Journal of Clinical Lipidology (2018) 12, 162–172

Journal of Clinical Lipidology

A randomized trial evaluating the efficacy and safety of alirocumab in South Korea and Taiwan (ODYSSEY KT)

Kwang Kon Koh, MD, PhD, FACC, Chang Wook Nam, MD, PhD, FACC, Ting-Hsing Chao, MD, FACC, FESC, Ming-En Liu, MD, Chiung-Jen Wu, MD, Dong-Soo Kim, MD, PhD, Chong-Jin Kim, MD, PhD, Ivy Li, MSc, Jianyong Li, MD, Marie T. Baccara-Dinet, MD, MSc, Pi-Jung Hsiao, MD, MS*, Chern-En Chiang, MD, PhD, FACC

Gachon University Gil Medical Center, Incheon, Korea (Dr Koh); Keimyung University Dongsan Medical Center, Daegu, South Korea (Dr Nam); Department of Internal Medicine, College of Medicine and Hospital, National Cheng Kung University, Tainan City, Taiwan (Dr Chao); Division of Cardiology, Department of Internal Medicine, Hsinchu Mackay Memorial Hospital, Hsinchu, Taiwan (Dr Liu); Division of Cardiology, Department of Internal Medicine, Chang Gung Memorial Hospital–Kaohsiung Medical Center, Chang Gung University College of Medicine, Tao–Yuan City, Taiwan (Dr Wu); Inje University Busan Paik Hospital, Busan, Korea (Dr D.-S. Kim); Kyung Hee University Hospital at Gangdong, Seoul, Korea (Dr C.-J. Kim); Sanofi R&D, Beijing, China (Dr I. Li); Sanofi R&D, Shanghai, China (Dr J. Li); Sanofi R&D, Montpellier, France (Dr Baccara-Dinet); Division of Endocrinology and Metabolism, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan (Dr Hsiao); and General Clinical Research Center, Division of Cardiology, Taipei Veterans General Hospital and National Yang–Ming University, Taipei, Taiwan (Dr Chiang)

KEYWORDS:
Alirocumab;
PCSK9;
LDL-C;
South Korea;
Taiwan;
ODYSSEY phase 3;
Hypercholesterolemia;
Lipid lowering;
Placebo-controlled;
Maximally tolerated statin

BACKGROUND: Alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9, has been shown to provide significant reductions in low-density lipoprotein cholesterol (LDL-C). Data about its efficacy and safety in patients from South Korea and Taiwan are limited.

OBJECTIVE: ODYSSEY KT assessed the efficacy and safety of alirocumab in patients from South Korea and Taiwan.

METHODS: Patients with hypercholesterolemia at high cardiovascular risk who were on maximally tolerated statin were randomized (1:1) to alirocumab (75 mg every 2 weeks, with dose increase to 150 mg every 2 weeks at week 12 if LDL-C ≥70 mg/dL at week 8) or placebo for 24 weeks. The primary efficacy endpoint was percentage change in LDL-C from baseline to week 24. Safety was assessed throughout.

RESULTS: At week 24, alirocumab changed LDL-C levels by −57.1% (placebo: +6.3%). In the alirocumab group, 9 patients (9.5%) received dose increase at week 12. At week 24, 85.8% of patients

Clinical Trial Registration: NCT02289963; clinicaltrials.gov.

Funding: The ODYSSEY KT study was funded by Sanofi and Regeneron Pharmaceuticals, Inc. The sponsors also had a role in study design and collection, analysis, and interpretation of data.

* Corresponding author. Kaohsiung Medical University Hospital, 100 Tzyou 1st Rd, Kaohsiung 807, Taiwan.

E-mail address: pjhsiao@cc.kmu.edu.tw

Submitted June 30, 2017. Accepted for publication September 27, 2017.

https://doi.org/10.1016/j.jacl.2017.09.007

in the alirocumab group reached LDL-C <70 mg/dL (placebo: 14.2%; $P \leq .0001$ vs placebo). Alirocumab significantly improved non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B, total cholesterol, lipoprotein (a), and HDL-C vs placebo ($P \leq .05$). Two consecutive calculated LDL-C values <25 mg/dL were recorded in 27.8% of alirocumab-treated patients. Overall, 58.8% (alirocumab) and 61.8% (placebo) of patients experienced treatment-emergent adverse events; 2.1% and 1.0% discontinued treatment due to treatment-emergent adverse events, respectively.

CONCLUSION: Alirocumab significantly improved LDL-C, apolipoprotein B, non-HDL-C, lipoprotein (a), HDL-C, and total cholesterol in Asian patients. Alirocumab was generally well tolerated. These findings are consistent with ODYSSEY findings to date.

Introduction

Elevated low-density lipoprotein cholesterol (LDL-C) levels correlate with an increased risk of coronary heart disease (CHD).[1] An increasing trend of cardiovascular (CV) mortality has been observed in Taiwan and South Korea.[2,3] Recent lipid guidelines have recommended LDL-C targets of <70 or <100 mg/dL in patients with very-high or high CV risk, respectively.[4,5] The CEPHEUS Pan-Asian survey showed that LDL-C goals were reached by 34.9% (LDL-C <70 mg/dL) and 55.4% (LDL-C <100 mg/dL) of patients with very-high and high CV risk, respectively.[6] Recent American College of Cardiology and European Society of Cardiology/European Atherosclerosis Society consensus statements recommend that proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors may be considered in patients with very-high or high CV risk who have high baseline LDL-C levels, despite maximally tolerated statin and ezetimibe therapies.[7,8] PCSK9 is a key regulator for cholesterol homeostasis, downregulating the low-density lipoprotein receptor protein and thus increasing LDL-C levels.[9]

Alirocumab, a fully human monoclonal antibody to PCSK9, with the dosing regimen 75 mg every 2 weeks (Q2W) (with possible dose increase to 150 mg Q2W) and 150 mg Q2W reduced LDL-C levels by up to 61% in addition to background statin therapy with or without other lipid-lowering therapies (LLTs) or as monotherapy in phase 3 ODYSSEY clinical studies.[10–16] Data regarding the efficacy and safety of alirocumab in patients from Asia are limited.[17,18] In phase 1 and 2 studies conducted in Japan, alirocumab treatment significantly reduced LDL-C levels and was well tolerated in healthy subjects or in patients with hypercholesterolemia.[18] In the phase 3 ODYSSEY Japan study, which enrolled Japanese patients with heterozygous familial hypercholesterolemia or high CV risk and hypercholesterolemia, the change in LDL-C levels from baseline to week 24 was −62.5% in the alirocumab 75/150 mg Q2W group (placebo: +1.6% increase).[17]

The phase 3 ODYSSEY KT study was a placebo-controlled study evaluating the efficacy and safety of alirocumab 75 mg Q2W (with possible dose increase to 150 mg Q2W) as add-on to statin therapy in patients with high CV risk and inadequately controlled hypercholesterolemia in South Korea and Taiwan. We also conducted a pooled safety analysis of alirocumab in a broader patient population from Asia, including an alirocumab phase 2 study from Japan and ODYSSEY phase 3 studies.

Methods

ODYSSEY KT was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study conducted in 27 active centers (which screened at least 1 patient) from 16 study centers in South Korea and 11 in Taiwan. The study was conducted in accordance with the ethical principles in the Declaration of Helsinki and applicable amendments, and the International Conference on Harmonization guidelines for Good Clinical Practice. The protocol was approved by the relevant institutional review boards or independent ethics committees. All participating patients provided written informed consent.

Patients

The study enrolled patients (aged ≥18 years) with high CV risk who had inadequately controlled hypercholesterolemia on maximally tolerated statin therapy at a stable dose for at least 4 weeks before screening. High CV risk was defined as history of CV disease (CVD), moderate chronic kidney disease, or diabetes with multiple risk factors. Inadequately controlled hypercholesterolemia was defined as LDL-C ≥70 mg/dL in patients with a history of documented CVD, or LDL-C ≥100 mg/dL in patients without such history. Maximally tolerated statin therapy was defined as atorvastatin 40 to 80 mg daily, rosuvastatin 20 mg daily, or simvastatin 40 mg daily. Patients were also eligible if they were receiving a daily dose of atorvastatin, rosuvastatin, or simvastatin considered appropriate by the investigator.

Background treatment with LLTs other than statins was allowed for all patients, provided that they had been on a stable dose for at least 4 weeks before the screening visit.

Patients were not eligible if they were receiving statins other than atorvastatin, rosuvastatin, or simvastatin; fibrates other than fenofibrate; or red yeast rice products. Patients were required to be on a stable diet (the National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes diet or equivalent) from screening visit to the end of study.

