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Efficacy and Safety of Alirocumab 150 mg Every 4 Weeks in Patients With Hypercholesterolemia Not on Statin Therapy: The ODYSSEY CHOICE II Study

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***Background*—**The PCSK9 antibody alirocumab (75 mg every 2 weeks; Q2W) as monotherapy reduced low-density lipoprotein-cholesterol (LDL-C) levels by 47%. Because the option of a monthly dosing regimen is convenient, ODYSSEY CHOICE II evaluated alirocumab 150 mg Q4W in patients with inadequately controlled hypercholesterolemia and not on statin (majority with statin-associated muscle symptoms), receiving treatment with fenofibrate, ezetimibe, or diet alone.

***Methods and Results*—**Patients were randomly assigned to placebo, alirocumab 150 mg Q4W or 75 mg Q2W (calibrator arm), with dose adjustment to 150 mg Q2W at week (W) 12 if W8 predefined LDL-C target levels were not met. The primary efficacy endpoint was LDL-C percentage change from baseline to W24. Mean baseline LDL-C levels were 163.9 mg/dL (alirocumab 150 mg Q4W, n=59), 154.5 mg/dL (alirocumab 75 mg Q2W, n=116), and 158.5 mg/dL (placebo, n=58). In the alirocumab 150 mg Q4W and 75 mg Q2W groups (49.1% and 36.0% of patients received dose adjustment, respectively), least-squares mean LDL-C changes from baseline to W24 were −51.7% and −53.5%, respectively (placebo [+4.7%]; both groups $P<0.0001$ versus placebo). In total, 63.9% and 70.3% of alirocumab-treated patients achieved their LDL-C targets at W24. Treatment-emergent adverse events occurred in 77.6% (alirocumab 150 mg Q4W), 73.0% (alirocumab 75 mg Q2W), and 63.8% (placebo) of patients, with injection-site reactions among the most common treatment-emergent adverse events.

***Conclusions*—**Alirocumab 150 mg Q4W can be considered in patients not on statin with inadequately controlled hypercholesterolemia as a convenient option for lowering LDL-C.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT02023879. **(*J Am Heart Assoc*. 2016;5: e003421 doi: 10.1161/JAHA.116.003421)**

Key Words: alirocumab • cardiovascular risk • low-density lipoprotein cholesterol • placebo-controlled • proprotein convertase subtilisin/kexin type 9

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Statins lower low-density lipoprotein cholesterol (LDL-C) by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A reductase and consistently reduce cardiovascular disease (CVD) risk by 30% to 40%.[1-3] Therefore, statin therapy is currently the recommended standard-of-care treatment for lowering LDL-C in patients at increased CVD risk.[2,3] In contrast to all major randomized controlled trials, which have found comparable rates of muscle adverse events (AEs)

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*An accompanying Appendix S1 which contains complete list of the ODYSSEY CHOICE II investigators, Tables S1 through S6 and Figures S1 through S4 are available at http://jaha.ahajournals.org/content/5/9/e003421/DC1/embed/inline-supplementary-material-1.pdf

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between statin and placebo arms,[4-6] observational studies reported higher rates of statin-associated muscle symptoms (SAMS) in 7% to 29% of patients.[7] As a consequence, patients with SAMS often receive a suboptimal statin dose or no statin therapy.[7] A substantial proportion of these, often high-risk, patients have persistently elevated LDL-C levels (>190 mg/dL),[8-10] placing them at a correspondingly high CVD risk.[3,11]

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a key regulator of cholesterol homeostasis, is a novel and attractive therapeutic target for lowering LDL-C levels via a 3-hydroxy-3-methylglutaryl-coenzyme A reductase-independent pathway. Alirocumab, a fully human monoclonal antibody that specifically binds to PCSK9, has been shown to significantly lower LDL-C levels across a range of dosing regimens, whether as monotherapy[12] or on a background of statin±-other lipid-lowering therapies.[13-16] A monthly dosing regimen may be convenient and effective,[17,18] with different doses being appropriate when used as monotherapy compared with background statin therapy. This is because statins are known to increase PCSK9 levels,[19] which reduce duration of alirocumab effect in the setting of every 4 weeks (Q4W) dosing.

Alirocumab 150 mg Q4W monotherapy demonstrated a 47.4% reduction in LDL-C levels from baseline in a phase 1 study.[17] However, in an early phase 2 study of patients with heterozygous familial hypercholesterolemia on statin, there was only an incremental LDL-C reduction of 28.9% at week 12 with alirocumab 150 Q4W.[18] The use of higher doses (200-300 mg Q4W) resulted in greater incremental LDL-C reductions (42.5-47.7% at week 12) when added to stable statin therapy.[18,20]

In this phase 3, placebo-controlled study (ODYSSEY CHOICE II, NCT02023879), we evaluated the efficacy and safety of alirocumab 150 mg Q4W (with possible adjustment to 150 mg Q2W; referred to as "150Q4W") as a therapeutic option for patients with hypercholesterolemia not receiving statin. This study also employed an alirocumab dosing regimen of 75 mg every 2 weeks (Q2W; with possible dose adjustment to 150 mg Q2W; referred to as "75Q2W") as a calibrator arm, a dose that has been extensively investigated across the phase 3 ODYSSEY clinical trials program.[12-16] CHOICE II followed a "treat-to-target" dosing strategy, based on the LDL-C reduction needed to provide best achievement of target LDL-C level at the lowest alirocumab dose.

Methods

ODYSSEY CHOICE II was a randomized, double-blind, placebo-controlled, phase 3 multinational study including 233 patients from 43 study sites from Australia (n=3), Belgium (n=3), Canada (n=6), Denmark (n=5), the Netherlands (n=9), New Zealand (n=2), Spain (n=7), and the United States (n=8). The study was initiated on December 16, 2013 (first patient screened) with the first patient randomized on January 2, 2014 and the last patient randomized on May 12, 2014. The study was conducted in accordance with the ethical principles in the Declaration of Helsinki and applicable amendments, and the International Conference on Harmonisation guidelines for Good Clinical Practice. The protocol was approved by the relevant institutional review boards or independent ethics committees. All participating patients provided written informed consent.

Patients

The study enrolled adult patients (≥18 years of age) with hypercholesterolemia receiving fenofibrate or ezetimibe or diet alone. Only patients not receiving a statin were eligible for the study, which corresponded to patients who (1) had SAMS (which was defined as statin intolerance in the protocol) with moderate, high, or very high cardiovascular risk or (2) were not receiving a statin but who did not fulfill the SAMS definition: only patients at moderate cardiovascular risk were included in this stratum. SAMS, as well as moderate, high, and very high cardiovascular risk, were defined as previously described.[21]

SAMS, defined as statin intolerance in the study protocol, was defined as the inability to tolerate at least 2 statins, consistent with other studies in the ODYSSEY clinical trial program[21]: 1 statin at the lowest daily starting dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg), and another statin at any dose, due to SAMS, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued.

The aim was for two-thirds of randomized patients to be receiving fenofibrate/ezetimibe, and for ≥50% of patients to fulfill the SAMS definition. Patients were instructed to maintain a stable diet (National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes diet or equivalent) throughout the entire study duration, including the screening period.[22] Use of fibrates (other than fenofibrate), niacin, bile acid-binding sequestrants, or red yeast rice products was not allowed during the study. A list of exclusion criteria is given in Table S1.

Hypercholesterolemia was defined based on cardiovascular risk: LDL-C ≥70 mg/dL if very high cardiovascular risk, or LDL-C ≥100 mg/dL if high or moderate risk. In addition, for those patients not fulfilling the SAMS definition, or who were being treated with diet alone, LDL-C also had to be ≥100 and <160 mg/dL.

Study Procedures

The study comprised a 3-week screening period, followed by 24 weeks of double-blind treatment and 8 weeks of follow-up (off treatment) for those patients who did not enter the open-label treatment period (Figure 1). After screening, the planned randomization was to follow a 2:1:1 treatment ratio for alirocumab 150Q4W, alirocumab 75Q2W (calibrator arm), and placebo Q2W, respectively. Randomization was stratified by SAMS status and by either ezetimibe/fenofibrate therapy or diet alone. However, owing to a systematic error in the algorithm managing treatment allocation at the study setup (where alirocumab 75Q2W was allocated to patients randomized to alirocumab 150Q4W during the entire double-blind period and vice versa), patients were actually randomized in a 1:2:1 ratio to receive alirocumab 150Q4W, 75Q2W, or placebo in a blinded manner. The blinding was maintained for patients randomized to alirocumab 150Q4W by alternating active and placebo injections; each patient received 12 injections during the study period. Each treatment was administered subcutaneously by 1-mL prefilled pen.

On-site visits took place during the double-blind period at weeks 0 (baseline, ie, the randomization visit), 4, 8, 9, 10, 11, 12, 16, and 24.

Patients in the alirocumab 150 mg Q4W or 75 mg Q2W treatment groups who did not achieve their target LDL-C levels (<70 or <100 mg/dL, depending on CVD risk), or who did not achieve a reduction of ≥30% in LDL-C level from baseline at week 8, had their alirocumab regimen changed to 150 mg Q2W at week 12 in a blinded fashion.

Patients also had the option of entering an open-label treatment period after completion of the double-blind treatment period. In this treatment period all patients received alirocumab 150Q4W at week 36 based on the investigator's judgment.

Endpoints

The primary efficacy endpoint was the percentage change in LDL-C (calculated using the Friedewald equation) from baseline to week 24 in the intent-to-treat (ITT) population, using all LDL-C values within 1 of the analysis windows up to week 24 regardless of adherence to treatment (ie, ITT approach). Efficacy endpoints were also assessed using an on-treatment approach, using all LDL-C values during the efficacy treatment period.

A hierarchical procedure was used to control type I error and handle multiple key secondary endpoints. Those endpoints included the percentage change in calculated LDL-C from baseline to week 24 using the on-treatment approach, the percentage change in calculated LDL-C from baseline to week 12 (also averaged for weeks 9-12), the proportion of patients achieving predefined LDL-C targets of <70 or <100 mg/dL, depending on cardiovascular risk, at weeks

