Alirocumab as Add-On to Atorvastatin Versus Other Lipid Treatment Strategies: ODYSSEY OPTIONS I Randomized Trial

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Context: Despite current standard of care, many patients at high risk of cardiovascular disease (CVD) still have elevated low-density lipoprotein cholesterol (LDL-C) levels. Alirocumab is a fully human monoclonal antibody inhibitor of proprotein convertase subtilisin/kexin type 9.

Objective: The objective of the study was to compare the LDL-C-lowering efficacy of adding alirocumab vs other common lipid-lowering strategies.

Design, Patients, and Interventions: Patients (n = 355) with very high CVD risk and LDL-C levels of 70 mg/dL or greater or high CVD risk and LDL-C of 100 mg/dL or greater on baseline atorvastatin 20 or 40 mg were randomized to one of the following: 1) add-on alirocumab 75 mg every 2 weeks (Q2W) sc; 2) add-on ezetimibe 10 mg/d; 3) double atorvastatin dose; or 4) for atorvastatin 40 mg regimen only, switch to rosuvastatin 40 mg. For patients not achieving protocol-defined LDL-C goals, the alirocumab dose was increased (blinded) at week 12 to 150 mg Q2W.

Main Outcome Measure: The primary end point was percentage change in calculated LDL-C from baseline to 24 weeks (intent to treat).

Results: Among atorvastatin 20 and 40 mg regimens, respectively, add-on alirocumab reduced LDL-C levels by 44.1% and 54.0% ($P < .001$ vs all comparators); add-on ezetimibe, 20.5% and 22.6%; doubling of atorvastatin dose, 5.0% and 4.8%; and switching atorvastatin 40 mg to rosuvastatin 40 mg, 21.4%. Most alirocumab-treated patients (87.2% and 84.6%) achieved their LDL-C goals. Most alirocumab-treated patients (86%) maintained their 75-mg Q2W regimen. Treatment-emergent adverse events occurred in 65.4% of alirocumab patients vs 64.4% ezetimibe and 63.8% double atorvastatin/switch to rosuvastatin (data were pooled).

Conclusions: Adding alirocumab to atorvastatin provided significantly greater LDL-C reductions vs adding ezetimibe, doubling atorvastatin dose, or switching to rosuvastatin and enabled greater LDL-C goal achievement. **(*J Clin Endocrinol Metab* 100: 3140–3148, 2015)**

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Abbreviations: ADA, antidrug antibody; AE, adverse event; ALT, alanine transferase; CHD, coronary heart disease; CV, cardiovascular; CVD, CV disease; ITT, intent to treat; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MMRM, mixed-effects model with repeated measures; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; TEAE, treatment-emergent AE.

Despite receiving current standard-of-care therapy, most patients with coronary heart disease (CHD) or CHD risk equivalents still have levels of low-density lipoprotein cholesterol (LDL-C) of 70 mg/dL or greater, with figures as high as 81% (1). Clinical outcome data suggest that patients may benefit from further LDL-C reductions to reduce CHD risk (2, 3); however, other lipid treatment strategies beyond statins result in modest additional LDL-C level reduction. Whereas results may vary among individual studies and individual patients, prior trials suggest that doubling the statin dose may further reduce LDL-C levels approximately 6%, switching to a higher-potency statin (eg, from atorvastatin to rosuvastatin) may further reduce LDL-C approximately 8%, or adding a nonstatin lipid-lowering drug (cholesterol absorption inhibitors, fibrates, bile acid sequestrants, etc) may further reduce LDL-C levels by approximately 10–20%. (4–6). In previous studies, alirocumab, an investigational monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), reduced LDL-C levels by 40%–70% when used as add-on to statin therapy or as a monotherapy (7–10). These studies reported rates of adverse events with alirocumab that were generally comparable with control groups (placebo or ezetimibe) (7–10). Longer-term cardiovascular disease outcomes studies are required for evaluation of lipid-lowering efficacy, safety, and impact on major cardiovascular events.

Patients do not always achieve desirable lipid levels with current lipid treatment strategies. The ODYSSEY OPTIONS I trial (ClinicalTrials.gov identifier NCT01730040) directly compared the efficacy and safety of alirocumab as an add-on therapy to atorvastatin vs commonly used lipid treatment strategies including the following: 1) addition of ezetimibe, 2) doubling the atorvastatin dose, or 3) switching from atorvastatin 40 mg to rosuvastatin 40 mg. Previous studies compared alirocumab with placebo or ezetimibe (with or without concomitant statin, usually with a range of statin doses). However, apart from one phase 2 trial that involved the uptitration of baseline atorvastatin from 10 to 80 mg (8), no trials compared alirocumab with changing the statin regimen in a manner consistent with how lipid-altering agents are often used in clinical practice. The OPTIONS I study was designed to test the hypothesis that adding alirocumab to atorvastatin would be more effective than the other lipid-altering pharmacotherapy treatment strategies, with study results intended to provide additional data regarding the clinical use of alirocumab. Another novel aspect of this study is that although prior studies have demonstrated the lipid-altering efficacy, lipid goal attainment efficacy, and safety of an uptitration approach of other lipid-altering pharmacotherapies (11, 12), the OPTIONS I study represents the first published report regarding the lipid efficacy, lipid goal attainment, and safety of a lipid-altering treatment dose-escalation approach compared with the addition of a PCSK9 inhibitor to statin-treated, dyslipidemic patients.

