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ORIGINAL ARTICLE

A subanalysis of Taiwanese patients from ODYSSEY South Korea and Taiwan study evaluating the efficacy and safety of alirocumab

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Abstract

Background: Alirocumab can provide significant reductions in low-density lipoprotein cholesterol (LDL-C). However, data regarding its efficacy and safety in Asians are limited.

Methods: A subgroup analysis of Taiwanese patients (n = 116) in a randomized trial evaluating the efficacy and safety of alirocumab in South Korea and Taiwan (ODYSSEY KT, clinicaltrials.gov Identifier: NCT02289963) was performed. Patients with hypercholesterolemia at high cardiovascular risk on maximally tolerated statin were randomized to alirocumab (75 mg every 2 weeks; with dose increased to 150 mg at Week 12 if LDL-C ≥ 70 mg/dL at Week 8) or placebo for 24 weeks. The primary efficacy endpoint was the percent change in LDL-C from baseline to Week 24. Safety was assessed for a total of 32 weeks.

Results: At Week 24, the percent change in calculated LDL-C in the alirocumab group (n = 57) was –51%, whereas that in the placebo group (n = 59) was 2.5%. Alirocumab significantly improved other lipid parameters, including non-high-density lipoprotein cholesterol, apolipoprotein B and A1, lipoprotein (a), high-density lipoprotein cholesterol, and total cholesterol. A significantly higher proportion of patients in the alirocumab group reached an LDL-C target below 70 mg/dL than those in the placebo group (81.3% vs 15.4%). The incidence of treatment-emergent adverse events was comparable between both groups.

Conclusion: Alirocumab treatment provided a favorable effect on LDL-C levels and other lipid parameters, and was generally well-tolerated in patients from Taiwan. The results of current analysis were consistent with the overall ODYSSEY phase 3 program.

Keywords: Alirocumab; High cardiovascular risk; Low-density lipoprotein cholesterol; Taiwanese

1. INTRODUCTION

The increasing incidence of cardiovascular (CV) events has become a serious public health challenge in Taiwan.[1,2] According to a report from the Taiwan Ministry of Health and Welfare in 2016, every 25 minutes a person dies of cardiovascular disease (CVD) in Taiwan.[3] The correlation between elevated low-density lipoprotein cholesterol (LDL-C) level and CVD is well-established.[4,5] Current guidelines suggest that the optimal LDL-C goals for patients with high or very-high CV risk are <100 mg/dL or <70 mg/dL, respectively.[6,7] 2017 Taiwan Lipid Guideline even recommended a goal of LDL-C <55 mg/dL for patients with comorbid acute coronary syndrome and diabetes mellitus.[7,8] However, Taiwanese Secondary Prevention for patients with AtheRosCLErotic disease (T-SPARCLE) study revealed that only 54.5% of Taiwanese patients with stable symptomatic atherosclerotic diseases achieved LDL-C <100 mg/dL.[9] In addition to T-SPARCLE study, the Centralized Pan-Asian survey on the under-treatment of hypercholesterolemia (CEPHEUS) Pan-Asian survey yielded a similar result in Taiwan and higher percentages of hypercholesterolemia patients in the high-risk categories failed to attain their LDL-C targets based on 2004 National Cholesterol Educational Program Adult Treatment Panel III.[10,11] For Taiwanese patients at very high risk with a

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LDL-C goal of <70 mg/dL, the lowest target achievement rate of 22% was reported, despite the use of conventional lipid-lowering therapies (LLTs) such as statin, ezetimibe, and fibrate.[11,12] With all these results revealing the suboptimal LDL-C control, a need for novel therapy has arisen and greater efforts are necessary in lipid control.[9–12] Proprotein convertase subtilisin/kexin type 9 (PCSK9), a member of the subtilisin family of serine proteases expressed primarily in the liver, promotes low-density lipoprotein receptor (LDLR) internalization and degradation through direct binding to LDLR, and thereby increases serum LDL-C.[13] Based on the consensus statements published by the American College of Cardiology and European Society of Cardiology/European Atherosclerosis Society, PCSK9 monoclonal antibody therapies including alirocumab may be considered in patients with high to very high CV risk.[14,15] The European Society of Cardiology/European Atherosclerosis Society Task Force further recommends that very high risk patients with verified statin intolerance may be considered for treatment with a PCSK9 inhibitor.[15] Therefore, PCSK9 inhibitors have become a promising alternative to achieve LDL-C targets for patients who did not respond well to a maximally tolerated daily dose of statin.