A list of exclusion criteria is given in Supplementary Table 1.

Study design

The study comprised an up to 3-week screening period, followed by 24 weeks of double-blind treatment and 8 weeks of follow-up (off treatment; Fig. 1). Eligible patients were randomized 1:1 to alirocumab 75 mg Q2W or placebo. Each treatment was administered subcutaneously via auto-injector. The patient or designated carer was trained to self-inject/inject using placebo. Randomization was stratified according to history of myocardial infarction or ischemic stroke, statin treatment (atorvastatin 40–80 mg or rosuvastatin 20 mg vs atorvastatin <40 mg, rosuvastatin <20 mg, or simvastatin any dose), and country.

Alirocumab-treated patients not achieving LDL-C levels of <70 mg/dL at week 8 had their dosing regimen changed to 150 mg Q2W from week 12 in a blinded fashion.

During the double-blind treatment period, on-site visits took place at weeks 0, 4, 8, 12, 16, and 24.

Endpoints

The primary efficacy endpoint was the percent change in calculated LDL-C from baseline to week 24 analyzed with an intent-to-treat (ITT) approach. The percent change in calculated LDL-C from baseline to week 24 was also assessed using an on-treatment approach. Other key secondary endpoints included the percent change in calculated LDL-C from baseline to week 12, the percent change in apolipoprotein (Apo) B, non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol, lipoprotein (a) [Lp(a)], HDL-C, triglycerides (TGs), and Apo A1 from baseline to weeks 12 and 24, and the proportion of patients reaching calculated LDL-C <70 mg/dL at week 24. Analyses of lipid samples were performed by a central laboratory using standard procedures. 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 by monitoring treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), laboratory parameters, and vital signs. TEAEs were defined as adverse events that occurred, worsened, or became serious during the period from first to last injection of study drug plus 70 days.

Adverse events of special interest included overdose with study drug, local injection-site reactions, allergy events, ophthalmologic events, neurologic events, neurocognitive events, pregnancy of female patient, increase in alanine aminotransferase (≥3 × upper limit of normal), and hemolytic anemia. For further details on safety events of interest and preferred terms of adverse event categories, see the Supplementary Material.

Anti-drug antibodies (ADAs) to alirocumab were assessed using a validated assay by Regeneron Pharmaceuticals, Inc (Tarrytown, NY). Blood samples were collected before study drug administration at baseline, at weeks 4, 12, 24/early termination, and 32 (follow-up).

Statistical analysis

A sample size of 40 patients (20 patients in each treatment group) was calculated to have 95% power to detect a difference of 30% in mean percent change in LDL-C at week 24 with 5% 2-sided significance level in the KT study, assuming a common standard deviation of 25% and these patients having an evaluable primary endpoint.

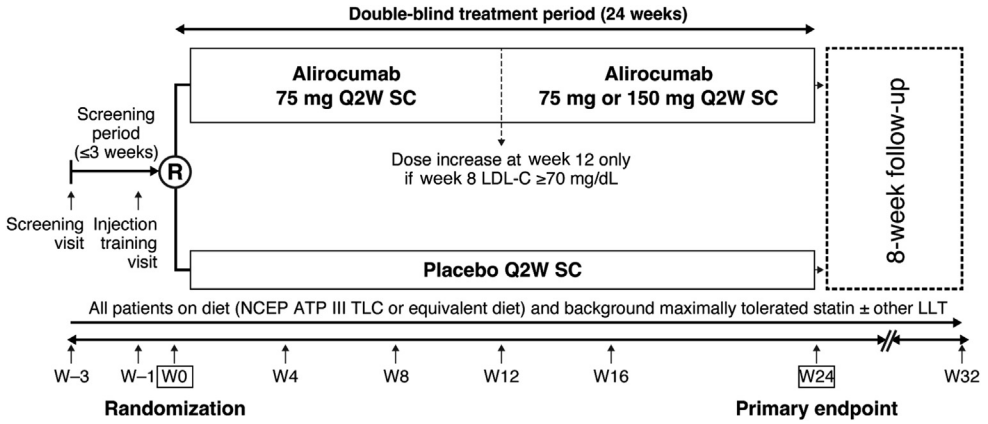

Figure 1 ODYSSEY KT study design. FU, follow-up; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; Q2W, every 2 weeks; R, randomization; SC, subcutaneously; TLC, therapeutic lifestyle changes; W, week.

Nevertheless, to meet the registration requirement and provide safety documentation in South Korea and Taiwan, the final total sample size was 199.

The primary efficacy analysis included a mixed effect model with repeated measures, with parameters to account for missing data as previously reported.[13,15,16,19,20] The mixed effect model with repeated measures included fixed categorical effects of treatment group (alirocumab vs placebo), time point (weeks 4, 8, 12, 16, and 24), randomization strata, treatment-by-time point interaction, and strata-by-time point interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. Alirocumab was compared with placebo using appropriate contrasts, and the 95% confidence interval of the difference was provided.

Key secondary lipid endpoints were analyzed in a predefined order using a hierarchical inferential approach to control type I error. Statistical significance of the primary endpoint at the 0.05 level was required before drawing inferential conclusions about the first secondary endpoint. Inferential conclusions about successive key secondary endpoints required statistical significance at the 0.05 level of prior ones. Continuous secondary endpoints with a normal distribution (eg, lipids other than Lp(a) and TGs) were analyzed as for the primary endpoint. Continuous secondary endpoints with non-normal distribution (eg, Lp(a) and TGs) were analyzed using the multiple imputation approach for handling missing values followed by robust regression. LDL-C goal achievement was analyzed by multiple imputations followed by logistic regression.

The ITT population included all randomized patients with an LDL-C measurement available at baseline and at least 1 of the post-randomization time points between weeks 4 and 24, regardless of treatment adherence. The modified ITT population used for the on-treatment analyses included all randomized patients who had received at least 1 dose or part of the study dose and had an evaluable primary endpoint during the treatment period. The safety population included randomized patients who received at least 1 dose or part of a dose of study drug during the treatment period.

The safety analysis included all randomized and treated patients. Safety data were analyzed by descriptive statistics. All statistical analyses were conducted using SAS (SAS Institute Inc, Cary, NC).

Post-hoc analysis: pooled safety analysis in patients from Asia

An additional safety analysis was performed on patient data pooled from studies conducted in Asia, including patients from this KT study, the placebo-controlled phase 2 study from Japan (NCT01812707; n = 100), and the phase 3 ODYSSEY Japan study (NCT02107898; n = 216), as well as patients from Asia who were included in the phase 3 ezetimibe-controlled ODYSSEY COMBO II study (NCT01644188, n = 42).[11,17,18]

The study populations were previously described.[11,17,18] Briefly, the Japan phase 2 study enrolled patients with hypercholesterolemia (≥100 mg/dL) who received atorvastatin (5–20 mg).[18] The phase 3 ODYSSEY Japan study enrolled patients with heterozygous familial hypercholesterolemia or high CV risk and hypercholesterolemia (LDL-C ≥100 mg/dL or ≥120 mg/dL, depending on prevention status according to the guidelines from the Japan Atherosclerosis Society).[17,21] These patients received a stable dose of daily statin therapy (neither type nor dose of statin was prespecified) with or without other LLTs. In ODYSSEY COMBO II, the study population comprised patients with documented CVD and LDL-C ≥70 mg/dL or those with high CV risk, no documented history of CVD, and LDL-C ≥100 mg/dL.[11] All patients received a stable dose of maximally tolerated statin.

Results

Patients

In total, 199 patients were randomized to treatment with alirocumab 75 mg Q2W (n = 97) or placebo (n = 102; Fig. 2). All patients were from South Korea (n = 83 [41.7%]) or Taiwan (n = 116 [58.3%]). Baseline characteristics and lipid parameters of the randomized population were generally similar between the groups (Table 1). The majority of patients were males (82.4%), regardless of treatment allocation. All patients received statin, with 72.4% of patients receiving high-intensity statin. Overall, 23.1% of patients received other LLTs in addition to statin (13.1% received ezetimibe). A total of 89.7% and 95.1% of patients completed the double-blind treatment period in the alirocumab and placebo groups, respectively.

In the pooled analysis of data from patients in Asia, 342 patients were randomized to alirocumab and 215 to control (Table 1). Patient baseline and lipid characteristics were generally similar between the control and alirocumab groups.

Efficacy

LDL-C reductions were observed from week 4 and maintained until week 24 (Fig. 3). At week 24, the least-squares mean (standard error) percent change in LDL-C from baseline was −57.1 (3.0)% in the alirocumab group and +6.3 (2.9)% in the placebo group for the ITT population, with a statistically significant difference between groups (−63.4 [4.2]%; $P < .0001$; Table 2). The results for the on-treatment population were similar at week 24 (alirocumab: −60.2 [2.8]%; placebo: +6.0 [2.7]%; difference: −66.2 [3.9]%; $P < .0001$).