Materials and Methods

OPTIONS I was a multicenter, randomized, double-blind, double-dummy, parallel-group, phase III trial in patients with hypercholesterolemia at high or very high cardiovascular disease (CVD) risk on a stable dose of atorvastatin 20 mg or 40 mg, carried out at 85 sites in Australia, Canada, France, Germany, Italy, Mexico, Spain, the United Kingdom, and the United States between October 2012 and May 2014. The study protocol was approved by the local Institutional Review Board and independent ethics committee at each site, and the study was conducted under the guidelines of the International Conference on Harmonization Good Clinical Practice guidance, the Declaration of Helsinki, and local regulatory requirements. Study participants underwent the informed consent process prior to participation, as evidenced by their written consent. Full details of the methods were previously published (13).

Patients

This study enrolled men and women aged 18 years or older at very high CVD risk (a history of CVD including CHD, or type 2 diabetes with target organ damage) and LDL-C of 70 mg/dL or greater or at high risk [no history of CVD or CHD but with other risk factors: calculated 10 y risk of fatal CVD of 5% or greater (Systematic Coronary Risk Evaluation [14]), moderate chronic kidney disease, or diabetes with no target organ damage] and LDL-C of 100 mg/dL or greater. Patients presented with these LDL-C levels despite receiving atorvastatin 20 mg or 40 mg/d with or without other lipid-lowering treatment (but not ezetimibe) for at least 4 weeks prior to screening. If not already on stable atorvastatin 20 mg or 40 mg/d, patients were enrolled into a run-in period to receive atorvastatin 20 mg or 40 mg/d for at least 4 weeks prior to screening and randomization.

Study design

The study consisted of a screening period of 2–6 weeks, a 24-week double-blind treatment period, and an 8-week follow-up period. Patients on a baseline statin regimen of atorvastatin 20 mg/d were randomized 1:1:1 to add-on therapy with sc alirocumab 75 mg every 2 weeks (Q2W), add-on therapy with oral ezetimibe 10 mg/d, or the doubling of the atorvastatin dose to 40 mg/d. Patients on a baseline statin regimen of atorvastatin 40 mg/d were randomized 1:1:1:1 to add-on therapy with sc alirocumab 75 mg Q2W, add-on therapy with ezetimibe 10 mg/d, doubling of atorvastatin dose to 80 mg/d, or a switch to rosuvastatin 40 mg/d. Blinding was maintained by using matching sc placebo-alirocumab, and overencapsulated tablets for ezetimibe, atorvastatin, and rosuvastatin to match the placebo for these comparators. Randomization was performed by the study sponsor using a permuted-block design. Within each baseline statin regimen, randomization was stratified according to history of myocardial infarction or ischemic stroke.

If, at week 8, lipid levels determined that the patient was above the prespecified, protocol-defined LDL-C treatment goal (≥70 mg/dL or 100 mg/dL in patients with or without documented CVD, respectively), the dose of alirocumab was increased to 150 mg Q2W at week 12 in an automated and blinded fashion. Alirocumab 75 mg or 150 mg doses (or sc placebo) were administered via single sc injections with a 1-mL prefilled pen. Injections could be administered at home by patients or designated caregivers (training was provided during the screening period). Patients could inject into the thigh, arm, or abdomen. Patients were provided with a dosing diary to document compliance with injectable and oral study drug dosing. All patients were instructed to adhere to a stable diet in line with National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes diet or equivalent.

Concomitant treatment with other statins, ezetimibe, fibrates (other than fenofibrate), and red yeast rice products was prohibited.

End points and assessments

The primary efficacy end point was the percentage change in calculated LDL-C from baseline to week 24 in an intent-to-treat (ITT) analysis. The efficacy of the alirocumab arm vs each of the comparator arms was evaluated for each entry baseline statin regimen, using five primary efficacy pairwise comparisons. Key secondary end points included percentage change in LDL-C from baseline to week 24 in an on-treatment analysis as well as percentage change in LDL-C at week 12, percentage change in other lipid parameters, proportion of patients achieving their protocol-defined LDL-C treatment goal (<100 mg/dL for high risk patients, <70 mg/dL for very high risk patients), and proportion of patients reaching calculated LDL-C less than 70 mg/dL at week 24, in both ITT and on-treatment analyses as well as the impact on other lipid parameters (see list in Supplemental Material) (13). On-site assessments were performed at baseline and then at weeks 4, 8, 12, 16, 24 (ie, to end of study treatment period), and the end-of-study follow-up visit at week 32. Fasting blood samples were collected in the morning. Lipid analyses were performed at a central laboratory and LDL-C was calculated using the Friedewald formula (15), except when triglyceride levels exceeded 400 mg/dL in which the measurement by β-quantification was performed. In addition, LDL-C was systematically measured via the β-quantification method at week 0 and week 24 for efficacy analyses. Lipoprotein (a) [Lp(a)] was analyzed using an immunoturbidometric assay on the Siemens BNII (Siemens) with a reference range of 1–30 mg/dL.

