Prevention and Rehabilitation

Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study

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Background The ODYSSEY COMBO I study (http://clinicaltrials.gov/show/NCT01644175) evaluated efficacy and safety of alirocumab as add-on therapy to stable maximally tolerated daily statin with or without other lipid-lowering therapy in high cardiovascular risk patients with suboptimally controlled hypercholesterolemia.

Methods This multicenter, phase 3, randomized (2:1 alirocumab vs placebo), double-blind, 52-week trial enrolled 316 patients with established coronary heart disease or coronary heart disease risk equivalents and hypercholesterolemia. Alirocumab (75 mg every 2 weeks [Q2W]) or placebo Q2W was self-administered subcutaneously via 1 mL prefilled pen. The alirocumab dose was increased to 150 mg Q2W (also 1 mL) at week 12 if week 8 low-density lipoprotein cholesterol (LDL-C) was ≥70 mg/dL. The primary efficacy end point was percent change in LDL-C from baseline to week 24 (intention-to-treat analysis).

Results At week 24, estimated mean (95% CI) changes in LDL-C from baseline were –48.2% (–52.0% to –44.4%) and –2.3% (–7.6% to 3.1%) for alirocumab and placebo, respectively, an estimated mean (95% CI) difference of –45.9% (–52.5% to –39.3%) ($P < .0001$). Low-density lipoprotein cholesterol <70 mg/dL was achieved by 75% alirocumab versus 9% placebo patients at week 24. At week 12, 83.2% of evaluable alirocumab-treated patients remained on 75-mg Q2W. Treatment-emergent adverse events were comparable between groups.

Conclusions Alirocumab treatment achieved a significantly greater reduction in LDL-C and allowed a greater proportion of patients to achieve LDL-C goals, versus placebo after 24 weeks in high cardiovascular risk patients with suboptimally controlled hypercholesterolemia at baseline despite receiving maximally tolerated statin with or without other lipid-lowering therapy. The frequency of treatment-emergent adverse events and study medication discontinuations were generally comparable between treatment groups. (Am Heart J 2015;169:906-915.e13.)

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Statin therapy is currently the most effective approved therapeutic intervention for lowering low-density lipoprotein cholesterol (LDL-C), with reductions of up to 55% depending on statin and dose.[1,2] The magnitude of clinical benefit attributable to statin therapy is directly proportional to the level of pretreatment atherosclerotic cardiovascular disease (ASCVD) risk and magnitude of reduction in LDL-C.[1-3] Currently, available nonstatin lipid-lowering therapies (LLTs) have limited efficacy, with bile acid resins, nicotinic acid, and fibrates decreasing LDL-C by 10% to 20% on average and ezetimibe-lowering LDL-C by 15% to 20% on average.[4,5] Therefore, considerable interest exists in the development of nonstatin therapies that more effectively reduce LDL-C and other atherogenic lipid parameters in high-risk patients on maximally tolerated doses of statin therapy and for those who are statin intolerant.

Recent interest has focused on proprotein convertase subtilisin/kexin type 9 (PCSK9) as a possible therapeutic target. Alirocumab, a fully human monoclonal antibody to PCSK9, has demonstrated significant reductions in LDL-C, non–high-density lipoprotein cholesterol (non–HDL-C), apolipoprotein B, and lipoprotein (a) when administered in clinical trials to patients with hypercholesterolemia despite statin therapy.[6-9]

ODYSSEY COMBO I (NCT01644175) is a randomized, placebo-controlled, 52-week efficacy and safety study of alirocumab administered every 2 weeks (Q2W) as add-on therapy to stable, maximally tolerated daily statin therapy (with or without other LLT) in patients at high ASCVD risk.[10] This study, and others within the ODYSSEY program, uses a treat-to-target dosing strategy whereby the alirocumab dose may be increased depending on individual patient response.

Methods

This study was performed at 76 sites in the United States in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice. The protocol was reviewed and approved by the institutional review board of each participating center, and all participants provided written informed consent.

Full methods have been previously reported.[10] Briefly, male or female patients aged ≥18 years could participate if they had either (*a*) LDL-C ≥70 mg/dL and established CVD or (*b*) LDL-C ≥100 mg/dL with coronary heart disease (CHD) risk equivalents (eg, diabetes mellitus with other risk factors or chronic kidney disease). All patients were receiving a stable, maximally tolerated statin dose (defined as atorvastatin, 40-80 mg; rosuvastatin, 20-40 mg; or simvastatin, 80 mg daily; or lower doses provided the investigator had a documented reason for not using the higher dose, eg, intolerance and local practice) with or without other LLT (bile acid sequestrant, ezetimibe, niacin, or omega-3 ≥1000 mg/day with stable dose ≥4 weeks; or fenofibrate with stable dose ≥6 weeks before enrollment). Exclusion criteria and definitions of CVD and CHD risk equivalents are given in the online Appendix.

Eligible patients were randomized 2:1 to receive either alirocumab 75-mg Q2W, self-administered subcutaneously via 1 mL prefilled pen, or a matching placebo. Randomization was stratified by history of myocardial infarction or ischemic stroke and intensity of concomitant statin treatment (high intensity [atorvastatin, 40-80 mg daily; and rosuvastatin, 20-40 mg daily] or not high intensity). If LDL-C level was ≥70 mg/dL at week 8, alirocumab was increased in an automated and blinded fashion without site or patient awareness to 150 mg subcutaneously Q2W (also 1 mL) at the week 12 visit.

On-site patient assessments were scheduled at randomization and subsequently at weeks 4, 8, 12, 16, 24, 36, and 52. Injections were performed at home by the patient or a designated caregiver. Training for the person performing the injection was provided during screening. After completion of double-blind treatment, patients were followed up for an additional 8 weeks off study medication.

End points and assessments

The primary efficacy end point was the percent change in LDL-C from baseline to week 24, analyzed using an intention-to-treat (ITT) approach. Key secondary efficacy end points included percent change in LDL-C from baseline to week 24 (on-treatment analysis), percent change in LDL-C at other defined time points, percent changes in other lipid parameters, and proportion of patients reaching LDL-C <70 mg/dL.[10]

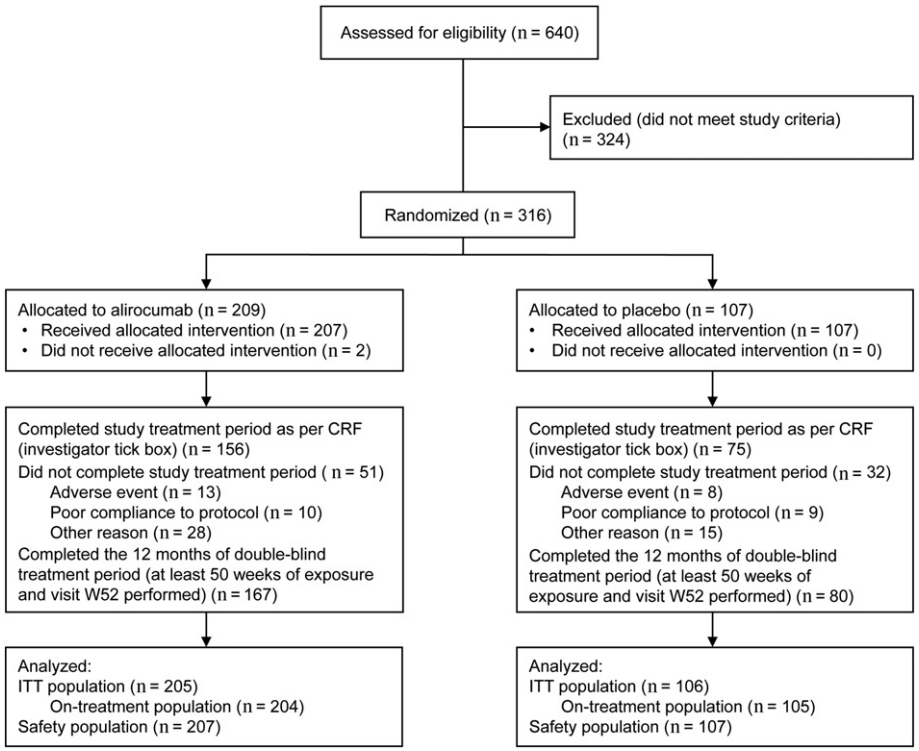
All lipid analyses were performed by a central laboratory (Medpace Reference Laboratories, Cincinnati, OH), and LDL-C was calculated by the Friedewald formula.[11] Low-density lipoprotein cholesterol was also measured via β quantification at randomization (week 0) and week 24 (and in cases where triglycerides exceeded 400 mg/dL [4.52 mmol/L]). All other lipid parameters were measured directly. Anti-alirocumab antibodies were assessed in all patients regardless of treatment allocation at baseline (week 0) as well as weeks 12, 24, 52, and 60 (follow-up).

