatively, DNA encoding the antigen-specific chimeric antibodies or the variable domains of the light and heavy chains may be isolated directly from antigen-specific lymphocytes.

[0077] Initially, high affinity chimeric antibodies are isolated having a human variable region and a mouse constant region. The antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc, using standard procedures known to those skilled in the art. The mouse constant regions are replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified IgG1 or IgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

[0078] In general, the antibodies that can be used in the methods of the present invention possess high affinities, as described above, when measured by binding to antigen either immobilized on solid phase or in solution phase. The mouse constant regions are replaced with desired human constant regions to generate the fully human antibodies of the invention. While

the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

[0079] Specific examples of human antibodies or antigen-binding fragments of antibodies that specifically bind PCSK9 which can be used in the context of the methods of the present invention include any antibody or antigen-binding fragment which comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1 and 11, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. Alternatively, specific examples of human antibodies or antigen-binding fragments of antibodies that specifically bind PCSK9 which can be used in the context of the methods of the present invention include any antibody or antigen-binding fragment which comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs 37, 45, 53, 61, 69, 77, 85, 93, 101, 109, 117, 125, 133, 141, 149, 157, 165, 173, 181, and 189, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. The antibody or antigen-binding fragment may comprise the three light chain CDRs (LCVR1, LCVR2, LCVR3) contained within a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6 and 15, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity. Alternatively, the antibody or antigen-binding fragment may comprise the three light chain CDRs (LCVR1, LCVR2, LCVR3) contained within a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs 41, 49, 57, 65, 73, 81, 89, 97, 105, 113, 121, 129, 137, 145, 153, 161, 169, 177, 185, and 193, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

[0080] In certain embodiments of the present invention, the antibody or antigen-binding fragment thereof comprises the six CDRs (HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3) from the heavy and light chain variable region amino acid sequence pairs (HCVR/LCVR) selected from the group consisting of SEQ ID NOs: 1/6 and 11/15. Alternatively, in certain embodiments of the present invention, the antibody or antigen-binding protein comprises the six CDRs (HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3) from the heavy and light chain variable region amino acid sequence pairs (HCVR/LCVR) selected from the group consisting of SEQ ID NOs:37/41, 45/49, 53/57, 61/65, 69/73, 77/81, 85/89, 93/97, 101/105, 109/113, 117/121, 125/129, 133/137, 141/145, 149/153, 157/161, 165/169, 173/177, 181/185, and 189/193.

[0081] In certain embodiments of the present invention, the anti-PCSK9 antibody, or antigen-binding fragment thereof, that can be used in the methods of the present invention has HCDR1/HCDR2/HCDR3/LCDR1/LCDR2/LCDR3 amino acid sequences selected from SEQ ID NOs: 2/3/4/7/8/10 (mAb316P) and 12/13/14/16/17/18 (mAb300N) (*See* US Patent App. Publ No. 2010/0166768).

[0082] In certain embodiments of the present invention, the antibody or antigen-binding fragment thereof comprises HCVR/LCVR amino acid sequence pairs selected from the group consisting of SEQ ID NOs: 1/6 and 11/15. Alternatively, in certain embodiments of the present invention, the antibody or antigen-binding protein comprises the heavy and light chain variable region amino acid sequence pairs (HCVR/LCVR) selected from the group consisting of SEQ ID NOs:37/41, 45/49, 53/57, 61/65, 69/73, 77/81, 85/89, 93/97, 101/105, 109/113, 117/121, 125/129, 133/137, 141/145, 149/153, 157/161, 165/169, 173/177, 181/185, and 189/193.

Pharmaceutical Compositions and Methods of Administration

[0083] The present invention includes methods which comprise administering a PCSK9 inhibitor to a high cardiovascular risk patient, wherein the PCSK9 inhibitor is contained within a pharmaceutical composition. The pharmaceutical compositions of the invention are formulated with suitable carriers, excipients, and other agents that provide suitable transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311.

[0084] Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, *e.g.*, encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al., 1987, J. Biol. Chem. 262:4429-4432). Methods of administration include, but are not limited to, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents.

[0085] A pharmaceutical composition of the present invention can be delivered

subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

[0086] Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Bergdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousand Oaks, CA), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.), and the HUMIRA™ Pen (Abbott Labs, Abbott Park IL), to name only a few.

[0087] In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, 1987, CRC Crit. Ref. Biomed. Eng. 14:201). In another embodiment, polymeric materials can be used; see, Medical Applications of Controlled Release, Langer and Wise (eds.), 1974, CRC Pres., Boca Raton, Florida. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose (see, *e.g.*, Goodson, 1984, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer, 1990, Science 249:1527-1533.

[0088] The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations

may be prepared by known methods. For example, the injectable preparations may be prepared, *e.g.*, by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

[0089] Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc.

Dosage

[0090] The amount of PCSK9 inhibitor (*e.g.*, anti-PCSK9 antibody) administered to a high cardiovascular risk subject according to the methods of the present invention is, generally, a therapeutically effective amount. As used herein, the phrase "therapeutically effective amount" means a dose of PCSK9 inhibitor that results in a detectable improvement (at least about 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, or more from baseline) in one or more parameters selected from the group consisting of LDL-C, ApoB, non-HDL-C, total cholesterol, HLDL-C, triglycerides, and Lp(a).

[0091] In the case of an anti-PCSK9 antibody, a therapeutically effective amount can be from about 0.05 mg to about 600 mg, *e.g.*, about 0.05 mg, about 0.1 mg, about 1.0 mg, about 1.5 mg, about 2.0 mg, about 10 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 75 mg, about 80 mg, about 90 mg, about 100 mg, about 110 mg, about 120 mg, about 130 mg, about 140 mg, about 150 mg, about 160 mg, about 170 mg, about 180 mg, about 190 mg, about 200 mg, about 210 mg, about 220 mg, about 230 mg, about 240 mg, about 250 mg, about 260 mg, about 270 mg, about 280 mg, about 290 mg, about 300 mg, about 310 mg, about 320 mg, about 330 mg, about 340 mg, about 350 mg, about 360 mg, about 370 mg, about 380 mg, about 390 mg, about 400 mg, about 410 mg, about 420 mg, about 430 mg, about 440 mg, about 450 mg, about 460 mg, about 470 mg, about 480 mg, about 490 mg, about 500 mg, about 510 mg, about 520 mg, about 530 mg, about 540 mg, about 550 mg, about 560 mg, about 570 mg, about 580 mg, about 590 mg, or about 600 mg, of the anti-PCSK9 antibody.

[0092] The amount of anti-PCSK9 antibody contained within the individual doses may be expressed in terms of milligrams of antibody per kilogram of patient body weight (*i.e.*, mg/kg). For example, the anti-PCSK9 antibody may be administered to a patient at a dose of about 0.0001 to about 10 mg/kg of patient body weight.

Combination Therapies

[0093] As described elsewhere herein, the methods of the present invention may comprise administering a PCSK9 inhibitor to a high cardiovascular risk patient in combination with the patient's previously prescribed stable daily maximum tolerated dose therapeutic statin regimen. According to certain embodiments of the present invention, additional therapeutic agents, besides a statin, may be administered to the patient in combination with the PCSK9 inhibitor. Examples of such additional therapeutic agents include *e.g.*, (1) an agent which inhibits cholesterol uptake and or bile acid re-absorption (*e.g.*, ezetimibe); (2) an agent which increase lipoprotein catabolism (such as niacin); and/or (3) activators of the LXR transcription factor that plays a role in cholesterol elimination such as 22-hydroxycholesterol.

Administration Regimens

[0094] According to certain embodiments of the present invention, multiple doses of a PCSK9 inhibitor (*i.e.*, a pharmaceutical composition comprising a PCSK9 inhibitor) may be administered to a subject over a defined time course (*e.g.*, on top of a daily therapeutic statin regimen). The methods according to this aspect of the invention comprise sequentially administering to a high cardiovascular risk subject multiple doses of a PCSK9 inhibitor. As used herein, "sequentially administering" means that each dose of PCSK9 inhibitor is administered to the subject at a different point in time, *e.g.*, on different days separated by a predetermined interval (*e.g.*, hours, days, weeks or months). The present invention includes methods which comprise sequentially administering to the high cardiovascular risk patient a single initial dose of a PCSK9 inhibitor, followed by one or more secondary doses of the PCSK9 inhibitor, and optionally followed by one or more tertiary doses of the PCSK9 inhibitor.

[0095] The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the individual doses of a pharmaceutical composition comprising a PCSK9 inhibitor. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of the PCSK9 inhibitor, but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of PCSK9

inhibitor contained in the initial, secondary and/or tertiary doses varies from one another (*e.g.*, adjusted up or down as appropriate) during the course of treatment. In certain embodiments, two or more (*e.g.*, 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as "loading doses" followed by subsequent doses that are administered on a less frequent basis (*e.g.*, "maintenance doses").

[0096] According to exemplary embodiments of the present invention, each secondary and/or tertiary dose is administered 1 to 26 (*e.g.*, 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, 15, 15½, 16, 16½, 17, 17½, 18, 18½, 19, 19½, 20, 20½, 21, 21½, 22, 22½, 23, 23½, 24, 24½, 25, 25½, 26, 26½, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of antigen-binding molecule which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

[0097] The methods according to this aspect of the invention may comprise administering to a high cardiovascular risk patient any number of secondary and/or tertiary doses of a PCSK9 inhibitor. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (*e.g.*, 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

[0098] In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the high cardiovascular risk patient 1 to 2, 4, 6, 8 or more weeks after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 1 to 2, 4, 6, 8 or more weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

[0099] The present invention includes administration regimens comprising an up-titration option (also referred to herein as "dose modification"). As used herein, an "up-titration option" means that, after receiving a particular number of doses of a PCSK9 inhibitor, if a patient has not achieved a specified reduction in one or more defined therapeutic parameters, the dose of the PCSK9 inhibitor is thereafter increased. For example, in the case of a therapeutic regimen

comprising administration of 75 mg doses of an anti-PCSK9 antibody to a high cardiovascular risk patient at a frequency of once every two weeks, if after 8 weeks (i.e., 5 doses administered at Week 0, Week 2 and Week 4, Week 6 and Week 8), the patient has not achieved a serum LDL-C concentration of less than 70 mg/dL, then the dose of anti-PCSK9 antibody is increased to *e.g.*, 150 mg administered once every two weeks thereafter (*e.g.*, starting at Week 12).

[00100] In certain embodiments, the anti-PCSK9 antibody is administered to a subject at a dose of about 150 mg every two weeks, for example for at least six doses.

[00101] In certain embodiments, the anti-PCSK9 antibody is administered to a subject at a dose of about 75 mg every two weeks, for example for at least six doses.

[00102] In some embodiments, the antibody is administered to a subject at a dose of about 75 mg every two weeks for 12 weeks, and the dose remains at 75 mg every two weeks if, at week 8, the subject's LDL-C value was less than 70 mg/dl.

[00103] In other embodiments, the antibody is administered to a subject at a dose of about 75 mg every two weeks for 12 weeks, and the dose is titrated up to about 150 mg every two weeks if, at week 8, the subject's LDL-C value was greater than or equal to 70 mg/dl.

EXAMPLES

[00104] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. Generation of Human Antibodies to Human PCSK9

[00105] Human anti-PCSK9 antibodies were generated as described in US Patent No. 8,062,640. The exemplary PCSK9 inhibitor used in the following Example is the human anti-PCSK9 antibody designated "mAb316P," also known as "Alirocumab." mAb316P has the following amino acid sequence characteristics: heavy chain variable region (HCVR) comprising SEQ ID NO:1; light chain variable domain (LCVR) comprising SEQ ID NO:6; heavy chain complementarity determining region 1 (HCDR1) comprising SEQ ID NO:2; HCDR2 comprising SEQ ID NO:3; HCDR3 comprising SEQ ID NO:4; light chain complementarity determining region 1 (LCDR1) comprising SEQ ID NO:7; LCDR2 comprising SEQ ID NO:8; and LCDR3 comprising SEQ ID NO:10.

Example 2: Efficacy and Safety of Alirocumab, a Fully Human PCSK9 Monoclonal Antibody ("mAb316P"), in High Cardiovascular Risk Patients with Uncontrolled Hypercholesterolemia on Maximally Tolerated Doses of Statins

INTRODUCTION

[00106] The objective of the COMBO I and II studies was to evaluate the efficacy and safety of alirocumab ("mAb316P") as add-on therapy to stable, maximally tolerated daily statin therapy, with or without other lipid-lowering therapy, in patients with hypercholesterolemia at high cardiovascular risk. COMBO I was placebo-controlled and patients may have received other lipid-lowering therapies in addition to statin therapy; COMBO II compared alirocumab with ezetimibe in patients receiving statin therapy (but no other lipid-lowering therapies). Each of the COMBO studies was randomized, double-blinded, and placebo-controlled. Both studies utilized a starting dose of alirocumab 75 mg every 2 weeks (Q2W; administered as a 1 ml solution via auto-injector). Patients with LDL-C levels ≥70 mg/dl after 8 weeks of treatment were up-titrated in a blinded manner at Week 12 to alirocumab 150 mg Q2W (also 1 ml auto-injector).

STUDY OBJECTIVES

[00107] The primary efficacy endpoint for each study was the difference between treatment arms in the percent change in LDL-C from baseline to Week 24.

[00108] The key secondary endpoints for each study were: percentage change in calculated LDL-C from baseline to Week 24 in the on-treatment population, using all low-density lipoprotein cholesterol (LDL-C) values during the efficacy treatment period (ITT estimand); percentage change in calculated LDL-C from baseline to Week 12 (ITT estimand); percentage change in calculated LDL-C from baseline to Week 12 (on-treatment estimand); percentage change in apoliprotein (Apo) B from baseline to Week 24 (ITT estimand); percentage change in Apo B from baseline to Week 24 (on-treatment estimand); percentage change in non high-density lipoprotein cholesterol (non-HDL-C) from baseline to Week 24 (ITT estimand); percentage change in non-HDL-C from baseline to Week 24 (on-treatment estimand); percentage change in total cholesterol from baseline to Week 24 (ITT estimand); percentage change in Apo B from baseline to Week 12 (ITT estimand); percentage change in non-HDL-C from baseline to Week 12 (ITT estimand); percentage change in total cholesterol from baseline to Week 12 (ITT estimand); percentage change in calculated LDL-C from baseline to Week 52 (ITT estimand); proportion of patients reaching calculated LDL-C <70 mg/dl (1.81 mmol/l) at Week 24 (ITT estimand); proportion of patients reaching calculated LDL-C <70 mg/dl (1.81 mmol/l) at Week 24 (on-treatment estimand); percentage change in lipoproten (a) (Lp(a)) from baseline to Week 24

(ITT estimand); percentage change in HDL-C from baseline to Week 24 (ITT estimand); percentage change in fasting triglycerides (TG) from baseline to Week 24 (ITT estimand); percentage change in Apo A1 from baseline to Week 24 (ITT estimand); percentage change in Lp(a) from baseline to Week 12 (ITT estimand); percentage change in HDL-C from baseline to Week 12 (ITT estimand); percentage change in fasting TG from baseline to Week 12 (ITT estimand); and percentage change in Apo A1 from baseline to Week 12 (ITT estimand). Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); TG, triglycerides.

STUDY DESIGN

[00109] COMBO I was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter, 52-week study. This study evaluated the efficacy and safety of alirocumab as add-on therapy to stable, maximally tolerated doses of daily statin, with or without other stable lipid lowering therapies, in high-risk patients with uncontrolled hypercholesterolemia (**Figure 1A**).

[00110] COMBO II was a Phase 3, randomized, double-blind, active-controlled, parallel-group, multinational 104-week study. Thestudy enrolled high-risk patients with uncontrolled hypercholesterolemia on stable, maximally tolerated daily statin therapy. Unlike COMBO I, with a placebo arm, COMBO II incorporated an active-treatment arm (ezetimibe) with double-dummy design (**Figure 1B**) and patients were not allowed to receive any other lipid lowering therapies besides statin and their randomized treatment.

PATIENT SELECTION

[00111] All patients in COMBO I and II had hypercholesterolemia and established CHD or CHD risk equivalents, with LDL-C inadequately controlled with a maximally tolerated daily dose of statin. In COMBO I only, patients were also permitted to receive other lipid lowering therapies on top of statin, provided both the statin and other lipid lowering therapies were at stable dose for at least 4 weeks (6 weeks for fenofibrate) prior to the screening visit; in COMBO II, statin dose was required to be stable for at least 4 weeks prior to the screening visit and other lipid lowering therapies were not permitted. At screening, patients either had LDL-C ≥70 mg/dl (≥1.81 mmol/l) with documented CVD or LDL-C ≥100 mg/dl (≥2.59 mmol/l) with no documented history of CVD.

[00112] The 'maximum tolerated dose' of statin was defined as either rosuvastatin 20 mg or 40 mg daily, atorvastatin 40 mg or 80 mg daily, or simvastatin 80 mg daily (if already on this dose for >1 year). However, patients not able to tolerate the above statin doses remained eligible for inclusion if they were on a lower dose of daily atorvastatin, rosuvastatin, or simvastatin provided that the investigator had a documented reason for not using the higher dose.

COMBO I

[00113] The inclusion criteria for the COMBO I study were as follows. Patients with hypercholesterolemia and established coronary heart disease (CHD) or CHD risk equivalents (see below for definitions) who are not adequately controlled with a maximally tolerated daily dose of statin with or without other lipid-lowering therapy (LLT), both at stable dose for at least 4 weeks prior to the screening visit (and 6 weeks for fenofibrate prior to the screening visit).

[00114] Definition of maximally tolerated dose (any of the following are acceptable): rosuvastatin 20 mg or 40 mg daily, atorvastatin 40 mg or 80 mg daily, or simvastatin 80 mg daily (if already on this dose for >1 year). Patients not able to be on any of the above statin doses were treated with the dose of daily atorvastatin, rosuvastatin, or simvastatin which is considered appropriate for the patient as per the investigator's judgment or concerns. Some examples of acceptable reasons for a patient taking a lower statin dose include: adverse effects on higher doses, advanced age, low body mass index (BMI), regional practices, local prescribing information, concomitant medications, and comorbid conditions such as impaired glucose tolerance/impaired fasting glucose.

[00115] Established CHD is defined as a documented history of CHD, including one or more of the following: acute myocardial infarction (MI), silent MI, unstable angina, coronary revascularization procedure (e.g., percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG] surgery), and clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging).

[00116] CHD risk equivalents includes one or more of the following 4 criteria: 1) documented peripheral arterial disease (PAD) (one of the following criteria [a, b, or c] must be satisfied): a) current intermittent claudication (muscle discomfort in the lower limb produced by exercise that is both reproducible and relieved by rest within 10 minutes) of presumed atherosclerotic origin together with ankle-brachial index equal to or less than 0.90 in either leg at rest, or b) history of intermittent together with endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease, or c) history of critical limb ischemia together with thrombolysis, endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease; 2) documented ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. Computed tomography (CT) or magnetic resonance imaging (MRI) must have been performed to rule out hemorrhage and non-ischemic neurological disease; 3) documented chronic kidney disease (CKD) as defined by estimated glomerular filtration rate (eGFR) of ≥30–<60 ml/min/1.73 m2 for 3 months or more, including the screening visit; and/or 4) known history of diabetes mellitus and 2 or more additional risk factors, including: a) history of hypertension (established on

antihypertensive medication), b) documented history of ankle-brachial index ≤0.90, c) documented history of microalbuminuria or macroalbuminuria or dipstick urinalysis at screening visit (Week -2) with >2+ protein, d) documented history of preproliferative or proliferative retinopathy or laser treatment for retinopathy, e) known family history of premature CHD (CHD in father or brother before 55 years of age; CHD in mother or sister before 65 years of age).

[00117] Patients who met all the above inclusion criteria were screened for the following exclusion criteria.

[00118] Exclusion criteria related to study methodology were as follows: Patients without established CHD or CHD risk equivalents; LDL-C <70 mg/dl (<1.81 mmol/l) at the screening visit in patients with an history of documented cardiovascular disease [CVD]); LDL-C <100 mg/dl (<2.59 mmol/l) at the screening visit in patients without history of documented CVD); those not on a stable dose of lipid lowering therapy (including statin) for at least 4 weeks and/or fenofibrate for at least 6 weeks, as applicable, prior to the screening visit and from screening to randomization; currently taking a statin other than simvastatin, atorvastatin, or rosuvastatin; simvastatin, atorvastatin, or rosuvastatin is not taken daily or not taken at a registered dose; daily doses above atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg (except for patients on simvastatin 80 mg for >1 year, who are eligible); use of fibrates, other than fenofibrate within 6 weeks of the screening visit or between screening and randomization visits; use of nutraceutical products or over-the-counter therapies that may affect lipids which have not been at a stable dose/amount for at least 4 weeks prior to the screening visit or between screening and randomization visits; use of red yeast rice products within 4 weeks of the screening visit or between screening and randomization visits; patients who have received plasmapheresis treatment within 2 months prior to the screening visit (Week -2), or have plans to receive it during the study; recent (within 3 months prior to the screening visit or between screening and randomization visits) MI, unstable angina leading to hospitalization, PCI, CABG, uncontrolled cardiac arrhythmia, stroke, transient ischemic attack, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease; planned to undergo scheduled PCI, CABG, carotid or peripheral revascularization during the study; systolic blood pressure (BP) >160 mmHg or diastolic BP >100 mmHg at screening visit or randomization visit; history of New York Heart Association (NYHA) Class III or IV heart failure within the past 12 months; known history of hemorrhagic stroke; age <18 years or legal age of majority at the screening visit, whichever is greater; patients not previously instructed on a cholesterol-lowering diet prior to the screening visit; newly diagnosed (within 3 months prior to randomization visit) or poorly controlled (glycated hemoglobin [HbA1c] >8.5% at the screening visit) diabetes; presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins (note: patients on thyroid replacement therapy can be included if the dosage has

been stable for at least 12 weeks prior to screening and between screening and randomization visits, and thyroid-stimulating hormone (TSH) level is within the normal range of the Central Laboratory at the screening visit); history of bariatric surgery within 12 months prior to the screening visit; unstable weight defined by a variation >5 kg within 2 months prior to the screening visit; known history of homozygous or heterozygous familial hypercholesterolemia (FH); known history of loss of function of proprotein convertase subtilisin kexin 9 (PCSK9) (i.e., genetic mutation or sequence variation); use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to randomization visit (note: topical, intra-articular, nasal, inhaled, and ophthalmic steroid therapies are not considered as 'systemic' and are allowed); use of continuous estrogen or testosterone hormone replacement therapy unless the regimen has been stable in the past 6 weeks prior to the screening visit (Week-2) and no plans to change the regimen during the study; history of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer; known history of HIV positivity; patients who have taken any investigational drugs other than the alirocumab training placebo kits within 1 month or 5 half-lives, whichever is longer; patients who have previously participated in any clinical trial of alirocumab or any other anti-PCSK9 therapy; patients who withdraw consent during the screening period (patients who are not willing to continue or fail to return).

[00119] Additional exclusion criteria were conditions/situations such as: any clinically significant abnormality identified at the time of screening that in the judgment of the investigator or any sub-investigator would preclude safe completion of the study or constrain endpoint assessment such as major systemic diseases or patients with short life expectancy; considered by the investigator or any sub-investigator as inappropriate for this study for any reason, e.g. deemed unable to meet specific protocol requirements, such as scheduled visits; deemed unable to administer or tolerate long-term injections based on the opinion of the patient or investigator; investigator or any sub-investigator, pharmacist, study coordinator, other study staff, or relative thereof directly involved in the conduct of the protocol, etc.; presence of any other conditions (e.g. geographic, social) actual or anticipated which the investigator feels would restrict or limit the patient's participation for the duration of the study.

[00120] Laboratory findings during the screening period (not including randomization assessments): positive test for hepatitis B surface antigen or hepatitis C antibody (confirmed by reflexive testing); positive serum beta-human chorionic gonadotropin (hCG) or urine pregnancy test (including Week 0) in women of childbearing potential; triglycerides >400 mg/dl (>4.52 mmol/l) (1 repeat assessment is allowed); eGFR <30 ml/min/1.73 m2; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 x upper limit of normal (ULN) (1 repeat

assessment is allowed); creatine phosphokinase (CPK) >3 x ULN (1 repeat assessment is allowed); thyroid stimulating hormone (TSH) <lower limit of normal (LLN) or >ULN.

[00121] Exclusion criteria related to background therapy were as follows. All contraindications to the background therapies or warning/precaution of use (when appropriate) as displayed in the respective National Product labeling.

[00122] Exclusion criteria related to alirocumab were as follows. Known hypersensitivity to monoclonal antibody therapeutics; pregnant or breast-feeding women; women of childbearing potential with no effective contraceptive method of birth control and/or who are unwilling or unable to be tested for pregnancy. Women of childbearing potential must have a confirmed negative pregnancy test at screening and randomization visits. They must use an effective contraceptive method throughout the study, and agree to repeat urine pregnancy test at designated visits. The applied methods of contraception have to meet the criteria for a highly effective method of birth control according to the note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. Postmenopausal women must be amenorrheic for at least 12 months.

COMBO II

[00123] The inclusion criteria for the COMBO II study were as follows. Patients with hypercholesterolemia and established CHD or CHD risk equivalents (see below for definitions) who are not adequately controlled with a maximally tolerated stable daily dose of statin for at least 4 weeks prior to the screening visit.

[00124] Definition of maximally tolerated dose (any of the following are acceptable): rosuvastatin 20 mg or 40 mg daily, atorvastatin 40 mg or 80 mg daily, and simvastatin 80 mg daily (if already on this dose for >1 year - see exclusion criterion). Patients not able to be on any of the above statin doses should be treated with the dose of daily atorvastatin, rosuvastatin, or simvastatin which is considered appropriate for the patient as per the investigator's judgment or concerns. Some examples of acceptable reasons for a patient taking a lower statin dose include: adverse effects on higher doses, advanced age, low BMI, regional practices, local prescribing information, concomitant medications, and comorbid conditions such as impaired glucose tolerance/impaired fasting glucose.

[00125] Established CHD includes one or more of the following: acute MI; silent MI; unstable angina; coronary revascularization procedure (e.g. PCI or CABG); clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography, or nuclear imaging).

[00126] CHD risk equivalents includes one or more of the following 4 criteria: 1) documented PAD (one of the following criteria [a, b, or c] must be satisfied): a) current intermittent claudication of resumed atherosclerotic origin together with ankle-brachial index equal to or less

than 0.90 in either leg at rest, or b) history of intermittent claudication together with endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease, or c) history of critical limb ischemia together with thrombolysis, endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease; 2) documented previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. CT or MRI must have been performed to rule out hemorrhage and non-ischemic neurological disease; 3) documented CKD as defined by eGFR ≥30– <60 ml/min/1.73 m2 for 3 months or more, including the screening visit; and/or 4) known history of diabetes mellitus and 2 or more additional risk factors: a) history of hypertension (established on antihypertensive medication), b) documented history of ankle-brachial index ≤0.90, c) documented history of microalbuminuria or macroalbuminuria or dipstick urinalysis at screening visit (Week -3) with >2+ protein, d) documented history of pre–proliferative or proliferative retinopathy or laser treatment for retinopathy, e) known family history of premature CHD (CHD in father or brother before 55 years of age; CHD in mother or sister before 65 years of age).

[00127] Patients who met all the above inclusion criteria were screened for the following exclusion criteria.

[00128] Exclusion criteria related to study methodology were as follows. Patients without established CHD or CHD risk equivalents; LDL-C <70 mg/dl (<1.81 mmol/l) at the screening visit in patients with an history of documented CVD; LDL-C <100 mg/dl (<2.59 mmol/l) at the screening visit in patients without history of documented CVD; change in statin dose or dose regimen from screening to randomization; currently taking a statin that is not simvastatin, atorvastatin, or rosuvastatin; simvastatin, atorvastatin, or rosuvastatin is not taken daily or not taken at a registered dose; daily doses above atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 40 mg (except for patients on simvastatin 80 mg for >1 year, who are eligible); use of cholesterol absorption inhibitor (i.e., ezetimibe), omega-3 fatty acid (at doses ≥1000 mg daily), nicotinic acid, bile acid-binding sequestrant, or red yeast rice products within the past 4 weeks prior to screening visit or between screening and randomization visits; use of fibrates in the past 6 weeks prior to screening visit; use of nutraceutical products or over-the-counter therapies that may affect lipids which have not been at a stable dose/amount for at least 4 weeks prior to the screening visit or between screening and randomization visits; patients who have received plasmapheresis treatment within 2 months prior to the screening visit, or have plans to receive it during the study; recent (within 3 months prior to the screening visit or between screening and randomization visits) MI, unstable angina leading to hospitalization, PCI, CABG, uncontrolled cardiac arrhythmia, stroke, transient ischemic attack, carotid revascularization, endovascular procedure or surgical intervention for peripheral vascular disease; planned to undergo

scheduled PCI, CABG, carotid or peripheral revascularization during the study; systolic BP >160 mmHg or diastolic BP >100 mmHg at screening visit or randomization visit; history of NYHA Class III or IV heart failure within the past 12 months; known history of hemorrhagic stroke; age <18 years or legal age of majority at the screening visit whichever is greater; patients not previously instructed on a cholesterol-lowering diet prior to the screening visit; newly diagnosed (within 3 calendar months prior to randomization visit) or poorly controlled (HbA1c >9% at the screening visit) diabetes; presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins (note: patients on thyroid replacement therapy can be included if the dosage has been stable for at least 12 weeks prior to screening and between screening and randomization visits, and TSH level is within the normal range of the Central Laboratory at the screening visit); history of bariatric surgery within 12 months prior to the screening visit; unstable weight defined by a variation >5 kg within 2 months prior to the screening visit; known history of homozygous or heterozygous FH; known history of loss of function of PCSK9 (i.e., genetic mutation or sequence variation); use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to randomization visit (note: topical, intra-articular, nasal, inhaled, and ophthalmic steroid therapies are not considered as 'systemic' and are allowed); use of continuous estrogen or testosterone hormone replacement therapy unless the regimen has been stable in the past 6 weeks prior to the screening visit and there are no plans to change the regimen during the study; history of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer; known history of a positive HIV test; patients who have taken any investigational drugs other than the alirocumab training placebo kits within 1 month or 5 half-lives, whichever is longer; patients who have been previously treated with at least 1 dose of alirocumab or any other anti-PCSK9 monoclonal antibody in other clinical trials; patients who withdraw consent during the screening period (patients who are not willing to continue or fail to return).

[00129] Additional exclusion criteria were conditions/situations such as any clinically significant abnormality identified at the time of screening that in the judgment of the investigator or any sub-investigator would preclude safe completion of the study or constrain endpoint assessment such as major systemic diseases; patients with short life expectancy; considered by the investigator or any sub-investigator as inappropriate for this study for any reason, e.g. deemed unable to meet specific protocol requirements such as scheduled visits; deemed unable to administer or tolerate long-term injections as per the patient or the investigator; investigator or any sub-investigator, pharmacist, study coordinator, other study staff or relative thereof directly involved in the conduct of the protocol, etc.; presence of any other conditions (e.g., geographic, social)

actual or anticipated, that the investigator feels would restrict or limit the patient's participation for the duration of the study.

[00130] Laboratory findings during the screening period (not including randomization assessments): positive test for Hepatitis B surface antigen or Hepatitis C antibody; positive serum beta-hCG or urine pregnancy test (including Week 0) in women of childbearing potential; triglycerides >400 mg/dl (>4.52 mmol/l) (1 repeat assessment is allowed); eGFR <30 ml/min/1.73 m2; ALT or AST >3 x ULN (1 repeat assessment is allowed); CPK >3 x ULN (one repeat assessment is allowed); TSH <LLN or >ULN (one repeat assessment is allowed).

[00131] Exclusion criteria related to the active comparator and mandatory background therapy were as follows. All contraindications to ezetimibe or warnings/precautions of use (when appropriate) as displayed in the respective National Product Labeling; all contraindications to the background statins or warning/precaution of use (when appropriate) as displayed in the respective National Product Labeling.

[00132] Exclusion criteria related to alirocumab were as follows. Known hypersensitivity to monoclonal antibody or any component of the drug product; pregnant or breast-feeding women; women of childbearing potential not protected by highly effective method(s) of birth control and/or who are unwilling or unable to be tested for pregnancy. Women of childbearing potential must have a confirmed negative pregnancy test at screening and randomization visits. They must use an effective contraceptive method throughout the entire duration of the study treatment, and for 10 weeks after the last intake of study medication (injection or capsule, whichever comes last), and agree to repeat urine pregnancy test at designated visits. (The applied methods of contraception have to meet the criteria for a highly effective method of birth control according to the "Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. Postmenopausal women must be amenorrheic for at least 12 months).

STUDY PROCEDURES

[00133] Patients meeting the inclusion criteria entered a screening period of up to 2 (COMBO I) or 3 (COMBO II) weeks prior to randomization. During screening, patients completed informed consent,inclusion/exclusion criteria were further assessed, patient information was collected and patients were trained in the use of the auto-injector device. In addition, vital signs were taken, a 12-lead electrocardiogram was performed, and fasting blood and urine samples were obtained for analysis. AEs were assessed from the screening visit throughout the study.

COMBO I

[00134] Eligible patients were randomized (2:1 alirocumab:placebo), with stratification by 1) prior history of myocardial infarction (MI) or ischemic stroke, and 2) intensity of statin treatment

to ensure balance between arms for these factors. After randomization, patients entered a double-blind treatment period of 52 weeks. In addition to existing statin and other existing lipid lowering therapies if appropriate, patients randomized to alirocumab received a 75-mg subcutaneous (SC) dose every 2 weeks (Q2W), administered as a single 1 ml injection utilizing an auto-injector, from randomization to Week 12. Patients randomized to placebo received a 1 ml SC placebo injection from an identical auto-injector.

[00135] At Week 12, patients randomized to alirocumab were up-titrated to 150 mg Q2W if the Week 8 LDL-C was ≥70 mg/dl (1.81 mmol/l). To maintain blinding, the patient and investigator were not informed of the Week 8 LDL-C levels (or any lipid values after randomization); continuation or up-titration of dose occurred in an automated and blinded manner. The 150 mg Q2W dose of alirocumab was also administered as a 1 ml solution in an auto-injector.

[00136] On-site patient assessments during the treatment period were scheduled at randomization and then Weeks 4, 8, 12, 16, 24, 36, and 52 (end of treatment visit) (**Figure 1A**). After the treatment period, there was an 8-week follow-up period.

COMBO II

[00137] Eligible patients were randomized (2:1 alirocumab:ezetimibe), with stratification for 1) prior history of MI or ischemic stroke, 2) intensity of statin treatment and 3) geographic region, to ensure balance between arms in these factors. After randomization, patients entered a double-blind, double-dummy treatment period of 104 weeks. Patients were randomized to either alirocumab 75 mg SC Q2W plus placebo for ezetimibe per os (PO) daily or placebo for alirocumab SC Q2W plus ezetimibe 10 mg PO daily. At Week 12, patients randomized to alirocumab were up-titrated to 150 mg Q2W if the Week 8 LDL-C was ≥70 mg/dl (1.81 mmol/l).

[00138] On-site patient assessments were scheduled at regular intervals from randomization to Week 104 (end of treatment visit) (**Figure 1B**). After the treatment period, there was an 8-week follow-up period.

COMBO I and II

[00139] In both studies, patients were asked to remain on a stable diet (National Cholesterol Education Program Adult Treatment Panel III therapeutic lifestyle changes diet or equivalent) and the daily statin dose should be stable throughout the entire study duration from screening to the follow-up visit. Modification to the statin (and in the case of COMBO I, other background lipid lowering therapy) was only allowed under special circumstances.

SAFETY ASSESSMENTS

[00140] Safety assessments during both studies were as follows. Safety was assessed through adverse event (AE) reporting (including adjudicated cardiovascular events), laboratory analyses, and vital signs measurement. Since the LDL-C-lowering effects of PCSK9 inhibition on top of a statin are unknown, a number of AEs were defined as being of special interest and were monitored, including alanine aminotransferase abnormalities, allergic events, hemolytic anemia, pregnancy, overdose with study drug, neurologic events, ophthalmic events, and local injection site reactions. AEs were determined to be of special interest based on review of previous clinical trials, correspondence with regulatory authorities and the Data Monitoring Committee, the use of a monoclonal antibody in this study, and the route of drug administration.

[00141] Safety Analyses were as follows. AEs (including adjudicated cardiovascular events), laboratory parameters, and vital signs were reported descriptively, based on the safety population (all randomized patients who received at least 1 dose or partial dose of study treatment). The safety analysis focused on the treatment-emergent AE period defined as the time from the first double-blind dose to the last double-blind dose of the investigational product + 70 days (10 weeks).

[00142] Safety: Occurrence of treatment emergent adverse events (TEAEs) reported by the patient or noted by the investigator, serious adverse events (SAEs), TEAEs leading to treatment discontinuation, AEs of special interest (local Injection site reactions, allergic events, selected neurological events and cardiovascular events with adjudication result), occurrence of PCSA (potentially clinically significant abnormalities) in laboratory parameters, specific analysis for diabetes or impaired glucose control and patients with 2 consecutives LDL-C < 25 mg/dL (O.65 mmol/L).

COMBO I: STATISTICAL METHODS

Sample size determination

[00143] The final total sample size was 306, with a randomization ratio of 2:1 (alirocumab 204: placebo 102).

Combo I: Analysis populations

[00144] The primary efficacy analysis population was the intent-to-treat (ITT) population, defined as all randomized patients who had an evaluable primary endpoint, that is, those with an available baseline calculated LDL-C value, and at least one available calculated LDL-C value within one of the analysis windows up to Week 24 (including all calculated LDL-C on-treatment and off-treatment).

[00145] The secondary efficacy analysis population was the modified intent-to-treat (mITT) population, defined as all randomized patients who took at least one dose or part of a dose of

the double-blind investigational medicinal product (IMP) and who had an available calculated LDL-C value at baseline and at least one within one of the analysis windows up to Week 24 during the efficacy treatment period. The efficacy treatment period was defined as the time from the first double-blind IMP administration up to 21 days after the last double-blind injection.

[00146] The safety population included all randomized patients who received at least one dose or part of a dose of the double-blind IMP.

Combo I: Efficacy analyses

[00147] Primary analyses of efficacy endpoints were conducted using an ITT approach (based on the ITT population defined above), including all lipid data, regardless of whether the patient was continuing therapy or not. This corresponds to ITT estimands, defined for primary and key secondary endpoints. In addition, analyses were also conducted using an on-treatment approach (based on the mITT population defined above), including lipid data collected during the efficacy treatment period. This corresponds to on-treatment estimands of key secondary endpoints.

[00148] The ITT approach analyzed all patients, irrespective of their adherence to the treatment; it assessed the benefit of the treatment strategy and reflected as much as possible the effect in a population of patients. The on-treatment approach analyzed the effect of treatment, restricted to the period during which patients actually received the treatment. It assessed the benefit that a treatment would achieve in patients adherent to treatment up to the considered time point.

[00149] Efficacy analyses were performed according to treatment as-randomized.

[00150] All measurements, scheduled or unscheduled, fasting or not fasting, were assigned to analysis windows in order to provide an assessment for Week 4 to Week 52 time points.

[00151] With regards to the primary efficacy analysis (ITT approach), the percent change in calculated LDL-C from baseline to Week 24 was analyzed using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available from Week 4 to Week 52 analysis windows were used and missing data were accounted for by the MMRM. The model included the fixed categorical effects of treatment group (placebo versus alirocumab), randomization strata (as per IVRS), time point (Week 4 to Week 52), treatment-by-time point interaction and strata-by-time point interaction, as well as, the continuous fixed covariates of baseline LDL-C value and baseline value-by-time- point interaction. This model provided baseline adjusted least-squares means (LSmeans) estimates at Week 24 for both treatment groups with their corresponding 95% confidence interval. To compare the alirocumab to the placebo group, an appropriate statement was used to test the differences of these estimates at the 5% alpha level.

[00152] A hierarchical procedure has been defined to test key secondary endpoints while controlling for multiplicity (using above order of key secondary endpoints). The first key secondary endpoint was the percent change in calculated LDL-C from baseline to Week 24 using an on-treatment approach.

