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Alirocumab Treatment and Achievement of Non-High-Density Lipoprotein Cholesterol and Apolipoprotein B Goals in Patients With Hypercholesterolemia: Pooled Results From 10 Phase 3 ODYSSEY Trials

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Background—Non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein (apo) B are better predictors of atherosclerotic cardiovascular disease risk than low-density lipoprotein cholesterol alone. US and European lipid management guidelines support non-HDL-C and apoB as targets for lipid-lowering therapy.

Methods and Results—This analysis evaluated the efficacy of alirocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor, on non-HDL-C and apoB. Data were derived from 4983 patients enrolled in 10 randomized, placebo- or ezetimibe-controlled Phase 3 ODYSSEY trials. Primary end point for this pooled analysis was percent reduction in non-HDL-C and apoB at Week 24; secondary end points included the percentage of patients achieving guideline-directed treatment goals (National Lipid Association guidelines: non-HDL-C <100 or <130 mg/dL for patients at very high and high cardiovascular risk, respectively; European Society of Cardiology/European Atherosclerosis Society guidelines: apoB <80 mg/dL for patients at very-high cardiovascular risk). Data were grouped according to comparator, alirocumab starting dose, and concomitant statin use. Compared with controls, alirocumab produced significantly greater reductions in non-HDL-C and apoB at Week 24 ($P<0.0001$), an effect extending up to 78 weeks. More alirocumab-treated patients achieved levels of non-HDL-C <100 mg/dL and apoB <80 mg/dL ($P\leq 0.0001$ versus control). By Week 24, >70% of alirocumab-treated patients on background statin achieved non-HDL-C <100 or <130 mg/dL, and apoB <80 mg/dL. Safety was comparable across pooled groups and in line with previous reports.

Conclusions—Alirocumab produced significant, sustained reductions in non-HDL-C and apoB, allowing more patients to achieve lipid goals compared with placebo or ezetimibe and irrespective of maximally tolerated statin use. (*J Am Heart Assoc.* 2017;6:e005639. DOI: 10.1161/JAHA.117.005639.)

Key Words: alirocumab • apolipoprotein B • cholesterol-lowering • hypercholesterolemia • non-high-density lipoprotein cholesterol • PCSK9

Guidelines for the management of dyslipidemia have traditionally recommended reductions in the level of low-density lipoprotein cholesterol (LDL-C) as the primary lipid target of therapy to reduce the risk of atherosclerotic cardiovascular disease (ASCVD). However, LDL-C has

limitations as a predictor of ASCVD risk, particularly in patients with elevated triglyceride levels.¹

Additional pro-atherogenic lipid parameters, such as non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein (apo) B, may provide important diagnostic

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Accompanying Data S1, Tables S1 through S3, and Figures S1 through S4 are available at <http://jaha.ahajournals.org/content/6/8/e005639/DC1/embed/inline-supplementary-material-1.pdf>

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Clinical Perspective

What Is New?

- Non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B (apoB) are specified as treatment targets by some international lipid guidelines.
- Alirocumab produced significant, sustained reductions in non-HDL-C and apoB, allowing more patients to achieve lipid goals.

What Are the Clinical Implications?

- Non-HDL-C and apoB are better predictors of atherosclerotic cardiovascular disease risk than calculated low-density lipoprotein cholesterol alone.
- Alirocumab effectively reduces non-HDL-C and apoB levels, allowing for better achievement of non-HDL-C and apoB levels corresponding to guideline treatment goals.

information to guide the assessment and management of dyslipidemia and ASCVD risk.² Current US National Lipid Association recommendations and European Society of Cardiology/European Atherosclerosis Society guidelines have recognized the importance of these lipid parameters. The National Lipid Association recommends non-HDL-C as a co-primary therapy target alongside LDL-C, and apoB as a secondary target, whereas European guidelines recommend both non-HDL-C and apoB as secondary targets.^{3,4} Although the 2013 American College of Cardiology/American Heart Association guidelines do not specify non-HDL-C treatment thresholds,⁵ recent recommendations from the 2016 American College of Cardiology Consensus Decision Pathway on the role of nonstatin therapies for LDL-C-lowering have introduced non-HDL-C thresholds in certain high-risk patient groups.⁶

Alirocumab is a monoclonal proprotein convertase subtilisin/kexin type 9 inhibitor that helps prevent LDL receptor degradation, thus increasing clearance of LDL-C and decreasing LDL-C blood levels. Alirocumab was evaluated in the ODYSSEY global Phase 3 clinical trial program comprising a comprehensive set of clinical studies in various patient populations. Individual studies^{7–14} and a pooled analysis of 8 studies in patients receiving background statin therapy¹⁵ have shown that alirocumab produces significant reductions in LDL-C compared with placebo or ezetimibe in patients at high cardiovascular risk.

The data for this analysis included 10 completed ODYSSEY studies in a broad range of patients with hypercholesterolemia: 8 studies including alirocumab administered to patients treated with background statin, the majority of whom received maximally tolerated statin, or other lipid-lowering therapies, and 2 studies involving alirocumab administered to

patients without background statin. The main aim of the analysis was to investigate the effect of alirocumab on levels of non-HDL-C and apoB.

Methods

Study Designs and Participants

In this analysis, data were pooled from 10 Phase 3 trials in the ODYSSEY program, involving 4983 patients with hypercholesterolemia. Detailed methods for each of the 10 studies were previously published elsewhere.^{7–14}

In 8 trials (pools 1, 3, and 4; total n=2535 patients), the alirocumab starting dose was 75 mg every 2 weeks (Q2W). If pre-defined ASCVD risk-based LDL-C goals were not achieved at Week 8, the alirocumab dose was increased in a blinded manner to 150 mg Q2W at Week 12.^{7–12} The alirocumab dose in these pooled groups is referred to herein as alirocumab 75/150 mg. In 2 trials (pool 2; total n=2448 patients), patients received alirocumab 150 mg Q2W from the outset.^{13,14}

As described above, trials were pooled into 1 of 4 groups: (1) alirocumab 75/150 mg Q2W versus placebo, on background statins (COMBO I, FH I, and FH II)^{8,10}; (2) alirocumab 150 mg Q2W versus placebo, on background statins (LONG TERM and HIGH FH)^{13,14}; (3) alirocumab 75/150 mg Q2W versus ezetimibe 10 mg daily, on background statins (COMBO II, OPTIONS I, and OPTIONS II)^{7–9}; and (4) alirocumab 75/150 mg Q2W versus ezetimibe 10 mg daily, without background statins (ALTERNATIVE and MONO)^{11,12} (Table S1).

Trial length ranged from 24 to 104 weeks. Efficacy analyses within each pool were performed to the time point for which data were available for all trials in that pool. For safety analyses, treatment-emergent adverse events (TEAEs) were defined as events occurring from the first dose of study treatment and up to 70 days after the last dose. All subcutaneous injections (alirocumab 75, 150 mg, or placebo) used a 1 mL injection volume. Patients provided written informed consent before their participation. The trial protocols were reviewed and approved by institutional review boards and independent ethics committees.

The primary efficacy end point for each of these trials was the percent change in calculated LDL-C levels from baseline to Week 24. Secondary end points included percent change in LDL-C at Week 12 and percent change from baseline in non-HDL-C, apoB, HDL-C, and triglyceride levels. Given their importance as highlighted in recent guidelines,^{3,4} the present analysis focuses on the reduction of non-HDL-C and apoB. As well as evaluating percent change from baseline, an additional end point was the percentage of patients achieving levels of these lipoproteins corresponding to guideline-directed treatment goals (non-HDL-C <100 or <130 mg/dL for patients at

very-high and high cardiovascular risk, respectively; apoB <80 mg/dL for patients at very-high cardiovascular risk, and <100 mg/dL for those at high risk).^{3,4}

The definition of cardiovascular risk in the Phase 3 studies included in this analysis varied by study. Detailed definitions can be found within Data S1. Given that the specified non-HDL-C goals are defined in guidelines according to the estimated degree of ASCVD risk for a given individual, our analysis of non-HDL-C goal attainment was performed for the entire population regardless of individual risk as well as stratification by very-high and high cardiovascular risk (the vast majority of patients in the present analysis were at very-high or high cardiovascular risk). Analysis of apoB goal attainment was performed for the entire population regardless of individual risk.

Statistical analyses were based on intention-to-treat (ITT) principles (including all data regardless of adherence to treatment) and the on-treatment (modified ITT) population. The modified ITT population was defined as all randomized and treated patients with a baseline non-HDL-C value and with on-treatment non-HDL-C values during at least 1 of the planned postbaseline time points. The on-treatment window was defined as the period up to 21 days after last injection. Patients who discontinued the study drug were required to return for further clinic visits and assessments until the scheduled final visits. Patients with missing data were accounted for using a mixed effect model with repeated measures. The model included fixed categorical effects of treatment group, study, randomization strata as per interactive voice system, time point, treatment-by-time point interaction, study-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline lipid value and baseline lipid value-by-time point interaction.

For analysis of safety, data were pooled into 2 groups according to the comparator in the individual trials, comprising (1) 5 placebo-controlled trials; and (2) 5 ezetimibe-controlled trials.

Results

Participants and Baseline Characteristics

A total of 4983 patients with inadequately managed hypercholesterolemia were randomized across the 10 trials. Baseline characteristics for the pool of patients analyzed here were reported previously¹⁶ and were generally similar between alirocumab and control patients within each pooled group (Table S1).

Pool 1 included the COMBO I study, which evaluated patients at high risk of ASCVD, and the FH I and FH II studies, which evaluated patients with heterozygous familial

hypercholesterolemia (HeFH). This pool thus included a higher proportion of patients receiving additional nonstatin lipid-lowering therapies and a higher proportion with familial hypercholesterolemia compared with the other pooled groups (Table S1).

Baseline mean LDL-C, non-HDL-C, and apoB levels exceeded National Lipid Association and European Society of Cardiology/European Atherosclerosis Society recommended goals for high-risk hypercholesterolemia patients (100, 130, and 100 mg/dL, respectively) in all pooled groups. Of note, mean baseline levels for these lipid parameters were considerably higher in the group not receiving statin therapy (pool 4) compared with those on statins (pools 1–3; Table S1). Median fasting triglyceride levels at baseline ranged from 111.0 to 147.5 mg/dL across all pooled groups.

Alirocumab dose was increased from 75 mg Q2W to 150 mg Q2W at Week 12 in 34.5% of patients in pool 1 (placebo-controlled, receiving background statins), 17.7% of patients in pool 3 (ezetimibe-controlled, receiving background statins), and 43.9% of patients in pool 4 (ezetimibe-controlled, no background statins). All alirocumab-treated patients in pool 2 received alirocumab 150 mg Q2W from the outset.