Safety

Safety was assessed throughout the study by adverse event (AE) reporting, laboratory parameters, vital signs, physical examination, and electrocardiogram (ECG). Treatment-emergent AEs (TEAEs) were defined as any AE that developed, worsened, or became serious during the period from the first injection to the last injection + 70 days. Certain AEs were designated of special interest and were to be monitored and managed in a prespecified manner, including allergic events; local injection site reactions; elevated alanine transferase (ALT); cardiovascular, neurological, neurocognitive, and ophthalmological events; development/worsening of diabetes mellitus or diabetic complications; overdose with study drug; consecutive calculated LDL-C less than 25 mg/d; and hemolytic anemia.

Antidrug antibodies

Antidrug antibodies (ADAs) to alirocumab were assessed in all patients at baseline, week 12 and week 24, and at the follow-up visit. Samples for ADA analysis were collected at clinic visits and before administration of study drug and were assayed using a validated immunoassay with adequate sensitivity by Regeneron Pharmaceuticals, Inc. The duration of the ADA response was classified as persistent (at least two consecutive postbaseline samples with positive ADA separated by at least a 12 wk period), indeterminate (ADA positive response present only at the last sampling time point), or transient (any treatment emergent positive ADA response considered neither persistent nor indeterminate).

Statistical analysis

A sample size of 50 patients per treatment arm was calculated to have 90% power to detect a difference in means of at least 20% in any one pairwise comparison of LDL-C percentage change from baseline to week 24 using a two-sided *t* test with 1% significance level for each of the five pairwise comparisons (thereby maintaining an overall 5% significance level), assuming a common SD of 25% based on previous experience with alirocumab (7).

The primary efficacy end point was assessed in the ITT population, which included all randomized patients, regardless of treatment adherence, with at least one available LDL-C value both at baseline and at one of the planned time points between weeks 4 and 24. A mixed-effects model with repeated measures (MMRM) was used to account for missing data. The model included the fixed categorical effects of treatment group randomization stratum, time point (weeks 4, 8, 12, 16, and 24), treatment-by-time point interaction, and stratum-by-time point interaction as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. The significance level of each of the five pairwise comparisons was $P = .01$ (rather than $P = .05$), adjusting for multiplicity to maintain a study α-level of .05 (13). A sensitivity analysis using a pattern mixture model (ie, a different imputation strategy to the MMRM) was also performed.

Secondary end points were analyzed in a hierarchical sequence to control type I error (see Supplemental Material). The on-treatment analysis used all available on-treatment measurements at planned time points from weeks 4 to 24.

The safety analysis included all randomized patients who received at least one dose or part of a dose of study treatment. Safety data are pooled (where appropriate) across atorvastatin baseline regimens (reported as the pooled alirocumab add-on group, pooled ezetimibe add-on group, and pooled atorvastatin dose increase/switch to rosuvastatin group); baseline data are also summarized in this way in the main text.

Results

Patients

In total, 355 patients were enrolled into one of the two atorvastatin baseline regimens (20 mg, n = 169; 40 mg, n = 186) and were then randomized to one of the treatment groups (n values were 55–57 for the three groups in the 20 mg regimen and 45–47 for the four groups in the 40

Table 1. Baseline Characteristics (All Randomized Patients)

	Entry Statin: Atorvastatin 20 mg (n = 169)			Entry Statin: Atorvastatin 40 mg (n = 186)			
	Alirocumab 75/150 mg Q2W + ATV 20 mg (n = 57)	EZE 10 mg + ATV 20 mg (n = 55)	ATV 40 mg (n = 57)	Alirocumab 75/150 mg Q2W + ATV 40 mg (n = 47)	EZE 10 mg + ATV 40 mg (n = 47)	ATV 80 mg (n = 47)	RSV 40 mg (n = 45)
Age, y, mean ± SD	62.2 ± 10.0	65.7 ± 9.0	63.0 ± 9.9	64.2 ± 10.4[a]	63.9 ± 10.3[a]	63.2 ± 10.9[a]	57.5 ± 10.0[a]
Male, n, %	33 (57.9)	31 (56.4)	35 (61.4)	31 (66.0)	36 (76.6)	33 (70.2)	32 (71.1)
Race, white n, %	48 (84.2)	48 (87.3)	50 (87.7)	43 (91.5)	43 (91.5)	41 (87.2)	33 (73.3)
BMI, kg/m^2, mean ± SD	32.2 ± 7.7	31.6 ± 6.0	31.4 ± 6.8	29.8 ± 5.4	30.8 ± 5.9	30.2 ± 6.0	30.8 ± 6.9
CHD history, n, %	22 (38.6)	28 (50.9)	29 (50.9)	33 (70.2)	35 (74.5)	31 (66.0)	22 (48.9)
CHD risk equivalent, n, %[b]	16 (28.1)	16 (29.1)	19 (33.3)	10 (21.3)	15 (31.9)	16 (34.0)	8 (17.8)
Hypertension, n, %	44 (77.2)	45 (81.8)	46 (80.7)	36 (76.6)	37 (78.7)	37 (78.7)	33 (73.3)
Type 2 diabetes, n, %	33 (57.9)	29 (52.7)	31 (54.4)	25 (53.2)	16 (34.0)	25 (53.2)	18 (40.0)
Baseline calculated LDL-C, mean ± SD, mg/dL	103.9 ± 34.9	100.4 ± 29.5	100.3 ± 29.8	116.4 ± 37.4	98.9 ± 29.2	108.6 ± 37.5	109.8 ± 39.0

Abbreviations: ATV, atorvastatin; BMI, body mass index; EZE, ezetimibe; RSV, rosuvastatin.