[00153] Continuous secondary variables anticipated to have a normal distribution (i.e., lipids other than TG and Lp(a)) were analyzed using the same MMRM model as for the primary endpoint. Continuous endpoints anticipated to have a non-normal distribution (i.e., TG and Lp(a)) were analyzed using multiple imputation approach for handling of missing values followed by robust regression model with endpoint of interest as response variable using M-estimation (using SAS ROBUSTREG procedure) with treatment group, randomization strata (as per IVRS) and corresponding baseline value(s) as effects to compare treatment effects. Combined estimate for mean in both treatment groups, as well as the differences of these estimates, with their corresponding SEs, 95% CIs and p-value were provided (through SAS MIANALYZE procedure).

[00154] Binary secondary efficacy endpoints were analyzed using multiple imputation approach for handling of missing values followed by stratified logistic regression with treatment group as main effect and corresponding baseline value(s) as covariate, stratified by randomization factors (as per IVRS). Combined estimates of odds ratio versus placebo, 95% CI, and p-value were provided (through SAS MIANALYZE procedure).

Combo I: Safety analyses

[00155] Safety analyses were descriptive, performed on the safety population according to treatment actually received. For analysis of TEAE and PCSA, the safety analysis focused on the TEAE period defined as the time from the first dose of double-blind IMP up to 70 days after the last double-blind injection. Analyses of laboratory data and vital signs overtime were performed on the period up to 21 days after the last IMP injection.

COMBO I: RESULTS

Patient Accountability

[00156] Of the 316 randomized patients, two patients in the alirocumab group were not treated, and therefore were not included in the safety population. Five randomized patients were not included in the ITT population (no LDL-C value within one analysis window through Week 24). Seven randomized patients were excluded from the mITT population (patients excluded from the ITT population and patients with no LDL-C value within one of the analysis window up to Week 24 during the efficacy treatment period).

Table 1 - Analysis populations

	Placebo	Alirocumab 75 Q2W/Up150 Q2W	All
Randomized population	107 (100%)	209 (100%)	316 (100%)
Efficacy populations			
Intent-to-Treat (ITT)	106 (99.1%)	205 (98.1%)	311 (98.4%)
Modified Intent-to-Treat (mITT)	105 (98.1%)	204 (97.6%)	309 (97.8%)
Safety population	107	207	314

Note: The safety population patients are tabulated according to treatment actually received (as treated).
For the other populations, patients are tabulated according to their randomized treatment.

[00157] In the alirocumab group, among the 191 patients who received at least one injection after Week 12, 32 (16.8%) patients received automatic up-titration at Week 12 from alirocumab 75 mg Q2W to 150 mg Q2W in a blinded manner.

COMBO I: Study disposition

[00158] Of 640 patients screened for eligibility, 316 were subsequently randomized to alirocumab (209) or placebo (107). Of the 316 randomized patients, 2 (alirocumab) were not treated; 231 patients (73.1%) completed the 52 week study treatment (75 placebo; 156 alirocumab); 311 (98.4%) comprised the ITT population (106 placebo; 205 alirocumab, 5 patients with missing LDL-C levels); 309 patients comprised the on-treatment population (105 placebo; 204 alirocumab) and 314 patients comprised the safety population (107 placebo; 207 alirocumab).

[00159] Over the 52-week double-blind period, adherence to study medication (receipt of ≥80% scheduled injections) was similar between treatment groups (98% alirocumab; 99% placebo). Based on week 8 LDL-C levels ≥70 mg/dL, 32/191 patients (16.8%) had their alirocumab dose increased to 150 mg subcutaneously every 2 weeks at week 12 (among patients with at least 1 injection after week 12).

[00160] The double-blind IMP was prematurely discontinued before Week 52 for 32 (29.9%) randomized patients in the placebo group and 51 (24.4%) randomized patients in the alirocumab group. The main reasons for study treatment discontinuation were "other reasons" and adverse events. These "other reasons" included the following: patient did not meet criteria for completion of treatment due to either missed / out of window Week 50 injection or out of window Week 52 visit (17 patients), subject withdrawal was not otherwise specified (8 patients), site closure (4 patients), sudden death / death (3 patients) (there was no decision of investigator to stop the treatment prior death), miscellaneous (2 patients).

COMBO I: Summary of Population Characteristics

[00161] Demographics characteristics, disease characteristics and lipid parameters at baseline were similar in the alirocumab group as compared to the placebo group. Baseline demographics characteristics are set forth in **Table 2**. Baseline lipid medication and lipid levels are set forth in **Table 3**. The definition of CHD included acute myocardial infarction (MI), silent MI, unstable angina, coronary revascularization, or clinically significant CHD diagnosed by invasive or non-invasive testing. CHD risk equivalents included peripheral arterial disease, ischemic stroke, chronic kidney disease (estimated glomerular filtration rate ≥30 to <60 mL/min/1.73 m^2 for ≥3 months), or diabetes mellitus in combination with 2 or more additional risk factors (hypertension, ankle-brachial index ≤0.90, micro- or macroalbuminuria, dipstick urinalysis with >2+ protein, retinopathy, or family history of premature CHD [<55 years in father/brother or <65 years in mother/sister]).

[00162] There were numerically higher proportions of female patients and patients with type 2 diabetes in the alirocumab group. Similarly, a higher percentage of patients in the placebo group were using other LLTs in addition to statin (49.5% versus 38.3% in the alirocumab group). However, these differences between the treatment groups were not found to be statistically significant.

[00163] All patients but one were treated with a statin, 57.6% receiving high intensity statin (atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily) and 8.2% receiving ezetimibe in addition to the statin. Mean (SD) calculated LDL-C at baseline was 102.2 (31.6) mg/dL (2.646 (0.820) mmol/L). Approximately 78% of the randomized population had a coronary heart disease (CHD) history (**Table 5**).

[00164] Exposure to injections was similar across treatment groups with a mean exposure of 46 weeks. In the alirocumab group, among the 191 patients who received at least one injection after Week 12, 32 (16.8%) patients received automatic up-titration at Week 12 from alirocumab 75 mg Q2W to 150 mg Q2W in a blinded manner.

Table 2 - Baseline demographic characteristics

Characteristic	Alirocumab (N=209)	Placebo (N=107)	P-value vs placebo†
Age, years, mean (SD)	63.0 (9.5)	63.0 (8.8)	0.77
Male, % (n)	62.7% (131)	72.0% (77)	0.11
Race			0.61
White, % (n)	81.3% (170)	82.2% (88)	
Black or African-American	16.3% (34)	15.9% (17)	
Ethnicity			0.44
Hispanic/Latino	12.0% (25)	8.4% (9)	
BMI, kg/m2, mean (SD)	32.6 (6.3)	32.0 (7.0)	0.23
CHD history, % (n)	78.5% (164)	77.6% (83)	0.97
Hypertension, % (n)	88.5% (185)	88.8% (95)	0.91
Type 2 diabetes, % (n)	45.0% (94)	39.3% (42)	0.39

All patients were on background maximally tolerated statin ±other LLT. †*P*-values comparing baseline data between treatment groups are provided for descriptive purpose, as a screening tool, using Fisher exact test for qualitative data and the asymptotic one-way ANOVA test for Wilcoxon scores (Kruskal-Wallis test) for continuous data.

Table 3 – Baseline lipid medication and lipid levels

All patients on background maximally tolerated statin ± other LLT	Alirocumab (N=209)	Placebo (N=107)	P-value vs placebo†
Any statin†,% (n)	99.5% (208)	100% (107)	1.00
High dose statin at screening††, % (n)	61.7% (129)	64.5% (69)	0.71
Other LLT‡, % (n)	38.3% (80)	49.5% (53)	0.07
Ezetimibe, % (n)	7.2% (15)	10.3% (11)	0.46
LDL-C, calculated	100.2 (29.5)	106.0 (35.3)	0.42
Median (IQR)	98.0 (81.0:114.0)	97.0 (86.0:120.0)	
LDL-C, measured‡‡	94.8 (29.3)	100.2 (34.4)	0.41
Non-HDL-C	130.0 (34.0)	133.4 (39.8)	0.72
Apo B	90.8 (21.4)	91.4 (24.1)	0.98
Lp(a), median (IQR)	31.0 (8:81)	38.0 (10:70)	0.70

Fasting TGs, median (IQR)	130.0 (92:189)	123.0 (95:177)	0.57
HDL-C	48.3 (14.4)	48.8 (12.7)	0.46

Table 4 - Disease characteristics and other relevant baseline data – Randomized population

	Placebo (N=107)	Alirocumab 75 Q2W/Up150 Q2W (N=209)	All (N=316)
Time from hypercholesterolemia diagnosis (years)			
Number	107	209	316
Mean (SD)	10.60 (7.98)	11.20 (8.01)	10.99 (7.99)
Median	9.70	10.05	9.84
Min : Max	0.2 : 42.4	0.4 : 46.1	0.2 : 46.1
Fredrickson classification of Hyperlipoproteinemia			
Number	99	188	287
IIa	42 (39.3%)	83 (39.7%)	125 (39.6%)
IIb	56 (52.3%)	96 (45.9%)	152 (48.1%)
IV	1 (0.9%)	9 (4.3%)	10 (3.2%)

5 **[00165]** There were 4 patients without fully documented CHD or CHD risk equivalents.

Table 5 - Medical history of specific interest: cardiovascular history and risk factors - Randomized population

	Placebo (N=107)	Alirocumab 75 Q2W/Up150 Q2W (N=209)	All (N=316)
Any cardiovascular history/risk factors	106 (99.1%)	206 (98.6%)	312 (98.7%)
Coronary heart disease [a]	83 (77.6%)	164 (78.5%)	247 (78.2%)
Acute Myocardial Infarction	47 (43.9%)	83 (39.7%)	130 (41.1%)
Silent Myocardial Infarction	2 (1.9%)	12 (5.7%)	14 (4.4%)
Unstable Angina	20 (18.7%)	34 (16.3%)	54 (17.1%)
Coronary Revascularization Procedures	60 (56.1%)	133 (63.6%)	193 (61.1%)
Other Clinically Significant CHD [b]	14 (13.1%)	38 (18.2%)	52 (16.5%)
CHD associated with 1 or more comorbidity (among hypertension, diabetes or moderate CKD) and/or associated with other CVD (ischemic stroke, PAD)	76 (71.0%)	150 (71.8%)	226 (71.5%)

Coronary heart disease risk equivalents [a]	51 (47.7%)	85 (40.7%)	136 (43.0%)
Ischemic Stroke	6 (5.6%)	21 (10.0%)	27 (8.5%)
Peripheral Arterial Disease	8 (7.5%)	3 (1.4%)	11 (3.5%)
Moderate Chronic Kidney Disease	24 (22.4%)	37 (17.7%)	61 (19.3%)
Known history of diabetes mellitus AND 2 or more additional risk factors	25 (23.4%)	42 (20.1%)	67 (21.2%)
At least 2 CHD risk equivalents or 1 CHD risk equivalent associated with hypertension or diabetes	50 (46.7%)	82 (39.2%)	132 (41.8%)

Note: A patient can be counted in several categories.
[a] according to the items pre-listed in the e-CRF.
[b] diagnosed by invasive or non-invasive testing.
PAD defined as Intermittent claudication TOGETHER WITH ankle-brachial index ≤ 0.90 OR TOGETHER WITH peripheral revascularization procedure/surgery OR critical limb ischemia TOGETHER WITH peripheral revascularization procedure/surgery or thrombolysis.

Table 6 - Medical history of specific interest: other medical history of special interest - Randomized population

	Placebo (N=107)	Alirocumab 75 Q2W/Up150 Q2W (N=209)	All (N=316)
Other medical history of special interest	102 (95.3%)	202 (96.7%)	304 (96.2%)
Hypertension [a]	95 (88.8%)	185 (88.5%)	280 (88.6%)
Type 1 Diabetes [a]	0	0	0
Type 2 Diabetes [a]	42 (39.3%)	94 (45.0%)	136 (43.0%)
Family history of premature coronary heart disease [a]	37 (34.6%)	72 (34.4%)	109 (34.5%)
Family history of type 2 diabetes [a]	31 (29.0%)	60 (28.7%)	91 (28.8%)
Menopause (females) [a]	23 (21.5%)	67 (32.1%)	90 (28.5%)

[a] according to the items pre-listed in the e-CRF.
Note: A patient can be counted in several categories.

Table 7 - Background LMT at randomization – Randomized population

	Placebo (N=107)	Alirocumab 75 Q2W/Up150 Q2W (N=209)	All (N=316)
Any statin	107 (100%)	208 (99.5%)	315 (99.7%)
Taking high intensity statin	60 (56.1%)	122 (58.4%)	182 (57.6%)
Atorvastatin daily dose (mg)	34 (31.8%)	70 (33.5%)	104 (32.9%)
10	0	2 (1.0%)	2 (0.6%)
20	5 (4.7%)	4 (1.9%)	9 (2.8%)
40	17 (15.9%)	40 (19.1%)	57 (18.0%)
80	12 (11.2%)	24 (11.5%)	36 (11.4%)
Other doses	0	0	0
Rosuvastatin daily dose (mg)	34 (31.8%)	66 (31.6%)	100 (31.6%)
5	1 (0.9%)	3 (1.4%)	4 (1.3%)
10	1 (0.9%)	5 (2.4%)	6 (1.9%)

	Placebo (N=107)	Alirocumab 75 Q2W/Up150 Q2W (N=209)	All (N=316)
20	16 (15.0%)	33 (15.8%)	49 (15.5%)
40	15 (14.0%)	25 (12.0%)	40 (12.7%)
Other doses	1 (0.9%)	0	1 (0.3%)
Simvastatin daily dose (mg)	39 (36.4%)	71 (34.0%)	110 (34.8%)
10	0	1 (0.5%)	1 (0.3%)
20	9 (8.4%)	16 (7.7%)	25 (7.9%)
40	21 (19.6%)	45 (21.5%)	66 (20.9%)
80	9 (8.4%)	8 (3.8%)	17 (5.4%)
Other doses	0	1 (0.5%)	1 (0.3%)
Any LMT other than statins[a]	53 (49.5%)	80 (38.3%)	133 (42.1%)
Any LMT other than nutraceuticals	46 (43.0%)	68 (32.5%)	114 (36.1%)
Ezetimibe	11 (10.3%)	15 (7.2%)	26 (8.2%)
Nutraceuticals	9 (8.4%)	15 (7.2%)	24 (7.6%)

[a] in combination with statins or not.
High intensity statin corresponds to atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily.

Table 8 - Lipid efficacy parameters at baseline – Quantitative summary in conventional units – Randomized population

	Placebo (N=107)	Alirocumab 75 Q2W/Up150 Q2W (N=209)	All (N=316)
Calculated LDL-C (mg/dL)			
Number	107	209	316
Mean (SD)	106.0 (35.3)	100.2 (29.5)	102.2 (31.6)
Median	97.0	98.0	97.0
Q1 : Q3	86.0 : 120.0	81.0 : 114.0	82.0 : 115.0
Min : Max	61 : 256	33 : 240	33 : 256
Measured LDL-C (mg/dL)			
Number	70	138	208
Mean (SD)	100.2 (34.4)	94.8 (29.3)	96.6 (31.2)
Median	92.0	91.0	91.5
Q1 : Q3	75.0 : 119.0	76.0 : 109.0	75.5 : 110.0
Min : Max	53 : 238	28 : 239	28 : 239
Non-HDL-C (mg/dL)			
Number	107	209	316
Mean (SD)	133.4 (39.8)	130.0 (34.0)	131.1 (36.0)
Median	125.0	125.0	125.0
Q1 : Q3	106.0 : 147.0	103.0 : 149.0	104.5 : 148.5
Min : Max	79 : 304	61 : 270	61 : 304

Total-C (mg/dL)			
Number	107	209	316
Mean (SD)	182.3 (39.6)	178.3 (35.7)	179.7 (37.0)
Median	176.0	173.0	174.0
Q1 : Q3	156.0 : 204.0	151.0 : 199.0	154.0 : 200.5
Min : Max	119 : 348	119 : 316	119 : 348
HDL-C (mg/dL)			
Number	107	209	316
Mean (SD)	48.8 (12.7)	48.3 (14.4)	48.5 (13.8)
Median	47.0	46.0	46.0
Q1 : Q3	40.0 : 55.0	39.0 : 56.0	39.0 : 55.0
Min : Max	26 : 98	17 : 109	17 : 109
Fasting TGs (mg/dL)			
Number	106	209	315
Mean (SD)	140.3 (64.3)	151.2 (93.2)	147.5 (84.6)
Median	123.0	130.0	127.0
Q1 : Q3	95.0 : 177.0	92.0 : 189.0	92.0 : 186.0
Min : Max	52 : 431	35 : 999	35 : 999
Lipoprotein-(a)(mg/dL)			
Number	101	191	292
Mean (SD)	49.4 (48.3)	49.6 (51.0)	49.5 (50.0)
Median	38.0	31.0	33.0
Q1 : Q3	10.0 : 70.0	8.0 : 81.0	9.5 : 79.5
Min : Max	2 : 184	2 : 248	2 : 248
Apo-B (mg/dL)			
Number	101	191	292
Mean (SD)	91.4 (24.1)	90.8 (21.4)	91.0 (22.3)
Median	88.0	87.0	87.5
Q1 : Q3	76.0 : 103.0	75.0 : 105.0	76.0 : 105.0
Min : Max	50 : 194	51 : 166	50 : 194
Apo-A1 (mg/dL)			
Number	101	191	292
Mean (SD)	145.1 (23.7)	143.1 (25.0)	143.8 (24.5)
Median	141.0	142.0	141.5
Q1 : Q3	129.0 : 161.0	125.0 : 157.0	128.0 : 158.0
Min : Max	96 : 217	69 : 262	69 : 262

Apo-B/Apo-A1 (ratio)			
Number	101	191	292
Mean (SD)	0.647 (0.207)	0.653 (0.192)	0.651 (0.197)
Median	0.620	0.620	0.620
Q1 : Q3	0.520 : 0.720	0.520 : 0.760	0.520 : 0.740
Min : Max	0.30 : 1.52	0.30 : 1.70	0.30 : 1.70
Total-C/HDL-C (ratio)			
Number	107	209	316
Mean (SD)	3.934 (1.199)	3.931 (1.211)	3.932 (1.205)
Median	3.711	3.750	3.750
Q1 : Q3	3.052 : 4.474	3.096 : 4.500	3.076 : 4.474
Min : Max	2.05 : 7.91	1.87 : 10.59	1.87 : 10.59

[00166] The collection of measured LDL-C was not planned in the initial protocol and was added in an amendment. Therefore measured LDL-C values are available for fewer patients compared to calculated LDL-C values.

COMBO I: Dosage and duration

[00167] Exposure to injections was similar across treatment groups with a mean exposure of approximately 46 weeks. In the alirocumab group, among the 191 patients who received at least one injection after Week 12, 32 (16.8%) patients received automatic up-titration at Week 12 from alirocumab 75 mg Q2W to 150 mg Q2W in a blinded manner.

COMBO I: Primary efficacy endpoint

[00168] The ITT analysis includes all LDL-C values collected on-treatment and off-treatment up to Week 52. The primary endpoint (percent change in calculated LDL-C from baseline to Week 24) analysis is provided based on a MMRM model on the ITT population, using LS means estimates at Week 24. Sixteen (7.8%) patients in the alirocumab group and 9 (8.5%) patients in the placebo group did not have a calculated LDL-C value at Week 24. These missing values were accounted for by the MMRM model.

[00169] Results of the primary endpoint analysis are presented in **Table 9**, in mmol/L and mg/dL.

[00170] A statistically significant decrease in percent change in LDL-C from baseline to Week 24 was observed in the alirocumab group (LS mean versus baseline - 48.2%) compared to the placebo group (LS mean versus baseline -2.3%) (LS mean difference vs. placebo of - 45.9%, $p < 0.0001$).

[00171] In the alirocumab group, LDL-C reduction from baseline was observed from Week 4 to Week 52.

[00172] A slight decrease in LDL-C reduction over time was observed in alirocumab group (LS mean versus baseline at Week 52 of -42.5 versus -48.2 at Week 24) probably due to the higher number of treatment discontinuations at Week 52 compared to Week 24 and as a result, higher number of post-treatment LDL-C included at Week 52 (8.8% at Week 52 versus 3.9% at Week 24).

[00173] Indeed the treatment effect is stable from Week 24 to Week 52 when only on-treatment LDL-C are considered (see **Figure 3**) whereas a slight decrease is observed when post-treatment LDL-C are also included (see **Figure 2**).

Table 9 - Percent change from baseline in calculated LDL-C and other lipid parameters at Week 24 (ITT or On-Treatment analyses as indicated)

All patients on maximally tolerated statin ± other LLT	Alirocumab	Placebo	Alirocumab vs. placebo		
			LS mean difference (SE) %	95% CI	p-value
ITT	n = 205	n = 106			
Baseline, mg/dL (Mean (SD))	100.3 (29.7)	104.6 (32.3)			
Median	98.0	96.5			
Min:Max	33:240	61:243			
LS mean (SE) change from baseline at week 24 (%)	-48.2 (1.9)	-2.3 (2.7)	-45.9 (3.3)	-52.5 to -39.3	< 0.0001
On-treatment	n = 204	n = 105			
Baseline, mg/dL	99.8 (29.0)	105.0 (32.2)			
Min:Max	33:240	61:243			
LS mean (SE) change from baseline at week 24 (%)	-50.7 (1.9)	-0.8 (2.6)	-49.9 (3.2)	-56.2 to -43.6	< 0.0001

Table 10 - Calculated LDL-C over time - ITT analysis - ITT population

	Placebo (N=106)			Alirocumab 75 Q2W/Up150 Q2W (N=205)		
Calculated LDL-C	Value	Change from baseline	Percent change from baseline	Value	Change from baseline	Percent change from baseline
LS Mean (SE) (mmol/L)						
Baseline [a]	2.709 (0.081)	NA	NA	2.597 (0.054)	NA	NA
Week 4	2.524 (0.062)	-0.112 (0.062)	-2.3 (2.4)	1.327 (0.045)	-1.308 (0.045)	-50.6 (1.7)
Week 8	2.592 (0.060)	-0.043 (0.060)	-0.4 (2.4)	1.264 (0.043)	-1.372 (0.043)	-51.6 (1.7)
Week 12	2.643 (0.071)	0.007 (0.071)	1.1 (2.5)	1.428 (0.051)	-1.207 (0.051)	-46.3 (1.8)
Week 16	2.595 (0.069)	-0.041 (0.069)	0.6 (2.6)	1.291 (0.049)	-1.345 (0.049)	-50.5 (1.9)
Week 24	2.533 (0.073)	-0.102 (0.073)	-2.3 (2.7)	1.332 (0.052)	-1.303 (0.052)	-48.2 (1.9)
Week 36	2.464 (0.078)	-0.172 (0.078)	-5.3 (3.4)	1.411 (0.057)	-1.225 (0.057)	-44.8 (2.5)
Week 52	2.586 (0.090)	-0.049 (0.090)	0.5 (3.6)	1.483 (0.063)	-1.153 (0.063)	-42.5 (2.5)
LS Mean (SE) (mg/dL)						
Baseline [a]	104.6 (3.1)	NA	NA	100.3 (2.1)	NA	NA
Week 4	97.5 (2.4)	-4.3 (2.4)	-2.3 (2.4)	51.2 (1.7)	-50.5 (1.7)	-50.6 (1.7)
Week 8	100.1 (2.3)	-1.7 (2.3)	-0.4 (2.4)	48.8 (1.7)	-53.0 (1.7)	-51.6 (1.7)
Week 12	102.0 (2.8)	0.3 (2.8)	1.1 (2.5)	55.1 (2.0)	-46.6 (2.0)	-46.3 (1.8)
Week 16	100.2 (2.7)	-1.6 (2.7)	0.6 (2.6)	49.8 (1.9)	-51.9 (1.9)	-50.5 (1.9)
Week 24	97.8 (2.8)	-3.9 (2.8)	-2.3 (2.7)	51.4 (2.0)	-50.3 (2.0)	-48.2 (1.9)
Week 36	95.1 (3.0)	-6.6 (3.0)	-5.3 (3.4)	54.5 (2.2)	-47.3 (2.2)	-44.8 (2.5)
Week 52	99.9 (3.5)	-1.9 (3.5)	0.5 (3.6)	57.2 (2.4)	-44.5 (2.4)	-42.5 (2.5)

[a] Baseline is described using means and standard errors.

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction

MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

COMBO I: Key secondary efficacy endpoints

[00174] Table 11 summarizes analysis results on key secondary endpoints in the hierarchical order. All key secondary endpoints are statistically significant according to the hierarchical testing procedure up to HDL-C endpoint at Week 24 (ITT estimand) included. Statistical significance was not reached for Fasting TG endpoint at week 24 (ITT estimand).

Table 11 – Key secondary efficacy endpoints

Endpoint	Analysis	Results	P-value
Calculated LDL-C - Percent change from baseline to Week 24	On-treatment	LS mean difference vs. placebo of -49.9%	<0.0001
Calculated LDL-C - Percent change from baseline to Week 12	ITT	LS mean difference vs. placebo of -47.4%	<0.0001
Calculated LDL-C - Percent change from baseline to Week 12	On-treatment	LS mean difference vs. placebo of -49.3%	<0.0001
Apo-B - Percent change from baseline to Week 24	ITT	LS mean difference vs. placebo of -35.8%	<0.0001
Apo-B - Percent change from baseline to Week 24	On-treatment	LS mean difference vs. placebo of -37.5%	<0.0001
Non-HDL-C - Percent change from baseline to Week 24	ITT	LS mean difference vs. placebo of -37.5%	<0.0001
Non-HDL-C - Percent change from baseline to Week 24	On-treatment	LS mean difference vs. placebo of -40.4%	<0.0001
Total-C - Percent change from baseline to Week 24	ITT	LS mean difference vs. placebo of -25%	<0.0001
Apo-B - Percent change from baseline to Week 12	ITT	LS mean difference vs. placebo of -38.2%	<0.0001
Non-HDL-C - Percent change from baseline to Week 12	ITT	LS mean difference vs. placebo of -40.1%	<0.0001
Total-C - Percent change from baseline to Week 12	ITT	LS mean difference vs. placebo of -26.4%	<0.0001
Calculated LDL-C - Percent change from baseline to Week 52	ITT	LS mean difference vs. placebo of -43%	<0.0001
Proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24	ITT	combined estimate for odds-ratio vs. placebo of 38.5	<0.0001
Proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24	On-treatment	combined estimate for odds-ratio vs. placebo of 50	<0.0001
Lp(a) - Percent change from baseline to Week 24	ITT	combined estimate for adjusted mean difference vs. placebo of -14.6%	<0.0001
HDL-C - Percent change from baseline to Week 24	ITT	LS mean difference vs. placebo of 7.3%	0.0001
Fasting TGs - Percent change from baseline to Week 24	ITT	combined estimate for adjusted mean difference vs. placebo of -1.2%	0.7597

[00175] The on-treatment analysis of LDL-C percent change from baseline to Week 24 shows consistent results with the ITT analysis with a LS mean difference vs. placebo of -49.9% in the on-treatment analysis versus - 45.9% in the ITT analysis. Indeed, few patients had LDL-C values collected post-treatment (ie more than 21 days after last injection) at Week 24: 5 patients (4.7%) in the placebo group and 8 patients (3.9%) in the alirocumab group.

[00176] A statistically significant decrease in percent change in LDL-C from baseline to Week 12 (i.e. before possible up-titration) in the ITT analysis was observed in the alirocumab group (LS mean versus baseline - 46.3%) compared to the placebo group (LS mean versus baseline + 1.1%) (LS mean difference vs. placebo of - 47.4%, $p < 0.0001$). The results obtained with the on-treatment analysis were similar.

[00177] Thirty-nine (19.5%) patients experienced two consecutive calculated LDL-C values <25 mg/dL. No particular safety concern has been observed in these 39 patients.

Table 12 - Number (%) of patients with 2 consecutive LDL-C < 25mg/dL (<0.65 mmol/L) during the treatment period– Safety population

	Placebo (N=107)	Alirocumab 75 Q2W/Up150 Q2W (N=207)
Patients with 2 consecutive calculated LDL-C value <25 mg/dL [1]	0/104	39/200 (19.5%)
Time to the first calculated LDL-C value < 25 mg/dL (weeks) [2]		
Number	0	39
Mean (SD)		11.48 (9.72)
Median		8.00
Min : Max		3.9 : 36.3
Patients with 2 consecutive calculated LDL-C value <15 mg/dL [1]	0/104	9/200 (4.5%)
Time to the first calculated LDL-C value < 15 mg/dL (weeks) [2]		
Number	0	9
Mean (SD)		12.51 (6.83)
Median		13.57
Min : Max		4.1 : 23.9

The number (n) represents the subset of the total number of patients who met the criteria
The denominator (/N) within a treatment group is the number of patients for the treatment group who had at least two calculated LDL-C values assessed at least 21 days apart in the efficacy period
[1] 2 consecutive values are considered if spaced out by at least 21 days
[2] First calculated LDL-C value <25 or <15 mg/dL among the first 2 consecutive calculated LDL-C values <25 or <15 mg/dL per patient

COMBO I: Summary Efficacy Results

[00178] At Week 24, the percent change from baseline in calculated LDL-C in the ITT population was significantly greater in the alirocumab group (LS mean versus baseline - 48.2%)

compared to the placebo group (LS mean versus baseline -2.3%) (LS mean difference vs. placebo of -45.9%, p < 0.0001) (see **Table 9**). The on-treatment analysis of LDL-C percent change from baseline to Week 24 shows consistent results with the ITT analysis with a LS mean difference vs. placebo of -49.9% in the on-treatment analysis (p<0.0001) (see **Table 9**).

[00179] At Week 12, before possible up-titration from 75 mg to 150 mg, statistical significance was also reached in the ITT population (LS mean versus baseline -46.3% and + 1.1%, for alirocumab and placebo groups respectively, LS mean difference vs. placebo of -47.4%; p <0.0001) (see **Table 11**).

[00180] In the alirocumab group, LDL-C reduction from baseline was observed from Week 4 to Week 52 (see **Table 10**). A slight decrease over time in LDL-C reduction was observed in alirocumab group (LS mean versus baseline at Week 52 of -42.5% versus -48.2% at Week 24) probably due to the higher number of treatment discontinuations at Week 52 compared to Week 24 and as a result, higher number of post-baseline LDL-C included at Week 52 (8.8% at Week 52 versus 3.9% at Week 24). Measured LDL-C results (beta-quantification) were consistent with those for calculated LDL-C. The results of a sensitivity analysis of the primary endpoint, using a pattern-mixture-model were consistent with the ITT analysis. Specifically, in the ITT group the combined estimate for LS mean (SE) change from baseline at week 24 (%) was -44.2 (2.1 for the alirocumab group and -1.5 (3.0) for the placebo group. The LS mean difference (SE) % for alirocumab vs. placebo was -42.7 (3.7) (95% CI of -49.9 to -35.4; p< 0.0001). The sensitivity analysis was conducted to further evaluate the impact of missing data on the primary endpoint. In this analysis, missing calculated LDL cholesterol values during the “on-treatment” period were multiply imputed using a model assuming Missing At Random and missing calculated LDL cholesterol values during the post-treatment period were multiply imputed using random draws from a normal distribution, with mean equal to subject’s own baseline value.

[00181] **Figure 4** shows LDL-C levels over time for alirocumab-treated patients with/without dose increase at week 12. In patients with dose increase, LDL-C was reduced by an additional mean 22.8% (SD 27.1) at week 24 compared with week 12. Among the 32 patients (16.8%) with alirocumab dose increase at week 12 (based on LDL-C at week 8 ≥70 mg/dL), achieved LDL-C was comparable at weeks 24, 36 and 52 to that observed among patients in whom no dose increment was performed (week 8 LDL-C <70 mg/dL).

[00182] The relative proportions of patients achieving LDL-C <70 mg/dL (<1.81 mmol/L) at week 24 among the ITT (75.0%) and on-treatment (77.5%) populations were significantly greater with alirocumab than placebo (9.0% and 8.0% respectively, p < 0.0001).

[00183] All key secondary endpoints including Apo B, non-HDL-C, Total-C, Lp(a), HDL-C at various time points were statistically significant according to the hierarchical testing procedure except for Fasting TG endpoint at week 24 (ITT estimand) (see **Table 11**). Significant

reductions from baseline to week 24 following therapy with alirocumab (vs. placebo) were observed in non-HDL-C (–39.1 [1.8] % alirocumab, –1.6 [2.5] % placebo), apolipoprotein B (–36.7 [1.6] % alirocumab, –0.9 [2.3] % placebo), total cholesterol (–27.9 [1.3] % alirocumab, –2.9 [1.8] % placebo) and lipoprotein(a) (–20.5 [2.0] % alirocumab, –5.9 [2.8] % placebo) (all $p < 0.0001$ alirocumab vs. placebo). No significant change was observed in triglyceride levels while a significant and directionally divergent increase in HDL-C (apolipoprotein A1) was observed the alirocumab group; 3.5 (1.1) % vs. –3.8 (1.5) % for placebo ($p < 0.0001$; see **Table 9**).

[00184] The percentage changes from baseline in LDL-C at week 24 by demographic characteristics and patient subgroups for alirocumab versus placebo are set forth in **Figure 5**. All of the 95% confidence intervals for differences in percent LDL-C reduction between alirocumab and placebo within each level of the subgroups defined by age, gender, race, ethnicity, intensity of background statin therapy, other LLT therapy (in addition to statin) and history of myocardial infarction or ischemic stroke are completely to the left of the no effect line. The treatment effect of was seen at every level within each subgroup. In addition, tests for interaction by age, gender, race, ethnicity, intensity of background statin therapy did not reach significance at the 5% level and hence demonstrate consistency of treatment effect within these subgroups. However, patients with other LLT therapy (in addition to statin) and those with a history of myocardial infarction or ischemic stroke demonstrated a relatively greater treatment effect (p-value for interaction 0.012 and 0.018 respectively; see **Figure 5**).

[00185] Two consecutive calculated LDL-C values <25 mg/dL (< 0.65 mmo/L) were observed in 39 (19.5%) patients. No particular safety concern has been observed in these patients.

COMBO I: Summary Safety Results

[00186] The percentages of patients who experienced treatment emergent adverse event (TEAE), serious TEAE, TEAE leading to death and TEAE leading to treatment discontinuation were similar between treatment groups. Safety data collected until last patient visit at week 52 is set forth in **Table 13.**

[00187] Of the 209 patients originally randomized to alirocumab, 2 did not receive treatment, meaning that the safety population comprised 207 patients for alirocumab. All randomized patients in the placebo arm received their allocated treatment, hence the safety population was 107 patients for placebo.

Table 13 - Adverse Events and Safety Laboratory Values (Safety Population)

No. (%) of patients All patients on maximally tolerated statin ± other LLT	**Alirocumab** (n = 207)	**Placebo** (n = 107)
TEAEs	157 (75.8)	81 (75.7)
Treatment-emergent SAEs	26 (12.6)	14 (13.1)
TEAE leading to death	2 (1.0)	3 (2.8)
TEAEs leading to discontinuation	13 (6.3)	8 (7.5)
TEAEs by preferred term occurring in ≥5% of patients in either group		
Upper respiratory tract infection	16 (7.7)	11 (10.3)
Arthralgia	8 (3.9)	8 (7.5)
Nasopharyngitis	15 (7.2)	5 (4.7)
Urinary tract infection	13 (6.3)	4 (3.7)
Dizziness	11 (5.3)	6 (5.6)
Non-cardiac chest pain	2 (1.0)	7 (6.5)
Sinusitis	11 (5.3)	4 (3.7)
Injection site reaction	11 (5.3)	3 (2.8)
AEs of special interest*		
Local injection site reactions	11 (5.3)	3 (2.8)
Potential general allergic reaction events	18 (8.7)	7 (6.5)
Neurological events	5 (2.4)	2 (1.9)
Neurocognitive disorders	0 (0)	1 (0.9)
Cardiovascular TEAEs confirmed by adjudication		
Any patients with treatment emergent cardiovascular events confirmed by adjudication**	– 6 (2.9)	3 (2.8)
Coronary heart disease death (including undetermined cause)	1 (0.5)	1 (0.9)
Non-fatal myocardial infarction	1 (0.5)	1 (0.9)
Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	– 2 (1.0)	0
Unstable angina requiring hospitalization	0	0
Congestive heart failure requiring hospitalization	0	1 (0.9)
Ischemia driven coronary revascularization procedure	3 (1.4)	1 (0.9)

*Company MedDRA Queries (CMQ). **One patient in the placebo group and 1 patient in the alirocumab group each experienced 2 events that were positively adjudicated: Non-fatal myocardial infarction and ischemia-driven coronary revascularization procedure. TEAEs are adverse events that developed, worsened, or became serious during the TEAE period (time from first to last injection of study treatment + 70 days). SAEs = serious adverse events; TEAEs = treatment-emergent adverse events; ULN = upper limit of normal.

The most frequently reported and noteworthy SOC with a higher frequency in alirocumab group as compared to placebo group were: "Infections and infestations": 37.2% in the alirocumab group vs 27.1% in the placebo group; “Metabolism and nutrition disorder”: 10.1% in the alirocumab group vs 5.6% in the placebo; and "Cardiac disorders": 8.2% in the alirocumab group vs 4.7% in the placebo group, although no striking imbalance was noted for a particular event, it is noteworthy that 9 ischemic events occurred in alirocumab group vs 3 in placebo group. When referring to the results of adjudication, 5 patients experienced cardiovascular events that were positively adjudicated (2.4%) against 2 patients in the placebo group (1.9%).

[00188] Among the SOCs with a lower frequency, the SOC "eye disorders" was observed in 4.3% of patients in the alirocumab group vs 0.9% in the placebo group with no imbalance for a particular event.

[00189] Two (1.0%) and 3 (2.8%) deaths occurred during treatment period in alirocumab (myocardial infarction and pulmonary embolism) and placebo (esophageal adenocarcinoma, dementia and sudden cardiac death) groups respectively. In addition one post-treatment death (aggravation of coronary artery disease) occurred in alirocumab group.

[00190] Adjudicated CV events include all CV AEs positively adjudicated. The adjudication categories are the following: CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, and ischemia-driven coronary revascularization procedure [PCI, CABG].

[00191] SAEs were reported by 12.6% patients in alirocumab and 13.1% in placebo during the TEAE period. There is no particular clinical pattern among SAEs preferred terms which were individually reported with low frequency.

[00192] No specific pattern was noted among the TEAEs leading to permanent treatment discontinuation.

[00193] Among the events of interest, no particular signal was detected for TEAEs related to neurological events and neurocognitive disorders.

[00194] Fourteen patients, 11 (5.3%) in alirocumab group and 3 (2.8%) in placebo group) experienced a treatment-emergent local injection site reaction. Among general allergic reactions, an imbalance was noted for asthma with 5 (2.4%) cases including 2 serious cases in the alirocumab group versus no case in the placebo group.

[00195] Five (7.4%) patients in the alirocumab group and 1 (2.7%) patient in the placebo group reported as being impaired glucose control at baseline were classified as diabetic in the TEAE period. No patient classified as having a normal status at baseline became diabetic.

[00196] Imbalance for PCSA values was noted for decrease of hemoglobin from baseline ≥20 g/L (6.3% in the alirocumab group vs 3.9% in placebo group) and for new cases of erythrocytes

values ≥6 Tera/L (2.5% in the alirocumab group vs no case in the placebo group). No other relevant abnormalities for PCSA was observed.

[00197] LDL-C levels <25 mg/dL (on 2 consecutive measurements ≥21 days apart) were observed in 39 alirocumab treated patients, of whom 9 had LDL-C <15 mg/dL. The overall adverse event profile appears similar to those patients without such low LDL-C levels, although there were slightly higher rates of myalgia (7.7% in patients with LDL-C <25 mg/dL vs 3.4% in the alirocumab group as a whole, 3.7% with placebo), osteoarthritis (7.7% vs 3.9% and 4.7%), arthralgia (5.1% vs 3.9% and 7.5%) and invertebral disc protusion (5.1% vs 1.0% and 0%).