Safety was assessed by adverse event (AE) reporting, including adjudicated CV events, laboratory analyses (including LDL-C <25 mg/dL on 2 consecutive measurements ≥21 days apart), and vital signs measurement. The safety population included all randomized patients who received ≥1 dose or an incomplete injection. The treatment-emergent AE (TEAE) period was defined as the time from first to last double-blind dose of study medication plus 70 days (10 weeks).

Statistical methodology

Statistical methods were described previously.[10] It was estimated that 45 randomized patients (30 alirocumab; 15

Figure 1



Patient flow through the study. Abbreviation: *CRF*, case report form.

placebo) would provide 95% power to detect a mean percent change in LDL-C of ≥30% from baseline to 24 weeks with a 0.05 two-sided significance level, assuming an SD of 25%. To accommodate a maximum estimated subject drop-out rate of 30% (based on previous trials) at 52 weeks and to provide greater safety data to the ODYSSEY Phase 3 program, the sample size was increased to 306 patients.

The primary end point was assessed in the ITT population, which included all randomized patients regardless of treatment adherence with ≥1 available LDL-C value both at baseline and at one of the planned time points between weeks 4 and 24. A mixed effect model with repeated measures was used to account for missing data. All available postbaseline data from week 4 to week 52 were used regardless of status on or off treatment. The model included fixed categorical effects of treatment group, randomization strata, time point, 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 estimates at week 24 for both treatment groups with their corresponding 95% CIs. The difference between these estimates will be provided with their corresponding 95% CI and *P* values.

A sensitivity analysis based on a pattern mixture model was conducted to evaluate the impact of missing data on the primary end point. In this approach, missing calculated LDL-C values during the on-treatment period were multiply imputed using a model assuming "missing at random"; missing calculated LDL-C values during the posttreatment period were multiply imputed using random draws from a normal distribution where the mean was equal to subject's own baseline value.

Secondary end points were analyzed in a predefined order using a hierarchical testing procedure to control type I error. These end points were analyzed with the same methodology as for the primary end point, except lipoprotein (a) and triglycerides, which were analyzed using a multiple imputation approach for handling of missing values followed by robust regression. The proportion of patients with LDL-C <70 mg/dL was analyzed using a multiple imputation approach for handling of missing values followed by logistic regression.

A prespecified on-treatment analysis was also conducted for the percent change in LDL-C from baseline to week 24 and key secondary end points, using all available

Table I. Baseline characteristics (all randomized patients)

All patients on maximally tolerated statin ± other LLT	Alirocumab (n = 209)	Placebo (n = 107)	*P* vs placebo
Age, y, mean (SD)	63.0 (9.5)	63.0 (8.8)	.77
Male, n (%)	131 (62.7)	77 (72.0)	.11
Race, n (%)			.61
White	170 (81.3)	88 (82.2)	
Black or African American	34 (16.3)	17 (15.9)	
Ethnicity, n (%)			.44
Hispanic/Latino	25 (12.0)	9 (8.4)	
BMI, kg/m^2, mean (SD)	32.62 (6.30)	32.03 (7.07)	.23
Any CV history/risk factors, n (%)	206 (98.6)	106 (99.1)	.88
CHD history, n (%)	164 (78.5)	83 (77.6)	.97
CHD risk equivalents, n (%)*	85 (40.7)	51 (47.7)	.28
Type 2 diabetes, n (%)	94 (45.0)	42 (39.3)	.39
Lipid medication, n (%)			
Any statin	208 (99.5)	107 (100)	1.00
High-dose statin use at screening†	129 (61.7)	69 (64.5)	.71
Other LLT use	80 (38.3)	53 (49.5)	.07
Ezetimibe use	15 (7.2)	11 (10.3)	.46
Lipid parameters, mg/dL, mean (SD)			
LDL-C (calculated)‡	100.2 (29.5)	106.0 (35.3)	.42
Median (Q1:Q3)	98.0 (81.0:114.0)	97.0 (86.0:120.0)	
Minimum:maximum	33:240	61:256	
LDL-C (measured)‡	94.8 (29.3)	100.2 (34.4)	.41
Non–HDL-C	130.0 (34.0)	133.4 (39.8)	.72
Apo B	90.8 (21.4)	91.4 (24.1)	.98
Lp(a)§	31.0 (8.0:81.0)	38.0 (10.0:70.0)	.70
Fasting TGs§	130.0 (92.0:189.0)	123.0 (95.0:177.0)	.57
HDL-C	48.3 (14.4)	48.8 (12.7)	.46

Abbreviations: *BMI*, Body mass index; *Apo*, apolipoprotein; *Lp(a)*, lipoprotein (a); *TGs*, triglycerides.
* Coronary heart disease risk equivalents were defined as ischemic stroke, peripheral artery disease, moderate chronic kidney disease, or diabetes (only if ≥2 risk factors present).
† High-dose statin: atorvastatin, 40 to 80 mg or rosuvastatin, 20 to 40 mg or simvastatin, 80 mg daily.
‡ Low-density lipoprotein cholesterol was calculated using the Friedewald formula and also measured by β quantification. 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 with calculated LDL-C values. At baseline, LDL-C was measured for 138 alirocumab and 70 placebo patients.
§ Median (Q1:Q3).

on-treatment measurements at planned time points from weeks 4 to 52.

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Results

Of 640 patients screened for eligibility, 316 were subsequently randomized to alirocumab (209) or placebo (107) (Figure 1). The ITT population included 311 (98.4%) patients (5 patients had missing LDL-C levels and were excluded from the ITT analysis); 309 patients comprised the on-treatment population, and 314 patients comprised the safety population. Baseline characteristics of randomized patients (Table I) were similar with no statistically significant differences between the treatment groups. 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 (16.8%) of 191 patients had their alirocumab dose increased to 150 mg subcutaneously Q2W at week 12 (among patients with ≥1 injection after week 12).

Primary and secondary efficacy analyses

Estimated mean (95% CI) percent change from baseline to week 24 in LDL-C was −48.2% (−52.0% to −44.4%) for alirocumab and −2.3% (−7.6% to 3.1%) for placebo in the ITT analysis and −50.7% (−54.4% to −47.0%) and −0.8% (−5.9% to 4.3%), respectively, for the on-treatment analysis (both $P < .0001$ for alirocumab vs placebo; Table II, Figure 2, and online Supplementary Table I). Measured LDL-C results (β quantification) were

Table II. Percent change in LDL-C and other lipid parameters (ITT analyses)

All patients on maximally tolerated statin ± other LLT	Alirocumab	Placebo	Alirocumab vs placebo		
			Estimated mean difference %	95% CI	*P*
ITT	n = 205	n = 106			
Baseline, mg/dL, mean (SD)	100.3 (29.7)	104.6 (32.3)			
Minimum:maximum	33:240	61:243			
Estimated mean (95% CI) change from baseline to week 12 (%)	−46.3 (−49.9 to −42.8)	1.1 (−3.9 to 6.1)	−47.4	−53.6 to −41.3	<.0001
Estimated mean (95% CI) change from baseline at week 24 (%)	−48.2 (−52.0 to −44.4)	−2.3 (−7.6 to 3.1)	−45.9	−52.5 to −39.3	<.0001
Estimated mean (95% CI) percent change in other lipid parameters from baseline to week 24					
ITT	n = 205	n = 106			
LDL-C (β quantification method)*	−46.1 (−50.9 to −41.4)	−0.2 (−7.1 to 6.6)	−45.9	−54.2 to −37.5	<.0001
Apo B	−36.7 (−39.9 to −33.5)	−0.9 (−5.4 to 3.5)	−35.8	−41.3 to −30.3	<.0001
Non–HDL-C	−39.1 (−42.6 to −35.6)	−1.6 (−6.6 to 3.3)	−37.5	−43.5 to −31.4	<.0001
Total cholesterol	−27.9 (−30.4 to −25.4)	−2.9 (−6.3 to 0.6)	−25.0	−29.3 to −20.7	<.0001
Lp(a)†	−20.5 (−24.4 to −16.6)	−5.9 (−11.3 to −0.5)	−14.6	−21.3 to −7.9	<.0001
TGs†	−6.0 (−10.5 to −1.6)	−5.4 (−11.7 to 0.9)	−0.6	−8.3 to 7.0	.8699
HDL-C	3.5 (1.4 to 5.6)	−3.8 (−6.8 to −0.8)	7.3	3.6 to 11.0	<.0001

Primary analyses were conducted using an ITT approach including all lipid data regardless of whether the patient was receiving study treatment.
* Sensitivity analysis; *P* value for descriptive purpose only.
† Combined estimate for adjusted mean (95% CI) shown for lipoprotein (a) and triglycerides.

