Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: The ODYSSEY OPTIONS II randomized trial

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ABSTRACT

Objective: To compare lipid-lowering efficacy of adding alirocumab to rosuvastatin versus other treatment strategies (NCT01730053).

Methods: Patients receiving baseline rosuvastatin regimens (10 or 20 mg) were randomized to: add-on alirocumab 75 mg every-2-weeks (Q2W) (1-mL subcutaneous injection via pre-filled pen); add-on ezetimibe 10 mg/day; or double-dose rosuvastatin. Patients had cardiovascular disease (CVD) and low-density lipoprotein cholesterol (LDL—C) ≥70 mg/dL (1.8 mmol/L) or CVD risk factors and LDL—C ≥100 mg/dL (2.6 mmol/L). In the alirocumab group, dose was blindly increased at Week 12 to 150 mg Q2W (also 1-mL volume) in patients not achieving their LDL—C target. Primary endpoint was percent change in calculated LDL—C from baseline to 24 weeks (intent-to-treat).

Results: 305 patients were randomized. In the baseline rosuvastatin 10 mg group, significantly greater LDL—C reductions were observed with add-on alirocumab (−50.6%) versus ezetimibe (−14.4%; p < 0.0001) and double-dose rosuvastatin (−16.3%; p < 0.0001). In the baseline rosuvastatin 20 mg group, LDL—C reduction with add-on alirocumab was −36.3% compared with −11.0% with ezetimibe and −15.9% with double-dose rosuvastatin (p = 0.0136 and 0.0453, respectively; pre-specified threshold for significance p < 0.0125). Overall, ~80% alirocumab patients were maintained on 75 mg Q2W. Of alirocumab-treated patients, 84.9% and 66.7% in the baseline rosuvastatin 10 and 20 mg groups, respectively, achieved risk-based LDL—C targets. Treatment-emergent adverse events occurred in 56.3% of alirocumab patients versus 53.5% ezetimibe and 67.3% double-dose rosuvastatin (pooled data).

Conclusions: The addition of alirocumab to rosuvastatin provided incremental LDL—C lowering versus adding ezetimibe or doubling the rosuvastatin dose.

1. Introduction

Among the therapies currently approved for lowering low-density lipoprotein cholesterol (LDL—C), statins are the most commonly prescribed and have shown the greatest ability to lower LDL—C and reduce coronary heart disease (CHD) events [1,2]. Recent studies have also shown that the addition of ezetimibe to

statins provides incremental reduction in CHD events in very high-risk patients [3]. Further, guidelines recommend higher intensity lipid-lowering therapy (LLT), primarily with statins, in very high-risk patient groups [2,4−6]. It should be noted, however, that some patients are unable to tolerate high-intensity statins [2]. Despite the availability of statins and other LLT, even when they are used in combination, many high-risk patients do not reach target LDL−C levels [7].

Alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), is currently in development for LDL−C-lowering. Phase 2 and 3 studies have shown that alirocumab significantly reduces LDL−C levels by 40−70% as monotherapy or when added to statins, with or without other LLTs [8−16]. Adverse events with alirocumab have generally been comparable to those observed in the control groups; however, injection-site reactions and pruritus occurred slightly more frequently in alirocumab-treated patients in the Phase 3 studies [8−16].

This study compared the lipid-lowering efficacy and safety of alirocumab, in a head-to-head fashion, with other current options for patients on rosuvastatin 10 or 20 mg with very-high or high cardiovascular (CV) risk according to European guidelines [6,7] and who had LDL−C levels above 70 or 100 mg/dL (1.8 or 2.6 mmol/L), respectively.

2. Methods

ODYSSEY OPTIONS II was a double-blind, double-dummy, randomized, Phase 3 study, and patients were enrolled in 79 sites in Australia, Germany, Italy, Spain, the United Kingdom, Mexico, the United States, and Canada from November 2012 to May 2014 (NCT01730053). The design and rationale for the trial have been published previously [17]. The protocol was reviewed and approved by the Institutional Review Board/Ethics Committee at each participating center and the study was conducted in accordance with International Conference on Harmonization/Good Clinical Practice, the Declaration of Helsinki and local regulations. All participants provided written informed consent.

2.1. Study participants

The study included adult patients with hypercholesterolemia at very-high or high CV risk receiving rosuvastatin 10 or 20 mg/day for at least 4 weeks prior to screening. Patients could also be receiving other LLTs except for ezetimibe; statins other than rosuvastatin were not allowed. Very-high CV risk patients with a history of CHD, non-CHD CV disease (CVD), or diabetes mellitus with target organ damage were included if LDL−C was ≥70 mg/dL (1.8 mmol/L) at screening. High-risk CV patients without documented CHD or CVD but with a 10-year risk of fatal CVD ≥5% (Systematic Coronary Risk Evaluation), moderate chronic kidney disease, or diabetes with no target organ damage, were included if LDL−C was ≥100 mg/dL (2.6 mmol/L).

2.2. Study design

Patients entered a 2- to 6-week screening period and were then randomized according to their baseline rosuvastatin regimen (10 mg or 20 mg/day) (Supplementary Fig. 1). Patients were randomized in a 1:1:1 ratio to 24 weeks' double-blind treatment with either (1) add-on therapy with subcutaneous (SC) alirocumab 75 mg every 2 weeks (Q2W), (2) add-on therapy with ezetimibe 10 mg/day, or (3) doubling of the rosuvastatin dose (i.e. 10 mg doubled to 20 mg/day, or 20 mg doubled to 40 mg/day). Patients also received SC or oral placebo as appropriate.

If Week 8 LDL−C levels were ≥70 mg/dL (1.8 mmol/L) in patients with documented CVD or diabetes mellitus with target organ damage, or ≥100 mg/dL (2.6 mmol/L) in all of the other patients, the alirocumab dose was increased to 150 mg Q2W at Week 12 in a blinded manner.