Efficacy

Changes in lipid parameters across pooled groups

The baseline levels of each lipid parameter for each of the pools are given in Table S1. Both alirocumab and ezetimibe reduced non-HDL-C and apoB levels from baseline. Patients allocated to placebo (ie, receiving background statin treatment with or without other lipid-lowering therapy only) experienced mild increases in these lipid parameters (Figure 1). In all 4 pools, alirocumab produced superior reductions in non-HDL-C and apoB at 12 and 24 weeks compared with placebo or ezetimibe, irrespective of alirocumab dose or background statin therapy ($P<0.0001$; Figure 1; Table S2). The benefit of alirocumab was apparent from the first lipid measurement (Week 4 for non-HDL-C; Week 12 for apoB) and was sustained throughout the trial periods for both lipid parameters in both the modified ITT (Figure 1) and ITT (Figure S1) population.

Data on other lipid parameters (calculated LDL-C, HDL-C, and fasting triglyceride) from pools 1 to 3 (patients receiving background statins) were reported previously.¹⁵ Briefly, treatment with alirocumab 75/150 mg Q2W or 150 mg Q2W added to statins resulted in significantly reduced LDL-C levels at Week 24 compared with both placebo and ezetimibe in all patient pools ($P<0.0001$; Table S2). In pool 4, in which patients did not receive statins, LDL-C was significantly

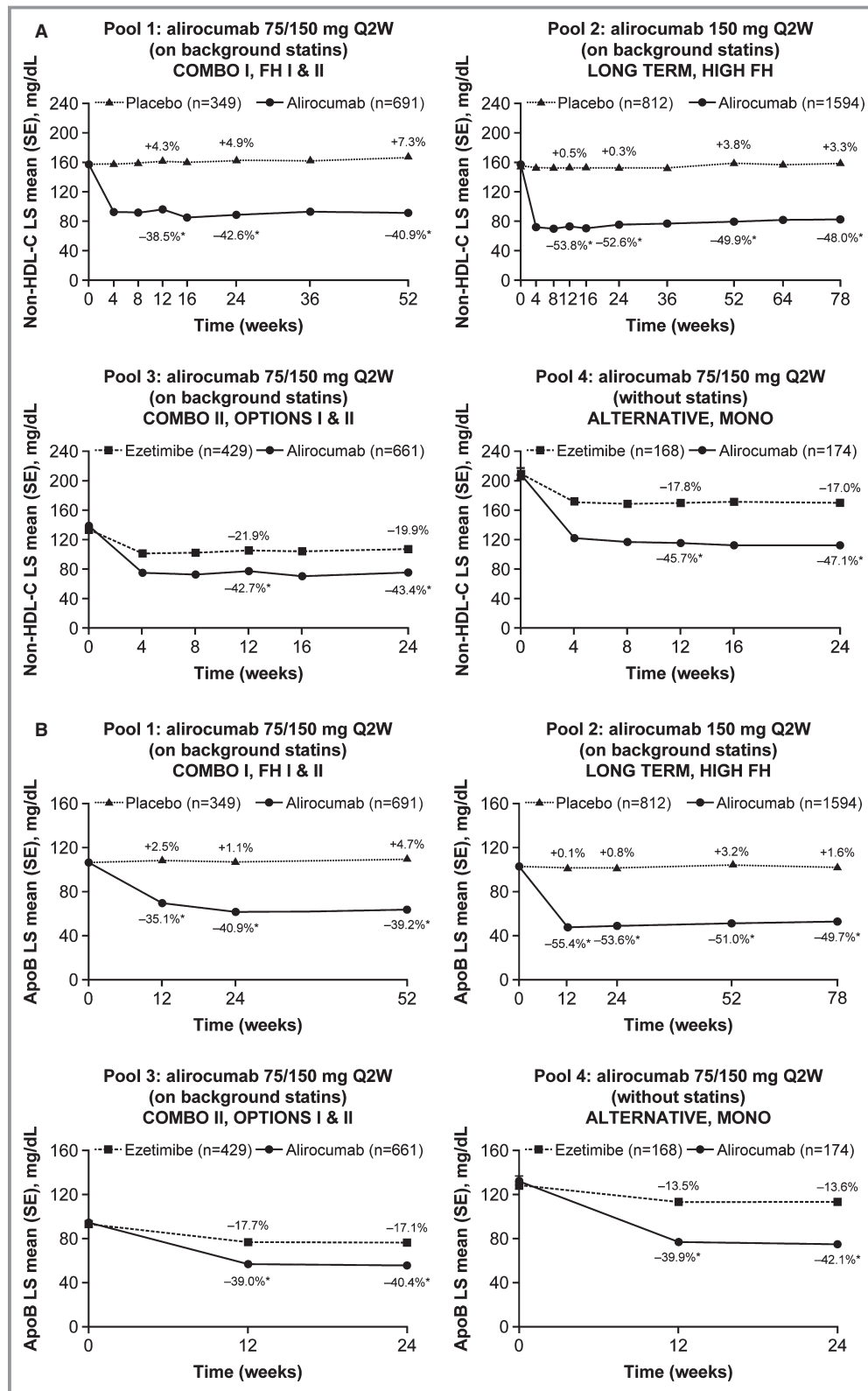


Figure 1. Change in non-HDL-C and apoB levels over time (on-treatment [mITT] population). A, Non-HDL-C. B, ApoB. The percent values represent the percent change from baseline at each time point. * $P < 0.0001$ vs control group. ApoB indicates apolipoprotein B; LS, least squares; mITT, modified intention-to-treat; non-HDL-C, non-high-density lipoprotein cholesterol; Q2W, every 2 weeks; SE, standard error.

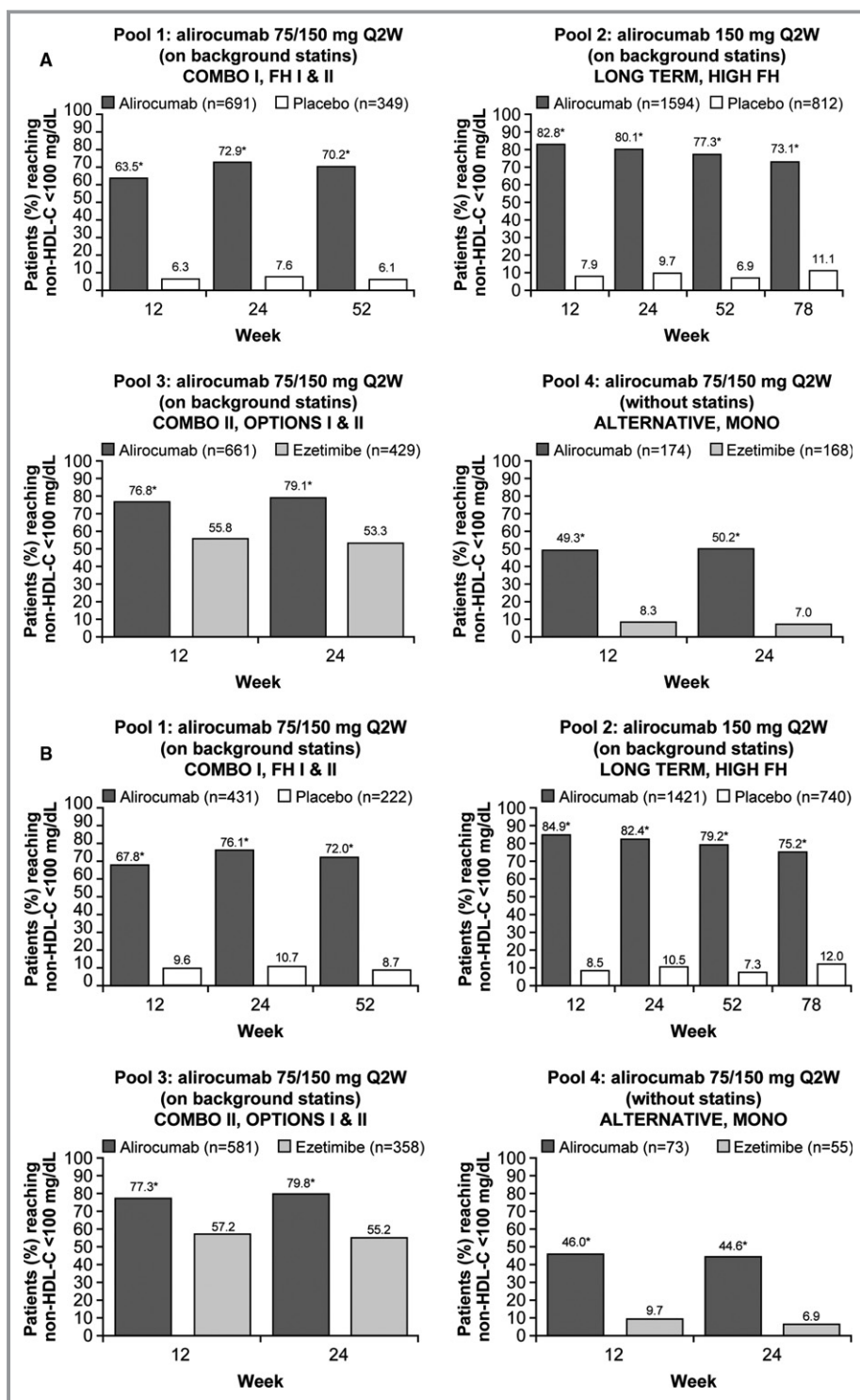


Figure 2. Percent of patients achieving non-HDL-C levels of <100 mg/dL during the studies, overall and by cardiovascular risk (on-treatment [mITT] population). A, All patients (regardless of cardiovascular risk). B, Patients with very-high cardiovascular risk. C, Patients with high cardiovascular risk. * $P < 0.0001$ vs control group at all time points in all study pools and patient categories, except for pool 3 and pool 4 of the “high cardiovascular risk” category where † $P = 0.0030$, ‡ $P = 0.0008$, § $P = 0.0159$, and ¶ $P = 0.0220$. mITT, modified intention-to-treat; non-HDL-C, non-high-density lipoprotein cholesterol; Q2W, every 2 weeks.

