



# Efficacy and safety of alirocumab in Korean patients with hypercholesterolemia and high cardiovascular risk: subanalysis of the ODYSSEY-KT study

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**Background/Aims:** Efficacy and safety data of alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), is not yet well established in the Korean population. We assessed them in ODYSSEY-KT through the pre-specified Korean subanalysis.

**Methods:** In the ODYSSEY-KT study, South Korean and Taiwanese patients with hypercholesterolemia and high cardiovascular risks were randomized (1:1) to alirocumab or placebo. Alirocumab was self-administered subcutaneously at 75 mg every 2 weeks with a maximally tolerated statin dose with or without other lipid-modifying therapies. Alirocumab dose was increased to 150 mg every 2 weeks at week 12 if low density lipoprotein cholesterol (LDL-C)  $\geq$  70 mg/dL at week 8. Primary endpoint was percent change in LDL-C from baseline to week 24. Results from Korean cohort (n = 83; 40 for alirocumab and 43 for placebo, respectively) analyses are reported here.

**Results:** In alirocumab group, the least square of mean change percent in LDL-C levels was -65.7% (placebo: 11.1%;  $p < 0.0001$ ) and 92.0% of them achieved LDL-C  $<$  70 mg/dL (placebo: 12.7%;  $p < 0.0001$ ) at week 24. Alirocumab also showed significantly greater improvements in high density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol, lipoprotein(a), and apolipoprotein B than placebo ( $p < 0.05$ ). Two consecutive calculated LDL-C values  $<$  25 mg/dL were observed in 37.5% of alirocumab-treated patients. Overall, 45.0% alirocumab-treated and 51.2% placebo-treated patients experienced treatment-emergent adverse events (TEAEs) without discontinuation of treatment due to TEAEs.

**Conclusions:** Alirocumab has demonstrated to be effective in improvement of LDL-C and related lipid profiles in Korean cohort. Alirocumab was generally well tolerated with no significant safety signals.

**Keywords:** PCSK9; Cholesterol, LDL; ODYSSEY; Hypercholesterolemia

## INTRODUCTION

Dyslipidemia is a major risk factor for cardiovascular disease (CVD), the second-leading cause of mortality in

Korea [1-3] and is also associated with increased prevalence of metabolic syndrome. In recent years, the prevalence of dyslipidemia has been increasing steadily in Korea [4,5]. The association between higher low density

lipoprotein cholesterol (LDL-C) level and CVD is well established and guidelines recommend  $< 70$  or  $< 100$  mg/dL as target levels in patients with very high or high CV risk, respectively [6,7].

Guidelines for the management of dyslipidemia in Korea were established in 2015 [8]. These guidelines recommend lifestyle modification and pharmacological management of dyslipidemia for prevention of CVD. The CEPHEUS Pan-Asian survey showed suboptimal achievement of target LDL-C and total cholesterol (TC) with existing treatments in Korea [9].

Among several lipid lowering therapies (LLTs), proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors modulate cholesterol homeostasis via its ability to upregulate LDL receptor expression on hepatocyte cell membrane and by decreasing plasma LDL-C levels [10]. Recent consensus statements from both the American College of Cardiology and European Society of Cardiology/European Atherosclerosis Society recommend the use of PCSK9 inhibitors or ezetimibe in patients with very high or high cardiovascular (CV) risk who have high baseline LDL-C levels (70 to 189 mg/dL) uncontrolled by maximally tolerated doses of statins [11,12]. Alirocumab is a fully human monoclonal antibody that inhibits PCSK9 and has been clinically evaluated for its ability to reduce LDL-C levels. Several ODYSSEY phase 3 studies have demonstrated that alirocumab can reduce LDL-C levels substantially when used as monotherapy or when combined with background statin therapy with or without other LLTs [13-21].

However, the safety and efficacy of alirocumab has not been established in the Korean population. The ODYSSEY KT study was performed to assess the safety and efficacy of alirocumab among Korean and Taiwanese patients with uncontrolled serum cholesterol levels and coronary heart disease (CHD) or those at risk for CHD [22]. Here we present a pre-specified subanalysis for Korean patients.

## METHODS

### Study design

The ODYSSEY KT study (NCT02289963) was a randomized, double-blind, placebo-controlled, parallel-group, and multicenter study [22]. The Korean cohort study was

conducted in 16 study centers across Korea between January 2015 and April 2016. The protocol was approved by the relevant independent Institutional Review Boards (Keimyung University Dongsan Medical Center IRB 2014-09-009). The study was performed according to the principles of the Declaration of Helsinki and applicable amendments and the International Conference on Harmonisation guidelines for Good Clinical Practice. All participating patients provided written informed consent.

### Patients

Eligible patients (aged  $\geq 18$  years) had established CHD or CHD risk equivalents and hypercholesterolemia that was inadequately controlled with a maximally tolerated statin dose (with or without other LLTs) at a stable dose  $\geq 4$  weeks prior to screening. CHD risk equivalents were defined as history of CVD, moderate chronic kidney disease, or diabetes with multiple risk factors. Inadequately controlled hypercholesterolemia was defined as LDL-C  $\geq 70$  mg/dL in patients with documented CVD history or  $\geq 100$  mg/dL in patients without CVD history. The following were considered maximally tolerated statin doses: atorvastatin, 40 to 80 mg/day; rosuvastatin, 20 mg/day; and simvastatin, 40 mg/day. Patients receiving daily dose of atorvastatin, rosuvastatin, or simvastatin dose and considered appropriate by the investigator were also eligible to participate. Exclusion criteria for this study are described in Supplementary Table 1.