The efficacy of alirocumab, a fully human monoclonal antibody to PCSK9, has been demonstrated in several phase three clinical studies.[16–18] In the ODYSSEY LONG TERM trial that enrolled 2341 patients at high CV risk who received statins therapy with or without other LLTs, LDL-C levels declined by 61% and approximately 80% of patients achieved their desired LDL-C goals in the treatment arm of receiving 150 mg of alirocumab every 2 weeks (Q2W).[17] The benefit of alirocumab was also observed in the ODYSSEY FH I and FH II conducted in heterozygous familial hypercholesterolemia (FH) population.[18] Nevertheless, the previously mentioned trials were conducted primarily in Western populations (up to 93%).[16–18] Considering the potential ethnic differences in drug response particularly between Asian and non-Asian, ODYSSEY Japan and ODYSSEY KT study that enrolled patients from Taiwan and South Korea were performed to provide data regarding the efficacy and safety of alirocumab in Asian patients with hypercholesterolemia at high CV risk.[19,20] ODYSSEY Japan study, which was conducted in 216 hypercholesterolemia patients, of whom 19.0% had heterozygous FH and 18.5% had coronary artery disease history, demonstrated that alirocumab significantly reduced LDL-C by 62.5% and was well-tolerated in Japanese patients over 52 weeks.[19] In ODYSSEY KT study that enrolled 199 hypercholesterolemia patients from Taiwan and South Korea, 96.0% of patients had coronary heart disease (CHD) history and patients with history of FH were excluded. A 57.1% of LDL-C reduction was observed in the alirocumab group (placebo: +6.3%) and 85.8% of patients in the treatment arm achieved LDL-C <70 mg/dL (placebo: 14.2%).[20] Notably, patients in the ODYSSEY Japan trial were on stable statin therapy, whereas maximally tolerated statin in ODYSSEY KT was used with up to 72.3% of patients having high-intensity statin. Despite the discrepancies in patient population and statin treatment, ODYSSEY Japan and ODYSSEY KT studies showed consistent efficacy in LDL-C reduction and were complimentary for alirocumab use in East Asian populations.[19,20]

Ethnic differences in drug response have recently been reported among East Asian populations including Chinese, Korean, and Japanese.[21–24] For instance, a subgroup analysis of a randomized controlled trial of stroke prevention in atrial fibrillation showed benefits of apixaban in Japanese and Korean populations but the benefits were absent in Chinese population.[24] Despite the underlying mechanisms remain equivocal, these observations are actually red flags to us, reminding us to take ethnic differences among East Asians into consideration when interpreting the outcomes of ODYSSEY KT study. Therefore, this study was designed to further investigate the efficacy and safety of alirocumab in the subset of Taiwanese patients who participated in the ODYSSEY KT study and to evaluate the consistency with the overall study population.

2. METHODS

The ODYSSEY KT study, a multicenter, double-blind, parallel group, randomized controlled trial, was carried out at 27 active sites across Taiwan and South Korea in accordance with the ethical principles enunciated in the Declaration of Helsinki and the International Conference on Harmonization guidelines for Good Clinical Practice. The study was registered in ClinicalTrials.gov (NCT02289963), and the protocol was approved by independent Ethics Committees of all participating sites. Prior to participation, written informed consent was provided by all patients. The study design of ODYSSEY KT has been previously published in detail.[20]

2.1. Patients and study design

All patients from 10 study sites across Taiwan in the ODYSSEY KT study were included. Patients were eligible to participate in the study if they fulfill all of the following criteria: (1) were equal to or older than 18 years; (2) had high CV risk with established CHD or CHD risk equivalents; (3) had inadequately controlled hypercholesterolemia (LDL-C ≥ 70 mg/dL in patients with documented CVD history; LDL-C ≥ 100 mg/dL in patients without documented CVD history); and (4) were on a maximally tolerated daily dose of statin with or without other LLTs, both at a stable dose for at least 4 weeks before the screening visit. Exclusion criteria are shown in Supplementary Table 1.