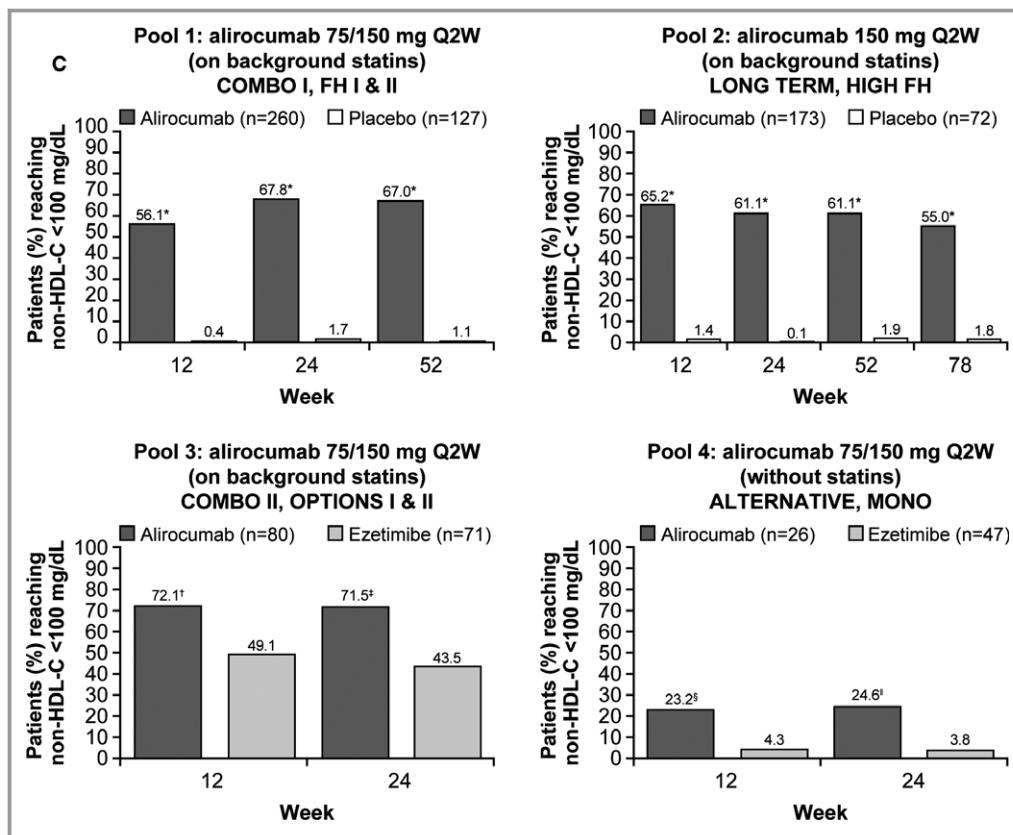


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reduced in the alirocumab 75/150 mg Q2W group versus ezetimibe ($P<0.0001$; Table S2). Alirocumab also produced a significant increase in HDL-C and decrease in fasting triglyceride compared with placebo at Week 24 ($P<0.0001$; Table S2).

Combined data from all patients in all 10 trials showed that average LDL-C, non-HDL-C, and apoB levels were highly correlated with one another throughout the treatment period (Pearson correlation coefficients ≥ 0.922 for the 3 pairwise comparisons comparing LDL-C with either non-HDL-C or apoB and comparing non-HDL-C with apoB; all $P<0.0001$).

Achievement of non-HDL-C and apoB levels corresponding to treatment goals

At 12 and 24 weeks, in all patients pooled regardless of cardiovascular risk categorization, alirocumab allowed a significantly higher percent of patients to achieve levels of non-HDL-C <100 mg/dL, non-HDL-C <130 mg/dL (except for pool 3 at Week 12), and apoB <80 mg/dL compared with placebo or ezetimibe ($P\leq 0.0001$; Figures 2A, 3A, and 4).

Data for each of the 4 individual pools are described as follows.

Pool 1: patients receiving alirocumab 75/150 mg Q2W or placebo with background statins (COMBO I, FH I, and FH II). At Week 12, before the potential protocol-directed alirocumab dose increase, alirocumab 75 mg Q2W allowed 63.5%, 81.5%, and 72.4% of patients to achieve levels of non-HDL-C <100 mg/dL, non-HDL-C <130 mg/dL, and apoB <80 mg/dL, respectively, in all patients pooled regardless of cardiovascular risk categorization (Figures 2A, 3A, and 4). By Week 24, following the potential alirocumab dose increase to 150 mg Q2W at Week 12, the percent of patients achieving these levels rose to 72.9%, 88.0%, and 82.0%, respectively. In contrast, 7.6%, 33.7%, and 18.3% of patients in the placebo group achieved non-HDL-C <100 mg/dL, non-HDL-C <130 mg/dL, and apoB <80 mg/dL levels, respectively, at Week 24 ($P<0.0001$ versus control). When stratified by cardiovascular risk, attainment of specified non-HDL-C goals with alirocumab 75/150 mg Q2W versus placebo in patients with very-high or high cardiovascular risk were in keeping with those observed in the whole population ($P<0.0001$ versus placebo at all time points; Figures 2B, 2C, 3B, and 3C).

Pool 2: patients receiving alirocumab 150 mg Q2W or placebo with background statins (LONG TERM and HIGH FH). The mean percent reductions at 24 weeks in

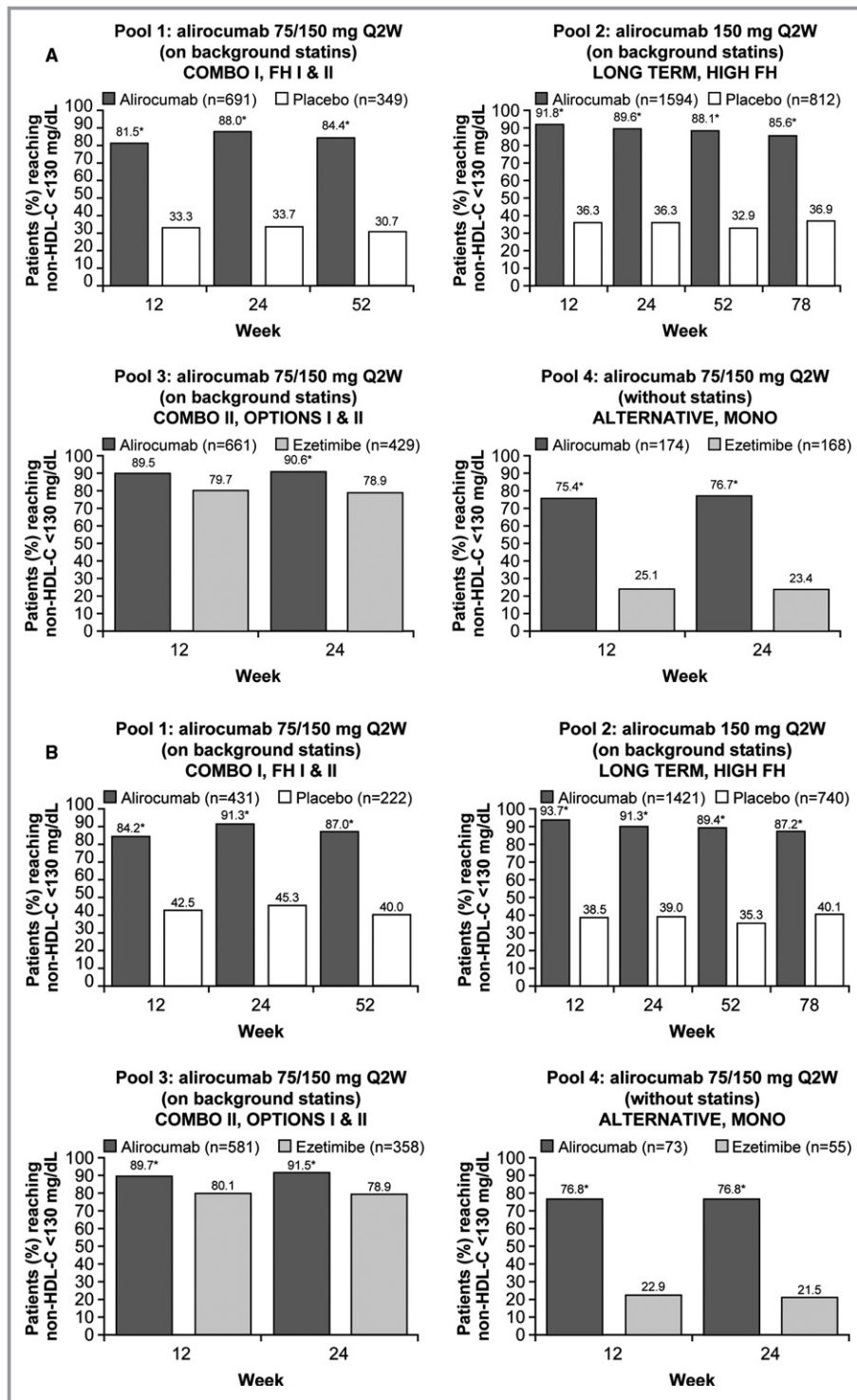


Figure 3. Percent of patients achieving non-HDL-C levels of <130 mg/dL during the studies, overall and by cardiovascular risk (on-treatment [mITT] population). A, All patients (regardless of cardiovascular risk). B, Patients with very-high cardiovascular risk. C, Patients with high cardiovascular risk. * $P < 0.0001$ vs control group at all time points in all study pools and patient categories, except for pool 4 of the “high cardiovascular risk” category where † $P = 0.0049$ and ‡ $P = 0.0018$. mITT, modified intention-to-treat; non-HDL-C, non-high-density lipoprotein cholesterol; Q2W, every 2 weeks.

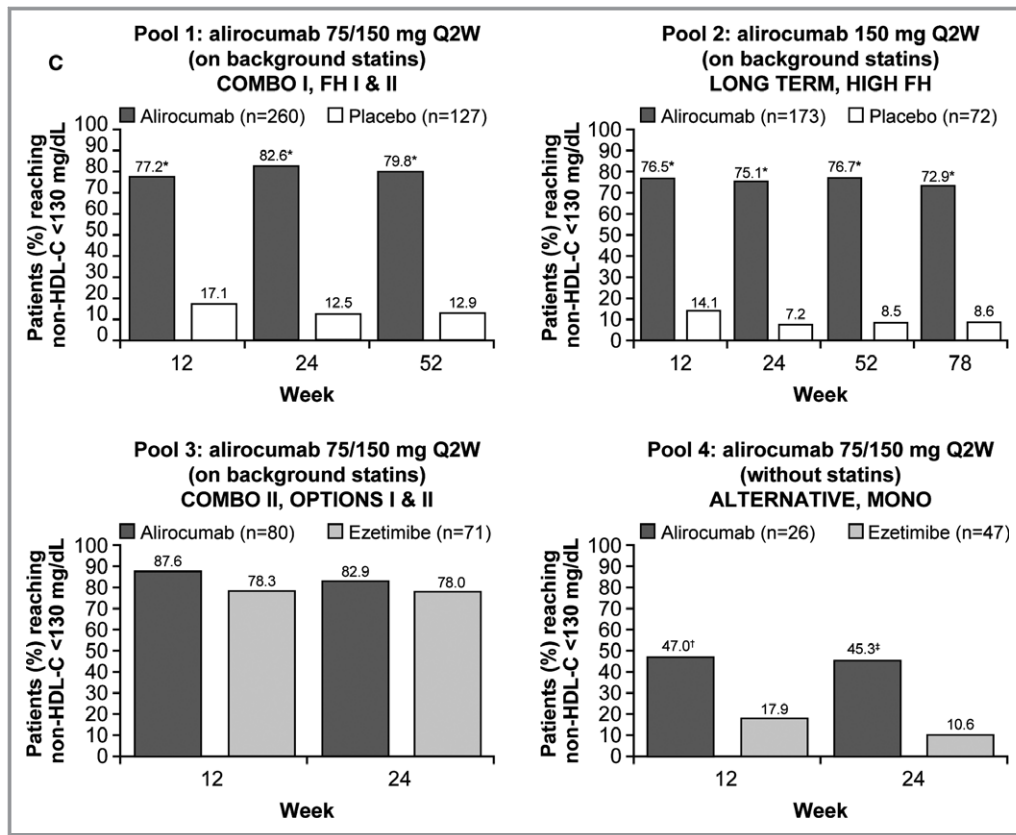


Figure 3. Continued.