### Treatment regimen

The total study duration was 35 weeks, consisting of a 3-week screening period, 24 weeks of double-blind treatment, and an 8-week follow-up period. Eligible patients were randomized 1:1 to receive either alirocumab 75 mg every 2 weeks or placebo every 2 weeks using an auto-injector device through the subcutaneous route. Study visits were on weeks 0, 4, 8, 12, 16, and 24. Follow visit was done 8 weeks after the end of treatment visit. Patients on alirocumab who did not achieve LDL-C  $< 70$  mg/dL at week 8 were uptitrated to alirocumab 150 mg every 2 weeks from week 12 onwards. Blinding was maintained in these patients.

### Endpoints

The primary efficacy endpoint was the percent change

in calculated LDL-C values between baseline and week 24 in the intent-to-treat (ITT) population. Other key endpoints included the percent change from baseline to week 24 in non-high density lipoprotein cholesterol (non-HDL-C), TC, HDL-C, fasting triglycerides (TGs), lipoprotein(a) (Lp(a)), apolipoprotein A<sub>1</sub> and apolipoprotein B (Apo B) and the proportion of patients reaching a calculated LDL-C < 70 mg/dL at week 24. Analyses of lipid samples were performed by a central laboratory using standard procedures and individual site laboratory tests for lipid parameters were not allowed during the study period. LDL-C levels were calculated using the Friedewald formula. LDL-C levels were reflexively measured via  $\beta$ -quantification when TG levels were > 400 mg/dL. In addition, LDL-C levels were systematically measured (via the  $\beta$ -quantification method) at weeks 0 and 24 for efficacy analysis purposes.

Safety was assessed throughout the study by monitoring treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory data, and vital signs. TEAEs were defined as adverse events (AEs) that occurred during the time from first administration of blinded study drug to 10 weeks after last administration of blinded study drug.

### Statistical analysis

The sample size calculation has been described previously [22]. Briefly, a total sample size of 40 patients (20 patients in each group) was required to achieve 95% power to detect a mean percent change difference in LDL-C of 30% with a 0.05 two-sided significance level and assuming a common standard deviation (SD) of 25% with all patients having an evaluable primary endpoint. At last, total sample size ( $n = 83$ ) was bigger than the estimated minimum size to satisfy the requirement because we also intended to identify the safety data as well as efficacy. Calculations were done using nQuery Advisor version 7.0 (Statsols, Cork, Ireland).

The primary efficacy endpoint was analyzed using a mixed effect model with repeated measures (MMRM) with all post-baseline data available and missing data accounted for. Fixed categorical effects of treatment group (alirocumab vs. placebo), time (weeks 4, 8, 12, 16, and 24), randomization strata, treatment-by-time point interaction, strata-by-time point interaction, and continuous fixed covariates of baseline LDL-C value and

baseline value-by-time point interaction were included in the MMRM. The 95% confidence intervals (CIs) of the differences were estimated from the model.

Other key endpoints were analyzed in a sequential order using a hierarchical inferential approach when the primary endpoint was significant at 5%  $\alpha$  level. Continuous secondary endpoints with an anticipated normal distribution were analyzed using MMRM. Continuous secondary endpoints with a normal distribution (lipids other than Lp(a) and TGs) were analyzed as for the primary endpoint while those without normal distribution (Lp(a) and TGs) and binary secondary endpoints were analyzed using multiple imputation approach followed by robust regression. Target achievement for LDL-C was analyzed by multiple imputations followed by logistic regression. The ITT population included all randomized patients with LDL-C values available at baseline and at least one other post-randomization time point till the end of study. The modified intent-to-treat (mITT) included the randomized patients who had received at least one dose or part of the study with an evaluable primary endpoint during the treatment period and within one of the analysis windows. All randomized patients who received at least one dose or part of a dose of the alirocumab comprised the safety set. Safety data were analyzed by descriptive statistics and were focused on the TEAE period. All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

### Patient characteristics

A total of 83 patients were enrolled in the Korean subgroup of the ODYSSEY KT study. Both the ITT and safety populations consisted of 83 patients (40 patients in the alirocumab group and 43 patients in the placebo group) while the mITT population comprised 82 patients (40 patients in the alirocumab group and 42 patients in the placebo group) (Fig. 1). Both treatment groups were matched for age, gender, weight, body mass index, medical history, and statin type by intensity. More patients in alirocumab group were taking ezetimibe than those in placebo group ( $n = 7$ , 17.5%; and  $n = 4$ , 9.3%, respectively), but it did not reach the significance level of 0.05