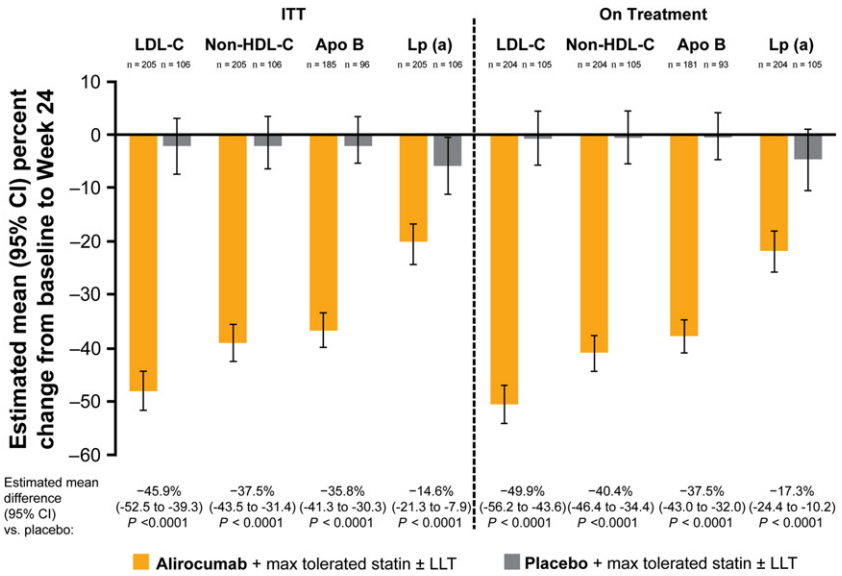
consistent with those for calculated LDL-C (Table II). Results of a sensitivity analysis of the primary end point were consistent with the ITT analysis (online Supplementary Table I). Achieved LDL-C reduction over time (Figure 3) demonstrates early (4 weeks) and sustained (52 weeks) reduction in LDL-C compared with placebo.

At week 12, before possible alirocumab dose increase (all alirocumab patients were receiving 75-mg Q2W), LDL-C reductions were 46.3% from baseline, comparable with those at week 24 (Table II). The main baseline factor predictive of a dose increase at week 12 was baseline LDL-C level; distributions of baseline and week 24 LDL-C levels are shown in online Supplementary Figure 1. 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 with that observed among patients in whom no dose increment was performed (week 8 LDL-C <70 mg/dL) (Figure 4). 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.

The relative proportions of patients achieving LDL-C <70 mg/dL (<1.81 mmol/L) at week 24 in the ITT (75.0%) and on-treatment (77.5%) analyses were significantly greater with alirocumab than placebo (9.0% and 8.0%, respectively; $P < .0001$) (Figure 5).

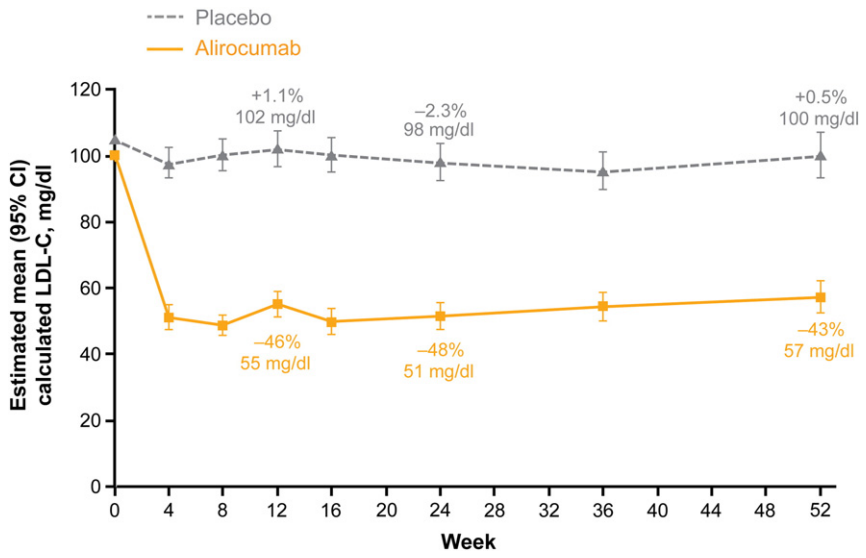
Significant reductions from baseline to week 24 after therapy with alirocumab ($P < .0001$ vs placebo) were observed in non–HDL-C (−39.1% [−42.6% to −35.6%] vs −1.6% [−6.6% to 3.3%]), apolipoprotein B (−36.7% [−39.9% to −33.5%] vs −0.9% [−5.4% to 3.5%]), total cholesterol (−27.9% [−30.4% to −25.4%] vs −2.9% [−6.3% to 0.6%]), and lipoprotein (a) (−20.5% [−24.4% to −16.6%] vs −5.9% [−11.3% to −0.5%]) (Table II, Figure 2, and online Supplementary Tables II-VIII); no significant change was observed in triglyceride levels, whereas a significant and directionally divergent increase in HDL-C was observed after alirocumab of 3.5% (1.4%-5.6%) (vs −3.8% [−6.8% to −0.8%] placebo; $P < .0001$) (Table II). Additional analysis of patients in the highest quartile of baseline lipoprotein (a) (>79.5 mg/dL; 73 patients) revealed a mean percent change in lipoprotein (a) from baseline to week 24 (alirocumab vs placebo) similar to that observed in the overall study population (−16.5% vs −14.6%, respectively). Patients in the highest quartile of baseline triglyceride (>186 mg/dL; 75 patients) had adjusted mean percent changes in triglyceride level from baseline to week 24 of −18.8%

Figure 2



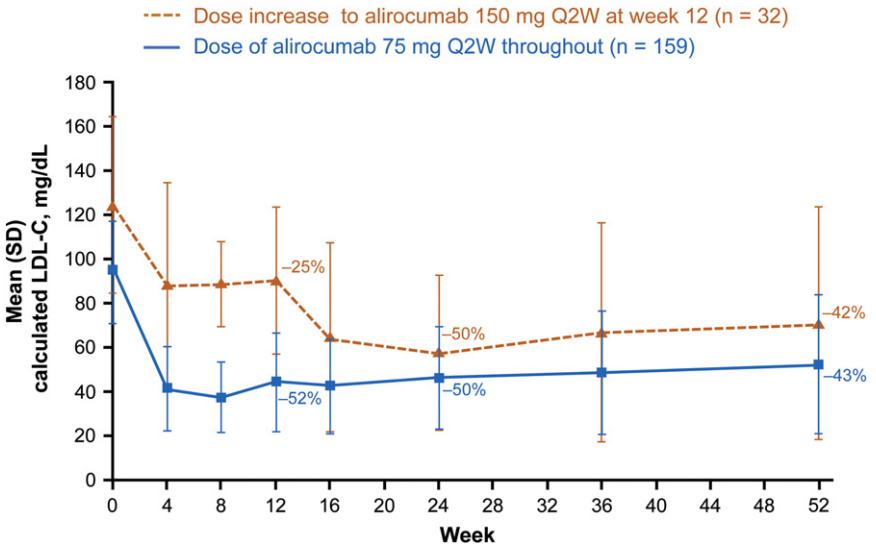
End point analysis: percent reduction in LDL-C and other lipid parameters from baseline to week 24.