non-HDL-C and apoB levels with alirocumab 150 mg Q2W were numerically greater than the corresponding reductions with alirocumab 75/150 mg Q2W observed in other groups (Table S2). In all patients (ie, regardless of cardiovascular risk) alirocumab 150 mg Q2W allowed 82.8% of patients to achieve non-HDL-C <100 mg/dL, with 91.8% achieving non-HDL-C <130 mg/dL and 88.8% achieving apoB <80 mg/dL at Week 12 (Figures 2A, 3A, and 4) compared with 7.9%, 36.3%, and 22.6% of patients who received placebo ($P<0.0001$ versus control). Similar results were obtained when the specified non-HDL-C goal attainments were stratified by cardiovascular risks ($P<0.0001$ versus placebo at all time points; Figures 2B, 2C, 3B, and 3C).

Pool 3: patients receiving alirocumab 75/150 mg Q2W or ezetimibe with background statins (COMBO II, OPTIONS I, and OPTIONS II). Alirocumab allowed 76.8% of all patients (pooled regardless of cardiovascular risk) to achieve non-HDL-C <100 mg/dL at Week 12, rising slightly to 79.1% at Week 24 after the protocol-directed dose increase (Figure 2A). Corresponding values were 89.5% (Week 12) and 90.6% (Week 24) for non-HDL-C <130 mg/dL (Figure 3A), and 83.9% (Week 12) and 85.6% (Week 24) for apoB <80 mg/dL (Figure 4). For each time point, alirocumab allowed a

significantly greater proportion of patients to achieve each of the specified levels than ezetimibe ($P\leq 0.0001$), except at Week 12 (before the potential protocol-directed alirocumab dose increase) for non-HDL-C <130 mg/dL where no significant difference between alirocumab and ezetimibe was found ($P=0.1222$; Figure 3A). In patients with very-high or high cardiovascular risk, achievement of specified non-HDL-C goals were generally higher with alirocumab 75/150 mg Q2W versus ezetimibe at all time points ($P\leq 0.0030$; Figures 2B, 2C, and 3B), except for non-HDL-C <130 mg/dL in patients with high cardiovascular risk where no significant differences between alirocumab and ezetimibe (Figure 3C) were found.

Pool 4: patients receiving alirocumab 75/150 mg Q2W or ezetimibe without background statin (ALTERNATIVE and MONO). The mean percent reductions in non-HDL-C and apoB levels at Week 24 were similar in this group compared with other pools receiving the same alirocumab dose regimen (75/150 mg Q2W; Table S2). However, patients in this pool who were not receiving background statin therapy had higher baseline lipid levels than patients in the pools with background statin (Table S1). Therefore, achievement of the specified lipid levels was less robust in this group (Figures 2A,

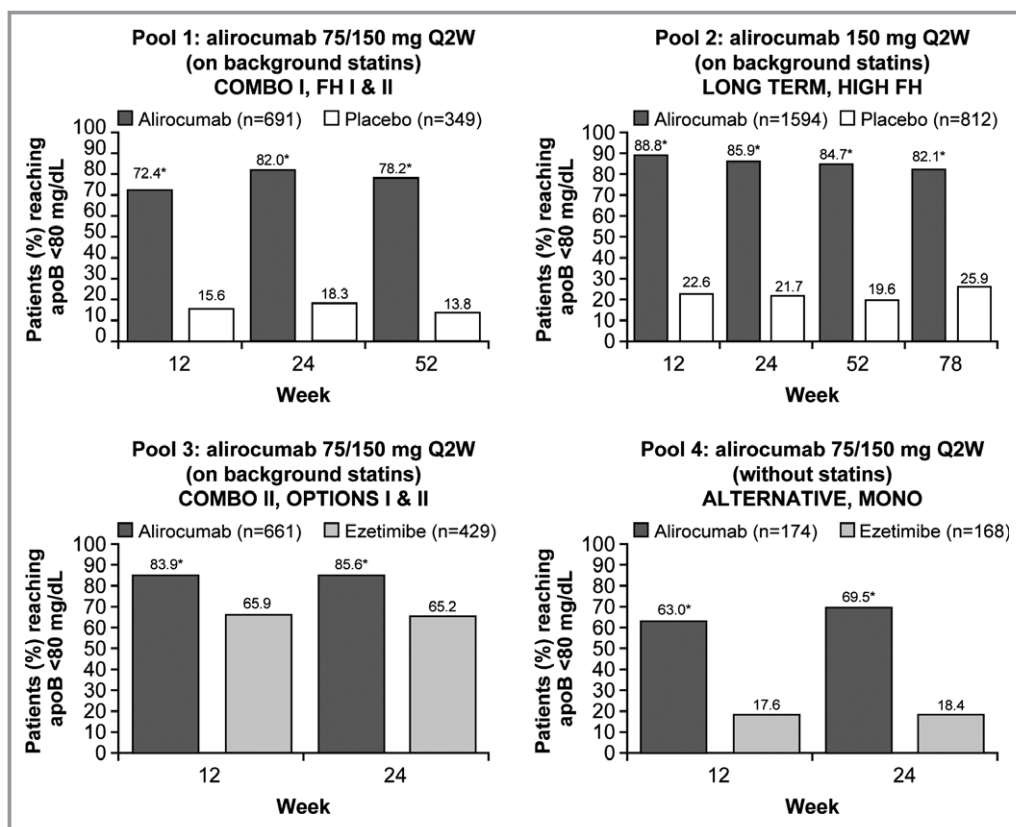


Figure 4. Percent of patients achieving apoB levels <80 mg/dL during the studies (mITT population). * $P < 0.0001$ vs control group at all time points and in all study pools. ApoB indicates apolipoprotein B; mITT, modified intention-to-treat; Q2W, every 2 weeks.

3A, and 4). Nevertheless, alirocumab allowed significantly more patients (regardless of cardiovascular risk) to achieve the specified non-HDL-C and apoB levels compared with ezetimibe ($P < 0.0001$; Figures 2A, 3A, and 4). Similar results were reported with alirocumab 75/150 mg Q2W in patients with very-high or high cardiovascular risk for specified non-HDL-C goals ($P \leq 0.0220$ versus ezetimibe; Figures 2B, 2C, 3B, and 3C). Corresponding results for all goal achievement data analyzed using the ITT population (Figures S2 through S4) were generally similar to the aforementioned results analyzed using the on-treatment (modified ITT) population.

Safety

Safety data for alirocumab across 14 Phase 2 and Phase 3 studies were previously reported,^{17,18} as were data from the 10 Phase 3 ODYSSEY studies included in the present analysis.^{16,18} In the 10 Phase 3 studies evaluating Q2W doses of alirocumab, the overall rates of TEAEs, serious TEAEs, and discontinuations because of TEAEs were similar for alirocumab versus control (Table S3). More patients experienced injection-site reactions in the alirocumab group compared with placebo (placebo-controlled studies:

alirocumab 7.2% versus 5.3% for placebo; ezetimibe-controlled studies: alirocumab 2.9% versus 2.1% for ezetimibe; Table S3).

Discussion

Non-HDL-C provides a measure of the cholesterol content of all pro-atherogenic particles including LDL-C, very low-density lipoprotein cholesterol, intermediate-density lipoprotein cholesterol, remnant lipoproteins, and lipoprotein (a). One molecule of apoB resides on each atherogenic lipoprotein.¹⁹ Therefore, in current US National Lipid Association recommendations and European guidelines, both non-HDL-C and apoB are considered important lipid treatment targets alongside LDL-C.^{3,4}

This analysis examined the effects of alirocumab on non-HDL-C and apoB from 10 ODYSSEY Phase 3 studies including 4983 patients with hypercholesterolemia, pooled into 4 groups according to dose of alirocumab, use of background statin therapy, and study control (placebo or ezetimibe). Alirocumab produced robust and sustainable reductions in non-HDL-C and apoB levels, as well as in LDL-C (the primary endpoint of the studies), and average non-HDL-C and apoB

levels highly correlated with average LDL-C throughout the treatment period. Compared with ezetimibe, treatment with alirocumab more than doubled the least-squares mean reduction in non-HDL-C and apoB levels. Substantial reductions were irrespective of concomitant statin therapy and alirocumab dose regimen (75/150 mg Q2W or 150 mg Q2W). Moreover, the effect of alirocumab was evident upon the first assessment from 4 weeks, and was sustained throughout the studies.