At week 12 (ie, before possible dose increase to 150 mg Q2W), a reduction of 57.9 (2.2)% in LDL-C was achieved with alirocumab (placebo: +4.7 [2.2]%; Table 2). In total,

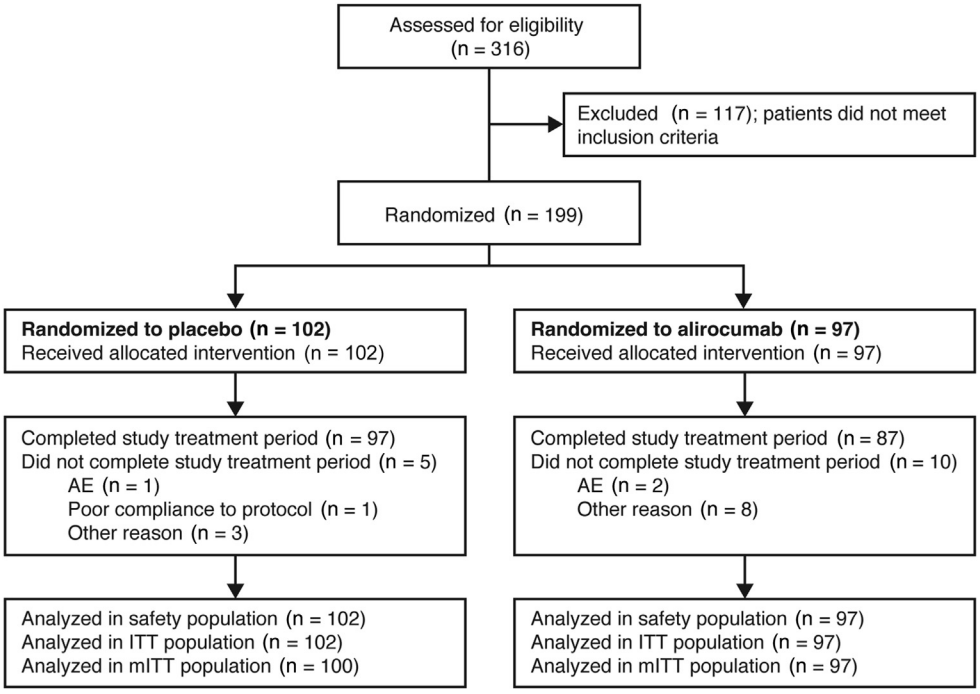

Figure 2 Patient flow through the ODYSSEY KT study. AE, adverse event; mITT, modified intent-to-treat; ITT, intent-to-treat.

9.5% of patients (n = 9) had a dose increase from 75 mg Q2W to 150 mg Q2W at week 12. Baseline LDL-C levels were higher in patients who received a dose increase to alirocumab 150 mg Q2W (n = 9; 123.2 [48.4] mg/dL) vs those remaining on 75 mg Q2W (n = 86; 94.1 [23.2] mg/dL). The adjusted dosing regimen was associated with additional lowering of LDL-C levels from week 12 (77.8 [45.3] mg/dL) to week 24 (42.0 [40.5] mg/dL). At week 24, 85.8% of patients in the alirocumab group and 14.2% in the placebo group achieved LDL-C levels of <70 mg/dL (difference vs placebo: $P < .0001$; Table 2). Alirocumab 75/150 mg Q2W significantly improved all key secondary efficacy lipid parameters vs placebo at week 24, with the exception of Apo A1 and TGs (Table 2).

Safety

Overall, in the KT study, 58.8% of patients in the alirocumab group experienced TEAEs vs 61.8% in the placebo group (Table 3). One death (1.0%) was reported in the alirocumab group and no deaths were reported in the placebo group. The patient who died was a 62-year-old male, who had type A influenza infection 3 days after the last injection of the investigational medical product and was hospitalized. The patient died 27 days later due to respiratory failure. The investigator and sponsor considered the event not to be related to the investigational medical product. The percentage of patients experiencing treatment-emergent SAEs was higher with alirocumab (17.5%) than with placebo (9.8%). No particular clinical pattern was observed among the SAEs. The percentage of patients with SAEs according to system organ class is presented in Supplementary Table 2. In total, 3 patients discontinued study treatment following at least 1 TEAE (alirocumab: 2.1%; placebo: 1.0%), with no specific clinical pattern. The TEAEs occurring in at least 2% of patients were similar in both groups, with nasopharyngitis (alirocumab: 6.2%; placebo: 3.9%) and dizziness (alirocumab: 6.2%; placebo: 2.9%) being among the most common (Supplementary Table 3).

Considering the TEAEs of special interest, a similar proportion of patients in both treatment groups of the KT study experienced general allergic reactions (Table 3). In the placebo group, 3 patients reported neurological events and 1 patient experienced a neurocognitive disorder (0 in the alirocumab group). Local injection-site reactions were reported by 2.1% (alirocumab) and 2.9% (placebo) of patients; most were mild in severity and did not result in study discontinuation. One patient in the alirocumab group experienced an ophthalmologic TEAE. Hepatic disorders were reported in a similar proportion of patients in the placebo and alirocumab groups. The TEAEs related to diabetes or diabetic complications were analyzed according to diabetes status at baseline. In the patient group without diabetes at baseline, 4 patients (6.2%) developed diabetes in the alirocumab group and 2 patients (3.1%) developed diabetes in the placebo group over a period of 6 months in the KT study ($P = .6801$). In the pooled analysis, 9 (4.7%) alirocumab and 5 (4.0%) control patients without diabetes at baseline developed diabetes over a treatment period of up to 52 weeks. Adjudicated treatment-emergent CV events were experienced by 3 alirocumab-treated patients (3.1%; all ischemia-driven coronary revascularization procedures) and by 5 patients (4.9%) in the placebo group (1 non-fatal

Table 1 Baseline characteristics (all randomized patients)

Parameters	ODYSSEY KT		Pooled data of patients from Asia	
	Placebo (n = 102)	Alirocumab (n = 97)	Control (placebo/ ezetimibe) (n = 215)	Alirocumab (n = 342)
Baseline demographics				
Age, y, mean (SD)	60.1 (9.1)	61.2 (10.4)	60.5 (9.1)	59.4 (10.4)
Male, n (%)	81 (79.4)	83 (85.6)	153 (71.2)	218 (63.7)
BMI, kg/m^2, mean (SD)	26.6 (3.8)	26.3 (4.0)	26.1 (3.5)	25.6 (4.1)
CHD history, n (%)*	95 (93.1)	96 (99.0)	123 (57.2)	142 (41.5)
CHD risk equivalent, n (%)†	26 (25.5)	21 (21.6)	33 (15.3)	29 (8.5)
Diabetes, n (%)	38 (37.3)	32 (33.0)	89 (41.4)	151 (44.2)
Lipid medication, n (%)				
Statin use	102 (100.0)	97 (100.0)	215 (100.0)	342 (100.0)
High-intensity statin use‡	73 (71.6)	71 (73.2)	81 (37.7)	89 (26.0)
Simvastatin 40 mg	22 (21.6)	17 (17.5)	23 (10.7)	18 (5.3)
LLT other than statins	24 (23.5)	22 (22.7)	37 (17.2)	41 (12.0)
Ezetimibe use	12 (11.8)	14 (14.4)	17 (7.9)	27 (7.9)
Nutraceuticals	0	0	0	1 (0.3)
Baseline lipid parameters, mg/dL				
LDL-C (calculated), mean (SD)	99.3 (25.2)	97.0 (27.8)	117.1 (32.6)	121.9 (33.0)
Non-HDL-C, mean (SD)	128.4 (30.3)	123.9 (29.0)	146.1 (36.3)	148.7 (35.0)
Total cholesterol, mean (SD)	174.5 (28.0)	169.4 (29.7)	196.5 (39.1)	201.8 (37.8)
Apo B, mean (SD)	85.6 (17.7)	81.7 (17.2)	97.9 (22.3)	98.3 (21.4)
Lp(a), median (Q1:Q3)	24.5 (12.0:57.0)	23.0 (12.5:54.5)	21.0 (8.8:43.0)	18.5 (9.3:38.3)
HDL-C, mean (SD)	46.1 (12.1)	45.5 (10.9)	50.4 (14.7)	53.2 (14.0)
Fasting TGs, median (Q1:Q3)	136.5 (103.0:167.0)	116.0 (85.0:170.0)	134.0 (99.0:174.0)	118.0 (91.0:166.0)
Apo A1, mean (SD)	132.1 (24.5)	131.7 (17.3)	143.9 (29.3)	149.2 (26.2)

Apo, apolipoprotein; BMI, body mass index; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); SD, standard deviation; TGs, triglycerides.