[00198] Antibodies to alirocumab were detected in a total of 18 patients (of 296 evaluable patients; 6.1%), with antibodies to alirocumab being detected at baseline in five total patients subsequently randomized to alirocumab (3/197; 1.5%) or placebo (2/99; 2.0%). Treatment-emergent low antibody positivity was observed in 13/197 (6.6%) alirocumab-treated patients with no titers exceeding 240. In seven of these patients, the antibodies were transient and resolved despite continued alirocumab treatment. The median time to detection of antibodies to alirocumab was 12 weeks; no specific clinical events were observed in antibody positive patients. However, the presence of anti-alirocumab antibodies had no observed effect on safety and efficacy.

COMBO I: Overall results

[00199] In this population of patients, with HeFH and high baseline levels of LDL-C despite maximally tolerated statin (with or without other LLT), the following observations were made: 1) self-administered alirocumab produced significantly greater LDL-C reductions versus placebo at Week 24; 2) the absolute mean decrease from baseline in LDL-C was –90.8 mg/dL at Week 24 with alirocumab versus –15.5 mg/dL with placebo; 3) the mean achieved LDL-C levels were 107 mg/dL at Week 24 with alirocumab versus 182 mg/dL with placebo; 4) 32% of alirocumab patients reached LDL-C <70 mg/dL despite baseline LDL-C >190 mg/dL; 5) 57% of alirocumab patients achieved LDL-C <100 mg/dL at Week 24; and 6) alirocumab was generally well tolerated and TEAEs were generally comparable with the placebo group.

COMBO II: STATISTICAL METHODS

Sample size determination

[00200] The final total sample size was 660 with a randomization ratio 2:1 (alirocumab 440: ezetimibe 220).

Combo II: Timing of analyses

[00201] The first step analysis included efficacy endpoints up to Week 52 (final efficacy analysis) and interim safety analysis, which was performed on all safety data up to the common

study cut-off date (last patient Week 52 visit). Analysis of lipid data beyond Week 52 was descriptive. These results are presented herein.

[00202] The second step (final) analysis will be conducted at the end of the study and will consist of the final analysis of efficacy endpoints up to Week 104 and final safety analysis.

Combo II: Analysis populations

[00203] The primary efficacy analysis population was the intent-to-treat (ITT) population, defined as all randomized patients who had an evaluable primary endpoint, that is, those with an available baseline calculated LDL-C value, and at least one available calculated LDL-C value within one of the analysis windows up to Week 24 (including all calculated LDL-C on-treatment and off-treatment).

[00204] The secondary efficacy analysis population was the modified intent-to-treat (mITT) population, defined as all randomized patients who took at least one dose or part of a dose of the double-blind investigational medicinal product (IMP) and who had an available calculated LDL-C value at baseline and at least one within one of the analysis windows up to Week 24 during the efficacy treatment period. The efficacy treatment period was defined as the time period from the first double-blind IMP administration (capsule or injection, whichever comes first) up to the day of last injection + 21 days or the day of last capsule intake + 3 days, whichever comes first.

[00205] The safety population included all randomized patients who received at least one dose or part of a dose of the double-blind IMP.

Combo II: Efficacy analyses

[00206] Primary analyses of efficacy endpoints were conducted using an ITT approach (based on the ITT population defined above), including all lipid data, regardless of whether the patient was continuing therapy or not. This corresponds to ITT estimands, defined for primary and key secondary endpoints. In addition, analyses were also conducted using an on-treatment approach (based on the mITT population defined above), including lipid data collected during the efficacy treatment period. This corresponds to on-treatment estimands of key secondary endpoints.

[00207] The ITT approach analyzed all patients, irrespective of their adherence to the treatment; it assessed the benefit of the treatment strategy and reflected as much as possible the effect in a population of patients. The on-treatment approach analyzed the effect of treatment, restricted to the period during which patients actually received the treatment. It assessed the benefit that a treatment would achieve in patients adherent to treatment up to the considered time point.

[00208] Efficacy analyses were performed according to treatment as-randomized.

[00209] All measurements, scheduled or unscheduled, fasting or not fasting, were assigned to analysis windows in order to provide an assessment for Week 4 to Week 104 time points.

[00210] With regards to the primary efficacy analysis (ITT approach), the percent change in calculated LDL-C from baseline to Week 24 was analyzed using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available from Week 4 to Week 52 analysis windows were used and missing data were accounted for by the MMRM. The model included the fixed categorical effects of treatment group (ezetimibe versus alirocumab), randomization strata (as per IVRS), time point (Week 4 to Week 52), treatment-by-time point interaction and strata-by-time point interaction, as well as, the continuous fixed covariates of baseline LDL-C value and baseline value-by-time- point interaction. This model provided baseline adjusted least-squares means (LSmeans) estimates at Week 24 for both treatment groups with their corresponding 95% confidence interval. To compare the alirocumab to the ezetimibe group, an appropriate statement was used to test the differences of these estimates at the 5% alpha level.

[00211] A hierarchical procedure has been defined to test key secondary endpoints while controlling for multiplicity (using above order of key secondary endpoints). The first key secondary endpoint was the percent change in calculated LDL-C from baseline to Week 24 using an on-treatment approach.

[00212] Continuous secondary variables anticipated to have a normal distribution (i.e., lipids other than TGs and Lp(a)) were analyzed using the same MMRM model as for the primary endpoint. Continuous endpoints anticipated to have a non-normal distribution (i.e., TGs and Lp(a)) were analyzed using multiple imputation approach for handling of missing values followed by robust regression model with endpoint of interest as response variable using M-estimation (using SAS ROBUSTREG procedure) with treatment group, randomization strata (as per IVRS) and corresponding baseline value(s) as effects to compare treatment effects. Combined estimate for mean in both treatment groups, as well as the differences of these estimates, with their corresponding SEs, 95% CIs and p-value were provided (through SAS MIANALYZE procedure).

[00213] Binary secondary efficacy endpoints were analyzed using multiple imputation approach for handling of missing values followed by stratified logistic regression with treatment group as main effect and corresponding baseline value(s) as covariate, stratified by randomization factors (as per IVRS). Combined estimates of odds ratio versus ezetimibe, 95% CI, and p-value were provided (through SAS MIANALYZE procedure).

<u>Combo II: Safety analyses</u>

[00214] Safety analyses were descriptive, performed on the safety population according to treatment actually received. For analysis of TEAE and PCSA, the safety analysis focused on

the TEAE period defined as the time from the first dose of double-blind IMP administration (capsule or injection, whichever comes first) up to 70 days after the last double-blind injection. Analyses of laboratory data and vital signs overtime were performed on the period up to 21 days after the last IMP injection.

COMBO II: RESULTS

Patient Accountability

[00215] Of the 720 randomized patients, all patients were treated and were therefore included in the safety population.

[00216] Thirteen randomized patients (12 in the alirocumab group and 1 in the ezetimibe group) were not included in the ITT population (no LDL-C value within one of the analysis windows through Week 24).

[00217] Twenty-one randomized patients were excluded from the mITT population (patients excluded from the ITT population and patients with no LDL-C value within one of the analysis windows up to Week 24 during the efficacy treatment period).

[00218] In the alirocumab group, among the 446 patients who received at least one injection after Week 12, 82 (18.4%) patients received automatic up-titration at Week 12 from alirocumab 75 mg Q2W to 150 mg Q2W in a blinded manner.

Table 14 - Analysis populations

	Ezetimibe 10	**Alirocumab 75 Q2W/Up150 Q2W**	**All**
Randomized population	241 (100%)	479 (100%)	720 (100%)
Efficacy populations			
Intent-to-Treat (ITT)	240 (99.6%)	467 (97.5%)	707 (98.2%)
Modified Intent-to-Treat (mITT)	235 (97.5%)	464 (96.9%)	699 (97.1%)
Safety population	241	479	720
Note: The safety population patients are tabulated according to treatment actually received (as treated). For the other populations, patients are tabulated according to their randomized treatment.			

Combo II: Study disposition

[00219] Study disposition, exposure and safety analyses were assessed using all data up to the study common cut-off date (defined as the date of the last patient's Week 52 visit). Therefore,

this first step analysis includes data beyond Week 52 for some patients. The results presented herein are from this first step analysis, and include efficacy data up to week 52, safety data up to week 52-102 (including all data collected until the last patient visit at W52).

[00220] No randomized patients completed the 104 weeks double-blind study treatment period and 612 (85.0%) randomized patients (N=406 in the alirocumab arm and N=206 in the ezetimibe arm) were treatment ongoing at the time of the first-step analysis cut-off date.

[00221] The double-blind IMP was prematurely discontinued before Week 104 for 73 (15.2%) randomized patients in the alirocumab group (including 71 patients who discontinued before Week 52) and 35 (14.5%) randomized patients in the ezetimibe group (including 33 patients who discontinued before Week 52).

[00222] The main reasons for study treatment discontinuation were adverse event and other reasons. The category "other" represented the most frequently reported and included the following: patient did not meet protocol inclusion/exclusion criteria (3 patients), subject withdrawal for personal reasons (14 patients), sudden death / death (5 patients) (there was no decision of investigator to stop the treatment prior death), lost to follow-up (1 patient). In this first step analysis, final results are available for the primary efficacy endpoint at Week 24 and key secondary efficacy endpoints assessed at Week 12, Week 24 and Week 52. At Week 24, the primary efficacy endpoint was available for 428 (91.6%) in the alirocumab and 221 (92.1%) in the ezetimibe groups. At Week 52, the primary efficacy endpoint was available for 414 (88.7%) in the alirocumab and 211 (87.9%) in the ezetimibe groups.

[00223] The primary endpoint was missing for 58 patients (39 patients (8.4%) in the alirocumab and 19 patients (7.9%) in the ezetimibe groups). At the Week 24 visit, the reasons for missingness were as follows: 29 samples not done due to earlier study discontinuation; 8 samples done outside analysis time window; 9 missing samples while visit Week 24 was done; 12 samples done but measurement could not be done (lipemia, insufficient quantity, TGs > 400 mg/dL [> 4.52 mmol/L], sample lost).

COMBO II: Demographics and baseline characteristics

[00224] Demographic characteristics, disease characteristics and lipid parameters at baseline were generally similar in the alirocumab group as compared to the ezetimibe group. For the alirocumab group (N=479), the age (mean years (SD)) was 61.7 (9.4), the percentage of males was 75.2% (N=360), the percentage white race was 84.3% (N=404), the percentage black or African American race was 4.4% (N=21), the percentage of other races was 11.3% (N=54), and the BMI (mean kg/m^2 (SD)) was 30.0 (5.4). For the ezetimibe group (N=241), the age (mean years (SD)) was 61.3 (9.2), the percentage of males was 70.5% (N=170), the percentage white

race was 85.5% (N=206), the percentage black or African American race was 2.9% (N=7), the percentage of other races was 11.6% (N=28), and the BMI (mean kg/m^2 (SD)) was 30.3 (5.1).

[00225] Baseline characteristics of the alirocumab and ezetimibe groups are set forth in **Tables 15-19**. Mean (SD) baseline LDL-C was 107.3 (35.7) mg/dL (2.778 (0.926) mmol/L). The HbA_{1c} (mean (SD), %) was 6.05 (0.75) for the alirocumab group and 6.07 (0.77) for the ezetimibe group. Approximately 90% of the randomized population had a history of CHD (i.e., at least one of the 5 below subcategories for CHD) and the remaining patients had CHD risk equivalents (**Table 16**), except for 2 patients, in the alirocumab group, who had no fully documented CHD or CHD risk equivalents. Globally 30% had a history of diabetes. All patients but one were treated with a statin, 66.7% receiving high intensity statin (atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily) and 2.1% receiving simvastatin 80 mg daily.

[00226] In summary, 1112 high cardiovascular risk patients were screened, 720 of whom were eligible and willing to participate in the study. Of these, 479 were randomly assigned to alirocumab and 241 to ezetimibe. The mean (SD) age was 61.6 (9.3) years, 73.6% of participants were men, 90.1% had coronary heart disease, 30.7% had type 2 diabetes, the mean (SD) baseline calculated LDL-C concentration was 107.3 (35.7) mg/dL, and 66.7% were taking high-intensity statin treatment (i.e. atorvastatin 40/80 mg/day or rosuvastatin 20/40 mg/day). Fifteen patients were on simvastatin 80 mg. Baseline characteristics were balanced between the two groups.

Table 15 - Disease characteristics and other relevant baseline data – Randomized population

	Ezetimibe 10 (N=241)	**Alirocumab 75 Q2W/Up150 Q2W (N=479)**	**All (N=720)**
Time from hypercholesterolemia diagnosis (years)			
Number	240	479	719
Mean (SD)	8.81 (7.62)	9.43 (7.23)	9.22 (7.36)
Median	7.48	7.89	7.85
Min : Max	0.1 : 53.9	0.1 : 46.8	0.1 : 53.9
Fredrickson classification of Hyperlipoproteinemia			
Number	185	369	554
IIa	113 (46.9%)	232 (48.4%)	345 (47.9%)
IIb	72 (29.9%)	137 (28.6%)	209 (29.0%)
IV	0	0	0

Table 16 - Medical history of specific interest: cardiovascular history and risk factors - Randomized population

	Ezetimibe 10 (N=241)	Alirocumab 75 Q2W/Up150 Q2W (N=479)	All (N=720)
Any cardiovascular history/risk factors	241 (100%)	477 (99.6%)	718 (99.7%)
Coronary heart disease [a]	212 (88.0%)	437 (91.2%)	649 (90.1%)
Acute Myocardial Infarction	139 (57.7%)	277 (57.8%)	416 (57.8%)
Silent Myocardial Infarction	4 (1.7%)	11 (2.3%)	15 (2.1%)
Unstable Angina	46 (19.1%)	106 (22.1%)	152 (21.1%)
Coronary Revascularization Procedures	165 (68.5%)	330 (68.9%)	495 (68.8%)
Other Clinically Significant CHD [b]	82 (34.0%)	184 (38.4%)	266 (36.9%)
CHD associated with 1 or more comorbidity (among hypertension, diabetes or moderate CKD) and/or associated with other CVD (ischemic stroke, PAD)	178 (73.9%)	366 (76.4%)	544 (75.6%)
Coronary heart disease risk equivalents [a]	72 (29.9%)	151 (31.5%)	223 (31.0%)
Ischemic Stroke	20 (8.3%)	40 (8.4%)	60 (8.3%)
Peripheral Arterial Disease	11 (4.6%)	24 (5.0%)	35 (4.9%)
Moderate Chronic Kidney Disease	23 (9.5%)	61 (12.7%)	84 (11.7%)
Known history of diabetes mellitus AND 2 or more additional risk factors	31 (12.9%)	59 (12.3%)	90 (12.5%)
At least 2 CHD risk equivalents or 1 CHD risk equivalent associated with hypertension or diabetes	67 (27.8%)	141 (29.4%)	208 (28.9%)

Note: A patient can be counted in several categories.

[a] according to the items pre-listed in the e-CRF.

[b] diagnosed by invasive or non-invasive testing.

PAD defined as Intermittent claudication TOGETHER WITH ankle-brachial index ≤ 0.90 OR TOGETHER WITH peripheral revascularization procedure/surgery OR critical limb ischemia TOGETHER WITH peripheral revascularization procedure/surgery or thrombolysis.

Table 17 - Medical history of specific interest: other medical history of special interest - Randomized population

	Ezetimibe 10 (N=241)	Alirocumab 75 Q2W/Up150 Q2W (N=479)	All (N=720)
Other medical history of special interest	219 (90.9%)	424 (88.5%)	643 (89.3%)
Hypertension [a]	198 (82.2%)	382 (79.7%)	580 (80.6%)
Type 1 Diabetes [a]	0	2 (0.4%)	2 (0.3%)
Type 2 Diabetes [a]	76 (31.5%)	145 (30.3%)	221 (30.7%)
Family history of premature coronary heart disease [a]	59 (24.5%)	94 (19.6%)	153 (21.3%)
Family history of type 2 diabetes [a]	38 (15.8%)	60 (12.5%)	98 (13.6%)
Menopause (females) [a]	65 (27.0%)	106 (22.1%)	171 (23.8%)

[a] according to the items pre-listed in the e-CRF.
Note: A patient can be counted in several categories.

Table 18 - Background LMT at randomization – Randomized population

	Ezetimibe 10 (N=241)	Alirocumab 75 Q2W/Up150 Q2W (N=479)	All (N=720)
Any statin	241 (100%)	478 (99.8%)	719 (99.9%)
Taking high intensity statin	160 (66.4%)	320 (66.8%)	480 (66.7%)
Atorvastatin daily dose (mg)	118 (49.0%)	237 (49.5%)	355 (49.3%)
10	6 (2.5%)	5 (1.0%)	11 (1.5%)
20	11 (4.6%)	26 (5.4%)	37 (5.1%)
40	55 (22.8%)	115 (24.0%)	170 (23.6%)
80	46 (19.1%)	90 (18.8%)	136 (18.9%)
Other doses	0	1 (0.2%)	1 (0.1%)
Rosuvastatin daily dose (mg)	75 (31.1%)	137 (28.6%)	212 (29.4%)
5	2 (0.8%)	9 (1.9%)	11 (1.5%)
10	14 (5.8%)	12 (2.5%)	26 (3.6%)
20	41 (17.0%)	80 (16.7%)	121 (16.8%)
40	17 (7.1%)	34 (7.1%)	51 (7.1%)
Other doses	1 (0.4%)	2 (0.4%)	3 (0.4%)
Simvastatin daily dose (mg)	49 (20.3%)	105 (21.9%)	154 (21.4%)
10	4 (1.7%)	5 (1.0%)	9 (1.3%)
20	16 (6.6%)	28 (5.8%)	44 (6.1%)
40	22 (9.1%)	61 (12.7%)	83 (11.5%)
80	5 (2.1%)	10 (2.1%)	15 (2.1%)
Other doses	2 (0.8%)	1 (0.2%)	3 (0.4%)
Any LMT other than statins[a]	12 (5.0%)	29 (6.1%)	41 (5.7%)
Any LMT other than nutraceuticals	4 (1.7%)	13 (2.7%)	17 (2.4%)

Nutraceuticals	8	(3.3%)	16	(3.3%)	24	(3.3%)

[a] in combination with statins or not.
High intensity statin corresponds to atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily.

Table 19 - Lipid efficacy parameters at baseline – Quantitative summary in conventional units – Randomized population

	Ezetimibe 10 (N=241)	Alirocumab 75 Q2W/Up150 Q2W (N=479)	All (N=720)
Calculated LDL-C (mg/dL)			
Number	241	479	720
Mean (SD)	104.6 (34.1)	108.6 (36.5)	107.3 (35.7)
Median	98.0	100.0	99.0
Q1 : Q3	81.0 : 122.0	83.0 : 126.0	83.0 : 124.0
Min : Max	38 : 243	22 : 303	22 : 303
Measured LDL-C (mg/dL)			
Number	213	429	642
Mean (SD)	101.1 (35.0)	103.8 (34.8)	102.9 (34.9)
Median	93.0	96.0	95.0
Q1 : Q3	75.0 : 118.0	79.0 : 120.0	78.0 : 119.0
Min : Max	47 : 237	26 : 284	26 : 284
Non-HDL-C (mg/dL)			
Number	241	479	720
Mean (SD)	136.8 (40.4)	139.1 (40.4)	138.3 (40.4)
Median	128.0	129.0	128.0
Q1 : Q3	109.0 : 154.0	110.0 : 161.0	110.0 : 158.0
Min : Max	65 : 317	61 : 322	61 : 322
Total-C (mg/dL)			
Number	241	479	720
Mean (SD)	183.9 (41.8)	186.5 (41.2)	185.6 (41.4)
Median	175.0	178.0	177.0
Q1 : Q3	156.0 : 201.0	159.0 : 209.0	157.0 : 206.5
Min : Max	117 : 347	90 : 411	90 : 411
HDL-C (mg/dL)			
Number	241	479	720
Mean (SD)	47.2 (13.5)	47.4 (13.3)	47.3 (13.4)
Median	44.0	45.0	45.0
Q1 : Q3	37.0 : 56.0	38.0 : 54.0	38.0 : 54.0
Min : Max	21 : 112	16 : 117	16 : 117

Fasting TGs (mg/dL)			
Number	241	479	720
Mean (SD)	159.2 (77.5)	153.9 (77.0)	155.7 (77.1)
Median	141.0	133.0	137.0
Q1 : Q3	106.0 : 198.0	98.0 : 193.0	100.0 : 195.0
Min : Max	47 : 456	46 : 532	46 : 532
Lipoprotein-(a)(mg/dL)			
Number	234	470	704
Mean (SD)	40.5 (45.0)	45.2 (46.3)	43.6 (45.9)
Median	23.0	28.0	25.0
Q1 : Q3	8.0 : 56.0	8.0 : 70.0	8.0 : 66.0
Min : Max	2 : 233	2 : 245	2 : 245
Apo-B (mg/dL)			
Number	234	470	704
Mean (SD)	93.5 (23.1)	94.3 (23.2)	94.0 (23.1)
Median	89.0	90.0	90.0
Q1 : Q3	78.0 : 105.0	78.0 : 108.0	78.0 : 107.0
Min : Max	43 : 193	45 : 180	43 : 193
Apo-A1 (mg/dL)			
Number	234	470	704
Mean (SD)	140.2 (25.5)	140.7 (23.6)	140.5 (24.2)
Median	137.0	139.0	139.0
Q1 : Q3	121.0 : 159.0	124.0 : 155.0	123.0 : 156.0
Min : Max	87 : 248	89 : 237	87 : 248
Apo-B/Apo-A1 (ratio)			
Number	234	470	704
Mean (SD)	0.688 (0.213)	0.689 (0.206)	0.689 (0.208)
Median	0.650	0.660	0.655
Q1 : Q3	0.540 : 0.790	0.540 : 0.810	0.540 : 0.800
Min : Max	0.33 : 1.65	0.30 : 1.79	0.30 : 1.79
Total-C/HDL-C (ratio)			
Number	241	479	720
Mean (SD)	4.155 (1.436)	4.188 (1.342)	4.177 (1.373)
Median	3.864	3.914	3.902
Q1 : Q3	3.228 : 4.761	3.254 : 4.818	3.249 : 4.815
Min : Max	2.10 : 11.57	1.87 : 9.40	1.87 : 11.57

[00227] The collection of measured LDL-C was not planned in the initial protocol and was added in an amendment. Therefore measured LDL-C values are available for fewer patients compared to calculated LDL-C values.

COMBO II: Dosage and duration

[00228] Exposure to injections (alirocumab or placebo) and to capsules (ezetimibe or placebo) was similar across treatment groups with a mean exposure of approximately 57 weeks.

[00229] In the alirocumab group, among the 446 patients who received at least one injection after Week 12, 82 (18.4%) patients received automatic up-titration at Week 12 from alirocumab 75 mg Q2W to 150 mg Q2W in a blinded manner.

[00230] The mean (SD) duration of injection exposures was 58.0 (18.7) weeks (with a mean [SD] of 26.6 [8.8] injections) in the alirocumab arm and 57.7 (19.0) weeks (26.6 [9.0] injections) in the ezetimibe arm. At the time of this analysis, 84.8% of patients in alirocumab arm and 85.5% in the ezetimibe arm had treatment ongoing (active or placebo). Eighty-two (18.4%) patients in the alirocumab arm had the dose increased at week 12 to the 150 mg Q2W dosing regimen because their LDL-C at week 8 was ≥70 mg/dL.

COMBO II: Primary efficacy endpoint

[00231] The ITT analysis includes all calculated LDL-C values collected on-treatment and off-treatment up to Week 52. The primary endpoint (percent change in calculated LDL-C from baseline to Week 24) analysis is provided based on a MMRM model on the ITT population, using LS means estimates at Week 24. Thirty-nine (8.4%) patients in the alirocumab group and 19 (7.9%) patients in the ezetimibe group did not have a calculated LDL-C value at Week 24. These missing values were accounted for by the MMRM model.

[00232] Results of the primary endpoint analysis are presented in **Table 20**, in mmol/L and mg/dL.

[00233] Statistically significant decrease in percent change in LDL-C from baseline to Week 24 was observed in the alirocumab group (LS mean versus baseline -50.6%) compared to the ezetimibe group (LS mean versus baseline -20.7%) (LS mean difference vs. ezetimibe of -29.8%, $p < 0.0001$).

[00234] In the alirocumab group, LDL-C reduction from baseline was observed from Week 4 to Week 52 (see **Figure 6** and **Table 20**). The LDL-C reduction was maintained up to Week 52 in the alirocumab group (LS mean versus baseline at Week 52 of -49.5% versus -50.6% at Week 24).

Table 20- Percent change from baseline in calculated LDL-C at Week 24: MMRM – ITT analysis - ITT population and On-treatment population

ITT POPULATION Calculated LDL Cholesterol	Ezetimibe 10 (N=240)	Alirocumab 75 Q2W/Up150 Q2W (N=467)
Baseline (mmol/L)		
Number	240	467
Mean (SD)	2.706 (0.884)	2.805 (0.946)
Median	2.538	2.590
Min : Max	0.98 : 6.29	0.57 : 7.85
Baseline (mg/dL)		
Number	240	467
Mean (SD)	104.5 (34.1)	108.3 (36.5)
Median	98.0	100.0
Min : Max	38 : 243	22 : 303
Week 24 percent change from baseline (%)		
LS Mean (SE)	-20.7 (1.9)	-50.6 (1.4)
LS mean difference (SE) vs ezetimibe		-29.8 (2.3)
95% CI		(-34.4 to -25.3)
p-value vs ezetimibe		<0.0001*

Table 21 - Calculated LDL-C over time - ITT analysis - ITT population

	Ezetimibe 10 (N=240)			Alirocumab 75 Q2W/Up150 Q2W (N=467)		
Calculated LDL-C	Value	Change from baseline	Percent change from baseline	Value	Change from baseline	Percent change from baseline
LS Mean (SE) (mmol/L)						
Baseline [a]	2.706 (0.057)	NA	NA	2.805 (0.044)	NA	NA
Week 4	2.002 (0.044)	-0.770 (0.044)	-25.3 (1.6)	1.254 (0.031)	-1.518 (0.031)	-54.7 (1.1)
Week 8	2.047 (0.045)	-0.725 (0.045)	-24.3 (1.7)	1.259 (0.032)	-1.512 (0.032)	-54.3 (1.2)
Week 12	2.102 (0.049)	-0.670 (0.049)	-21.8 (1.8)	1.350 (0.035)	-1.422 (0.035)	-51.2 (1.3)
Week 16	2.069 (0.048)	-0.702 (0.048)	-23.0 (1.8)	1.194 (0.035)	-1.578 (0.035)	-56.4 (1.3)
Week 24	2.138 (0.051)	-0.634 (0.051)	-20.7 (1.9)	1.337 (0.036)	-1.435 (0.036)	-50.6 (1.4)
Week 36	2.187 (0.058)	-0.585 (0.058)	-19.3 (2.0)	1.337 (0.041)	-1.434 (0.041)	-51.2 (1.4)
Week 52	2.210 (0.061)	-0.562 (0.061)	-18.3 (2.1)	1.381 (0.044)	-1.390 (0.044)	-49.5 (1.5)
LS Mean (SE) (mg/dL)						

Calculated LDL-C	Ezetimibe 10 (N=240) Value	Ezetimibe 10 (N=240) Change from baseline	Ezetimibe 10 (N=240) Percent change from baseline	Alirocumab 75 Q2W/Up150 Q2W (N=467) Value	Alirocumab 75 Q2W/Up150 Q2W (N=467) Change from baseline	Alirocumab 75 Q2W/Up150 Q2W (N=467) Percent change from baseline
Baseline [a]	104.5 (2.2)	NA	NA	108.3 (1.7)	NA	NA
Week 4	77.3 (1.7)	-29.7 (1.7)	-25.3 (1.6)	48.4 (1.2)	-58.6 (1.2)	-54.7 (1.1)
Week 8	79.0 (1.7)	-28.0 (1.7)	-24.3 (1.7)	48.6 (1.2)	-58.4 (1.2)	-54.3 (1.2)
Week 12	81.1 (1.9)	-25.9 (1.9)	-21.8 (1.8)	52.1 (1.4)	-54.9 (1.4)	-51.2 (1.3)
Week 16	79.9 (1.9)	-27.1 (1.9)	-23.0 (1.8)	46.1 (1.3)	-60.9 (1.3)	-56.4 (1.3)
Week 24	82.5 (2.0)	-24.5 (2.0)	-20.7 (1.9)	51.6 (1.4)	-55.4 (1.4)	-50.6 (1.4)
Week 36	84.4 (2.2)	-22.6 (2.2)	-19.3 (2.0)	51.6 (1.6)	-55.4 (1.6)	-51.2 (1.4)
Week 52	85.3 (2.4)	-21.7 (2.4)	-18.3 (2.1)	53.3 (1.7)	-53.7 (1.7)	-49.5 (1.5)

[a] Baseline is described using means and standard errors.

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction

MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

COMBO II: Key secondary efficacy endpoints and additional analyses

[00235] The following table summarizes analysis results on key secondary endpoints in the hierarchical order. All key secondary endpoints are statistically significant according to the hierarchical testing procedure up to HDL-C endpoint at Week 24 (ITT estimand) included.

[00236] Statistical significance was not reached for fasting TG at Week 24 (ITT estimand) and therefore the testing procedure was stopped, p-values are provided from this endpoint for descriptive purpose only.

Table 22

Endpoint	Analysis	Results	Results	P-value
Calculated LDL-C - Percent change from baseline to Week 24	On-treatment	LS mean difference vs. ezetimibe of -30.6%	LS mean difference vs. baseline of -52.4%	<0.0001
Calculated LDL-C - Percent change from baseline to Week 24, beta – quantification method	ITT	LS mean difference vs. ezetimibe of -29.7%	LS mean difference vs. baseline of -47.7%	<0.0001
Calculated LDL-C - Percent change from baseline to Week 12	ITT	LS mean difference vs. ezetimibe of -29.4%	LS mean difference vs. baseline of -51.2 %	<0.0001
Calculated LDL-C - Percent change from baseline to Week 12	On-treatment	LS mean difference vs. ezetimibe of -29.7%	LS mean difference vs. baseline of -52.4	<0.0001

Apo-B - Percent change from baseline to Week 24	ITT	LS mean difference vs. ezetimibe of -22.4%	LS mean difference vs. baseline of -40.7	<0.0001
Apo-B - Percent change from baseline to Week 24	On-treatment	LS mean difference vs. ezetimibe of -23%	LS mean difference vs. baseline of -42.1	<0.0001
Non-HDL-C - Percent change from baseline to Week 24	ITT	LS mean difference vs. ezetimibe of -22.9%	LS mean difference vs. baseline of -42.1	<0.0001
Non-HDL-C - Percent change from baseline to Week 24	On-treatment	LS mean difference vs. ezetimibe of -23.5%	LS mean difference vs. baseline of -43.7	<0.0001
Total-C - Percent change from baseline to Week 24	ITT	LS mean difference vs. ezetimibe of -14.7%	LS mean difference vs. baseline of -29.3	<0.0001
Apo-B - Percent change from baseline to Week 12	ITT	LS mean difference vs. ezetimibe of -22.5%	LS mean difference vs. baseline of -39.7	<0.0001
Non-HDL-C - Percent change from baseline to Week 12	ITT	LS mean difference vs. ezetimibe of -22%	LS mean difference vs. baseline of -42.6	<0.0001
Total-C - Percent change from baseline to Week 12	ITT	LS mean difference vs. ezetimibe of -14.3%	LS mean difference vs. baseline of -29.4	<0.0001
Calculated LDL-C - Percent change from baseline to Week 52	ITT	LS mean difference vs. ezetimibe of -31.2%	LS mean difference vs. baseline of -49.5	<0.0001
Proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24	ITT	combined estimate for odds-ratio vs. ezetimibe of 5.4		<0.0001
Proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24	On-treatment	combined estimate for odds-ratio vs. ezetimibe of 5.9		<0.0001
Lp(a) - Percent change from baseline to Week 24	ITT	combined estimate for adjusted mean difference vs. ezetimibe of -21.7%	LS mean difference vs. baseline of -27.8	<0.0001
HDL-C - Percent change from baseline to Week 24	ITT	LS mean difference vs. ezetimibe of 8.1%	LS mean difference vs. baseline of _+8.6	<0.0001
Fasting TGs - Percent change from baseline to Week 24	ITT	combined estimate for adjusted mean difference vs. ezetimibe of -0.3%		0.9117
Apolipoprotein A-1	ITT	LS mean difference vs. ezetimibe of 6.3%	LS mean difference vs. baseline of +5.0	<0.0001

[00237] The on-treatment analysis of the LDL-C percent change from baseline to Week 24 shows very consistent results with the ITT analysis (LS mean difference vs. ezetimibe of -30.6% in the on-treatment analysis versus -29.8% in the ITT analysis).

[00238] The following key secondary endpoints including Apo B, non-HDL-C, Total-C, Lp(a), HDL-C at various time points as well as the proportion of patients reaching their LDL-C goals at Week 24 were statistically significant according to the hierarchical testing procedure.

[00239] Most high cardiovascular risk patients receiving Alirocumab on background statin achieved their LDL-C goal. The proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24 was significantly higher in the alirocumab than in the ezetimibe group (combined estimate for proportion of 77.0% in the alirocumab group vs. 45.6% in the ezetimibe group, p<0.0001).

[00240] The difference in percent change in fasting TGs from baseline to Week 24 in the ITT analysis was non-statistically significant. The LS mean versus baseline was -13.0% in the alirocumab group and -12.8% in the ezetimibe group (LS mean difference vs. ezetimibe of -0.3%, p=0.9117).

[00241] One hundred and five (22.8%) patients experienced two consecutive calculated LDL-C values <25 mg/dL. No particular safety concern has been observed in these 105 patients.

Table 23 - Number (%) of patients with 2 consecutive LDL-C < 25mg/dL (<0.65 mmol/L) during the treatment period– Safety population

	Ezetimibe 10 (N=241)	**Alirocumab 75 Q2W/Up150 Q2W (N=479)**
Patients with 2 consecutive calculated LDL-C value <25 mg/dL [1]	0/230	105/460 (22.8%)
Time to the first calculated LDL-C value < 25 mg/dL (weeks) [2]		
Number	0	105
Mean (SD)		12.56 (12.31)
Median		5.14
Min : Max		3.1 : 64.1
Patients with 2 consecutive calculated LDL-C value <15 mg/dL [1]	0/230	31/460 (6.7%)
Time to the first calculated LDL-C value < 15 mg/dL (weeks) [2]		
Number	0	31
Mean (SD)		15.07 (13.15)
Median		9.14
Min : Max		3.1 : 52.1

The number (n) represents the subset of the total number of patients who met the criteria
The denominator (/N) within a treatment group is the number of patients for the treatment group who had at least two calculated LDL-C values assessed at least 21 days apart in the efficacy period
[1] 2 consecutive values are considered if spaced out by at least 21 days
[2] First calculated LDL-C value <25 or <15 mg/dL among the first 2 consecutive calculated LDL-C values <25 or <15 mg/dL per patient

Table 24 - Percent change from baseline to week 24 in LDL-C and secondary lipid parameters (on-treatment analysis)

	Alirocumab 75 mg SC Q2W (n=464)	Ezetimibe 10 mg ezetimibe daily (n=235)	Alirocumab vs ezetimibe		
			LS mean difference (SE) %	95% CI	*P* Value
LDL-C	-52.4 (1.3)	-21.8 (1.8)	-30.6 (2.2)	-34.9 to -26.2	<.0001
Apo B	-42.1 (1.0)	-19.1 (1.4)	-23.0 (1.8)	-26.5 to -19.6	<.0001
Non–HDL-C	-43.7 (1.1)	-20.2 (1.6)	-23.5 (1.9)	-27.2 to -19.7	<.0001
Total cholesterol	-30.4 (0.9)	-15.2 (1.2)	-15.1 (1.5)	-18.0 to -12.2	<.0001
Lipoprotein(a)	-28.1 (1.4)	-5.6 (1.9)	-22.5 (2.4)	-27.2 to -17.8	<.0001
Triglycerides (fasted)	-13.5 (1.4)	-13.3 (2.0)	-0.2 (2.5)	-5.1 to 4.6	.93
HDL-C	9.0 (0.8)	0.8 (1.1)	8.2 (1.4)	5.6 to 10.9	<.0001

COMBO II: Summary efficacy results

[00242] At Week 24, the percent change from baseline in calculated LDL-C in the ITT population was significantly greater in the alirocumab group (LS mean versus baseline - 50.6%) compared to the ezetimibe group (LS mean versus baseline -20.7%) (LS mean difference versus ezetimibe of -29.8%, p < 0.0001) (**Table 20**). The on-treatment analysis of LDL-C percent change from baseline to Week 24 shows consistent results with the ITT analysis with a LS mean difference versus ezetimibe of -30.6% in the on-treatment analysis (p<0.0001) (**Table 24**).

[00243] The time-course of changes in LDL-C concentrations in the alirocumab and ezetimibe arms from baseline to 52 weeks is shown in **Figure 6**. Mean LDL-C concentrations dropped rapidly in the first 4 weeks, but to a greater degree in the alirocumab arm. In the alirocumab group, LDL-C reduction from baseline was observed from Week 4 and maintained up to Week 52 (LS mean versus baseline at Week 52 of -49.5% versus -50.6% at Week 24) (Table 21).

[00244] The distribution of baseline and achieved LDL-C values at 24 weeks are shown in **Figure 7.** The median was 40 mg/dL for alirocumab compared and 70 mg/dL for ezetimibe. Mean achieved LDL-C at week 24 was 51.6 (1.4) mg/dL with alirocumab and 82.5 (2.0) mg/dL with ezetimibe; these differences were maintained to week 52.

[00245] The time-course of changes in LDL-C concentrations according to dose-increase status in the alirocumab arm is shown in **Figure 8**. Only 18% percent of the patients in alirocumab group had the dose increased to 150 mg SC Q2W. These patients had much higher baseline LDL-C values versus patients who did not require a dose increase (140.4 [47.4] mg/dL vs. 101.1 [29.7] mg/dL), and the percent reductions in LDL-C achieved at weeks 12 and 24 were lower. The dose increase at 12 weeks led to an additional reduction of 12.4%. Moreover, the absolute

reduction in LDL-C by week 24 was slightly greater in the dose-increased group (63.5 vs 56.9 mg/dL) relative to the remainder of the alirocumab group.

[00246] For key secondary efficacy endpoints, statistically significant reductions were observed for Apo B (22.4%), Lp(a) (21.7%), and non–HDL-C (22.9%) (all *P*<.0001), and there was an 8.1% increase in HDL-C at week 24 in the alirocumab arm compared with ezetimibe (*P*<.0001) (**Table 22**). Statistically significant difference was not reached with fasting TGs at Week 24 (reduced from baseline by 13.5% in the alirocumab group and 13.3% in the ezetimibe group) and therefore the testing procedure was stopped from this endpoint. Alirocumab efficacy versus ezetimibe was consistent across several subgroups in the ITT population (**Figure 9**). **In Table 22**, the beta-quantification method for determining LDL-C percent change from baseline to week 24 was a sensitivity analysis conducted in 180 patients in the ezetimibe group and 361 patients in the alirocumab group.

COMBO II: Summary safety results

[00247] Rates of treatment-emergent adverse events (TEAEs) over a mean of 58 (19) weeks' follow-up are shown in **Table 25**. The overall percentage of patients who experienced at least one TEAE was 71.2% in the alirocumab arm and 67.2% in the ezetimibe arm. A TEAE leading to death occurred in 2 (0.4%) patients in the alirocumab arm (both of cardiac origin) and in 4 (1.7%) patients in the ezetimibe arm (two of cardiac origin). Similar percentages of subjects in both groups experienced a serious adverse event (18.8% alirocumab vs 17.8% ezetimibe). A higher proportion of patients in the alirocumab group experienced TEAEs leading to treatment discontinuation (7.5% vs 5.4%), with no specific pattern at the preferred term level **(Table 25)**.

[00248] There was no indication of imbalance in TEAEs at the system organ class level, with the exception of slightly higher rates with alirocumab for infections and infestations (27.1% vs 25.3% ezetimibe), musculoskeletal and connective tissue disorders (19.6% vs 17.0%), and gastrointestinal disorders (15.0% vs 13.7%) **(Table 25)**. Adjudicated cardiovascular events were also more frequent in the alirocumab group (4.8%, n =23; vs 3.7%, n = 9) due to higher rates of non-fatal myocardial infarctions and coronary revascularizations.