In addition, alirocumab allowed a high percentage of patients to achieve non-HDL-C and apoB levels that correspond to guideline-directed goals, which were sustained throughout the studies. For example, compared with statins alone (ie, in patients receiving placebo), alirocumab allowed a more than 2-fold higher achievement of non-HDL-C levels of <130 mg/dL and an almost 10-fold higher achievement of the more stringent non-HDL-C target of <100 mg/dL at Week 24. Moreover, in the absence of background statins, alirocumab produced an almost 3-fold increase in the percent of patients achieving non-HDL-C <130 mg/dL and an almost 6-fold increase in the percent achieving <100 mg/dL compared with ezetimibe. With concomitant statin therapy, alirocumab also allowed a significantly greater percentage of patients to achieve the specified non-HDL-C levels than ezetimibe. These were consistent overall with the results from analysis where patients were grouped according to cardiovascular risk categories. Results from the present analysis are in general agreement with achievement of LDL-C goals in a previous analysis of 8 ODYSSEY studies in patients receiving concomitant statin (corresponding to pools 1–3 in the current analysis).⁹ In that analysis, LDL-C goal attainment was investigated in patients grouped according to whether the patient was at very high (LDL-C goal <70 mg/dL) or high risk (goal <100 mg/dL) and overall 75.2–79.0% of patients achieved these risk-based LDL-C goals.¹⁵

LDL-C in isolation may be an inadequate measure of total ASCVD risk, as it fails to account for cholesterol carried by other lipoproteins, such as triglyceride-rich lipoproteins. When triglyceride levels are high, the levels of remnant atherogenic lipoproteins are also elevated; in these circumstances, the risk predicted by LDL-C alone is underestimated.¹ In addition, discordance between LDL-C, non-HDL-C, and apoB levels may exist in a significant proportion of patients with dyslipidemia, including those with metabolic syndrome, type 2 diabetes mellitus, and obesity.^{20–22} For example, the Very Large Database of Lipids 2 study showed that, among patients achieving an LDL-C goal of ≤ 70 mg/dL, 15% may still have a non-HDL-C level ≥ 100 mg/dL, increasing to 22% among patients with high triglyceride levels (150–199 mg/dL).²²

Such discordance means that residual ASCVD risk may be overlooked with LDL-C-centric treatment.¹ A number of studies have demonstrated that non-HDL-C and apoB are

superior markers of ASCVD risk compared with LDL-C alone.^{19,23–29} Indeed, some studies suggest that apoB levels may have the strongest association with risk.^{23,24,26}

Because most ASCVD outcomes trials have utilized LDL-C as the primary lipid outcome parameter, the conclusions of the current analysis are limited by the lack of studies demonstrating the correlation of non-HDL-C or apoB levels as a primary endpoint with ASCVD risk. Nevertheless, a meta-analysis of ASCVD outcomes trials has supported the association between reduced non-HDL-C and apoB levels with reduced ASCVD events.³⁰ Moreover, the randomized, double-blind Helsinki Heart study, one of the few ASCVD outcomes studies that evaluated non-HDL-C as the primary lipid outcome, demonstrated an association between reduction in non-HDL-C levels and cardiovascular events.³¹ Furthermore, a recently published post-hoc analysis from the 10 ODYSSEY trials used in the present study showed that reductions in non-HDL-C and apoB were associated with improved cardiovascular outcomes, regardless of the treatment received during the trials.³²

At the time of writing, the correlation between the lipid effects of alirocumab and ASCVD events are unproven. However, the ongoing ODYSSEY OUTCOMES trial (NCT01663402) is evaluating the potential benefits of alirocumab in reducing major cardiovascular events in patients with acute coronary syndrome within 1 year who have not achieved lipid management goals with intense statin therapy.

Conclusion

Non-HDL-C and apoB are useful in assessment of ASCVD risk, and are specified as treatment targets by international lipid guidelines. Data from this analysis of 4983 patients derived from 4 pooled groups support the role of alirocumab in effectively reducing levels of non-HDL-C, and apoB levels, as well as allowing substantially better achievement of non-HDL-C and apoB levels that correspond to guideline-directed goals compared with placebo or ezetimibe.

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Supplemental Material

Data S1.

Supplemental Methods

Definition of cardiovascular risk in the Phase 3 studies included in this analysis

The definition of cardiovascular risk and corresponding LDL-C targets in the Phase 3 studies included in this analysis were based on US and EU guidelines in effect at the time of clinical development plan finalization of each studies with focus on coronary heart disease (CHD) and CHD risk equivalents. In FH I, FH II, HIGH FH, OPTIONS I, and OPTIONS II, patients with CHD (including acute or silent myocardial infarction, unstable angina, coronary revascularization procedure, or other clinically significant CHD) or CHD risk equivalent (including peripheral arterial disease [PAD], ischemic stroke, moderate chronic kidney disease, and known history of diabetes mellitus and ≥ 2 additional risk factors) were categorized as having very-high cardiovascular risk; all other patients were included in the “high cardiovascular risk” category.

In LONG TERM, heterozygous familial hypercholesterolemia (HeFH) patients with CHD or CHD risk equivalents (as defined above) and non-familial hypercholesterolemia patients were included in the “very-high cardiovascular risk” category (as defined above); all other patients were included in the “high cardiovascular risk” category (as defined above). All patients from COMBO I and COMBO II were assigned to the “very-high cardiovascular risk” category (as defined above), whereas patients from MONO were assigned to the “moderate cardiovascular risk” category defined as a 10 year risk Systematic Coronary Risk Estimation (SCORE) of $\geq 1\%$ and $< 5\%$.

In ALTERNATIVE, very-high cardiovascular risk was defined as any documented history of CHD (defined above), ischemic stroke, PAD, transient ischemic attack, abdominal aortic aneurysm, carotid artery occlusion >50% without symptoms, carotid endarterectomy or carotid artery stent procedure, renal artery stenosis, renal stent procedure, or diabetes with target organ damages. Furthermore, in ALTERNATIVE, high cardiovascular risk was defined as a calculated 10-year fatal cardiovascular disease risk SCORE of $\geq 5\%$, moderate chronic kidney disease, HeFH with no history of CHD or CHD risk equivalent, and diabetes without target organ damages. Moderate cardiovascular disease was defined as a above.

Table S1. Overview of studies included in the pooled analysis and baseline characteristics (n=4983 patients with hypercholesterolemia)

	Pool 1 (3 studies)		Pool 2 (2 studies)		Pool 3 (3 studies)		Pool 4 (2 studies)	
Studies	1. COMBO I (NCT01644175) <ul style="list-style-type: none"> • 52 weeks* • Alirocumab, n=209 • Placebo, n=107 2. FH I (NCT01623115) <ul style="list-style-type: none"> • 78 weeks* • Alirocumab, n=323 • Placebo, n=163 3. FH II (NCT01709500) <ul style="list-style-type: none"> • 78 weeks* • Alirocumab, n=167 • Placebo, n=82 		1. LONG TERM (NCT01507831) <ul style="list-style-type: none"> • 78 weeks* • Alirocumab, n=1553 • Placebo, n=788 2. HIGH FH (NCT01617655) <ul style="list-style-type: none"> • 78 weeks* • Alirocumab, n=72 • Placebo, n=35 		1. COMBO II (NCT01644188) <ul style="list-style-type: none"> • 104 weeks*[†] • Alirocumab, n=479 • Ezetimibe, n=241 2. OPTIONS I (NCT01730040) <ul style="list-style-type: none"> • 24 weeks[‡] • Alirocumab, n=104 • Ezetimibe, n=102 3. OPTIONS II (NCT01730053) <ul style="list-style-type: none"> • 24 weeks[‡] • Alirocumab, n=103 • Ezetimibe, n=101 		1. ALTERNATIVE (NCT01709513) <ul style="list-style-type: none"> • 24 weeks • Alirocumab, n=126 • Ezetimibe, n=125 2. MONO (NCT01644474) <ul style="list-style-type: none"> • 24 weeks • Alirocumab, n=52 • Ezetimibe, n=51 	
Alirocumab dose	75/150 mg Q2W [§]		150 mg Q2W		75/150 mg Q2W [§]		75/150 mg Q2W [§]	
Statin/other LLT	Concomitant statin ± other LLT		Concomitant statin ± other LLT		Concomitant statin ± other LLT		No concomitant statin	
Baseline characteristics Value is mean (SD) unless stated otherwise	Alirocumab (n=699)	Placebo (n=352)	Alirocumab (n=1625)	Placebo (n=823)	Alirocumab (n=686)	Ezetimibe (n=444)	Alirocumab (n=178)	Ezetimibe (n=176)
Age, years	55.6 (12.9)	55.5 (12.5)	60.0 (10.8)	60.2 (10.6)	61.6 (9.7)	62.3 (9.7)	63.1 (8.1)	61.9 (9.1)
Male, n (%)	397 (56.8)	216 (61.4)	1018 (62.6)	496 (60.3)	483 (70.4)	294 (66.2)	98 (55.1)	94 (53.4)
Race, white, n (%)	634 (90.7)	312 (88.6)	1505 (92.6)	760 (92.3)	582 (84.8)	385 (86.7)	163 (91.6)	163 (92.6)
BMI, kg/m ²	30.0 (5.5)	30.1 (6.0)	30.1 (5.7)	30.5 (5.4)	30.3 (5.9)	30.7 (5.6)	29.7 (6.4)	28.4 (5.5)

CV risk per protocol, n (%) [#]								
High	261 (37.3)	128 (36.4)	174 (10.7)	72 (8.7)	85 (12.4)	73 (16.4)	29 (16.3)	47 (26.7)
Very-high	438 (62.7)	224 (63.6)	1451 (89.3)	751 (91.3)	601 (87.6)	371 (83.6)	73 (41.0)	62 (35.2)
HeFH, n (%)	490 (70.1)	245 (69.6)	348 (21.4)	174 (21.1)	26 (3.8)	18 (4.1)	14 (7.9)	25 (14.2)
Patients on statin, n (%)	697 (99.7)	352 (100.0)	1624 (99.9)	822 (99.9)	685 (99.9)	444 (100.0)	3 (1.7)	10 (5.7)
Patients on LLTs other than statin, n (%)	395 (56.5)	217 (61.6)	487 (30.0)	244 (29.6)	74 (10.8)	54 (12.2)	51 (28.7)	66 (37.5)
Non-HDL-C, mg/dL	155.5 (50.0)	155.8 (48.4)	155.8 (49.4)	155.4 (48.6)	139.3 (39.7)	135.4 (41.8)	211.7 (75.1)	210.8 (77.4)
ApoB, mg/dL	106.1 (29.3)	105.6 (27.8)	103.5 (28.9)	103.3 (28.8)	94.3 (23.0)	92.3 (23.5)	131.0 (38.7)	128.6 (36.6)
LDL-C, calculated, mg/dL	129.0 (47.3)	130.3 (45.4)	125.9 (45.9)	125.3 (44.5)	109.4 (35.6)	105.0 (36.2)	176.5 (66.8)	177.4 (66.0)
HDL-C, mg/dL	50.5 (15.4)	49.7 (14.4)	49.8 (12.3)	49.8 (12.4)	48.0 (13.2)	48.3 (13.1)	50.5 (15.7)	53.3 (16.3)
Fasting TG, mg/dL (median [Q1–Q3])	114.0 (85.0–161.0)	111.0 (86.0–156.0)	132.0 (93.8–182.3)	134.5 (94.7–188.5)	129.0 (96.0–185.0)	134.0 (97.0–187.0)	147.5 (105.0–218.0)	130.0 (89.5–201.5)

Efficacy data were pooled according to study design.

*Concomitant statin at maximally tolerated doses (defined as atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg; lower doses were allowed with an investigator-approved reason).

†No concomitant non-statin LLT allowed in COMBO II.