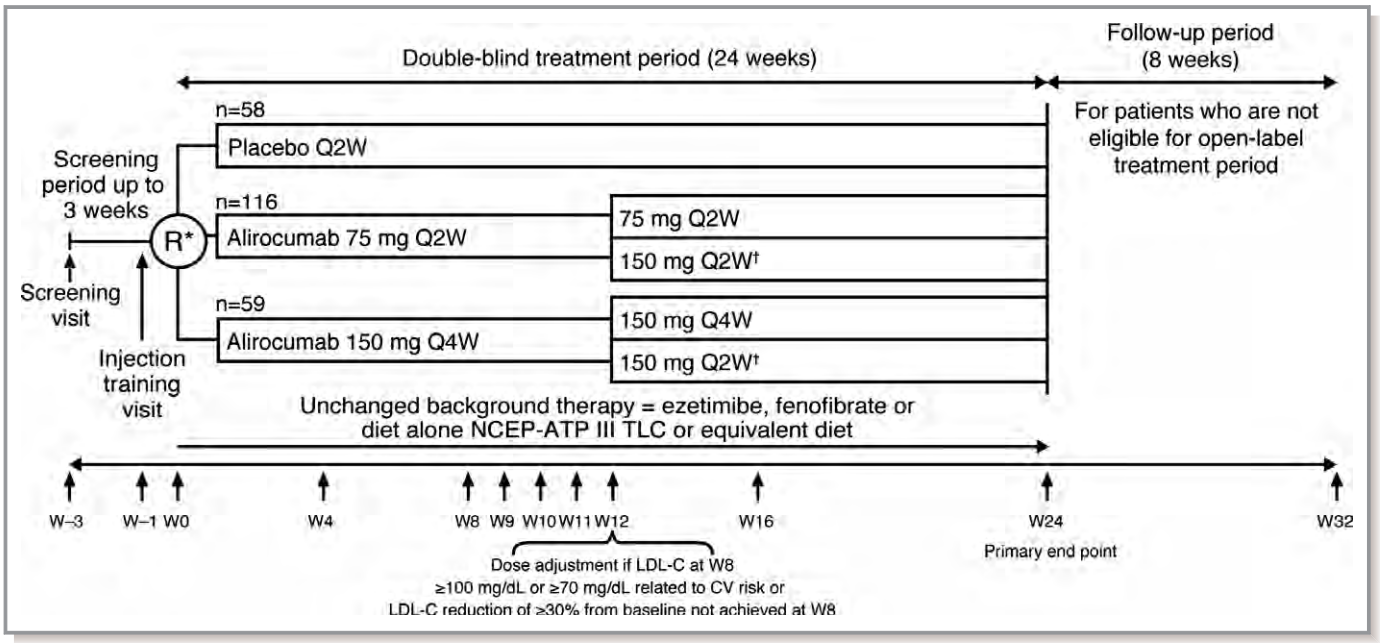

Figure 1. CHOICE II study design. *Patients were to be randomized to 2:1:1 alirocumab 150Q4W: alirocumab 75Q2W: placebo. However, a systematic randomization error occurred in alirocumab treatment allocation. †Blind was maintained in all patients, including those receiving dose adjustments, by giving the study treatment as a single 1-mL subcutaneous injection Q2W in all groups. 75Q2W indicates 75 mg every 2 weeks (with possible dose adjustment to 150 mg every 2 weeks); 150Q4W, 150 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks); LDL-C, low-density lipoprotein cholesterol; NCEP ATP III TLC, National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes; Q2W, every 2 weeks; Q4W, every 4 weeks; R, randomization; W, week.

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12 and 24, and the percentage change in other lipid parameters such as apolipoprotein B, non-high-density lipoprotein cholesterol, total cholesterol, lipoprotein(a) (Lp [a]), fasting triglycerides, high-density lipoprotein cholesterol, and apolipoprotein A1 from baseline to weeks 12 and 24. All comparisons with the alirocumab 75 mg Q2W treatment arm were classed as other secondary endpoints.

Analyses of lipid samples were conducted by a central laboratory. Lp(a) was analyzed using an immunoturbidimetric assay on a Siemens BNII analyzer (Siemens, Erlangen, Germany), with a reference range of 1 to 30 mg/dL. If triglyceride values exceeded 400 mg/dL (4.52 mmol/L), LDL-C was measured via β-quantification rather than by calculation. (LDL-C ultracentrifugation was performed using a Beckman Ultracentrifuge with an ultracentrifuge rotor, Type 50.4; LDL-C concentration was assessed using a Beckman Coulter chemistry analyzer.) LDL-C was also measured via the β-quantification method at weeks 0 and 24 in all patients.

Safety was assessed primarily from the reporting of treatment-emergent AEs (TEAEs), defined as those occurring during the period from first to last study drug injection plus 70 days or up to the first open-label injection, whichever came first.

Certain events were classed as safety events of interest, requiring completion of a special electronic case report form (e-CRF), including general allergic reactions, cardiovascular events, injection-site reactions, hemolytic anemia, neurologic events, ophthalmologic events, and increased alanine aminotransferase (ALT) levels. See Appendix S1 for further details on safety events of interest and preferred terms for the adverse events categories.

To assess development of antidrug antibodies to alirocumab, blood samples were collected before study drug administration at baseline and scheduled clinic visits at weeks 4, 8, 12, 16, 24, and at the follow-up visit. These samples were analyzed using a validated nonquantitative, titer-based bridging immunoassay by Regeneron Pharmaceuticals, Inc (Tarrytown, NY), using a tiered approach involving 3 potential steps: initial screen, confirmation, and a titer measurement. Assay sensitivity was ~5.6 ng/mL based on the positive control monoclonal antibody, and the drug tolerance limit was 191 μg/mL of alirocumab for 500 ng/mL of monoclonal antibody positive control. Positive samples were tested for the presence of antidrug antibody using a validated, nonquantitative, competitive ligand-binding assay with sensitivity based on a monoclonal positive control neutralizing antibody of 470 ng/mL. Drug tolerance limit was 547 ng/mL of alirocumab in neat serum for 500 ng/mL of monoclonal antibody positive control. Free PCSK9 levels were determined using a specific validated enzyme-linked immunosorbent assay (Regeneron Pharmaceuticals, Tarrytown, NY). The lower limits of detection were 31.2 ng/mL.

Statistical Analysis

A sample size of 39 patients (26 in alirocumab 150Q4W and 13 in placebo arms, respectively) was estimated to have 90% power to detect a between-treatment-group difference in mean percentage change in LDL-C of 30%, with a 5% 2-sided significance level and assuming a common standard deviation of 25%, and a 5% nonevaluable primary endpoint. To obtain additional safety data on the administration of a 150Q4W regimen in non-statin-treated patients, the total planned sample size was increased and rounded to 200 (100 for alirocumab 150Q4W, 50 for alirocumab 75Q2W, and 50 for placebo). Thus, the systematic allocation error was not anticipated to have an impact on the power of the study.

The primary efficacy analysis was conducted in the ITT population, which included all randomized patients with an evaluable primary endpoint. Analysis utilized a mixed-effect model with repeated measures to account for missing data as used in previous alirocumab studies.[23]

Secondary lipid endpoints were analyzed as for the primary endpoint, except Lp(a) and triglycerides (analyzed by multiple imputation followed by a robust regression model) and LDL-C goal achievement (analyzed by multiple imputation followed by logistic regression). The modified ITT population used for on-treatment analyses included all randomized patients with an evaluable primary endpoint during the treatment period who had received at least 1 dose or part of a dose of study treatment.

The safety population included all randomized patients who had received at least 1 dose or part of a dose of study drug. Safety data were analyzed by descriptive statistics.

Device-Handling Questionnaire

At weeks 0 and 12, an optional device-handling questionnaire assessed experience of participants performing self-injection using the alirocumab prefilled pen.

Participants rated 7 manipulations/steps to inject alirocumab/placebo (7-point scale from “not easy at all” [1] to “extremely easy” [7]), how many clicks they heard during injection, satisfaction with duration of injection (7-point scale from “extremely unsatisfied” [1] to “extremely satisfied” [7]), and the overall experience performing self-injection (7-point scale from “extremely unsatisfied” [1] to “extremely satisfied” [7]).

Results

Patients

A total of 233 patients were randomly assigned to alirocumab 150Q4W (n=59), 75Q2W (n=116), and placebo (n=58) (Figure 1, Figure S1). The ITT, modified ITT, and safety populations comprised 230, 228, and 231 patients,

respectively. A total of 158 (90.3%) randomized patients receiving alirocumab completed the 24-week treatment period. Reasons for study discontinuation are given in Table S2.

Baseline characteristics and lipid parameters were generally balanced between groups (Table 1). A total of 90.1% of patients fulfilled the criteria for SAMS as the reason for statin discontinuation. The majority of patients with additional lipid-lowering therapy received ezetimibe (60.1%) and/or fenofibrate (8.6%). Across the different treatment groups, 32.2% of patients received treatment with diet alone and 3.4% received nutraceuticals (Table 1).

Efficacy Analyses

Alirocumab (both dose regimens) maintained LDL-C reductions from week 4 (first sampling point) until week 24 (Figure 2; Table 2).

Week 12

Before any dose adjustment (ie, up to week 12), the mean percentage change in LDL-C from baseline to averaged weeks 9 to 12 was −52.3% in the alirocumab 150Q4W group and 3.2% in the placebo group. However, in the alirocumab 150Q4W group the mean percentage reduction in LDL-C from baseline to weeks 9 to 11 was greater (54.5% to 57.2%) compared with that observed at week 12 (41.7%; Table 2). Absolute LDL-C levels over time are shown in Figure 2. In the alirocumab 75Q2W calibrator arm, percentage reduction in LDL-C from baseline to averaged weeks 9 to 12 was 53.6% (Table 2), whereas percentage reduction in LDL-C from baseline to weeks 9 to 11 (51.6% to 56.3%) was comparable to that at week 12 (50.8%).

At week 12, 26 patients (49.1%) received a dose adjustment from alirocumab 150 mg Q4W to 150 mg Q2W because these patients did not achieve their predefined LDL-C target levels at week 8 (with 36.0% of patients in the 75 mg Q2W group also increasing to 150 mg Q2W). In general, subjects in both groups with dose adjustment were characterized by higher LDL-C levels at baseline (197.5 mg/dL in the 150Q4W group and 188.6 mg/dL in the 75Q2W group) compared with those who did not require dose adjustment (130.3 and 137.3 mg/dL, respectively) (Figure 3, Table S3). Mean LDL-C levels in patients who received dose adjustment from 150 mg Q4W to 150 mg Q2W were reduced further from 120.5 mg/dL at week 12 to 79.0 mg/dL at week 24, a decrease from week 12 of 34.4%, corresponding to an incremental benefit of ~19% compared with baseline (Figure 3). Of patients allocated to alirocumab 150Q4W, 50.9% did not need dose adjustment and were maintained on this dose until the end of the study. In the calibrator arm, 64.0% of patients remained on the 75 mg Q2W dose. For patients who received dose adjustment from 75 mg Q2W to 150 mg Q2W, an LDL-C reduction from week 12 to week 24 of 15.8% was observed, corresponding to an incremental benefit of ~11% compared with baseline (week 12, 106.6 mg/dL; week 24, 89.8 mg/dL) (Figure S2).

Week 24

At week 24 (primary endpoint), the mean (standard error) percentage change in LDL-C from baseline to week 24 was greater in the alirocumab 150Q4W group (−51.7%) versus placebo (+4.7%) in the ITT analysis, with a statistically significant mean difference of −56.4% ($P<0.0001$; Table 2). The on-treatment analysis demonstrated consistent results (alirocumab 150Q4W −54.6%; placebo +5.1%; $P<0.0001$) (Table S4). Data were comparable when either measured or calculated LDL-C was used (Table S5).

At week 24, 63.9% of patients allocated to alirocumab 150Q4W achieved their LDL-C target levels versus 1.8% of patients allocated to placebo (70.3% in the alirocumab 75Q2W group) (Table 2).

Across various patient subgroups the reductions in LDL-C were similar to the primary endpoint data at week 24 (Figure S3), although patients with baseline free PCSK9 levels above the median tended to see a greater reduction in LDL-C compared with those with baseline levels below the median (Figure S3). Considering concomitant therapies (ezetimibe and/or fenofibrate or diet alone), LDL-C reductions were consistent in the alirocumab 150Q4W group at week 24 (Figure S3).

At week 24, significant ($P<0.05$) improvements in secondary efficacy endpoints including apolipoprotein B, non-high-density lipoprotein cholesterol, and Lp(a) were observed following treatment with alirocumab 150Q4W (Table 2).

Free PCSK9

In general, predictable dynamics were observed following alirocumab administration, with free PCSK9 levels decreasing concomitantly with LDL-C level reduction in the alirocumab 150Q4W group (or 75Q2W group) (Figure 2). Despite similar baseline free PCSK9 levels, alirocumab-treated patients receiving dose adjustment to 150 mg Q2W at week 12 had a less pronounced decrease in mean free PCSK9 levels during the first 12 weeks than those remaining on the initial alirocumab dose (Figure 3; Figure S2). Following dose adjustment, an additional reduction in mean free PCSK9 levels was observed with mean values close to 0, ranging from 1.6 to 3.6 ng/mL (Figure 3; Figure S2).

Device-Handling Questionnaire

At Weeks 0 and 12, 135 and 117 of all study participants completed the device-handling questionnaire, respectively.