2.3. Study assessments and endpoints

Patients returned to the clinic for assessment at Weeks 4, 8, 12, 16, 24 (end of treatment), and Week 32 (end of study follow-up visit). Adherence to injectable and oral study drug dosing was documented in a dosing diary, and measured in terms of mean injection and daily capsule frequency as well as injection and capsule compliance intervals.

The primary efficacy endpoint was the percent change from baseline in calculated LDL−C at Week 24, on-treatment or off-treatment, in the intent-to-treat (ITT) population. The ITT population was defined as all randomized patients with a baseline calculated LDL−C value and post-baseline calculated LDL−C value during at least one of the planned time points, regardless of the patient's adherence to study treatment. The primary ITT analysis compared the efficacy of the alirocumab arm versus each comparator arm via pairwise comparisons for each baseline entry rosuvastatin regimen, for a total of four comparisons. In an additional pre-specified analysis, pooled data from the alirocumab groups from the two baseline rosuvastatin dose regimens were pooled and compared with pooled data from the comparator groups.

In a pre-specified hierarchical order [17], key secondary endpoints included the percent change from baseline in calculated LDL−C on-treatment at Week 24 in the modified ITT (mITT) population (on-treatment analysis), percent change in LDL−C from baseline to Week 12 (ITT and on-treatment), the percent change in other lipid parameters, and the proportion of very-high and high CV risk patients reaching LDL−C <70 mg/dL (1.8 mmol/L) or <100 mg/dL (2.6 mmol/L) at Week 24, respectively, in both ITT and on-treatment analyses. The mITT population was defined as all randomized and treated patients with a baseline calculated LDL−C value and with on-treatment calculated LDL−C values during at least one of the planned post-baseline time points. The on-treatment window was defined as the period up to 21 days after last injection/3 days after last capsule (whichever came first) at planned time points from Weeks 4−24.

Safety was evaluated by adverse events (AEs), laboratory tests, vital signs, physical examination, and electrocardiogram. The treatment-emergent AE (TEAE) period was defined as the period between the first dose of study drug up to 70 days after last injection. Certain safety events were designated of special interest based on the alirocumab mode of action, theoretical risks raised in the literature or potential risks based on any findings in preclinical studies.

Anti-drug antibodies (ADAs) to alirocumab were assessed in all patients. Samples were collected at clinic visits, before administration of study drug, and were assayed using a validated immunoassay by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY, USA). The duration of the ADA response was classified as: "persistent", at least 2 consecutive post-baseline samples with positive ADA separated by at least a 12-week period; "indeterminate", ADA positive response present only at the last sampling point; or "transient", any treatment-emergent positive ADA response neither considered persistent nor indeterminate.

2.4. Statistical analysis

A total sample size of 300 patients (50 in each of the six

treatment arms), was determined to provide 90% power to detect a difference in means of at least 20% in any of the 4 pairwise comparisons of the primary efficacy endpoint, using a 2-sided *t*-test with an adjusted significance level of 1.25% for each of the 4 pairwise comparisons (i.e. Bonferroni adjustment giving 5% significance overall). If any of the 4 pairwise comparisons had $p < 0.0125$, it would therefore be declared significant. This assumed a standard deviation of 25% in change from baseline in LDL−C (based on previous experience with alirocumab) [10]. The multiplicity for testing key secondary efficacy endpoints was adjusted for by hierarchical procedure within each of the 4 pairwise comparisons. Inferential conclusions about successive key secondary parameters for pairwise comparisons require statistical significance of the primary and prior key secondary efficacy endpoints within the same pairwise comparison hierarchy.

To estimate treatment effects at the specified time points for primary and key secondary efficacy endpoints that were approximately normal distributions, a mixed-effect model with a repeated measures approach was used to account for missing data [18,19]. Least-squares means estimates were calculated, and treatment differences between patients treated with alirocumab and comparators were tested through pairwise comparisons for each entry statin dose. A sensitivity analysis using a pattern mixture model was also performed.

For the non-normal lipoprotein (a) (Lp[a]) and triglycerides, a robust regression model was used. The proportion of patients with LDL−C <70 mg/dL (1.8 mmol/L) and <100 mg/dL (2.6 mmol/L) was analyzed using a stratified exact conditional logistic regression model. The treatment group was treated as the main effect and

baseline LDL−C value as a covariate stratified by randomization factor in both models. Missing values were handled by the multiple imputation approach.

The safety analysis included all randomized patients who received at least one dose or part of a dose of study treatment (safety population). Safety data are pooled (where appropriate) across rosuvastatin baseline regimens and are reported as the pooled alirocumab add-on group, pooled ezetimibe add-on group, and pooled rosuvastatin group.

3. Results

3.1. Patients

Across the two rosuvastatin baseline regimens (10 and 20 mg respectively), a total of 305 patients were randomized to one of the six treatment groups (Supplementary Fig. 2). The safety population included all 305 patients, and the ITT and mITT populations excluded 7 and 10 patients, respectively, due to missing post-baseline LDL−C values. Combining both baseline rosuvastatin groups, 87 (84.5%), 84 (83.2%), and 90 (89.1%) patients randomized to the alirocumab add-on, ezetimibe add-on, and double-dose rosuvastatin groups, respectively, completed 24 weeks of the double-blind treatment period (defined as at least 22 weeks of treatment and Week 24 visit performed). Baseline patient characteristics were generally similar across treatment groups (Table 1). Treatment adherence to study drug injections was high in all treatment groups within the pooled dose regimen, with a mean overall adherence of 97.5% in the alirocumab add-on group, 98.6% in

Table 1
Baseline characteristics (all randomized patients).