Figure 3



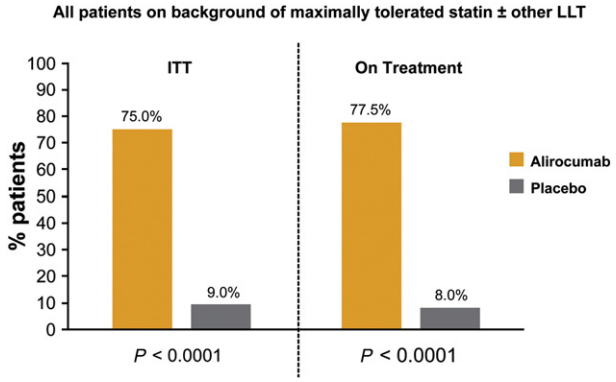
Achieved calculated LDL-C levels over time with alirocumab and placebo on background maximally tolerated statin with or without other LLT (ITT analysis). Baselines are described using mean; all other time points are estimated mean (95% CI). Values above and below data points indicate estimated mean percent change from baseline and estimated mean achieved LDL-C levels.

Figure 4



Low-density lipoprotein cholesterol percent reduction in patients with and without alirocumab dose increase.

Figure 5



Proportion of patients reaching LDL-C <70 mg/dL (1.81 mmol/L) at week 24. Multiple imputation method is used to address missing values in the ITT and modified ITT populations. Combined estimate for proportion of patients is obtained by averaging out all the imputed proportions of patients reaching the level of interest. The *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.

and −23.6% after alirocumab or placebo, respectively. There was no difference in response between placebo and alirocumab-treated patients (combined estimate for adjusted mean percent difference vs placebo of 4.8; *P* = .6069).

Subgroup analyses

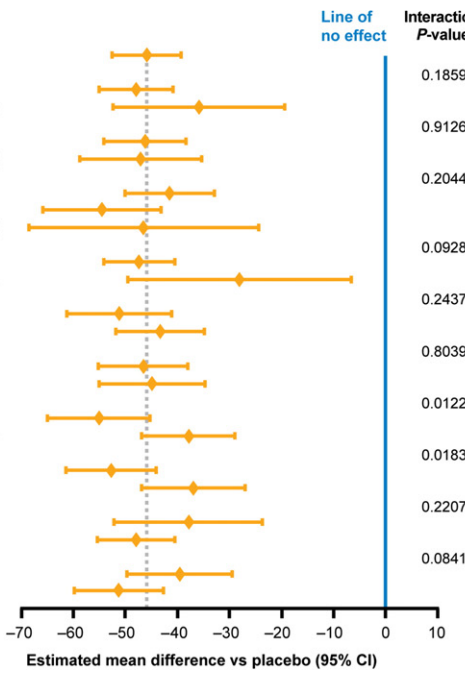
Alirocumab produced 40% to 55% mean reduction in LDL-C across prespecified subgroups including age, gender, race, ethnicity, intensity of background statin therapy, other LLT therapy (in addition to statin), and history of myocardial infarction or ischemic stroke (Figure 6). Greater variation in LDL-C reductions was observed with placebo for some subgroups, particularly those with small sample sizes (such as ethnicity [Hispanic/Latino]), producing large CIs for the difference in treatment effect for alirocumab versus placebo. Although treatment effect was generally consistent across subgroups, some heterogeneity in treatment effect (*P* value for interaction < .05) was observed for patients with other LLT therapy (in addition to statin) and those with a history of myocardial infarction or ischemic stroke.

Safety measures

The incidences of TEAEs and serious TEAEs were similar between treatment groups (Table III and online Supplementary Table IX). Treatment-emergent AEs leading to death or study medication discontinuation were uncommon in both groups (Table III). Local injection site reactions, reported by 5.3% alirocumab-treated patients (vs 2.8% placebo), were mild in severity and did not prompt study medication discontinuation. Adverse events related to potential general allergic reactions occurred in 8.7% alirocumab versus 6.5% placebo patients. There were few neurologic or neurocognitive events. Laboratory assessments were similar between groups and between alirocumab patients maintained on the 75-mg dose or those increased to 150-mg Q2W.

Figure 6

Subgroup	Alirocumab n	Alirocumab Estimated mean	Alirocumab 95% CI	Placebo n	Placebo Estimated mean	Placebo 95% CI	Interaction *P*-value	Consistency of effect
Overall	205	-48.2	(-52.0 to -44.4)	106	-2.3	(-7.6 to 3.1)		
Race							0.1859	Yes
White	167	-50.6	(-54.8 to -46.4)	88	-2.7	(-8.4 to 3.1)		
Black/African American	33	-36.3	(-45.7 to -26.9)	17	-0.4	(-14.0 to 13.1)		
Gender							0.9126	Yes
Male	129	-50.5	(-55.3 to -45.7)	76	-4.2	(-8.4 to 3.1)		
Female	76	-44.4	(-50.7 to -38.0)	30	2.6	(-14.0 to 13.1)		
Age							0.2044	Yes
<65	123	-44.0	(-48.9 to -39.0)	59	-2.4	(-9.5 to 4.6)		
65 to <75	59	-55.3	(-62.4 to -48.3)	39	-0.9	(-9.8 to 8.1)		
≥75	23	-52.5	(-64.0 to -41.0)	8	-6.0	(-24.7 to 12.8)		
Ethnicity							0.0928	Yes
Not Hispanic/Latino	180	-47.8	(-51.9 to -43.8)	97	-0.5	(-6.0 to 5.1)		
Hispanic/Latino	25	-50.6	(-61.8 to -39.4)	9	-22.5	(-40.9 to -4.0)		
BMI							0.2437	Yes
<30	78	-53.5	(-59.8 to -47.3)	47	-2.3	(-10.3 to 5.7)		
≥30	126	-45.4	(-50.3 to -40.6)	59	-2.1	(-9.2 to 5.0)		
Statin treatment							0.8039	Yes
High-intensity statin*	121	-46.8	(-51.7 to -41.9)	62	-0.2	(-7.3 to 6.9)		
No high-intensity statin	84	-50.2	(-56.3 to -44.0)	44	-5.2	(-13.7 to 2.3)		
Other LLT at randomization							0.0122	No
Statin with other LLT	77	-51.0	(-57.2 to -44.7)	52	4.1	(-3.6 to 11.8)		
Statin without other LLT	128	-46.5	(-51.2 to -41.7)	54	-8.6	(-16.2 to -1.0)		
History of MI or ischemic stroke							0.0183	No
Prior history MI or stroke	118	-52.3	(-57.3 to -47.3)	60	0.4	(-6.6 to 7.5)		
No prior MI or stroke	87	-42.6	(-48.4 to -36.8)	46	-5.7	(-13.7 to 2.3)		
Moderate CKD at randomization							0.2207	Yes
Moderate CKD	36	-42.3	(-51.1 to -33.4)	24	-4.3	(-15.5 to 6.9)		
No moderate CKD	169	-49.6	(-53.8 to -45.4)	82	-1.6	(-7.7 to 4.4)		
Diabetes at randomization							0.0841	Yes
Diabetes	94	-42.2	(-47.8 to -36.6)	41	-2.6	(-11.1 to 5.8)		
No diabetes	111	-53.2	(-58.4 to -48.1)	65	-2.0	(-8.8 to 4.8)		



Differences versus placebo for percent change from baseline in calculated LDL-C at week 24 by demographic characteristics and subgroup analysis (ITT population). All patients on background of maximally tolerated statin ± other LLT. Abbreviations: *CKD*, chronic kidney disease; *MI*, myocardial infarction. *High-intensity statin: atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily.

Low-density lipoprotein cholesterol 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 AE profile appeared similar to those patients without such low LDL-C levels (online Supplementary Table X). No placebotreated patients reached LDL-C levels of <25 mg/dL on 2 consecutive measurements.