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Table 1. Baseline Characteristics (Randomized Population)

	Placebo (n=58)	Alirocumab	
		75Q2W (n=116)	150Q4W (n=59)
Baseline demographics			
Age, y, mean (SD)	63.1 (10.7)	62.5 (9.9)	64.2 (10.0)
Male, n (%)	31 (53.4)	69 (59.5)	30 (50.8)
Race, white, n (%)	56 (96.6)	108 (93.1)	55 (93.2)
Race, black or African American, n (%)	1 (1.7)	3 (2.6)	1 (1.7)
Ethnicity, Hispanic/Latino, n (%)	1 (1.7)	7 (6.0)	4 (6.8)
BMI, kg/m^2, mean (SD)	28.5 (4.6)	29.4 (5.6)	28.2 (5.2)
HeFH, n (%)	5 (8.6)	15 (12.9)	9 (15.3)
Diagnosis of HeFH, n	5	15	9
By genotyping, n (%)	4 (80.0)	8 (53.3)	6 (66.7)
By WHO/Simon Broome criteria, n (%)	1 (20.0)	7 (46.7)	3 (33.3)
SAMS status, n (%)			
SAMS	51 (87.9)	106 (91.4)	53 (89.8)
Non-SAMS	7 (12.1)	10 (8.6)	6 (10.2)
CHD history, n (%)	27 (46.6)	57 (49.1)	32 (54.2)
CHD risk equivalent*, n (%)	10 (17.2)	23 (19.8)	11 (18.6)
Hypertension, n (%)	37 (63.8)	69 (59.5)	36 (61.0)
Type 2 diabetes, n (%)	9 (15.5)	22 (19.0)	7 (11.9)
Categorization of cardiovascular risk, n (%)			
Very-high cardiovascular risk	31 (53.4)	66 (56.9)	36 (61.0)
High cardiovascular risk	13 (22.4)	23 (19.8)	10 (16.9)
Moderate cardiovascular risk	14 (24.1)	27 (23.3)	13 (22.0)
Lipid medication, n (%)			
Any LLT other than statins	41 (70.7)	82 (70.7)	42 (71.2)
Ezetimibe	35 (60.3)	70 (60.3)	35 (59.3)
Fenofibrate	3 (5.2)	12 (10.3)	5 (8.5)
Nutraceuticals	1 (1.7)	3 (2.6)	4 (6.8)
Diet alone†	20 (34.5)	35 (30.2)	20 (33.9)
Baseline lipid parameters, mg/dL, mean (SD)			
LDL-C (calculated)	158.5 (47.3)	154.5 (44.6)	163.9 (69.1)
LDL-C (calculated), median (Q1:Q3)	148.5 (136.0:166.0)	146.0 (124.5:173.5)	148.0 (127.0:179.0)
LDL-C (measured)	156.6 (46.6)	154.1 (42.4)	167.5 (69.0)
Non-HDL-C	191.9 (51.0)	188.0 (49.9)	195.9 (76.4)
Total cholesterol	244.7 (50.8)	239.1 (50.2)	250.8 (75.7)
Apo B	120.3 (27.6)	120.2 (27.1)	126.5 (44.8)
Lp(a), median (Q1:Q3)	10.5 (4.0:31.0)	16.0 (5.0:46.0)	19.0 (5.0:41.0)
HDL-C	52.8 (16.6)	51.1 (15.1)	54.9 (13.4)
Fasting triglycerides, median (Q1:Q3)	154.5 (105.0:218.0)	147.5 (107.0:225.0)	145.0 (102.0:211.0)
Apo A1	151.0 (27.7)	150.5 (27.3)	154.8 (25.8)

75Q2W indicates 75 mg every 2 weeks (with possible dose adjustment to 150 mg every 2 weeks); 150Q4W, 150 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks); Apo, apolipoprotein; BMI, body mass index; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); SAMS, statin-associated muscle symptoms; SD, standard deviation; WHO, World Health Organization.
*CHD risk equivalents were defined as abdominal aortic aneurysm, carotid artery occlusions >50% without symptoms, peripheral arterial disease, carotid endarterectomy or carotid artery stent procedure, type 1 or 2 diabetes mellitus, with target organ damage, ischemic stroke, renal artery stenosis, and transient ischemic attack.
†Patients not taking fenofibrate or ezetimibe.

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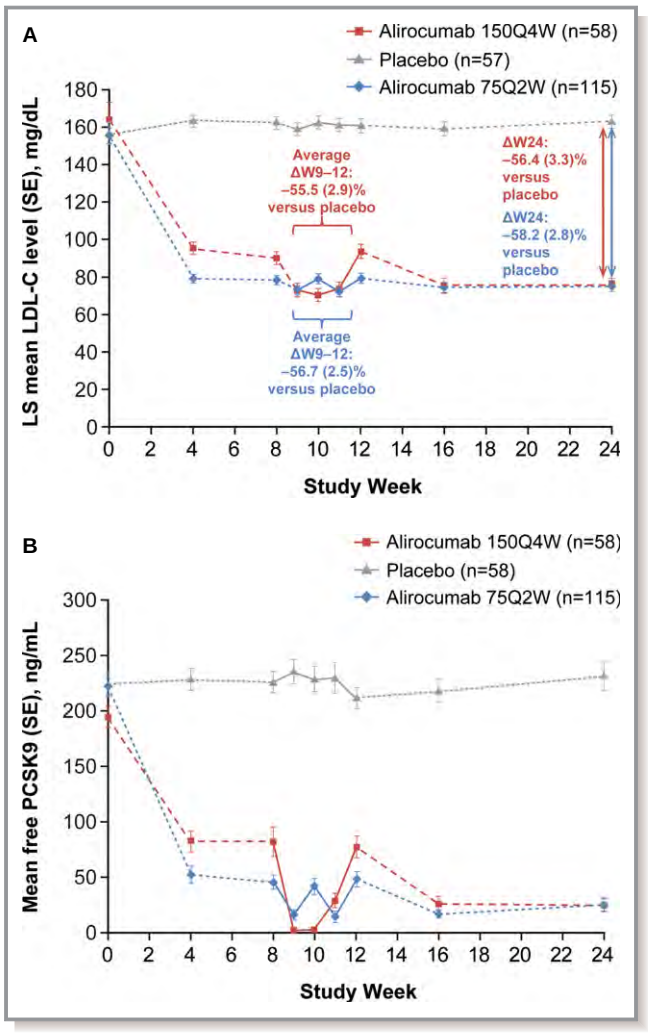

Figure 2. Calculated LDL-C mean (SE) absolute values from baseline (ITT analysis) (A) and free PCSK9 levels (B) over time (PK analysis). ΔW 9 to 12 defined as percentage change in calculated LDL-C from baseline to averaged values from weeks 9 to 12 vs placebo in the ITT analysis; ΔW 24 defined as percentage change in calculated LDL-C from baseline to week 24 vs placebo in the ITT analysis. 75Q2W indicates 75 mg every 2 weeks (with possible dose adjustment to 150 mg every 2 weeks); 150Q4W indicates150 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks); ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least-squares; PCSK9, proprotein convertase subtilisin/kexin type 9; SE, standard error.

Overall, the provided ratings at each time point were similar. The overall experience in performing home self-injection was rated as 6 or 7 (7=extremely satisfied) by 93% of the patients. In addition, 92% of patients (n=125) were very satisfied with the duration of injection (rating 6 or 7).

Safety

As described below and compared with placebo, alirocumab was generally well tolerated at any dose regimen. The number of patients with at least 1 TEAE was 45 (77.6%) in the alirocumab 150Q4W group, 37 (63.8%) in the placebo group, and 84 (73.0%) in the alirocumab 75Q2W group (Table 3). Permanent discontinuations due to TEAEs occurred in 6.9% and 3.4% of patients treated with alirocumab 150Q4W and placebo, respectively (1.7% in the alirocumab 75Q2W group). No deaths were reported during this study (Table 3). Serious TEAEs were reported by 7 (12.1%) patients in the alirocumab 150Q4W group and 4 (6.9%) in the placebo group (6 [5.2%] in the alirocumab 75Q2W group).

A list of TEAEs by preferred term occurring in ≥2% of patients in either group is given in Table S6.

In regard to TEAEs of special interest, injection-site reactions were experienced by 8 (13.8%) alirocumab 150Q4W-treated patients (vs 4 [3.5%] in alirocumab 75Q2W-treated patients and 0 [0%] in the placebo group). The intensity of all injection-site reactions was mild, except for 1 of moderate intensity in the alirocumab 75 mg Q2W group (Table S6). Injection-site reactions occurred earlier and were of longer duration in the alirocumab 150Q4W group; however, none of the injection-site reactions led to treatment discontinuation. No particular safety findings were detected for neurological events. Neurocognitive events were reported by 1 patient in the alirocumab 150Q4W group (1.7%; aphasia) and 1 patient in the alirocumab 75Q2W group (0.9%; amnesia). These neurocognitive events were not serious and did not lead to treatment discontinuation. A positively adjudicated case of nonfatal myocardial infarction and of ischemia-driven coronary revascularization were observed in 1 (1.7%) patient receiving alirocumab 150Q4W and in 1 (0.9%) patient receiving alirocumab 75Q2W.

Three (2.7%) patients in the alirocumab 75Q2W group had calculated LDL-C levels of <25 mg/dL on ≥2 consecutive occasions (0 in the alirocumab 150Q4W group). No specific safety concern was identified in these patients.

Antidrug Antibodies

The presence of antidrug antibodies had no observed effect on LDL-C-lowering efficacy (Figure S4). A total of 1/109 (0.9%) patient in the alirocumab 75Q2W group developed a low-titer, treatment-emergent persistent positive response for the antialirocumab antibody assay (0 in the alirocumab 150Q4W group). Five patients in this study had positive alirocumab-neutralizing activity: 1 patient (1/56; 1.8%) from the alirocumab 150Q4W group and 4 patients (4/109; 3.7%) from the alirocumab 75Q2W group.

Discussion

In ODYSSEY CHOICE II, patients with hypercholesterolemia not on statin therapy were treated with

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Table 2. Change From Baseline in Lipid End Points and Achievement of LDL-C Goals (ITT Analysis)