The pooled data analysis included patients from Asia from the following studies: NCT02289963, NCT01812707, NCT02107898, and NCT01644188.

*CHD was defined as acute/silent myocardial infarction, unstable angina, coronary revascularization procedures, or clinically significant CHD diagnosed by noninvasive testing (for ODYSSEY KT CHD was also diagnosed by invasive testing).

†CHD risk equivalents were defined as ischemic stroke, moderate chronic kidney disease, and diabetes mellitus (only if 2 or more risk factors present).

‡High-intensity statin therapy was defined as atorvastatin 40 to 80 mg daily or rosuvastatin 20 mg daily.

myocardial infarction and ischemia-driven coronary revascularization procedures; 1 non-fatal ischemic stroke; 3 ischemia-driven coronary revascularization procedures).

The adverse events and safety laboratory values from the pooled Asian study data, including patients who were treated for a period of up to 52 weeks in the Japanese studies and 104 weeks in the COMBO II study, were generally similar to the safety data reported in the KT study. The incidence of patients experiencing an SAE (alirocumab: 9.1%; control: 7.4%) and positively adjudicated CV events (alirocumab: 1.8%; control: 2.8%) was slightly lower in the pooled analysis than in the KT study

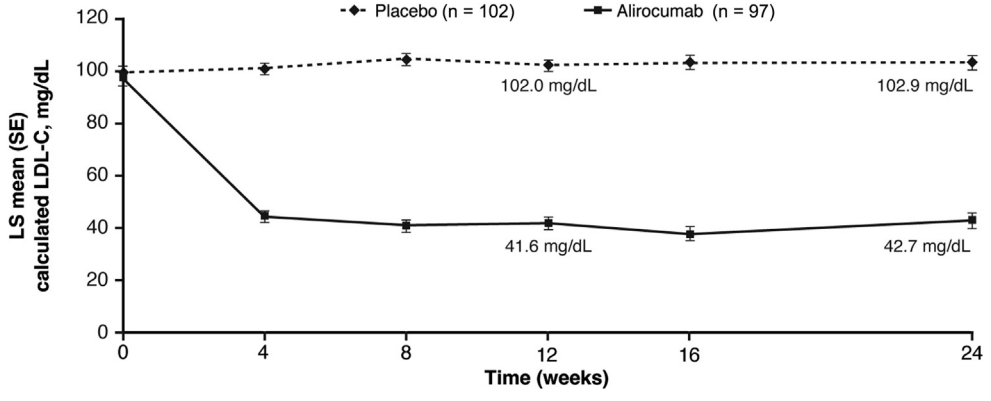

Figure 3 Calculated LDL-C levels over time (ITT analysis). ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least squares; SE, standard error.

Table 2 Effect of alirocumab vs placebo on LDL-C, secondary lipid parameters, and achievement of LDL-C target levels in the KT study (ITT analysis)

Parameters	Placebo (n = 102)	Alirocumab (n = 97)	Alirocumab vs placebo		
			Difference vs placebo	95% CI	*P* value
Baseline LDL-C, LS mean (SE), mg/dL	99.3 (2.5)	97.0 (2.8)			
Absolute change in calculated LDL-C from baseline to week 24, LS mean (SE), mg/dL	4.7 (3.0)	−55.5 (3.1)	−60.1 (4.3)	−68.60 to −51.65	<.0001
Change in calculated LDL-C from baseline to week 24, LS mean (SE), %	6.3 (2.9)	−57.1 (3.0)	−63.4 (4.2)	−71.6 to −55.2	<.0001*
Proportion of patients reaching calculated LDL-C <70 mg/dL at week 24, %	14.2†	85.8†	46.9‡	18.4 to 119.4	<.0001*
Change in calculated LDL-C from baseline to week 12, LS mean, %	4.7 (2.2)	−57.9 (2.2)	−62.5 (3.2)	−68.8 to −56.3	<.0001*
Change from baseline to week 24 in other lipid parameters, LS mean (SE), %					
Non-HDL-C	4.3 (2.4)	−47.2 (2.5)	−51.5 (3.5)	−58.4 to −44.6	<.0001*
Apo B	4.1 (2.3)	−42.3 (2.4)	−46.3 (3.4)	−53.0 to −39.7	<.0001*
Total cholesterol	4.0 (1.8)	−31.2 (1.8)	−35.2 (2.6)	−40.3 to −30.1	<.0001*
Lp(a)§	−2.3 (3.0)	−35.9 (3.0)	−33.6 (4.2)	−41.9 to −25.3	<.0001*
HDL-C	6.2 (1.7)	13.8 (1.8)	7.5 (2.5)	2.6 to 12.4	.0029*
TGs§	−3.6 (3.1)	−8.1 (3.2)	−4.5 (4.5)	−13.3 to 4.2	.3110
Apo A1	3.2 (1.2)	4.5 (1.2)	1.3 (1.7)	−2.0 to 4.6	.4363

Apo, apolipoprotein; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LS, least squares; SE, standard error; TGs, triglycerides.

**P* value is statistically significant according to the fixed hierarchical approach used to ensure a strong control of the overall type-I error rate at the 0.05 level.

†Combined estimate for proportion of patients reaching the level.

‡Combined estimate for odds ratio.

§Combined estimate for adjusted mean.

data (Table 3). In the pooled analysis, the treatment-emergent SAEs were similar to those in this study, with numerical differences observed regarding cardiac disorders, injury, poisoning, procedural complications, and vascular disorders (Supplementary Table 2).

In total, 27 patients (27.8%) in the alirocumab group had LDL-C levels <25 mg/dL on at least 2 consecutive occasions, among whom 9 experienced 2 consecutive LDL-C values <15 mg/dL (Supplementary Table 4). No specific safety concerns were identified with any of these patients during this short-term study.

In the pooled safety analysis, 17.0% of alirocumab-treated patients (n = 58) had LDL-C levels <25 mg/dL on at least 2 consecutive occasions, with 19 patients (5.6%) experiencing 2 consecutive LDL-C values <15 mg/dL (Supplementary Table 4).

Immunogenicity

In the KT study, 5 patients (5.2%) developed a treatment-emergent positive ADA response in the alirocumab treatment group. All ADA responses were classified as transient responses. Only 1 patient with a positive ADA response (titer <240) had a positive neutralizing status on a single occasion, at the follow-up visit.

Overall, the generation of ADAs and the neutralizing antibody response did not appear to impact LDL-C efficacy. No particular safety pattern was observed in patients with a positive ADA response compared with patients without an ADA response in the alirocumab group.

Discussion

ODYSSEY KT is the first dedicated study of a PCSK9 inhibitor to assess the efficacy and safety of alirocumab in patients with high CV risk and inadequately controlled hypercholesterolemia in South Korea and Taiwan. In this study of patients with high CV risk and baseline LDL-C 97.0 to 99.3 mg/dL who received maximally tolerated statin with/without other LLTs, alirocumab 75 mg Q2W (with possible dose increase to 150 mg Q2W) significantly reduced LDL-C

Table 3 AEs and safety laboratory values (safety population)