After screening, all participants were randomly assigned to receive either 75 mg of alirocumab or placebo Q2W for 24 weeks in a ratio of 1:1, stratified by history of CVD, daily dose of statin, and country. For patients on alirocumab therapy with LDL-C levels ≥ 70 mg/dL at Week 8, their dose of alirocumab was titrated to 150 mg Q2W from Week 12 per protocol. On-site visits including collection of blood samples were scheduled at weeks 0, 4, 8, 12, 16, 24, and 32.[20]

2.2. Efficacy and safety assessments

The primary endpoint of this study was identical to that of the ODYSSEY KT study, which was the percent change from baseline in calculated LDL-C at week 24 via intent-to-treat (ITT) analysis. The secondary endpoints were the percent change from baseline in calculated LDL-C at Week 12, the percent change from baseline in other lipid parameters, including apolipoprotein A1 and B, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, lipoprotein (a), total cholesterol, and triglyceride at Week 12 and Week 24, and the percentage of patients whose calculated LDL-C < 70 mg/dL at Week 24.

Safety profiles, including treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events, laboratory data and vital signs, were monitored and recorded. TEAEs in this study were defined as adverse events that emerged or worsened from the time of the first injection to 70 days after the last injection. Key adverse events of interest comprised injection site reactions, general allergic reactions, hepatic disorders, and nervous system disorders.

To assess the generation of antidrug antibodies (ADAs) against alirocumab, ADAs were measured at weeks 0, 4, 12, 24, and 32, via a validated, competitive ligand binding assay provided by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY).

2.3. Statistical analysis

A minimum of 40 patients was imputed for 95% statistical power to detect 30% change in LDL-C level from baseline to Week 24 at a two-sided significance level of 0.05. The population was assumed to be evaluable for the primary endpoint and have a common SD of 25%. Since the number of patients from Taiwan was 116, which is still larger than 40, the sample size was sufficient to provide statistically significant outcomes related to efficacy.

To manage missing data, a mixed effect model with repeated measures was used to evaluate the primary efficacy endpoint. Besides, a hierarchical inferential procedure was used in

analyzing principal secondary endpoints to control type 1 error caused by multiple independent endpoints. To analyze continuous secondary endpoints with non-normal distribution (lipoprotein [a] and triglycerides [TGs]), a multiple imputation method followed by robust regression was selected to handle missing data. A multiple imputation method followed by logistic regression was used to analyze LDL-C goal attainment.

The ITT population included all randomly assigned patients with recorded data of LDL-C level at baseline and at one of the postrandomization evaluation points. The safety population included all randomly assigned patients who were treated with at least part of a dose of study drug within the study duration.

Safety analyses that included all treated patients were reported descriptively in this study. All statistical analyses mentioned earlier were performed on SAS version 9.4 (SAS Institute Inc., Cary, NC).

3. RESULTS

3.1. Study patients

Among 199 patients in the ODYSSEY KT study, 116 patients (58.3%) from 10 clinical sites in Taiwan were identified and treated with at least one dose to fulfill the criteria for both ITT and safety population. Fifty-seven of the patients from Taiwan were randomized to receive 75 mg of alirocumab Q2W, whereas 59 of them were assigned to receive placebo (Fig. 1). The baseline demographics and lipid profiles of patients from Taiwan and overall population are shown in Table 1, based on their randomized group (alirocumab vs placebo). The Taiwanese population had a mean age of 60.7 years and 83.6% of them were male. Most of the characteristics were similar between the Taiwan population and the original ODYSSEY KT population. However, in comparison to the overall study population, patients from Taiwan had a higher rate of receiving high-intensity statins (overall, 72.4%; Taiwan, 83.6%) and prevalence of diabetes mellitus (overall, 35.2%; Taiwan, 44.0%).