[a] $P = .0065$ for comparison of mean age between groups in the atorvastatin 40 mg entry regimen. No statistical differences ($P > .05$) were observed for comparisons of all other baseline characteristics.

[b] CHD risk equivalents were defined as ischemic stroke, peripheral artery disease, moderate chronic kidney disease, diabetes (only if two or more risk factors were present).

mg regimen; Supplemental Figure 1). Overall, 86.5%, 81.4%, and 88.6% of patients randomized to alirocumab add-on, ezetimibe add-on, or atorvastatin dose increase/switch to rosuvastatin, respectively, completed 24 weeks of double-blind treatment (defined as at least 22 wk of treatment and wk 24 visit performed). Median follow-up for patients who did not complete the study was 9.5, 12.4, and 12.1 weeks, respectively. Baseline characteristics were generally similar across the treatment groups (Table 1 and Supplemental Table 1). Mean baseline LDL-C levels were 100–104 mg/dL in the 20-mg atorvastatin baseline regimen and 99–116 mg/dL in the 40-mg atorvastatin baseline regimen (Table 1). Persistent use of study drug injections (ie, alirocumab/placebo, with compliance based on mean injection frequency) was high (>98%) across the pooled treatment groups. Greater than 70% of patients received all planned injections. Treatment injection exposure was similar among treatment groups, with a mean (SD) exposure of 22.0 (6.3) weeks in the pooled alirocumab add-on group, 22.1 (5.4) weeks in the pooled ezetimibe add-on group, and 22.7 (4.8) weeks in the pooled atorvastatin dose increase/switch to rosuvastatin group.

Efficacy

Among atorvastatin 20- and 40-mg regimens respectively, add-on alirocumab reduced LDL-C levels at week 24 by 44.1% and 54.0% ($P < .001$ vs all comparators); add-on ezetimibe, 20.5% and 22.6%; doubling of atorvastatin dose, 5.0% and 4.8%; and switching atorvastatin 40 mg to rosuvastatin 40 mg, 21.4% (Figure 1). Reductions were maintained from week 4 to week 24 (Figure 2). Calculated LDL-C reductions at week 24 were consistent with those derived using on-treatment and pattern-mixture analysis methods, and using LDL-C measured by β-quantification (Supplemental Tables 2–4). Alirocumab dose was increased from 75 mg to 150 mg Q2W at week 12 in 8.0% and 20.9% of patients on baseline atorvastatin 20 mg or 40 mg, respectively. Overall, the majority (86%) of patients in the alirocumab add-on groups (with at least one injection postrandomization at wk 12) were main-

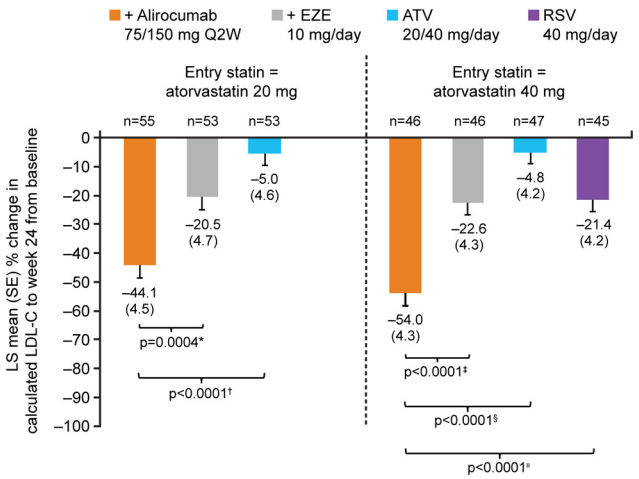

Figure 1. Primary end point. LS mean (SE) percentage change from baseline in calculated LDL-C to week 24 (ITT analysis). LS mean (SE) percentage difference in calculated LDL-C vs comparator agents at week 24: *, −23.6 (6.6); †, −39.1 (6.4); ‡, −31.4 (6.1); §, −49.2 (6.1); ‖, −32.6 (6.0). LS means, SE, and *P* value taken from mixed-model with repeated-measures analysis. ATV, atorvastatin; EZE, ezetimibe; LS, least squares; RSV, rosuvastatin.