‡Concomitant statin and doses in OPTIONS I were atorvastatin 20 or 40 mg, and rosuvastatin 10 or 20 mg in OPTIONS II. Concomitant treatment with other statins, ezetimibe, fibrates (other than fenofibrate), and red yeast rice products was prohibited.

§75/150 mg Q2W indicates starting dose of 75 mg Q2W increasing to 150 mg Q2W at Week 12, if pre-specified LDL-C goal was not met at Week 8.

^lConcomitant non-statin LLT (excluding ezetimibe) allowed in ALTERNATIVE; no concomitant LLT allowed in MONO.

[#]Excludes patients with moderate CV risk from the ALTERNATIVE and MONO pools (71 and 65 patients for alirocumab and ezetimibe, respectively).

Apo, apolipoprotein; BMI, body mass index; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolemia; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; non-HDL-C, non-high-density lipoprotein cholesterol; Q1, 25th percentile; Q2W, every 2 weeks; Q3, 75th percentile; SD, standard deviation; TG, triglyceride.

n = number of patients in ITT population.

For a more detailed report of the baseline characteristics of the patients included in the pooled analysis, please see ^{1,2} (<http://dx.doi.org/10.1016/j.ijcard.2016.08.273>, <http://dx.doi.org/10.1016/j.amjcard.2016.09.010>)

Table S2. Change from baseline in lipid parameters at Week 24 (ITT population)

Value (LS mean % [SE] change, unless stated otherwise)	Pool 1: alirocumab 75/150 mg Q2W (on background statins) COMBO I, FH I & II		Pool 2: alirocumab 150 mg Q2W (on background statins) LONG TERM, HIGH FH		Pool 3: alirocumab 75/150 mg Q2W (on background statins) COMBO II, OPTIONS I & II		Pool 4: alirocumab 75/150 mg Q2W (without statins) ALTERNATIVE, MONO	
	Alirocumab (n=693)	Placebo (n=350)	Alirocumab (n=1601)	Placebo (n=815)	Alirocumab (n=669)	Ezetimibe (n=436)	Alirocumab (n=178)	Ezetimibe (n=173)
Calculated LDL-C	-48.6 (1.0)	4.2 (1.5)	-60.4 (0.7)	0.5 (1.0)	-48.9 (1.4)	-19.3 (1.7)	-45.6 (1.8)	-14.8 (1.8)
LS mean difference vs comparator (95% CI)	-52.7 (-56.3 to -49.2)		-60.9 (-63.3 to -58.5)		-29.6 (-33.8 to -25.3)		-30.9 (-35.9 to -25.9)	
<i>P</i> -value vs comparator	<0.0001		<0.0001		<0.0001		<0.0001	
Non-HDL-C	-41.7 (1.0)	4.7 (1.3)	-51.1 (0.6)	0.4 (0.9)	-41.1 (1.1)	-17.8 (1.4)	-40.4 (1.5)	-14.7 (1.5)
LS mean difference vs comparator (95% CI)	-46.4 (-49.6 to -43.2)		-51.6 (-53.7 to -49.5)		-23.3 (-26.8 to -19.9)		-25.7 (-29.8 to -21.6)	
<i>P</i> -value vs comparator	<0.0001		<0.0001		<0.0001		<0.0001	
ApoB	-40.2 (0.8)	1.0 (1.1)	-52.2 (0.7)	0.7 (0.9)	-38.6 (1.0)	-15.9 (1.2)	-36.5 (1.4)	-11.2 (1.4)
LS mean difference vs comparator (95% CI)	-41.3 (-44.0 to -38.6)		-52.9 (-55.2 to -50.7)		-22.7 (-25.8 to -19.6)		-25.3 (-29.1 to -21.5)	
<i>P</i> -value vs comparator	<0.0001		<0.0001		<0.0001		<0.0001	
HDL-C	6.6 (0.6)	-1.0 (0.8)	4.1 (0.4)	-0.4 (0.5)	8.1 (0.7)	0.8 (0.8)	7.2 (1.3)	5.3 (1.3)
LS mean difference vs comparator (95% CI)	7.6 (5.6 to 9.6)		4.5 (3.3 to 5.8)		7.4 (5.3 to 9.4)		1.9 (-1.7 to 5.6)	

<i>P</i> -value vs comparator	<0.0001		<0.0001		<0.0001		0.3059	
Fasting TG (combined estimate for adjusted mean [SE] % change)	-8.9 (1.1)	1.4 (1.5)	-15.3 (0.8)	1.7 (1.1)	-13.0 (1.2)	-11.2 (1.5)	-10.3 (2.2)	-6.0 (2.3)
Combined estimate for adjusted mean difference vs comparator (95% CI)	-10.3 (-14.0 to -6.6)		-17.0 (-19.7 to -14.3)		-1.7 (-5.4 to 2.0)		-4.3 (-10.6 to 2.0)	
<i>P</i> -value	<0.0001		<0.0001		0.3556		0.1827	

Apo, apolipoprotein; CI, confidence interval; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least squares; non-HDL-C, non-high-density lipoprotein cholesterol; Q2W, every 2 weeks; SE, standard error; TG, triglyceride.

Data in patients receiving background statin therapy (pools 1 to 3) have been reported previously

Table S3. Safety analysis (pool of 10 Phase 3 trials*)

n (%)	Placebo-controlled trials		Ezetimibe-controlled trials	
	Alirocumab (n=2318)	Placebo (n=1174)	Alirocumab (n=864)	Ezetimibe (n=618)
Patients with any TEAE	1851 (79.9)	954 (81.3)	657 (76.0)	457 (73.9)
Patients with any serious TEAE	385 (16.6)	202 (17.2)	147 (17.0)	86 (13.9)
Patients with any TEAE leading to death	16 (0.7)	13 (1.1)	6 (0.7)	9 (1.5)
Patients with any TEAE leading to permanent treatment discontinuation	144 (6.2)	67 (5.7)	84 (9.7)	66 (10.7)
TEAE occurring in ≥5% of patients in any pool				
Nasopharyngitis	291 (12.6)	142 (12.1)	52 (6.0)	41 (6.6)
Upper respiratory tract infection	162 (7.0)	94 (8.0)	62 (7.2)	40 (6.5)
Myalgia	111 (4.8)	46 (3.9)	62 (7.2)	48 (7.8)
Injection site reaction	167 (7.2)	62 (5.3)	25 (2.9)	13 (2.1)
Arthralgia	118 (5.1)	76 (6.5)	42 (4.9)	26 (4.2)
Accidental overdose	30 (1.3)	17 (1.4)	54 (6.3)	24 (3.9)
Influenza	147 (6.3)	63 (5.4)	37 (4.3)	23 (3.7)
Back pain	123 (5.3)	70 (6.0)	33 (3.8)	26 (4.2)
Headache	119 (5.1)	64 (5.5)	43 (5.0)	24 (3.9)
Urinary tract infection	128 (5.5)	65 (5.5)	21 (2.4)	25 (4.0)
Diarrhea	123 (5.3)	57 (4.9)	30 (3.5)	21 (3.4)

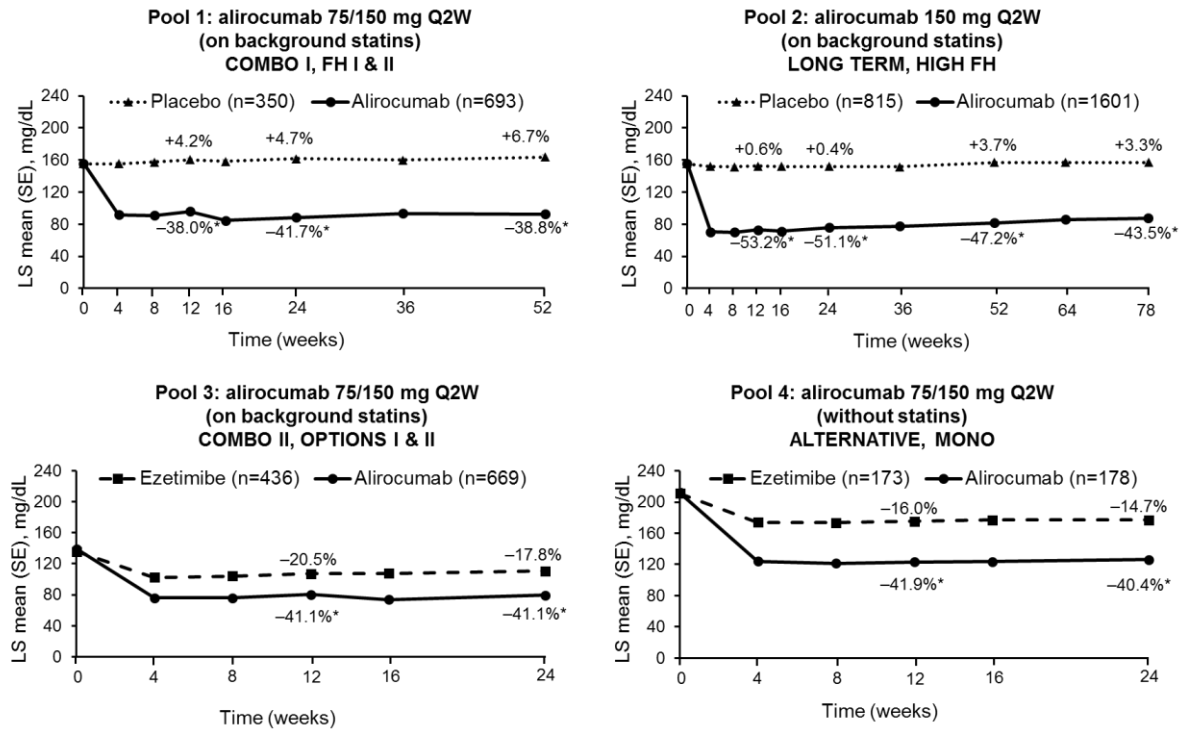
*Placebo-controlled studies include COMBO I, FH I, FH II, LONG TERM, HIGH FH; ezetimibe-controlled studies include COMBO II, OPTIONS I, OPTIONS II, ALTERNATIVE, MONO.

TEAE, treatment-emergent adverse event.