[00249] Rates of treatment-emergent local injection site reactions appeared slightly higher in the alirocumab arm (2.5% vs 0.8% for ezetimibe) **(Table 25)**. Reactions were of mild intensity, except for one of moderate intensity and none were serious. Two events led to discontinuation in the alirocumab group. A low percentage of patients in both groups developed myalgia.

[00250] Abnormalities in laboratory measurements were uncommon and occurred at similar rates in both groups with the exception of alanine aminotrasaminase and aspartate aminotransferase, which were more frequent in the alirocumab group, and impaired glucose control, which was less frequent in the alirocumab group (**Table 25**).

[00251] One-hundred and five (22.8% of 460) patients in the alirocumab arm and none in the ezetimibe arm had two consecutive LDL-C values of <25 mg/dL during the treatment period. Rates of TEAEs in this group were similar to those in the ezetimibe group, with the exception of nasopharyngitis, which was more frequent in the alirocumab group (**Table 25**).

Table 25 - TEAEs and laboratory parameters (safety population) at 52 weeks by system-organ class and preferred term (including those occurring in patients with two LDL-C values <25 mg/dl alirocumab treatment)

All patients on maximal statin therapy ± other lipid-lowering therapy	**Alirocumab 75 mg SC Q2W (n = 479)**	**Ezetimibe 10 mg daily (n = 241)**	**Alirocumab 75 mg SC Q2W With Two Consecutive LDL-C ≤25 mg/dL (n=105)**
Patients experiencing any TEAE	341 (71.2)	162 (67.2)	72 (68.6)
TEAEs by system organ class occurring in ≥3% of patients in either group			
Infections and infestations	130 (27.1)	61 (25.3)	35 (33.3)
Musculoskeletal and connective tissue disorders	94 (19.6)	41 (17.0)	19 (18.1)
Nervous system disorders	77 (16.1)	40 (16.6)	17 (16.2)
Gastrointestinal disorders	72 (15.0)	33 (13.7)	19 (18.1)
Injury, poisoning, and procedural complications	61 (12.7)	33 (13.7)	10 (9.5)
Cardiac disorders	60 (12.5)	29 (12.0)	14 (13.3)
General disorders and administration site conditions	56 (11.7)	26 (10.8)	10 (9.5)
Respiratory, thoracic, and mediastinal disorders	45 (9.4)	22 (9.1)	11 (10.5)
Investigations	35 (7.3)	21 (8.7)	7 (6.7)
Vascular disorders	33 (6.9)	20 (8.3)	4 (3.8)
Skin and subcutaneous tissue disorders	35 (7.3)	15 (6.2)	10 (9.5)
Metabolism and nutrition disorders	27 (5.6)	18 (7.5)	6 (5.7)
Psychiatric disorders	21 (4.4)	12 (5.0)	2 (1.9)
Renal and urinary disorders	21 (4.4)	13 (5.4)	7 (6.7)
Eye disorders	23 (4.8)	9 (3.7)	2 (1.9)
Blood and lymphatic system disorders	11 (2.3)	8 (3.3)	4 (3.8)
Neoplasms, benign, malignant and unspecified (including cysts and polyps)	15 (3.1)	7 (2.9)	5 (4.8)
Reproductive system and breast disorders	12 (2.7)	2 (0.8)	4 (3.8)
TEAEs by preferred term occurring in ≥3% of patients in either group or TEAEs of interest			
Accidental overdose	30 (6.3)	16 (6.6)	6 (5.7)

Upper respiratory tract infection	31 (6.5)	14 (5.8)	4 (3.8)
Dizziness	23 (4.8)	13 (5.4)	5 (4.8)
Myalgia	21 (4.4)	12 (5.0)	4 (3.8)
Headache	21 (4.4)	10 (4.1)	4 (3.8)
Arthralgia	19 (4.0)	9 (3.7)	5 (4.8)
Nasopharyngitis	18 (3.8)	9 (3.7)	10 (9.5)
Hypertension	18 (3.8)	10 (4.1)	3 (2.9)
Influenza	17 (3.5)	7 (2.9)	3 (2.9)
Angina pectoris	12 (2.5)	11 (4.6)	2 (1.9)
Laboratory parameters			
Blood glucose increased[c]	1 (0.2)	3 (1.2)	1 (1.0)
Hemoglobin decreased[c]	4 (0.8)	2 (0.8)	3 (2.9)

COMBO II: Overall results

[00252] In this population of high CV risk patients who had poorly controlled LDL-C on maximally tolerated statin therapy the following observations were made: 1) self-administered alirocumab produced significantly greater LDL-C reductions than ezetimibe after 24 weeks (LS mean difference –29.8%); 2) self-administered alirocumab had good compliance and was well-tolerated; 3) 77% of alirocumab patients achieved LDL-C goal of <0.81 mmol/L (70 mg/dL) at Week 24; LDL-C reductions of ~50% vs. baseline maintained to Week 52 with alirocumab; 4) mean LDL-C levels of 1.4 mmol/L (53.3 mg/dL) were achieved at Week 52 with alirocumab; 5) approximately 80% of patients did not require uptitration to alirocumab 150mg Q2W suggesting that 75 mg Q2W may be sufficient for most patients; and 6) TEAEs occurred in a similar frequency in alirocumab and ezetimibe arms.

Example 3: Long-term safety and tolerability of Alirocumab in high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipid modifying therapy: a randomized, double-blind, placebo-controlled study

INTRODUCTION

[00253] This study was undertaken to assess the long-term safety and tolerability of alirocumab in patients at high cardiovascular risk who are not at LDL-C goal. This population that is not at LDL-C goal on optimized LMT represents a highest risk group with a well identified unmet medical need that can be addressed by adding alirocumab to their LDL-C modifying therapies. Two sets of results are reported: (1) a pre-specified interim analysis was performed when all patients reached one year and approximately 25 percent of patients reached 18 months of treatment; and (2) the final analysis of the safety population, when all patients had completed the study.

STUDY OBJECTIVES

[00254] The primary study objective was to evaluate the long-term safety and tolerability of alirocumab in high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their lipid modifying therapy.

[00255] The secondary study objectives were: 1) to evaluate the effect of alirocumab on low-density lipoprotein cholesterol (LDL-C) levels after 24 weeks of treatment in comparison with placebo; 2) to evaluate the efficacy of alirocumab on LDL-C levels at other time points; 3) to evaluate the effect of alirocumab on Apolipoprotein B (Apo B), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (total-C), lipoprotein a (Lp [a]), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) levels, and apolipoprotein A-1 (Apo A-1) after 24 weeks of treatment and at other time points in comparison with placebo; 4) to evaluate the development of anti-alirocumab antibodies; and 5) to evaluate the pharmacokinetics (PK) of alirocumab.

STUDY DESIGN

[00256] This was a randomized, double-blind, placebo-controlled, unbalanced (2:1, alirocumab:placebo), parallel-group, multi-center, multi-national study evaluating the long-term safety and tolerability of alirocumab in high cardiovascular risk patients with hypercholesterolemia who were not adequately controlled with a maximally tolerated daily registered dose of a statin with or without other lipid modifying therapy. See **Figure 10**. Patients were stratified according to heFH population, prior history of MI or ischemic stroke, statin treatment and geographic region. Patients at high cardiovascular risk were defined as 1) having heFH (who may or may not have CHD/CHD risk equivalents) or 2) no prior diagnosis of heFH but having hypercholesterolemia together with established CHD or CHD risk equivalents. Patients must be hypercholesterolemic and not adequately controlled (i.e., LDL-C ≥70 mg/dL [≥1.81 mmol/L]) despite therapy with maximally tolerated daily registered dose of a statin with or without other lipid modifying therapy at a stable dose for at least 4 weeks (6 weeks for fenofibrate) prior to screening.

Description of the protocol

[00257] Patients randomized to alirocumab received 150 mg every 2 weeks. The treatment scheme could be adjusted, if needed, during the course of the study, through a protocol amendment, to introduce a lower dose with a titration scheme.

[00258] The study consisted of 3 periods: screening, double-blind treatment, and follow up. The screening period was up to 3 weeks in duration including an intermediate visit during which the patient (or another designated person such as spouse, relative, etc.) was trained to self-inject/inject with placebo. Eligibility assessments were performed to permit the randomization of

the patients into the study. The double-blind treatment period was a randomized, double-blind study treatment period of 18 months. The first injection during the double-blind period was done at the site on the day of randomization and as close as possible after randomization into the study. The subsequent injections were done by the patient (self-injection), or another designated person (such as spouse, relative, etc.) at a patient-preferred location (home...). The follow-up period was a period of 8 weeks after the end of the double-blind treatment period.

[00259] Patients who achieved 2 consecutive calculated LDL-C levels < 25 mg/dL (0.65 mmol/L) during the study were monitored and managed.

[00260] Statin and other lipid modifying therapy (if applicable) should be stable (including dose) during the first 24 weeks of the double-blind treatment period barring exceptional circumstances whereby overriding concerns (including but not limited to triglyceride alert posted by the central lab) warrant such changes, as per the investigator's judgment. At Week 24 onwards, background lipid modifying therapy could be modified only under certain conditions.

[00261] Patients were to be on a stable diet (NCEP-ATPIII TLC diet or equivalent) throughout the entire study duration from screening. The dietician or site staff with appropriate training reviewed the patient's diet at the screening visit and periodically throughout the study. **Table 26** provides a summary of TLC Diet for high cholesterol.

Table 26

Total Fat	25% - 35% total calories*
Saturated fat*	< 7% total calories
Polyunsaturated fat	up to 10% total calories
Monounsaturated fat	up to 20% total calories
Carbohydrates†	50% - 60% total calories*
Protein	~15% total calories
Cholesterol	< 200 mg/day (5.172 mmol/†day)
Plant Sterols	2g
Soluble Fiber such as psyllium	10g - 25g

* ATP III allows an increase of total fat to 35 percent of total calories and a reduction in carbohydrate to 50 percent for persons with the metabolic syndrome. Any increase in fat intake should be in the form of either polyunsaturated or monounsaturated fat. Trans fatty acids are another LDL-raising fat that should be kept at a low intake.

†Carbohydrate should derive predominantly from foods rich in complex carbohydrates including grains—especially whole grains—fruits, and vegetables.

[00262] Patients with cardiovascular events from randomization until the final follow up visit had an adjudication package prepared and sent to the independent Clinical Events Committee.

[00263] Patients underwent color vision testing periodically throughout the study. An ophthalmologic sub-study was conducted in a sub-set of the study population.

Duration of study participation

[00264] The study duration included up to 3 weeks of screening period, 18 months of double-blind study treatment period, and 8 weeks of follow up period. Thus, the study duration per patient was approximately 20 months. The end of the study per patient was the last protocol planned visit or the resolution/stabilization of all SAEs, and AESI, whichever came last. The end of the study was defined as being the last visit of the follow-up period for each patient.

SELECTION OF PATIENTS

[00265] The study was designed to randomize approximately 2100 patients in a 2:1 randomization ratio to the following: Alirocumab - approximately 1400 patients; placebo - approximately 700 patients.

[00266] Patients meeting the following criteria were considered for enrollment into the study: 1) patients with heterozygous Familial Hypercholesterolemia (heFH)* with or without established coronary heart disease (CHD) or CHD risk equivalents who are not adequately controlled with a maximally tolerated stable daily dose of statin** for at least 4 weeks prior to the screening visit (Week -3) with or without other lipid modifying therapy (LMT); or 2) patients with hypercholesterolemia and established CHD or CHD risk equivalents (see below for definitions) who are not adequately controlled with a maximally tolerated stable daily dose of statin** for at least 4 weeks prior to the screening visit (Week -3) with or without other lipid modifying therapy (LMT).

[00267] *Diagnosis of heFH must be made either by genotyping or by clinical criteria. For those patients not genotyped, the clinical diagnosis may be based on either the WHO criteria/Dutch Lipid Clinical Network criteria with a score > 8 points or the Simon Broome register diagnostic criteria with a criterion for definite FH.

[00268] ** Definition of maximally tolerated dose (any of the following are acceptable): 1) rosuvastatin 20 mg or 40 mg daily; 2) atorvastatin 40 mg or 80 mg daily; 3) simvastatin 80 mg daily (if already on this dose for >1 year); 4) patients not able to be on any of the above statin doses, should be treated with the dose of daily atorvastatin, rosuvastatin or simvastatin which is considered appropriate for the patient as per the investigator's judgment or concerns. Some examples of acceptable reasons for a patient taking a lower statin dose include, but are not limited to: adverse effects on higher doses, advanced age, low body mass index, regional practices, local prescribing information, concomitant medications, co-morbid conditions such as impaired glucose tolerance/impaired fasting glucose. The reason(s) had to be documented.

[00269] Documented history of CHD includes one or more of the following: i) acute myocardial infarction (MI); ii) silent myocardial infarction; iii) unstable angina; iv) coronary revascularization procedure (eg, percutaneous coronary intervention [PCI] or coronary artery bypass graft surgery [CABG]); and/or v) clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging).

[00270] CHD risk equivalents includes one or more of the following 4 criteria: i) Documented peripheral arterial disease (one of the following criteria [a, b, or c] must be satisfied): current intermittent claudication (muscle discomfort in the lower limb that is both reproducible and produced by exercise and relieved by rest within 10 minutes) of presumed atherosclerotic origin together with ankle-brachial index < 0.90 in either leg at rest, or b) history of intermittent claudication (muscle discomfort in the lower limb that is both reproducible and produced by exercise and relieved by rest within 10 minutes) together with endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease or c) history of critical limb ischemia together with thrombolysis, endovascular procedure or surgical intervention in one or both legs because of atherosclerotic disease; ii) Documented previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 hours, considered as being of atherothrombotic origin. CT or MRI must have been performed to rule out hemorrhage and non-ischemic neurological disease; iii) Documented moderate chronic kidney disease (CKD) as defined by 30 ≤ eGFR <60 mL/min/1.73 m^2 for 3 months or more, including the screening visit; iv) Known history of diabetes mellitus AND 2 or more additional risk factors (as listed below): *a* history of hypertension (established on antihypertensive medication), *b* Documented history of ankle-brachial index ≤0.90, *c* Documented history of microalbuminuria or macroalbuminuria OR dipstick urinalysis at screening visit (Week-3) with >2+ protein, d Documented history of pre–proliferative or proliferative retinopathy or laser treatment for retinopathy, e Known family history of premature CHD (CHD in father or brother before 55 years of age; CHD in mother or sister before 65 years of age).

[00271] According to the Simon Broome Register Diagnostic Criteria for Heterozygous Familial Hypercholesterolemia, definite familial hypercholesterolemia is defined as: Total-C >6.7 mmol/l (260 mg/dL) or LDL cholesterol above 4.0 mmol/l (155 mg/dL) in a child <16 years or Total-C >7.5 mmol/l (290 mg/dL) or LDL cholesterol above 4.9 mmol/l (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment) PLUS Tendon xanthomas in patient, or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt) OR DNA-based evidence of an LDL receptor mutation or familial defective apo B-100.

[00272] According to the Simon Broome Register Diagnostic Criteria for Heterozygous Familial Hypercholesterolemia, possible familial hypercholesterolemia is defined as: Total-C >6.7 mmol/l

(260 mg/dL) or LDL cholesterol above 4.0 mmol/l (155 mg/dL) in a child <16 years or Total-C >7.5 mmol/l (290 mg/dL) or LDL cholesterol above 4.9 mmol/l (190 mg/dL) in an adult. (Levels either pre-treatment or highest on treatment) and at least one of the following: family history of myocardial infarction below 50 years of age in 2nd degree relative or below 60 years of age in 1st degree relative, or family history of raised cholesterols >7.5 mmol/l (290 mg/dL) in adult 1st or 2nd degree relative or >6.7 mmol/l (260 mg/dL) in child or sibling under 16 years of age.

[00273] The WHO Criteria (Dutch Lipid Network clinical criteria) for diagnosis of Heterozygous Familial Hypercholesterolemia (heFH) is set forth in **Table 27**.

Table 27

Diagnostic Scoring for Heterozygous Familial Hypercholesterolemia			
Family history			
a First degree relative with known premature (men <55 yrs, women <60 yrs) coronary and			1
b First degree relative with known LDL-cholesterol >95th percentile for age and sex.			
and/or			
a First degree relative with tendon xanthomata and/or arcus cornealis.			2
b Children below 18 yrs. with LDL-cholesterol >95th percentile for age			
Clinical history			
a Patient has premature (men <55 yrs, women <60 yrs) coronary artery			2
b Patient has premature (men <55 yrs, women <60 yrs) cerebral or			1
Physical examination			
a Tendon xanthomata			6
b Arcus cornealis below the age of 45 yrs.			4
Laboratory analysis			
	mmol/L	mg/dL	
a LDL-cholesterol	>8.5	>330	8
b LDL-cholesterol	6.5-8.4	250-	5
c LDL-cholesterol	5.0-6.4	190-	3
d LDL-cholesterol	4.0-4.9	155-	1
(HDL-cholesterol and triglycerides are normal)			
DNA-analysis			
a Functional mutation low-density lipoprotein receptor gene present			8
Diagnosis of heFH is:			
Certain When		>8 points	

Probable When	6-8 points
Possible When	3-5 points

[00274] Patients who met all the above inclusion criteria were screened for the following exclusion criteria.

[00275] Exclusion criteria related to study methodology were: 1) Without established history of CHD or CHD risk equivalents or without a diagnosis of heFH based on genotyping or clinical criteria; 2) LDL-C <70 mg/dL (<1.81 mmol/L) at the screening visit (Week-3); 3) Not on a stable dose of LMT (including statin) for at least 4 weeks and/or fenofibrate for at least 6 weeks, as applicable, prior to the screening visit (Week -3) and from screening to randomization; 4) Currently taking a statin that is not simvastatin, atorvastatin, or rosuvastatin; 5) Simvastatin, atorvastatin, or rosuvastatin is not taken daily or not taken at a registered dose; 6) Daily doses above atorvastatin 80 mg, rosuvastatin 40 mg or simvastatin 40 mg (except for patients on simvastatin 80 mg for more than one year, who are eligible); 7) Use of fibrates other than fenofibrate within 6 weeks prior to screening visit (Week -3) or between screening and randomization visits; 8) Use of nutraceutical products or over-the-counter therapies that may affect lipids which have not been at a stable dose for at least 4 weeks prior to the screening visit (Week -3) or between screening and randomization visits; 9) Use of red yeast rice products within 4 weeks of the screening visit (Week-3) or between screening and randomization visits; 10) Patient who has received plasmapheresis treatment within 2 months prior to the screening visit (Week -3), or has plans to receive it; 11) Recent (within 3 months prior to the screening visit [Week -3] or between screening and randomization visits) MI, unstable angina leading to hospitalization, uncontrolled cardiac arrhythmia, CABG, PCI, carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease; 12) Planned to undergo scheduled PCI, CABG, carotid or peripheral revascularization during the study; 13) History of New York Heart Association (NYHA) Class III or IV heart failure within the past 12 months; 14) Systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg at screening visit or randomization visit; 15) Known history of hemorrhagic stroke; 16) Age < 18 years or legal age of majority at the screening visit (Week-3), whichever is greater; 17) Known history of active optic nerve disease; 18) Patients not previously instructed on a cholesterol-lowering diet prior to the screening visit (Week-3); 19) Known history of homozygous FH; 20) Known history of loss of function of PCSK9 (ie, genetic mutation or sequence variation); 21) Use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks prior to randomization. Note: topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are not considered as “systemic” and are allowed; 22) Use of continuous hormone replacement therapy unless the regimen has been stable in the past 6

weeks prior to the Screening visit (Week-3) and no plans to change the regimen during the study; 23) History of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ cervical cancer; 24) Known history of HIV positivity; 25) Conditions/situations such as: a) Any clinically significant abnormality identified at the time of screening that in the judgment of the Investigator or any sub-Investigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases, patients with short life expectancy, b) Patients considered by the Investigator or any sub-Investigator as inappropriate for this study for any reason, eg.: i) Those deemed unable to meet specific protocol requirements, such as scheduled visits; ii) Those deemed unable to administer or tolerate long-term injections as per the patient or the investigator; iii) Investigator or any sub-Investigator, pharmacist, study coordinator, other study staff or relative thereof directly involved in the conduct of the protocol, etc; iv) Presence of any other conditions (eg, geographic, social....) actual or anticipated, that the Investigator feels would restrict or limit the patient's participation for the duration of the study; 26) Patient who has been previously treated with at least one dose of alirocumab or any other anti-PCSK9 monoclonal antibody in other clinical trials; 27) Patient who has taken any investigational drugs other than alirocumab training placebo kits within 1 month or 5 half lives, whichever is longer; 28) Patient who withdraws consent during the screening period (patient who is not willing to continue or fails to return); 29) Laboratory findings during the screening period (not including randomization labs): A) Positive test for Hepatitis B surface antigen and/or Hepatitis C antibody (confirmed by reflexive testing), B) Triglycerides (TG) >400 mg/dL (>4.52 mmol/L) (1 repeat lab is allowed); C) Positive serum or urine pregnancy test in women of childbearing potential; D) eGFR <30 mL/min/1.73 m^2 according to 4-variable MDRD equation; E) HbA_{1c} >10%; F) ALT or AST >3 x ULN (1 repeat lab is allowed); G) CPK >3 x ULN (1 repeat lab is allowed).

[00276] Physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life, as shown in **Table 28**.

Table 28

Class	Patient Symptoms
Class I (mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV	Unable to carry out any physical activity without discomfort. Symptoms of cardiac

(severe)	insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

[00277] Exclusion criteria related to the active comparator and/or mandatory background therapies were: 30) all contraindications to the background therapies or warning/precaution of use (when appropriate) as displayed in the respective National Product Labeling.

[00278] Exclusion criteria related to the current knowledge of alirocumab were: 31) Known hypersensitivity to monoclonal antibody therapeutics; 32) Pregnant or breast-feeding women; 33) Women of childbearing potential not protected by highly-effective method(s) of birth control and/or who are unwilling or unable to be tested for pregnancy. Note: Women of childbearing potential must have a confirmed negative serum pregnancy test at screening and urine pregnancy test at randomization visit. They must use effective contraceptive methods throughout the study and agree to repeat urine pregnancy test at designated visits. The applied methods of contraception have to meet the criteria for a highly effective method of birth control according to the "Note for guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals (CPMP/ICH/286/95)". Postmenopausal women must be amenorrheic for at least 12 months.

STUDY TREATMENTS

[00279] Sterile alirocumab drug product (IMP) was supplied at a concentration of 150 mg/mL as 1 mL volume filled into syringe. During the double-blind treatment period, alirocumab or placebo was administered subcutaneously as 1 mL injection every 2 weeks, starting at Week 0 continuing up to the last injection (ie, Week 76) which was at 2 weeks before the end of the double blind treatment period. IMP should have ideally been administered every two weeks subcutaneously at approximately the same time of the day, however it was acceptable to have a window period of ± 3 days.

[00280] The following classes of drugs were identified as non-investigational medicinal products (NIMP) because the medication was either a background therapy or a potential rescue medication: statins (rosuvastatin, atorvastatin, simvastatin); cholesterol absorption inhibitors (ezetimibe); bile acid-binding sequestrants (such as cholestyramine, colestipol, colesevelam); nicotinic acid; fenofibrate; omega-3 fatty acids (≥ 1000 mg daily).

[00281] Patients were randomized to receive either placebo or alirocumab during the double-blind study treatment period. The randomization ratio alirocumab:placebo was 2:1. The randomization was stratified by heFH population (Yes, No), prior history of acute or silent MI or ischemic stroke (Yes, No), statin treatment (atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily, vs. simvastatin whatever the daily dose, atorvastatin below 40 mg daily or rosuvastatin below 20 mg daily) and region (North America, Western Europe, Eastern Europe and Rest of World).

[00282] A concomitant medication was any treatment received by the patient concomitantly to the study (until follow-up visit). Concomitant medications were to be kept to a minimum during the study. However, if these were considered necessary for the patient's welfare and unlikely to interfere with the IMP, they could given at the discretion of the Investigator, with a stable dose (when possible). Besides the specific information related to concomitant medications provided in this section, any other concomitant medication(s) will be allowed and will have to be recorded. If the patient had an LDL-C ≥160 mg/dL (4.14 mmol/L) at the screening visit (Week -3) and was treated with a statin only, ie, without additional LMT, the investigator had to report the reason for the patient not being on a second LMT. Nutraceutical products or over-the-counter therapies that may affect lipids were allowed only if they wereused at a stable dose for at least 4 weeks prior to screening visit, during the screening period and maintained during the first 24 weeks of the double-blind treatment period. After the Week 24 visit, modification to these nutraceutical products or over-the-counter therapieswais allowed but in general should be avoided. Examples of such nutraceutical products or over-the-counter therapies included omega-3 fatty acids at doses <1000 mg, plant stanols such as found in Benecol, flax seed oil, and psyllium.

[00283] Patients were on maximally tolerated daily registered doses of statins with or without other lipid modifying therapy during the study. From the screening visit (Week -3) until the first 24 weeks of the double-blind treatment period (Week 24), the background lipid modifying therapy should not be changed. No dose adjustment, discontinuation or initiation of other statins or other lipid modifying therapy should take place during this time, barring exceptional circumstances whereby overriding concerns (including but not limited to triglyceride alert posted by the central lab) warrant such changes, as per the investigator's judgment.

[00284] The following therapies were not allowed during the study (including the screening period until the follow-up visit): fibrates other than fenofibrate; red yeast rice products; and statin other than simvastatin, atorvastatin, or rosuvastatin.

SAFETY ASSESSMENT

[00285] Safety was assessed by the following parameters: recording of adverse events (including adjudicated cardiovascular events); standard laboratory tests (hematology, chemistry and urinalysis); liver panel (ALT, AST, Alkaline Phosphatase [ALP], and total bilirubin); creatine phospho kinase (CPK); hepatitis C Antibody (if positive, then confirmed with reflexive testing); vitamin E (alpha-tocopherol) and other fat soluble vitamins; cortisol (with reflexive ATCH levels, as needed, and followed by ACTH stimulation test, as needed); gonadal hormone assessments; electrocardiogram (ECG); vital signs (systolic and diastolic blood pressure and heart rate); physical examination (including neurological exam); color vision test (as a screening test for more comprehensive ophthalmological testing, as needed). Safety parameters (adverse events

[including adjudicated cardiovascular events], laboratory data, vital signs, and ECG) were assessed throughout the study.

[00286] Patients who achieve 2 consecutive calculated LDL-C <25 mg/dL (0.65 mmol/L) will be monitored.

[00287] Patients who have a titer at or above 240 for anti-alirocumab antibody at the Follow Up visit will have additional antibody sample(s) at 6 to 12 months after the last dose and thereafter, about every 3 to 6 months until titer returns below 240.

[00288] Safety endpoints assessed in this trial were: cardiovascular events; allergic events; local tolerability at injection site; other adverse events (including hemolytic anemia); laboratory tests: urinalysis, hematology (red blood cell count, red blood cell distribution width (RDW), reticulocyte count, hemoglobin, hematocrit, platelets, white blood cell count with differential blood count), standard chemistry (sodium, potassium, chloride, bicarbonate, calcium, phosphorous, urea nitrogen, creatinine, uric acid, total protein, albumin, LDH, γ Glutamyl Transferase [γGT]), Vitamin E (alpha tocopherol) and other Fat Soluble Vitamins, cortisol (and reflexive ACTH levels, as needed, followed by ACTH stimulation test, as needed), Gonadal Hormone Assessments, Hepatitis C antibody, liver panel (ALT, AST, ALP, and total bilirubin), and CPK; vital signs including heart rate and blood pressure; and 12-lead ECG.

STUDY PROCEDURES

[00289] For all visits after Day 1/Week 0 (randomization visit), a timeframe of a certain number of days was allowed. The window period for visits at Weeks 12 and 24 were ± 3 days, at Week it was 52 ± 5 days, and for all other site visits it was ± 7 days during the double-blind treatment period, and follow-up period. A window period of +3 days was allowed for the randomization visit (Day1/Week 0) and ± 7 days was allowed for the screening visit for injection training (Week -1). A window period of ± 7 days was allowed for all phone call visits. For all visits after Day 1/randomization visit, if one visit date was changed, then the next visit took place according to the original schedule.

OPHTHALMOLOGIC SUB-STUDY

[00290] Despite evidence that ocular abnormalities noted during toxicology studies in rats were not due to the administration of alirocumab, thorough ophthalmic evaluations were conducted in a sub-set of patients in the protocol to verify the ophthalmic safety of alirocumab.

[00291] The primary objective was to assess the clinical ophthalmic safety of alirocumab in high cardiovascular risk patients with hypercholesterolemia not adequately controlled with their LMT.

[00292] Patients underwent ophthalmologic assessments by ophthalmologists/optometrists at the screening period. If the patients were deemed eligible for the main study trial and fulfilled

the additional eligibility criteria for the sub-study, then the patients underwent ophthalmologic assessments every 6 months during the 18-month double-blind treatment period

[00293] The primary endpoint was adverse events related to ophthalmologic abnormalities (using SMQ “optic nerve disorders”, “retinal disorders” and “corneal disorders”) over the study duration.

[00294] Approximately 270 patients were expected to participate in this sub-study. All subjects must meet eligibility criteria for the main study and the additional eligibility criteria outlined for this sub-study in order to be eligible for this sub-study.

[00295] The only additional inclusion criteria was signed written informed consent.

[00296] Additional exclusion criteria for the sub-study were: patient who withdraws consent for Ophthalmologic Sub-study during the screening period (patient who is not willing to continue); patient unable to complete all of the ophthalmologic assessments during the screening period; patient with active optic nerve disease (eg, optic neuritis) detected during the ophthalmologic assessments at the screening period. Note - Patient with controlled open-angle glaucoma may be eligible for the study; and patient with active chorio-retinal disease detected during the ophthalmologic assessments at the screening period.

Statistical methods:

Sample size determination:

[00297] For safety assessment, a sample size of 2100 patients (randomization ratio 2:1, i.e., alirocumab:1400 and placebo:700) allows the collection of long-term safety data in a broad database (at least 1000 patients exposed to alirocumab for a minimum of 12 months, of which approximately 900 patients exposed to alirocumab for 18 months).

[00298] With this sample size and the following assumptions: duration of recruitment of 16 months, 44% of patients recruited in the first 9 months, and a dropout rate of 25% and 35% at 12 months and 18 months, respectively, the expected number of patients exposed to alirocumab for a minimum of 12 months and 18 months of treatment is given below:

[00299] Expected number of patients exposed to alirocumab according to timing of analysis:

Analysis	Patients exposed ≥12 months	Patients exposed 18 months
First step analysis [a]	970 patients	400 patients
Final analysis	1050 patients	910 patients

[a] First step analysis planned when approximately 600 patients have completed 18 months of the double-blind treatment period

[00300] Moreover, a sample size of 1400 patients treated with alirocumab allows detecting adverse event with a rate ≥0.002 with 95% confidence in the alirocumab group. It was anticipated that between 122 and 142 patients exposed to alirocumab would be evaluated in the ophthalmologic sub-study for at least 12 months considering a sample size of 270 patients and

assuming a discontinuation rate of 25% over 12 months. This would allow detection of an ophthalmological event with a true occurrence between 0.021 and 0.024 in the alirocumab group, with 95% confidence.

Timing of analyses:

[00301] The first step analysis included final efficacy endpoints up to Week 52 (including primary efficacy endpoint at Week 24) and interim safety analysis, which was performed on all safety data up to the common study cut-off date (date when approximately 600 randomized patients had completed 18 months of the double-blind treatment period). Analysis of lipid data beyond Week 52 was descriptive. Results are presented herein.

[00302] The second step (final) analysis will be conducted at the end of the study and will consist of the final analysis of efficacy data at time points beyond time points analyzed at first step analysis and final safety analysis.

Analysis populations:

[00303] The primary efficacy analysis population was the intent-to-treat (ITT) population, defined as all randomized patients who had an evaluable primary efficacy endpoint, that is, those with an available baseline calculated LDL-C value, and at least one available calculated LDL-C value within one of the analysis windows up to Week 24 (including all calculated LDL-C on-treatment and off-treatment).

[00304] The secondary efficacy analysis population was the modified intent-to-treat (mITT) population, defined as all randomized patients who took at least one dose or part of a dose of the double-blind investigational medicinal product (IMP) and who had an available calculated LDL-C value at baseline and at least one available calculated LDL-C value within one of the analysis windows up to Week 24 during the efficacy treatment period. The efficacy treatment period was defined as the time from the first double-blind IMP administration up to 21 days after the last double-blind injection.

[00305] The safety population included all randomized patients who received at least one dose or part of a dose of the double-blind IMP.

Efficacy analyses:

[00306] Primary analyses of efficacy endpoints were conducted using an ITT approach (based on the ITT population defined above), including all lipid data, regardless of whether the patient was continuing therapy or not. This corresponds to ITT estimands, defined for primary and key secondary endpoints. In addition, analyses were also conducted using an on-treatment approach (based on the mITT population defined above), including lipid data collected during the efficacy treatment period. This corresponds to on-treatment estimands of key secondary endpoints.

[00307] The ITT approach analyzed all patients, irrespective of their adherence to the treatment; it assessed the benefit of the treatment strategy and reflected as much as possible the effect in a population of patients. The on-treatment approach analyzed the effect of treatment, restricted to the period during which patients actually received the treatment. It assessed the benefit that a treatment would achieve in patients adherent to treatment up to the considered time point.

[00308] Efficacy analyses were performed according to treatment as-randomized.

[00309] All measurements, scheduled or unscheduled, fasting or not fasting, were assigned to analysis windows in order to provide an assessment from Week 4 to Week 78 time points.

[00310] With regards to the primary efficacy analysis (ITT approach), the percent change in calculated LDL-C from baseline to Week 24 was analyzed using a mixed-effect model with repeated measures (MMRM) approach. All post-baseline data available from Week 4 to Week 52 analysis windows were used and missing data were accounted for by the MMRM. The model included the fixed categorical effects of treatment group (placebo versus alirocumab), randomization strata (as per IVRS), time point (Week 4 to Week 52), treatment-by-time point interaction and strata-by-time point interaction, as well as, the continuous fixed covariates of baseline LDL-C value and baseline value-by-time- point interaction. This model provided baseline adjusted least-squares means (LSmeans) estimates at Week 24 for both treatment groups with their corresponding SEs and 95% confidence intervals. To compare the alirocumab to the placebo group, an appropriate contrast statement was used to test the differences of these estimates at the 5% alpha level.

[00311] A hierarchical procedure has been defined to test key secondary endpoints while controlling for multiplicity (using above order of key secondary endpoints). The first key secondary endpoint was the percent change in calculated LDL-C from baseline to Week 24 using an on-treatment approach.

[00312] Continuous secondary variables anticipated to have a normal distribution (i.e., lipids other than TGs and Lp(a)) were analyzed using the same MMRM model as for the primary endpoint. Continuous endpoints anticipated to have a non-normal distribution (i.e., TG and Lp(a)) were analyzed using multiple imputation approach for handling of missing values followed by robust regression model with endpoint of interest as response variable using M-estimation (using SAS ROBUSTREG procedure) with treatment group, randomization strata (as per IVRS) and corresponding baseline value(s) as effects to compare treatment effects. Combined estimate for mean in both treatment groups, as well as the differences of these estimates, with their corresponding SEs, 95% CIs and p-value were provided (through SAS MIANALYZE procedure).

[00313] Binary secondary efficacy endpoints were analyzed using multiple imputation approach for handling of missing values followed by stratified logistic regression with treatment group as main effect and corresponding baseline value(s) as covariate, stratified by randomization factors (as per IVRS). Combined estimates of odds ratio versus placebo, 95% CI, and p-value were provided (through SAS MIANALYZE procedure).

Safety analyses:

[00314] Safety analyses were descriptive, performed on the safety population according to treatment actually received. The safety analysis focused on the TEAE period defined as the time from the first dose of double-blind injection up to 70 days after the last double-blind injection. TEAE which developed, worsened or became serious or PCSA occurring after the patient's first injection in the open-label extension study (LTS13643) were not considered in the TEAE period. TEAE period was truncated at the common study cut-off date.

RESULTS I- PRE-SPECIFIED ANALYSIS

Patient accountability

[00315] A pre-specified interim analysis was performed when all patients reached one year and approximately 25 percent of patients reached 18 months of treatment. Of the 2341 randomized patients, three patients were not treated and were not therefore included in the safety population.

[00316] Thirty-one randomized patients were not included in the ITT population (No LDL-C value within one of the analysis windows up to week 24).

[00317] Forty-one randomized patients were excluded from the mITT population (patients excluded from the ITT population and patients with no LDL-C value within one of the analysis windows up to week 24 during the efficacy treatment period).

Table 29- Analysis populations

	Placebo	Alirocumab 150 Q2W	All
Randomized population	788 (100%)	1553 (100%)	2341 (100%)
Efficacy populations			
Intent-to-Treat (ITT)	780 (99.0%)	1530 (98.5%)	2310 (98.7%)
Modified Intent-to-Treat (mITT)	777 (98.6%)	1523 (98.1%)	2300 (98.2%)
Safety population	788	1550	2338

Note: The safety population patients are tabulated according to treatment actually received (as treated). For the other populations, patients are tabulated according to their randomized treatment.

Study disposition

[00318] At the cut-off date in this pre-specified analysis, 607 (25.9%) patients have completed the 18-months double-blind treatment period (defined as an exposure of at least 76 weeks and a Week 78 visit performed), including at least 400 patients in the alirocumab group, as agreed with Health Authorities during "End of Phase 2" meeting consultation: 405 patients (26.1%) in the alirocumab group and 202 patients (25.6%) in the placebo group.

[00319] In the alirocumab group, 1550 of the 1553 actually received alirocumab. 23% (n=349) of these patients completed 78 weeks, 20% (n=311) discontinued treatment, and 57% (n=890) are still receiving treatment. Alirocumab-group patients that discontinued treatment did so because of poor compliance to the protocol (n = 54), an adverse event (n = 98), or another reason (n = 159). The ITT safety populations for the alirocumab group were 1530 and 1550 patients, respectively. In the placebo group, all 788 received placebo. 22% (n=176) of these patients completed 78 weeks, 19% (n=146) discontinued treatment and 59% (n=466) are still receiving treatment. Placebo-group patients that discontinued treatment did so because of poor compliance to the protocol (n = 34), an adverse event (n = 44), or another reason (n = 67). The ITT safety populations for the alirocumab group were 780 and 788 patients, respectively. Patients in the ITT population were included in all efficacy endpoints up to Week 52. Patients in the safety population received either alirocumab or placebo for at least 52 weeks.

[00320] Study disposition, exposure and safety analyses were assessed using all data up to the study common cut-off date and therefore include data beyond week 52 and up to week 78 or up to the Follow-up visit. Final results for primary efficacy endpoint (at Week 24) and key secondary efficacy endpoints (assessed up to Week 52) are provided in this first step analysis.

[00321] There were in total 525 (22.4%) randomized patients who completed the study treatment period up to the cut-off date in this pre-specified analysis, i.e. last IMP injection was taken (Week 76) and end of treatment visit (Week 78) was performed within 21 days after the last IMP injection and at least 525 days after randomization.

[00322] The double-blind IMP was prematurely discontinued for 455 (19.4%) randomized patients (310 (20.0%) patients in the alirocumab group and 145 (18.4%) patients in the placebo group). For 1358 (58.0%) randomized patients, treatment was ongoing at the time of the first-step analysis cut-off date.

[00323] Overall, the main reasons for study treatment discontinuation were "other reasons - other" and "adverse event": These "other reasons" included the following: subject refusal to continue (93 patients), patient did not meet eCRF criteria for completion of treatment due to either missed/out of window week 78 visit (71 patients), death (6 patients) (there was no decision of investigator to stop the treatment prior to death), miscellaneous (5 patients), lost-to-follow-up (4 patients), site closure (3 patients) and subject moved (2 patients).

[00324] In addition, among these 455 patients who prematurely discontinued, 219 (14.1%) randomized patients had prematurely discontinued the double-blind IMP before the Week 52 visit in the alirocumab group and 111 (14.1%) in the placebo group.