		Alirocumab	
	Placebo (n=57)	75Q2W (n=115)	150Q4W (n=58)
Baseline, LS mean (SD)	156.7 (45.7)	155.1 (44.4)	164.4 (69.6)
Calculated LDL-C, LS mean (SE), mg/dL			
Week 24 absolute LDL-C value	162.9 (3.7)	75.0 (2.6)	75.8 (3.7)
Absolute change from baseline to week 24	5.1 (3.7)	−82.9 (2.6)	−82.1 (3.7)
Percentage change from baseline to week 24 (primary end point)	4.7 (2.3)%	−53.5 (1.6)%	−51.7 (2.3)%
Percenaget difference vs placebo; *P*-value*		−58.2 (2.8)%; <0.0001	−56.4 (3.3)%; <0.0001†
Percentage change from baseline to week 12	3.2 (2.5)%	−50.8 (1.7)%	−41.7 (2.4)%
Percentage difference vs placebo; *P*-value*		−54.0 (3.0)%; <0.0001	−44.9 (3.5)%; <0.0001†
Percentage change from baseline to averaged weeks 9 to 12	3.2 (2.0)%	−53.6 (1.4)%	−52.3 (2.0)%
Percentage difference vs placebo; *P*-value*		−56.7 (2.5)%; <0.0001	−55.5 (2.9)%; <0.0001†
Percentage of patients achieving LDL-C goals <70 mg/dL or <100 g/dL at week 24; *P*-value vs placebo	1.8%	70.3%; <0.0001	63.9%; <0.0001†
Percentage of patients achieving LDL-C <70 mg/dL at week 24 (LOCF); *P*-value vs placebo	0	60.0%; <0.0001	50.0%; <0.0001
Percentage change from baseline to week 24 in other lipid parameters, LS mean (SE)			
Apo B	7.5 (2.1)%	−39.7 (1.5)%	−38.9 (2.2)%
Percentage difference vs placebo; *P*-value*		−47.2 (2.6)%; <0.0001	−46.4 (3.0)%; <0.0001†
Non-HDL-C	4.8 (2.1)%	−45.3 (1.5)%	−44.2 (2.1)%
Percentage difference vs placebo; *P*-value*		−50.1 (2.6)%; <0.0001	−49.0 (3.0)%; <0.0001†
Total cholesterol	3.0 (1.6)%	−34.0 (1.1)%	−32.3 (1.6)%
Percentage difference vs placebo; *P*-value*		−37.0 (2.0)%; <0.0001	−35.3 (2.3)%; <0.0001†
Lp(a)‡	4.1 (3.7)%	−21.8 (2.6)%	−15.5 (3.7)%
Percentage difference vs placebo; *P*-value*		−25.9 (4.5)%; <0.0001	−19.6 (5.2)%; 0.0002†
Fasting triglycerides‡	1.1 (3.8)%	−10.6 (2.7)%	−9.2 (3.9)%
Percentage difference vs placebo; *P*-value*		−11.8 (4.6)%; 0.0109	−10.4 (5.4)%; 0.0556
HDL-C	−2.4 (1.9)%	7.4 (1.4)%	7.7 (2.0)%
Percentage difference vs placebo; *P*-value*		9.8 (2.4)%; <0.0001	10.1 (2.8)%; 0.0003
Apo A1	3.4 (1.5)%	8.2 (1.1)%	10.0 (1.5)%
Percentage difference vs placebo; *P*-value*		4.8 (1.8)%; 0.0104	6.6 (2.1)%; 0.0025

75Q2W indicates 75 mg every 2 weeks (with possible dose adjustment to 150 mg every 2 weeks); 150Q4W, 150 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks); Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LOCF, last observation carried forward; Lp(a), lipoprotein(a); LS, least squares; SD, standard deviation; SE, standard error.

**P*-values are for the comparison with placebo.

†*P*-value is 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 (only applicable to comparison of alirocumab 150Q4W arm vs placebo).

‡Combined estimate for adjusted mean (SE).

alirocumab 150Q4W, resulting in LDL-C reductions of 51.7% at week 24 (placebo +4.7%). ODYSSEY CHOICE II was the first phase 3 study to use this alirocumab dose, with results suggesting that 150Q4W may be convenient for patients with hypercholesterolemia not on statin therapy. The dose adjustment strategy would allow the physician to modify the dose to Q2W if LDL-C targets were not met.

The current study included weekly sample collection from weeks 8 to 12, thereby allowing detailed assessment of LDL-C levels as well as PCSK9 levels. In line with previous studies,[17,18] alirocumab 150Q4W (and 75Q2W) led to a rapid and robust reduction in mean free PCSK9 levels, which persisted for at least 3 weeks (as shown between weeks 9 and 11) following alirocumab 150Q4W administration. With administration of alirocumab 75Q2W, mean free PCSK9 levels remained below

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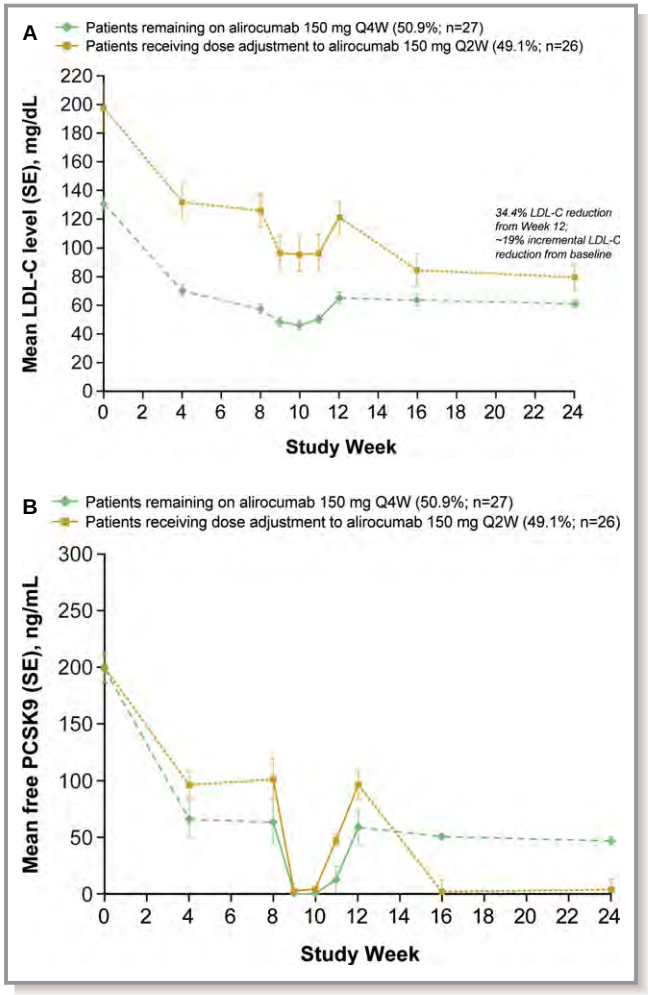

Figure 3. Impact of dosing regimen adjustment on LDL-C levels (ITT analysis*) (A) and free PCSK9 levels (B) in patients in the 150 mg Q4W alirocumab cohort: time profile from baseline to Week 24 (PK analysis*). *Patients who received dose adjustment at Week 12 and had at least 1 subsequent injection. LDL-C indicates low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error.

Table 3. Adverse Events and Safety Laboratory Values (Safety Population)

	Placebo (n=58)	Alirocumab 75Q2W (n=115)	Alirocumab 150Q4W (n=58)
TEAEs, n (%)	37 (63.8)	84 (73.0)	45 (77.6)
Treatment-emergent SAEs, n (%)	4 (6.9)	6 (5.2)	7 (12.1)
TEAEs leading to death, n (%)	0	0	0
TEAEs leading to discontinuation, n (%)	2 (3.4)	2 (1.7)	4 (6.9)
Safety terms of interest, n (%)			
Adjudicated cardiovascular events*	0	1 (0.9)	1 (1.7)
General allergic reactions	4 (6.9)	5 (4.3)	6 (10.3)
General allergic serious TEAE (CMQ)	0	0	0
Neurological TEAE	2 (3.4)	5 (4.3)	4 (6.9)
Neurocognitive disorders	0	1 (0.9%)	1 (1.7%)
Laboratory parameters†, n (%)			
Alanine aminotransferase >3 times ULN	0/58	1/115 (0.9)	0/58
Aspartate aminotransferase >3 times ULN	0/58	0/115	0/58
Creatine kinase >3 times ULN	1/57 (1.8)	8/115 (7.0)	4/57 (7.0)

75Q2W indicates 75 mg every 2 weeks (with possible dose adjustment to 150 mg every 2 weeks); 150Q4W, 150 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks); CHD, coronary heart disease; CMQ, Custom Medical Dictionary of Regulatory Activities Query; SAE, serious adverse event; TEAE, treatment-emergent adverse events; ULN, upper limit of normal.
*Includes CHD death, nonfatal myocardial infarction, fatal and nonfatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, and ischemia-driven coronary revascularization procedure.
†Regardless of baseline status.

25% of baseline levels throughout the 4-week period. However, in the 150Q4W group, there was a modest increase of free PCSK9 levels between weeks 11 and 12 that coincided with a small tailing off of LDL-C efficacy.

At week 12, before possible dose modification, when patients remained on either alirocumab 150 mg Q4W or 75 mg Q2W, 45.9% and 60.7% of patients, respectively, achieved their predefined LDL-C target levels despite none of them being on a statin.

The dose adjustment at week 12 (based on LDL-C values at week 8) resulted in an additional reduction in LDL-C of 34.4% (alirocumab 150Q4W) and 15.8% (alirocumab 75Q2W) from weeks 12 to 24, corresponding to an incremental benefit of ~19% and ~11% compared with baseline, respectively. At week 24, after possible dose modification, 63.9% of patients in the alirocumab 150Q4W group had achieved their predefined LDL-C targets (alirocumab 75Q2W group 70.3%). Higher LDL-C levels at baseline were associated with dose adjustment at week 12, with duration of effect across the dosing interval also being a contributory factor toward some patients receiving a dose adjustment.

At week 24, LDL-C reductions were 51.7% in the alirocumab 150Q4W arm and 53.5% in the 75Q2W arm. Importantly, alirocumab 75Q2W used as a calibrator arm demonstrated results that are consistent with LDL-C-lowering efficacy and with safety data of alirocumab used as add-on or monotherapy in previously published studies from the ODYSSEY clinical trials program.[12-14] Significant reductions in LDL-C levels have also been seen with Q4W dosing of another PCSK9 inhibitor, evolocumab, in statin-

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intolerant patients.[8] In that study, mean percentage reductions from baseline in LDL-C at week 12 were 56.1% with evolocumab 140 mg Q2W and 52.6% with evolocumab 420 mg Q4W. The effectiveness of alirocumab 300 mg Q4W has also been investigated in patients receiving concomitant statin therapy in the ODYSSEY CHOICE I study. The changes in LDL-C from baseline to week 24 were −58.8% (placebo −0.1%) with alirocumab 300 mg Q4W (with possible dose adjustment to 150 mg Q2W at week 12) in patients on statin, and at week 12, only 19.3% of those patients required dose adjustment.[24]

Despite the fact that 90.1% of patients included in this study had a history of experiencing intolerable SAMS on multiple statins, we observed a low rate of muscle-related symptoms with alirocumab treatment. These data support the concept that LDL-C lowering per se is not a pivotal factor in SAMS and/or causation of myopathy.[7] It should be noted that patients with perceived SAMS not utilizing statin therapy are unlikely to experience the degree of LDL-C lowering needed to reduce cardiovascular risk with other traditional lipid-lowering therapies.[7] Causality of SAMS is debated, with randomized, blinded, and placebo-controlled trials often reporting similar rates of muscle AEs between statin and placebo arms and with lower rates of muscle symptoms compared with observational studies.[25] These findings imply that perceived SAMS, besides potential pharmacological and pharmacogenetic factors, are also likely to include a behavioral component from the expectation that statins can cause muscle symptoms.[7,25] In support, many patients who discontinue statins due to SAMS can be successfully rechallenged.[7,10,26]

Injection-site reactions were reported at a higher rate in patients receiving 150Q4W alirocumab versus comparator arms. Here, it should be emphasized that the number of patients was relatively small in this treatment arm. Furthermore, all injection-site reactions in the 150Q4W arm were of mild intensity and of limited duration. Because of the sample size per group in this study, small percentage differences between treatment groups may not be clinically meaningful, as similar trends were not observed in previously published larger alirocumab studies.[13,14,27]

Conclusions

Overall, these data suggest that alirocumab 150Q4W may provide an additional option to further optimize the treatment of patients with SAMS not receiving statin treatment. However, this dosing strategy may not provide adequate LDL-C reduction in all patients, for example, those receiving concomitant statin or those with higher baseline LDL-C levels. In these patients, either a higher dose of alirocumab 300Q4W or alirocumab 75 mg Q2W (with possible dose adjustment to 150 mg Q2W) is likely to be preferred.

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Disclosures

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Supplementary Materials

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Data Monitoring Committee

DMC Chairman: Anders Olsson (Bromma, Sweden). Members: David Waters, MD (Division of Cardiology, San Francisco General Hospital, San Francisco, CA, USA); Dominique Larrey (Hôpital Saint-Eloi Service d'hépato-gastro-entérologie, Montpellier, France); Robert S. Rosenson (Director, Cardiometabolic Disorders, Mount Sinai Heart; Professor of Medicine, Mount Sinai School of Medicine, New York, NY, USA); Peter A. Patriarca (Biologics Consulting Group, Inc., Alexandria, VA, USA); Geert Molenberghs, Biostatistician (Center for Statistics [CenStat], Diepenbeek, Belgium).