	Entry statin 10 mg RSV ($n = 145$)			Entry statin 20 mg RSV ($n = 160$)		
	ALI + 10 mg RSV ($n = 49$)	EZE + 10 mg RSV ($n = 48$)	RSV 20 mg ($n = 48$)	ALI + 20 mg RSV ($n = 54$)	EZE + 20 mg RSV ($n = 53$)	RSV 40 mg ($n = 53$)
Age, years mean (SD)	62.2 (11.1)	60.4 (10.4)	61.5 (11.1)	57.9 (8.9)	63.1 (10.2)	60.6 (10.1)
Male, n (%)	31 (63.3)	26 (54.2)	33 (68.8)	28 (51.9)	31 (58.5)	38 (71.7)
Race, n (%)						
White	45 (91.8)	42 (87.5)	37 (77.1)	42 (77.8)	46 (86.8)	44 (83.0)
Black or African-American	2 (4.1)	6 (12.5)	6 (12.5)	6 (11.1)	2 (3.8)	5 (9.4)
Ethnicity, Hispanic/Latino, n (%)	7 (14.3)	6 (12.5)	6 (12.5)	5 (9.3)	7 (13.2)	10 (18.9)
BMI, kg/m², mean (SD)	31.8 (7.7)	32.1 (7.3)	32.0 (6.2)	30.2 (6.0)	30.2 (5.4)	31.5 (6.7)
HeFH, n (%)	8 (16.3)	6 (12.5)	4 (8.3)	6 (11.1)	8 (15.1)	9 (17.0)
CHD history, n (%)	23 (46.9)	29 (60.4)	25 (52.1)	32 (59.3)	32 (60.4)	36 (67.9)
CHD risk equivalent, n (%)[a]	16 (32.7)	12 (25.0)	15 (31.3)	11 (20.4)	11 (20.8)	14 (26.4)
Hypertension, n (%)	36 (73.5)	33 (68.8)	34 (70.8)	40 (74.1)	36 (67.9)	42 (79.2)
Type II diabetes, n (%)	19 (38.8)	23 (47.9)	28 (58.3)	18 (33.3)	21 (39.6)	17 (32.1)
Use of LLT other than statins, n (%)	11 (22.4)	8 (16.7)	11 (22.9)	11 (20.4)	13 (24.5)	9 (17.0)
Baseline lipid parameters, mg/dL, *mmol/L or g/L*						
LDL−C (calculated)						
Mean (SD)	107.3 (26.4)	102.4 (41.9)	105.9 (36.0)	118.3 (32.2)	119.0 (48.0)	112.9 (43.3)
Mean (SD)	*2.780 (0.684)*	*2.653 (1.085)*	*2.743 (0.933)*	*3.065 (0.834)*	*3.082 (1.243)*	*2.924 (1.122)*
LDL−C (measured)						
Mean (SD)	106.0 (29.1)	94.7 (33.6)	100.2 (37.1)	114.1 (30.0)	115.2 (48.4)	108.6 (43.3)
Mean (SD)	*2.745 (0.753)*	*2.453 (0.870)*	*2.594 (0.960)*	*2.955 (0.777)*	*2.984 (1.254)*	*2.813 (1.120)*
Non-HDL−C, mean (SD)	138.0 (37.5)	131.7 (48.8)	136.9 (41.7)	145.8 (36.6)	149.0 (49.7)	143.6 (44.4)
Mean (SD)	*3.575 (0.971)*	*3.411 (1.263)*	*3.546 (1.079)*	*3.777 (0.949)*	*3.859 (1.288)*	*3.720 (1.151)*
Apo B, mean (SD)	93.4 (22.6)	89.0 (25.9)	92.7 (25.2)	97.8 (20.4)	100.8 (25.9)	96.7 (23.6)
Mean (SD)	*0.934 (0.226)*	*0.890 (0.259)*	*0.927 (0.252)*	*0.978 (0.204)*	*1.008 (0.259)*	*0.967 (0.236)*
Lp(a), median (Q1:Q3)	22.0 (8.0:74.0)	38.5 (14.0:106.0)	26.0 (8.0:48.0)	49.5 (16.0:105.0)	35.5 (15.0:76.0)	28.0 (6.0:70.0)
Median (Q1:Q3)	*0.22 (0.080:0.740)*	*0.385 (0.140:1.060)*	*0.260 (0.080:0.480)*	*0.495 (0.160:1.050)*	*0.355 (0.150:0.760)*	*0.280 (0.060:0.700)*
Fasting TGs, median (Q1:Q3)	116.0 (86.0:199.0)	127.0 (95.0:163.5)	130.5 (90.5:203.0)	116.0 (91.0:179.0)	143.0 (93.0:192.0)	143.0 (108.0:190.0)
Median (Q1:Q3)	*1.311 (0.972:2.249)*	*1.435 (1.074:1.848)*	*1.475 (1.023:2.294)*	*1.311 (1.028:2.023)*	*1.616 (1.051:2.170)*	*1.616 (1.220:2.147)*
HDL-C, mean (SD)	49.4 (12.7)	51.0 (13.0)	48.5 (14.2)	51.8 (11.0)	52.2 (13.7)	46.9 (13.6)
Mean (SD)	*1.281 (0.329)*	*1.322 (0.336)*	*1.257 (0.369)*	*1.342 (0.284)*	*1.352 (0.355)*	*1.216 (0.353)*

ALI, alirocumab; Apo, apolipoprotein; BMI, body mass index; CHD, coronary heart disease; EZE, ezetimibe; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL−C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); RSV, rosuvastatin; SD, standard deviation; TGs, triglycerides.

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

the ezetimibe add-on group, and 98.7% in the double-dose rosuvastatin group. Of the 92 patients in the pooled alirocumab group who received at least one injection of study drug, 17 (18.5%) patients had their dose increased to alirocumab 150 mg Q2W at Week 12: 7 (15.9%) patients in the baseline rosuvastatin 10 mg regimen and 10 (20.8%) patients in the baseline rosuvastatin 20 mg regimen.

3.2. Efficacy

In the baseline rosuvastatin 10 mg regimen ITT analysis, alirocumab add-on treatment significantly reduced LDL−C levels at Week 24 versus the other comparators ($p < 0.0001$) (Fig. 1). From baseline, add-on alirocumab reduced LDL−C by 50.6%, add-on ezetimibe reduced LDL−C by 14.4%, and double-dose (20 mg) rosuvastatin reduced LDL−C by 16.3%. LDL−C reductions in the alirocumab add-on group were observed by Week 4 and were maintained through Week 24 (Supplementary Fig. 3).