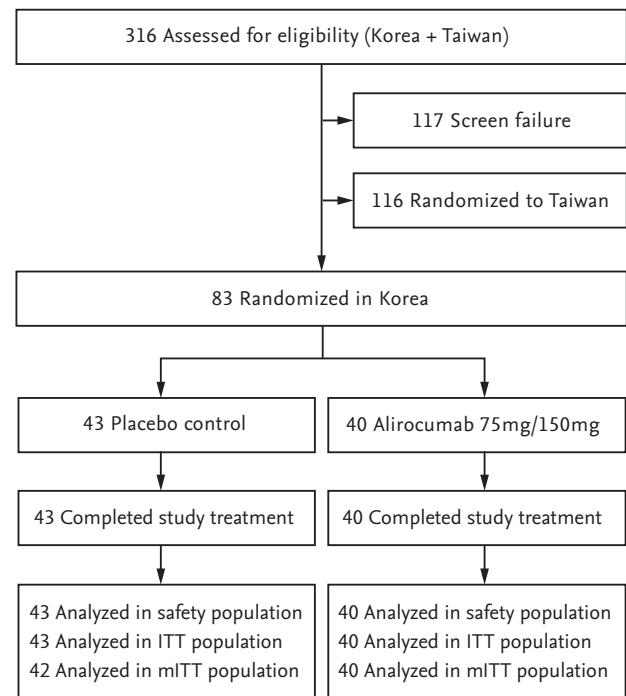
in the *post hoc* chi-square test (Table 1). Additionally, no significant differences were found in lipid parameters between alirocumab and placebo groups at baseline ( $p > 0.05$ ; *post hoc t* tests) (Table 2).

### Efficacy analyses

There was a reduction in LDL-C levels at week 4 and it was maintained till week 24. The calculated least squares mean (LSM)  $\pm$  standard error (SE) of LDL-C levels in the ITT population receiving alirocumab decreased from  $90.7 \pm 3.6$  mg/dL at baseline to  $33.8 \pm 4.5$  mg/dL at week 24 (Fig. 2). In comparison, LSM  $\pm$  SE of LDL-C levels increased from  $95.1 \pm 4.1$  at baseline to  $102.9 \pm 4.4$  at week 24 in patients receiving placebo. The percent change in LSM  $\pm$  SE of LDL-C from baseline to week 24 was  $-65.7\% \pm 4.4\%$  in the alirocumab group in comparison with  $11.1\% \pm 4.2\%$  in the placebo group. The difference in LSM  $\pm$  SE for alirocumab versus placebo was  $-76.7\% \pm 6.1\%$  (95% CI,  $-88.9$  to  $-64.6$ ;  $p < 0.0001$ ) (Table 3 and Fig. 3). Similarly, the percent change in LDL-C from baseline for the mITT population given as LSM  $\pm$  SE was  $-67.3\% \pm 4.4\%$  in the alirocumab group in comparison with  $11.1\% \pm 4.2\%$  in the placebo group and the difference in LSM  $\pm$  SE for alirocumab versus placebo was  $-78.5\% \pm 6.1\%$  (95% CI,  $-90.6$  to  $-66.3$ ;  $p < 0.0001$ ) (Fig. 4).

Significant differences in LSM  $\pm$  SE for alirocumab versus placebo were observed at week 24 in the following lipid parameters: non-HDL-C ( $-62.4\% \pm 4.5\%$ ; 95% CI,  $-71.4$  to  $-53.4$ ;  $p < 0.0001$ ), HDL-C ( $9.0\% \pm 4.2\%$ ; 95% CI,  $0.7$  to  $17.4$ ;  $p = 0.034$ ), TC ( $-41.9\% \pm 3.4\%$ ; 95% CI,  $-48.6$  to  $-35.3$ ;  $p < 0.0001$ ), Lp(a) ( $-40.9\% \pm 7.7\%$ ; 95% CI,  $-56.1$  to  $-25.7$ ;  $p < 0.0001$ ), and ApoB ( $-57.0\% \pm 4.5\%$ ; 95% CI,  $-66.0$  to  $-48.1$ ;  $p < 0.0001$ ) (Table 3 and Fig. 3). The same trend was found in mITT comparisons (Supplementary Table 2).

The proportion of patients achieving LDL-C  $< 70$  mg/dL at week 24 was 92.0% in the alirocumab group and 12.7% in the placebo group (combined estimate for odds ratio, 157.4; 95% CI, 19.0 to 1,306.7;  $p < 0.0001$ ). Three alirocumab-treated patients (7.5%) had LDL-C values  $\geq 70$  mg/dL at week 8 and were uptitrated to alirocumab 150 mg every 2 weeks at week 12. During the treatment period, 15 alirocumab-treated patients (37.5%) had two consecutive calculated LDL-C values  $< 25$  mg/dL, among whom four patients (10.0%) displayed two consecutive LDL-C values  $< 15$  mg/dL.



**Figure 1.** Patient flow: CONSORT diagram. ITT, intent-to-treat; mITT, modified intent-to-treat.

### Safety analysis

A total of 18 patients (45.0%) in the alirocumab group and 22 patients (51.2%) in the placebo group experienced a TEAE. The most commonly reported TEAEs in the alirocumab group by system organ class (SOC) and preferred term (PT) classification were nervous system disorders ( $n = 5$ , 12.5%), majority of which were headaches ( $n = 4$ , 10.0%); followed by infections and infestations ( $n = 4$ , 10.0%), majority of which were nasopharyngitis ( $n = 3$ , 7.5%); and injury, poisoning, and procedural complications ( $n = 4$ , 10.0%), majority of which were due to fall ( $n = 2$ , 5.0%) (Table 4). The most commonly reported TEAEs in placebo group by SOC and PT classification were infections and infestations ( $n = 6$ , 14.0%), followed by gastrointestinal disorders ( $n = 5$ , 11.6%) and general disorders and administration site conditions ( $n = 5$ , 11.6%) (Table 4). Among alirocumab-treated patients who had two consecutive calculated LDL-C  $< 25$  mg/dL ( $n = 15$ ), one case of hepatobiliary disorders (hepatitis acute) and one case of injury, poisoning and procedural complications (fall and radius fracture for the same case) were identified.