Anti-alirocumab antibodies

A total of 13 alirocumab-treated patients (of 197 evaluable patients; 6.6%) had a positive response for the anti-alirocumab antibody assay. Five patients randomized to alirocumab (3/197; 1.5%) or placebo (2/99; 2.0%) had preexisting immunoreactivity. Treatment-emergent and low-titer antibody response was observed in 13 (6.6%) of 197 alirocumab-treated patients, in 7 of whom the antibodies were transient and resolved despite continued alirocumab treatment. Dose increase at week 12 did not appear to contribute to the development of antibodies. Of 8 patients with a positive response for the anti-alirocumab antibody assay at week 24, 2 had a dose increase in alirocumab to 150-mg Q2W at week 12; in both of these patients, antibodies were transient and resolved by week 52. Of the 13 alirocumab-treated patients positive in the anti-alirocumab antibody assay, 4 were positive for alirocumab-neutralizing antibodies; each of these resolved (became negative) within 24 weeks. The median time to detection of antibodies to alirocumab was 12 weeks, and no specific clinical events were observed in antibody-positive patients. The presence of anti-alirocumab antibodies had no observed effect on LDL-C–lowering efficacy (online Supplementary Figure 2) or safety.

Discussion

Self-administered alirocumab versus placebo added to maximally tolerated statin therapy with or without other LLT was associated with (*a*) a 48% reduction from baseline (pretreatment) to 24 weeks in LDL-C, corresponding to achieved estimated mean LDL-C levels of 51 mg/dL (vs 98 mg/dL with placebo); (*b*) significant reductions in non–HDL-C, total cholesterol, apolipoprotein B, and lipoprotein (a); and (*c*) a greater portion of patients who achieved LDL-C <70 mg/dL (75% vs 9%). These efficacy data complement clinical trial results using alirocumab as monotherapy[8] and are consistent with previous phase 2 trial results.[6,7,9]

COMBO I used a treat-to-target level dosing strategy based on individual patient responses to alirocumab

Table III. Adverse events and safety laboratory values (safety population)

n (%) of patients	Alirocumab	Placebo
All patients on maximally tolerated statin ± other LLT	(n = 207)	(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)
Noncardiac chest pain	2 (1.0)	7 (6.5)
Sinusitis	11 (5.3)	4 (3.7)
Injection site reaction	11 (5.3)	3 (2.8)
Safety terms of interest*		
Local injection site reactions	11 (5.3)	3 (2.8)
Potential general allergic reaction events	18 (8.7)	7 (6.5)
Neurologic events	5 (2.4)	2 (1.9)
Neurocognitive disorders	0 (0)	1 (0.9)
CV TEAEs confirmed by adjudication		
Any patients with treatment-emergent CV events confirmed by adjudication†	6(2.9)	3 (2.8)
CHD death (including undetermined cause)	1(0.5)	1 (0.9)
Nonfatal myocardial infarction	1(0.5)	1 (0.9)
Fatal and nonfatal 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)

Abbreviations: *SAEs*, Serious AEs.
*Neurocognitive events were selected using a company Medical Dictionary for Regulatory Activities query based on the following 5 high-level group terms: *deliria* (including confusion), *cognitive and attention disorders and disturbances, dementia and amnestic conditions, disturbances in thinking and perception*, and *mental impairment disorders*.
† One patient in the placebo group and 1 patient in the alirocumab group each experienced 2 events that were positively adjudicated: nonfatal myocardial infarction and ischemia-driven coronary revascularization procedure.

treatment. Most (83% of those with an injection after week 12) high CV risk patients on background statin therapy achieved an LDL-C <70 mg/dL on the 75-mg Q2W alirocumab dose regimen at week 8 and did not need dose increase to 150-mg Q2W. These patients demonstrated consistent efficacy over time. Low-density lipoprotein cholesterol reduction for weeks 24 to 52 was comparable among those patients in whom alirocumab dose was increased to 150 mg at week 12 (LDL-C ≥70 mg/dL at week 8) and those who remained on alirocumab 75 mg throughout the duration of the study. In this study, increase in alirocumab dose produced an additional 22.8% reduction in LDL-C, providing rationale for initiation of alirocumab therapy using the 75-mg dose with the potential to increase to 150 mg if further LDL-C reduction is required.

When administered in conjunction with maximally tolerated statin with or without additional LLT, alirocumab treatment appeared to be generally well tolerated over 52 weeks of therapy, with incidences of TEAEs and serious AEs largely comparable with those observed on placebo. Injection site reactions occurred more frequently in alirocumab-treated patients versus placebo; however, consistent with previous reports,[6-9] they were mostly graded mild in severity. Development of anti-alirocumab antibodies was observed in 6.6% of evaluable alirocumab-treated patients; however, these were transient (despite continued treatment) in almost two-thirds of cases, and there was no association between development of antibodies and clinical sequelae or LDL-C lowering. Overall safety findings were similar to other alirocumab studies reported thus far[6-9] and for other PCSK9 inhibitors.[12]

Although sufficiently powered to detect the primary end point of LDL-C reduction from baseline to week 24, this study remains relatively small with respect to subgroup analyses. Analysis using pooled data from the multinational ODYSSEY phase 3 program will provide more comprehensive assessment in terms of consistency of alirocumab treatment effect across subgroups (including in patients with LDL-C <25 mg/dL) and patient populations. COMBO I provided further demonstration of the LDL-C–lowering efficacy and safety of alirocumab in a high CV risk population; however, clinical outcomes data

(currently being collected in the OUTCOMES trial NCT01663402) are required to corroborate any potential benefit with respect to CV events.

In patients at high ASCVD risk with hypercholesterolemia despite treatment with maximally tolerated statin (with or without other LLT), alirocumab reduced LDL-C through 52 weeks of treatment and was well tolerated. Alirocumab 75-mg Q2W was sufficient for a majority of patients to achieve LDL-C <70 mg/dL without the need for subsequent dose increase to 150 mg. These findings provide support for initiating alirocumab therapy at 75-mg Q2W in patients on maximized standard of care who have suboptimally controlled hypercholesterolemia, with dose increase to 150-mg Q2W in those patients not achieving LDL-C lower than 70 mg/dL.

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Appendix

Key inclusion/exclusion criteria

Full details of the study design have been published previously.[10]

The definitions of CHD included acute myocardial infarction, silent myocardial infarction, unstable angina, coronary revascularization, or clinically significant CHD diagnosed by invasive or noninvasive testing. Coronary heart disease risk equivalents included peripheral arterial disease, ischemic stroke, chronic kidney disease (estimated glomerular filtration rate ≥30 to <60 mL/min per 1.73 m^2 for ≥3 months), or diabetes mellitus in combination with ≥2 additional risk factors (hypertension, ankle-brachial index ≤0.90, microalbuminuria 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]). Specific protocol-defined exclusion criteria included known hypersensitivity to monoclonal antibody therapeutics, women of childbearing potential with no effective contraceptive method, uncontrolled diabetes with hemoglobin A1C >8.5% or diagnosed within 3 months, clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins, blood pressure >160/100 mm Hg, major CV event within 3 months, New York Heart Association class III or IV, heart failure within 12 months, fasting serum triglycerides >400 mg/dL (4.52 mmol/L), thyroid-stimulating hormone either below or above the upper limit of normal, alanine aminotransferase, aspartate aminotransferase, or creatine phosphokinase >3× upper limit of normal.

Additional statistical methodology

A mixed effect model with repeated measures was used to account for missing data and included fixed categorical effects of treatment group, randomized strata, time point, 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-bytime point interaction. A sensitivity analysis based on a pattern mixture model was conducted to evaluate the impact of missing data on the primary end point; in this approach, missing calculated LDL-C values during the on-treatment period were multiply imputed using a model assuming "missing at random"; missing calculated LDL-C values during the posttreatment period were multiply imputed using random draws from a normal distribution where the mean was equal to subject's own baseline value.

Secondary end points were analyzed in a predefined order using a hierarchical testing procedure to control type I error. Secondary lipid end points were analyzed as for the primary end point, except lipoprotein (a) and triglycerides, which were analyzed using a multiple imputation approach for handling of missing values followed by robust regression. The proportion of patients with LDL-C <70 mg/dL was analyzed by logistic regression.

A prespecified on-treatment analysis was also conducted for the percent change in LDL-C from baseline to week 24 and key secondary end points, using all available on-treatment measurements at planned time points from weeks 4 to 52.