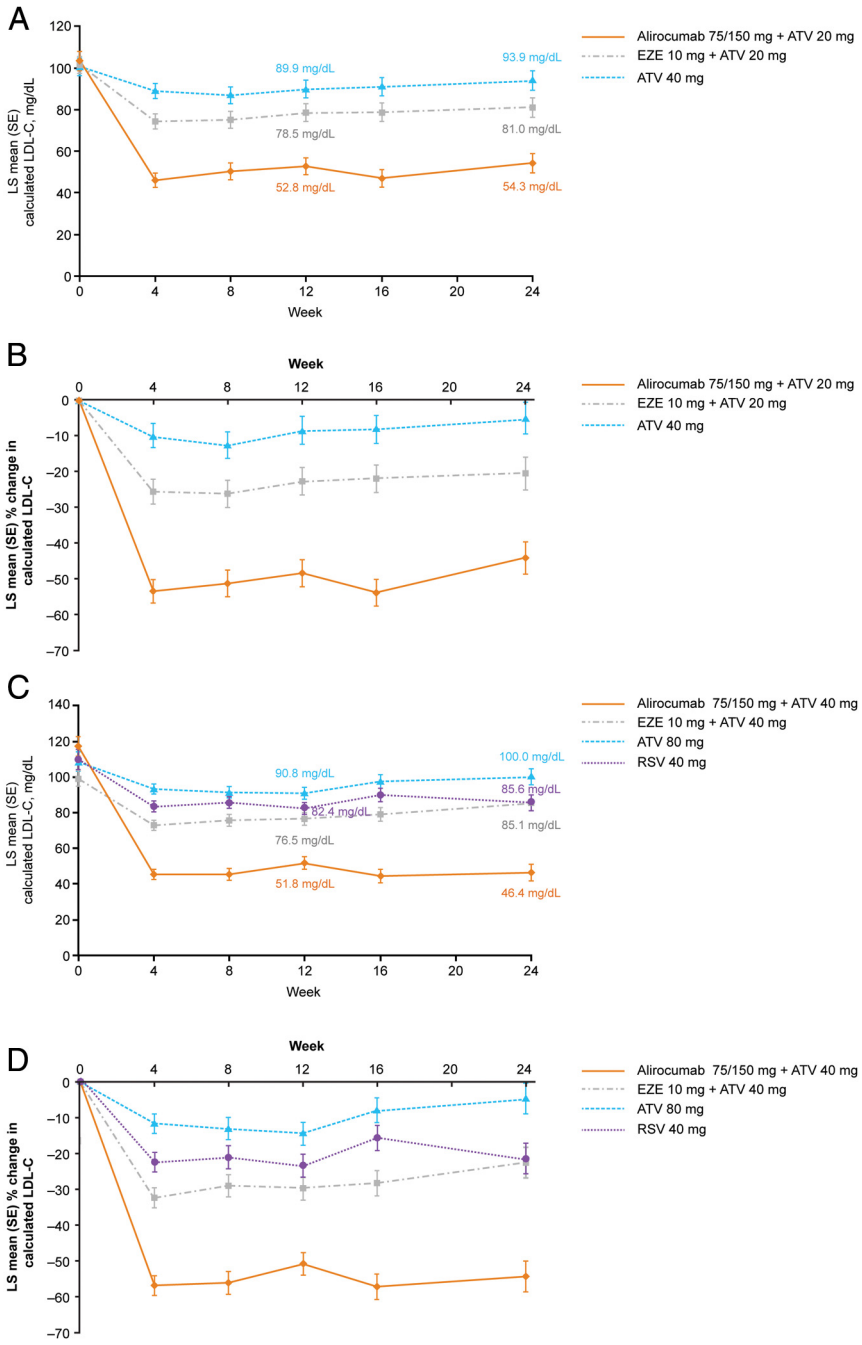

Figure 2. Absolute levels and percentage change from baseline in calculated LDL-C over time for patients entering on atorvastatin 20 mg (A and B) and atorvastatin 40 mg (C and D) (ITT analysis). Actual mean LDL-C values are shown for data points at weeks 12 and 24 in panels A and C. ATV, atorvastatin; EZE, ezetimibe; LS, least squares; RSV, rosuvastatin.

tained on the 75-mg Q2W dose after week 12 because their week 8 LDL-C was below the predefined threshold (<70 or <100 mg/dL, depending on CVD risk); LDL-C reductions were consistent over time in these patients (Supplemental Figure 2).

For patients receiving alirocumab added to background atorvastatin 20 mg and 40 mg, the combined proportion of high and very-high CVD risk patients achieving protocol predefined LDL-C goals of less than 70 mg/dL and less than 100 mg/dL, respectively, at week 24, was greater than 80% when using calculated LDL-C values (Figure 3). Furthermore, achievement of the more stringent LDL-C goal of less than 70 mg/dL was achieved by 77%–79% of patients in the alirocumab add-on groups, when using calculated LDL-C values (Figure 3). When using LDL-C values measured by β-quantification, achievement of LDL-C less than 70 mg/dL or less than 100 mg/dL was similar to those when calculated LDL-C was used for most groups (Supplemental Figure 3). Alirocumab reduced apolipoprotein B and nonhigh-density lipoprotein cholesterol (non-HDL-C) from baseline to week 24 vs all comparators, regardless of background atorvastatin regimen, and significantly reduced Lp(a) when compared with all comparators on a background of atorvastatin 40 mg (all $P < .001$, Table 2).

Results of subanalyses according to baseline characteristics are shown in Supplemental Figure 4.

Safety

TEAEs occurred in 65.4% of patients receiving alirocumab as an add-on, 6.7% of which led to discontinuation. These were comparable with rates reported in patients receiving ezetimibe as an add-on or atorvastatin dose increase/switch to rosuvastatin (64.4% and 63.8% TEAEs, respectively, with 4.0% and 5.4% leading to discontinuation) (Table 3). Serious AEs were reported by 5.4% of patients overall, with no discernible pattern. Two patients not receiving alirocumab died during the study, both from the ezetimibe add-on group in the atorvastatin 20-mg baseline regimen. The causes of death were determined to be acute respiratory distress syndrome (according to the investigator, underlying cause was pneumonia and aspiration) and cardiac arrest in the other patient with a medical history of acute myocardial infarction. Of potential allergic events (Table 3), allergic rhinitis and urticaria were the only