In the baseline rosuvastatin 20 mg regimen ITT analysis, mean reductions from baseline in LDL−C at Week 24 were greater in the alirocumab add-on group versus the other comparators (Fig. 1). LDL−C reductions were 36.3% in the add-on alirocumab group, compared with 11.0% in the add-on ezetimibe group ($p = 0.0136$) and with 15.9% in the double-dose (40 mg) rosuvastatin group ($p = 0.0453$). However, the pre-specified threshold p-value for these 4-way comparisons was 0.0125, therefore both primary comparisons failed to reach statistical significance and, as a result, all key secondary efficacy endpoints were not tested for statistical significance with respect to the two comparisons in the baseline rosuvastatin 20 mg regimen. Investigation of the data suggests a larger variability in the baseline rosuvastatin 20 mg regimen (Fig. 1) than previously observed. In part, the larger variability can be attributed to an outlying observation in one patient in the rosuvastatin 20 mg + ezetimibe group, caused by the low, Day 1, pre-dose calculated LDL−C value of 13 mg/dL (~0.34 mmol/L). However, this patient's low calculated LDL−C at baseline had been confirmed against the measured LDL−C (beta-quantification) for the same blood draw and deemed by the central lipid laboratory to be correct. The mean LDL−C reductions from baseline over time in the alirocumab groups compared with the ezetimibe add-on and double-dose rosuvastatin treatment groups are shown in Supplementary Fig. 3.

Between group differences in LDL−C reductions in the on-treatment analysis were consistent with the primary analysis (Supplementary Table 1) as were results with LDL−C measured using beta quantification and pattern mixture model analysis (Supplementary Tables 2 and 3).

An analysis which pooled data from both the baseline rosuvastatin 10 mg and 20 mg regimens confirmed a greater LDL−C-lowering effect for alirocumab add-on treatment compared with the double-dose rosuvastatin treatment and ezetimibe add-on treatment at Week 12 (ITT analysis) and Week 24 (ITT and on-treatment analyses). In these pooled analyses, measures of variability were less affected by individual values and the overall sample numbers were larger. Accordingly, the nominal p-value was <0.0001 for all comparisons (alirocumab add-on versus ezetimibe add-on and alirocumab add-on versus double-dose rosuvastatin treatment) at Week 12 (ITT analysis) and Week 24 (ITT and on-treatment analyses) (Supplementary Table 4). Of further note, in the pooled dose regimen in patients who received a dose increase, the mean percent change from baseline in calculated LDL−C at Week 12 was −20.3%. When the alirocumab dose was increased from 75 to 150 mg, there was a further 14% decrease in LDL−C observed at Week 24 (−34.4% from baseline) (Supplementary Fig. 4).

3.2.1. Proportion of patients achieving LDL−C goals

In the baseline rosuvastatin 10 mg regimen groups, the proportion of patients at very-high and high CV risk who reached a LDL−C level of <70 mg/dL (1.8 mmol/L) or <100 mg/dL (2.6 mmol/L) at Week 24, depending on risk status, was significantly greater in the alirocumab add-on group (84.9%) compared with the ezetimibe add-on group (57.2%; $p = 0.0007$) and the rosuvastatin 20 mg group (45.0%; $p < 0.0001$) (Fig. 2). The proportion of patients who reached the more stringent LDL−C level of <70 mg/dL (1.8 mmol/L) at Week 24 was also significantly greater in the alirocumab add-on group (77.8%) compared with the ezetimibe add-on and rosuvastatin 20 mg groups (43.1%; $p < 0.0001$ and 31.3%; $p < 0.0001$), respectively (Fig. 2).
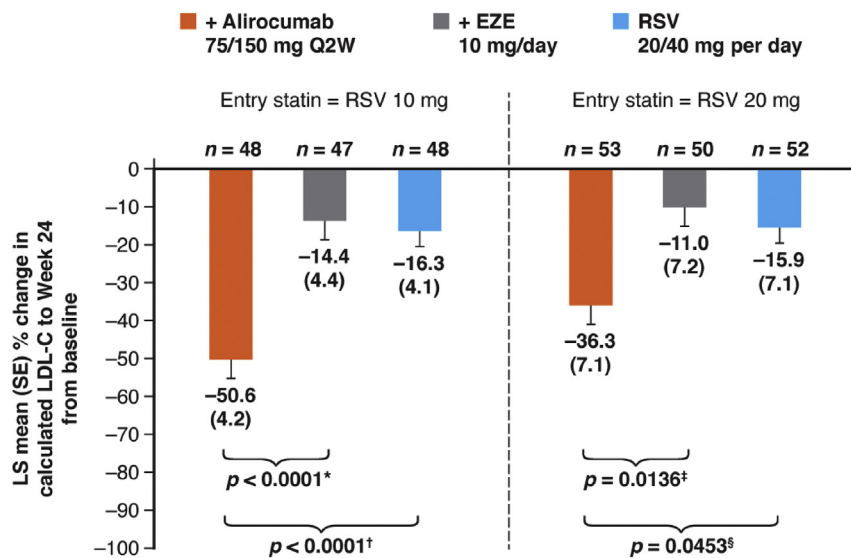