**Table 1. Patient characteristics at baseline**

Characteristic	Placebo (n = 43)	Alirocumab 75 mg/150 mg q2w (n = 40)	Total (n = 83)
Age, yr	60.2 ± 9.4	60.8 ± 9.4	60.5 ± 9.3
Age group, yr			
< 45	2 (4.7)	3 (7.5)	5 (6.0)
≥ 45 to < 65	26 (60.5)	22 (55.0)	48 (57.8)
≥ 65 to < 75	13 (30.2)	12 (30.0)	25 (30.1)
≥ 75	2 (4.7)	3 (7.5)	5 (6.0)
Sex			
Male	35 (81.4)	32 (80.0)	67 (80.7)
Female	8 (18.6)	8 (20.0)	16 (19.3)
Weight, kg	71.03 ± 13.75	72.48 ± 12.67	71.73 ± 13.18
BMI, kg/m <sup>2</sup>	25.91 ± 3.67	25.88 ± 3.35	25.90 ± 3.50
BMI group, kg/m <sup>2</sup>			
< 30	39 (90.7)	35 (87.5)	74 (89.2)
≥ 30	4 (9.3)	5 (12.5)	9 (10.8)
CV history/risk factors	43 (100.0)	40 (100.0)	83 (100.0)
CHD	40 (93.0)	40 (100)	80 (96.4)
Coronary revascularization procedures	33 (76.7)	29 (72.5)	62 (74.7)
Acute MI	16 (37.2)	16 (40.0)	32 (38.6)
Unstable angina	9 (20.9)	16 (40.0)	25 (30.1)
Silent MI	7 (16.3)	4 (10.0)	11 (13.3)
Other clinically significant CHD	20 (46.5)	16 (40.0)	36 (43.4)
CHD associated with ≥ 1 comorbidity and/or associated with other CVD	29 (67.4)	29 (72.5)	58 (69.9)
CHD risk equivalents	9 (20.9)	5 (12.5)	14 (16.9)
Ischemic stroke	4 (9.3)	1 (2.5)	5 (6.0)
Moderate CKD	4 (9.3)	4 (10.0)	8 (9.6)
Known history of T2DM and ≥ 2 additional risk factors	1 (2.3)	0	1 (1.2)
At least 2 or more CHD risk equivalents or one CHD risk equivalent associated with hypertension or T2DM	8 (18.6)	3 (7.5)	11 (13.3)
Prior history of MI or ischemic stroke	27 (62.8)	24 (60.0)	51 (61.4)
Intensity of statins prescribed			
High	24 (55.8)	22 (55.0)	46 (55.4)
Low/moderate	19 (44.2)	18 (45.0)	37 (44.6)
Any LLT other than statins	14 (32.6)	14 (35.0)	28 (33.7)
Ezetimibe	4 (9.3)	7 (17.5)	11 (13.3)

Values are presented as mean ± SD or number (%).

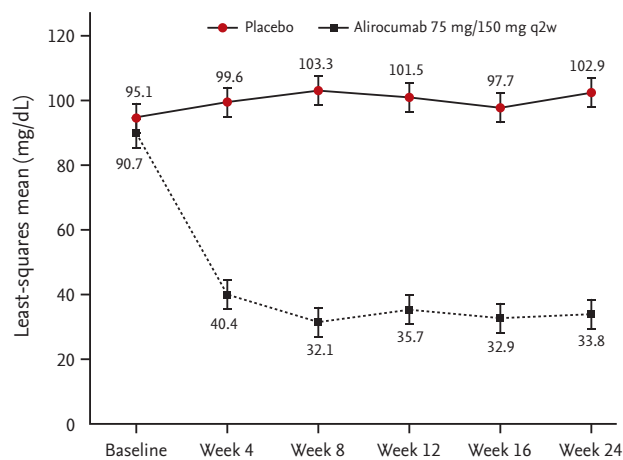
q2w, every 2 weeks; BMI, body mass index; CV, cardiovascular; CHD, coronary heart disease; MI, myocardial infarction; CVD, cardiovascular disease; CKD, chronic kidney disease; T2DM, type 2 diabetes mellitus; LLT, lipid lowering therapy.

**Table 2. Baseline lipid profile of study patients**

Variable	Placebo (n = 43)	Alirocumab 75 mg/ 150 mg q2w (n = 40)	Total (n = 83)
LDL-C, mg/dL	95.1 ± 27.0	90.7 ± 22.9	93.0 ± 25.0
Non-HDL-C, mg/dL	124.4 ± 32.6	117.4 ± 27.0	121.0 ± 30.1
HDL-C, mg/dL	48.5 ± 13.1	45.9 ± 10.6	47.3 ± 11.9
Fasting TG, mg/dL	146.2 ± 67.9	144.2 ± 117.1	145.3 ± 94.3
TC, mg/dL	172.9 ± 28.4	163.3 ± 28.0	168.3 ± 28.4
Lp(a), mg/dL	43.4 ± 36.4	37.0 ± 36.8	40.4 ± 36.5
Apo A1, mg/dL	136.2 ± 25.1	134.0 ± 16.9	135.1 ± 21.5
Apo B, mg/dL	84.6 ± 18.2	79.3 ± 14.7	82.1 ± 16.7

Values are presented as mean ± SD.

q2w, every 2 weeks; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; Lp(a), lipoprotein(a); Apo A1, apolipoprotein A1; Apo B, apolipoprotein B.