[00325] Finally, 139 (5.9%) patients participated in the optional ophthalmologic sub-study (instead of the planned 270 patients).

[00326] In this first step analysis, final results are available for primary efficacy endpoint at Week 24 and key secondary efficacy endpoints assessed at Week 12, Week 24 and Week 52. At week 24, the primary efficacy endpoint was available for 1384 (90.5%) in the alirocumab group and 708 (90.8%) in the placebo group.

[00327] The primary efficacy endpoint was missing for 218 patients. At the week 24 visit, the reasons for missingness were as follows: 108 samples not done due to earlier study discontinuation; 47 samples done outside analysis windows; 10 samples not done; 51 samples done but measurement could not be done (insufficient quantity, TGs>400 mg/dL (4.52 mmol/L) ...); and 2 samples not done for patients randomized but not treated.

Demographics and baseline characteristics

[00328] A total of 2341 patients were randomized in the study (1553 in alirocumab versus 788 in placebo group). Demographics characteristics, disease characteristics and lipid parameters at baseline were similar in the alirocumab group as compared to the placebo group. For the alirocumab group (N=1553), the age (mean years (SD)) was 60.4 (10.4), the percentage of males was 63.3% (N=983), the percentage white race was 92.8% (N=1441), and the BMI (mean kg/m^2 (SD)) was 30.2 (5.7). For the placebo group (N=788), the age (mean years (SD)) was 60.6 (10.4), the percentage of males was 60.2% (N=474), the percentage white race was 92.6% (N=730), and the BMI (mean kg/m^2 (SD)) was 30.5 (5.5).

[00329] 17.7% of patients (17.8% (N=276) of the alirocumab patients and 17.6% (N=139) of the placebo group) had heFH with or without established CHD or CHD risk equivalents. 82.3% of patients were enrolled with non-familial hypercholesterolemia with established CHD or CHD risk equivalents. A large majority of the randomized population (90.6%) had a history of Coronary Heart Disease (CHD) or CHD risk equivalents. CHD was reported for 68.6% of patients. 91.5% of the patients were classified as very high risk (see the note below).

[00330] Demographics characteristics, disease characteristics and lipid parameters at baseline were similar in the alirocumab group as compared to the placebo group. Mean (SD) baseline calculated LDL-C was 122.4 (42.2) mg/dL (3.171 (1.092) mmol/L). With regards to background lipid modifying therapy, 1032 (44.1%) patients took high intensity statin at randomization (i.e. atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg daily) and 334 (14.3%) were receiving ezetimibe in addition to the statin.

[00331] A summary of the baseline characteristics of the alirocumab and placebo groups is set forth in **Table 34**.

[00332] Exposure to injections was similar across treatment groups with a median exposure of 68 weeks. At the cut-off date (7 May 2014), 607 (25.9%) patients have completed the 18-months double-blind treatment period (ie. at least 76 weeks of exposure and the Week 78 visit completed), including at least 400 patients in the alirocumab group, as agreed with Health Authorities during End of Phase 2 meeting consultation: 405 patients (26.1%) in the alirocumab group and 202 patients (25.6%) in the placebo group.

Table 30 - Disease characteristics and other relevant baseline data – Randomized population

	Placebo (N=788)	Alirocumab 150 Q2W (N=1553)	All (N=2341)
Type of hypercholesterolemia			
Heterozygous Familial Hypercholesterolemia (heFH)	139 (17.6%)	276 (17.8%)	415 (17.7%)
Non-Familial Hypercholesterolemia (non-FH)	649 (82.4%)	1277 (82.2%)	1926 (82.3%)
Non-Familial Hypercholesterolemia patients			
Time from hypercholesterolemia diagnosis (years)			
Number	647	1273	1920
Mean (SD)	8.95 (7.29)	9.13 (7.65)	9.07 (7.53)
Median	7.36	7.46	7.44
Min : Max	-0.0 : 42.1	0.0 : 49.4	-0.0 : 49.4
Fredrickson classification of Hyperlipoproteinemia			
Number	649	1277	1926
IIa	455 (57.7%)	885 (57.0%)	1340 (57.2%)
IIb	194 (24.6%)	392 (25.2%)	586 (25.0%)
IV	0	0	0
Heterozygous Familial Hypercholesterolemia patients			
Time from hypercholesterolemia diagnosis (years)			
Number	139	276	415
Mean (SD)	10.58 (10.66)	11.09 (11.40)	10.92 (11.15)
Median	7.37	7.22	7.24
Min : Max	-1.4 : 44.2	-1.5 : 48.2	-1.5 : 48.2
Confirmation of diagnosis			
By genotyping	56 (7.1%)	111 (7.1%)	167 (7.1%)
By WHO/Simon Broome[a]	83 (10.5%)	165 (10.6%)	248 (10.6%)

[a] for heFH diagnosis not confirmed by genotyping.

Table 31 - Medical history of specific interest: cardiovascular history and risk factors – Randomized population

	Placebo (N=788)	Alirocumab 150 Q2W (N=1553)	All (N=2341)
Any cardiovascular history/risk factors	719 (91.2%)	1403 (90.3%)	2122 (90.6%)
Coronary heart disease [a]	552 (70.1%)	1055 (67.9%)	1607 (68.6%)
Acute Myocardial Infarction	309 (39.2%)	563 (36.3%)	872 (37.2%)
Silent Myocardial Infarction	16 (2.0%)	53 (3.4%)	69 (2.9%)
Unstable Angina	108 (13.7%)	183 (11.8%)	291 (12.4%)
Coronary Revascularization Procedures	368 (46.7%)	713 (45.9%)	1081 (46.2%)
Other Clinically Significant CHD [b]	233 (29.6%)	445 (28.7%)	678 (29.0%)
CHD associated with 1 or more comorbidity (among hypertension, diabetes or moderate CKD) and/or associated with other CVD (ischemic stroke, PAD)	449 (57.0%)	845 (54.4%)	1294 (55.3%)
Coronary heart disease risk equivalents [a]	323 (41.0%)	639 (41.1%)	964 (41.2%)
Ischemic Stroke	74 (9.4%)	158 (10.2%)	232 (9.9%)
Peripheral Arterial Disease	42 (5.3%)	80 (5.2%)	122 (5.2%)
Moderate Chronic Kidney Disease	103 (13.1%)	223 (14.4%)	326 (13.9%)
Known history of diabetes mellitus AND 2 or more additional risk factors	171 (21.7%)	316 (20.3%)	487 (20.8%)
At least 2 CHD risk equivalents or 1 CHD risk equivalent associated with hypertension or diabetes	308 (39.1%)	592 (38.1%)	900 (38.4%)
Categorization of CV risk per protocol			
Very high CV risk	728 (92.4%)	1413 (91.0%)	2141 (91.5%)
High CV risk	60 (7.6%)	140 (9.0%)	200 (8.5%)

Note: A patient can be counted in several categories.

[a] according to the items pre-listed in the e-CRF.

[b] diagnosed by invasive or non-invasive testing.

PAD defined as Intermittent claudication TOGETHER WITH ankle-brachial index ≤ 0.90 OR TOGETHER WITH peripheral revascularization procedure/surgery OR critical limb ischemia TOGETHER WITH peripheral revascularization procedure/surgery or thrombolysis.

Very high CV risk is defined as heFH patients with CHD or CHD risk equivalents or non-FH patients.

High CV risk is defined as heFH patients without CHD or CHD risk equivalents.

[00333] Note: 219 patients had neither a medical history of coronary heart disease nor a medical history of coronary heart disease risk equivalents. 200 of them are heFH patients (corresponding to high CV risk category). The other 19 are non-FH without established history

of CHD or CHD risk equivalents (i.e. exclusion criterion E01). By convention at the program level, these 19 patients with deviation are taken into account in the very high CV risk category.

[00334] The following summarizes the history of Lipid Modifying Therapy (LMT) including statin at screening: 1245 (53.2%) patients did not take atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg or simvastatin 80 mg daily. The most common reason was the regional practice and local labeling. Among the 656 (28.0%) patients who did not take high intensity statin or simvastatin 80 mg daily due to regional practice/local labeling, 375 (57.2%) patients took simvastatin 40 mg.

Table 32 - Background LMT at randomization – Randomized population

	Placebo (N=788)	Alirocumab 150 Q2W (N=1553)	All (N=2341)
Any statin	787 (99.9%)	1552 (>99.9%)	2339 (>99.9%)
Taking high intensity statin	342 (43.4%)	690 (44.4%)	1032 (44.1%)
Atorvastatin daily dose (mg)	283 (35.9%)	623 (40.1%)	906 (38.7%)
10	33 (4.2%)	67 (4.3%)	100 (4.3%)
20	62 (7.9%)	138 (8.9%)	200 (8.5%)
40	112 (14.2%)	240 (15.5%)	352 (15.0%)
80	73 (9.3%)	174 (11.2%)	247 (10.6%)
Other doses	3 (0.4%)	4 (0.3%)	7 (0.3%)
Rosuvastatin daily dose (mg)	199 (25.3%)	362 (23.3%)	561 (24.0%)
5	9 (1.1%)	20 (1.3%)	29 (1.2%)
10	34 (4.3%)	66 (4.2%)	100 (4.3%)
20	74 (9.4%)	134 (8.6%)	208 (8.9%)
40	80 (10.2%)	140 (9.0%)	220 (9.4%)
Other doses	2 (0.3%)	2 (0.1%)	4 (0.2%)
Simvastatin daily dose (mg)	306 (38.8%)	567 (36.5%)	873 (37.3%)
10	21 (2.7%)	43 (2.8%)	64 (2.7%)
20	84 (10.7%)	150 (9.7%)	234 (10.0%)
40	166 (21.1%)	323 (20.8%)	489 (20.9%)
80	30 (3.8%)	39 (2.5%)	69 (2.9%)
Other doses	5 (0.6%)	12 (0.8%)	17 (0.7%)
Any LMT other than statins[a]	220 (27.9%)	437 (28.1%)	657 (28.1%)
Any LMT other than nutraceuticals	176 (22.3%)	337 (21.7%)	513 (21.9%)
Ezetimibe	118 (15.0%)	216 (13.9%)	334 (14.3%)
Nutraceuticals	68 (8.6%)	134 (8.6%)	202 (8.6%)

[a] in combination with statins or not.

High intensity statin corresponds to atorvastatin 40 to 80 mg daily or rosuvastatin 20 to 40 mg daily.

Note: two patients, one in each group, did not receive statin at randomization and received the IMP (up to Week 10 for one patient and up to Week 74 for the other patient).

Table 33 - Lipid efficacy parameters at baseline – Quantitative summary in conventional units – Randomized population

	Placebo (N=788)	Alirocumab 150 Q2W (N=1553)	All (N=2341)
Calculated LDL-C (mg/dL)			
Number	788	1553	2341
Mean (SD)	121.9 (41.4)	122.7 (42.6)	122.4 (42.2)
Median	112.7	114.7	114.0
Q1 : Q3	95.0 : 140.9	94.2 : 141.0	94.6 : 140.9
Min : Max	19 : 404	39 : 424	19 : 424
Measured LDL-C (mg/dL)			
Number	677	1322	1999
Mean (SD)	115.6 (38.1)	117.2 (39.0)	116.7 (38.7)
Median	108.9	110.4	109.7
Q1 : Q3	91.5 : 132.0	90.3 : 134.0	90.7 : 132.8
Min : Max	17 : 358	30 : 359	17 : 359
Non-HDL-C (mg/dL)			
Number	788	1553	2341
Mean (SD)	152.0 (45.8)	152.6 (46.6)	152.4 (46.3)
Median	142.5	144.8	144.0
Q1 : Q3	122.0 : 174.5	121.2 : 173.0	121.6 : 174.0
Min : Max	31 : 420	54 : 475	31 : 475
Total-C (mg/dL)			
Number	788	1553	2341
Mean (SD)	201.9 (47.0)	202.4 (47.4)	202.2 (47.3)
Median	192.8	194.2	193.8
Q1 : Q3	170.3 : 225.3	171.0 : 223.2	170.7 : 224.7
Min : Max	78 : 477	108 : 521	78 : 521
HDL-C (mg/dL)			
Number	788	1553	2341
Mean (SD)	50.0 (12.4)	49.8 (12.2)	49.9 (12.3)
Median	48.6	48.0	48.3
Q1 : Q3	41.7 : 56.8	41.3 : 56.4	41.3 : 56.4
Min : Max	13 : 109	14 : 113	13 : 113
Fasting TGs (mg/dL)			
Number	787	1553	2340
Mean (SD)	151.5 (79.7)	150.7 (85.3)	150.9 (83.4)
Median	135.0	132.0	132.7
Q1 : Q3	94.7 : 188.5	93.8 : 183.2	94.0 : 185.0
Min : Max	35 : 650	31 : 1422	31 : 1422

Lipoprotein-(a)(mg/dL)			
Number	777	1521	2298
Mean (SD)	42.1 (47.2)	43.5 (48.7)	43.0 (48.2)
Median	20.9	22.2	22.0
Q1 : Q3	6.5 : 66.8	7.6 : 66.5	7.3 : 66.7
Min : Max	2 : 262	2 : 363	2 : 363
Apo-B (mg/dL)			
Number	778	1523	2301
Mean (SD)	101.4 (27.3)	101.9 (27.7)	101.7 (27.6)
Median	97.0	98.0	98.0
Q1 : Q3	84.0 : 115.0	83.0 : 116.0	83.0 : 115.0
Min : Max	18 : 247	42 : 268	18 : 268
Apo-A1 (mg/dL)			
Number	778	1523	2301
Mean (SD)	147.3 (27.3)	146.5 (25.1)	146.8 (25.9)
Median	145.0	145.0	145.0
Q1 : Q3	130.0 : 162.0	129.0 : 161.0	129.0 : 161.0
Min : Max	30 : 291	30 : 295	30 : 295
Apo-B/Apo-A1 (ratio)			
Number	778	1523	2301
Mean (SD)	0.713 (0.250)	0.719 (0.267)	0.717 (0.261)
Median	0.670	0.680	0.670
Q1 : Q3	0.560 : 0.830	0.550 : 0.830	0.560 : 0.830
Min : Max	0.12 : 3.17	0.27 : 4.80	0.12 : 4.80
Total-C/HDL-C (ratio)			
Number	788	1553	2341
Mean (SD)	4.228 (1.295)	4.252 (1.367)	4.244 (1.343)
Median	3.965	4.040	4.020
Q1 : Q3	3.355 : 4.835	3.350 : 4.820	3.350 : 4.830
Min : Max	1.66 : 12.61	1.81 : 16.64	1.66 : 16.64

Note: Measured LDL-C was assessed via the beta-quantification method.

Table 34 - Summary of Baseline Characteristics of the Alirocumab and Placebo Groups

Characteristic	**Alirocumab** (n=1553)	**Placebo** (n=788)
Age, years, mean (*SD*)	60.4 (*10.4*)	60.6 (*10.4*)
Male, % (n)	63.3% (983)	60.2% (474)
Race, White	92.8% (1441)	92.6% (730)
Race, Black or African-American	3.4% (53)	3.0% (24)
Hispanic/Latino	5.5% (85)	4.6% (36)

BMI, kg/m^2, mean (*SD*)	30.2 (*5.7*)	30.5 (*5.5*)
HeFH, % (n)	17.8% (276)	17.6% (139)
Diagnosis by genotyping	7.1% (111)	7.1% (56)
Clinical diagnosis (WHO/Simon Broome)	10.6% (165)	10.5% (83)
CHD history, % (n)	67.9% (1055)	70.1% (552)
Type 2 diabetes, % (n)	34.9% (542)	33.9% (267)
Current smoker, % (n)	20.9% (325)	20.2% (159)
Any statin[†], % (n)	99.9% (1552)	99.9% (787)
High-intensity statin[‡], % (n)	44.4% (690)	43.4% (342)
Any LLT other than statins, % (n)	28.1% (437)	27.9% (220)
High-dose statin [a]	46.9% (728)	46.8% (369)
Ezetimibe, % (n)	13.9% (216)	15.0% (118)
LDL-C, calculated mean (*SD*), mmol/L [mg/dL]	3.2 (*1.1*) [122.7 (*42.6*)]	3.2 (*1.1*) [121.9 (*41.4*)]
Median (IQR)	114.7 (94.2-141.0)	112.7 (95.0-140.9)
Range	39-424	19-404
LDL-C, measured mean (*SD*), mg/dL	117.2 (39.0)	115.6 (38.1)
Median (IQR)	110.4 (90.3-134.0)	108.9 (91.5-132.0)
Range	30-359	17-358
Non-HDL-C, mean (SD), mmol/L [mg/dL]	4.0 (1.2) [152.6 (46.6)]	3.9 (1.2) [152.0 (45.8)]
Apo B, mean (SD), mg/dL	101.9 (27.7)	101.4 (27.3)
Lp(a), mg/dL, median (IQR)	22.2 (7.6-66.5)	20.9 (6.5-66.8)
Fasting triglycerides, median (IQR)	132 (93.8-183.2)	135 (94.7-188.5)
HDL-C, mean (SD)	49.8 (12.2)	50.0 (12.4)
Apo A1, mean (SD), mg/dL	146.5 (25.1)	147.3 (27.3)

All patients on background of max-tolerated statin ± other lipid-lowering therapy. [†]Patients should receive either rosuvastatin 20-40 mg, atorvastatin 40-80 mg daily, or simvastatin 80 mg daily unless not tolerated and/or appropriate other dose given according to the judgement of the investigator.

[‡]High-intensity statin: atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily.

[a] High-dose statin: atorvastatin 40-80 mg, rosuvastatin 20-40 mg daily, or simvastatin 80 mg daily.

Dosage and duration

[00335] Exposure to injections was similar across treatment groups with a median exposure of 68 weeks. Of note, 817 (35.0%) patients were treated at least 76 weeks (543 (35.0%) patients in the alirocumab group and 274 (34.6%) patients in the placebo group). Among those 817

patients, 607 patients also completed the Week 78 visit at the time of the first step analysis cut-off date.

Primary efficacy endpoint

[00336] The ITT analysis includes all LDL-C values collected on-treatment and off-treatment up to Week 52. The primary endpoint (percent change in calculated LDL-C from baseline to Week 24) analysis is provided based on a MMRM model on the ITT population, using LS means estimates at Week 24. 146 (9.5%) patients in the alirocumab group and 72 (9.2%) patients in the placebo group did not have a calculated LDL-C value at Week 24. These missing values were accounted for by the MMRM model.

[00337] Results of the primary endpoint analysis are presented in **Table 35**, in mmol/L and mg/dL.

[00338] A statistically significant decrease in percent change in LDL-C from baseline to Week 24 was observed in alirocumab group (LS mean versus baseline - 61.0%) compared to the placebo group (LS mean versus baseline 0.8%) (LS mean difference vs. placebo of - 61.9%, $p<0.0001$).

[00339] In the alirocumab group, a consistent LDL-C reduction from baseline was observed from week 4 to Week 52. Calculated LDL-C values, change from baseline, and percent change from baseline for this period are presented in **Table 36** and **Figure 11** (ITT analysis of all available measurements over the 52 week observation period), and demonstrate a marked difference between the alirocumab and placebo treated groups.

Table 35 - Percent change from baseline in calculated LDL-C at Week 24: MMRM – ITT analysis – ITT population

Calculated LDL Cholesterol	Placebo (N=780)	Alirocumab 150 Q2W (N=1530)
Baseline (mmol/L)		
Number	780	1530
Mean (SD)	3.159 (1.077)	3.180 (1.106)
Median	2.920	2.974
Min : Max	0.49 : 10.47	1.01 : 10.99
Baseline (mg/dL)		
Number	780	1530
Mean (SD)	122.0 (41.6)	122.8 (42.7)
Median	112.7	114.8
Min : Max	19 : 404	39 : 424
Absolute level at week 24 (mg/dL)	118.9 (1.2)	48.3 (0.9)
Week 24 percent change from baseline (%)		
LS Mean (SE)	0.8 (1.0)	-61.0 (0.7)
LS mean difference (SE) vs placebo		-61.9 (1.3)
95% CI		(-64.3 to -59.4)

Calculated LDL Cholesterol	Placebo (N=780)	Alirocumab 150 Q2W (N=1530)
p-value vs placebo		<0.0001*

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point and strata-by-time point interaction, as well as the continuous fixed covariates of baseline calculated LDL-C value and baseline calculated LDL-C value-by-time point interaction

MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

The p-value is followed by a '*' if statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level

Table 36 - Calculated LDL-C over time – ITT analysis – ITT population

	Placebo (N=780)			Alirocumab 150 Q2W (N=1530)		
Calculated LDL-C	Value	Change from baseline	Percent change from baseline	Value	Change from baseline	Percent change from baseline
LS Mean (SE) (mmol/L)						
Baseline [a]	3.159 (0.039)	NA	NA	3.180 (0.028)	NA	NA
Week 4	3.109 (0.025)	-0.064 (0.025)	1.1 (0.9)	1.145 (0.018)	-2.028 (0.018)	-64.8 (0.6)
Week 8	3.084 (0.026)	-0.089 (0.026)	1.0 (0.9)	1.111 (0.019)	-2.061 (0.019)	-65.8 (0.7)
Week 12	3.112 (0.029)	-0.061 (0.029)	1.5 (1.0)	1.184 (0.020)	-1.989 (0.020)	-63.3 (0.7)
Week 16	3.076 (0.029)	-0.097 (0.029)	0.9 (1.0)	1.143 (0.021)	-2.030 (0.021)	-64.5 (0.7)
Week 24	3.081 (0.031)	-0.092 (0.031)	0.8 (1.0)	1.252 (0.022)	-1.921 (0.022)	-61.0 (0.7)
Week 36	3.066 (0.032)	-0.107 (0.032)	0.3 (1.1)	1.278 (0.023)	-1.895 (0.023)	-59.5 (0.8)
Week 52	3.187 (0.036)	0.014 (0.036)	4.4 (1.2)	1.376 (0.026)	-1.797 (0.026)	-56.8 (0.8)
LS Mean (SE) (mg/dL)						
Baseline [a]	122.0 (1.5)	NA	NA	122.8 (1.1)	NA	NA
Week 4	120.0 (1.0)	-2.5 (1.0)	1.1 (0.9)	44.2 (0.7)	-78.3 (0.7)	-64.8 (0.6)
Week 8	119.1 (1.0)	-3.4 (1.0)	1.0 (0.9)	42.9 (0.7)	-79.6 (0.7)	-65.8 (0.7)
Week 12	120.1 (1.1)	-2.4 (1.1)	1.5 (1.0)	45.7 (0.8)	-76.8 (0.8)	-63.3 (0.7)
Week 16	118.8 (1.1)	-3.7 (1.1)	0.9 (1.0)	44.1 (0.8)	-78.4 (0.8)	-64.5 (0.7)
Week 24	118.9 (1.2)	-3.6 (1.2)	0.8 (1.0)	48.3 (0.9)	-74.2 (0.9)	-61.0 (0.7)

Calculated LDL-C	Placebo (N=780) Value	Placebo (N=780) Change from baseline	Placebo (N=780) Percent change from baseline	Alirocumab 150 Q2W (N=1530) Value	Alirocumab 150 Q2W (N=1530) Change from baseline	Alirocumab 150 Q2W (N=1530) Percent change from baseline
Week 36	118.4 (1.2)	-4.1 (1.2)	0.3 (1.1)	49.3 (0.9)	-73.2 (0.9)	-59.5 (0.8)
Week 52	123.0 (1.4)	0.5 (1.4)	4.4 (1.2)	53.1 (1.0)	-69.4 (1.0)	-56.8 (0.8)

[a] Baseline is described using means and standard errors.

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis. The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, time point, treatment-by-time point interaction, strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction

MMRM model and baseline description run on patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model.

[00340] Of note, as part of the model assumption checks, the homogeneity of treatment effect across lipids baseline levels has been assessed and shows a significant treatment-by baseline LDL-C level interaction ($p<0.0001$). To further explore this interaction, the treatment effect on the primary efficacy endpoint, according to 4 classes of baseline LDL-C level, is presented below. It shows a decreased treatment effect versus placebo for higher baseline LDL-C levels (from -75.0% for patients with baseline LDL-C < 100 mg/dL to -41.3% for patients with LDL-C ≥ 160 mg/dL). This observation appears to be due to changes in the placebo group, where the percent change in LDL-C from baseline to Week 24 decreases with increasing baseline LDL-C categories. Conversely, the percent change in LDL-C from baseline to Week 24 is consistent across the different sub-categories of LDL-C within the alirocumab group.

Table 37 - Percent change from baseline in calculated LDL-C at Week 24: Subgroup analysis according to calculated LDL-C at baseline - ITT analysis

Subgroup factor Percent change from baseline in calculated LDL-C at week 24 (%)	Placebo (N=780)	Alirocumab 150 Q2W (N=1530)	Interaction p-value
Baseline calculated LDL-C			<0.0001
<100 mg/dL / <2.59 mmol/L			
Number	241	470	
LS means (SE)	13.6 (1.8)	-61.3 (1.3)	
LS mean difference (SE) vs placebo		-75.0 (2.2)	
95% CI		(-79.3 to -70.6)	
LS mean absolute LDL-C reduction, mg/dL	9.5	-51.6	

≥ 100 to <130 mg/dL / ≥ 2.59 to <3.37 mmol/L			
Number		285	562
LS means (SE)		0.5 (1.7)	-62.0 (1.2)
LS mean difference (SE) vs placebo			-62.5 (2.0)
95% CI			(-66.5 to -58.4)
LS mean absolute LDL-C reduction, mg/dL		0.0	-71.2
≥ 130 to <160 mg/dL / ≥ 3.37 to <4.14 mmol/L			
Number		143	271
LS means (SE)		-5.2 (2.4)	-59.8 (1.7)
LS mean difference (SE) vs placebo			-54.6 (2.9)
95% CI			(-60.3 to -48.8)
LS mean absolute LDL-C reduction, mg/dL		-7.6	-85.3
≥ 160 mg/dL / ≥ 4.14 mmol/L			
Number		111	227
LS means (SE)		-18.2 (2.8)	-59.5 (1.9)
LS mean difference (SE) vs placebo			-41.3 (3.3)
95% CI			(-47.8 to -34.8)
LS mean absolute LDL-C reduction, mg/dL		-33.7	-115.8
Baseline HDL-C				0.0989
<40 mg/dL / <1.04 mmol/L			
Number		151	306
LS means (SE)		0.5 (2.3)	-65.5 (1.6)
LS mean difference (SE) vs placebo			-66.1 (2.8)
95% CI			(-71.6 to -60.5)
≥ 40 mg/dL / ≥ 1.04 mmol/L			
Number		629	1224
LS means (SE)		0.9 (1.1)	-59.9 (0.8)
LS mean difference (SE) vs placebo			-60.8 (1.4)
95% CI			(-63.6 to -58.1)

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis.

The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, subgroup factor, time point, and the interactions treatment-by-time point, strata-by-time point, subgroup factor-by-time point, treatment group-by-subgroup factor, and treatment group-by-subgroup factor-by-time point for baseline LDL-C as subgroup factor.

For other subgroup factors, the model also includes the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction.

Number corresponds to number of patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model

The p-value is provided for descriptive purpose only

Key secondary efficacy endpoints

[00341] Table 38 summarizes analysis results on key secondary endpoints in the hierarchical order. All key secondary endpoints are statistically significant according to the hierarchical testing procedure.

Table 38

Endpoint	Analysis	Results	P-value
Calculated LDL-C - Percent change from baseline to Week 24	On-treatment	LS mean difference vs. placebo of -63.5%	<0.0001
Calculated LDL-C - Percent change from baseline to Week 12	ITT	LS mean difference vs. placebo of -64.8%	<0.0001
Calculated LDL-C - Percent change from baseline to Week 12	On-treatment	LS mean difference vs. placebo of -65.5%	<0.0001
Measured LDL-C (by ultracentrifugation) - Percent change from baseline to Week 24	ITT	LS mean difference vs. placebo of -61.3%	<0.0001
Apo-B - Percent change from baseline to Week 24	ITT	LS mean difference vs. placebo of -54%	<0.0001
Apo-B - Percent change from baseline to Week 24	On-treatment	LS mean difference vs. placebo of -55.5%	<0.0001
Non-HDL-C - Percent change from baseline to Week 24	ITT	LS mean difference vs. placebo of -52.3%	<0.0001
Non-HDL-C - Percent change from baseline to Week 24	On-treatment	LS mean difference vs. placebo of -53.7%	<0.0001
Total-C - Percent change from baseline to Week 24	ITT	LS mean difference vs. placebo of -37.5%	<0.0001
Apo-B - Percent change from baseline to Week 12	ITT	LS mean difference vs. placebo of -56%	<0.0001
Non-HDL-C - Percent change from baseline to Week 12	ITT	LS mean difference vs. placebo of -54.6%	<0.0001
Total-C - Percent change from baseline to Week 12	ITT	LS mean difference vs. placebo of -39%	<0.0001
Proportion of very high CV risk patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C < 100 mg/dL (2.59 mmol/L) at Week 24	ITT	combined estimate for odds-ratio vs. placebo of 71.5	<0.0001

Proportion of very high CV risk patients reaching calculated LDL-C < 70 mg/dL (1.81 mmol/L) or high CV risk patients reaching calculated LDL-C < 100 mg/dL (2.59 mmol/L) at Week 24	On-treatment	combined estimate for odds-ratio vs. placebo of 93.4	<0.0001
Proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24	ITT	combined estimate for odds-ratio vs. placebo of 74.6	<0.0001
Proportion of patients reaching calculated LDL-C <70 mg/dL (1.81 mmol/L) at Week 24	On-treatment	combined estimate for odds-ratio vs. placebo of 97.3	<0.0001
Lp(a) - Percent change from baseline to Week 24	ITT	combined estimate for adjusted mean difference vs. placebo of -25.6%	<0.0001
HDL-C - Percent change from baseline to Week 24	ITT	LS mean difference vs. placebo of 4.6%	<0.0001
Fasting TGs - Percent change from baseline to Week 24	ITT	combined estimate for adjusted mean difference vs. placebo of -17.3%	<0.0001
Apolipoprotein A1 - Percent change from baseline to Week 24	ITT	LS mean difference vs. placebo of 2.9%	<0.0001
Lp(a) - Percent change from baseline to Week 12	ITT	combined estimate for adjusted mean difference vs. placebo of -25.1%	<0.0001
HDL-C - Percent change from baseline to Week 12	ITT	LS mean difference vs. placebo of 5.6%	<0.0001
Fasting TGs - Percent change from baseline to Week 12	ITT	combined estimate for adjusted mean difference vs. placebo of -17.9%	<0.0001
Apolipoprotein A1 - Percent change from baseline to Week 12	ITT	LS mean difference vs. placebo of 4%	<0.0001

Table 39 - Percent change from baseline in lipid parameters at Week 24 (ITT population[a])

Secondary endpoints	**Placebo (N=780)**	**Alirocumab 150 Q2W (N=1530)**
Proportion (%) of patients reaching calculated LDL-C levels at Week 24		
<70 mg/dL (very high risk) or <100 mg/dL (high risk)	8.5	80.7
p-value vs placebo		<0.0001*
<70 mg/dL (regardless of risk)	8.0	79.3
p-value vs placebo		<0.0001
Percentage change from baseline to Week 78 in calculated LDL-C	3.6 (1.3)	-52.4 (0.9)
LS mean difference (SE) vs placebo		-56.0 (1.6)
95% CI		-59.1 to -52.8
p-value vs placebo		<0.001
LS mean (SE) change from baseline to Week 24 (%) in secondary lipid parameters		
Non-HDL-C	0.7 (0.9)	-51.6 (0.6)
LS mean difference (SE) vs placebo		-52.3 (1.1)
95% CI		-54.4 to -50.2

p-value vs placebo		<0.0001
Apo B	1.2 (1.0)	-52.8 (0.7)
LS mean difference (SE) vs placebo		-54.0 (1.2)
95% CI		-56.3 to -51.7
p-value vs placebo		<0.0001
Total cholesterol	-0.3 (0.7)	-37.8 (0.5)
LS mean difference (SE) vs placebo		-37.5 (0.8)
95% CI		-39.1 to -35.9
p-value vs placebo		<0.0001
Lipoprotein (a)[b]	-3.7 (1.0)	-29.3 (0.7)
LS mean difference (SE) vs placebo		-25.6 (1.3)
95% CI		-28.1 to -23.1
p-value vs placebo		<0.0001
Fasting triglycerides[b]	1.8 (1.2)	-15.6 (0.8)
LS mean difference (SE) vs placebo		-17.3 (1.4)
95% CI		-20.1 to -14.6
p-value vs placebo		<0.0001
HDL-C	-0.6 (0.5)	4.0 (0.4)
LS mean difference (SE) vs placebo		4.6 (0.7)
95% CI		3.3 to 5.9
p-value vs placebo		<0.0001
Apo A1	1.2 (0.6)	4.0 (0.4)
LS mean difference (SE) vs placebo		2.9 (0.7)
95% CI		1.6 to 4.2
p-value vs placebo		<0.0001
Number of patients with measured LDL-C[C] values available	652	1278
LS mean (SE) change from baseline to Week 24 in measured LDL-C, %	3.5 (1.1)	-57.8 (0.8)
LS mean difference (SE) vs placebo		-61.3 (1.4)
95% CI		-64.0 to -58.5
p-value vs placebo		<0.0001

Abbreviations: CI, confidence intervals; HDL, high-density lipoprotein; ITT, intention-to-treat; LDL, low-density lipoprotein; LS, least squares; LLT, lipid-lowering therapy; SD, standard deviation; SE, standard error.

[a] Primary and secondary efficacy analyses were conducted using an ITT approach including patients with baseline calculated LDL -cholesterol value and at least one calculated LDL-cholesterol value on or off-treatment within one of the analysis windows up to week 24. LS means, SE and p-value taken from mixed-effect model with repeated measures analysis. The p-values are significant according to the fixed hierarchical approach used to ensure control of the overall type-1 error rate at the 0.05 level.

[b] Combined estimate for adjusted mean (SE) shown for lipoprotein (a) and triglycerides.

[C] LDL-cholesterol measured by beta-quantification.

Table 40 - Percent change from baseline in lipid parameters at Week 24 – On-Treatment analysis[a]

	Placebo (N=777)	Alirocumab 150 Q2W (N=1523)
Calculated LDL-C		
Baseline, mean (SD) mg/dL	121.9 (41.5)	122.8 (42.7)
Range	19-404	39-424
LS mean (SE) change from baseline to Week 24 (%)	0.7 (1.0)	-62.8 (0.7)
LS mean difference (SE) vs placebo		-63.5 (1.2)
95% CI		-65.9 to -61.2
p-value vs placebo		<0.0001
LS mean (SE) change from baseline to Week 24 (%) in secondary lipid parameters		
Non-HDL-C	0.6 (0.9)	-53.1 (0.6)
LS mean difference (SE) vs placebo		-53.7 (1.0)
95% CI		-55.7 to -51.6
p-value vs placebo		<0.0001
Apo B	1.2 (0.9)	-54.3 (0.7)
LS mean difference (SE) vs placebo		-55.5 (1.2)
95% CI		-57.7 to -53.2
p-value vs placebo		<0.0001
Total cholesterol	-0.4 (0.6)	-38.8 (0.5)
LS mean difference (SE) vs placebo		-38.4 (0.8)
95% CI		-39.9 to -36.9
p-value vs placebo		<0.0001
Lipoprotein (a)[b]	-3.9 (1.0)	-30.2 (0.7)
LS mean difference (SE) vs placebo		-26.3 (1.3)
95% CI		-28.8 to -23.8
p-value vs placebo		<0.0001
Triglycerides[b]	1.4 (1.2)	-15.8 (0.8)
LS mean difference (SE) vs placebo		-17.2 (1.4)
95% CI		-20.0 to -14.4
p-value vs placebo		<0.0001
HDL-C	-0.7 (0.5)	4.2 (0.4)
LS mean difference (SE) vs placebo		4.9 (0.7)
95% CI		3.6 to 6.1
p-value vs placebo		<0.0001
Apo A1	1.2 (0.6)	4.2 (0.4)
LS mean difference (SE) vs placebo		2.9 (0.7)
95% CI		1.6 to 4.3
p-value vs placebo		<0.0001

Abbreviations: CI, confidence intervals; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LS, least squares; LLT, lipid-lowering therapy; SE, standard error.

[a] Only patients who were receiving study treatment were included in the on-treatment analysis. The on-treatment analysis excluded any patients without a calculated LDL-cholesterol value available between the first dose of study treatment up until 21 days after last injection.

[b] Combined estimate for adjusted mean (SE) shown for lipoprotein (a) and triglycerides.

P values taken from mixed-effect model with repeated measures analysis.

Table 41 - Percent change from baseline in calculated LDL-C at Week 24 (Pattern Mixture Model[a])

	Placebo (N=780)	Alirocumab 150 Q2W (N=1523)
Calculated LDL-C		
Baseline, mean (SD) mg/dL	122.0 (41.6)	122.7 (42.7)
Range	19-404	39-424
LS mean (SE) change from baseline to Week 24 (%)	0.7 (1.1)	-57.8 (0.8)
LS mean difference (SE) vs placebo		-58.5 (1.3)
95% CI		-61.1 to -55.8
p-value vs placebo		<0.0001

Abbreviations: CI, confidence intervals; LDL, low-density lipoprotein; LS, least squares; LLT, lipid-lowering therapy; SE, standard error.
[a] This sensitivity analysis has been conducted to further evaluate the impact of missing data on the primary endpoint: in this approach, missing calculated LDL-cholesterol values during the "on-treatment" period were multiply imputed using a model assuming Missing At Random and missing calculated LDL-cholesterol values during the post-treatment period were multiply imputed using random draws from a normal distribution, with mean equal to subject's own baseline value.

[00342] Detailed analyses for each key secondary endpoint is described herein.

[00343] The on-treatment analysis of calculated LDL-C percent change from baseline to Week 24 shows consistent results with the ITT analysis with a LS mean difference vs. placebo of -63.5% in the on-treatment analysis versus -61.9% in the ITT analysis. Indeed, few patients had LDL-C values collected post-treatment (i.e. more than 21 days after last injection at week 24: 37 patients (2.4%) in the alirocumab group versus 20 (2.6%) in the placebo group. Percent change from baseline in lipid parameters at Week 24 in the ITT population and the on-treatment population can be seen in **Table 39** and **Table 40**, respectively. The pattern mixture model analysis of percent change from baseline in calculated LDL-C at Week 24 can be seen in **Table 41**.

[00344] The ITT and on-treatment analyses of calculated LDL-C percent change from baseline to Week 12 also shows consistent results.

[00345] At Week 24, the treatment effect on measured LDL-C is comparable to the effect on calculated LDL-C. Results on measured LDL-C will be further investigated, including the correlation between calculated and measured LDL-C.

[00346] ITT analysis was performed on Apo B, non-HDL-C and total-C at Week 12 and 24. On-treatment analysis was also performed at Week 24 for Apo B and non-HDL-C. Results of ITT and on-treatment analyses are similar for these 2 lipid parameters. The alirocumab group exhibited a significant reduction in non-HDL-C, ApoB and Lp(a) levels relative to placebo at 24 weeks.

[00347] On the ITT analysis at Week 24, 80.7% of very high CV risk or high CV risk patients reached calculated LDL-C < 70 mg/dL or < 100 mg/dL, respectively, in the alirocumab group versus 8.5% in placebo group ($p < 0.0001$). Regarding the on-treatment analysis at Week 24, 82.8% of very high CV risk or high CV risk patients reached calculated LDL-C < 70 mg/dL or < 100 mg/dL, respectively, in the alirocumab group versus 8.5% in placebo group.

[00348] Proportion of patients reaching calculated LDL-C <70 mg/dL was studied on ITT and on-treatment analysis at Week 24. 79.3% of patients from the alirocumab group reached this level on the ITT analysis (81.2% on the on-treatment analysis) versus 8.0% in the placebo group on the ITT analysis (8.0% in the on-treatment analysis).

Primary efficacy endpoint according to subgroup status

[00349] As described next, comparisons of the primary efficacy endpoint in various subgroups were analyzed, including HeFH status, demographic groups, medical history, and patients who reached to consecutive LDL-C <25 mg/dL.