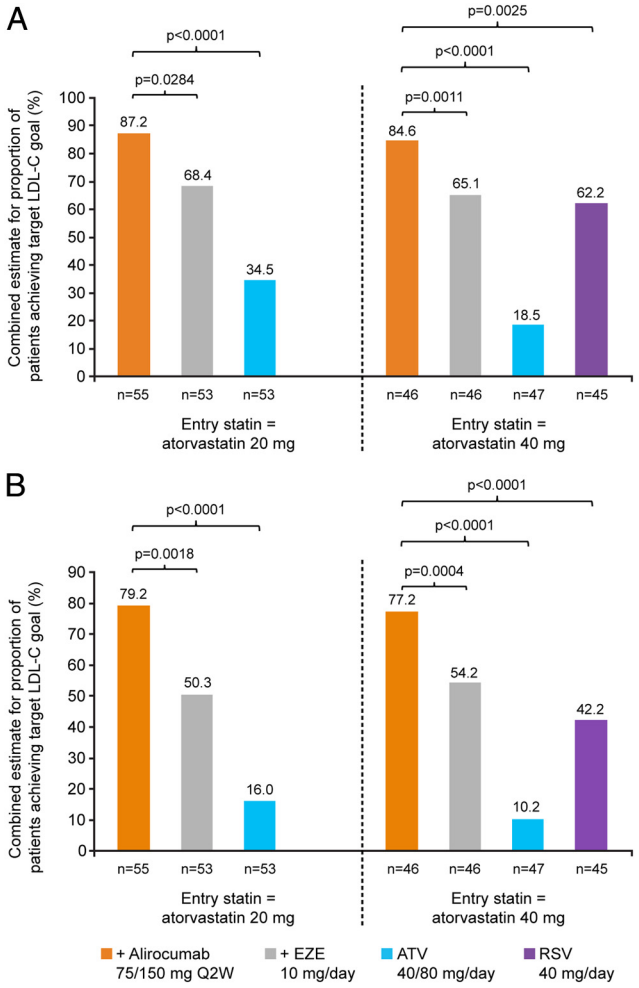

Figure 3. Proportion of patients achieving LDL-C goals at week 24: LDL-C less than 70 mg/dL (very high CVD risk) or less than 100 mg/dL (high CVD risk) (A) or less than 70 mg/dL (regardless of risk) (calculated LDL-C; ITT analysis) (B). Multiple-imputation approach was followed by a stratified exact conditional logistic regression stratified by randomization factor, with treatment group as the main effect and baseline LDL-C as a covariate. ATV, atorvastatin; EZE, ezetimibe; RSV, rosuvastatin.

events to occur in more than one patient, with each reported by two patients (1.3%) in the pooled atorvastatin dose increase/rosuvastatin switch group. Pruritus occurred in one patient (in the pooled atorvastatin dose increase/rosuvastatin switch group). No serious allergic events were reported. Injection site reactions were reported with similar proportions of patients in each group (2%–3%, Table 3); all injection-site reactions were graded mild in intensity and none led to discontinuation of study treatment. Neurologic TEAEs (Table 3) led to discontinuation in one patient (0.7%) in the pooled atorvastatin dose increase/switch to rosuvastatin group. This patient, who had a history of type 2 diabetes mellitus and proliferative diabetic retinopathy, experienced two nonserious TEAEs of increased peripheral neuropathy of severe intensity, requiring treatment including oxycodone hydrochloride. The patient also experienced increased blood glucose levels. No patients in any treatment group experienced ophthalmological or neurocognitive TEAEs, and no events of hemolytic anemia were reported. Two cardiovascular TEAEs were confirmed by adjudication: the aforementioned cardiac death in the ezetimibe plus atorvastatin 20 mg group, and one event of ischemia-driven coronary revascularization procedure in the alirocumab plus atorvastatin 20 mg group. Elevation of ALT (greater than 3 times the upper limit of normal) was reported in one patient (randomized to atorvastatin 80 mg). Few muscle-related AEs were reported (<5% patients). Further details on adverse events are given in Supplemental Table 5.

Antidrug antibodies

A baseline positive response in the ADA assay was observed in one patient (1.0%) in the pooled alirocumab add-on group and in four patients in the control treatment groups: three patients (3.2%) in the pooled ezetimibe add-on group and one patient (0.7%) in the pooled atorvastatin dose increase/switch to rosuvastatin group. These results indicate either a high serum background or preexisting immunoreactivity and not a treatment-emergent ADA response. No patient in this study had previously been exposed to a PCSK9 monoclonal antibody. Treatment-emergent ADA positive responses were observed in 5 of 99 patients (5.1%) in the pooled alirocumab add-on group. Of these five patients, three had persistent responses, one had a transient response, and the other had an indeterminate response. One of the three patients with a persistent ADA response also had a positive neutralizing antibody assay response. One patient in the pooled statin dose increase/switch to rosuvastatin group also exhibited a treatment-emergent response in the ADA assay. Overall, immunogenicity was low and ADA positivity did not have an effect on the LDL-C-lowering efficacy of alirocumab during this study (Supplemental Figure 5), nor were any specific TEAEs considered related to the development of ADAs.