Parameters	ODYSSEY KT		Pooled data of patients from Asia	
	Placebo (n = 102)	Alirocumab (n = 97)	Control (placebo/ezetimibe) (n = 215)	Alirocumab (n = 341)
TEAEs, n (%)	63 (61.8)	57 (58.8)	128 (59.5)	225 (66.0)
Treatment-emergent SAEs, n (%)	10 (9.8)	17 (17.5)	16 (7.4)	31 (9.1)
TEAEs leading to death, n (%)	0	1 (1.0)	0	1 (0.3)
TEAEs leading to treatment discontinuation, n (%)	1 (1.0)	2 (2.1)	4 (1.9)	13 (3.8)
AEs of interest, n (%)				
Injection-site reactions	3 (2.9)	2 (2.1)	7 (3.3)	24 (7.0)
General allergic reactions	4 (3.9)	4 (4.1)	9 (4.2)	19 (5.6)
Hepatic disorders	5 (4.9)	3 (3.1)	7 (3.3)	8 (2.3)
Neurological events	3 (2.9)	0	4 (1.9)	4 (1.2)
Neurocognitive disorders	1 (1.0)	0	1 (0.5)	0
Ophthalmologic disorders	0	1 (1.0)	1 (0.5)	4 (1.2)
Positively adjudicated CV events, n (%)	5 (4.9)	3 (3.1)	6 (2.8)	6 (1.8)
Non-fatal MI	1 (1.0)	0	1 (0.5)	2 (0.6)
Fatal and non-fatal ischemic stroke (including stroke not otherwise specified)	1 (1.0)	0	1 (0.5)	0
Ischemia-driven coronary revascularization procedure	4 (3.9)	3 (3.1)	5 (2.3)	6 (1.8)
TEAEs related to diabetes mellitus or diabetic complications (CMQ),* according to baseline diabetes status				
Patients with diabetes at baseline, n†	38	32	89	150
Diabetes mellitus or diabetic complications (CMQ), n (%)	1 (2.6)	1 (3.1)	3 (3.4)	10 (6.7)
Diabetes mellitus (PT), n (%)	0	0	0	4 (2.7)
Type II diabetes mellitus (PT), n (%)	1 (2.6)	0	1 (1.1)	4 (2.7)
Diabetes mellitus inadequate control (PT), n (%)	0	1 (3.1)	0	1 (0.7)
Diabetic neuropathy (PT), n (%)	0	0	1 (1.1)	0
Diabetic retinopathy (PT), n (%)	0	0	1 (1.1)	1 (0.7)
Patients without diabetes at baseline, n†	64	65	126	191
Diabetes mellitus or diabetic complications (CMQ), n (%)	2 (3.1)	4 (6.2)	5 (4.0)	9 (4.7)
Diabetes mellitus (PT), n (%)	1 (1.6)	2 (3.1)	2 (1.6)	5 (2.6)
Type II diabetes mellitus (PT), n (%)	1 (1.6)	1 (1.5)	2 (1.6)	2 (1.0)
Blood glucose increased (PT), n (%)	0	0	0	1 (0.5)
Glycosylated hemoglobin increased (PT), n (%)	0	1 (1.5)	0	1 (0.5)
Hyperglycemia (PT), n (%)	0	0	1 (0.8)	0
Laboratory values, n (%)				
Alanine aminotransferase >3 times ULN	1/102 (1.0)	1/97 (1.0)	2/215 (0.9)	5/340 (1.5)
Aspartate aminotransferase >3 times ULN	1/102 (1.0)	1/96 (1.0)	2/215 (0.9)	5/340 (1.5)
Creatine kinase >3 times ULN	6/100 (6.0)	2/96 (2.1)	6/213 (2.8)	6/339 (1.8)

AE, adverse event; CMQ, Custom MedDRA Queries; CV, cardiovascular; HLGT, high-level group term; HLT, high-level term; MedDRA, Medical Dictionary of Regulatory Activities; MI, myocardial infarction; PT, preferred term; SAE, serious adverse event; SMQ, standardized MedDRA Queries; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

TEAEs were encoded as PTs using MedDRA (version 18.0) according to the verbatim account entered by the investigator. TEAEs were further categorized according to standard MedDRA definitions (HLT, HLGT, and SMQ) or using custom groupings (CMQs) as defined by the sponsors.

*Selection of PTs is based on the HLGT "diabetic complications," HLT "diabetes mellitus," and HLT "carbohydrate tolerance analyses (including diabetes)," excluding PT "blood glucose decreased" and PT "hyperglycemia."

†According to medical history. The pooled data analysis included patients from Asia from the following studies: NCT02289963, NCT01812707, NCT02107898, and NCT01644188.

levels compared with placebo at week 24 ($P < .0001$). At week 12, only 9.5% of patients received a dose increase from 75 to 150 mg Q2W. In this study, alirocumab 75/150 mg Q2W changed LDL-C from baseline to week 24 by −57.1%; the change observed with alirocumab 75/150 mg Q2W in patients with high CV risk in Western societies who were included in the total patient population of COMBO II was −50.6%.[11] The LDL-C reductions from baseline to week 24 were similar in patients at high CV risk in Japan who received alirocumab 75/150 mg Q2W (LDL-C reduction: 62.5%).[17] Consistent with previous ODYSSEY phase 3 studies with similar patient inclusion criteria, most alirocumab-treated patients (85.8%) reached LDL-C levels <70 mg/L at week 24.[16,17]

At baseline, the proportion of patients on high-intensity statin was greater and LDL-C levels were lower in this study compared with the pooled data of patients from Asia because of differences in patient inclusion criteria and prescribing practices, particularly in Japan.[17,18] The Japan Atherosclerosis Society Guidelines recommend LDL-C levels of <120 mg/dL in patients with high CV risk and <100 mg/dL for those with very-high CV risk, which are higher than guideline recommendations from Europe (100 and 70 mg/dL, respectively).[4,21] The phase 2 dose-ranging study in Japan enrolled patients with hypercholesterolemia who were on atorvastatin 5 to 20 mg (n = 100) and had a lower CV risk than those studied later during the phase 3 studies. As a result, the proportion of patients with CHD history and CHD risk equivalents is lower in the pooled analysis, also resulting in a lower rate of patients receiving high-intensity statin.

Beneficial effects were shown for most secondary lipid parameters. Increased levels of Lp(a) have been previously associated with increased CV risk.[22] In this study, Lp(a) percent change from baseline to week 24 was −35.9% and −2.3% in the alirocumab and placebo groups, respectively. A pooled analysis of 10 ODYSSEY phase 3 studies (n = 4915) demonstrated Lp(a) reduction from baseline to week 24 by 23% to 27% with alirocumab 75 mg Q2W (with possible dose adjustment to 150 mg Q2W) and 29% with alirocumab 150 mg Q2W.[23] No significant difference in TG levels was observed between the alirocumab and placebo groups. Considering the low number of patients included in this study, the high variability of TG parameters and the lower levels of TGs at baseline in alirocumab-treated patients (116.0 mg/dL) vs the placebo group (136.5 mg/dL), the data should be interpreted with caution.

Because of the lower levels of LDL-C at baseline in this KT study (97.0–99.3 mg/dL) compared with ODYSSEY Japan (141.2 mg/dL), 27.8% of patients in the alirocumab group had 2 consecutive LDL-C values of <25 mg/dL compared with 12.1% of patients in ODYSSEY Japan.[17] In the pooled analysis, compared with the KT study, a lower rate of patients with at least 2 consecutive LDL-C values of <25 mg/dL was observed, likely due to the inclusion of ODYSSEY Japan data. No particular safety signals were reported with LDL-C <25 mg/dL in these short-term studies. In a pooled analysis of 14 phase 2 and 3 alirocumab studies (n = 5234), LDL-C <25 mg/dL was not associated with an increase in TEAEs except for a small but statistically significant increase in the incidence of cataracts.[24] In the KT study, the incidence of TEAEs was similar between the alirocumab and placebo groups. The incidence of discontinuation due to TEAEs was similar between this study (alirocumab: 2.1%; placebo: 1.0%) and the pooled data analysis of patients from Asia (alirocumab: 3.8%; control: 1.9%). The higher percentage of patients experiencing an SAE in the alirocumab group in the KT study (17.5%; n = 17) was not confirmed in the pooled analysis (9.1%; n = 31). In alirocumab-treated patients, the overall rate of adverse events of special interest was low and similar to that seen in the pooled analysis of Asian patients.

Meta-analyses have indicated that statins slightly increase the risk of developing type II diabetes.[25] Despite numerous investigations, the underlying mechanisms of this observation are not fully understood.[26,27] In the KT study, the number of patients developing diabetes was too low in the alirocumab (n = 4) and placebo groups (n = 2) to draw any conclusion. Similarly, the small number of patients without diabetes included in the pooled analysis of patients from Asia did not allow for generalization of the diabetes findings (n = 317). In a previously published analysis including 10 phase 3 studies from the ODYSSEY program (n = 3448), no evidence was found that alirocumab affects the incidence of new-onset diabetes and the hemoglobin A_{1c} levels in patients with no diabetes at baseline with a follow-up period of 6 to 18 months.[28] The occurrence of new-onset diabetes will be further investigated in the on-going ODYSSEY OUTCOMES study, which is assessing CV morbidity and mortality in patients treated with alirocumab.[29]

CV events were adjudicated in all phase 3 ODYSSEY studies including this KT study. Regardless of treatment status, the rate of positively adjudicated CV events was slightly lower in the pooled data of patients from Asia (alirocumab: 1.8%; control: 2.8%) vs the KT population (alirocumab: 3.1%; placebo: 4.9%), which is consistent with a lower proportion of patients with CHD history in the pooled patient population (pooled analysis: alirocumab [41.5%] and control [57.2%]; KT study: alirocumab [99.0%] and placebo [93.1%]) and male patients (pooled analysis: alirocumab [63.7%] and control [71.2%]; KT study: alirocumab [85.6%] and placebo [79.4%]). In a post-hoc analysis of the LONG TERM trial, it was suggested that alirocumab reduced the incidence of CV events compared with placebo (1.7% vs 3.3%; hazard ratio: 0.52).[16] The ODYSSEY OUTCOMES study of more than 18,000 patients will be completed by the end of 2017 and will report efficacy on CV events as well as long-term safety data.[29] Approximately 2300 patients from Asia were enrolled in OUTCOMES, including patients from Taiwan, South Korea, China, India, Japan, Philippines, Singapore, Sri Lanka, and Thailand.