[00350] A comparison in the percent change in LDL-C from baseline to week 24 between patients who have heterozygous familial hypercholesterolemia ("HeFH"), and those who do not, is provided in Table 43 and Figures 12A-C. **Figure 12B** shows a comparison between the population of HeFH patients that have baseline LDL-C levels of <160 mg/dL or ≥ 160 mg/dL; **Figure 12C** shows a comparison between the population of HeFH patients that have baseline LDL-C levels of <190 mg/dL or ≥ 190 mg/dL. All patients were on a background treatment including maximally tolerated statins and optional further lipid lowering therapies. The decrease in percent change in LDL-C from baseline to Week 24 was statistically significant in the alirocumab groups compared to the placebo groups regardless of whether the patients had HeFH (see Figure 12A). The decrease in percent change in LDL-C from baseline to Week 24 was also statistically significant in the alirocumab groups compared to the placebo groups regardless of and whether the patients with HeFH had LDL-C ≥ 160 mg/dL or <160 mg/dL (see **Figure 12B**) or LDL-C ≥ 190 mg/dL or <190 mg/dL (see **Figure 12C**).

[00351] The difference seen between LS mean (SE) percent change from baseline to Week 24 for LDL-C in alirocumab treated patients (compared to placebo patients) was also consistent in patients with PCSK9 levels that were less or more than the median total or free PCSK9 value. Median total PCSK9 levels were 637 ng/mL in the alirocumab group and 640 ng/mL in the placebo group. Total PCSK9 levels are defined as all circulating PCSK9, which includes PCSK9 that is free (unbound) as well as PCSK9 that is bound by anti-PCSK9 antibodies (and inactive). For patients with total PCSK9 levels below the median, the percent change from baseline in calculated LDL-C was significantly greater in the alirocumab group (LS mean versus baseline -60.1%) compared to the placebo group (LS mean versus baseline -2.8%) (LS mean difference

vs. placebo of –57.3%, p < 0.0001). For patients with total PCSK9 levels at or above the median, the percent change from baseline in calculated LDL-C was significantly greater in the alirocumab group (LS mean versus baseline -62.1%) compared to the placebo group (LS mean versus baseline 4.1%) (LS mean difference vs. placebo of -66.0%, p < 0.0001). The percent change in LDL-C from baseline to Week 24 showed a statistically greater reduction in subjects with total PCSK9 levels at or above the median compared to those with total PCSK9 levels below the median (interaction p-value 0.0003).

[00352] Similarly, for patients with free PCSK9 levels below the median, the percent change from baseline in calculated LDL-C was significantly greater in the alirocumab group (LS mean versus baseline -59.4%) compared to the placebo group (LS mean versus baseline -1.6%) (LS mean difference vs. placebo of –58.0%, p < 0.0001). For patients with free PCSK9 levels at or above the median, the percent change from baseline in calculated LDL-C was significantly greater in the alirocumab group (LS mean versus baseline -62.7%) compared to the placebo group (LS mean versus baseline 3.0%) (LS mean difference vs. placebo of -66.0%, p < 0.0001). The percent change in LDL-C from baseline to Week 24 showed a statistically greater reduction in subjects with free PCSK9 levels at or above the median compared to those with free PCSK9 levels below the median (interaction p-value 0.0015).

[00353] The decrease in percent change in LDL-C from baseline to Week 24 seen in this study was also statistically significant in the alirocumab groups compared to the placebo groups in both males and females. In men, the percent change from baseline in calculated LDL-C was significantly greater in the alirocumab group (LS mean versus baseline -65.5%) compared to the placebo group (LS mean versus baseline -0.7%) (LS mean difference vs. placebo of -64.7%, p < 0.0001). In women, the percent change from baseline in calculated LDL-C was significantly greater in the alirocumab group (LS mean versus baseline -53.4%) compared to the placebo group (LS mean versus baseline 3.2%) (LS mean difference vs. placebo of -56.6%, p < 0.0001). The percent change in LDL-C from baseline to Week 24 showed a statistically greater reduction in men than women (interaction p-value 0.0014).

[00354] The decrease in percent change in LDL-C from baseline to Week 24 seen in the ODDYSEY LONG TERM study was also statistically significant in the alirocumab groups compared to the placebo groups in different subgroups, including race, age, BMI, moderate chronic kidney disease, diabetes status, and baseline fasting TG levels (see **Figure 13**), different statin and lipid-lowering therapy (LLT) subgroups (see **Figure 14**). All patients were on a background statin (at the maximum tolerated level). A subset of patients also received a further lipid lowering therapy.

[00355] Two consecutive calculated LDL-C values <25 mg/dL (< 0.65 mmo/L) were observed in 562 (37.4%) patients. An analysis was made on the frequency of TEAEs (PT) vs. the overall

alirocumab group assessing for marked imbalances. TEAEs that were AESI which occurred in patients with two consecutive calculated LDL-C values <25 mg/dL (< 0.65 mmo/L) were compared for frequency with the overall alirocumab group. Finally, theoretical AEs were reviewed to ensure that no such reported term existed, and if present were further investigated at the patient level data. No particular safety concern has been observed from such analysis in these patients.

Table 42 - Number (%) of patients with 2 consecutive LDL-C < 25mg/dL (<0.65 mmol/L) during the treatment period– Safety population (at the time of the pre-specified analysis)

	Placebo (N=788)	Alirocumab 150 Q2W (N=1550)
Patients with 2 consecutive calculated LDL-C value <25 mg/dL [1]	0/767	562/1503 (37.4%)
Time to the first calculated LDL-C value < 25 mg/dL (weeks) [2]		
Number	0	562
Mean (SD)		11.03 (11.51)
Median		4.86
Min : Max		2.3 : 65.1
Patients with 2 consecutive calculated LDL-C value <15 mg/dL [1]	0/767	223/1503 (14.8%)
Time to the first calculated LDL-C value < 15 mg/dL (weeks) [2]		
Number	0	223
Mean (SD)		12.99 (12.43)
Median		8.14
Min : Max		3.1 : 64.6

The number (n) represents the subset of the total number of patients who met the criteria
The denominator (/N) within a treatment group is the number of patients for the treatment group who had at least two calculated LDL-C values assessed at least 21 days apart in the efficacy period
[1] 2 consecutive values are considered if spaced out by at least 21 days
[2] First calculated LDL-C value <25 or <15 mg/dL among the first 2 consecutive calculated LDL-C values <25 or <15 mg/dL per patient

Table 43 - Percent change from baseline in calculated LDL-C at Week 24: according to heFH status at randomization - ITT population

Subgroup factor Percent change from baseline in calculated LDL-C at week 24 (%)	Placebo (N=780)	Alirocumab 150 Q2W (N=1530)	Interaction p-value
HeFH			0.6038
HeFH population			
Number	145	271	
LS means (SE)	7.0 (2.4)	-56.3 (1.9)	
LS mean difference (SE) vs placebo		-63.2 (2.9)	
95% CI		(-69.0 to -57.5)	

Subgroup factor Percent change from baseline in calculated LDL-C at week 24 (%)	Placebo (N=780)	Alirocumab 150 Q2W (N=1530)	Interaction p-value
Non-HeFH population			
Number	635	1259	
LS means (SE)	-0.5 (1.1)	-62.1 (0.8)	
LS mean difference (SE) vs placebo		-61.5 (1.4)	
95% CI		(-64.3 to -58.8)	

Note: Least-squares (LS) means, standard errors (SE) and p-value taken from MMRM (mixed-effect model with repeated measures) analysis.
The model includes the fixed categorical effects of treatment group, randomization strata as per IVRS, subgroup factor, time point, and the interactions treatment-by-time point, strata-by-time point, subgroup factor-by-time point, treatment group-by-subgroup factor, and treatment group-by-subgroup factor-by-time point, as well as the continuous fixed covariates of baseline LDL-C value and baseline LDL-C value-by-time point interaction.
Number corresponds to number of patients with a baseline value and a post-baseline value in at least one of the analysis windows used in the model
The p-value is provided for descriptive purpose only

Summary efficacy results:

[00356] At Week 24, the percent change from baseline in calculated LDL-C in the ITT population was significantly greater in the alirocumab group (LS mean versus baseline -61.0%) compared to the placebo group (LS mean versus baseline 0.8%) (LS mean difference vs. placebo of -61.9%, $p < 0.0001$) (see **Table 35**). The on-treatment analysis of LDL-C percent change from baseline to Week 24 shows consistent results with the ITT analysis with a LS mean difference vs. placebo of -63.5% in the on-treatment analysis ($p<0.0001$). Indeed, at Week 24, few patients (2.5% of patients overall) had LDL-C values collected post-treatment (i.e. more than 21 days after last injection). At Week 24, the treatment effect on measured LDL-C (LS mean versus baseline -61.3%) is comparable to the effect on calculated LDL-C (ITT analysis).

[00357] In the alirocumab group, a consistent LDL-C reduction from baseline was observed from week 4 to Week 52.

[00358] The homogeneity of treatment effect across lipids baseline levels was assessed and it showed a significant treatment-by baseline LDL-C level interaction ($p<0.0001$). This observation appears to be due to changes in the placebo group. Indeed the change in LDL-C from baseline to Week 24 is consistent across the different sub-categories of LDL-C within the alirocumab group. The LS mean (SE) percent change from baseline to Week 24 for LDL-C in alirocumab group patients was statistically significant and consistent across a range of LDL-C baseline values (**Table 37**).

[00359] All key secondary endpoints were statistically significant according to the hierarchical testing procedure.

[00360] Two consecutive calculated LDL-C values <25 mg/dL (< 0.65 mmo/L) were observed in 562 (37.4%) patients. No particular safety concern has been observed in these patients.

Summary safety results:

[00361] For the purposes of this study, TEAE are adverse events that developed, worsened, or became serious during the TEAE period (time from the first dose of the double-blind treatment to seventy days after the last dose). At the time of the pre-specified analysis, the percentages of patients who experienced TEAE, serious TEAE and TEAE leading to treatment discontinuation were similar between treatment groups (see **Table 44**).

[00362] The most frequently reported SOC in both treatment groups (≥ 10%) were "infections and infestations" (45.5% in the alirocumab group versus 46.1% in the placebo group), "musculoskeletal and connective tissue disorders" (27.2% in the alirocumab group vs. 28.6% in the placebo group), "gastrointestinal disorders" (18.6% in the alirocumab group vs.18.8% in the placebo group), "nervous system disorders" (17.0% in the alirocumab group vs.17.8% in the placebo group) "general disorders and administration site conditions" (15.4% in the alirocumab group vs. 17% in the placebo group), "injury, poisoning and procedural complications" (13.4% in the alirocumab group vs. 14.2% in the placebo group), and "respiratory, thoracic and mediastinal disorders" (11.0% vs. 10.9%). **Table 45** lists the number of TEAEs for selected system-organ-classes. **Table 46** lists the percentage of different TEAEs in alirocumab and placebo treated groups as well as specifically listing the TEAEs observed in alirocumab-treated patients (by percentage of patients) with two consecutive LDL-C measurements of less than 25 mg/dL. All patients were on a background statin (at the maximum tolerated level). A subset of patients also received a further lipid lowering therapy. Patients who have acheived LDL-C levels of less than 25 mg/dL in two or more consecutive periods make up 36.3% of the patient population treated with alirocumab (562 patients out of 1550). Certain laboratory values of interest (alanine aminotransferase > 3 x ULN, aspartate aminiotransferase > 3 x ULN, and creatine kinase >3 x ULN) are shown in **Table 47**. Few alirocumab patients (31 out of 1461, 2.1%) had decreased plasma vitamin E levels below the outer limit of normal during the TEAE period (compared to 1 patient out of 738 in the placebo group, 0.1%).

[00363] No marked imbalance was observed on the frequency of TEAE (Preferred Term). The following TEAEs were the most frequently reported in both treatment groups (≥ 5% in any group): nasopharyngitis (12.6% in alirocumab vs. 12.7% in placebo group), upper respiratory tract infection (7.0% vs. 8.0%), injection site reaction (5.7% vs. 4.3%), influenza (5.4% vs. 5.5%), diarrhea (5.3% vs 5.1%), urinary tract infection (5.2% vs. 6.2%), bronchitis (5.2% vs. 4.7%) and headache (4.8% vs. 5.6%). Most injection site reactions (treatment-emergent local injection site reactions) were of mild or moderate intensity, with the first reaction occurring in the

first three months of therapy (57 days of alirocumab cersus 100 days of placebo) for the majority of patients.

[00364] TEAE of special interest included: treatment-emergent local injection site reactions; general allergic reaction events; neurological events; neurocognitive disorders; adjudicated cardiovascular events; neurocognitive disorders; and haemolytic anaemia. The prevalence of these events in the alirocumab and placebo groups is set forth in **Table 48**. The prevalence of specific neurocognitive adverse events in the alirocumab and placebo groups is set forth in **Table 49**.

[00365] Nineteen (19) deaths were reported during the study (11 (0.7%) in the alirocumab group versus 8 (1.0%) in the placebo group). Focusing on the TEAE leading to death, 7 (0.5%) deaths were reported in the alirocumab group versus 8 (1.0%) in the placebo group. Per adjudication, the primary cause of death was cardiovascular in both treatment groups (during TEAE period, 5 (0.3%) cardiovascular death in alirocumab group versus 5 (0.6%) in placebo group).

[00366] SAEs were reported by 394 patients (255 (16.5%) patients in the alirocumab group and 139 (17.6%) patients in the placebo group) during the TEAE period. No imbalance between groups is observed.

[00367] No specific pattern was noted among the TEAEs leading to permanent treatment discontinuation.

[00368] Among the events of interest, no particular signal was detected for TEAEs related to neurological events and ophthalmological events (including in the ophthalmological sub-study). For neurocognitive disorders, 18 (1.2%) were observed in the alirocumab group versus 4 (0.5%) in the placebo group including mainly amnesia, memory impairment and confusional state. No case of hemolytic anaemia was reported.

[00369] With regards to general allergic reaction, similar proportions of patients reported at least one such event in alirocumab (140 [9.0%]) vs. placebo (71 [9.0%]) groups.

[00370] 124 (5.3%) patients (90 (5.8%) patients from alirocumab group and 34 (4.3%) patients from placebo group) experienced a treatment-emergent local injection site reaction. Most of these events were of mild or moderate intensity.

[00371] According to the “diabetes and impaired glucose control” exploratory analysis, a total of 36 (6.3%) patients in the alirocumab group and 10 (3.6%) patients in the placebo group classified as having "impaired glucose control" at baseline were defined as diabetic in the TEAE period. Two patients classified with normal status at baseline became diabetic (one in each treatment group).

[00372] There was no imbalance for PCSA of laboratory parameters, ECG and vital signs.

Table 44 - Treatment Emergent Adverse Events (at the time of the pre-specified analysis)

% (n) of patients[a] All patients on background of max tolerated statin ± other lipid-lowering therapy	Alirocumab (n=1550)	Alirocumab with two consecutive LDL-C <25 mg/dL (n = 562; 36%)	Placebo (n=788)
TEAEs[b]	78.6% (1218)	71.9% (404)	80.6% (635)
Treatment-emergent SAEs	16.5% (255)	14.6% (82)	17.6% (139)
TEAE leading to death	0.5% (7)	0.5% (3)	1.0% (8)
TEAEs leading to discontinuation	6.2% (96)	3.6% (20)	5.5% (43)

[a] Safety results from a first-step analysis (52 weeks for all patients continuing treatment, and including ~600 patients exposed for 78 weeks).

[b] TEAEs are adverse events that developed, worsened, or became serious during the TEAE period (time from first to last injection of study treatment + 70 days).

Table 45 - TEAEs by System-Organ-Class (≥2%) in any Group (at the time of the pre-specified analysis)

% (n) of patients All patients on background of max tolerated statin ± other LLT	Alirocumab (n=1550)	Alirocumab with two consecutive LDL-C <25 mg/dL (n = 562; 36%)	Placebo (n=788)
Infections and infestations	45.5% (705)	39.0% (219)	46.1% (363)
Musculoskeletal and connective tissue disorders	27.2% (422)	22.6% (127)	28.6% (225)
Gastrointestinal disorders	18.6% (288)	13.7% (77)	18.8% (148)
Nervous system disorders	17.0% (264)	11.2% (63)	17.8% (140)
General disorders and administration site conditions	15.4% (238)	11.0% (62)	17.0% (134)
Injury, poisoning, and procedural complications	13.4% (207)	10.5% (59)	14.2% (112)

Respiratory, thoracic, and mediastinal disorders	11.0% (171)	7.7% (43)	10.9% (86)
Cardiac disorders	9.1% (141)	7.5% (42)	11.8% (93)
Skin and subcutaneous tissue disorders	9.1% (141)	6.9% (39)	8.5% (67)
Metabolism and nutrition disorders	9.1% (141)	8.0% (45)	8.4% (66)
Vascular disorders	7.9% (122)	5.0% (28)	8.9% (70)
Eye disorders	6.5% (100)	6.4% (36)	6.1% (48)
Investigations (lab parameters)	6.1% (95)	3.7% (21)	5.2% (41)
Psychiatric disorders	5.9% (91)	4.3% (24)	8.0% (63)
Renal and urinary disorders	4.6% (72)	3.6% (20)	6.0% (47)
Neoplasms, benign, malignant (incl cysts/polyps)	2.5% (38)	3.0% (17)	3.4% (27)
Reproductive system and breast disorders	2.5% (38)	2.0% (11)	3.2% (25)
Blood and lymphatic system disorders	2.4% (37)	1.6% (9)	3.0% (24)
Ear and labyrinth disorders	2.0% (31)	1.2% (7)	2.9% (23)

Table 46 - TEAEs listed by patient subgroup (at the time of the pre-specified analysis)

TEAE % (n) of patients	Alirocumab (n=1550)	Alirocumab with two consecutive LDL-C <25 mg/dL (n = 562; 36%)	Placebo (n=788)
Nasopharyngitis	12.6% (196)	10.0% (56)	12.7% (100)
Upper respiratory tract infection (URTI)	7.0% (109)	5.7% (32)	8.0% (63)
Injection site reaction	5.7% (89)	3.6% (20)	3.4% (34)
Influenza	5.4% (84)	4.1% (23)	5.5% (43)
Diarrhea	5.3% (82)	3.9% (22)	5.1% (40)
Urinary tract infection	5.2% (81)	5.5% (31)	6.2% (49)
Bronchitis	5.2% (80)	5.2% (29)	4.7% (37)
Myalgia	4.9% (76)	3.0% (17)	3.0% (24)
Headache	4.8% (74)	1.8% (10)	5.6% (44)
Back pain	4.7% (73)	5.0% (28)	6.0% (47)

Arthralgia	4.5% (70)	3.2% (18)	6.0% (47)
Muscle spasms	3.7% (58)	2.8% (16)	3.2% (25)
Fatigue	3.0% (47)	3.0% (17)	3.8% (30)
Pain in extremity	3.0% (46)	2.1% (12)	4.4% (35)
Hypertension	3.5% (54)	2.0% (11)	3.4% (27)
Cough	3.2% (49)	2.0% (11)	2.2% (17)
Lower respiratory tract infection (LRTI)	3.0% (46)	2.8% (16)	2.9% (23)
Fall	2.8% (43)	1.6% (9)	4.1% (32)
Sinusitis	2.6% (40)	3.0% (17)	2.4% (19)
Dizziness	2.5% (38)	1.4% (8)	3.7% (29)
Gastoenteritis	2.4% (37)	0.7% (4)	2.8% (22)
Nausea	2.4% (37)	0.9% (5)	2.5% (20)
Musculoskeletal pain	2.3% (36)	1.4% (8)	1.9% (15)
Osteoarthritis	2.3% (35)	2.1% (12)	3.0% (24)
Confusion	2.3% (35)	1.2% (7)	0.8% (6)
Angina pectoris	2.1% (32)	1.8% (10)	2.9% (23)
Constipation	1.9% (30)	1.6% (9)	1.8% (14)
Depression	1.8% (28)	1.4% (8)	3.2% (25)
Non-cardiac chest pain	1.8% (28)	2.0% (11)	1.9% (15)
Diabetes in patients with no history of diabetes[a]	19		9
Diabetes in patients with history of diabetes[a]	48		22
Type-2 diabetes mellitus	1.7% (27)	2.5% (14)	1.3% (10)
Rhinitis	1.4% (22)	1.2% (7)	2.2% (17)
Atrial fibrillation	1.4% (22)	1.6% (9)	2.2% (17)
Cellulitis	1.4% (22)	1.6% (9)	1.0% (8)
ALT increase	1.1%	0.7%	0.5%
CPK increase	0.5%	0.2%	0.5%
AST increase	0.2%	0%	0%

Abbreviations: CHD, coronary heart disease; CV, cardiovascular; MI, myocardial infarction; LDL, low-density lipoprotein; LLN, lower limit of normal; LLT, lipid-lowering therapy; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; ULN, upper limit of normal.

[a] The selection of preferred terms is based on Company MedDRA Query “diabetes” and includes the preferred terms “diabetes mellitus”, “diabetes mellitus inadequate control”, “fulminant type 1 diabetes mellitus”, “insulin resistant diabetes”, “insulin requiring type 2 diabetes mellitus”, “type 1

diabetes mellitus", "type 2 diabetes mellitus", "diabetes mellitus malnutrition-related", and "diabetes mellitus management" and excluding "blood glucose decreased".

Table 47 – Laboratory values of interest (at the time of the pre-specified analysis)

TEAE % (n) of patients	Alirocumab	Placebo
Alanine aminotransferase > 3 x ULN	25/1532 (1.6)	13/779 (1.7)
Aspartate aminiotransferase > 3 x ULN	19/1532 (1.2)	15/779 (1.9)
Creatine kinase >3 x ULN	50/1507 (3.3)	32/771 (4.2)

Table 48 - Adverse Events of Special Interest (at the time of the pre-specified analysis)

% (n) of patients All patients on background of max tolerated statin ± other lipid-lowering therapy	Alirocumab (n=1550)	Alirocumab with two consecutive LDL-C <25 mg/dL (n = 562; 36%)	Placebo (n=788)
Treatment-emergent local injection site reactions	5.8% (90)	6.2%	4.3% (34)
General allergic reaction events	9.0% (140)	8.0%	9.0% (71)
Neurological events ‡[a]	4.2% (65)	3.2%	3.9% (31)
All adjudicated cardiovascular events†	4.0% (62)	4.3%	4.4% (35)
Neurocognitive disorders ‡	1.2% (18)	0.7%	0.5% (4)
Ophthalmological events ‡	2.5% (38)	2.5%	1.9% (15)
Haemolytic anaemia	0	0	0

† Adjudicated CV events. Adjudicated CV events include all CV AEs positively adjudicated. The adjudication categories are the following: CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalisation, congestive heart failure requiring hospitalisation, ischemia driven coronary revascularisation procedure [PCI, CABG]. ‡Company MedDRA Queries (CMQ)[a] The selection of preferred terms is based on Standardized MedDRA Query including 'demyelination' (broad + narrow), 'peripheral neuropathy' (broad + narrow) and 'Guillain-Barre syndrome' (broad + narrow) excluding the preferred terms 'acute respiratory distress syndrome', 'asthenia', 'respiratory arrest' and 'respiratory failure'.

Table 49 - Neurocognitive Adverse Events (at the time of the pre-specified analysis)

% (n) of patients All patients on background of max tolerated statin ± other lipid-lowering therapy	Alirocumab (n=1550)	Alirocumab with two consecutive LDL-C <25 mg/dL (n = 562; 36%)	Placebo (n=788)
Any neurocognitive disorder [a]	1.2% (18)	0.7%	0.5% (4)
Amnesia	0.3% (5)	0	0% (0)
Memory impairment	0.3% (5)	0	0.1% (1)
Confusional state	0.3% (4)	0.2% (1)	0.1% (1)
Confusion postoperative	<0.1% (1)	0	0% (0)
Dementia	<0.1% (1)	0.2% (1)	0.1% (1)
Disorientation	<0.1% (1)	0	0% (0)
Disturbance in attention	<0.1% (1)	0	0.1% (1)
Frontotemporal dementia	<0.1% (1)	0.2% (1)	0% (0)
Transient global amnesia	<0.1% (1)	0	0% (0)

[a] The selection of preferred terms is based on Company MedDRA Query.

RESULTS II- FINAL ANALYSIS

[00373] Although all of the primary and secondary efficacy endpoints were completed at the time of the pre-specified interim analysis, the study continued until completion, allowing analysis of the complete safety population.

Summary safety population characteristics:

[00374] Mean study-drug exposure was 70 weeks in the 2338 patients included in the safety analysis (1550 in alirocumab and 788 in placebo groups), providing 2061 patient-years of exposure to alirocumab 150 mg every two weeks. Overall mean adherence to study treatment (i.e. the percentage of days that a patient took their injections as per the planned dosing schedule) was 98.0% and 97.6% in alirocumab and placebo groups, respectively. Mean duration of follow-up (regardless of treatment adherence) in the safety population was 80.9 weeks for alirocumab and 80.1 weeks for placebo. Study treatment discontinuation rates were 28% for alirocumab and 25% for placebo.

Efficacy

[00375] A consistent LDL cholesterol reduction from baseline was observed from week 4 to 78 in the alirocumab group (Figure 15). Measured LDL cholesterol results were consistent with

those for calculated LDL cholesterol. The percent decrease in LDL cholesterol was slightly lower at Week 78 (52%) versus Week 24 (61%) in the intention-to-treat analysis; this observation was influenced by values collected after premature treatment discontinuation.

Safety

[00376] Similar percentages of patients experienced treatment-emergent adverse events in both treatment groups (81% with alirocumab versus 83% with placebo) (Table 50). Treatment-emergent adverse events leading to study-drug discontinuation occurred in 7.2% of alirocumab patients and 5.8% of placebo patients. With regard to specific adverse events, there were differences between the alirocumab and placebo groups in rates of injection-site reactions (5.9% versus 4.2%, respectively), myalgia (5.4% versus 2.9%, respectively), neurocognitive events (1.2% versus 0.5%, respectively), and ophthalmological events (2.9% versus 1.9%, respectively; Table 50).

[00377] Among the alirocumab patients, 575 (38% of the total) had two consecutive calculated LDL cholesterol levels of less than 25 mg/dL. Rates of treatment-emergent adverse events among these patients were comparable with those among the overall alirocumab group.

Table 50. AEs of Interest and Safety Laboratory Values (Safety Analysis)

No. of patients	**Alirocumab**	**Placebo**	**P-value**
Patients on maximally tolerated statin ± other LLT	(N=1550)	(N=788)	
Summary of TEAEs*			
TEAEs	1255 (81.0)	650 (82.5)	0.3983
Treatment-emergent SAEs	290 (18.7)	154 (19.5)	0.6555
TEAEs leading to death	8 (0.5)	10 (1.3)	0.0760
TEAEs leading to discontinuation	111 (7.2)	46 (5.8)	0.2559
Cardiovascular AEs of interest			
CHD death including unknown cause	4 (0.3)	7 (0.9)	0.2559
Non-fatal MI	14 (0.9)	18 (2.3)	0.0129
Fatal and non-fatal ischemic stroke	9 (0.6)	2 (0.3)	0.3528
Unstable angina requiring hospitalization	0	1 (0.1)	0.337
Congestive heart failure requiring hospitalization	9 (0.6)	3 (0.4)	0.761
Ischemia-driven coronary revascularization procedure	48 (3.1)	24 (3.0)	1
Positively adjudicated cardiovascular events (including all cardiovascular AEs listed above)	72 (4.6)	40 (5.1)	0.682
Post hoc analysis of a subgroup of adjudicated MACE†	27 (1.7)	26 (3.3)	0.0116
Other AEs of interest			
General allergic reaction events	156 (10.1)	75 (9.5)	0.7142
Local injection site reaction	91 (5.9)	33 (4.2)	0.0968
Myalgia	84 (5.4)	23 (2.9)	0.0063

Neurological events[‡]	65 (4.2)	35 (4.4)	0.8289
Neurocognitive disorders[§]	18 (1.2)	4 (0.5)	0.1727
Amnesia	5 (0.3)	0	0.1747
Memory impairment	4 (0.3)	1 (0.1)	0.6686
Confusional state	4 (0.3)	1 (0.1)	0.6686
Ophthalmological events[¶]	35 (2.9)	15 (1.9)	0.6516
Hemolytic anemia	0	0	NC
Diabetes in patients with no history of diabetes, n/N (%)[‖]	18/994 (1.8)	10/509 (2.0)	0.8419
Worsening of diabetes in patients with history of diabetes, n/N (%)[‖]	72/556 (12.9)	38/279 (13.6)	0.8284
Laboratory values of interest			
Alanine aminotransferase >3 times ULN, n/N (%)	28/1533 (1.8)	16/779 (2.1)	0.748
Aspartate aminotransferase >3 times ULN, n/N (%)	22/1533 (1.4)	18/779 (2.3)	0.1316
Creatine kinase >3 times ULN, n/N (%)	56/1507 (3.7)	38/771 (4.9)	0.1819

P-values calculated using Fisher exact test and not adjusted for multiplicity. Provided for descriptive purpose only.

Overall Summary

[00378] This study is the largest and longest double-blind study of a PCSK9 inhibitor. The current analysis provides about 1900 patient-years of double-blind patient exposure to alirocumab 150 mg Q2W. In high CV risk patients on maximally-tolerated statin ± other lipid lowering therapy the following observations were made: 1) self-administered alirocumab treatment produced significantly greater LDL-C reductions than placebo at Week 24 (LS mean difference –61.9%); efficacy remained consistent throughout treatment, and at week 78 alirocumab reduced LDL-C from baseline by an additional 56 percent versus placebo; 2) 79% of alirocumab patients achieved LDL-C goal of <0.81 mmol/L (70 mg/dL) at Week 24; 3) reductions in LDL-C levels were observed in alirocumab patients by Week 4 and alirocumab patients achieved mean LDL-C levels of 1.4 mmol/L (53.1 mg/dL) at Week 52; and 4) TEAEs occurred in a similar frequency in the alirocumab and placebo arms as well as a subset of alirocumab-treated patients (n = 562) with two consecutive LDL-C levels of <25 mg/dL.

[00379] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

CLAIMS

What is claimed is:

1. A method for treating a high cardiovascular risk patient with hypercholesterolemia and established coronary heart disease (CHD) or CHD risk equivalents that are not adequately controlled by maximum tolerated dose statin therapy with or without other lipid lowering therapy comprising administering one or more doses of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to the patient, wherein the patient exhibits inadequate control of the hypercholesterolemia despite treatment with the maximum tolerated dose statin therapy with or without other lipid lowering therapy in the absence of the PCSK9 inhibitor.

2. The method of claim 1, wherein the established CHD is defined by a history of CHD, including one or more of the following: acute myocardial infarction (MI), silent MI, unstable angina, coronary revascularization procedure, and clinically significant CHD diagnosed by invasive or non-invasive testing.

3. The method of claim 1, wherein the CHD risk equivalents include one or more of the following four criteria: 1) peripheral arterial disease (PAD); 2) ischemic stroke; 3) chronic kidney disease; and/or 4) a history of diabetes mellitus and 2 or more additional risk factors, including: a) history of hypertension, b) history of ankle-brachial index ≤0.90, c) history of microalbuminuria or macroalbuminuria or dipstick urinalysis with >2+ protein, d) history of preproliferative or proliferative retinopathy or laser treatment for retinopathy, and e) known family history of premature CHD.

4. The method of any one of claims 1 to 3, wherein the PCSK9 inhibitor is an antibody or an antigen-binding fragment thereof that specifically binds PCSK9.

5. The method of claim 4, wherein the antibody or antigen-binding fragment thereof comprises the heavy and light chain complementarity determining regions (CDRs) of a heavy chain variable region/light chain variable region (HCVR/LCVR) amino acid sequence pair selected from the group consisting of SEQ ID NOs: 1/6 and 11/15.

6. The method of claim 5, wherein the antibody or antigen-binding fragment thereof comprises heavy and light chain CDR amino acid sequences having SEQ ID NOs:12, 13, 14, 16, 17, and 18.

7. The method of claim 6, wherein the antibody or antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:11 and an LCVR having the amino acid sequence of SEQ ID NO:15.

8. The method of claim 5, wherein the antibody or antigen-binding fragment thereof comprises heavy and light chain CDR amino acid sequences having SEQ ID NOs:2, 3, 4, 7, 8, and 10.

9. The method of claim 8, wherein the antibody or antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:1 and an LCVR having the amino acid sequence of SEQ ID NO:6.

10. The method of claim 4, wherein the antibody or antigen-binding fragment thereof binds to the same epitope on PCSK9 as an antibody comprising heavy and light chain CDR amino acid sequences having SEQ ID NOs: 12, 13, 14, 16, 17, and 18; or SEQ ID NOs: 2, 3, 4, 7, 8, and 10.

11. The method of claim 4, wherein the antibody or antigen-binding fragment thereof competes for binding to PCSK9 with an antibody comprising heavy and light chain CDR amino acid sequences having SEQ ID NOs: 12, 13, 14, 16, 17, and 18; or SEQ ID NOs: 2, 3, 4, 7, 8 and 10.

12. The method of claim 4, wherein the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is administered to the patient at a dose of about 75 mg at a frequency of once every two weeks.

13. The method of claim 12, wherein the about 75 mg dose is maintained if the patient's LDL-C measured after five or more doses is <70 mg/dL.

14. The method of claim 12, wherein the about 75 mg dose is discontinued if the patient's LDL-C measured after five or more doses remains ≥70 mg/dL, and the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is subsequently administered to the patient at a dose of about 150 mg at a frequency of once every two weeks.

15. The method of claim 4, wherein the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is administered to the patient at a dose of about 150 mg at a frequency of once every two weeks.

16. The method of any one of claims 1 to 15, wherein the PCSK9 inhibitor is administered to the patient in combination with the maximum tolerated dose statin therapy.

17. The method of any one of claims 1 to 16, wherein the maximum tolerated dose statin therapy comprises a daily dose of about 40 mg to about 80 mg of atorvastatin.

18. The method of any one of claims 1 to 16, wherein the maximum tolerated dose statin therapy comprises a daily dose of about 20 mg to about 40 mg of rosuvastatin.

19. The method of any one of claims 1 to 16, wherein the maximum tolerated dose statin therapy comprises a daily dose of about 80 mg of simvastatin.

20. The method of any one of claims 1 to 19, wherein the PCSK9 inhibitor is administered to the patient in combination with the other lipid lowering therapy, wherein the other lipid lowering therapy comprises a therapeutic agent selected from the group consisting of ezetimibe, a fibrate, niacin, an omega-3 fatty acid, and a bile acid resin.

21. The method of any one of claims 1-20, wherein the method improves at least one hypercholesterolemia-associated parameter selected from the group consisting of:

(a) reduction of the patient's low density lipoprotein cholesterol (LDL-C) by at least 40%;

(b) reduction of the patient's apolipoprotein B100 (ApoB) by at least 35%;

(c) reduction of the patient's non-high density lipoproprotein cholesterol (non-HDL-C) by at least 35%;

(d) reduction of the patient's total cholesterol by at least 20%;

(e) increase of the patient's high density lipoprotein cholesterol (HDL-C) by at least 1%;

(f) reduction of the patient's triglycerides by at least 1%;

(g) reduction of the patient's lipoprotein a (Lp(a)) by at least 10%; and

(h) increase of the patient's apolipoprotein A1 by at least 1%.

22. A method for reducing low-density lipoprotein cholesterol (LDL-C) in a high cardiovascular risk patient with hypercholesterolemia and established coronary heart disease (CHD) or CHD risk equivalents that is not adequately controlled by maximum tolerated dose statin therapy with or without other lipid lowering therapy comprising administering one or more doses of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to the patient, wherein the patient

exhibits inadequate control of LDL-C despite treatment with a maximum tolerated dose statin therapy with or without other lipid lowering therapy in the absence of the PCSK9 inhibitor.

23. The method of claim 22, wherein the established CHD is defined by a history of CHD, including one or more of the following: acute myocardial infarction (MI), silent MI, unstable angina, coronary revascularization procedure, and clinically significant CHD diagnosed by invasive or non-invasive testing.

24. The method of claim 22, wherein the CHD risk equivalents include one or more of the following four criteria: 1) peripheral arterial disease (PAD); 2) ischemic stroke; 3) chronic kidney disease; and/or 4) a history of diabetes mellitus and 2 or more additional risk factors, including: a) history of hypertension, b) history of ankle-brachial index ≤0.90, c) history of microalbuminuria or macroalbuminuria or dipstick urinalysis at screening visit with >2+ protein, d) history of preproliferative or proliferative retinopathy or laser treatment for retinopathy, and e) known family history of premature CHD.

25. The method of any one of claims 22 to 24, wherein the PCSK9 inhibitor is an antibody or an antigen-binding fragment thereof that specifically binds PCSK9.

26. The method of claim 25, wherein the antibody or antigen-binding fragment thereof comprises the heavy and light chain complementarity determining regions (CDRs) of a heavy chain variable region/light chain variable region (HCVR/LCVR) amino acid sequence pair selected from the group consisting of SEQ ID NOs: 1/6 and 11/15.

27. The method of claim 26, wherein the antibody or antigen-binding fragment thereof comprises heavy and light chain CDR amino acid sequences having SEQ ID NOs: 12, 13, 14, 16, 17, and 18.

28. The method of claim 27, wherein the antibody or antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:11 and an LCVR having the amino acid sequence of SEQ ID NO:15.

29. The method of claim 26, wherein the antibody or antigen-binding fragment thereof comprises heavy and light chain CDR amino acid sequences having SEQ ID NOs:2, 3, 4, 7, 8, and 10.

30. The method of claim 29, wherein the antibody or antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:1 and an LCVR having the amino acid sequence of SEQ ID NO:6.

31. The method of claim 25, wherein the antibody or antigen-binding fragment thereof binds to the same epitope on PCSK9 as an antibody comprising heavy and light chain CDR amino acid sequences having SEQ ID NOs: 12, 13, 14, 16, 17, and 18; or SEQ ID NOs: 2, 3, 4, 7, 8 and 10.

32. The method of claim 25, wherein the antibody or antigen-binding fragment thereof competes for binding to PCSK9 with an antibody comprising heavy and light chain CDR amino acid sequences having SEQ ID NOs: 12, 13, 14, 16, 17, and 18; or SEQ ID NOs: 2, 3, 4, 7, 8 and 10.

33. The method of claim 25, wherein the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is administered to the patient at a dose of about 75 mg at a frequency of once every two weeks.

34. The method of claim 33, wherein the about 75 mg dose is maintained if the patient's LDL-C measured after five or more doses is <70 mg/dL.

35. The method of claim 33, wherein the about 75 mg dose is discontinued if the patient's LDL-C measured after five or more doses remains ≥70 mg/dL, and the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is subsequently administered to the patient at a dose of about 150 mg at a frequency of once every two weeks.

36. The method of claim 33, wherein the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is administered to the patient at a dose of about 150 mg at a frequency of once every two weeks.

37. The method of any one of claims 22 to 36, wherein the PCSK9 inhibitor is administered to the patient in combination with the maximum tolerated dose statin therapy.

38. The method of any one of claims 22 to 37, wherein the maximum tolerated dose statin therapy comprises a daily dose of about 40 mg to about 80 mg of atorvastatin.

39. The method of any one of claims 22 to 37, wherein the maximum tolerated dose statin therapy comprises a daily dose of about 20 mg to about 40 mg of rosuvastatin.

40. The method of any one of claims 22 to 37, wherein the maximum tolerated dose statin therapy comprises a daily dose of about 80 mg of simvastatin.

41. The method of any one of claims 22 to 39, wherein the PCSK9 inhibitor is administered to the patient in combination with the other lipid lowering therapy, wherein the other lipid lowering therapy comprises a therapeutic agent selected from the group consisting of ezetimibe, a fibrate, niacin, an omega-3 fatty acid, and a bile acid resin.

42. The method of any one of claims 22-41, wherein the method improves at least one hypercholesterolemia-associated parameter selected from the group consisting of:

(a) reduction of the patient's low density lipoprotein cholesterol (LDL-C) by at least 40%;

(b) reduction of the patient's apolipoprotein B100 (ApoB) by at least 35%;

(c) reduction of the patient's non-high density lipoproprotein cholesterol (non-HDL-C) by at least 35%;

(d) reduction of the patient's total cholesterol by at least 20%;

(e) increase of the patient's high density lipoprotein cholesterol (HDL-C) by at least 1%;

(f) reduction of the patient's triglycerides by at least 1%;

(g) reduction of the patient's lipoprotein a (Lp(a)) by at least 10%; and

(h) increase of the patient's apolipoprotein A1 by at least 1%.