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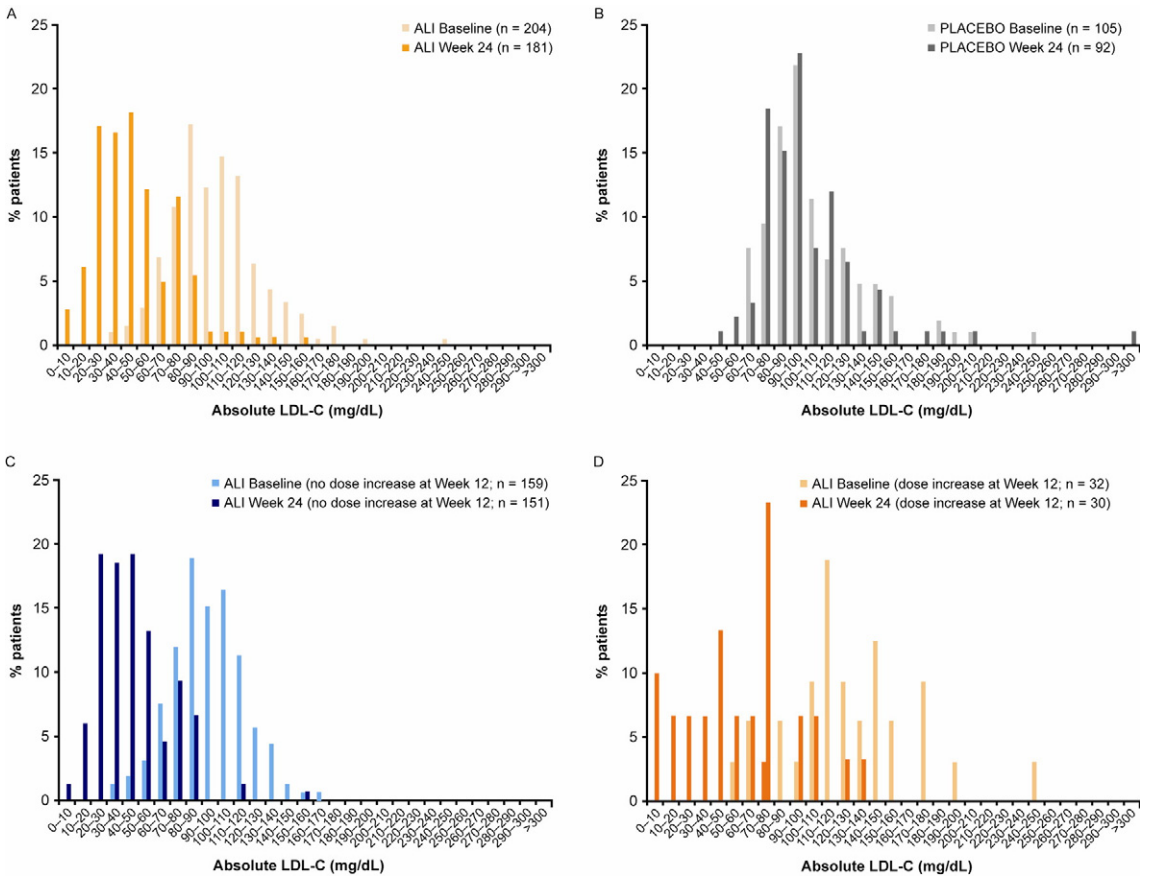
Independent Physicians

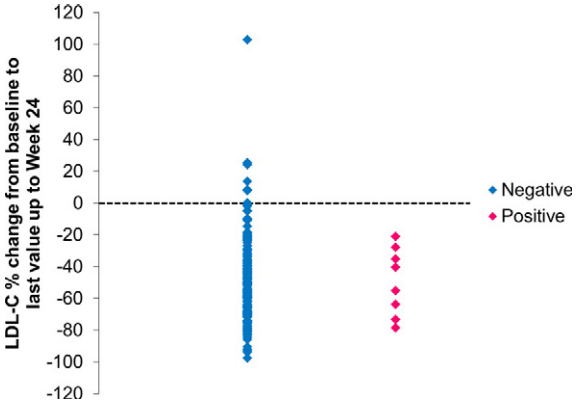
Independent physicians monitoring two consecutive LDL < 0.65 mmol/L: Karen Alexander, and Chiara Melloni (Duke Clinical Research Institute, Durham, NC USA).

Supplementary Figure 1



Distribution of absolute LDL-C levels at baseline and week 24 for (**A**) all alirocumab-treated patients and (**B**) all placebo-treated patients (on treatment analyses). **C** and **D,** show the distribution within the alirocumab group for (**C**) alirocumab-treated patients who remained on a dose of 75-mg Q2W through the study and (**D**) alirocumab-treated patients who received a dose increase to 150-mg Q2W at week 12 if their LDL-C was ≥70 mg/dL at week 8.

Supplementary Figure 2



Percent reduction in LDL-C from baseline to week 24 by anti-alirocumab antibody status.

Supplementary Table I. Percent change from baseline in calculated LDL-C: on-treatment and sensitivity (pattern mixture model—ITT analysis—randomized population) analyses

All patients on maximally tolerated statin ± other LLT	Alirocumab	Placebo	Alirocumab vs placebo		
			Estimated mean difference		
			%	95% CI	*P*
On-treatment analysis	n = 204	n = 105			
Baseline, mg/dL, mean (SD)	99.8 (29.0)	105.0 (32.2)			
Minimum:maximum	33:240	61:243			
Estimated mean (95% CI) change from baseline to week 12 (%)	−47.6 (−51.1 to −44.1)	1.7 (−3.1 to 6.5)	−49.3	−55.3 to −43.3	<.0001
Estimated mean (95% CI) change from baseline at week 24 (%)	−50.7 (−54.4 to −47.0)	−0.8 (−5.9 to 4.3)	−49.9	−56.2 to −43.6	<.0001
Sensitivity analysis	n = 205	n = 106			
Baseline, mg/dL	100.3 (29.7)	104.6 (32.3)			
Min:max	33:240	61:243			
Combined estimate for mean (95% CI) change from baseline at week 24 (%)	−44.2 (−48.4 to −40.1)	−1.5 (−7.4 to 4.4)	−42.7	(−49.9 to −35.4)	<.0001

Values are mean (SD) unless stated.
Only patients who were receiving study treatment were included in the on-treatment analysis (modified ITT).
The sensitivity analysis has been conducted to further evaluate the impact of missing data on the primary end point: in this approach, missing calculated LDL-C values during the "on-treatment" period were multiply imputed using a model assuming missing at random, and missing calculated LDL-C values during the posttreatment period were multiply imputed using random draws from a normal distribution, with mean equal to subject's own baseline value.

Supplementary Table II. Calculated LDL-C over time (raw data, ITT analysis)

	Alirocumab (n = 205)			Placebo (n = 106)		
Calculated LDL-C (mg/dL)	Value	Change from baseline	Percent change from baseline	Value	Change from baseline	Percent change from baseline
Baseline						
No. of patients	205	NA	NA	106	NA	NA
No. of missing data	–			–		
Mean (SD)	100.3 (29.7)			104.6 (32.3)		
Week 4						
No. of patients	198	198	198	102	102	102
No. of missing data	7	7	7	4	4	4
Mean (SD)	49.8 (31.1)	−50.2 (25.4)	−50.9 (23.6)	99.2 (31.7)	−4.7 (28.4)	−1.8 (25.6)
Week 8						
No. of patients	196	196	196	101	101	101
No. of missing data	9	9	9	5	5	5
Mean (SD)	47.2 (26.6)	−52.5 (28.5)	−51.8 (26.1)	101.7 (31.6)	−3.0 (23.4)	−0.8 (21.1)
Week 12						
No. of patients	193	193	193	99	99	99
No. of missing data	12	12	12	7	7	7
Mean (SD)	53.8 (31.4)	−46.1 (28.2)	−46.5 (26.0)	104.7 (41.5)	−0.2 (30.7)	1.3 (25.3)
Week 16						
No. of patients	185	185	185	96	96	96
No. of missing data	20	20	20	10	10	10
Mean (SD)	47.7 (28.4)	−52.2 (31.2)	−51.4 (26.4)	102.5 (33.0)	−3.0 (28.2)	0.2 (24.8)
Week 24						
No. of patients	189	189	189	97	97	97
No. of missing data	16	16	16	9	9	9
Mean (SD)	50.4 (28.6)	−49.3 (33.4)	−47.9 (29.1)	100.0 (35.2)	−5.3 (30.2)	−2.5 (24.9)
Week 36						
No. of patients	168	168	168	90	90	90
No. of missing data	37	37	37	16	16	16
Mean (SD)	52.0 (32.7)	−46.4 (35.5)	−44.9 (37.6)	97.7 (33.3)	−5.7 (21.4)	−4.6 (20.0)
Week 52						
No. of patients	167	167	167	79	79	79
No. of missing data	38	38	38	27	27	27
Mean (SD)	56.6 (37.1)	−43.8 (37.3)	−42.4 (35.2)	98.8 (25.7)	−1.4 (25.8)	1.4 (27.7)

Abbreviation: *NA*, Not applicable.