Fig. 1. Percent change in calculated LDL−C from baseline to Week 24 (ITT analysis). EZE, ezetimibe; ITT, intent-to-treat; LDL−C, low-density lipoprotein cholesterol; LS, least squares; RSV, rosuvastatin; SE, standard error. p-values achieved statistical significance at the 0.0125 level; nominal p-values are provided for descriptive purposes only. LS mean (SE) % difference in calculated LDL−C versus comparator agents at Week 24: *−36.1 (6.1); †−34.2 (5.9); ‡−25.3 (10.1); §−20.3 (10.1). LS means, SE, and p-value taken from mixed-model with repeated measures analysis.
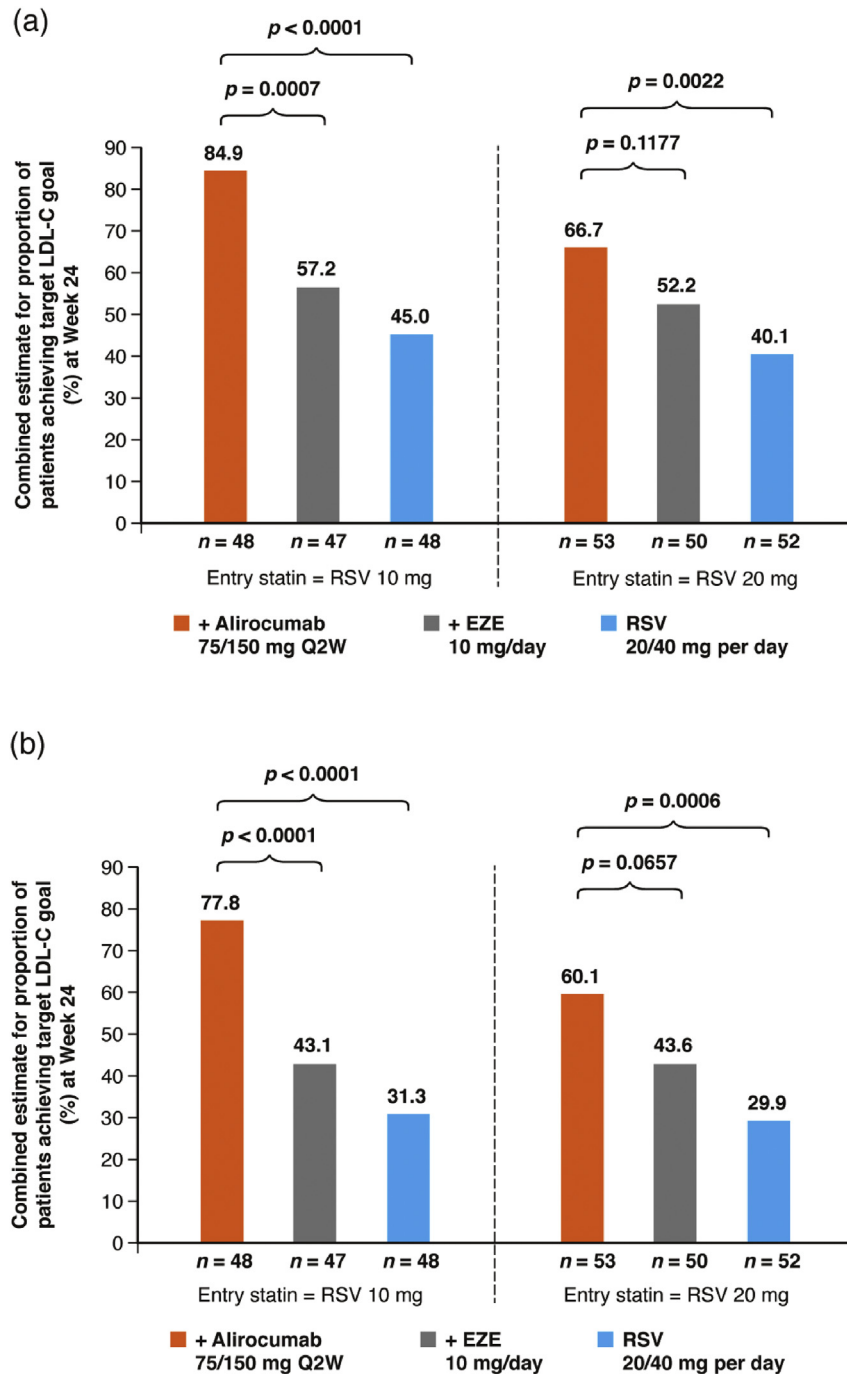
(a)

(b)

Fig. 2. Proportion of patients achieving LDL–C goals at Week 24: (a) LDL–C <70 mg/dL (very-high CV risk) or <100 mg/dL (high CV risk); (b) LDL–C <70 mg/dL (regardless of CV risk). CV, cardiovascular; EZE, ezetimibe; LDL–C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; RSV, rosuvastatin. LDL–C goals: very-high risk, <70 mg/dL (1.8 mmol/L), high-risk: <100 mgdL (2.6 mmol/L). *p*-values are for pairwise comparisons between alirocumab and comparator groups within each baseline regimen. Differences were significant for the baseline rosuvastatin 10 mg regimen according to the hierarchical testing procedure, with a significance threshold of 0.0125 to account for 4 primary pairwise comparisons. The primary comparisons for the baseline rosuvastatin 20 mg regimen were significant versus the rosuvastatin 40 mg treatment group but not versus add-on ezetimibe and *p*-values are shown for descriptive purposes only.

In the baseline rosuvastatin 20 mg regimen groups, the proportion of very-high and high risk patients who reached a LDL–C level of <70 mg/dL (1.8 mmol/L) or <100 mg/dL (2.6 mmol/L) at Week 24, depending on risk status, was 66.7% in the alirocumab add-on group, 52.2% in the ezetimibe add-on group (nominal $p = 0.1177$), and 40.1% in the rosuvastatin 40 mg treatment group (nominal $p = 0.0022$) (Fig. 2). The proportion of patients who reached a LDL–C level of <70 mg/dL (1.8 mmol/L) at Week 24 was 60.1% in the alirocumab add-on group, 43.6% in the ezetimibe add-

on group (nominal $p = 0.0657$), and 29.9% in the rosuvastatin 40 mg group (nominal $p = 0.0006$) (Fig. 2).

3.2.2. Other lipid parameters

Significant reductions in apolipoprotein (Apo) B, non-high-density lipoprotein cholesterol (non-HDL–C), and Lp(a) were seen in the alirocumab add-on group versus other comparators in the baseline rosuvastatin 10 mg regimen (Table 2). The alirocumab add-on group also produced modest reductions in triglycerides and

Table 2
Percent change from baseline in key secondary lipid endpoints (ITT analysis).