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Clinical Events Committee (Reviewers)

Clinical Events Committee, Duke Clinical Research Institute, Durham, NC, USA; Pierluigi Tricoci, CEC Principal Investigator, Cardiology; Kenneth W. Mahaffey, CEC Director, Cardiology; Renato D. Lopes, Cardiology; Bimal R. Shah, Cardiology; Rajendra H. Mehta, Cardiology; Matthew T. Roe, Cardiology; Zubin Eapen, Cardiology; Luciana Armaganijan, Cardiology; Adriana Bertolami, Cardiology; Sergio Leonardi, Cardiology; Bradley J. Kolls, Neurology; J. Dedrick Jordan, Neurology; Grégory Ducrocq, Cardiology; Etienne Puymirat, Cardiology; Robin Mathews, Cardiology.

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Safety Events of Interest

The selection of preferred terms for the AE categories was based on Standard Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) or Custom Standard MedDRA queries.

The safety events of interest and other potentially significant AEs were identified as follows for analysis purposes:

- Local injection site reactions, selected using the e-CRF-specific tick-box on the AE page
- Allergic events
  - General allergic events, selected using the SMQ “hypersensitivity” (broad and narrow) excluding the following preferred terms (PTs) linked to local injection site reactions (“infusion site dermatitis,” “infusion site hypersensitivity,” “infusion site rash,” “infusion site urticaria,” “injection site dermatitis,” “injection site hypersensitivity,” “injection site rash,” “injection site urticaria”, and “injection site vasculitis”)
  - General allergic events and local allergic reactions at investigational medicinal product (IMP) injection site based on the above selection for general allergic event and on the following selection of PTs from the symptoms complementary form for local injection site reaction (“injection site dermatitis,” “injection site hypersensitivity,” “injection site edema,” “injection site rash,” “injection site urticaria,” “injection site eczema,” “injection site vasculitis,” “injection site swelling,” “infusion site dermatitis,” “infusion site hypersensitivity,” “infusion site edema,” “infusion site rash,” “infusion site urticaria,” and “infusion site swelling”)

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- ALT ≥3 × upper limit of normal (ULN) (if baseline ALT <ULN) or ALT ≥2 times the baseline value (if baseline ALT ≥ULN), selected using laboratory data
- Hemolytic anemia, selected using e-CRF-specific tick-box on the AE page and confirmed final diagnosis provided in the AE complementary form
- Neurologic events
  - Neurologic event, selected using SMQs “demyelination” (broad and narrow), “peripheral neuropathy” (broad and narrow), and “Guillain-Barre syndrome” (broad and narrow) excluding the following PTs: “acute respiratory distress syndrome,” “asthenia,” “respiratory arrest”, and “respiratory failure”;
- Neurocognitive events were analyzed based on 2 different groupings
  - Sponsor CMQ grouping: neurocognitive events were selected using a CMQ, based on the following 5 high-level group terms (HLGTs): “deliria (including confusion),” “cognitive and attention disorders and disturbances,” “dementia and amnestic conditions,” “disturbances in thinking and perception,” and “mental impairment disorders.”
  - CMQ grouping requested by a health authority: This grouping included the following terms: PT “amnesia,” PT “amnestic disorder,” PT “anterograde amnesia,” PT “behavioral and psychiatric symptoms of dementia,” PT ”change in sustained attention,” lowest-level term “cognitive deterioration,” PT “cognitive disorder,” lowest-level term “confusion,” lowest-level term “confusion aggravated,” PT “confusional state,” PT “delirium,” PT “dementia,” PT “dementia Alzheimer's type,” lowest-level term “dementia not otherwise specified (NOS),” lowest-level term “dementia NOS aggravated,” lowest-level

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term “dementia of the Alzheimer's type NOS,” PT “dementia with Lewy bodies,” PT “disorientation,” PT “disturbance in attention,” PT “executive dysfunction,” PT “frontotemporal dementia,” lowest-level term “global amnesia,” PT “illogical thinking,” PT “impaired reasoning,” PT “incoherent,” PT “judgement impaired,” PT “memory impairment,” PT “mental impairment,” lowest-level term “mental impairment NOS,” lowest-level term “mental state abnormal aggravated,” PT “mental status changes,” PT “mini mental status examination abnormal,” PT “presenile dementia,” PT “retrograde amnesia,” PT “senile dementia,” lowest-level term “senile dementia NOS,” lowest-level term “short-term memory loss,” PT “thinking abnormal,” lowest-level term “thinking slowed,” PT “transient global amnesia,” PT “vascular dementia.”

- Ophthalmologic events selected using the SMQs “optic nerve disorders” (broad and narrow), “retinal disorders” (narrow), and “corneal disorders” (narrow)

- Overdose with IMP (symptomatic or asymptomatic), selected using high-level term (HLT) “Overdose” and the tick box “Overdose with IMP” in the AE complementary e-CRF form

- Pregnancy (female patients or male patient’s partners) selected using appropriate MedDRA codes.

Analysis of Other Potentially Significant AEs

Additional grouping of AEs was identified as follows for analysis purposes:

- Hepatic disorder events using SMQ “hepatic disorder”

- Diabetes mellitus or diabetic complications using HLGT “diabetes complications,” HLT “diabetes mellitus,” HLT “carbohydrate tolerance analyses (including

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diabetes)" excluding the PT "blood glucose decreased" but including the PT "hyperglycemia" and the microvascular complications, which pertain to the secondary system organ class (SOC) included in the defined HLGT/HLTs, secondary SOCs in the MedDRA coding system.

Analysis of Cardiovascular Events

Suspected cardiovascular events and all deaths that occurred from randomization until the follow-up visit were to be submitted to the Clinical Events Committee (CEC) for adjudication. An analysis of adjudicated cardiovascular events was performed. Adjudicated cardiovascular events included all cardiovascular AEs and procedures positively adjudicated as defined in the CEC charter

- Coronary heart disease death
- Non-fatal myocardial infarction
- Fatal and non-fatal ischemic stroke
- Unstable angina requiring hospitalization (of note, a strict definition was applied for this end point, which was only considered when there was definite evidence of progression of the ischemic condition)
- Congestive heart failure requiring hospitalization
- Ischemia-driven coronary revascularization procedure.

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Supplemental Material

Table S1. Exclusion Criteria

	Exclusion criteria
1	Patients defined as statin intolerant and at very high CV risk with LDL-C <70 mg/dL (1.81 mmol/L) at the screening visit (Week –3, Visit 1)
2	Patients defined as statin intolerant and high or moderate CV risk with LDL-C <100 mg/dL (< 2.59 mmol/L) at the screening visit (Week –3, Visit 1)
3	Patients not fulfilling the statin intolerant definition and who are at moderate CV risk with LDL-C < 100 mg/dL (<2.59 mmol/L) at the screening visit (Week –3, Visit 1)
4	Patients with LDL-C ≥160 mg/dL (≥ 4.1 mmol/L) at the screening visit (Week –3, Visit 1) if receiving treatment with diet only, whatever the statin intolerance status or if non-fulfilling statin intolerance definition at moderate CV risk and treated with ezetimibe or fenofibrate
5	Patients with a 10-year fatal CVD risk SCORE <1% (ESC/EAS 2011) at the screening visit (Week –3, Visit 1)
6	Patients newly diagnosed (within 3 months prior to randomization visit [Week 0]) or poorly controlled (HbA1c >9%) diabetes
7	Patients with use of statin, red yeast rice products, niacin, or bile acid sequestrant within 4 weeks of the screening visit (Week –3) or between screening and randomization visits
8	Patients not on a stable dose of ezetimibe or fenofibrate for at least 4 weeks prior to the screening visit (Week –3, Visit 1) or between screening and randomization visits
9	Patients with use of fibrates, other than fenofibrate, within 4 weeks of the screening visit (Week –3, Visit 1) or between screening and randomization visits
10	Patients with use of nutraceuticals or over-the-counter therapies known to affect lipids, at a dose/amount that has not been stable for at least 4 weeks, prior to the screening visit (Week –3, Visit 1) or between screening and randomization visits
11	Patients planned to undergo scheduled PCI, CABG, or carotid or peripheral revascularization during the study
12	Patients with systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg at screening (Week –3, Visit 1) and/or randomization (Week 0) visits
13	Patients with history of New York Heart Association Appendix B Class III or IV heart failure within the past 12 months
14	Patients with history of a myocardial infarction, unstable angina leading to hospitalization, CABG, PCI, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack, carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease within 3 months prior to the screening visit (Week –3, Visit 1)
15	Patients with known history of hemorrhagic stroke
16	Patients aged <18 years or legal age of majority at the screening visit (Week –3, Visit 1) whichever is older

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17 Patients not previously instructed on a cholesterol-lowering diet prior to the screening visit (Week –3, Visit 1)

18 Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins (note: patients on thyroid replacement therapy could be included if the dosage of thyroxin has been stable for at least 12 weeks prior to screening and TSH level is within the normal range of the central laboratory at the screening visit)

19 Patients with history of bariatric surgery within 12 months prior to the screening visit (Week –3, Visit 1)

20 Patients with unstable weight defined by a variation >5 kg within 2 months prior to the screening visit (Week –3, Visit 1)

21 Patients with known history of homozygous familial hypercholesterolemia

22 Patients with known history of loss of function of PCSK9 (i.e., genetic mutation or sequence variation)

23 Patients with 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 were not considered as “systemic” and were allowed)

24 Patients with 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

25 Patients with known history of a positive HIV test

26 Patients who have taken any active investigational drugs within 1 month or 5 half-lives, whichever is longer

27 Patients who have been previously treated with at least 1 dose of alirocumab or any other anti-PCSK9 monoclonal antibody in other clinical trials

28 Patients with 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

29 Patients who withdraw consent during the screening period (patient who is not willing to continue or fails to return)

30 Conditions/situations or laboratory findings, 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 end points assessment such as major systemic diseases, patients with short life expectancy

Patients considered by the investigator or any sub-investigator as inappropriate for this study for any reason, e.g.:

Those deemed unable to meet specific protocol requirements, such as scheduled visits

Those 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

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	study
31	Laboratory findings during the screening period (not including randomization labs): Positive test for hepatitis B surface antigen or hepatitis C antibody Positive serum or urine pregnancy (including Week 0) test in women of childbearing potential Triglycerides >400 mg/dL (>4.52 mmol/L) (1 repeat lab was allowed) eGFR <30 mL/min/1.73 m^2 according to 4-variable MDRD study equation (calculated by central lab) ALT or AST >3 x ULN (1 repeat lab is allowed) CPK >3 x ULN (1 repeat lab is allowed) TSH <LLN or >ULN
32	Patients with known hypersensitivity to monoclonal antibody or any component of the drug product
33	Pregnant or breast-feeding women. Women of childbearing potential not protected by highly-effective method(s) of birth control (as defined in the informed consent form and/or in a local protocol addendum) and/or who are unwilling or unable to be tested for pregnancy. (Note: 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 IMP, 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 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. M3(R2): guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. ICH. 2009 Jun:1-25. Postmenopausal women must be amenorrheic for at least 12 months.
34	Significant protocol deviation in the double-blind period based on the Investigator judgment, such as non-compliance by the patient
35	Any patient who experienced an adverse event leading to permanent discontinuation from IMP during the double-blind period
36	Patients having any new condition or worsening of existing condition which in the opinion of the investigator would make the patient unsuitable for enrollment, or could interfere with the patient participating in or completing the study
37	Patients with known hypersensitivity to monoclonal antibody or any component of the drug product
38	Patients with positive pregnancy test at last visit of the double-blind period (Week 24, Visit 11)
39	Women of childbearing potential not willing to continue highly-effective method(s) of birth control (as defined in the informed consent form and/or in a local protocol addendum) and/or who are unwilling or unable to be tested for pregnancy

ALT indicates alanine aminotransferase; AST, aspartate transferase; CABG, coronary artery bypass graft; CPK, creatine phosphokinase; CV, cardiovascular; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; HbA1c, glycated hemoglobin; IMP, investigational medicinal product; LDL-C, low-density lipoprotein cholesterol; LLN, lower limit of normal; MDRD, modification of diet in renal disease; PCI, percutaneous coronary intervention; PCSK9, proprotein

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convertase subtilisin/kexin type 9; SCORE, Systematic COronary Risk Evaluation; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

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Table S2. Reasons for Not Completing the Study Treatment Period (Randomized Population)

n (%)	Placebo (n=58)	Alirocumab 75Q2W (n=116)	Alirocumab 150Q4W (n=59)
Discontinued due to adverse event	2 (3.4)	2 (1.7)	5 (8.5)
Discontinued due to poor compliance to protocol	0	2 (1.7)	1 (1.7)
Life events made continuing too difficult	0	1 (0.9)	0
Other reasons	0	1 (0.9)	1 (1.7)
Other reasons	2 (3.4)	4 (3.4)	2 (3.4)
Physician decision	0	1 (0.9)	0
Other	2 (3.4)	3 (2.6)	2 (3.4)

75Q2W indicates 75 mg every 2 weeks (with possible dose adjustment to 150 mg every 2 weeks); 150Q4W, 150 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks).