3.2. Efficacy outcomes

After 24 weeks of double-blind treatment, the mean percent change in calculated LDL-C from baseline was −51% with alirocumab and +2.5% with placebo, for a significant difference of −53.5% between two groups (95% CI, −64.4 to −42.6; $p < 0.0001$). At Week 12, alirocumab reduced LDL-C level by 54.7% (+1.1% with placebo), with a significant difference of −55.8% in comparison to placebo (95% CI, −63.7 to −47.9; $p < 0.0001$) (Table 2). In alirocumab-treated group, a reduction in LDL-C concentrations was observed from Week 4 to Week 24 in Taiwan cohort (Fig. 2). Consistent efficacy was noticed in both Taiwan and the overall population.

In total, 10.9% of patients in the alirocumab group (n = 6) had a dose up-titration at Week 12. At Week 24, a significantly higher proportion of patients in the alirocumab group reached an LDL-C target below 70 mg/dL than those in the placebo group (81.3% vs 15.4%; $p < 0.0001$) (Fig. 3). Moreover, alirocumab showed highly significant improvement ($p < 0.0001$) in other secondary lipid parameters, including apolipoprotein B, lipoprotein (a), non-high-density lipoprotein cholesterol, and total cholesterol (Table 2). Apolipoprotein A1 and high-density lipoprotein cholesterol were also significantly improved in the alirocumab group ($p < 0.05$).

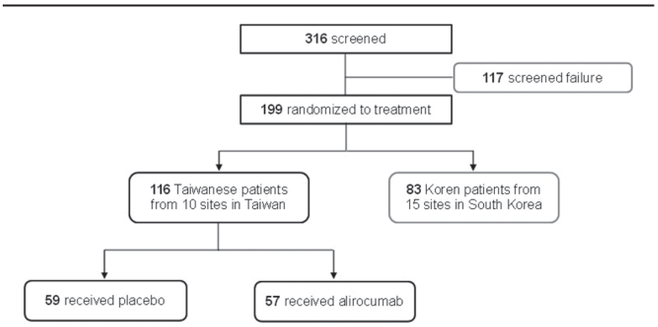

Fig. 1 Patient flow through the ODYSSEY-KT study for a subgroup analysis of Taiwanese patients.

3.3. Safety outcomes

Among 116 Taiwanese patients, 39 patients in the alirocumab group and 41 patients in the placebo group reported TEAEs (Table 3). By comparison with the overall population, the incidence of TEAEs in Taiwan population was higher in both groups (alirocumab vs placebo, respectively: Taiwan, 68.4% vs 69.5%; overall, 58.8% vs 61.8%). Being consistent with the findings in the overall population, the rate of treatment-emergent serious adverse events was less frequent with placebo compared with alirocumab in Taiwan patients (alirocumab vs placebo, respectively: Taiwan, 21.1% vs 8.5%; overall, 17.5% vs 9.8%). But the treatment-emergent serious adverse events were sporadically reported and no particular clinical pattern was observed.

One fatal TEAE was reported in the alirocumab group. A 62-year-old male from Taiwan had type A influenza infection and was hospitalized 3 days after the last injection of alirocumab (Day 158, Week 22). The patient died on Day 185 due to respiratory failure. The primary cause of death was considered non-CV and not related to alirocumab. Few patients discontinued the study drug due to TEAEs (two patients in alirocumab group vs one patient in placebo group).

The most common TEAEs (occurring in ≥5% of patients in either group) in Taiwanese patients observed in this study were nasopharyngitis (5.3% with alirocumab vs 3.4% with placebo), upper respiratory infection (3.5% with alirocumab vs 10.2% with placebo), headache (1.8% with alirocumab vs 5.1% with placebo), diarrhea (8.8% with alirocumab vs 1.7% with placebo), dizziness (8.8% with alirocumab vs 5.1% with placebo), and cough (1.8% with alirocumab vs 6.8% with placebo). In addition, a few injection-site reactions were observed (<2% in each group). The incidences of patients experiencing positively adjudicated CV events were low and highly comparable between alirocumab and placebo group (three events in alirocumab group vs two events in placebo group). Besides, TEAEs related to diabetes mellitus were also similar in both alirocumab-treated and placebo-treated patients regardless of their diabetic status at baseline and were summarized in Supplementary Table 2. The adverse events and laboratory data in Taiwanese patients were generally similar to the safety outcomes of the entire ODYSSEY KT population.