Discussion

This study demonstrated that among patients at high CVD risk treated with atorvastatin 20 or 40 mg for at least 4 weeks prior to screening or randomization, adding alirocumab to a background of atorvastatin provided greater reductions in LDL-C levels compared with adding ezetimibe, doubling the atorvastatin dose, or switching to rosuvastatin. Specifically, among the atorvastatin 20 mg and 40 mg regimens, respectively, add-on alirocumab reduced LDL-C levels by 44.1% and 54.0%, add-on

Table 2. Percentage Change From Baseline in Key Secondary Lipid End Points (ITT Analysis)

	Entry Statin: ATV 20 mg			Entry Statin: ATV 40 mg			
LS Mean (SE) Change From Baseline, %	Alirocumab 75/150 mg Q2W + ATV 20 mg (n = 55)	EZE 10 mg + ATV 20 mg (n = 53)	ATV 40 mg (n = 53)	Alirocumab 75/150 mg Q2W + ATV 40 mg (n = 46)	EZE 10 mg + ATV 40 mg (n = 46)	ATV 80 mg (n = 47)	RSV 40 mg (n = 45)
Calculated LDL-C, week 12	−48.4 (3.8)	−22.6 (3.9)	−8.5 (3.9)	−50.5 (3.2)	−29.7 (3.2)	−14.5 (3.2)	−23.3 (3.2)
Difference, alirocumab vs comparator		−25.8 (5.4)[a]	−39.8 (5.4)[a]		−20.9 (4.6)[a]	−36.0 (4.5)[a]	−27.3 (4.6)[a]
Apo B, week 24	−33.7 (3.4)	−10.1 (3.6)	−4.4 (3.5)	−41.9 (3.4)	−14.3 (3.3)	−3.5 (3.3)	−10.9 (3.2)
Difference, alirocumab vs comparator		−23.6 (4.9)[a]	−29.3 (4.9)[a]		−27.6 (4.8)[a]	−38.4 (4.8)[a]	−30.9 (4.7)[a]
Non-HDL-C, week 24	−36.7 (3.9)	−15.1 (4.0)	−6.3 (3.9)	−47.6 (3.7)	−21.0 (3.7)	−6.5 (3.6)	−17.4 (3.6)
Difference, alirocumab vs comparator		−21.6 (5.6)[b]	−30.4 (5.5)[a]		−26.6 (5.3)[a]	−41.1 (5.2)[a]	−30.2 (5.2)[a]
Lp(a), week 24	−23.6 (4.0)	−10.6 (4.4)	−20.2 (4.0)	−30.8 (4.1)	0.2 (3.9)	−9.7 (4.1)	−4.9 (3.7)
Difference, alirocumab vs comparator		−13.0 (6.0)	−3.4 (5.7)		−31.0 (5.7)[a]	−21.1 (5.9)[b]	−25.9 (5.5)[a]
Fasting triglycerides, week 24	−12.0 (3.7)	−3.3 (4.1)	−6.7 (3.7)	−19.1 (4.1)	−13.9 (4.1)	−7.3 (4.1)	−0.5 (4.0)
Difference, alirocumab vs comparator		−8.6 (5.4)	−5.3 (5.2)		−5.2 (5.7)	−11.8 (5.8)	−18.7 (5.7)[b]
HDL-C, week 24	4.8 (2.0)	−0.1 (2.1)	1.9 (2.0)	7.7 (2.7)	2.0 (2.7)	4.7 (2.7)	5.7 (2.7)
Difference, alirocumab vs comparator		4.9 (2.9)	2.9 (2.9)		5.6 (3.8)	2.9 (3.8)	2.0 (3.8)

Abbreviations: Apo, apolipoprotein; ATV, atorvastatin; EZE, ezetimibe; HDL-C, high-density lipoprotein cholesterol; LS, least squares; RSV, rosuvastatin.

LS means, SE, and *P* value were taken from a mixed-model with repeated measures analysis with hierarchical procedure to control for type I error except for Lp(a) and triglycerides, which were analyzed using multiple imputation approach to account for missing values, followed by robust regression model with the end point of interest as the response variable and the treatment group and corresponding baseline values as effects. The proportion of patients achieving LDL-C goals was analyzed using a multiple imputation approach followed by a logistic regression.

[a] $P < .0001$.

[b] $P < .01$.

ezetimibe reduced LDL-C levels by 20.5% and 22.6%, doubling of atorvastatin dose reduced LDL-C levels by 5.0% and 4.8%, and switching atorvastatin 40 mg to rosuvastatin 40 mg reduced LDL-C levels by 21.4%. In the treatment groups not receiving alirocumab, the LDL-C reductions observed with ezetimibe add-on (20.5%–22.6%) and atorvastatin dose increase (5.0%–4.8%) were consistent with previous reports (5, 6). The 21.4% reduction in LDL-C levels when switching from atorvastatin 40 mg/d to rosuvastatin 40 mg/d was higher than the approximately 8% reduction reported elsewhere (5).

This study used a treat-to-goal dosing strategy, whereby the alirocumab dose was increased from 75 mg to 150 mg Q2W if LDL-C was greater than 70 mg/dL or greater than 100 mg/dL, depending on the patient's CVD risk. Most alirocumab-treated patients (86%) maintained their 75-mg Q2W regimen for the duration of the study. A greater proportion of patients received alirocumab dose increase to 150 mg Q2W in the atorvastatin 40 mg per day group vs the atorvastatin 20 mg per day group. Reasons for this difference may be 2-fold: 1) patients in the atorvastatin 40 mg group had a somewhat higher mean LDL-C level at baseline (116 vs 104 mg/dL; $P = .0540$) and 2) a greater proportion of patients on the higher atorvastatin dose of 40 mg/d presented with a history of CVD ($P = .0016$) that, per protocol, required more aggressive LDL-C treatment goals.