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Table S3. Baseline Characteristics According to Dose Adjustment Status (Safety Population*)

	Alirocumab 150Q4W		Alirocumab 75 mg Q2W	
	Patients remaining on 150 mg Q4W (n=27)	**Patients with dose adjustment to 150 mg Q2W† (n=26)**	**Patients remaining on 75 mg Q2W (n=71)**	**Patients with dose adjustment to 150 mg Q2W† (n=40)**
Baseline demographics				
Age, y, mean (SD)	64.0 (10.3)	62.7 (9.0)	64.3 (9.1)	59.5 (11.0)
Male, n (%)	17 (63.0)	11 (42.3)	42 (59.2)	24 (60.0)
Race, White, n (%)	25 (92.6)	25 (96.2)	64 (90.1)	39 (97.5)
Race, Black or African-American, % (n)	0	0	2 (2.8)	1 (2.5)
Ethnicity, Hispanic/Latino, n (%)	1 (3.7)	2 (7.7)	5 (7.0)	2 (5.0)
BMI, kg/m^2, mean (SD)	27.3 (4.4)	28.9 (6.1)	28.8 (5.2)	30.5 (6.5)
HeFH, n (%)	1 (3.7)	7 (26.9)	1 (1.4)	14 (35.0)
Diagnosis of HeFH, n	1	7	1	14
By genotyping, n (%)	0	6 (85.7)	0	8 (57.1)
By WHO/Simon Broome criteria, n (%)	1 (100)	1 (14.3)	1 (100)	6 (42.9)
Free PSCK9‡, ng/mL, mean (SD)	198.9 (72.6)	199.7 (66.8)	227.7 (83.5)	208.0 (69.4)
Total PSCK9‡, ng/mL, mean (SD)	469.0 (159.0)	562.3 (167.1)	504.0 (178.3)	523.9 (185.3)

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LDL-C (calculated) , mean (SD)	130.3 (25.3)	197.5 (86.9)	137.3 (26.0)	188.6 (52.2)
≥70 to <100 mg/dL, n (%)	4 (14.8)	0	4 (5.6)	0
≥100 to <130 mg/dL, n (%)	10 (37.0)	1 (3.8)	26 (36.6)	4 (10.0)
≥130 to <160 mg/dL, n (%)	10 (37.0)	9 (34.6)	29 (40.8)	11 (27.5)
≥160 to <190 mg/dL, n (%)	3 (11.1)	8 (30.8)	8 (11.3)	8 (20.0)
≥190 mg/dL, n (%)	0	8 (30.8)	4 (5.6)	17 (42.5)
LDL-C (calculated), median (Q1:Q3)	127.0 (113.0:148.0)	178.0 (143.0:212.0)	134.0 (122.0:151.0)	179.5 (146.5:223.0)
LDL-C (measured), mean (SD)	133.4 (26.7)	199.5 (85.7)	136.9 (24.4)	187.1 (50.0)
Non-HDL-C, mean (SD)	160.0 (32.8)	232.8 (95.3)	171.0 (34.0)	222.7 (56.9)
Total cholesterol, mean (SD)	213.0 (31.9)	288.9 (92.5)	222.7 (34.3)	272.8 (58.0)
Apo B, mean (SD)	105.4 (21.6)	145.1 (53.6)	110.9 (18.7)	138.5 (31.4)
Lp(a), median (Q1:Q3)	7.0 (4.0:41.0)	21.5 (9.0:42.0)	16.0 (6.0:41.0)	15.0 (3.0:72.0)
<30 mg/dL, n (%)	20 (74.1)	16 (61.5)	46 (64.8)	22 (56.4)
≥30 to <50 mg/dL, n (%)	3 (11.1)	4 (15.4)	14 (19.7)	5 (12.8)
≥50 mg/dL, n (%)	4 (14.8)	6 (23.1)	11 (15.5)	12 (30.8)
HDL-C, mean (SD)	52.9 (13.6)	56.1 (13.7)	51.7 (14.9)	50.1 (16.2)

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<40 mg/dL, n (%)	4 (14.8)	2 (7.7)	18 (25.4)	11 (27.5)
≥40 mg/dL, n (%)	23 (85.2)	24 (92.3)	53 (74.6)	29 (72.5)
Fasting triglycerides, median (Q1:Q3)	117.0 (95.0:205.0)	156.0 (115.0:234.0)	137.0 (96.0:228.0)	164.0 (123.0:226.0)
<150 mg/dL, n (%)	16 (59.3)	12 (46.2)	37 (52.1)	16 (40.0)
≥150 to <200 mg/dL, n (%)	3 (11.1)	4 (15.4)	9 (12.7)	11 (27.5)
≥200 mg/dL, n (%)	8 (29.6)	10 (38.5)	25 (35.2)	13 (32.5)
Apo A1, mean (SD)	147.9 (24.4)	157.7 (25.5)	152.6 (26.8)	146.0 (28.1)

*Patients who had at least 1 subsequent injection.

†Patients who received dose adjustment at Week 12 and had at least 1 subsequent injection.

‡Including patients from the pharmacokinetic population (patients with ≥1 injection post-IVRS transaction at Week 12).

150Q4W indicates 150 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks); Apo, apolipoprotein; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation; WHO, World Health Organization.

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Table S4. Percent Change from Baseline in Calculated LDL-C at Week 24: Mixed-Effect Model with Repeated Measures (On-Treatment Analysis – Modified ITT Population)

		Alirocumab	
	Placebo (n=56)	75Q2W (n=115)	150Q4W (n=57)
Baseline, mean (SD), mg/dL	156.0 (45.8)	155.1 (44.4)	165.0 (70.1)
LS mean (SE) change from baseline to Week 24 in measured LDL-C, %	5.1 (2.1)	–55.3 (1.5)	–54.6 (2.1)
LS mean difference (SE) versus placebo		–60.4 (2.6)	–59.7 (3.0)
95% confidence interval		(–65.4 to –55.4)	(–65.6 to –53.8)
P-value versus placebo		<0.0001	<0.0001*

**P*-value is 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 (only applicable to comparison of alirocumab 150Q4W arm versus placebo).

75Q2W indicates 75 mg every 2 weeks (with possible dose adjustment to 150 mg every 2 weeks); 150Q4W, 150 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks); LDL-C, low-density lipoprotein cholesterol; LS, least-squares; SD standard deviation; SE, standard error

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Table S5. Percent Change from Baseline in Measured LDL-C at Week 24: Analysis of Covariance – Complete Case Analysis (ITT Analysis – ITT Population)

		Alirocumab	
	Placebo (n=57)	75Q2W (n=115)	150Q4W (n=58)
Number of patients with measured LDL-C values available	54	108	53
Baseline, mean (SD), mg/dL	158.1 (46.9)	154.5 (43.4)	168.4 (71.9)
LS mean (SE) change from baseline to Week 24 in measured LDL-C, %	3.7 (2.2)	–50.4 (1.6)	–50.7 (2.3)
LS mean difference (SE) versus placebo		–54.1 (2.7)	–54.4 (3.2)
95% confidence interval		(–59.5 to –48.7)	(–60.7 to –48.1)
P-value versus placebo		<0.0001	<0.0001

75Q2W indicates 75 mg every 2 weeks (with possible dose adjustment to 150 mg every 2 weeks); 150Q4W, 150 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks); ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least-squares; SD, standard error; SE, standard error

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Table S6. Adverse Events by Preferred Term Occurring in ≥2% of Patients in Either Group (Safety Population)

		Alirocumab	
	Placebo (n=58)	75Q2W (n=115)	150Q4W (n=58)
TEAEs occurring in ≥2% patients in either group, n (%)			
Infections and infestations	13 (22.4)	32 (27.8)	22 (37.9)
Nasopharyngitis	3 (5.2)	10 (8.7)	5 (8.6)
Urinary tract infection	1 (1.7)	4 (3.5)	4 (6.9)
Upper respiratory tract infection	4 (6.9)	4 (3.5)	3 (5.2)
Influenza	0	3 (2.6)	1 (1.7)
Psychiatric disorders	0	9 (7.8)	2 (3.4)
Insomnia	0	3 (2.6)	0
Nervous system disorders	8 (13.8)	17 (14.8)	12 (20.7)
Headache	3 (5.2)	10 (8.7)	5 (8.6)
Dizziness	4 (6.9)	1 (0.9)	4 (6.9)
Eye disorders	0	5 (4.3)	2 (3.4)
Vision blurred	0	3 (2.6)	1 (1.7)
Vascular disorders	4 (6.9)	1 (0.9)	4 (6.9)
Hypertension	2 (3.4)	0	2 (3.4)
Respiratory, thoracic and mediastinal disorders	4 (6.9)	11 (9.6)	4 (6.9)
Cough	0	3 (2.6)	1 (1.7)
Dyspnea	0	3 (2.6)	0
Nasal congestion	2 (3.4)	0	0

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Gastrointestinal disorders	8 (13.8)	20 (17.4)	10 (17.2)
Nausea	2 (3.4)	6 (5.2)	3 (5.2)
Diarrhea	3 (5.2)	5 (4.3)	1 (1.7)
Abdominal pain	0	3 (2.6)	1 (1.7)
Gastroesophageal reflux disease	0	5 (4.3)	1 (1.7)
Toothache	2 (3.4)	2 (1.7)	0
Skin and subcutaneous tissue disorders	6 (10.3)	9 (7.8)	8 (13.8)
Rash	0	1 (0.9)	3 (5.2)
Pruritus	2 (3.4)	1 (0.9)	1 (1.7)
Musculoskeletal and connective tissue disorders	12 (20.7)	33 (28.7)	14 (24.1)
Arthralgia	2 (3.4)	7 (6.1)	7 (12.1)
Muscle spasms	0	8 (7.0)	3 (5.2)
Myalgia	3 (5.2)	7 (6.1)	3 (5.2)
Pain in extremity	1 (1.7)	4 (3.5)	3 (5.2)
Back pain	0	6 (5.2)	2 (3.4)
Muscular weakness	1 (1.7)	4 (3.5)	0
Musculoskeletal pain	1 (1.7)	3 (2.6)	0
Musculoskeletal stiffness	0	3 (2.6)	0
Osteoarthritis	2 (3.4)	0	0
Renal and urinary disorders	2 (3.4)	9 (7.8)	2 (3.4)
Renal failure	1 (1.7)	4 (3.5)	0
General disorders and administration site conditions	8 (13.8)	20 (17.4)	12 (20.7)
Injection site reaction	0	4 (3.5)	8 (13.8)

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Mild intensity*	0	3 (75.0)	8 (100)
Moderate intensity*	0	1 (25.0)	0
Severe intensity*	0	0	0
Fatigue	0	5 (4.3)	4 (6.9)
Feeling hot	2 (3.4)	0	0
Non-cardiac chest pain	2 (3.4)	3 (2.6)	0
Edema peripheral	4 (6.9)	3 (2.6)	0
Injury, poisoning and procedural complications	6 (10.3)	12 (10.4)	5 (8.6)
Fall	2 (3.4)	6 (5.2)	0
Post-traumatic pain	0	3 (2.6)	1 (1.7)

*In case of several occurrences, the maximal intensity is reported.