Two consecutive LDL-C values <25 mg/dL were observed in 12 alirocumab-treated patients (21.1%), of whom five patients experienced LDL-C levels <15 mg/dL at two consecutive points. However, no related safety problem was noticed in these patients during the study duration (data not shown).

In patients from Taiwan, three cases of treatment-emergent ADA positive responses were observed in the alirocumab group and all cases were transient (data not shown). Overall, no particular difference in efficacy and safety outcomes was noticed between patients with positive ADA response and patients without positive ADA response.

4. DISCUSSION

ODYSSEY KT-Taiwan is a subgroup analysis of ODYSSEY KT study to provide complete data regarding the efficacy and safety of alirocumab in Taiwanese patients and further evaluate its consistency with the overall KT population. In this subgroup analysis of Taiwanese population, a significant reduction in LDL-C from baseline was observed at Week 24 in alirocumab-treated population and was comparable to the outcome of ODYSSEY KT.[20] Consistent with ODYSSEY KT study, the incidence of

Table 1

Baseline characteristics (all randomized patients)

	ODYSSEY KT		KT-TW[a]	
	Placebo (n = 102)	Alirocumab (n = 97)	Placebo (n = 59)	Alirocumab (n = 57)
Baseline demographics				
Age, y, mean, SD	60.1 (9.1)	61.2 (10.4)	60.0 (8.9)	61.5 (11.1)
Male, n, %	81 (79.4)	83 (85.6)	46 (78.0)	51 (89.5)
BMI, kg/m^2, mean, SD	26.6 (3.8)	26.3 (4.0)	27.0 (3.8)	26.7 (4.4)
CHD history[b], n, %	95 (93.1)	96 (99.0)	55 (93.2)	56 (98.2)
CHD risk equivalents[c], n, %	26 (25.5)	21 (21.6)	17 (28.8)	16 (28.1)
Diabetes, n, %	38 (37.3)	32 (33.0)	27 (45.8)	24 (42.1)
Lipid medication, n, %				
Any statin	102 (100)	97 (100)	59 (100)	57 (100)
High-intensity statin[d]	73 (71.6)	71 (73.2)	49 (83.1)	48 (84.2)
Simvastatin 40 mg	22 (21.6)	17 (17.5)	6 (10.2)	5 (8.8)
LMT other than statins	24 (23.5)	22 (22.7)	10 (16.9)	8 (14.0)
Ezetimibe use	12 (11.8)	14 (14.4)	8 (13.6)	7 (12.3)
Baseline lipid parameters, mg/dL				
Calculated LDL-C, mean, SD	99.3 (25.2)	97.0 (27.8)	102.4(23.6)	101.5 (30.3)
Non-HDL-C, mean, SD	128.4 (30.3)	123.9 (29.0)	131.3 (28.4)	128.5 (29.6)
Total cholesterol, mean, SD	174.5 (28.0)	169.4 (29.7)	175.6 (28.0)	173.6 (30.3)
Apo B, mean, SD	85.6 (17.7)	81.7 (17.2)	86.3 (17.5)	83.3 (18.6)
Lp(a), median (Q1:Q3)	24.5 (12.0:57.0)	23.0 (12.5:54.5)	24.0 (7.0:55.0)	23.0 (12.0:52.0)
Fasting TGs, median (Q1:Q3)	136.5 (103.0:167.0)	116.0 (85.0:170.0)	136.0 (103.0:167.0)	125.0 (90.0:181.0)
HDL-C, mean, SD	46.1 (12.1)	45.5 (10.9)	44.3 (11.0)	45.1 (11.2)
Apo A1, mean, SD	132.1 (24.5)	131.7 (17.3)	129.2 (23.8)	130.0 (17.6)

Apo = apolipoprotein; BMI = body mass index; CHD = coronary heart disease; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LMT = lipid-modifying therapy; Lp(a) = lipoprotein(a); TGs = triglycerides.

[a]KT-TW-Taiwan population: Taiwanese patients identified by investigators in the CRF and enrolled from 10 sites in Taiwan in ODYSSEY KT study.