ODYSSEY KT was designed to assess the efficacy and safety of alirocumab vs placebo in patients with hypercholesterolemia from South Korea and Taiwan over a period of 24 weeks. The efficacy and safety of alirocumab 75 mg Q2W (with possible dose increase to 150 mg Q2W) in patients with high CV risk in this particular population were demonstrated. The relatively small number of enrolled patients in the KT study and the 6 months' study duration may limit the generalization of these findings. Therefore, the safety results particularly should be interpreted with caution and must be considered in the context of a larger pool of patients from Asia, as well as the complete ODYSSEY program.

Acknowledgments

The authors would like to thank the study patients and investigators, and the following persons from the sponsors for their contributions to data collection and analysis, assistance with statistical analysis, or critical review of the article: Regeneron Pharmaceuticals, Inc: Carol Hudson, Robert Pordy, Desmond Thompson; Sanofi: Robeta Chi, Jay Edelberg, Michael Howard, Joohwan Lee, and L. Veronica Lee. A full list of principal investigators and committee members is shown in the supplement. Medical writing support was provided by Susanne Ulm of Prime, Knutsford, Cheshire, UK, funded by Sanofi and Regeneron Pharmaceuticals, Inc. Responsibility for all opinions, conclusions, and data interpretation lies with the authors.

Authors' contributions: K.K.K., C.W.N., T.-H.C., M.-E.L., C.-J.W., D.-S.K., C.-J.K., P.-J.H., and C.-E.C. contributed to data acquisition, analysis or interpretation of data, revising the article critically for important intellectual content, and gave approval of the version to be submitted. I.L., J.L., and M.T.B.-D. contributed to concept or design, analysis or interpretation of data, revising the article critically for important intellectual content, and gave approval of the version to be submitted.

Financial disclosure

K.K.K. holds a certificate of patent, 10-1579656 (pravastatin+valsartan). C.W.N. received research grant support from Pfizer, Medtronic, and Biosensors. T.-H.C. received speaker's bureau fees from Abbott Laboratories, AstraZeneca Pharmaceuticals, Bayer Healthcare Pharmaceuticals, Boehringer-Ingelheim, Daiichi Sankyo, Pfizer, Merck & Co., Inc., Novartis Corporation, Otsuka Pharmaceutical Co., Sanofi-Aventis. M.-E.L., C.-J.W., D.-S.K., C.-J.K., and P.-J.H. had no conflict of interest. I.L., J.L., and M.T.B.-D. are employees of and stockholders in Sanofi. C.-E.C. received consultant fees/honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Chugai, Daiichi Sankyo, GSK, MSD, Novartis, Pfizer, Roche, Sanofi-Aventis, Servier, Tanabe, Takeda, and TTY.

References

1. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
2. Welfare TMoHa. 2010 statistics of causes of death Available at: https://www.mohw.gov.tw/dl-30367-ac1e22be-ce5c-4e76-a803-81deccdf2ebc.html. Accessed November 8, 2017.
3. Kim HJ, Kim Y, Cho Y, Jun B, Oh KW. Trends in the prevalence of major cardiovascular disease risk factors among Korean adults: results from the Korea National Health and Nutrition Examination Survey, 1998-2012. *Int J Cardiol*. 2014;174:64–72.
4. Authors/Task Force Members, Catapano AL, Graham I, et al. 2016 ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis*. 2016;253:281–344.
5. Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1–full report. *J Clin Lipidol*. 2015;9:129–169.
6. Park JE, Chiang CE, Munawar M, et al. Lipid-lowering treatment in hypercholesterolaemic patients: the CEPHEUS Pan-Asian survey. *Eur J Prev Cardiol*. 2012;19:781–794.
7. Landmesser U, John Chapman M, Farnier M, et al. European Society of Cardiology/European Atherosclerosis Society Task Force consensus statement on proprotein convertase subtilisin/kexin type 9 inhibitors: practical guidance for use in patients at very high cardiovascular risk. *Eur Heart J*. 2017;38:2245–2255.
8. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC Expert Consensus Decision Pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on clinical expert consensus documents. *J Am Coll Cardiol*. 2016;68:92–125.
9. Seidah NG. New developments in proprotein convertase subtilisin-kexin 9's biology and clinical implications. *Curr Opin Lipidol*. 2016;27:274–281.
10. Bays H, Gaudet D, Weiss R, et al. Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial. *J Clin Endocrinol Metab*. 2015;100:3140–3148.
11. Cannon CP, Cariou B, Blom D, et al. Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur Heart J*. 2015;36:1186–1194.
12. Farnier M, Jones P, Severance R, et al. 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. *Atherosclerosis*. 2016;244:138–146.
13. Kastelein JJ, Ginsberg HN, Langslet G, et al. ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J*. 2015;36:2996–3003.
14. Kereiakes DJ, Robinson JG, Cannon CP, et al. Efficacy and safety of the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: The ODYSSEY COMBO I study. *Am Heart J*. 2015;169:906–915.e913.
15. Moriarty PM, Thompson PD, Cannon CP, et al. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: The ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol*. 2015;9:758–769.
16. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med*. 2015;372:1489–1499.

17. Teramoto T, Kobayashi M, Tasaki H, et al. Efficacy and safety of alirocumab in Japanese patients with heterozygous familial hypercholesterolemia or at high cardiovascular risk with hypercholesterolemia not adequately controlled with statins - ODYSSEY JAPAN randomized controlled trial. *Circ J*. 2016;80:1980–1987.
18. Teramoto T, Kobayashi M, Uno K, et al. Efficacy and safety of alirocumab in Japanese subjects (Phase 1 and 2 studies). *Am J Cardiol*. 2016;118:56–63.
19. Colhoun HM, Robinson JG, Farnier M, et al. Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials. *BMC Cardiovasc Disord*. 2014;14:121.
20. Ginsberg HN, Rader DJ, Raal FJ, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia and LDL-C of 160 mg/dl or higher. *Cardiovasc Drugs Ther*. 2016;30:473–483.
21. Teramoto T, Sasaki J, Ishibashi S, et al. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -2012 version. *J Atheroscler Thromb*. 2013;20:517–523.
22. Verbeek R, Sandhu MS, Hovingh GK, et al. Lipoprotein(a) improves cardiovascular risk prediction based on established risk algorithms. *J Am Coll Cardiol*. 2017;69:1513–1515.
23. Gaudet D, Watts GF, Robinson JG, et al. Effect of alirocumab on lipoprotein(a) over >/=1.5 years (from the Phase 3 ODYSSEY program). *Am J Cardiol*. 2017;119:40–46.
24. Robinson JG, Rosenson RS, Farnier M, et al. Safety of very low low-density lipoprotein cholesterol levels with alirocumab: pooled data from randomized trials. *J Am Coll Cardiol*. 2017;69:471–482.
25. Lim S, Sakuma I, Quon MJ, Koh KK. Differential metabolic actions of specific statins: clinical and therapeutic considerations. *Antioxid Redox Signal*. 2014;20:1286–1299.
26. Ference BA, Robinson JG, Brook RD, et al. Variation in PCSK9 and HMGCR and risk of cardiovascular disease and diabetes. *N Engl J Med*. 2016;375:2144–2153.
27. Koh KK, Sakuma I, Quon MJ. Differential metabolic effects of distinct statins. *Atherosclerosis*. 2011;215:1–8.
28. Colhoun HM, Ginsberg HN, Robinson JG, et al. No effect of PCSK9 inhibitor alirocumab on the incidence of diabetes in a pooled analysis from 10 ODYSSEY Phase 3 studies. *Eur Heart J*. 2016;37:2981–2989.
29. Schwartz GG, Bessac L, Berdan LG, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. *Am Heart J*. 2014;168:682–689.

Supplementary Material

Principal investigators

South Korea: Jei Keon Chae (Jeollabuk-do); Ki Yuk Chang (Seoul); Ho Myung Jeong (Gwangju); Sang-Ho Jo (Gyeonggi-do); Chongjin Kim (Seoul); Dong-Soo Kim (Busan); Moo Hyun Kim (Busan); Sanghyun Kim (Seoul); Youngkwon Kim (Gyeonggi-do); Kwang Kon Koh (Incheon); Chang Wook Nam (Daegu); Kyungmi Oh (Seoul); Cheol Young Park (Seoul); Woo-Keun Seo (Seoul); Eunseok Shin (Ulsan); Kyung-Ho Yu (Gyeonggi-do).