75Q2W indicates 75 mg every 2 weeks (with possible dose adjustment to 150 mg every 2 weeks); 150Q4W, 150 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks); TEAEs, treatment-emergent adverse events

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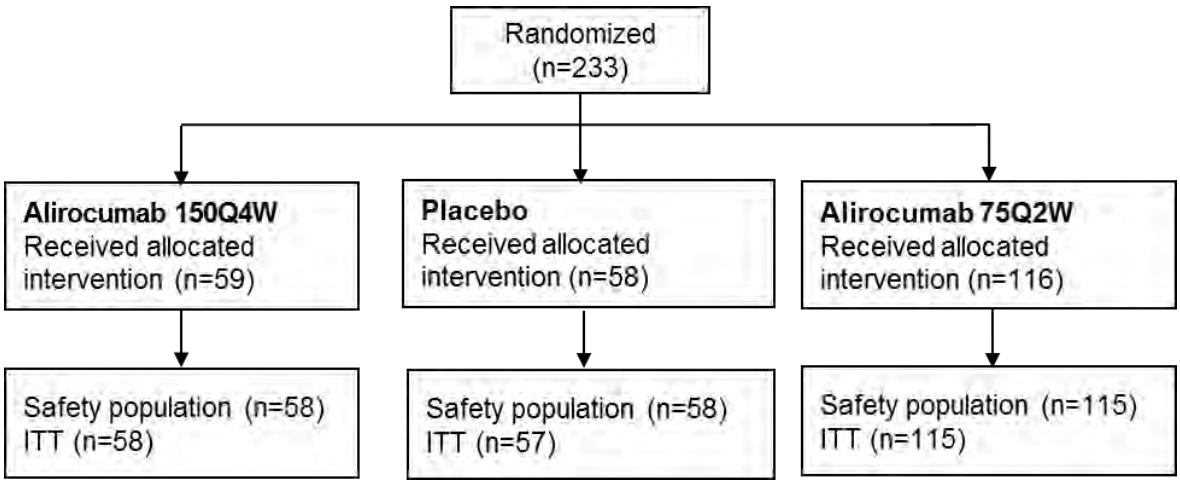
Figure S1. Patient disposition for CHOICE II study



75Q2W indicates 75 mg every 2 weeks (with possible dose adjustment to 150 mg every 2 weeks); 150Q4W, 150 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks); ITT, intent-to-treat

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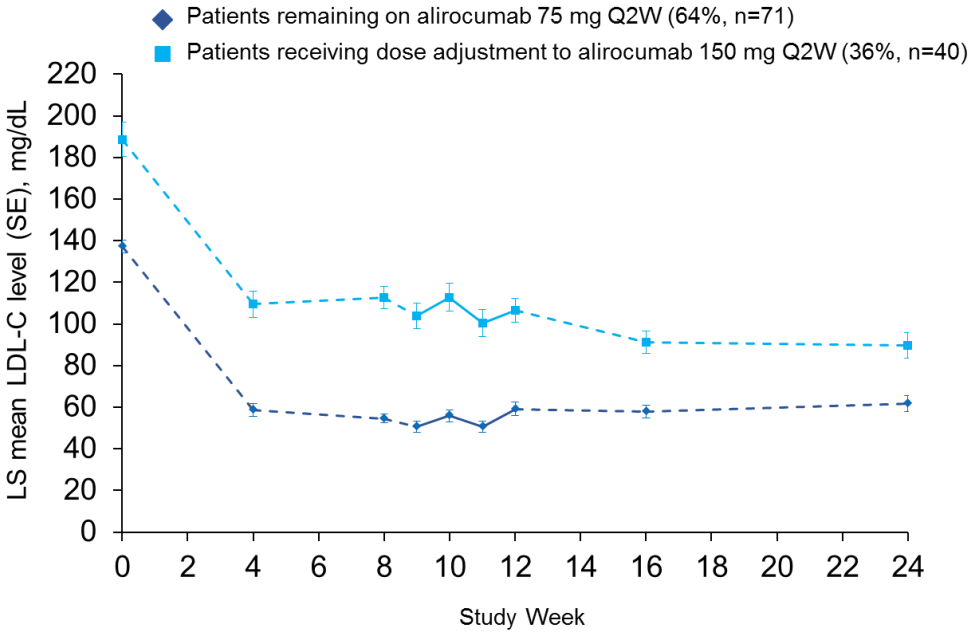
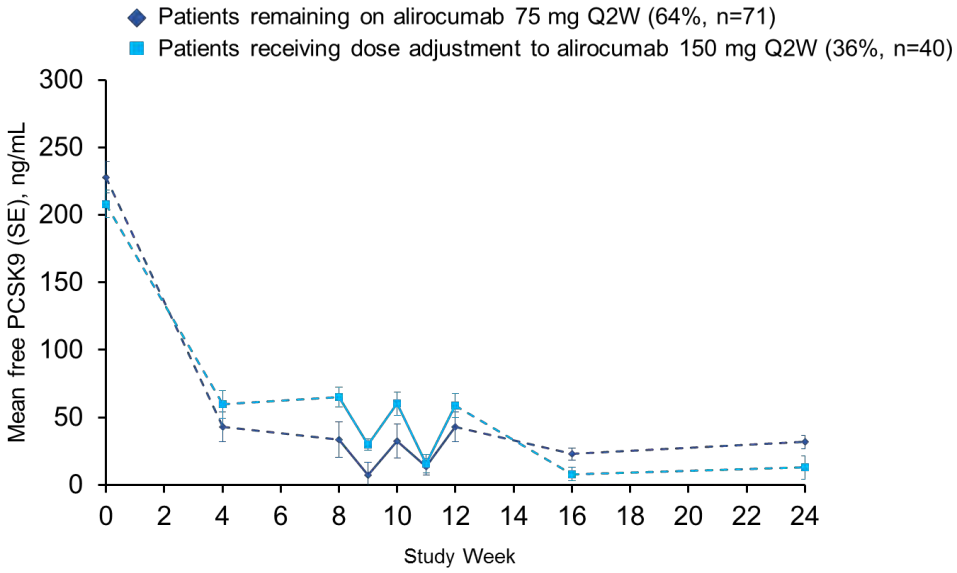
Figure S2. Impact of dosing regimen adjustment on LDL-C levels (A) and free PCSK9 levels (B) in patients in the 75 mg Q2W alirocumab cohort: time profile from baseline to Week 24 (ITT analysis)

(A)



(B)



Patients who received dose adjustment at Week 12 and had at least 1 subsequent injection.

LDL-C indicates low-density lipoprotein cholesterol; LS, least-squares; Q2W, every 2 weeks; SE, standard error

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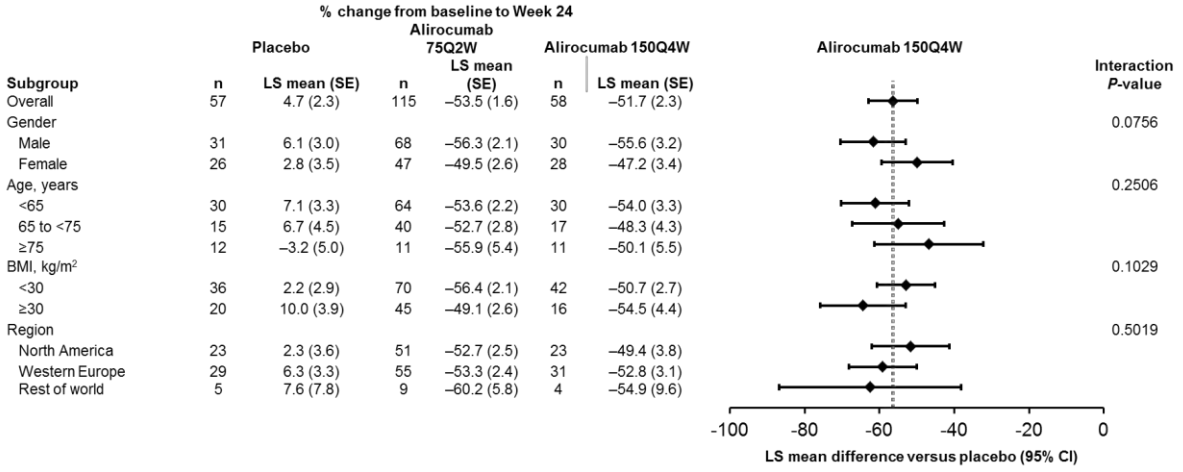
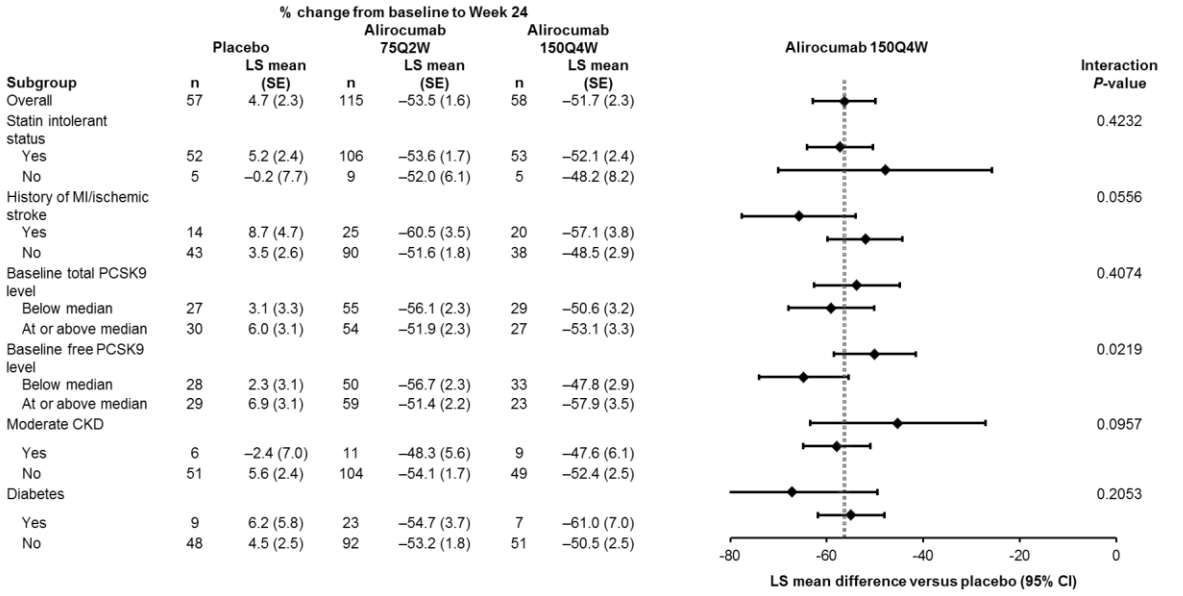
Figure S3. The difference in percent change from baseline to Week 24 in LDL-C (alirocumab 150Q4W versus placebo) according to baseline subgroup: Demographics (A), medical history and PCSK9 levels (B), Lipids (C), and medication (D) (ITT analysis)