**Figure 2.** Calculated low density lipoprotein cholesterol levels (least-squares mean ± standard error) in intent-to-treat population during treatment phase. q2w, every 2 weeks.

Eight treatment-emergent SAEs were experienced by five patients (12.5%) from the alirocumab group. These SAEs were unstable angina, brachiocephalic artery stenosis, traumatic fracture, radius fracture (one patient each) and two ligament sprains and two muscle strains (one patient). Eight treatment-emergent SAEs were experienced by five patients (11.6%) from the placebo group. These SAEs were road traffic accident and arterial injury (one patient); acute myocardial infarction on two occasions (one patient); unstable angina and peripheral arterial disease (one patient); pulmonary tuberculosis (one patient) and coronary artery stenosis (one patient). None of the reported SAEs were deemed related to study drug by both the investigator and the sponsor. No treat-

ment-related discontinuation or death was reported due to TEAEs in either group.

## DISCUSSION

The ODYSSEY KT study was the first to evaluate the safety and efficacy of alirocumab 75 mg (with a provision to uptitrate the dose to 150 mg) every 2 weeks for 24 weeks in Korean patients with inadequately controlled hypercholesterolemia and at high risk of CVD. The main findings are as follows. (1) The percent change of LDL-C from baseline in the ITT population was -65.7% in the alirocumab group and the difference of LDL-C versus placebo was -76.7% ( $p < 0.0001$ ). (2) Alirocumab treatment additionally improved lipid parameters including HDL-C, non-HDL-C, TC, Lp(a), and Apo B versus placebo in the Korean cohort ( $p < 0.05$ ). (3) Alirocumab did not induce higher rates of TEAEs and SAEs than placebo. None of the eight treatment-emergent SAEs in the alirocumab group, were deemed related to alirocumab.

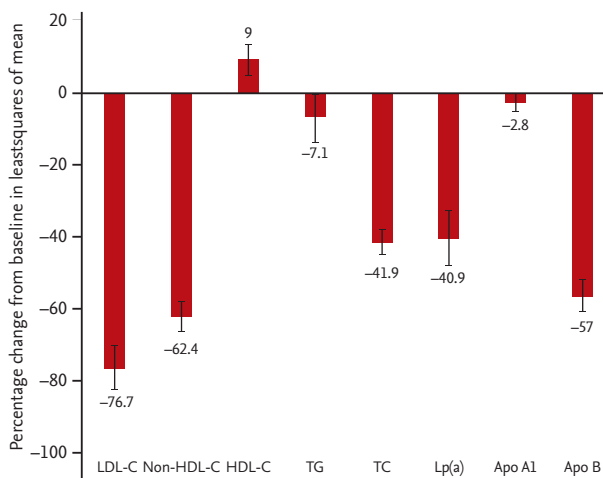
In recent years, improvements in laboratory lipid measurements through PCSK9 inhibition have revealed to be associated with better clinical prognosis. Evolocumab reduced the risk of CV events (composite of CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization) by 15% at 3 years of follow-up in FOURIER clinical trial [23]. Most recently in ODYSSEY outcomes trial, alirocumab proved 15% reduction in CV events (composite of CHD death, non-fatal myocardial infarction, fatal or non-fatal

**Table 3. Least squares mean differences (vs. placebo) in LDL-C and secondary lipid parameters in patients of alirocumab group in intent-to-treat population**

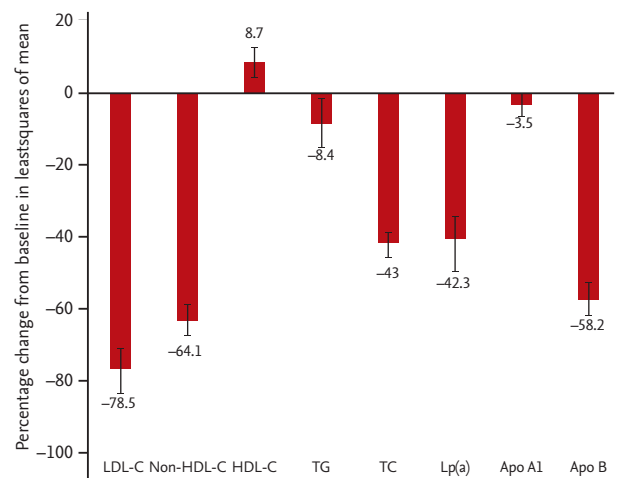
Lipid parameter	% Change at week 24 from baseline		Difference of % change compared to placebo group	95% CI	p value
	Placebo (n = 43)	Alirocumab (n = 40)			
LDL-C	11.1 ± 4.2	-65.7 ± 4.4	-76.7 ± 6.1	-88.9 to -64.6	< 0.0001
Non-HDL-C	8.1 ± 3.1	-54.2 ± 3.2	-62.4 ± 4.5	-71.4 to -53.4	< 0.0001
HDL-C	7.5 ± 2.9	16.6 ± 3.0	9.0 ± 4.2	0.7 to 17.4	0.0344
Fasting TG	-1.6 ± 4.9	-8.7 ± 5.0	-7.1 ± 7.0	-20.8 to 6.5	0.3048
TC	7.1 ± 2.3	-34.9 ± 2.4	-41.9 ± 3.4	-48.6 to -35.3	< 0.0001
Lp(a)	4.8 ± 5.4	-36.1 ± 5.5	-40.9 ± 7.7	-56.1 to -25.8	< 0.0001
Apo A1	6.2 ± 2.1	3.4 ± 2.1	-2.8 ± 3.0	-8.8 to 3.1	0.3479
Apo B	8.1 ± 3.1	-48.9 ± 3.2	-57.0 ± 4.5	-66.0 to -48.1	< 0.0001

Values are presented as mean ± SE.