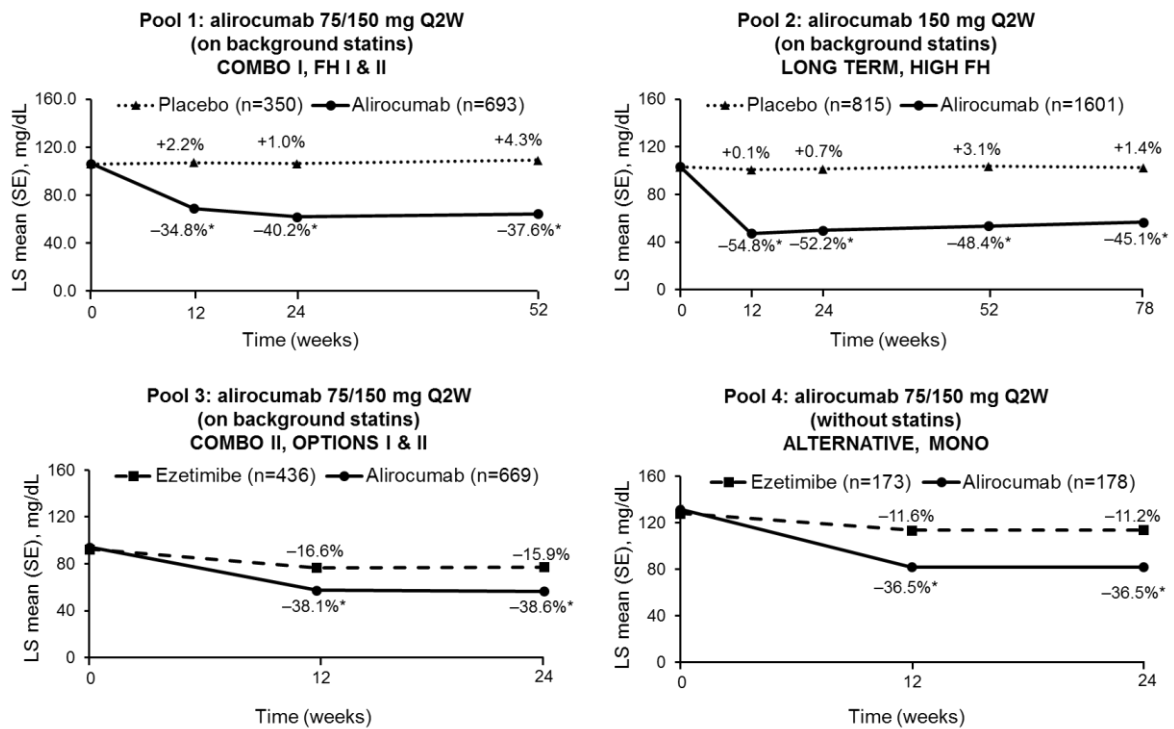
Adapted with permission from Gaudet et al.²

Figure S1. Change in non-HDL-C and apoB levels over time (ITT population)

(A) Non-HDL-C



(B) ApoB



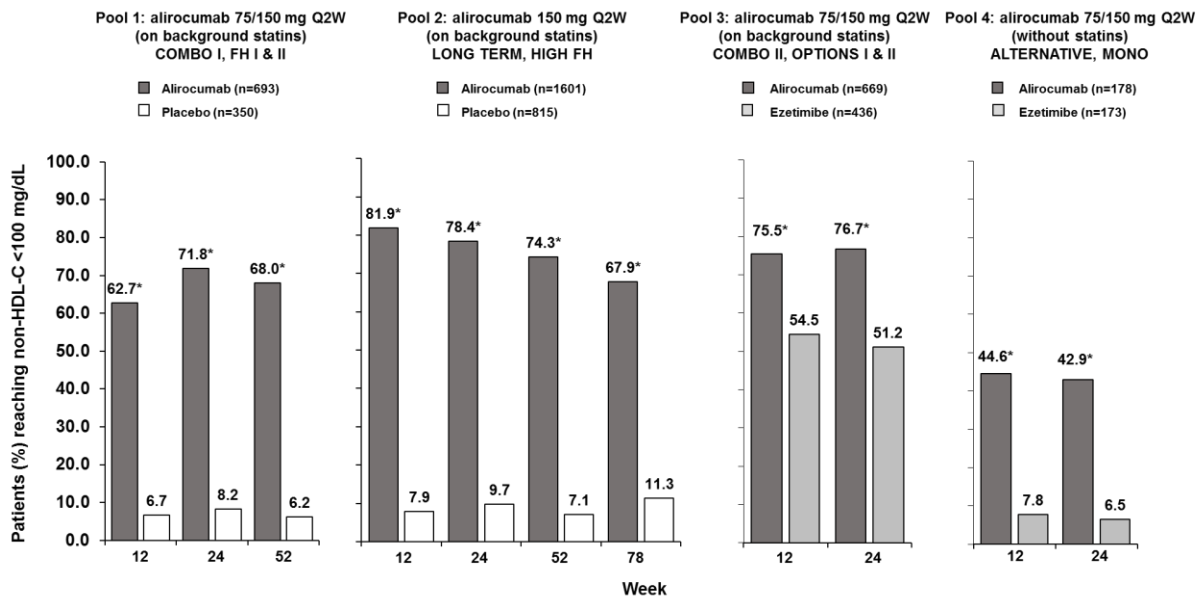
The percent values represent the percent change from baseline at each time point.

* $P < 0.0001$ versus control group.

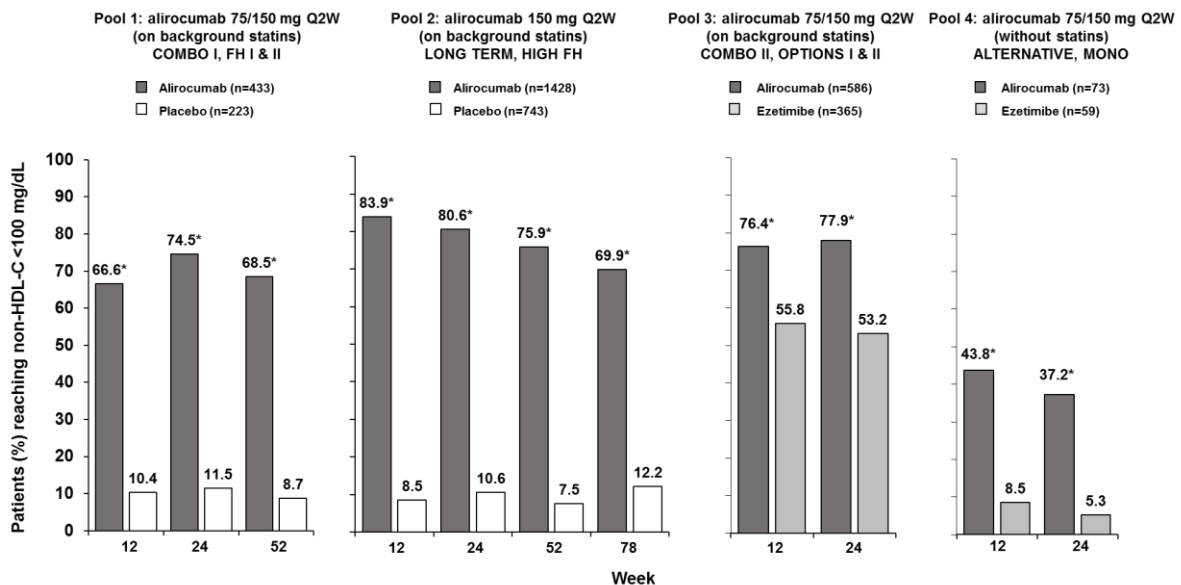
ApoB, apolipoproteinB; ITT, intention-to-treat; LS, least squares; non-HDL-C, high-density lipoprotein cholesterol; Q2W, every 2 weeks; SE, standard error.

Figure S2. Percent of patients achieving non-HDL-C levels of <100 mg/dL during the studies, overall and by cardiovascular risk (ITT population)

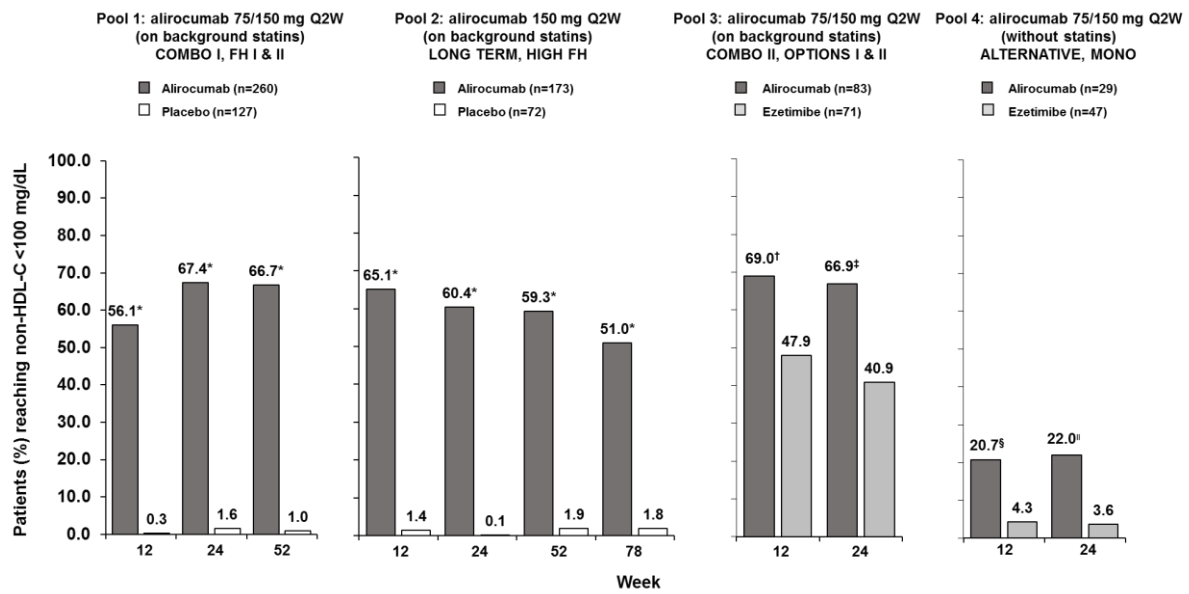
(A) All patients (regardless of cardiovascular risk)