(A)



Subgroup	Placebo n	Placebo LS mean (SE)	Alirocumab 75Q2W n	Alirocumab 75Q2W LS mean (SE)	Alirocumab 150Q4W n	Alirocumab 150Q4W LS mean (SE)	Interaction *P*-value
Overall	57	4.7 (2.3)	115	–53.5 (1.6)	58	–51.7 (2.3)	
Gender							0.0756
Male	31	6.1 (3.0)	68	–56.3 (2.1)	30	–55.6 (3.2)	
Female	26	2.8 (3.5)	47	–49.5 (2.6)	28	–47.2 (3.4)	
Age, years							0.2506
<65	30	7.1 (3.3)	64	–53.6 (2.2)	30	–54.0 (3.3)	
65 to <75	15	6.7 (4.5)	40	–52.7 (2.8)	17	–48.3 (4.3)	
≥75	12	–3.2 (5.0)	11	–55.9 (5.4)	11	–50.1 (5.5)	
BMI, kg/m^2							0.1029
<30	36	2.2 (2.9)	70	–56.4 (2.1)	42	–50.7 (2.7)	
≥30	20	10.0 (3.9)	45	–49.1 (2.6)	16	–54.5 (4.4)	
Region							0.5019
North America	23	2.3 (3.6)	51	–52.7 (2.5)	23	–49.4 (3.8)	
Western Europe	29	6.3 (3.3)	55	–53.3 (2.4)	31	–52.8 (3.1)	
Rest of world	5	7.6 (7.8)	9	–60.2 (5.8)	4	–54.9 (9.6)	

(B)



Subgroup	Placebo n	Placebo LS mean (SE)	Alirocumab 75Q2W n	Alirocumab 75Q2W LS mean (SE)	Alirocumab 150Q4W n	Alirocumab 150Q4W LS mean (SE)	Interaction *P*-value
Overall	57	4.7 (2.3)	115	–53.5 (1.6)	58	–51.7 (2.3)	
Statin intolerant status							0.4232
Yes	52	5.2 (2.4)	106	–53.6 (1.7)	53	–52.1 (2.4)	
No	5	–0.2 (7.7)	9	–52.0 (6.1)	5	–48.2 (8.2)	
History of MI/ischemic stroke							0.0556
Yes	14	8.7 (4.7)	25	–60.5 (3.5)	20	–57.1 (3.8)	
No	43	3.5 (2.6)	90	–51.6 (1.8)	38	–48.5 (2.9)	
Baseline total PCSK9 level							0.4074
Below median	27	3.1 (3.3)	55	–56.1 (2.3)	29	–50.6 (3.2)	
At or above median	30	6.0 (3.1)	54	–51.9 (2.3)	27	–53.1 (3.3)	
Baseline free PCSK9 level							0.0219
Below median	28	2.3 (3.1)	50	–56.7 (2.3)	33	–47.8 (2.9)	
At or above median	29	6.9 (3.1)	59	–51.4 (2.2)	23	–57.9 (3.5)	
Moderate CKD							0.0957
Yes	6	–2.4 (7.0)	11	–48.3 (5.6)	9	–47.6 (6.1)	
No	51	5.6 (2.4)	104	–54.1 (1.7)	49	–52.4 (2.5)	
Diabetes							0.2053
Yes	9	6.2 (5.8)	23	–54.7 (3.7)	7	–61.0 (7.0)	
No	48	4.5 (2.5)	92	–53.2 (1.8)	51	–50.5 (2.5)	

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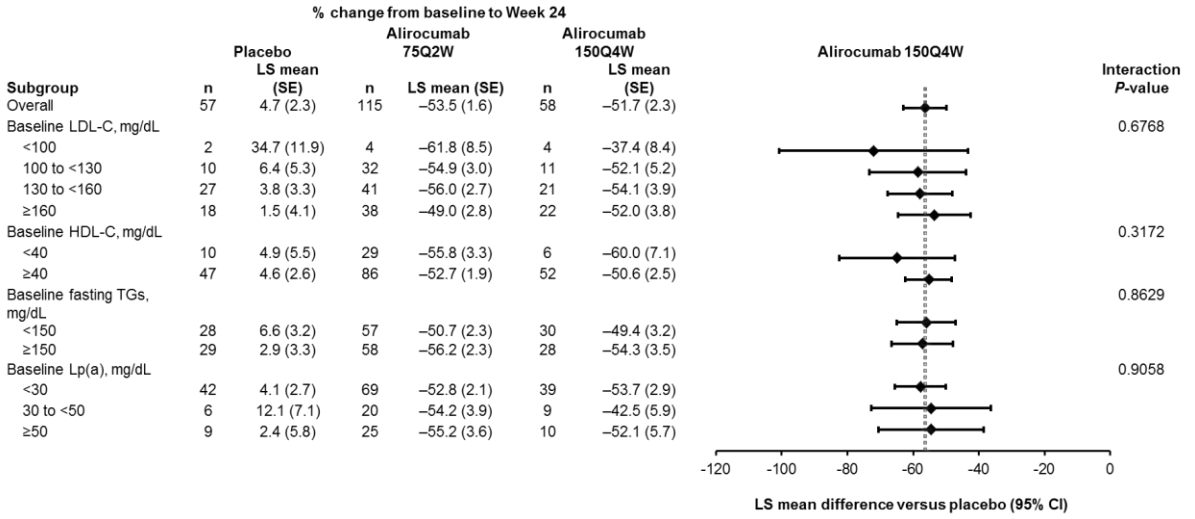
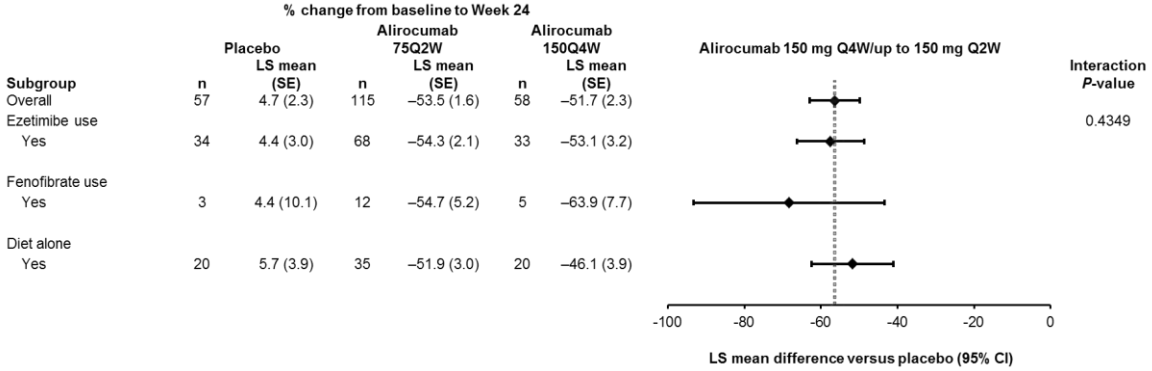
(C)



(D)



75Q2W indicates 75 mg every 2 weeks (with possible dose adjustment to 150 mg every 2 weeks); 150Q4W, 150 mg every 4 weeks (with possible dose adjustment to 150 mg every 2 weeks); BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LS, least-squares; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; SE, standard error; TGs, triglycerides.

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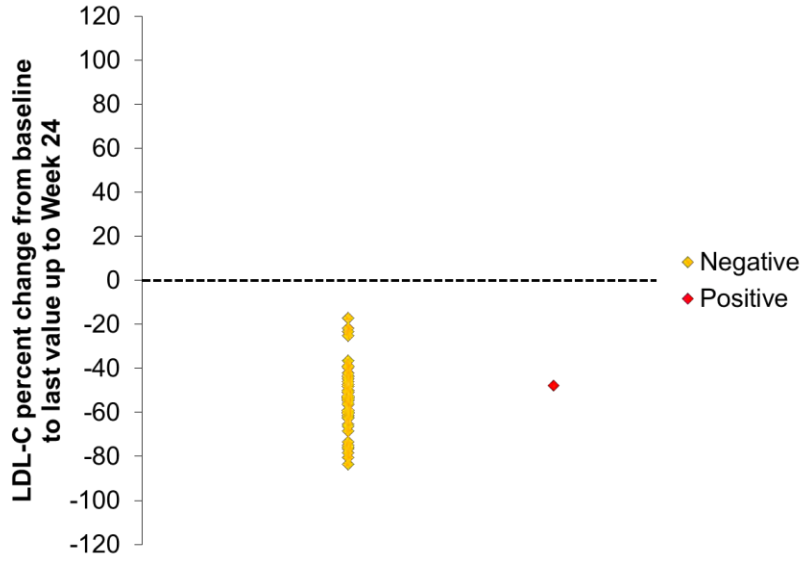
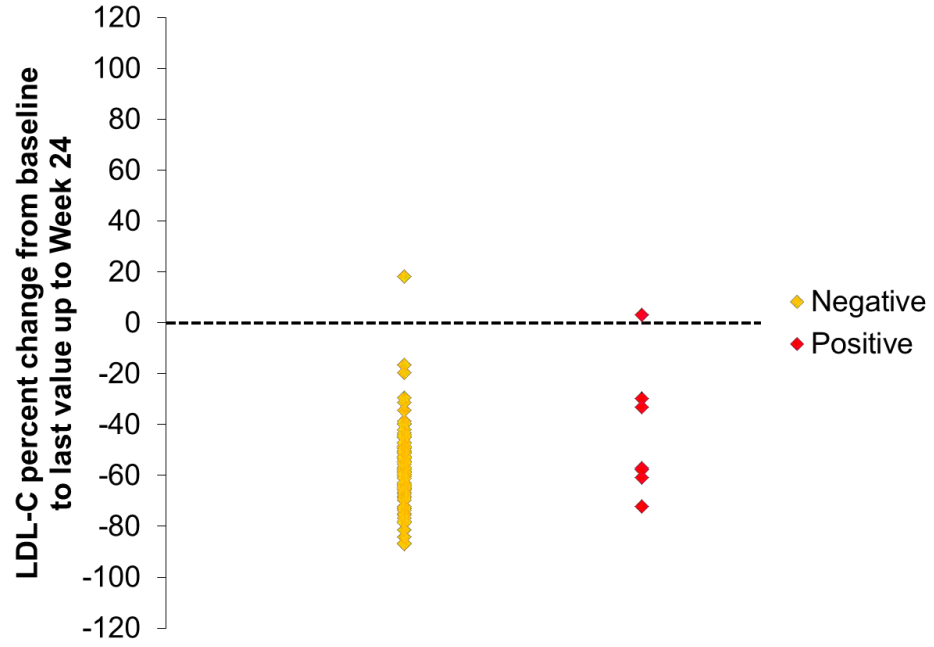
Figure S4. Percent reduction in LDL-C at last value up to Week 24 by anti-alirocumab antibody status in the alirocumab 150Q4W group (A) and 75Q2W group (B) (on-treatment analysis – modified ITT population).

(A)



(B)



LDL-C indicates low-density lipoprotein-cholesterol.

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Efficacy and Safety of Alirocumab 150 mg Every 4 Weeks in Patients With Hypercholesterolemia Not on Statin Therapy: The ODYSSEY CHOICE II Study

Erik Stroes, John R. Guyton, Norman Lepor, Fernando Civeira, Daniel Gaudet, Gerald F. Watts, Marie T. Baccara-Dinet, Guillaume Lecorps, Garen Manvelian, Michel Farnier and the ODYSSEY CHOICE II Investigators

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