Supplementary Table III. Apolipoprotein B over time (raw data, ITT analysis)

	Alirocumab		Placebo	
	(n = 205)		(n = 106)	
Apolipoprotein B (mg/dL)	Value	Percent change from baseline	Value	Percent change from baseline
Baseline				
No. of patients	189	NA	100	NA
No. of missing data	16		6	
Mean (SD)	90.8 (21.5)		90.4 (21.9)	
Week 12				
No. of patients	195	181	98	93
No. of missing data	10	24	8	13
Mean (SD)	59.6 (24.4)	−34.7 (22.1)	93.4 (30.3)	3.5 (22.0)
Week 24				
No. of patients	192	181	97	92
No. of missing data	13	24	9	14
Mean (SD)	56.3 (21.5)	−36.5 (23.2)	89.6 (24.0)	−1.1 (21.4)
Week 52				
No. of patients	176	167	81	76
No. of missing data	29	38	25	30
Mean (SD)	63.0 (27.3)	−30.6 (29.4)	90.6 (19.7)	4.3 (23.1)

Supplementary Table IV. Non–HDL-C over time (raw data, ITT analysis)

	Alirocumab (n = 205)		Placebo (n = 106)	
Non-HDL cholesterol (mg/dL)	Value	Percent change from baseline	Value	Percent change from baseline
Baseline				
No. of patients	205	NA	106	NA
No. of missing data	–		–	
Mean (SD)	130.1 (34.3)		131.7 (36.3)	
Week 4				
No. of patients	200	200	102	102
No. of missing data	5	5	4	4
Mean (SD)	76.5 (36.4)	–41.7 (19.9)	125.2 (36.5)	–2.5 (21.3)
Week 8				
No. of patients	199	199	102	102
No. of missing data	6	6	4	4
Mean (SD)	72.1 (29.2)	–43.4 (21.0)	129.9 (35.3)	–0.1 (18.4)
Week 12				
No. of patients	196	196	99	99
No. of missing data	9	9	7	7
Mean (SD)	81.1 (42.2)	–37.3 (28.0)	134.2 (44.2)	2.8 (21.0)
Week 16				
No. of patients	188	188	98	98
No. of missing data	17	17	8	8
Mean (SD)	73.1 (34.3)	–42.7 (24.0)	130.4 (37.3)	0.2 (21.8)
Week 24				
No. of patients	192	192	97	97
No. of missing data	13	13	9	9
Mean (SD)	77.3 (34.0)	–39.0 (25.8)	128.0 (41.7)	–1.6 (25.1)
Week 36				
No. of patients	177	177	90	90
No. of missing data	28	28	16	16
Mean (SD)	82.2 (41.3)	–35.2 (28.3)	125.9 (37.1)	–2.4 (18.1)
Week 52				
No. of patients	175	175	81	81
No. of missing data	30	30	25	25
Mean (SD)	85.4 (42.8)	–32.5 (32.8)	128.8 (29.6)	3.4 (25.0)

Supplementary Table V. Total cholesterol over time (raw data, ITT analysis)

	Alirocumab (n = 205)		Placebo (n = 106)	
Cholesterol (mg/dL)	Value	Percent change from baseline	Value	Percent change from baseline
Baseline				
No. of patients	205	NA	106	NA
No. of missing data	–		–	
Mean (SD)	178.5 (36.0)		180.7 (36.3)	
Week 4				
No. of patients	200	200	102	102
No. of missing data	5	5	4	4
Mean (SD)	126.6 (37.7)	−29.1 (14.7)	173.3 (37.4)	−2.6 (17.0)
Week 8				
No. of patients	199	199	102	102
No. of missing data	6	6	4	4
Mean (SD)	122.0 (32.0)	−30.7 (15.8)	177.1 (35.6)	−1.1 (13.2)
Week 12				
No. of patients	196	196	99	99
No. of missing data	9	9	7	7
Mean (SD)	132.1 (43.2)	−25.2 (21.5)	181.3 (43.2)	0.9 (16.2)
Week 16				
No. of patients	188	188	98	98
No. of missing data	17	17	8	8
Mean (SD)	123.0 (34.8)	−30.0 (17.8)	177.4 (38.1)	−1.3 (16.6)
Week 24				
No. of patients	192	192	97	97
No. of missing data	13	13	9	9
Mean (SD)	126.5 (34.0)	−27.7 (18.4)	174.4 (40.9)	−3.1 (18.7)
Week 36				
No. of patients	177	177	90	90
No. of missing data	28	28	16	16
Mean (SD)	130.3 (40.3)	−25.2 (20.9)	172.3 (35.9)	−3.4 (13.5)
Week 52				
No. of patients	175	175	81	81
No. of missing data	30	30	25	25
Mean (SD)	136.2 (44.1)	−22.4 (23.4)	175.1 (30.3)	0.5 (16.1)

Supplementary Table VI. Lipoprotein (a) over time (raw data, ITT analysis)

	Alirocumab (n = 205)		Placebo (n = 106)	
Lipoprotein (a) (mg/dL)	Value	Percent change from baseline	Value	Percent change from baseline
Baseline				
No. of patients	189	NA	100	NA
No. of missing data	16		6	
Median	31.0		38.0	
Q1:Q3	8.0:81.0		10.0:71.0	
Min:max	2:248		2:184	
Week 12				
No. of patients	195	181	98	93
No. of missing data	10	24	8	13
Median	26.0	–16.7	35.0	0.0
Q1:Q3	5.0:71.0	–35.4:0.0	11.0:75.0	–13.7:14.3
Min:max	2:206	–85:771	2:254	–60:600
Week 24				
No. of patients	192	181	97	92
No. of missing data	13	24	9	14
Median	20.0	–20.8	30.0	–5.4
Q1:Q3	6.0:65.0	–37.8:0.0	10.0:67.0	–18.2:5.9
Min:max	2:197	–85:657	2:243	–63:67
Week 52				
No. of patients	176	167	81	76
No. of missing data	29	38	25	30
Median	20.0	–25.0	26.0	–14.8
Q1:Q3	5.0:60.5	–45.6:0.0	9.0:69.0	–25.8:0.0
Min:max	2:189	–85:543	2:167	–65:100

Supplementary Table VII. TGs over time (raw data, ITT analysis)