43. A method for treating hypercholesterolemia in a high cardiovascular risk patient with hypercholesterolemia and established coronary heart disease (CHD) or CHD risk equivalents that are not adequately controlled by maximum tolerated dose statin therapy with or without other lipid lowering therapy comprising administering one or more doses of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to the patient, wherein the patient exhibits inadequate control of the hypercholesterolemia despite treatment with the maximum tolerated dose statin therapy with or without other lipid lowering therapy in the absence of the PCSK9 inhibitor.

44. The method of claim 43, wherein the established CHD is defined by a history of CHD, including one or more of the following: acute myocardial infarction (MI), silent MI, unstable angina, coronary revascularization procedure, and clinically significant CHD diagnosed by invasive or non-invasive testing.

45. The method of claim 43, wherein the CHD risk equivalents include one or more of the following four criteria: 1) peripheral arterial disease (PAD); 2) ischemic stroke; 3) chronic kidney disease (CKD); and/or 4) history of diabetes mellitus and 2 or more additional risk factors, including: a) history of hypertension, b) history of ankle-brachial index ≤0.90, c) history of microalbuminuria or macroalbuminuria or dipstick urinalysis at screening visit with >2+ protein, d) history of preproliferative or proliferative retinopathy or laser treatment for retinopathy, and e) known family history of premature CHD.

46. The method of any one of claims 43 to 45, wherein the PCSK9 inhibitor is an antibody or an antigen-binding fragment thereof that specifically binds PCSK9.

47. The method of claim 46, wherein the antibody or antigen-binding fragment thereof comprises the heavy and light chain complementarity determining regions (CDRs) of a heavy chain variable region/light chain variable region (HCVR/LCVR) amino acid sequence pair selected from the group consisting of SEQ ID NOs: 1/6 and 11/15.

48. The method of claim 47, wherein the antibody or antigen-binding fragment thereof comprises heavy and light chain CDR amino acid sequences having SEQ ID NOs: 12, 13, 14, 16, 17, and 18.

49. The method of claim 48, wherein the antibody or antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:11 and an LCVR having the amino acid sequence of SEQ ID NO:15.

50. The method of claim 47, wherein the antibody or antigen-binding fragment thereof comprises heavy and light chain CDR amino acid sequences having SEQ ID NOs:2, 3, 4, 7, 8 and 10.

51. The method of claim 50, wherein the antibody or antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:1 and an LCVR having the amino acid sequence of SEQ ID NO:6.

52. The method of claim 46, wherein the antibody or antigen-binding fragment thereof binds to the same epitope on PCSK9 as an antibody comprising heavy and light chain CDR amino acid sequences having SEQ ID NOs: 12, 13, 14, 16, 17, and 18; or SEQ ID NOs: 2, 3, 4, 7, 8, and 10.

53. The method of claim 46, wherein the antibody or antigen-binding fragment thereof competes for binding to PCSK9 with an antibody comprising heavy and light chain CDR amino acid sequences having SEQ ID NOs: 12, 13, 14, 16, 17, and 18; or SEQ ID NOs: 2, 3, 4, 7, 8, and 10.

54. The method of claim 46, wherein the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is administered to the patient at a dose of about 75 mg at a frequency of once every two weeks.

55. The method of claim 54, wherein the about 75 mg dose is maintained if the patient's LDL-C measured after five or more doses is <70 mg/dL.

56. The method of claim 54, wherein the about 75 mg dose is discontinued if the patient's LDL-C measured after five or more doses remains ≥70 mg/dL, and the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is subsequently administered to the patient at a dose of about 150 mg at a frequency of once every two weeks.

57. The method of claim 46, wherein the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is administered to the patient at a dose of about 150 mg at a frequency of once every two weeks.

58. The method of any one of claims 43 to 57, wherein the PCSK9 inhibitor is administered to the patient in combination with the maximum tolerated dose statin therapy.

59. The method of any one of claims 43 to 58, wherein the maximum tolerated dose statin therapy comprises a daily dose of about 40 mg to about 80 mg of atorvastatin.

60. The method of any one of claims 43 to 58, wherein the maximum tolerated dose statin therapy comprises a daily dose of about 20 mg to about 40 mg of rosuvastatin.

61. The method of any one of claims 43 to 58, wherein the maximum tolerated dose statin therapy comprises a daily dose of about 80 mg of simvastatin.

62. The method of any one of claims 43 to 61, wherein the PCSK9 inhibitor is administered to the patient in combination with the other lipid lowering therapy, wherein the other lipid

lowering therapy comprises a therapeutic agent selected from the group consisting of ezetimibe, a fibrate, niacin, an omega-3 fatty acid, and a bile acid resin.

63. The method of any one of claims 43-62, wherein the method improves at least one hypercholesterolemia-associated parameter selected from the group consisting of:

(a) reduction of the patient's low density lipoprotein cholesterol (LDL-C) by at least 40%;

(b) reduction of the patient's apolipoprotein B100 (ApoB) by at least 35%;

(c) reduction of the patient's non-high density lipoproprotein cholesterol (non-HDL-C) by at least 35%;

(d) reduction of the patient's total cholesterol by at least 20%;

(e) increase of the patient's high density lipoprotein cholesterol (HDL-C) by at least 1%;

(f) reduction of the patient's triglycerides by at least 1%;

(g) reduction of the patient's lipoprotein a (Lp(a)) by at least 10%; and

(h) increase of the patient's apolipoprotein A1 by at least 1%.

64. A method for improving the serum level of one or more lipid components in a high cardiovascular risk patient with hypercholesterolemia and established coronary heart disease (CHD) or CHD risk equivalents that are not adequately controlled by maximum tolerated dose statin therapy with or without other lipid lowering therapy comprising administering one or more doses of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to the patient, wherein the patient exhibits inadequate control of the lipid component despite treatment with the maximum tolerated dose statin therapy with or without other lipid lowering therapy in the absence of the PCSK9 inhibitor, wherein the improvement in the serum level of one or more lipid components is selected from the group consisting of:

(a) a reduction of the patient's low density lipoprotein cholesterol (LDL-C) by at least 40%;

(b) a reduction of the patient's apolipoprotein B100 (ApoB) by at least 35%;

(c) a reduction of the patient's non-high density lipoproprotein cholesterol (non-HDL-C) by at least 35%;

(d) a reduction of the patient's total cholesterol by at least 20%;

(e) an increase of the patient's high density lipoprotein cholesterol (HDL-C) by at least 1%;

(f) a reduction of the patient's triglycerides by at least 1%;

(g) a reduction of the patient's lipoprotein a (Lp(a)) by at least 10%; and

(h) an increase of the patient's apolipoprotein A1 by at least 1%.

65. The method of claim 64, wherein the established CHD is defined by a history of CHD, including one or more of the following: acute myocardial infarction (MI), silent MI, unstable angina, coronary revascularization procedure, and clinically significant CHD diagnosed by invasive or non-invasive testing.

66. The method of claim 64, wherein the CHD risk equivalents include one or more of the following four criteria: 1) peripheral arterial disease (PAD); 2) ischemic stroke; 3) chronic kidney disease; and/or 4) known history of diabetes mellitus and 2 or more additional risk factors, including: a) history of hypertension, b) history of ankle-brachial index ≤0.90, c) history of microalbuminuria or macroalbuminuria or dipstick urinalysis at screening visit with >2+ protein, d) history of preproliferative or proliferative retinopathy or laser treatment for retinopathy, and e) known family history of premature CHD.

67. The method of any one of claims 64 to 66, wherein the PCSK9 inhibitor is an antibody or an antigen-binding fragment thereof that specifically binds PCSK9.

68. The method of claim 67, wherein the antibody or antigen-binding fragment thereof comprises the heavy and light chain complementarity determining regions (CDRs) of a heavy chain variable region/light chain variable region (HCVR/LCVR) amino acid sequence pair selected from the group consisting of SEQ ID NOs: 1/6 and 11/15.

69. The method of claim 68, wherein the antibody or antigen-binding fragment thereof comprises heavy and light chain CDR amino acid sequences having SEQ ID NOs: 12, 13, 14, 16, 17, and 18.

70. The method of claim 69, wherein the antibody or antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:11 and an LCVR having the amino acid sequence of SEQ ID NO:15.

71. The method of claim 68, wherein the antibody or antigen-binding fragment thereof comprises heavy and light chain CDR amino acid sequences having SEQ ID NOs:2, 3, 4, 7, 8, and 10.

72. The method of claim 71, wherein the antibody or antigen-binding fragment thereof comprises an HCVR having the amino acid sequence of SEQ ID NO:1 and an LCVR having the amino acid sequence of SEQ ID NO:6.

73. The method of claim 67, wherein the antibody or antigen-binding fragment thereof binds to the same epitope on PCSK9 as an antibody comprising heavy and light chain CDR amino acid sequences having SEQ ID NOs: 12, 13, 14, 16, 17, and 18; or SEQ ID NOs: 2, 3, 4, 7, 8, and 10.

74. The method of claim 67, wherein the antibody or antigen-binding fragment thereof competes for binding to PCSK9 with an antibody comprising heavy and light chain CDR amino acid sequences having SEQ ID NOs: 12, 13, 14, 16, 17, and 18; or SEQ ID NOs: 2, 3, 4, 7, 8, and 10.

75. The method of claim 67, wherein the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is administered to the patient at a dose of about 75 mg at a frequency of once every two weeks.

76. The method of claim 75, wherein the about 75 mg dose is maintained if the patient's LDL-C measured after five or more doses is <70 mg/dL.

77. The method of claim 75, wherein the about 75 mg dose is discontinued if the patient's LDL-C measured after five or more doses remains ≥70 mg/dL, and the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is subsequently administered to the patient at a dose of about 150 mg at a frequency of once every two weeks.

78. The method of claim 75, wherein the antibody or antigen-binding fragment thereof that specifically binds PCSK9 is administered to the patient at a dose of about 150 mg at a frequency of once every two weeks.

79. The method of any one of claims 64 to 78, wherein the PCSK9 inhibitor is administered to the patient in combination with the maximum tolerated dose statin therapy.

80. The method of any one of claims 64 to 79, wherein the maximum tolerated dose statin therapy comprises a daily dose of about 40 mg to about 80 mg of atorvastatin.

81. The method of any one of claims 64 to 79, wherein the maximum tolerated dose statin therapy comprises a daily dose of about 20 mg to about 40 mg of rosuvastatin.

82. The method of any one of claims 64 to 79, wherein the maximum tolerated dose statin therapy comprises a daily dose of about 80 mg of simvastatin.

83. The method of any one of claims 64 to 82, wherein the PCSK9 inhibitor is administered to the patient in combination with the other lipid lowering therapy, wherein the other lipid lowering therapy comprises a therapeutic agent selected from the group consisting of ezetimibe, a fibrate, niacin, an omega-3 fatty acid, and a bile acid resin.

84. The method of claim 64, wherein the lipid component is LDL-C and the reduction in serum level of LDL-C is compared to baseline.

85. The method of claim 64, wherein the lipid component is Apo B, and the reduction in serum level of Apo B is compared to baseline.

86. The method of claim 64, wherein the lipid component is non-HDL-C and the reduction in serum level of non-HDL-C is compared to baseline.

87. The method of claim 64, wherein the lipid component is total cholesterol and the reduction in serum level of total cholesterol is compared to baseline.

88. The method of claim 64, wherein the lipid component is Lp(a) and the reduction in serum level of Lp(a) is compared to baseline.

89. The method of claim 64, wherein the lipid component is triglycerides and the reduction in serum level of triglycerides is compared to baseline.

90. The method of claim 64, wherein the lipid component is Apo A1 and the reduction in serum level of Apo A1 is compared to baseline.

91. The method of claim 64, wherein the lipid component is HDL-C and the reduction in serum level of HDL-C is compared to baseline.

Fig. 1A ODYSSEY COMBO I

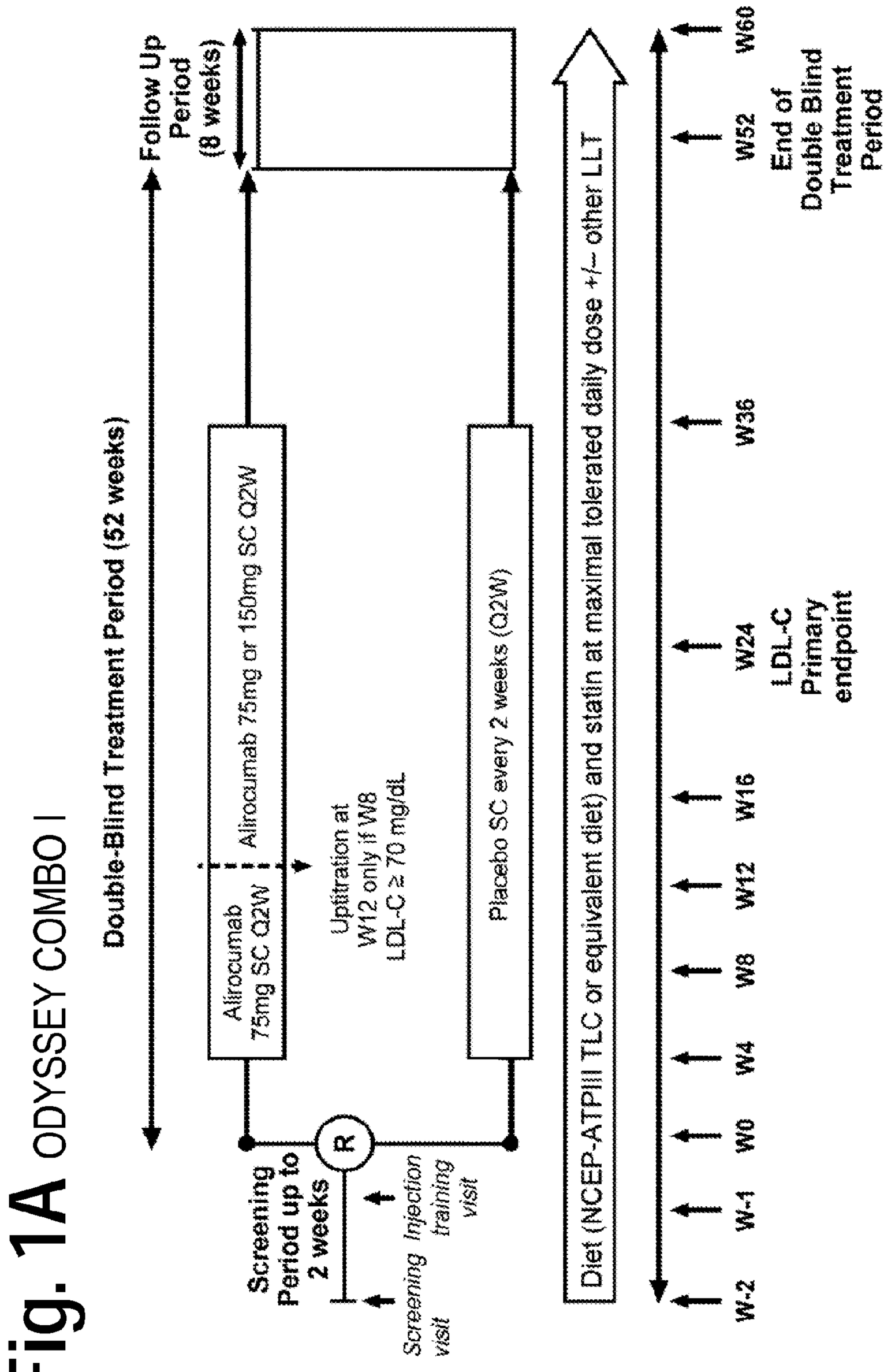
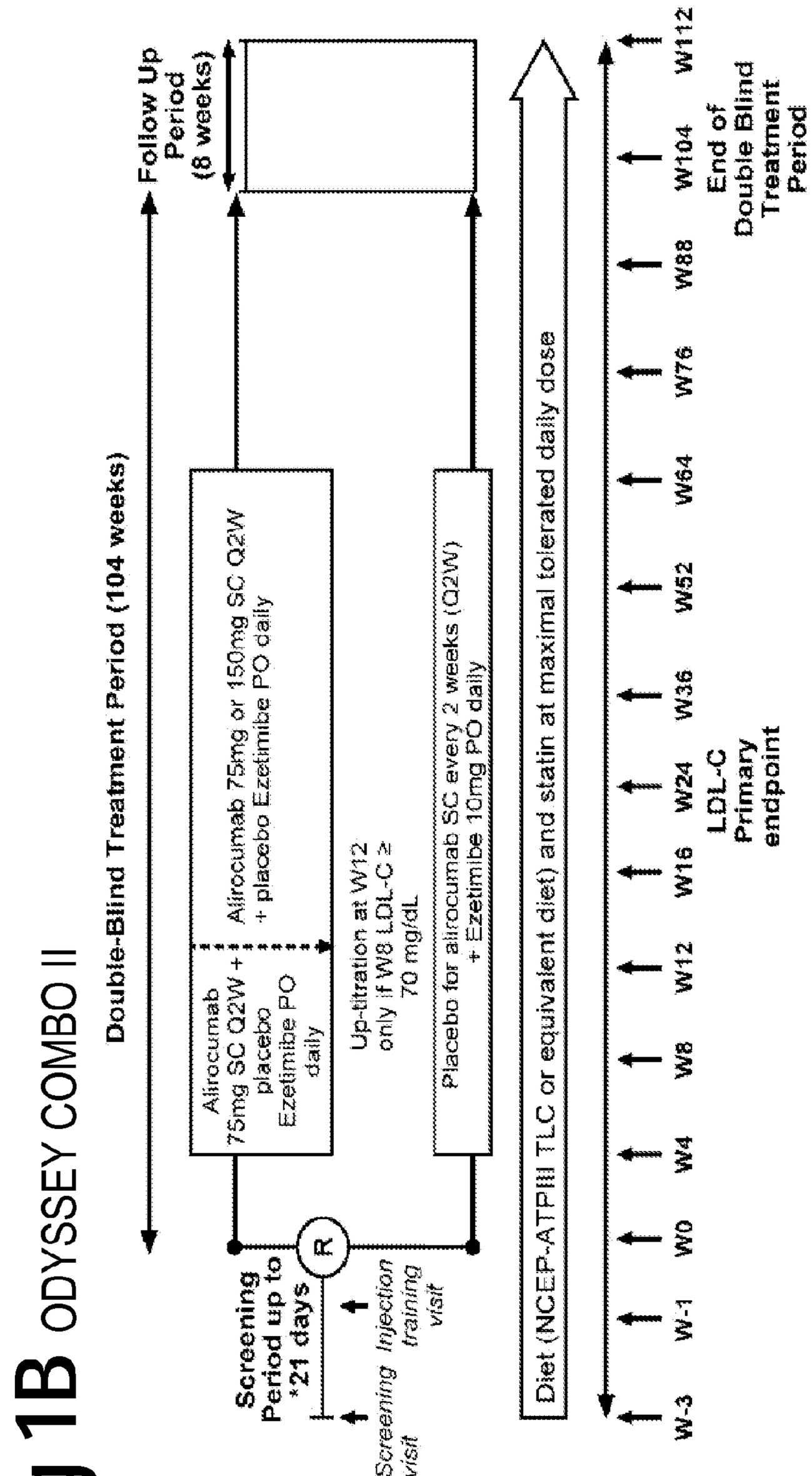


Fig 1B ODYSSEY COMBO II



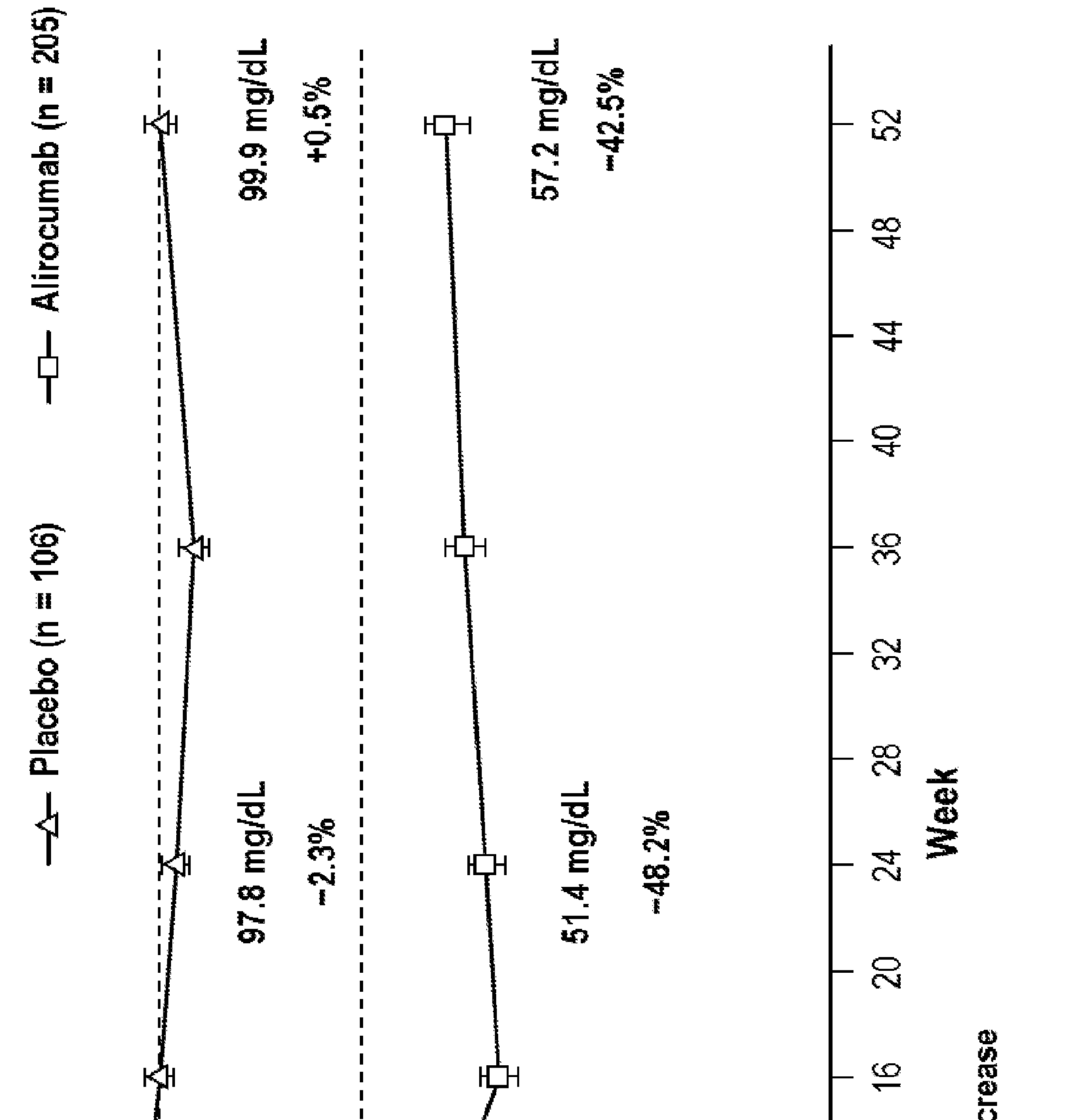

Alirocumab (n = 205)
Placebo (n = 106)
99.9 mg/dL
+0.5%
57.2 mg/dL
−42.5%
97.8 mg/dL
−2.3%
51.4 mg/dL
−48.2%
LDL-C, LS mean (SE), mg/dL
120
100
80
60
40
20
0
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Week
Per-protocol dose increase
ITT analysis.

Fig. 2

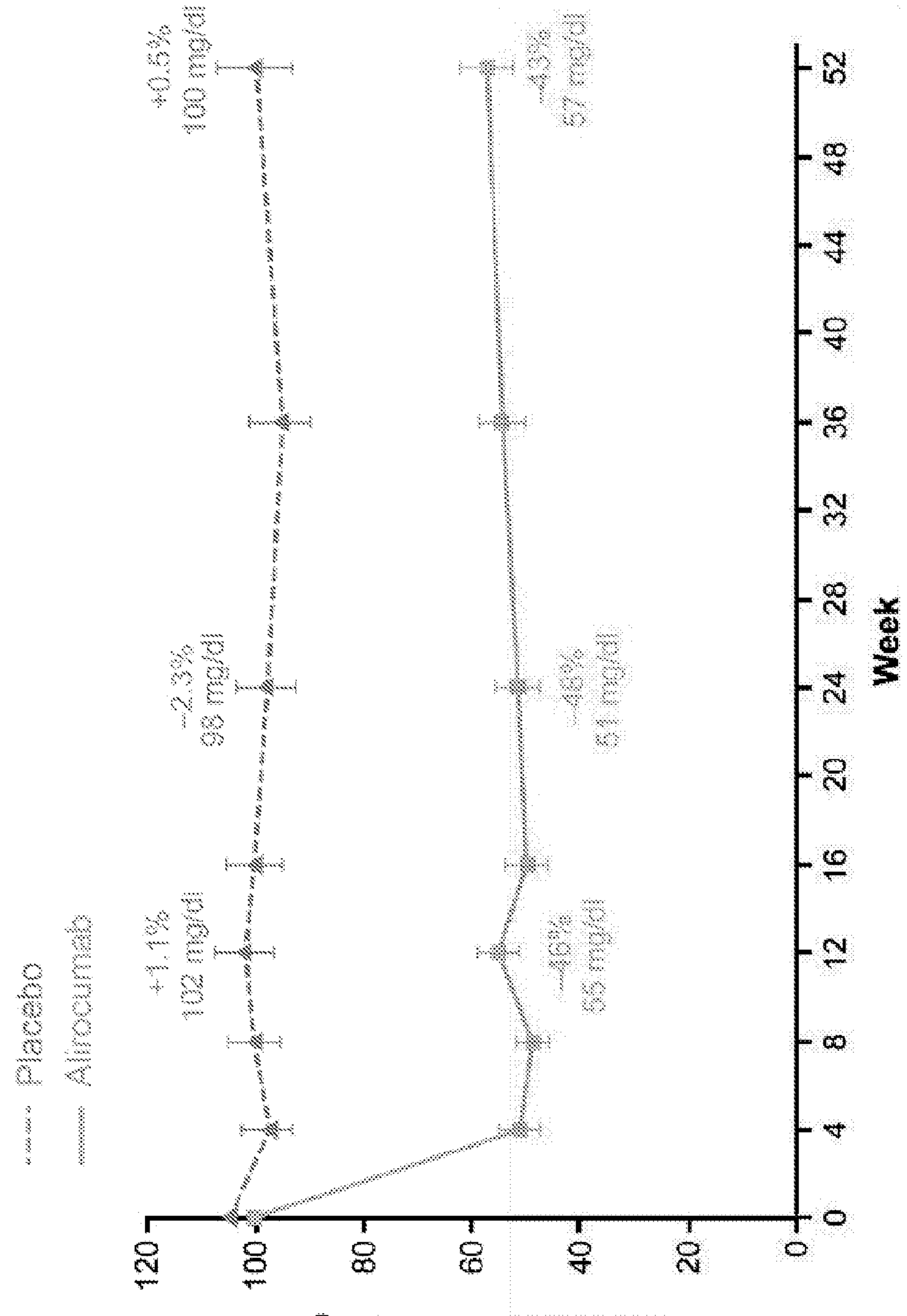

Placebo
Alirocumab
+0.5%
100 mg/dl
−2.3%
98 mg/dl
+1.1%
102 mg/dl
−48%
57 mg/dl
−46%
55 mg/dl
−48%
61 mg/dl
Estimated mean (95% CI)
calculated LDL-C, mg/dl
120
100
80
60
40
20
0
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Week

Fig. 3

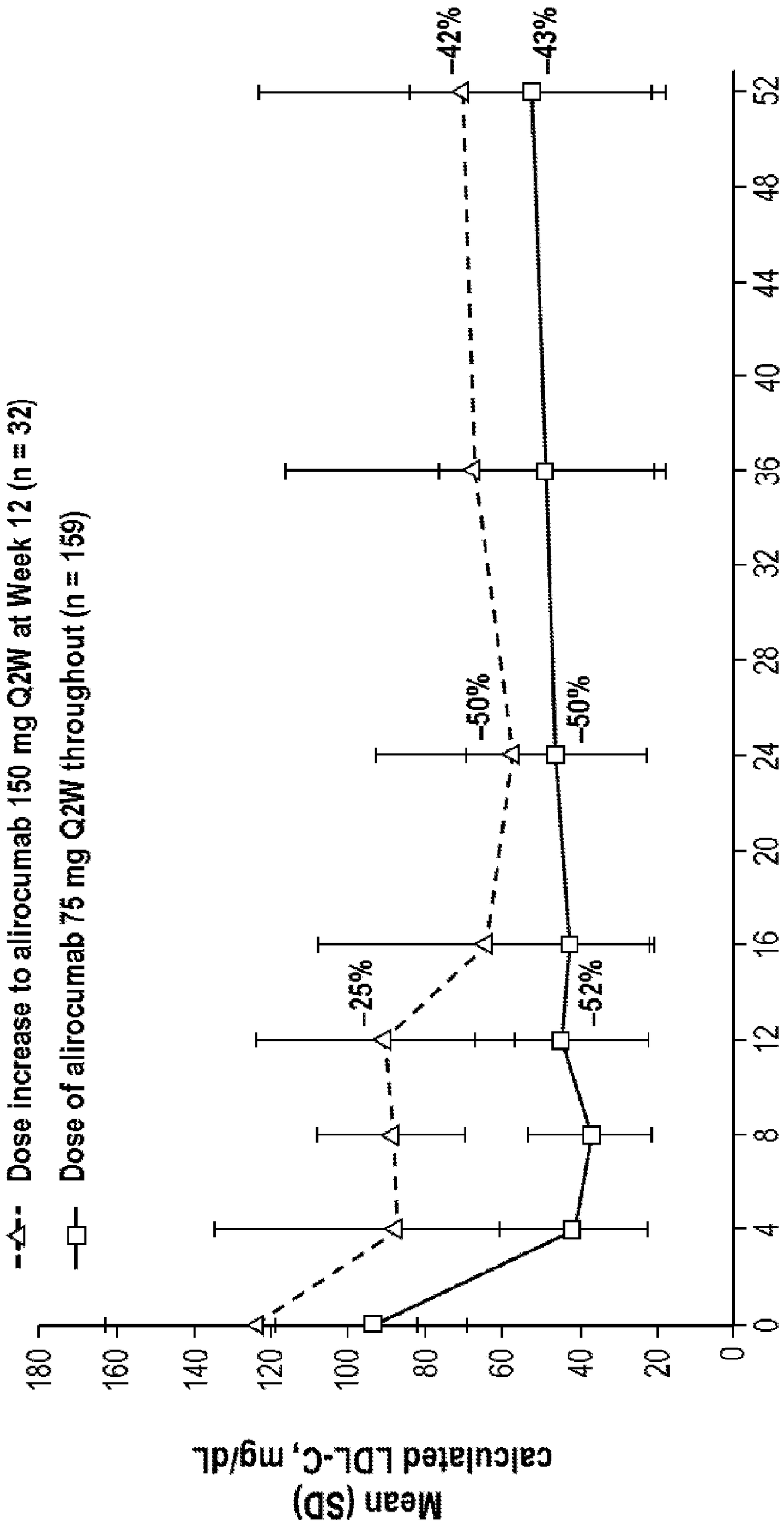
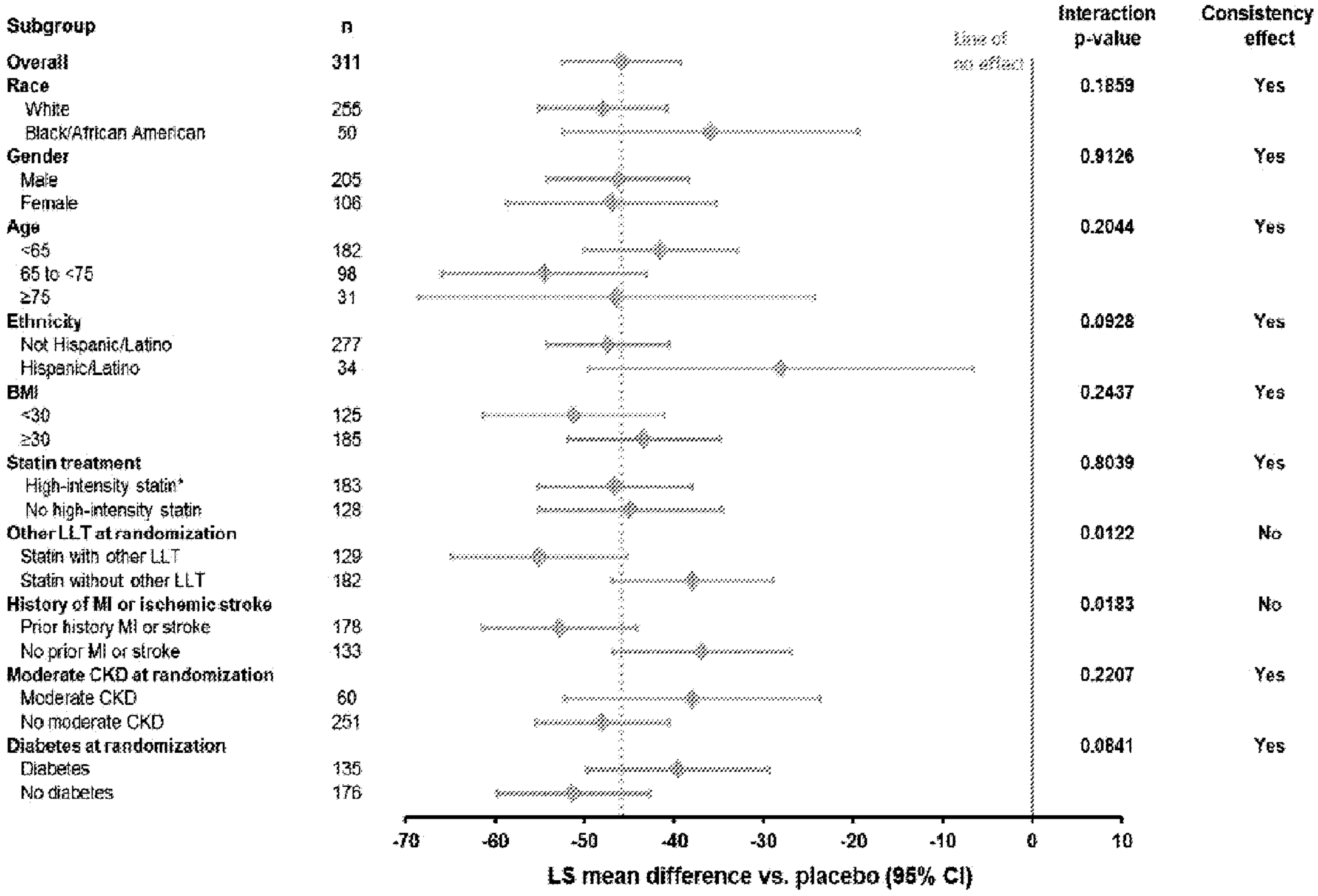

Mean (SD) calculated LDL-C, mg/dL
180
160
140
120
100
80
60
40
20
0
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Week
Per-protocol dose increase
ITT analysis; % values indicated at Weeks 12, 24, and 52 show % change from baseline.
-42%
-43%
-50%
-50%
-25%
-52%
Dose increase to alirocumab 150 mg Q2W at Week 12 (n = 32)
Dose of alirocumab 75 mg Q2W throughout (n = 159)

Fig. 4



*High-intensity statin: atorvastatin 40–80 mg or rosuvastatin 20–40 mg daily

Fig. 5

CA 02955304 2017-01-13

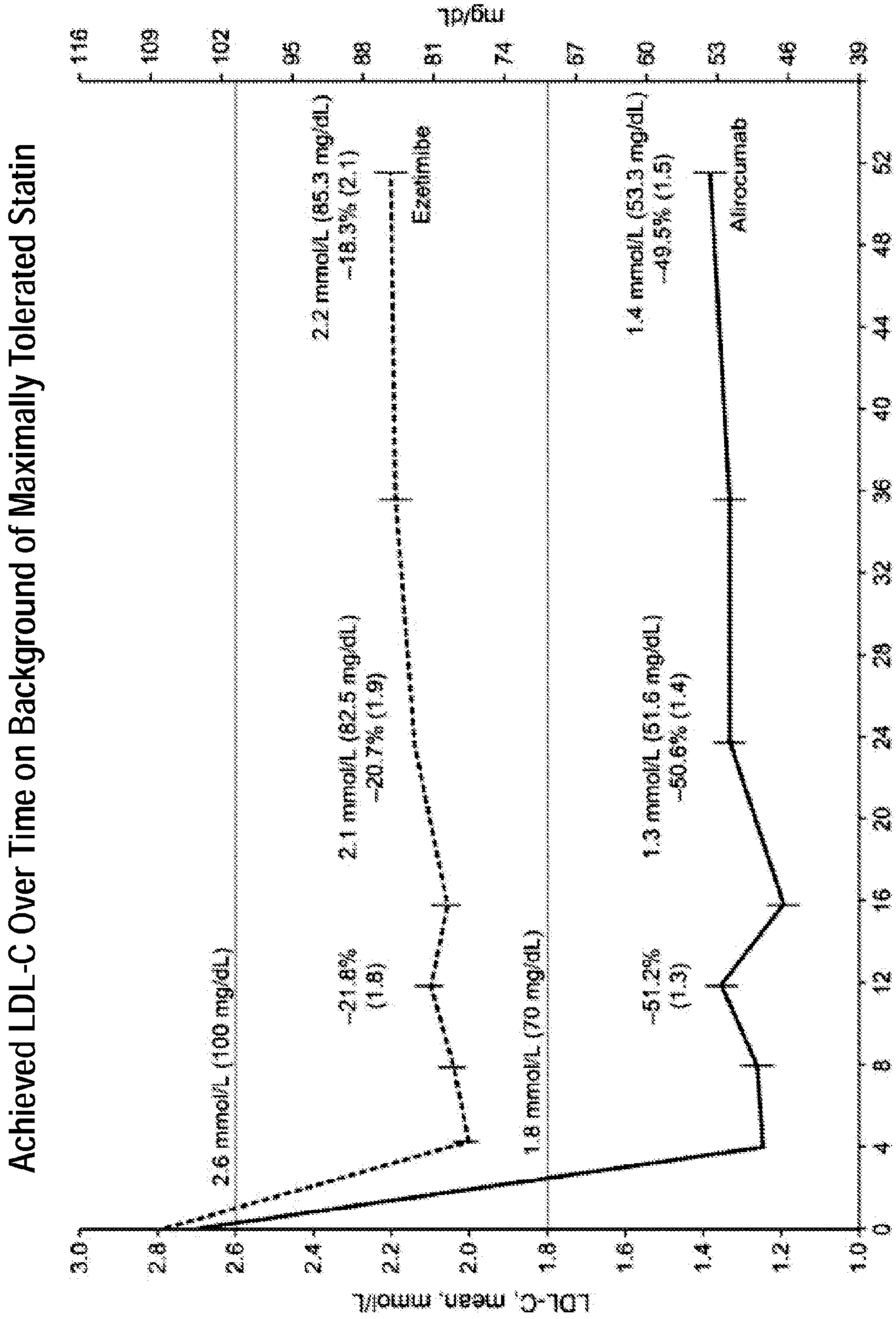

Achieved LDL-C Over Time on Background of Maximally Tolerated Statin
LDL-C, mean, mmol/L
mg/dL
116
109
102
95
88
81
74
67
60
53
46
39
3.0
2.8
2.6
2.4
2.2
2.0
1.8
1.6
1.4
1.2
1.0
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Week
2.6 mmol/L (100 mg/dL)
–21.8%
(1.8)
2.1 mmol/L (82.5 mg/dL)
–20.7% (1.9)
1.8 mmol/L (70 mg/dL)
–51.2%
(1.3)
1.3 mmol/L (51.6 mg/dL)
–50.6% (1.4)
2.2 mmol/L (85.3 mg/dL)
–18.3% (2.1)
Ezetimibe
1.4 mmol/L (53.3 mg/dL)
–49.5% (1.5)
Alirocumab