[b]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).

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

[d]High-intensity statin: atorvastatin 40-80 mg or rosuvastatin 20 mg daily.

TEAEs was similar between alirocumab and placebo groups.[20] Moreover, the LDL-C reduction effect was sustained and alirocumab was well-tolerated over 24-weeks of study duration. In general, no major differences regarding efficacy and safety of alirocumab were observed between Taiwanese population and overall ODYSSEY KT population.[20]

Since LDL-C concentration is highly commensurate with the CV risk, statin, with its well-established efficacy in LDL-C lowering, has achieved great success in reducing CV events for decades.[25] However, recent studies including T-SPARCLE and CEPHEUS-TW revealed an astonishing fact that approximately half of the Taiwanese patients with high CV risk failed to reach their LDL-C goal and residual risk persists.[9,11] These findings should be interpreted in the context of current National Health Insurance restriction in Taiwan, setting the LDL-C goal for patients with CV history at 100 mg/dL, which is higher than

Table 2

Effect of alirocumab vs placebo on LDL-C, secondary lipid parameters, and achievement of LDL-C target levels in Taiwanese patients (ITT analysis)

			Alirocumab vs Placebo		
	Placebo (n = 59)	Alirocumab (n = 57)	Difference vs Placebo	95% CI	*p*
Baseline LDL-C, LS mean (SE), mg/dL	102.4 (3.1)	101.5 (4.0)			
Absolute change in calculated LDL-C from baseline to week 24, LS mean (SE), mg/dL	0.3 (4.0)	–52.5 (4.0)	–52.7 (5.7)	–63.9 to –41.5	<0.0001
Change in calculated LDL-C from baseline to week 24, LS mean (SE), %	2.5 (3.8)	–51.0 (3.9)	–53.5 (5.5)	–64.4 to –42.6	<0.0001*
Proportion of patients reaching calculated LDL-C <70 mg/dL at week 24, %	15.4[a]	81.3[a]	28.5[b]	9.6 to 84.5	<0.0001*
Change in calculated LDL-C from baseline to week 12, LS mean, %	1.1 (2.8)	–54.7 (2.8)	–55.8 (4.0)	–63.7 to –47.9	<0.0001
Change from baseline to week 24 in other lipid parameters, LS mean (SE), %					
Non-HDL-C	1.5 (3.4)	–42.2 (3.5)	–43.6 (4.9)	–53.4 to –33.9	<0.0001*
Apo B	1.1 (3.3)	–37.6 (3.3)	–38.7 (4.7)	–47.9 to –29.4	<0.0001*
Total cholesterol	1.7 (2.5)	–28.5 (2.6)	–30.2 (3.6)	–37.3 to –23.0	<0.0001*
Lp(a)[c]	–5.2 (3.6)	–35.9 (3.6)	–30.8 (5.1)	–40.7 to –20.8	<0.0001*
HDL-C	5.4 (2.2)	11.6 (2.2)	6.2 (3.1)	0.0 to 12.4	0.0484
TGs[c]	–5.7 (4.1)	–7.6 (4.2)	–1.9 (5.9)	–13.5 to 9.7	0.7508
Apo A1	1.1 (1.3)	5.2 (1.4)	4.1 (1.9)	0.3 to 7.8	0.0343*

*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.

Apo = apolipoprotein; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); TGs = triglycerides; ITT = intention-to-treat; LS = least squares.

[a]Combined estimate for proportion of patients reaching the level.

[b]Combined estimate for odds ratio.

[c]Combined estimate for adjusted mean.