LS mean (SE) change from baseline, %	Entry statin RSV 10 mg			Entry statin RSV 20 mg		
	ALI + RSV 10 mg (n = 48)	EZE + RSV 10 mg (n = 47)	RSV 20 mg (n = 48)	ALI + RSV 20 mg (n = 53)	EZE + RSV 20 mg (n = 50)	RSV 40 mg (n = 52)
Calculated LDL—C Week 12	−49.6 (4.1)	−17.4 (4.2)	−17.1 (4.1)	−32.3 (5.2)	−19.3 (5.4)	−22.1 (5.3)
Difference ALI vs comparator	–	−32.2 (5.8)	−32.5 (5.8)	–	−12.9 (7.5)	−10.2 (7.4)
p-value	–	<0.0001*	<0.0001*	–	0.0861	0.1747
Non-HDL—C Week 24	−42.7 (3.5)	−13.4 (3.7)	−11.3 (3.4)	−31.4 (5.2)	−12.9 (5.2)	−11.2 (5.1)
Difference ALI vs comparator	–	−29.3 (5.1)	−31.4 (4.9)	–	−18.4 (7.3)	−20.1 (7.3)
p-value	–	<0.0001*	<0.0001*	–	0.0133	0.0063
Apo B Week 24	−36.5 (3.1)	−9.7 (3.1)	−7.3 (3.0)	−28.3 (4.3)	−11.2 (4.3)	−9.8 (4.1)
Difference ALI vs comparator	–	−26.8 (4.4)	−29.2 (4.3)	–	−17.1 (6.1)	−18.5 (6.0)
p-value	–	<0.0001*	<0.0001*	–	0.0057	0.0024
Lp(a), Week 24	−27.9 (4.1)	−4.3 (4.5)	−4.0 (4.3)	−22.7 (5.1)	−5.8 (4.6)	−5.2 (4.8)
Difference ALI vs comparator	–	−23.6 (6.2)	−23.9 (5.9)	–	−16.9 (6.8)	−17.5 (7.0)
p-value	–	0.0001*	<0.0001*	–	0.0131	0.0123
Fasting TG Week 24	−11.2 (4.6)	−8.3 (4.8)	−1.8 (4.5)	−8.7 (4.5)	−11.1 (4.3)	−9.9 (4.1)
Difference ALI vs comparator	–	−2.9 (6.6)	−9.3 (6.4)	–	2.4 (6.2)	1.2 (6.1)
p-value	–	0.6639	0.1454	–	0.7039	0.8459
HDL-C Week 24	9.1 (2.4)	4.0 (2.5)	1.7 (2.4)	7.2 (2.3)	−1.8 (2.3)	1.5 (2.3)
Difference ALI vs comparator	–	5.1 (3.5)	7.4 (3.4)	–	9.0 (3.3)	5.7 (3.3)
p-value	–	0.1491	0.0311	–	0.0072	0.0866

ALI, alirocumab; Apo, apolipoprotein; EZE, ezetimibe; HDL-C, high-density lipoprotein cholesterol; ITT, intent-to-treat; LDL—C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); LS, least squares; RSV, rosuvastatin; SD, standard deviation; SE, standard error; TG, triglycerides.
LS means, SE, and p-value taken from a mixed-model with repeated measures analysis with hierarchical procedure to control for type I error except for Lp(a) and TG, which were analyzed using multiple imputation approach to account for missing values, followed by robust regression model with the endpoint of interest as the response variable and the treatment group and corresponding baseline values as effects.
p-values are for alirocumab versus comparator.
*p-values with an asterisk were formally tested based on the predefined hierarchical sequence and achieved statistical significance at the 0.0125 level; nominal p-values are provided for descriptive purposes only.

increases in HDL-C (Table 2).

In the baseline rosuvastatin 20 mg regimen, decreases in Apo B, non-HDL—C, and Lp(a) were observed in the alirocumab add-on group when compared with the ezetimibe add-on and rosuvastatin 40 mg groups (Table 2).

3.3. Safety

The summary of safety results are presented by the treatment groups of pooled rosuvastatin dose regimens in order to maximize the detection of potential safety signals. For pooled data, 3 treatment groups were formed by combining treatment groups in each of the baseline rosuvastatin regimens: the add-on alirocumab treatment group, pooling the alirocumab + rosuvastatin 10 mg group and the alirocumab + rosuvastatin 20 mg group; the double-dose rosuvastatin treatment group, pooling the placebo-alirocumab + rosuvastatin 20 mg group and the placebo-alirocumab + rosuvastatin 40 mg group; and the add-on ezetimibe treatment group, pooling the ezetimibe + rosuvastatin 10 mg group and the ezetimibe + rosuvastatin 20 mg group.

The incidence of TEAEs was generally similar across treatment groups in the pooled dose regimens, with 58 patients (56.3%) experiencing a TEAE in the alirocumab add-on group, 54 patients (53.5%) in the ezetimibe add-on group, and 68 patients (67.3%) in the double-dose rosuvastatin group (Table 3). A total of 22 patients (7.2%) experienced a serious AE (SAE): 6 patients (5.8%) in the alirocumab add-on group, 8 patients (7.9%) in the ezetimibe add-on group, and 8 patients (7.9%) in the double-dose rosuvastatin group. One patient (0.3%) who was randomized to the ezetimibe + rosuvastatin 20 mg group died of a subdural hematoma during the course of the study; the death was adjudicated as a CV death. A total of 18 patients (5.9%) discontinued treatment prematurely due to a TEAE: 5 (4.9%) in the alirocumab add-on group, 8 (7.9%) in the ezetimibe add-on group and 5 (5.0%) in the double-dose rosuvastatin group. Nine patients (8.7%) in the