Fig. 6

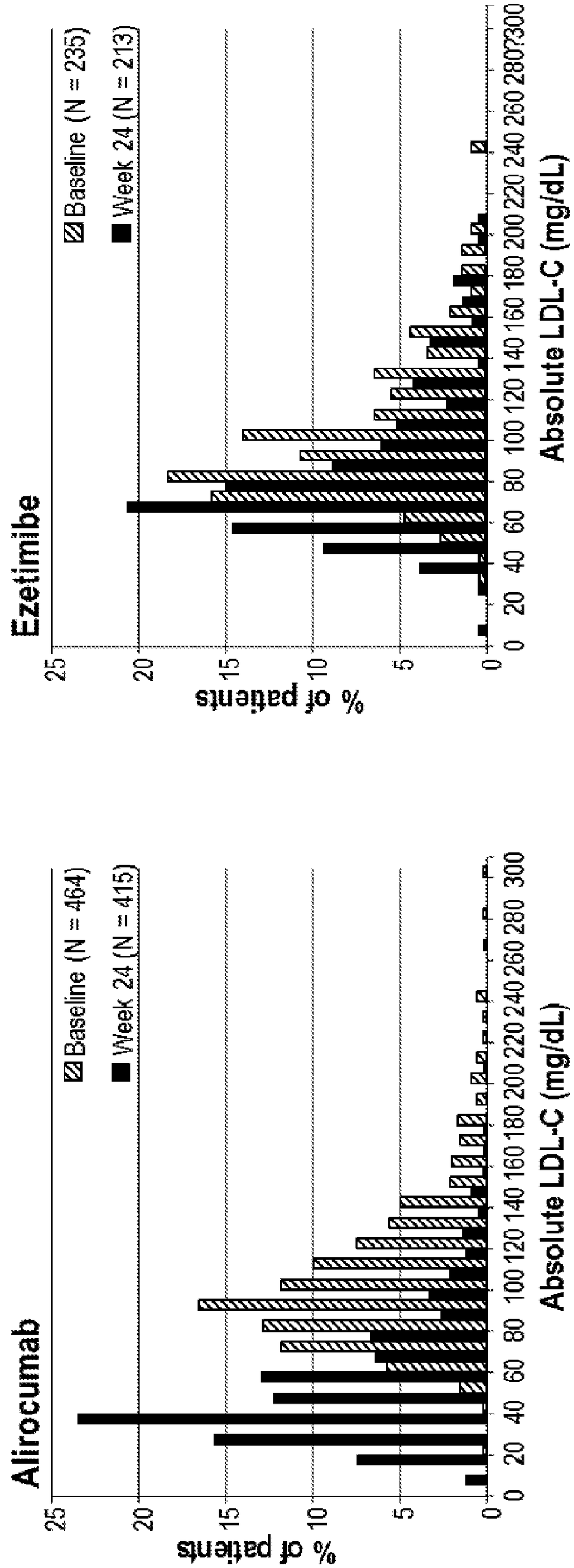
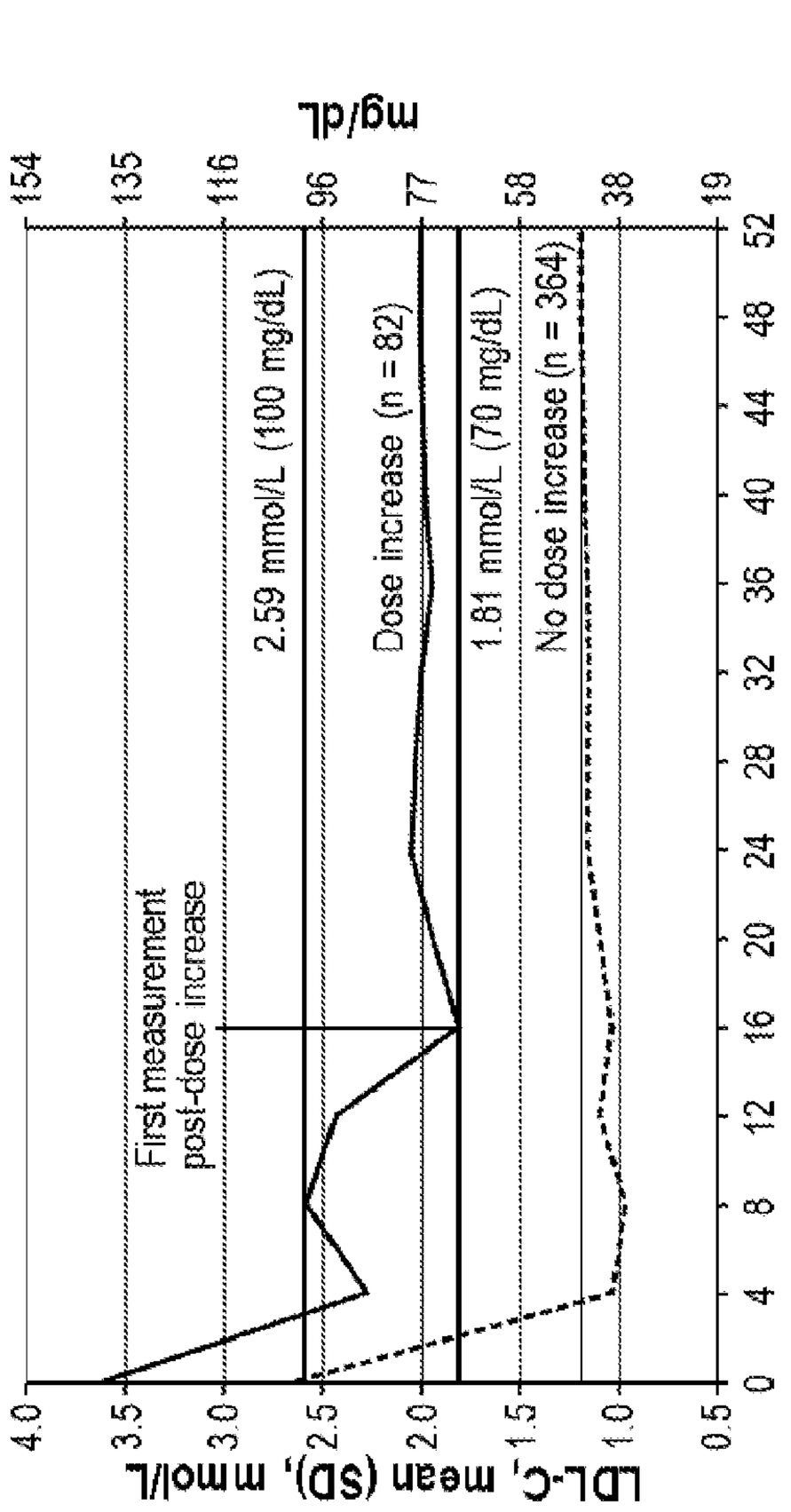

Ezetimibe
Baseline (N = 235)
Week 24 (N = 213)
% of patients
25
20
15
10
5
0
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300
Absolute LDL-C (mg/dL)
Alirocumab
Baseline (N = 464)
Week 24 (N = 415)
% of patients
25
20
15
10
5
0
0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300
Absolute LDL-C (mg/dL)

Fig. 7

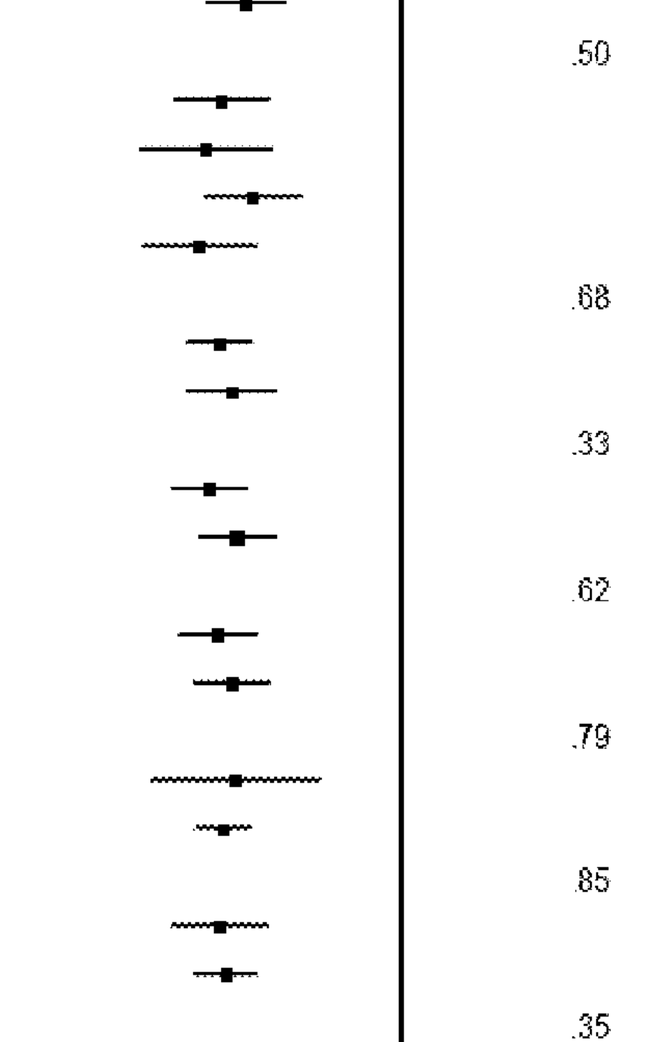


Dose-increase status	Baseline	Week 12	Week 24	Week 52
Dose increase at week 12 (n = 82)				
Mean LDL-C (mg/dL)	140.4 (47.4)	95.1 (44.2)	79.5 (47.2)	77.6 (57.6)
Mean (SD) change from baseline		–46.5 (48.6)	–63.5 (51.9)	–62.4 (62.8)
Mean (SD) percent change from baseline		–30.1 (33.5)	–42.5 (33.7)	–42.5 (42.7)
No dose increase at week 12 (n = 364)				
Mean LDL-C (mg/dL)	101.1 (29.7)	41.9 (21.6)	44.3 (23.5)	46.1 (28.0)
Mean (SD) change from baseline		–59.2 (29.0)	–56.9 (31.9)	–55.4 (32.2)
Mean (SD) percent change from baseline		–57.6 (19.9)	–54.7 (24.3)	–53.9 (27.2)

Fig. 8

Fig. 9

Subgroup	No. of Patients: Alirocumab 75mg SC Q2W	No. of Patients: Ezetimibe 10 mg daily	LS mean difference (vs ezetimibe) (95% CI)	P value for interaction
Race				
White	396	205	−30.8 (−35.8 to −25.8)	.13
Black or African American	20	7	−9.8 (−36.5 to 17.0)	
Hispanic or Latino				
Yes	14	6	−31.9 (−65.2 to 1.5)	.91
No	451	232	−29.9 (−34.5 to −25.3)	
Gender				
Male	354	170	−30.9 (−36.3 to −25.6)	.36
Female	113	70	−26.1 (−34.9 to −17.4)	
Age group, years				
<65	276	149	−27.8 (−33.4 to −21.9)	.27
?65 to <75	152	73	−30.6 (−38.7 to −22.4)	
?75	39	16	−41.7 (−58.2 to −25.3)	
BMI, kg/m2				
<30	289	128	−32.9 (−39.1 to −26.8)	.14
?30	198	112	−26.0 (−32.8 to −19.2)	
Regiona				
North America	151	79	−30.2 (−38.4 to −22.0)	.50
Western Europe	72	36	−32.9 (−44.3 to −21.5)	
Eastern Europe	143	73	−25.0 (−33.1 to −16.8)	
Other	101	52	−34.0 (−43.7 to −24.2)	
History of MI or stroke a				
Yes	303	157	−30.6 (−36.2 to −24.9)	.68
No	164	83	−28.5 (−36.2 to −20.8)	
Baseline total PCSK9 level				
<Median	221	115	−32.3 (−38.8 to −25.8)	.33
?Median	226	109	−27.6 (−34.2 to −20.9)	
Baseline free PCSK9 level				
<Median	234	101	−30.8 (−37.5 to −24.1)	.62
?Median	212	123	−28.5 (−34.9 to −22.0)	
Moderate CKD				
Yes	61	23	−27.9 (−42.2 to −13.5)	.79
No	406	217	−29.9 (−34.6 to −25.1)	
Diabetes				
Yes	142	76	−30.5 (−38.6 to −22.3)	.85
No	325	164	−29.6 (−35.0 to −24.1)	
High-intensity statin treatment a				
Yes	302	152	−28.2 (−33.9 to −22.5)	.35
No	165	88	−32.8 (−40.4 to −25.1)	
Baseline calculated LDL-C				
<100 mg/dL/<2.59 mmol/L	231	126	−32.8 (−39.2 to −26.5)	.66
?100 to <130 mg/dL/<2.59 to <3.37 mmol/L	136	64	−27.3 (−36.0 to −18.5)	
?130 to <160 mg/dL/?3.37 to <4.14 mmol/L	59	33	−29.6 (−42.0 to −17.1)	
?160 mg/dL/?4.14 mmol/L	41	17	−24.1 (−40.8 to −7.3)	
Baseline HDL-C				.08
<40 mg/dL/<1.04 mmol/L	144	74	−36.0 (−44.2 to −27.8)	
?40 mg/dL/?1.04 mmol/L	323	166	−27.1 (-32.6to −21.6)	
Fasting TGs				.22
<150 mg/dL/<1.7 mmol/L	273	136	−27.4 (−33.3 to −21.4)	
?150 mg/dL/?1.7 mmol/L	194	104	−33.1 (−40.2 to −26.1)	
Baseline Lp(a)				.87
<30 mg/dL/<0.3 g/L	238	132	−29.7 (−35.9 to −23.5)	
?30 to <50 mg/dL/?0.3 to <0.5 g/L	51	32	−29.0 (−41.8 to −16.1)	
?50 mg/dL/?0.5 g/L	170	69	−32.2 (−40.4 to −24.0)	



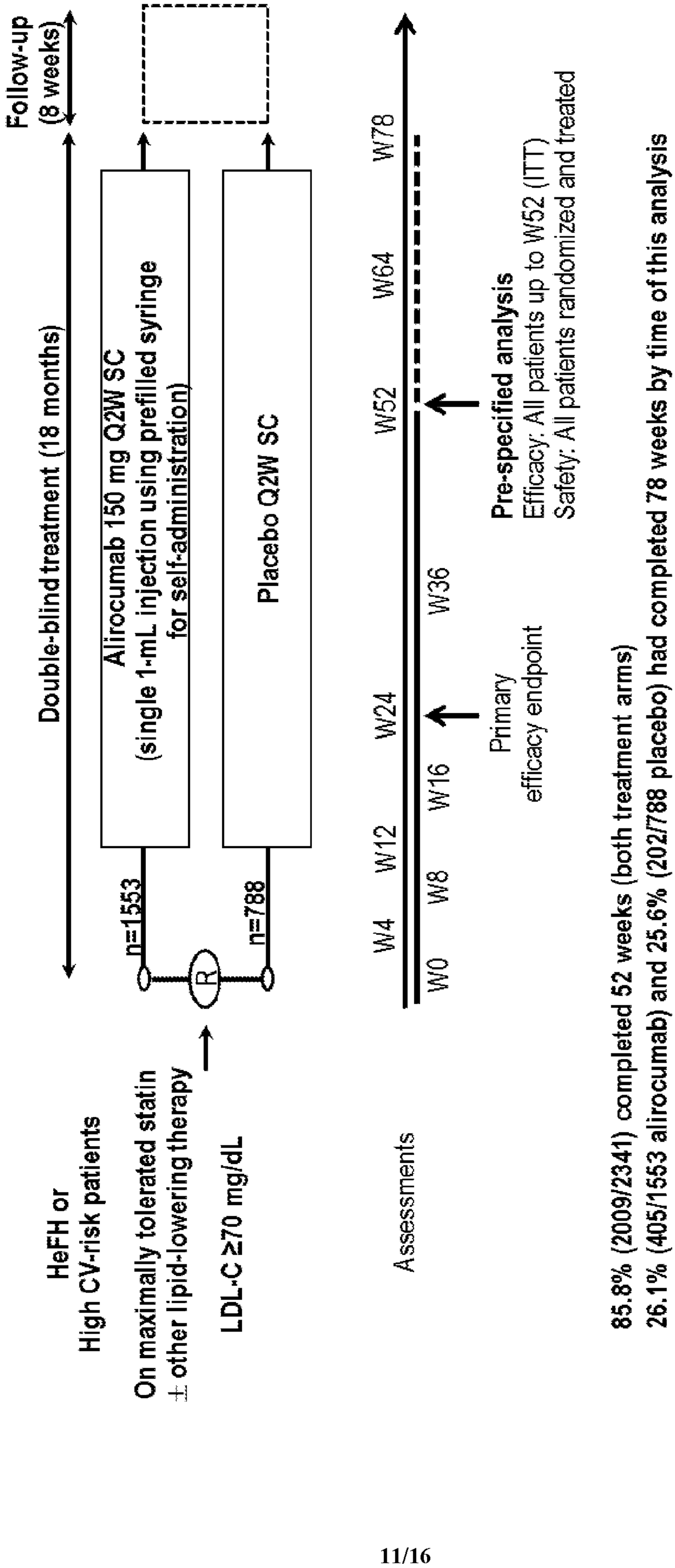

HeFH or
High CV-risk patients
On maximally tolerated statin
± other lipid-lowering therapy
LDL-C ≥70 mg/dL
Assessments
W0
W4
W8
W12
W16
W24
W36
W52
W64
W78
R
n=1553
n=788
Alirocumab 150 mg Q2W SC
(single 1-mL injection using prefilled syringe
for self-administration)
Placebo Q2W SC
Double-blind treatment (18 months)
Follow-up
(8 weeks)
Primary
efficacy endpoint
Pre-specified analysis
Efficacy: All patients up to W52 (ITT)
Safety: All patients randomized and treated
his analysis
85.8% (2009/2341) completed 52 weeks (both treatment arms)
26.1% (405/1553 alirocumab) and 25.6% (202/788 placebo) had completed 78 weeks by time of this analysis
Mean treatment duration: 65 weeks (both treatment arms)
ClinicalTrials.gov identifier: NCT01507831.

Fig. 10

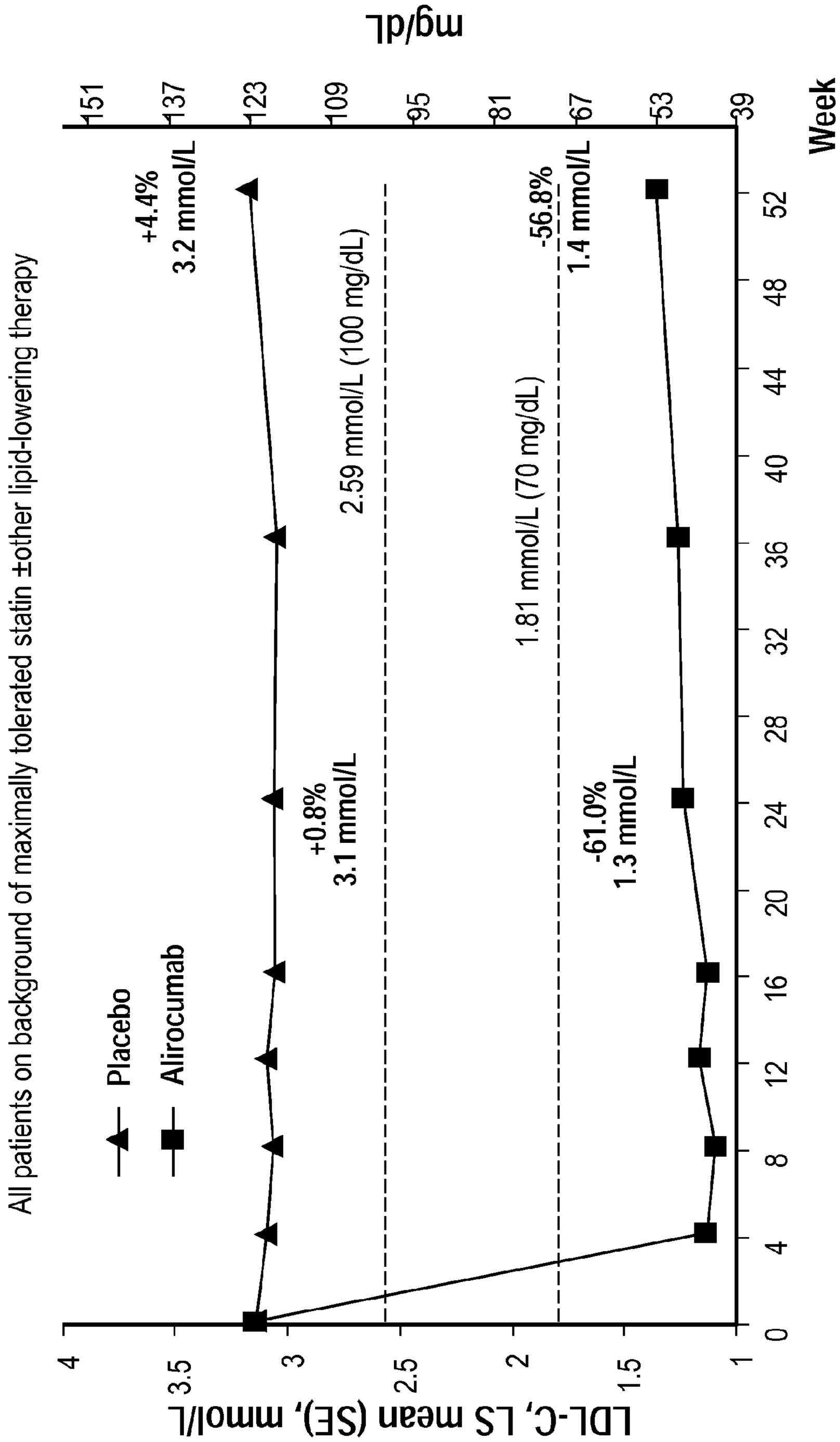

Achieved LDL-C Over Time
All patients on background of maximally tolerated statin ±other lipid-lowering therapy
Placebo
Alirocumab
+0.8%
3.1 mmol/L
-61.0%
1.3 mmol/L
+4.4%
3.2 mmol/L
-56.8%
1.4 mmol/L
2.59 mmol/L (100 mg/dL)
1.81 mmol/L (70 mg/dL)
LDL-C, LS mean (SE), mmol/L
4
3.5
3
2.5
2
1.5
1
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Week
39
53
67
81
95
109
123
137
151
mg/dL

Fig. 11

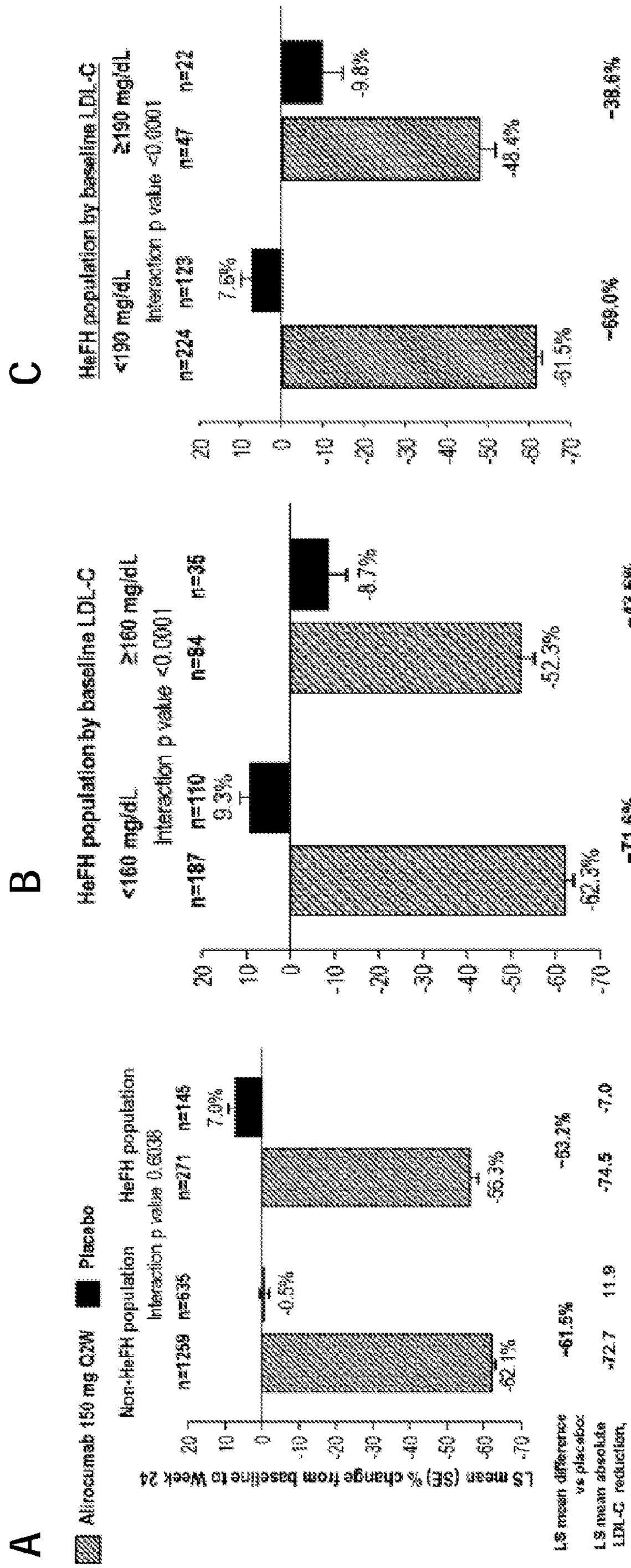

A
Alirocumab 150 mg Q2W
Placebo
Non-HeFH population
Interaction p value 0.6038
n=1259 n=635
LS mean (SE) % change from baseline to Week 24
20
10
0
-10
-20
-30
-40
-50
-60
-70
-0.5%
-52.1%
LS mean difference vs placebo
-51.5%
LS mean absolute LDL-C reduction, mg/dL
-72.7
11.9
B
HeFH population
Interaction p value 0.6038
n=271 n=145
7.0%
-55.3%
-63.2%
-74.5
-7.0
HeFH population by baseline LDL-C
<160 mg/dL
Interaction p value <0.0001
n=187 n=110
9.3%
-62.3%
-71.6%
≥160 mg/dL
n=84 n=35
-8.7%
-52.3%
-43.6%
C
HeFH population by baseline LDL-C
<190 mg/dL
Interaction p value <0.0001
n=224 n=123
7.5%
-51.5%
-59.0%
≥190 mg/dL
n=47 n=22
-9.8%
-48.4%
-38.6%

Fig. 12

Subgroup	Alirocumab n	Alirocumab LS mean	Placebo n	Placebo LS mean	Interaction p-value
Overall	1530	-61.0	780	0.8	
Race					0.2227
White	1419	-61.6	722	0.8	
Black/African American	53	-49.5	24	4.3	
Age					0.1313
<65	963	-60.4	498	-0.1	
65 to <75	442	-62.9	221	3.0	
≥75	125	-59.5	61	0.5	
BMI					0.3396
<30	852	-61.5	406	1.3	
≥30	674	-60.3	371	0.1	
Moderate CKD					0.0210
Yes	73	-62.0	174	8.7	
No	1356	-60.9	707	0.0	
Diabetes					0.0957
Yes	545	-60.0	273	-1.0	
No	985	-61.6	507	1.8	
Baseline fasting TGs, mg/dL					0.3431
<150	928	-58.8	450	2.2	
≥150	602	-64.5	329	-1.1	

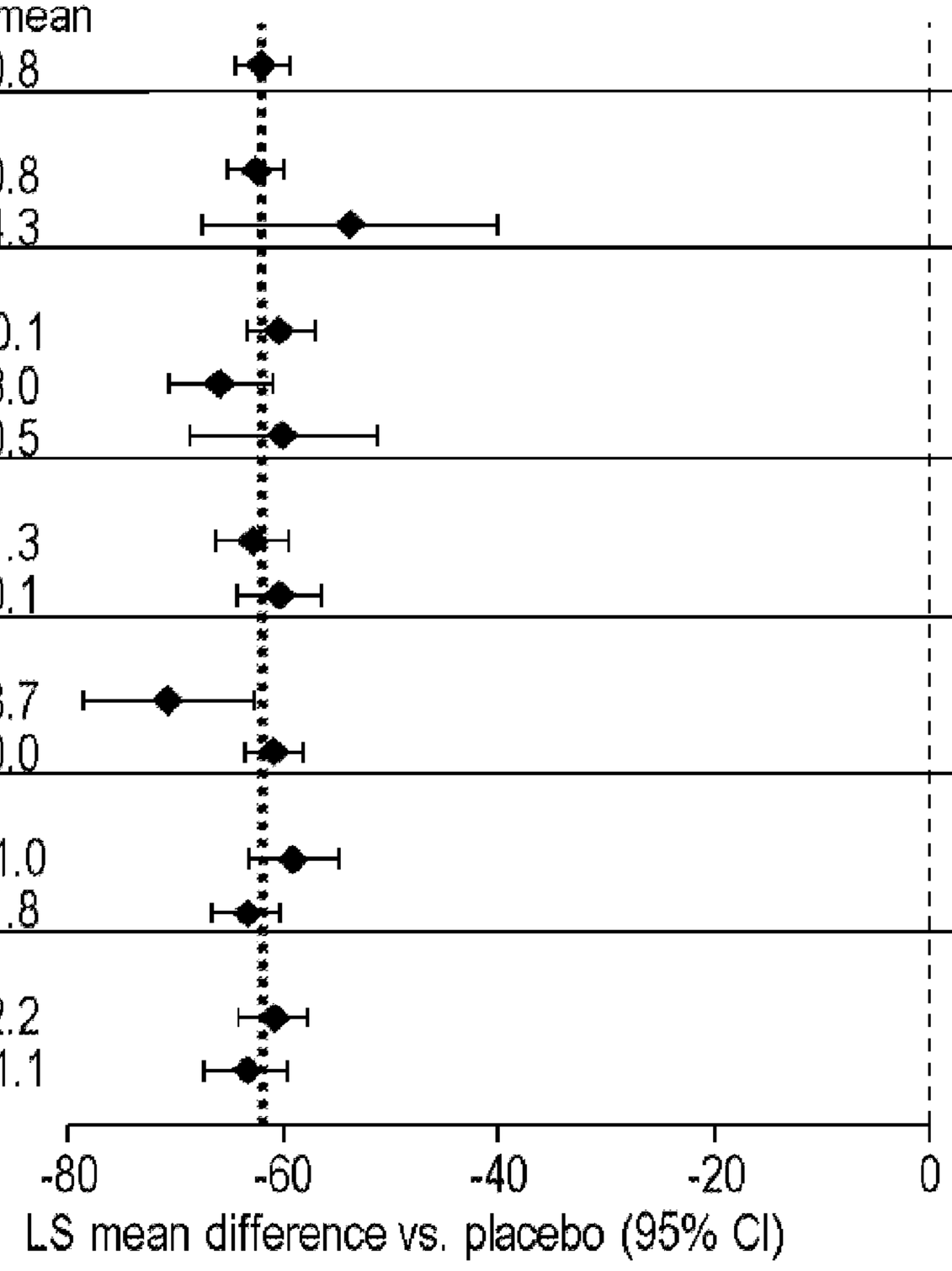


Fig. 13

CA 02955304 2017-01-13

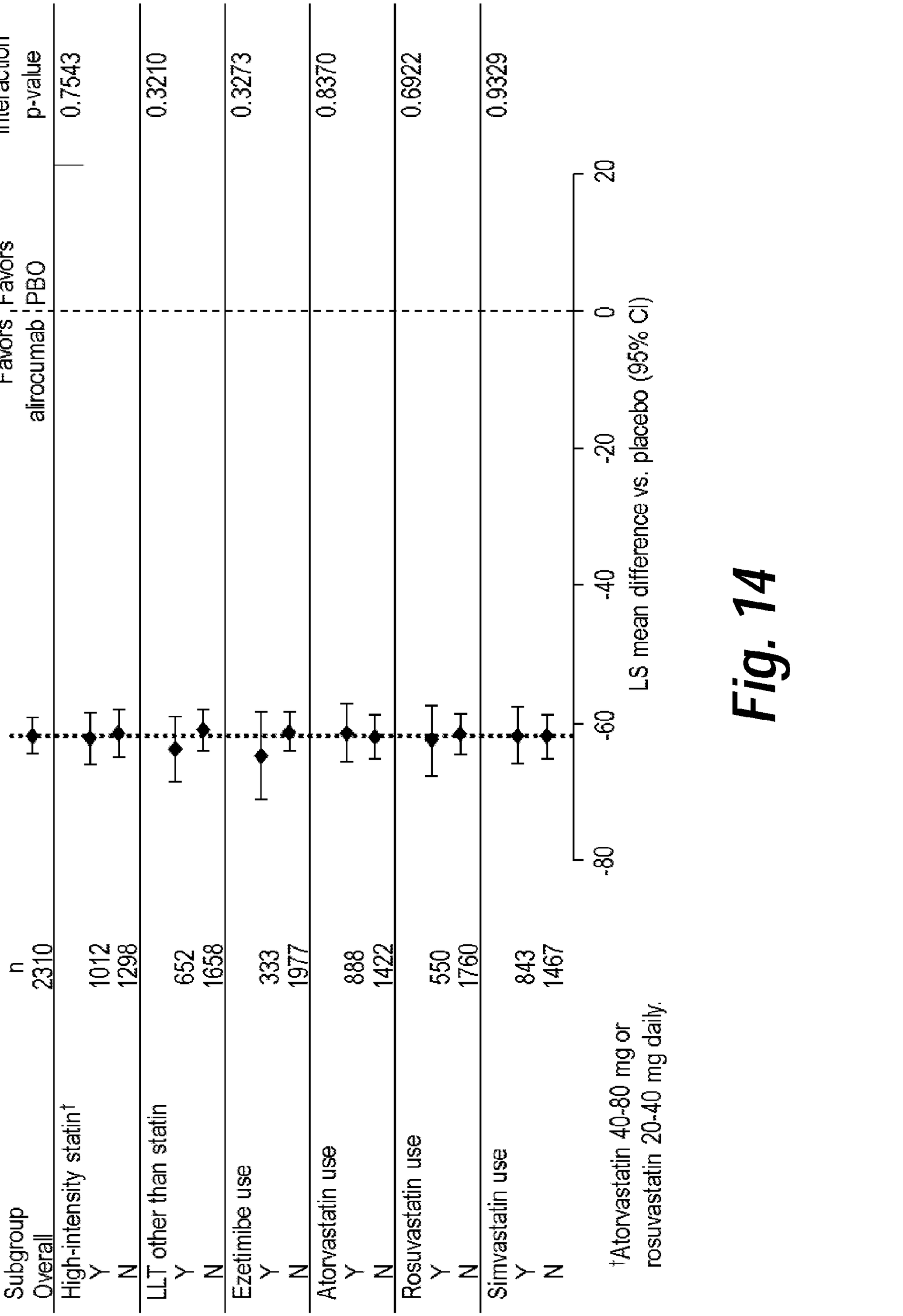

Subgroup
Overall
High-intensity statin†
Y
N
LLT other than statin
Y
N
Ezetimibe use
Y
N
Atorvastatin use
Y
N
Rosuvastatin use
Y
N
Simvastatin use
Y
N
n
2310
1012
1298
652
1658
333
1977
888
1422
550
1760
843
1467
Interaction
p-value
0.7543
0.3210
0.3273
0.8370
0.6922
0.9329
Favors alirocumab
Favors PBO
20
0
-20
-40
-60
-80
LS mean difference vs. placebo (95% CI)
†Atorvastatin 40-80 mg or
rosuvastatin 20-40 mg daily.

Fig. 14

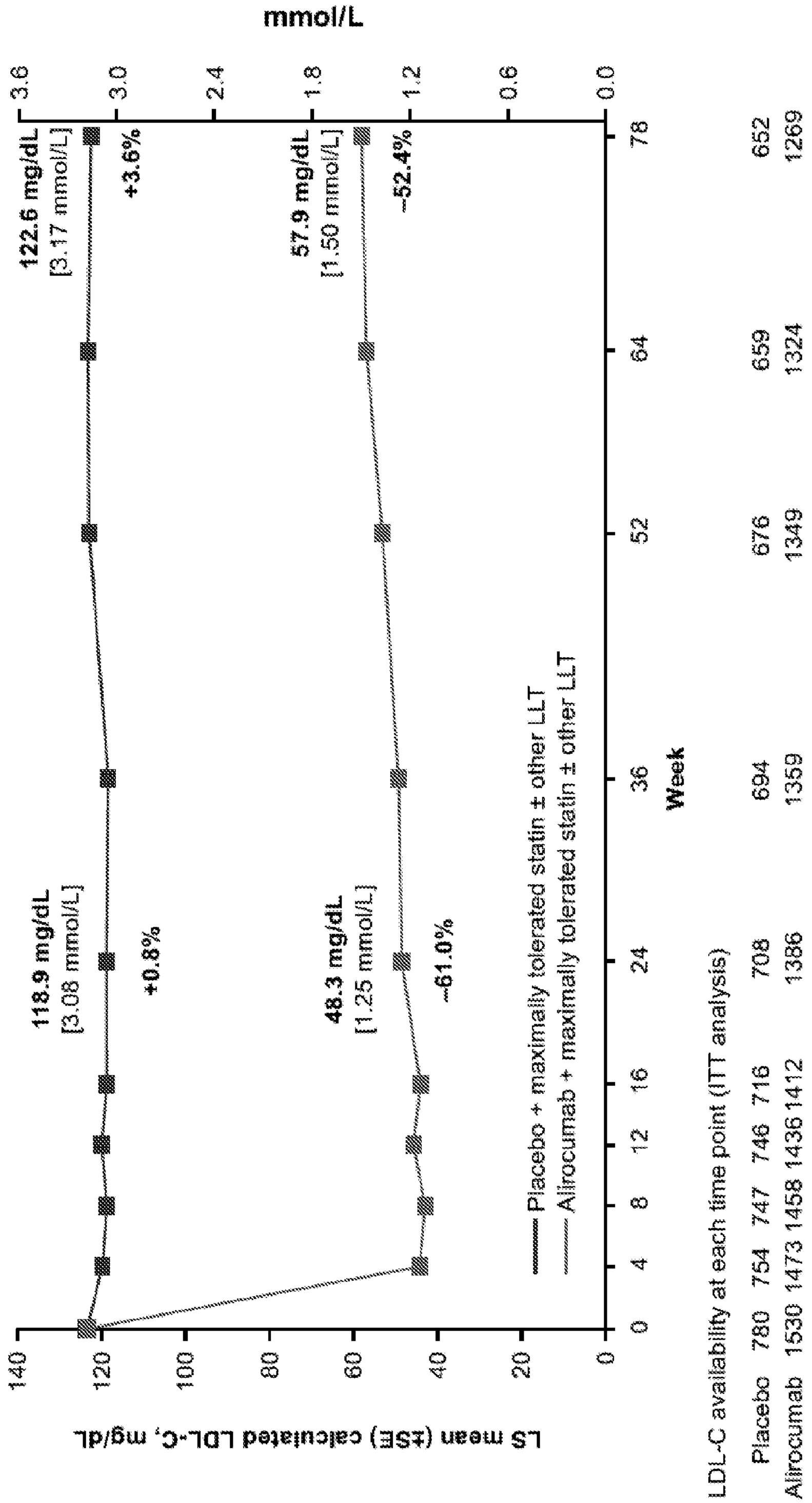

mmol/L
3.6
3.0
2.4
1.8
1.2
0.6
0.0
122.6 mg/dL
[3.17 mmol/L]
+3.6%
57.9 mg/dL
[1.50 mmol/L]
−52.4%
118.9 mg/dL
[3.08 mmol/L]
+0.8%
48.3 mg/dL
[1.25 mmol/L]
−61.0%
Placebo + maximally tolerated statin ± other LLT
Alirocumab + maximally tolerated statin ± other LLT
LS mean (±SE) calculated LDL-C, mg/dL
140
120
100
80
60
40
20
0
0 4 8 12 16 24 36 52 64 78
Week
LDL-C availability at each time point (ITT analysis)
Placebo 780 754 747 746 716 708 694 676 659 652
Alirocumab 1530 1473 1458 1436 1412 1386 1359 1349 1324 1269

Fig. 15