LDL-C, low density lipoprotein cholesterol; CI, confidence interval; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; Lp(a), lipoprotein(a); Apo A1, apolipoprotein A1; Apo B, apolipoprotein B.



**Figure 3.** Least squares mean difference (vs. placebo) in low density lipoprotein cholesterol (LDL-C) and secondary lipid parameters in patients in the alirocumab group in intent-to-treat population. LDL-C levels given were calculated values. Triglyceride levels were ascertained under fasting conditions. HDL-C, high density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; Lp(a), lipoprotein(a); Apo A1, apolipoprotein A1; Apo B, apolipoprotein B.



**Figure 4.** Least squares mean difference (vs. placebo) in low density lipoprotein cholesterol (LDL-C) and secondary lipid parameters in patients in the alirocumab group in modified intent-to-treat population. LDL-C levels given were calculated values. Triglyceride levels were ascertained under fasting conditions. HDL-C, high density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; Lp(a), lipoprotein(a); Apo A1, apolipoprotein A1; Apo B, apolipoprotein B.

ischemic stroke, or unstable angina requiring hospitalization) and appeared associated with 15% lower rate of all-cause death at 4 years of follow-up among patients with “recent acute coronary syndrome” defined as an index hospitalization for acute myocardial infarction or unstable angina 1 to 12 months before the enrollment [24]. In summary, it can be implicated that the improve-

ments in LDL-C and related lipid parameters observed in current study might lead to clinical benefits in CV morbidity and mortality among Korean population. It requires further investigation.

There were several findings in the current Korean cohort that were unique relative to the entire ODYSSEY KT population [22]. The use of high-intensity statins was

lower in the Korean cohort in comparison to the entire KT population (55.4% vs. 72.4%). In contrast, the use of LLTs other than statins were higher in the Korean cohort that in the study population (33.7% vs. 23.1%). Additionally, baseline Lp(a) and fasting TG levels were higher in the Korean cohort. Compared to the entire ODYSSEY KT study population, nominally larger percent change in LDL-C from baseline in the alirocumab group appeared at week 12 (−62.3% vs. −57.9%) and was maintained week 24 (−65.7% vs. −57.1%) in the Korean cohort. Similarly, among alirocumab group, the proportion of patients achieving LDL-C values < 70 mg/dL (92.0% vs. 85.8%) and the proportion of patients with two consecutive LDL-C values < 15 mg/dL (10.0% vs. 9.3%) or < 25 mg/dL (37.5% vs. 27.8%) were nominally higher in the Korean cohort. In short, LDL-C reduction through alirocumab treatment in Korean cohort appeared at least consistent with the results from whole ODYSSEY KT cohort. With regards to safety data, a smaller proportion of overall patients in the Korean cohort displayed TEAEs in comparison to the ODYSSEY KT study population (48.2% vs. 60.3%). Similarly, the incidence of TEAEs in the alirocumab-treated patients was lower in the Korean cohort in comparison to those in the ODYSSEY KT population (45.0% vs. 58.8%). In addition, neither death nor permanent discontinuation due to TEAE were observed in the Korean cohort, whereas one death (influenza A infection) and three permanent discontinuations due to TEAEs (one in placebo group and two in alirocumab group) were reported in the Taiwanese study population.

The results show that, with similar design and inclusion criteria, Korean patients exhibited consistent LDL-C reduction with previous ODYSSEY trials. In the ODYSSEY COMBO I and II studies, treatment with add-on alirocumab to background statin therapy reduced LDL-C levels by at least 48.2% [14,17]. In the ODYSSEY OPTIONS I and II studies, add-on alirocumab to atorvastatin 20 or 40 mg resulted in a reduction of LDL-C levels of 44.1% and 54%, respectively [13], while add-on alirocumab to rosuvastatin 10 or 20 mg resulted in a reduction of LDL-C levels of 50.6% and 36.3%, respectively [15]. In patients with heterozygous familial hypercholesterolemia (heFH), alirocumab treatment reduced LDL-C levels by at least 51.4% [16]. In patients with statin intolerance, alirocumab treatment reduced LDL-C levels by 45% [18]. Another study reported that 150 mg of

**Table 4. Adverse events and laboratory evaluations in safety population (with incidence of ≥ 5.0% in alirocumab group)**

Variable	Placebo (n = 43)	Alirocumab 75 mg/150 mg q2w (n = 40)
Patients with any TEAE	22 (51.2)	18 (45.0)
Patients with any treatment-emergent SAE	5 (11.6)	5 (12.5)
Classification according to SOC and PT		
Nervous system disorders	2 (4.7)	5 (12.5)
Headache	0	4 (10.0)
Dizziness	0	1 (2.5)
Infections and infestations	6 (14.0)	4 (10.0)
Nasopharyngitis	2 (4.7)	3 (7.5)
URTI	0	1 (2.5)
Injury, fall, and procedural complications	3 (7.0)	4 (10.0)
Fall	1 (2.3)	2 (5.0)
Facial bones fracture	0	1 (2.5)
Gastrointestinal disorders	5 (11.6)	2 (5.0)
Chronic gastritis	0	1 (2.5)
Dyspepsia	0	1 (2.5)
Skin and subcutaneous tissue disorders	1 (2.3)	2 (5.0)
Eczema	0	1 (2.5)
Rash	0	1 (2.5)