(B) Patients with very-high cardiovascular risk



(C) Patients with high cardiovascular risk

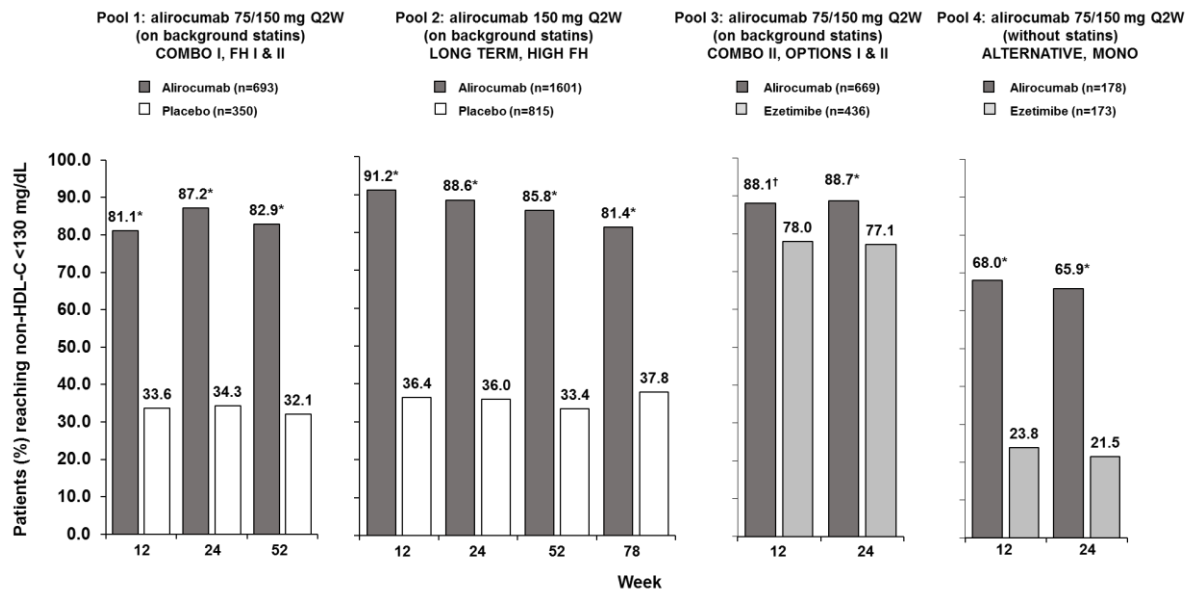


* $P < 0.0001$ versus control group at all time points in all study pools and patient categories, except for pool 3 and pool 4 of the 'high cardiovascular risk' category where [†] $P = 0.0050$, [‡] $P = 0.0015$, [§] $P = 0.0187$, and ^{||} $P = 0.0249$.

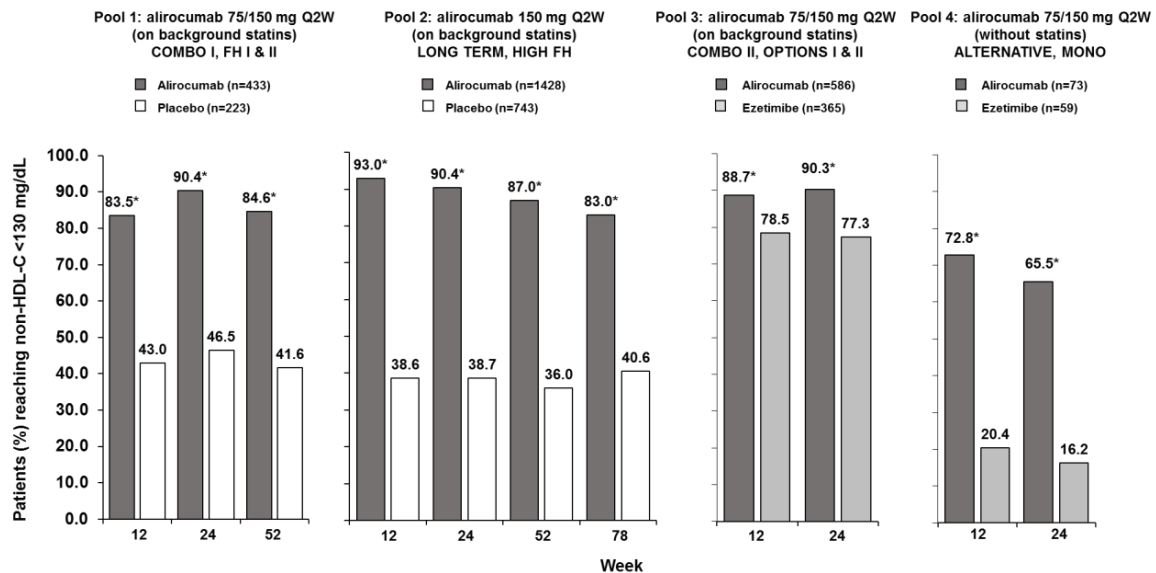
ITT, intention-to-treat; non-HDL-C, high-density lipoprotein cholesterol; Q2W, every 2 weeks.

Figure S3. Percent of patients achieving non-HDL-C levels of <130 mg/dL during the studies, overall and by cardiovascular risk (ITT population)

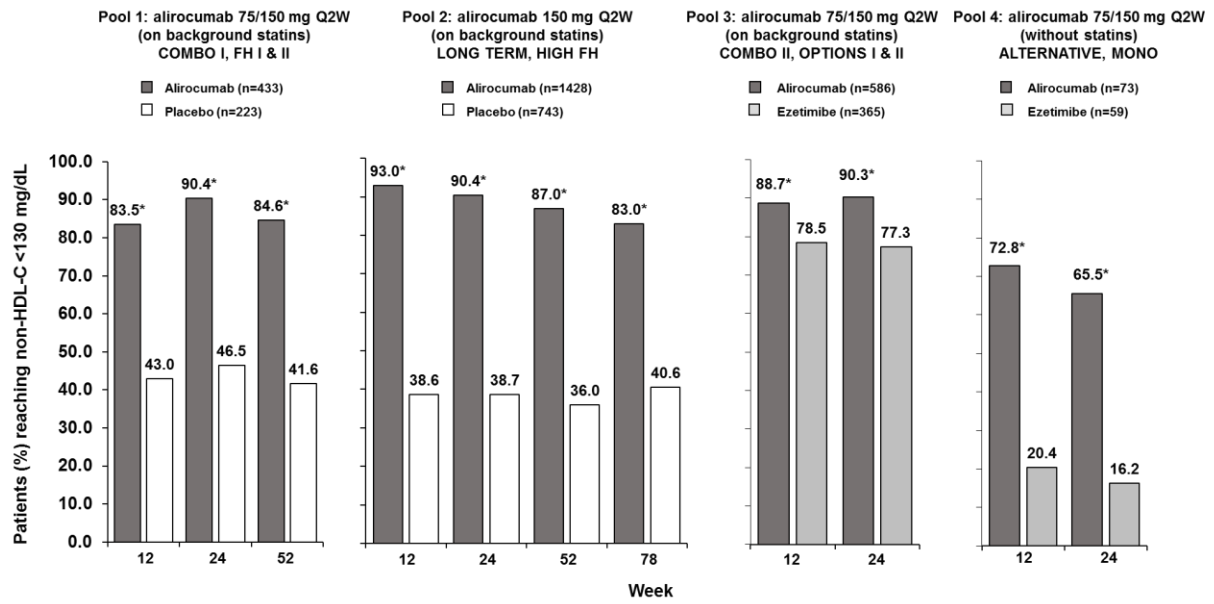
(A) All patients (regardless of cardiovascular risk)



(B) Patients with very-high cardiovascular risk



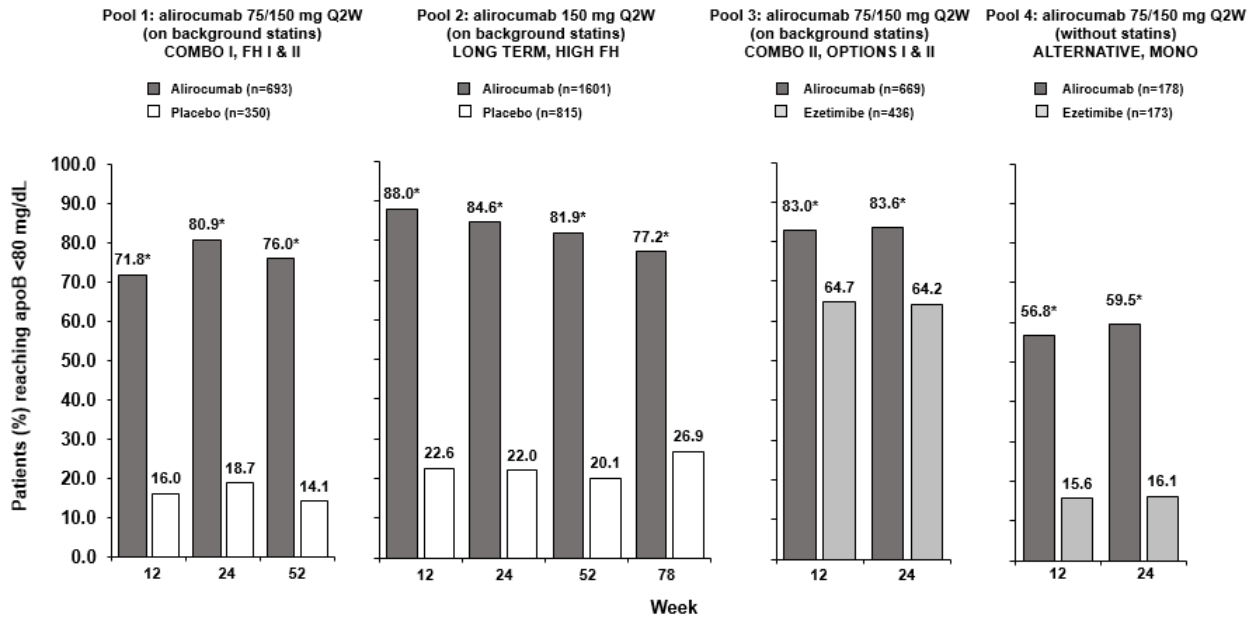
(C) Patients with high cardiovascular risk



* $P < 0.0001$ versus control group at all time points in all study pools and patients categories, except for pool 3 of the “all patients” category where † $P = 0.0002$ and pool 4 of the ‘high cardiovascular risk’ category where ‡ $P = 0.0063$ and § $P = 0.0058$.

ITT, intention-to-treat, non-HDL-C, non-high-density lipoprotein cholesterol; Q2W, every 2 weeks.

Figure S4. Percent of patients achieving apoB levels <80 mg/dL during the studies (ITT population)



* $P < 0.0001$ versus control group at all time points and in all study pools.

ApoB, apolipoproteinB; ITT, intention-to-treat; Q2W, every 2 weeks.

Supplemental References:

1. Farnier M, Gaudet D, Valcheva V, Minini P, Miller K, Cariou B. Efficacy of alirocumab in high cardiovascular risk populations with or without familial hypercholesterolemia: Pooled analysis of eight ODYSSEY Phase 3 clinical program trials. *Int J Cardiol.* 2016;223:750-757.
2. Gaudet D, Watts GF, Robinson JG, Minini P, Sasiela WJ, Edelberg J, Louie MJ, Raal FJ. Effect of alirocumab on lipoprotein(a) over ≥ 1.5 years (from the Phase 3 ODYSSEY program). *Am J Cardiol.* 2017;119:40-46.



Alirocumab Treatment and Achievement of Non–High–Density Lipoprotein Cholesterol and Apolipoprotein B Goals in Patients With Hypercholesterolemia: Pooled Results From 10 Phase 3 ODYSSEY Trials

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