alirocumab add-on group, 2 patients (2.0%) in the ezetimibe add-on group and 7 patients (6.9%) in the double-dose rosuvastatin group had a potential general allergic TEAE. Of these, 2 patients (1.9%) in the alirocumab add-on group experienced a general allergic TEAE that led to study drug being permanently discontinued. In terms of safety events of interest, local injection-site reactions, all mild in intensity, were experienced by 4 patients (3.9%) in the alirocumab add-on group, 2 patients (2.0%) in the double-dose rosuvastatin group, and none in the ezetimibe group; none of the local injection-site reactions led to treatment discontinuation. Neurological TEAEs of interest were reported in 2 patients (1.9%) in the alirocumab add-on group, 3 patients (3.0%) in the ezetimibe add-on group, and 2 patients (2.0%) in the double-dose rosuvastatin group. One patient (1.0%) in each group within the pooled dose regimen experienced a neurocognitive TEAE. No neurocognitive TEAEs were considered SAEs and none led to permanent study drug discontinuation. One patient (1.0%) in each of the ezetimibe add-on and double-dose rosuvastatin groups experienced a CV TEAE that was confirmed by adjudication. The CV event in the ezetimibe add-on group (ezetimibe + rosuvastatin 20 mg) was adjudicated as non-fatal myocardial infarction; the CV event in the double-dose rosuvastatin group (rosuvastatin 20 mg) was adjudicated in the category of fatal and non-fatal ischemic stroke. Creatine kinase more than 3 times the upper limit of normal was observed in 3 patients (3.1%) in the ezetimibe add-on group, 2 patients (2.0%) in the double-dose rosuvastatin group, and none in the alirocumab add-on group. One patient (1.0%) in the alirocumab add-on group had an increase in alanine aminotransferase (ALT) over 3 times the upper limit of normal; no patients in any treatment group had both ALT over 3 times the upper limit of normal and total bilirubin over 2 times the upper limit of normal. Further, no patients in any treatment group experienced a confirmed hemolytic anemia TEAE or experienced an ophthalmological TEAE during the study (Table 3). Further details on AEs are provided in Supplementary Table 5.

Table 3
Safety analysis (safety population pooled across statin entry regimens).

% (n) of patients	Pooled ALI 75/150 ($n = 103$)	Pooled EZE ($n = 101$)	Pooled double RSV ($n = 101$)
Any TEAEs	56.3 (58)	53.5 (54)	67.3 (68)
Treatment-emergent SAEs	5.8 (6)	7.9 (8)	7.9 (8)
TEAE leading to death	0	1.0 (1)	0
TEAEs leading to discontinuation	4.9 (5)	7.9 (8)	5.0 (5)
Most frequently reported TEAEs by preferred term ($\geq$5% of patients in any group)			
Nasopharyngitis	3.9 (4)	5.0 (5)	6.9 (7)
Upper respiratory tract infections	5.8 (6)	4.0 (4)	8.9 (9)
Dizziness	2.9 (3)	2.0 (2)	5.0 (5)
Pain in extremity	1.9 (2)	3.0 (3)	7.9 (8)
Safety events of special interest			
Allergic events[a]	8.7 (9)	2.0 (2)	6.9 (7)
Injection-site reactions	3.9 (4)	0	2.0 (2)
Adjudicated CV events[b]	0	1.0 (1)	1.0 (1)
Hemolytic anemia	0	0	0
Neurocognitive disorders[c]	1.0 (1)	1.0 (1)	1.0 (1)
Neurologic disorders[d]	1.9 (2)	3.0 (3)	2.0 (2)
Ophthalmologic events[e]	0	0	0
Laboratory values			
ALT >3 × ULN, % (n/N)	1.0 (1/101)	0/99	0/100
Creatine kinase >3 × ULN, % (n/N)	0/98	3.1 (3/97)	2 (2/100)

ALI, alirocumab; ALT, alanine aminotransferase; CV, cardiovascular; EZE, ezetimibe; RSV, rosuvastatin; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

[a] The selection of preferred terms is based on Standardized MedDRA (Medical Dictionary for Regulatory Activities) Queries: "hypersensitivity" (broad + narrow) excluding the following preferred terms: "infusion-site dermatitis", "infusion-site hypersensitivity", "infusion-site rash", "injection-site rash", "injection-site urticaria", and "injection-site vasculitis".

[b] Adjudicated CV events include all CV adverse events positively adjudicated. The adjudication categories are the following: CHD death, non-fatal myocardial infarction, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalization, congestive heart failure requiring hospitalization, and ischemia-driven revascularization procedure (percutaneous coronary intervention, coronary artery bypass graft).

[c] The selection of preferred terms is based on a Custom MedDRA Query that was based on the following five 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."

[d] The 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").

[e] The selection of preferred terms is based on Standardized MedDRA Queries: "optic nerve disorders" (broad + narrow), "retinal disorders" (narrow), and "corneal disorders" (narrow).

3.4. Anti-drug antibodies

Two patients (2.5%) in the alirocumab add-on group were negative at baseline in the ADA assay but positive in one or more post-dose samples. Both patients appeared to demonstrate a treatment-emergent ADA response, but all samples exhibited low levels of reactivity in the assay. Of these 2 patients, 1 patient had a transient response while the other patient had an indeterminate response. Overall, in these 2 patients who developed ADAs, immunogenicity was low and ADA assay positivity did not have an effect on the LDL–C-lowering efficacy of alirocumab during this study, nor were any particular safety concerns observed.

4. Discussion

Many patients at high or very-high risk for CVD do not achieve LDL–C treatment goals with existing therapies [20,21]. While statins are recommended as first-line therapy for LDL–C-lowering [1,2], their use, even when used in combination with other therapies, does not always enable patients to reach their individual LDL–C target levels [7]. This study compared adding alirocumab therapy versus adding ezetimibe or doubling the rosuvastatin dose in patients at high or very-high CV risk.