	Alirocumab (n = 205)		Placebo (n = 106)	
Fasting triglycerides (mg/dL)	Value	Percent change from baseline	Value	Percent change from baseline
Baseline				
No. of patients	205	NA	105	NA
No. of missing data	–		1	
Median	130.0		123.0	
Q1:Q3	92.0:189.0		95.0:175.0	
Min:max	35:999		52:431	
Week 4				
No. of patients	197	197	101	100
No. of missing data	8	8	5	6
Median	118.0	−11.7	122.0	−5.8
Q1:Q3	85.0:157.0	−28.1:7.0	89.0:160.0	−17.3:16.8
Min:max	34:438	−72:125	48:365	−68:84
Week 8				
No. of patients	197	197	101	101
No. of missing data	8	8	5	5
Median	113.0	−13.6	130.0	0.0
Q1:Q3	84.0:145.0	−30.6:7.7	87.0:171.0	−18.8:22.6
Min:max	33:508	−58:127	41:442	−53:131
Week 12				
No. of patients	196	196	98	98
No. of missing data	9	9	8	8
Median	110.5	−14.1	129.0	3.5
Q1:Q3	84.5:159.0	−30.8:11.2	102.0:184.0	−11.1:23.4
Min:max	30:1247	−77:277	47:384	−46:172
Week 16				
No. of patients	186	186	98	98
No. of missing data	19	19	8	8
Median	116.0	−12.6	132.0	2.7
Q1:Q3	82.0:151.0	−29.2:9.8	95.0:173.0	−13.8:23.2
Min:max	36:627	−69:160	53:427	−57:110
Week 24				
No. of patients	191	191	96	96
No. of missing data	14	14	10	10
Median	116.0	−8.4	113.0	−6.4
Q1:Q3	84.0:157.0	−27.1:17.8	87.5:154.0	−20.2:22.9
Min:max	36:511	−66:287	46:669	−69:142
Week 36				
No. of patients	176	176	88	88
No. of missing data	29	29	18	18
Median	123.5	−4.5	125.5	−1.0
Q1:Q3	89.0:176.0	−24.7:26.2	96.5:173.0	−16.1:20.3
Min:max	35:1776	−58:238	53:365	−43:113
Week 52				
No. of patients	175	175	80	80
No. of missing data	30	30	26	26
Median	126.0	−3.3	129.5	5.0
Q1:Q3	95.0:171.0	−25.3:26.7	96.5:174.5	−12.4:33.4
Min:max	28:683	−70:413	65:476	−67:258

Supplementary Table VIII. High-density lipoprotein cholesterol over time (raw data, ITT analysis)

	Alirocumab (n = 205)		Placebo (n = 106)	
HDL cholesterol (mg/dL)	Value	Percent change from baseline	Value	Percent change from baseline
Baseline				
No. of patients	205	NA	106	NA
No. of missing data	–		–	
Mean (SD)	48.3 (14.5)		48.8 (12.8)	
Week 4				
No. of patients	200	200	102	102
No. of missing data	5	5	4	4
Mean (SD)	49.9 (14.1)	4.3 (12.9)	48.1 (12.0)	–0.8 (11.4)
Week 8				
No. of patients	199	199	102	102
No. of missing data	6	6	4	4
Mean (SD)	49.9 (13.7)	4.8 (14.4)	47.2 (11.5)	–1.3 (11.9)
Week 12				
No. of patients	196	196	99	99
No. of missing data	9	9	7	7
Mean (SD)	51.0 (15.0)	6.6 (15.8)	47.1 (12.9)	–2.8 (13.4)
Week 16				
No. of patients	188	188	98	98
No. of missing data	17	17	8	8
Mean (SD)	49.9 (13.8)	4.0 (14.4)	46.9 (13.7)	–3.0 (15.7)
Week 24				
No. of patients	192	192	97	97
No. of missing data	13	13	9	9
Mean (SD)	49.2 (13.4)	3.7 (16.3)	46.4 (12.5)	–4.3 (16.4)
Week 36				
No. of patients	177	177	90	90
No. of missing data	28	28	16	16
Mean (SD)	48.1 (13.8)	1.6 (16.2)	46.4 (11.3)	–4.7 (14.1)
Week 52				
No. of patients	175	175	81	81
No. of missing data	30	30	25	25
Mean (SD)	50.9 (13.5)	6.7 (18.8)	46.3 (12.3)	–3.9 (16.4)

Supplementary Table IX. Treatment-emergent AEs occurring in ≥2% of patients in either group (safety population)

n (%) of patients	Alirocumab	Placebo
All patients on maximally tolerated statin ± other LLT	(n = 207)	(n = 107)
TEAEs occurring in ≥2% of patients in either group		
Infections and infestations	77 (37.2)	29 (27.1)
Upper respiratory tract infection	16 (7.7)	11 (10.3)
Nasopharyngitis	15 (7.2)	5 (4.7)
Urinary tract infection	13 (6.3)	4 (3.7)
Sinusitis	11 (5.3)	4 (3.7)
Bronchitis	10 (4.8)	5 (4.7)
Influenza	6 (2.9)	0
Herpes zoster	2 (1.0)	3 (2.8)
Musculoskeletal and connective tissue disorders	49 (23.7)	23 (21.5)
Arthralgia	8 (3.9)	8 (7.5)
Osteoarthritis	8 (3.9)	5 (4.7)
Pain in extremity	8 (3.9)	3 (2.8)
Myalgia	7 (3.4)	4 (3.7)
Back pain	5 (2.4)	4 (3.7)
Injury, poisoning, and procedural complications	29 (14.0)	22 (20.6)
Contusion	7 (3.4)	5 (4.7)
Fall	7 (3.4)	5 (4.7)
Gastrointestinal disorders	39 (18.8)	17 (15.9)
Diarrhea	8 (3.9)	3 (2.8)
Nausea	8 (3.9)	0
Constipation	6 (2.9)	3 (2.8)
Gastroesophageal reflux disease	3 (1.4)	4 (3.7)
Nervous system disorders	24 (11.6)	17 (15.9)
Dizziness	11 (5.3)	6 (5.6)
Headache	7 (3.4)	3 (2.8)
General disorders and administration-site conditions	26 (12.6)	16 (15.0)
Injection-site reaction	11 (5.3)	3 (2.8)
Edema peripheral	5 (2.4)	2 (1.9)
Noncardiac chest pain	2 (1.0)	7 (6.5)
Respiratory, thoracic, and mediastinal disorders	28 (13.5)	14 (13.1)
Asthma	5 (2.4)	0
Cough	5 (2.4)	4 (3.7)
Vascular disorders	14 (6.8)	6 (5.6)
Hypertension	10 (4.8)	2 (1.9)
Psychiatric disorders	12 (5.8)	5 (4.7)
Depression	5 (2.4)	2 (1.9)
Blood and lymphatic system disorders	5 (2.4)	3 (2.8)
Anemia	5 (2.4)	2 (1.9)

Supplementary Table X. Incidence of TEAEs including alirocumab-treated patients with 2 consecutive LDL-C values ≤25 mg/dL (safety population)

n (%) of patients	Alirocumab	Alirocumab 2 consecutive	Placebo
All patients on maximally tolerated statin ± other LLT	(n = 207)	LDL-C ≤25 mg/dL (n = 39)	(n = 107)
TEAEs (any class)	157 (75.8)	29 (74.4)	81 (75.7)
TEAEs by preferred term occurring in ≥5% of patients in any group			
Infections and infestations	77 (37.2)	11 (28.2)	29 (27.1)
Upper respiratory tract infection	16 (7.7)	1 (2.6)	11 (10.3)
Nasopharyngitis	15 (7.2)	2 (5.1)	5 (4.7)
Urinary tract infection	13 (6.3)	2 (5.1)	4 (3.7)
Sinusitis	11 (5.3)	1 (2.6)	4 (3.7)
Bronchitis	10 (4.8)	3 (7.7)	5 (4.7)
Musculoskeletal and connective tissue disorders	49 (23.7)	12 (30.8)	23 (21.5)
Arthralgia	8 (3.9)	2 (5.1)	8 (7.5)
Osteoarthritis	8 (3.9)	2 (5.1)	5 (4.7)
Myalgia	7 (3.4)	3 (7.7)	4 (3.7)
Intervertebral disc protrusion	2 (1.0)	2 (5.1)	0 (0)
Gastrointestinal disorders	39 (18.8)	4 (10.3)	17 (15.9)
Nausea	8 (3.9)	2 (5.1)	0 (0)
General disorders and administration-site conditions	26 (12.6)	3 (7.7)	16 (15.0)
Injection-site reaction	11 (5.3)	2 (5.1)	3 (2.8)
Noncardiac chest pain	2 (1.0)	1 (2.6)	7 (6.5)
Injury, poisoning, and procedural complications	29 (14.0)	5 (12.8)	22 (20.6)
Contusion	7 (3.4)	2 (5.1)	5 (4.7)
Fall	7 (3.4)	2 (5.1)	5 (4.7)
Nervous system disorders	24 (11.6)	1 (2.6)	17 (15.9)
Dizziness	11 (5.3)	1 (2.6)	6 (5.6)
Ear and labyrinth disorders	4 (1.9)	3 (7.7)	4 (3.7)
Cerumen impaction	2 (1.0)	2 (5.1)	0 (0)