Values are presented as number (%). q2w, every 2 weeks; TEAE, treatment-emergent adverse event; SAE, serious adverse event; SOC, system organ class; PT, preferred term; URTI, upper respiratory tract infection.

alirocumab every 2 weeks induced −62.0% of change in LDL-C level at week 24 from baseline [19]. Considering that only three out of 40 patients were uptitrated to 150 mg in Korean cohort, it might suggest that 75 mg every 2 weeks is enough for the majority of Korean dyslipidemic patients. In studies on Japanese patients (with or without heFH), alirocumab treatment reduced LDL-C levels by at least 40% [20,21]. Similar to the results observed in this Korean population, a pooled analysis of eight ODYSSEY phase 3 trials (n = 4,629) indicated that alirocumab provided consistent reductions in LDL-C regardless of the statin dose and type [25]. In the ODYSSEY LONG TERM trial (n = 2,341), TEAEs were observed



in 81% of alirocumab-treated patients [19], which is more than that observed in the Korean cohort (45%). The most common TEAEs in the ODYSSEY LONG TERM trial of alirocumab-treated patients were general allergic reactions (10.1%) and local injection-site reactions (5.9%) [19], while the most common TEAEs in the Korean cohort were headache (10.0%) and nasopharyngitis (7.5%) (Table 4).

While the patients in the ODYSSEY KT study were receiving background statin therapy, it is important to note that high-dose statins are known to upregulate PCSK9 expression [26] and could therefore interfere with PCSK9 inhibitors.

Although several reports suggested that low-to-moderate dose statins are sufficient in Korean population [27,28], it still appears to be inadequate in achieving the goal of LDL-C < 70 mg/dL in patients with very high CV risk [6-8]. Further investigations are needed to assess the necessity of more aggressive treatment policy including combination of alirocumab for Korean dyslipidemic patients.

There are several limitations to this study. The relatively small number of patients (n = 40) in the alirocumab group may not be representative of the relevant Korean population. There was a 4:1 ratio of males to females in the study, and very few patients were < 45 or > 75 years. As this study recruited patients already on statins or other LLTs, it is not known how the Korean population would respond to alirocumab as monotherapy. The small number of patients and the limited trial period may be insufficient to capture all relevant AEs.

In conclusion, this study demonstrated that alirocumab showed significantly greater efficacy in reduction of LDL-C levels, as well as improvements in HDL-C, non-HDL-C, TC, Lp(a), and Apo B than placebo in Korean patients. In addition, alirocumab was generally well tolerated. These results indicate that Korean dyslipidemic patients could achieve higher efficacy in LDL-C reduction with alirocumab augmentation than with conventional LLTs only.

## KEY MESSAGE

1. Alirocumab add on treatment can make an additional low density lipoprotein cholesterol level

reduction up to 65% to 75% compared with statin only therapy.

2. Alirocumab treatment additionally improved lipid parameters including high density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol, lipoprotein(a), and apolipoprotein B versus placebo in the Korean patients.
3. Although alirocumab showed stronger effect on lipid modification than placebo, alirocumab did not induce higher rates of treatment-emergent adverse events and serious adverse events than statin only therapy.

## Conflict of interest

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**Supplementary Table 1. Exclusion criteria**

1	Patients without established CHD or CHD risk equivalents
2	LDL-C, 70 mg/dL at the screening visit in patients with a history of documented CVD
3	LDL-C, 100 mg/dL at the screening visit in patients without history of documented CVD
4	Not on a stable dose of lipid lowering therapy (including statin) for $\geq 4$ weeks before the screening visit or between screening and randomization visits
5	Currently taking a statin that is not atorvastatin, rosuvastatin, or simvastatin
6	Atorvastatin, rosuvastatin, or simvastatin is not taken daily or not taken at a registered dose
7	Daily dose above atorvastatin 80 mg, rosuvastatin 20 mg, or simvastatin 40 mg
8	Use of fibrates, other than fenofibrate in the past 4 weeks before screening visit or between screening and randomization visits
9	Use of nutraceutical products or over-the-counter therapies that may affect lipids which have not been at a stable dose/amount for $\geq 4$ weeks before the screening visit or between screening and randomization visits
10	Use of red yeast rice products within 4 weeks of the screening visit or between screening and randomization visits
11	Patient who has received plasmapheresis treatment within 2 months before the screening visit or has plans to receive this during the study
12	History of a MI, unstable angina leading to hospitalization, CABG, PCI, uncontrolled cardiac arrhythmia, carotid surgery or stenting, stroke, transient ischemic attack, carotid revascularization, endovascular procedure, or surgical intervention for peripheral vascular disease within 3 months before the screening visit
13	Planned to undergo scheduled PCI or CABG, or carotid or peripheral revascularization, during the study
14	Systolic blood pressure (160 mmHg) or diastolic blood pressure (100 mmHg) at screening visit or randomization visit
15	History of New York Heart Association Class III or IV heart failure within the past 12 months
16	Known history of hemorrhagic stroke
17	Age, 18 years or legal age of majority at the screening visit, whichever is greater
18	Patients not previously instructed on a cholesterol-lowering diet before the screening visit
19	Newly diagnosed (within 3 months before randomization visit) or poorly controlled (HbA <sub>1c</sub> > 9% at the screening visit) diabetes
20	Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins
21	History of bariatric surgery within 12 months before the screening visit
22	Unstable weight defined by a variation > 5 kg within 2 months before the screening visit
23	Known history of homozygous or heterozygous familial hypercholesterolemia
24	Known history of loss of function of PCSK9 (i.e., genetic mutation or sequence variation)
25	Use of systemic corticosteroids, unless used as replacement therapy for pituitary/adrenal disease with a stable regimen for at least 6 weeks before randomization
26	Use of continuous estrogen or testosterone hormone replacement therapy unless the regimen has been stable in the past 6 weeks before the screening visit and no plans to change the regimen during the study
27	History of cancer within the past 5 years, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or <i>in situ</i> cervical cancer
28	Known history of a positive HIV test
29	Patient who has taken any investigational drugs other than the alirocumab training placebo kits within 1 month or 5 half-lives, whichever is longer
30	Patient who has been previously treated with at least 1 dose of alirocumab or any other anti-PCSK9 monoclonal antibody in other clinical trials
31	Patient who withdraws consent during the screening period (patient who is not willing to continue or fails to return)