Taiwan: Ting-Hsing Chao (Tainan); Zhih-Cherng Chen (Tainan); Ching-Pei Cheng (Changhua); Chern-En Chiang (Taipei); Fu-Tien Chiang (Taipei); Pi-Jung Hsiao (Kaohsiung); Tsong-Hai Lee (Taoyuan County); Chung-Hsiang Liu (Taichung); Ming-En Liu (Hsinchu); Chiung-Jen Wu (Kaohsiung); Hung-I Yeh (Taipei).

Steering committee

Christopher P. Cannon (Boston, USA); Helen Colhoun (Dundee, United Kingdom); Michel Farnier (Dijon, France); Henry N. Ginsberg (New York, USA); Yong Huo (Beijing, China); John J.P. Kastelein (Amsterdam, the Netherlands); Daniel J. Rader (Philadelphia, USA); Jennifer G. Robinson (Iowa City, USA).

Data monitoring committee

Dominique Larrey (Montpellier, France); Geert Molenberghs (Diepenbeek, Belgium); Anders G. Olsson (Bromma, Sweden); Peter A. Patriarca (Alexandria, USA); Robert S. Rosenson (New York, USA); David D. Waters (San Francisco, USA).

Independent biostatistician

Geneviève Sturbois (Louvain-la-Neuve, Belgium).

Safety events of interest

The selection of preferred terms (PTs) for the adverse event (AE) categories was based on Standard Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQs) or Custom MedDRA Queries (CMQ). The safety events of interest and other potentially significant AEs were identified as follows for the analysis purpose.

- Overdose with study investigational medical product (IMP; symptomatic or asymptomatic): selection of PTs was based on high-level term (HLT) "Overdose."
- Local injection-site reactions: selection of PTs based on electronic case report form (e-CRF)-specific tick box on the AE page.
- Allergy events.
  - Selection of PTs was based on SMQs: "hypersensitivity" (broad and narrow) excluding the following PTs linked to local injection-site reactions ("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-site vasculitis").
  - General allergic events and local allergic reactions at IMP injection site: selection of PTs based on the selection for general allergic event and the following selection of PTs from the symptoms complementary form for local injection-site reaction ("injection-site dermatitis," "injection-site hypersensitivity," "injection-site edema," "injection-site rash," "injection-site urticaria," "injection-site eczema," "injection-site vasculitis," "injection-site swelling," "infusion-site dermatitis," "infusion-site hypersensitivity," "infusion-site edema," "infusion-site rash," "infusion-site urticaria," "infusion-site swelling").
- Ophthalmologic events: selection was based on the SMQs "optic nerve disorders" (broad and narrow), "retinal disorders" (narrow), and "corneal disorders" (narrow), and the HLT "cataract conditions."
- Neurologic events: selection of PTs was based on the SMQs "demyelination" (broad and narrow), "peripheral neuropathy" (broad and narrow), and "Guillain-Barré syndrome" (broad and narrow) excluding the PTs "acute respiratory distress syndrome," "asthenia," "respiratory arrest," and "respiratory failure."
- Neurocognitive events: selection of PTs was based on the CMQ of the following 5 high-level group terms (HLGTs): "deliria (including confusion)," "cognitive and attention disorders and disturbances," "dementia and amnestic conditions," "disturbances in thinking and perception," and "mental impairment disorders."
- Pregnancy of female patient or partner of male patient: selection of PTs was based on appropriate MedDRA codes.
- Hemolytic anemia: selection of PTs was based on e-CRF-specific tick box on the AE page and confirmed final diagnosis provided in the AE complementary form.
- Alanine aminotransferase (ALT) $\geq$3 upper limit of normal range (ULN; if baseline ALT $<$ ULN) or ALT $\geq$2 times the baseline value (if baseline ALT $\geq$ ULN), selected using laboratory data.

Analysis of other potentially significant AEs

The following additional grouping of AEs was identified for analysis purposes.

- Hepatic disorder events using the SMQ "hepatic disorder."
- Diabetes, (ie, investigator-reported, treatment-emergent diabetes and worsening of pre-existing diabetes) selected using the CMQ "diabetes": HLGT "diabetes complications," HLT "diabetes mellitus," and HLT "carbohydrate

tolerance analyses (including diabetes)" excluding PT "blood glucose decreased" and using the PT "hyperglycemia." Diabetes was assessed separately in patients with diabetes at baseline and those without.

Cardiovascular events

Suspected CV events that occured from randomization until the follow-up visit were submitted to the Clinical Events Committee (CEC) for adjudication. An analysis of adjudicated CV events was performed. Adjudicated CV events include all CV AEs positively adjudicated as defined in the CEC charter. The following categories were described:

- Coronary heart disease death.
- Non-fatal myocardial infarction.
- Fatal and non-fatal ischemic stroke.
- Unstable angina requiring hospitalization.
- Congestive heart failure requiring hospitalization.
- Ischemia-driven coronary revascularization procedure.

Deaths

The deaths were defined according to the observation period.

- Death on-study: deaths occurring during the on-study observation period.
  - Death on-treatment: deaths occurring during the TEAE period.
- Death post-study: deaths occurring after the last planned protocol visit.

Supplementary Table 1 Exclusion criteria

	Exclusion criteria
1	Patients without established CHD or CHD risk equivalents
2	LDL-C <70 mg/dL at the screening visit (week −3) in patients with a history of documented CVD
3	LDL-C <100 mg/dL at the screening visit (week −3) in patients without history of documented CVD
4	Not on a stable dose of LTT (including statin) for ≥4 wk before the screening visit (week −3) 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 wk before screening visit (week −3) 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 ≥4 wk before the screening visit (week −3) or between screening and randomization visits
10	Use of red yeast rice products within 4 wk of the screening visit (week −3) or between screening and randomization visits
11	Patient who has received plasmapheresis treatment within 2 mo before the screening visit (week −3) or has plans to receive this during the study
12	History of an 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 mo before the screening visit (week −3, visit 1)
13	Planned to undergo scheduled PCI or CABG, or carotid or peripheral revascularization, during the study
14	Systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg at screening visit or randomization visit
15	History of New York Heart Association Class III or IV heart failure within the past 12 mo
16	Known history of hemorrhagic stroke
17	Age <18 y or legal age of majority at the screening visit (week −3), whichever is greater
18	Patients not previously instructed on a cholesterol-lowering diet before the screening visit (week −3)
19	Newly diagnosed (within 3 mo before randomization visit [week 0]) or poorly controlled (HbA1c >9% at the screening visit [week −3]) diabetes
20	Presence of any clinically significant uncontrolled endocrine disease known to influence serum lipids or lipoproteins
21	History of bariatric surgery within 12 mo before the screening visit (week −3)
22	Unstable weight defined by a variation >5 kg within 2 mo before the screening visit (week −3)
23	Known history of homozygous or heterozygous familial hypercholesterolemia
24	Known history of loss of function of *PCSK9* (ie, 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 wk before randomization (week 0)
26	Use of continuous estrogen or testosterone hormone replacement therapy unless the regimen has been stable in the past 6 wk before the screening visit (week −3) and no plans to change the regimen during the study
27	History of cancer within the past 5 y, except for adequately treated basal cell skin cancer, squamous cell skin cancer, or in situ 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 mo 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)
32	Conditions/situations such as: Any clinically significant abnormality identified at the time of screening that in the judgment of the investigator or any subinvestigator would preclude safe completion of the study or constrain endpoints assessment such as major systemic diseases or patients with a short life expectancy. Considered by the investigator or any subinvestigator as inappropriate for this study for any reason, eg, • Deemed unable to meet specific protocol requirements, such as scheduled visits • Deemed unable to administer or tolerate long-term injections as per the patient or the investigator • Investigator or any subinvestigator, pharmacist, study coordinator, other study staff, or relative thereof directly involved in the conduct of the protocol, etc. • Presence of any other conditions (eg, geographic, social), actual or anticipated, that the investigator feels would restrict or limit the patient's participation for the duration of the study

(*continued on next page*)

Supplementary Table 1 (*continued*)

	Exclusion criteria
33	Laboratory findings during the screening period (not including randomization week 0 labs): • Positive test for hepatitis B surface antigen or hepatitis C antibody (confirmed by reflexive testing) • Positive serum beta-human chorionic gonadotropin or urine pregnancy test (including week 0) in women of childbearing potential • Triglycerides >400 mg/dL (1 repeat laboratory is allowed) • eGFR <30 mL/min/1.73 m^2 • ALT or AST >3 × ULN (1 repeat laboratory is allowed) • CPK >3 × ULN (1 repeat laboratory is allowed) • TSH < lower limit of normal or > ULN (1 repeat laboratory is allowed)
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

ALT, alanine aminotransferase; AST, aspartate transferase; CABG, coronary artery bypass graft; CHD, coronary heart disease; CPK, creatine phosphokinase; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HIV, human immunodeficiency virus; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MI, myocardial infarction; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; TSH, thyroid-stimulating hormone; ULN, upper limit of normal.