Although LDL-C treatment goals are at present no longer recommended by the American College of Cardiology/American Heart Association lipid treatment guidelines (6), other US and international guidelines and recommendations continue to support the use of LDL-C treatment goals (14, 16–22). Alirocumab significantly improved protocol-predefined LDL-C goal achievement vs all comparators, with 87.2%–84.6% of patients in the alirocumab add-on groups achieving their LDL-C goals (<70 mg/dL or <100 mg/dL, depending on risk) vs comparators. Alirocumab also significantly reduced apolipoprotein B and non-HDL-C vs the comparators and also reduced Lp(a) by 23.6%–30.8%. The impact of alirocumab on cardiovascular (CV) events will be discerned in the ongoing 18 000-patient ODYSSEY OUTCOMES study (23).

The incidence of TEAEs in patients who received alirocumab was comparable with that observed in the other treatment groups, with a similar number of discontinuations because of TEAEs between groups. The occurrence of potential allergic events, neurological events, or injection site reactions was low in all groups. Development of antibodies to alirocumab (ADAs) were observed in five patients after alirocumab treatment and did not affect overall efficacy or safety. Overall, the safety findings of this study were comparable with other alirocumab trials (7–10) and trials of other PCSK9 inhibitors (24).

In conclusion, in patients at high and very high CV risk not achieving LDL-C goals of less than 100 mg/dL or less than 70 mg/dL, respectively, with commonly used doses of atorvastatin, alirocumab as add-on to atorvastatin 20 mg

Table 3. Safety Analysis (Pooled Data Across Atorvastatin 20 mg and 40 mg Entry Regimens)

Patients, %, n	Pooled Alirocumab (n = 104)	Pooled EZE (n = 101)	Pooled Double ATV or RSV Switch (n = 149)	*P* Value
TEAEs[a]	65.4 (68)	64.4 (65)	63.8 (95)	.9796
Treatment-emergent SAEs	3.8 (4)	6.9 (7)	5.4 (8)	.6036
TEAE leading to death	0	2.0 (2)	0	.0808
TEAEs leading to discontinuation	6.7 (7)	4.0 (4)	5.4 (8)	.6950
TEAEs in 5% or more of patients in any group				
Back pain	6.7 (7)	3.0 (3)	4.0 (6)	.4409
Nasopharyngitis	4.8 (5)	3.0 (3)	5.4 (8)	.7254
Upper respiratory tract infection	4.8 (5)	8.9 (9)	4.7 (7)	.3479
Hypertension	4.8 (5)	5.9 (6)	0.7 (1)	.315
Urinary tract infection	2.9 (3)	7.9 (8)	5.4 (8)	.2690
Diarrhea	1.9 (2)	3.0 (3)	5.4 (8)	.3726
Nausea	1.0 (1)	4.0 (4)	7.4 (11)	.0390
AEs of interest				
Potential allergic event[b]	1.9 (2)	5.0 (5)	4.0 (6)	.4858
Injection-site reactions	2.9 (3)	3.0 (3)	2.0 (3)	.8354
Neurological events[c]	2.9 (3)	1.0 (1)	2.0 (3)	.6485
Adjudicated CV events	1.0 (1)	1.0 (1)	0	.3347
ALT greater than 3 × ULN, %, n/N	0 (0/101)	0 (0/99)	0.7 (1/147)[d]	1.000
Creatine kinase greater than 3 × ULN, %, n/N[e]	3.0 (3/100)	1.0 (1/98)	5.4 (8/147)	.1859

Abbreviations: ATV, atorvastatin; EZE, ezetimibe; MedDRA, Medical Dictionary for Regulatory Activities; RSV, rosuvastatin; SAE, serious AE; ULN, upper limit of normal.

[a] TEAE period is the time from first dose to the last dose + 70 days.

[b] Selection of preferred terms based on standardized MedDRA queries: hypersensitivity (broad + narrow) excluding the following preferred terms: infusion site dermatitis, infusion site hypersensitivity, infusion site rash, infusion site urticaria, injection site dermatitis, injection site hypersensitivity, injection site rash, injection site urticaria, and injection side vasculitis.

[c] Selection of preferred terms is based on standardized MedDRA queries: demyelination (broad + narrow), peripheral neuropathy (broad + narrow), and Guillain-Barre syndrome (broad + narrow) excluding the following preferred terms: acute respiratory distress syndrome, asthenia, respiratory arrest, and respiratory failure.

[d] Bilirubin levels were not elevated (defined as >2 × ULN) in the patient with ALT >3 × ULN).

[e] No patients had creatine kinase greater than 5 × or greater than 10 × the ULN.

or 40 mg, produced significantly greater LDL-C reductions at week 24 vs the addition of ezetimibe, doubling the atorvastatin dose, or switching to rosuvasatin. The LDL-C-lowering effect with alirocumab was seen from week 4 and was maintained until the end of the treatment. In high CV risk patients, the addition of alirocumab may provide an effective means to achieve significantly greatly LDL-C reductions and higher levels of LDL-C level goal attainment compared with commonly used strategies for improving LDL-C control.

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