**Supplementary Table 1. Continued**

32	<p>Conditions/situations such as:</p> <p>Any clinically significant abnormality identified at the time of screening that in the judgment of the investigator or any sub-investigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases or patients with a short life expectancy.</p> <p>Considered by the investigator or any sub-investigator as inappropriate for this study for any reason, e.g.,</p> <p>Deemed unable to meet specific protocol requirements, such as scheduled visits</p> <p>Deemed unable to administer or tolerate long-term injections as per the patient or the investigator</p> <p>Investigator or any sub-investigator, pharmacist, study coordinator, other study staff, or relative thereof directly involved in the conduct of the protocol, etc.</p> <p>Presence of any other conditions (e.g., geographic, social), actual or anticipated, that the investigator feels would restrict or limit the patient's participation for the duration of the study</p>
33	<p>Laboratory findings during the screening period:</p> <p>Positive test for hepatitis B surface antigen or hepatitis C antibody (confirmed by reflexive testing)</p> <p>Positive serum <math>\beta</math>-human chorionic gonadotropin or urine pregnancy test in women of childbearing potential</p> <p>Triglycerides &gt; 400 mg/dL (1 repeat laboratory is allowed)</p> <p>eGFR &lt; 30 mL/min/1.73 m<sup>2</sup></p> <p>ALT or AST &gt; 3 <math>\times</math> ULN (1 repeat laboratory is allowed)</p> <p>CPK &gt; 3 <math>\times</math> ULN (1 repeat laboratory is allowed)</p> <p>TSH &lt; lower limit of normal or &gt; ULN (1 repeat laboratory is allowed)</p>
34	All contraindications to the background therapies or warning/precaution of use (when appropriate) as displayed in the respective National Product Labeling
35	Known hypersensitivity to monoclonal antibody or any component of the drug products
36	Pregnant or breastfeeding women
37	Women of childbearing potential not protected by highly effective method(s) of birth control and/or who are unwilling or unable to be tested for pregnancy

CHD, coronary heart disease; LDL-C, low density lipoprotein cholesterol; CVD, cardiovascular disease; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; HbA<sub>1c</sub>, glycated hemoglobin; PCSK9, proprotein convertase subtilisin/kexin type 9; HIV, human immunodeficiency virus; eGFR, estimated glomerular filtration rate; ALT, alanine aminotransferase; AST, aspartate transferase; ULN, upper limit of normal; CPK, creatine phosphokinase; TSH, thyroid stimulating hormone.

**Supplementary Table 2. Least squares mean differences (vs. placebo) in LDL-C and secondary lipid parameters in patients of alirocumab group in modified intent-to-treat population**

Lipid parameter	% Change at week 24 from baseline		Difference of % change compared to placebo group	95% CI	p value
	Placebo (n = 43)	Alirocumab (n = 40)			
LDL-C	11.1 ± 4.2	-67.3 ± 4.4	-78.5 ± 6.1	-90.6 to -66.3	< 0.0001
non-HDL-C	8.2 ± 3.1	-55.9 ± 3.2	-64.1 ± 4.4	-72.9 to -55.3	< 0.0001
HDL-C	8.1 ± 2.9	16.9 ± 3.0	8.7 ± 4.2	0.4 to 17.1	0.0412
Fasting TG	-0.05 ± 4.9	-8.3 ± 5.0	-8.3 ± 7.0	-22.0 to 5.3	0.2298
TC	7.1 ± 2.3	-35.9 ± 2.4	-43.0 ± 3.3	-49.7 to -36.4	< 0.0001
Lp(a)	5.3 ± 5.7	-37.0 ± 5.6	-42.3 ± 8.0	-58.0 to -26.6	< 0.0001
Apo A1	7.2 ± 2.1	3.7 ± 2.2	-3.5 ± 3.0	-9.6 to 2.5	0.2482
Apo B	7.9 ± 3.1	-50.4 ± 3.2	-58.2 ± 4.5	-67.2 to -49.2	< 0.0001

Values are presented as mean ± SE.

LDL-C, low density lipoprotein cholesterol; CI, confidence interval; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; TC, total cholesterol; Lp(a), lipoprotein(a); Apo A1, apolipoprotein A1; Apo B, apolipoprotein B.