Supplementary Table 2 Patients with treatment-emergent SAE according to primary system organ class (safety population)

	ODYSSEY KT		Pooled data of patients from Asia	
n (%)	Placebo (n = 102)	Alirocumab (n = 97)	Control (placebo/ ezetimibe) (n = 215)	Alirocumab (n = 341)
Any class	10 (9.8)	17 (17.5)	16 (7.4)	31 (9.1)
Cardiac disorders	4 (3.9)	6 (6.2)	5 (2.3)	10 (2.9)
Injury, poisoning, and procedural complications	1 (1.0)	5 (5.2)	1 (0.5)	7 (2.1)
Vascular disorders	1 (1.0)	1 (1.0)	8 (3.7)	13 (3.8)
Nervous system disorders	2 (2.0)	3 (3.1)	3 (1.4)	7 (2.1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	2 (2.1)	1 (0.5)	6 (1.8)
Infections and infestations	2 (2.0)	1 (1.0)	3 (1.4)	2 (0.6)
Musculoskeletal and connective tissue disorders	0	1 (1.0)	2 (0.9)	6 (1.8)
Gastrointestinal disorders	0	0	2 (0.9)	5 (1.5)
Product issues*	0	1 (1.0)	0	1 (0.3)
Respiratory, thoracic, and mediastinal disorders	1 (1.0)	0	2 (0.9)	2 (0.6)
Ear and labyrinth disorders	0	0	1 (0.5)	2 (0.6)
Eye disorders	0	0	0	2 (0.6)
Renal and urinary disorders	0	0	1 (0.5)	2 (0.6)
General disorders and administration-site conditions	0	0	1 (0.5)	0
Reproductive system and breast disorders	0	0	1 (0.5)	1 (0.3)
Skin and subcutaneous tissue disorders	0	0	0	1 (0.3)

SAE, serious adverse event.
The pooled data analysis included patients from Asia from the following studies: NCT02289963, NCT01812707, NCT02107898, and NCT01644188.
*Defined as implant failure for left patella fracture.

Supplementary Table 3 TEAEs occurring in ≥2% of patients (safety population)

n (%)	ODYSSEY KT		Pooled data of patients from Asia	
	Placebo (n = 102)	Alirocumab (n = 97)	Control (placebo/ ezetimibe) (n = 215)	Alirocumab (n = 341)
TEAEs occurring in ≥2% patients in either group				
Infections and infestations	19 (18.6)	16 (16.5)	44 (20.5)	97 (28.4)
Nasopharyngitis	4 (3.9)	6 (6.2)	18 (8.4)	63 (18.5)
Upper respiratory tract infection	6 (5.9)	3 (3.1)	6 (2.8)	9 (2.6)
Blood and lymphatic system disorders	0	3 (3.1)	0	5 (1.5)
Anemia	0	2 (2.1)	0	4 (1.2)
Metabolism and nutrition disorders	6 (5.9)	6 (6.2)	9 (4.2)	21 (6.2)
Type II diabetes mellitus	2 (2.0)	1 (1.0)	3 (1.4)	6 (1.8)
Nervous system disorders	10 (9.8)	14 (14.4)	14 (6.5)	38 (11.1)
Dizziness	3 (2.9)	6 (6.2)	3 (1.4)	11 (3.2)
Headache	3 (2.9)	5 (5.2)	3 (1.4)	15 (4.4)
Ear and labyrinth disorders	3 (2.9)	2 (2.1)	5 (2.3)	7 (2.1)
Vertigo	3 (2.9)	1 (1.0)	4 (1.9)	3 (0.9)
Cardiac disorders	9 (8.8)	9 (9.3)	11 (5.1)	20 (5.9)
Angina pectoris	3 (2.9)	3 (3.1)	4 (1.9)	6 (1.8)
Atrial fibrillation	0	2 (2.1)	0	2 (0.6)
Coronary artery disease	1 (1.0)	2 (2.1)	1 (0.5)	2 (0.6)
Respiratory, thoracic, and mediastinal disorders	10 (9.8)	2 (2.1)	15 (7.0)	13 (3.8)
Cough	4 (3.9)	1 (1.0)	7 (3.3)	3 (0.9)
Gastrointestinal disorders	19 (18.6)	12 (12.4)	34 (15.8)	52 (15.2)
Diarrhea	1 (1.0)	5 (5.2)	3 (1.4)	8 (2.3)
Dyspepsia	0	2 (2.1)	0	4 (1.2)
Constipation	2 (2.0)	1 (1.0)	2 (0.9)	4 (1.2)
Gastritis	2 (2.0)	1 (1.0)	2 (0.9)	5 (1.5)
Abdominal pain	3 (2.9)	0	3 (1.4)	1 (0.3)
Abdominal pain upper	3 (2.9)	0	6 (2.8)	2 (0.6)
Vomiting	2 (2.0)	0	3 (1.4)	2 (0.6)
Musculoskeletal and connective tissue disorders	9 (8.8)	5 (5.2)	29 (13.5)	54 (15.8)
Intervertebral disc protrusion	0	2 (2.1)	0	3 (0.9)
Back pain	3 (2.9)	1 (1.0)	7 (3.3)	15 (4.4)
Renal and urinary disorders	6 (5.9)	4 (4.1)	9 (4.2)	8 (2.3)
Hematuria	2 (2.0)	2 (2.1)	3 (1.4)	3 (0.9)
Reproductive system and breast disorders	0	4 (4.1)	1 (0.5)	6 (1.8)
Benign prostatic hyperplasia	0	3 (3.1)	0	4 (1.2)
General disorders and administration-site conditions	9 (8.8)	5 (5.2)	19 (8.8)	43 (12.6)
Chest discomfort	1 (1.0)	2 (2.1)	1 (0.5)	4 (1.2)
Injection-site reaction	3 (2.9)	2 (2.1)	7 (3.3)	24 (7.0)
Mild	3 (100)	1 (50.0)	6 (85.7)	23 (95.8)
Moderate	0	1 (50.0)	0	1 (4.2)
Severe	0	0	1 (14.3)	0
Asthenia	3 (2.9)	0	3 (1.4)	1 (0.3)
Non-cardiac chest pain	2 (2.0)	0	3 (1.4)	4 (1.2)
Injury, poisoning, and procedural complications	3 (2.9)	10 (10.3)	5 (2.3)	32 (9.4)
Fall	1 (1.0)	3 (3.1)	1 (0.5)	10 (2.9)
Contusion	0	2 (2.1)	1 (0.5)	8 (2.3)

TEAE, treatment-emergent adverse event.

The pooled data analysis included patients from Asia from the following studies: NCT02289963, NCT01812707, NCT02107898, and NCT01644188.

Supplementary Table 4 Percent of patients with 2 consecutive calculated LDL-C values <25 and <15 mg/dL (safety population)

Parameters	ODYSSEY KT		Pooled data of patients from Asia	
	Placebo (n = 102)	Alirocumab (n = 97)	Control (placebo/ ezetimibe) (n = 215)	Alirocumab (n = 341)
Patients with 2 consecutive calculated LDL-C values <25 mg/dL, n (%)*	0	27 (27.8)	0	58 (17.0)
Time to the first calculated LDL-C value <25 mg/dL, wk†				
Mean (SD)	0	7.5 (4.2)	0	9.0 (9.9)
Median (Min:Max)	0	7.6 (3.6:16.3)	0	7.6 (2.0:64.4)
Patients with 2 consecutive calculated LDL-C values <15 mg/dL, n (%)*	0	9 (9.3)	0	19 (5.6)
Time to the first calculated LDL-C value <15 mg/dL, wk†				
Mean (SD)	0	7.6 (3.0)	0	12.9 (20.5)
Median (Min:Max)	0	8.1 (3.6:11.9)	0	7.9 (2.1:77.1)

LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.

The pooled data analysis included patients from Asia from the following studies: NCT02289963, NCT01812707, NCT02107898, and NCT01644188.

*Two consecutive values were considered if spaced out by at least 21 d.

†First calculated LDL-C value <25 or <15 mg/dL among the first 2 consecutive calculated LDL-C values <25 or <15 mg/dL per patient.