In the baseline rosuvastatin 10 mg regimen, treatment with add-on alirocumab therapy significantly reduced calculated LDL–C levels at Week 24 when compared with doubling the dose of rosuvastatin regimen or ezetimibe add-on therapy. In the rosuvastatin 10 mg baseline regimen group, alirocumab add-on therapy also significantly improved key secondary endpoints, such as levels of Apo B, non-HDL–C, and Lp(a), as well as the proportion of patients achieving pre-specified LDL–C levels.

Consistent with the results in the baseline rosuvastatin 10 mg treatment regimen, greater reductions in calculated LDL–C levels were observed in the group receiving add-on alirocumab to rosuvastatin 20 mg when compared with doubling the rosuvastatin dose or an ezetimibe add-on treatment regimen. However, these differences did not reach the p-value threshold of 0.0125 for these multiple comparisons. The failure to reach statistical significance could be explained, in part, by the large standard error in the LDL–C values in the baseline rosuvastatin 20 mg group compared with the baseline rosuvastatin 10 mg group (7.1 versus 4.2, respectively), which was greater than estimated in the original power calculations.

Further, it should be noted that the findings in both baseline rosuvastatin treatment regimens are inconsistent with LDL–C-lowering effects seen in the literature. In the add-on ezetimibe groups, LDL–C reductions of 14.4% and 11.0% were found in the baseline rosuvastatin 10 mg and 20 mg regimens, respectively, compared with an average 20% reduction seen in published studies [22]. In addition, a greater than expected LDL–C level reduction was observed with doubling of the statin dose, 16.3% in the baseline rosuvastatin 10 mg regimen and 15.9% in the baseline rosuvastatin 20 mg regimen, which is more than the expected reduction of a further 6% as seen in other studies in which the statin dose is doubled [23]. These observed differences may be due to the small number of patients studied and a high inter-individual variability. Measures of variability were less affected by individual values in the pooled analysis; the nominal p-value for the change in LDL–C was <0.0001 for all comparisons between treatment groups at Week 12 (ITT analysis) and Week 24 (ITT and on-treatment analyses).

In this study, alirocumab demonstrated consistent LDL–C reductions in patients receiving stable rosuvastatin therapy, as well as

consistent decreases in Apo B, non-HDL–C, and Lp(a). In previous studies in patients with non-familial hypercholesterolemia on various, stable doses of statins, or those with heterozygous familial hypercholesterolemia on stable doses of statin with or without ezetimibe, alirocumab demonstrated robust, consistent, and significant reductions in LDL–C levels by 40%–70%, as well as reductions in Apo B, non-HDL–C, and Lp(a) [8–16]. Reports of other PCSK9 inhibitors have also shown reductions in LDL–C and other lipoproteins across a range of patient populations and background therapies [24–27]. In addition, these data confirm earlier reports that substantial reductions in Lp(a) are observed in patients receiving alirocumab.

A flexible alirocumab dosing regimen, which allowed for the alirocumab dose to be increased only when patients did not reach their individual LDL–C goals (depending on their CV risk) by a pre-specified time point (Week 8), was also evaluated in this study. All patients receiving alirocumab began the study on a regimen of 75 mg Q2W and more than 80% of patients were maintained on the 75 mg Q2W dose; in the pooled alirocumab treatment groups, 17 patients (18.5%) had their dose increased to alirocumab 150 mg Q2W at Week 12 in a blinded manner.

Patients who remained on 75 mg Q2W maintained the reduction in calculated LDL–C levels observed from Week 12 to Week 24, while patients who had their dose increased to 150 mg at the Week 12 visit showed a further reduction in LDL–C levels from Week 12 to Week 24. In the pooled dose regimen in patients who received a dose increase to 150 mg Q2W, the mean percent change from baseline in calculated LDL–C at Week 12 was −20.3% with a further 14% reduction observed at Week 24.

Overall, the addition of alirocumab produced greater LDL–C-lowering than its comparators over the entire 24-week study period, demonstrating durability of effect over this time period. Alirocumab was well tolerated and the numbers of patients reporting TEAEs were similar across treatment groups. No safety signals were detected for alirocumab add-on therapy when compared with doubling the statin dose or ezetimibe add-on therapy. The overall rate of AEs of special interest, which were chosen based on the alirocumab mode of action, theoretical risks raised from literature, or potential risks based on any findings in preclinical studies, was low. There were few reports of allergic reactions or local injection-site reactions, although more frequent in the alirocumab group than in the comparator groups. In addition, the rates of ALT and creatine kinase over 3 times the upper limit of normal were low and no patients in any treatment group had ALT over 3 times the upper limit of normal and total bilirubin over 2 times the upper limit of normal. Antibodies to alirocumab were observed in 2 patients receiving alirocumab but did not impact overall safety, nor was there an effect on efficacy. Further, this study reflects the safety profile demonstrated by alirocumab across Phase 2 and 3 studies, in which a total of 5234 patients with hypercholesterolemia were included in the double-blind safety pool; 3340 patients received alirocumab for an overall exposure of 3451 patient-years. In the Phase 2 and 3 pooled safety analysis, the rates of TEAEs, treatment-emergent SAEs, and TEAEs leading to permanent treatment discontinuation were similar between the alirocumab and control groups. Among the common TEAEs, injection-site reactions (7.3% versus 5.2%) and pruritus (1.1% versus 0.4%) were identified as more common in patients receiving alirocumab than control. In addition, the rates of neurologic events, neurocognitive events, hepatic disorders, and clinically meaningful changes in glycemic control were generally similar to placebo and ezetimibe in the pooled data [28].

As many high-risk patients do not achieve LDL–C goals on current therapies, there is an unmet need for new therapeutic options to reduce risk in such patients. In patients with hypercholesterolemia at high or very-high CV risk, alirocumab provided clinically important and incremental reductions in LDL–C compared with the currently available options, namely the addition of ezetimibe or doubling the statin dose. Both alirocumab 75 mg and 150 mg are well tolerated, allowing a treat-to-target approach in patients not at their LDL–C goal. Further studies, including the ODYSSEY Outcomes trial (NCT01663402), will provide additional efficacy and safety data on alirocumab.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://

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