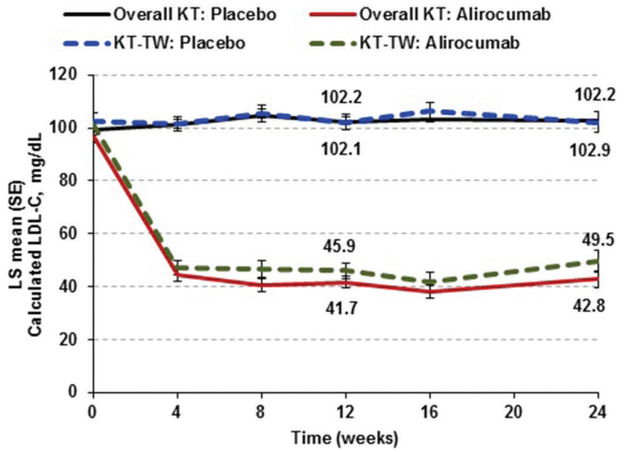

Fig. 2 Calculated LDL-C levels over time (ITT analysis). ITT, intention to treat; KT, ODYSSEY KT trial; KT-TW, the subanalysis of Taiwanese patients from the ODYSSEY KT trial; LS, least squares; LDL-C, low-density lipoprotein cholesterol.

international guideline recommendation.[10,26] Notably, vulnerable patients who were at the highest CV risk had the lowest LDL-C attainment rate of 22% among all patients in the CEPHEUS-TW study despite conventional LLTs use.[11] Given these caveats, medical societies started to question the statin monotherapy strategy and its applicability to high CV risk patients.[27,28] In this subgroup analysis of ODYSSEY KT study, the LDL-C goal attainment rate was up to 81.3% after 24 weeks of alirocumab treatment in patients on maximally tolerated statin. The high attainment rate in ODYSSEY KT trial is comparable to that in ODYSSEY LONG TERM study as well as the ODYSSEY COMBO I/II studies.[16,17,29] With recent data demonstrating the favorable results in combination lipid therapy, an issue concerning which additional LLT should be applied has been aroused.[8,17,20,29] In ODYSSEY OPTIONS I study, adding alirocumab to 40 mg daily of atorvastatin therapy further reduced LDL-C by 54.0% in contrast to 22.6% of LDL-C reduction with additional ezetimibe therapy.[30] In addition, ODYSSEY COMBO II study supports the benefits of alirocumab by demonstrating a 73% achievement rate of LDL-C <70 mg/dL with alirocumab, in comparison to 40% in ezetimibe-treated patients on maximally tolerated statin.[30] We noted that the LDL-C reduction in the present study was 51%, while it reached 61% in ODYSSEY LONG TERM trial.[17] In addition, the TG lowering effect did not show in this subgroup analysis but it was significant in the LONG TERM trial. In the current study, alirocumab treatment regimen is the same as most global trials, starting at 75 mg Q2W with titration to 150 mg as necessary and >90% of alirocumab patients stayed at 75 mg

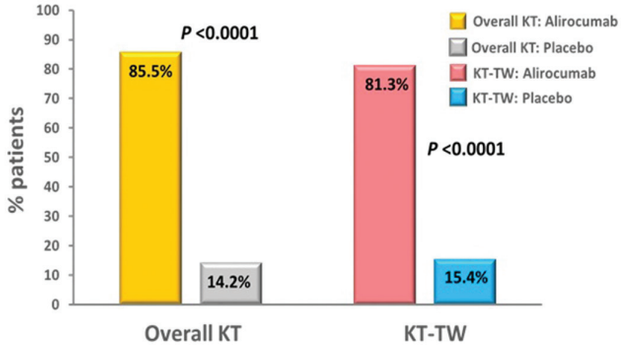

Fig. 3 Proportion of patients achieving LDL-C < 70 mg/dL at week 24 (ITT analysis). ITT, intention to treat; KT, ODYSSEY KT trial; KT-TW, the subanalysis of Taiwanese patients from the ODYSSEY KT trial; LS, least squares; LDL-C, low-density lipoprotein cholesterol.

Q2W over the study period, whereas alirocumab patients in ODYSSEY LONG TERM trial received 150 mg Q2W throughout the study. The differences in LDL-C and TG reduction effects could be attributed to different dosing regimens of alirocumab. In conclusion, alirocumab that can substantially reduce LDL-C may become a new option for patients who remained at high CV risk despite maximally tolerated statin.[31,32]

Despite not having an elucidated mechanism, ethnic differences in statins have recently been reported among Caucasian, Chinese, and other Asian populations.[33,34] Consequently, ethnic difference is a potential issue for alirocumab since both statins and PCSK9 inhibitors have the ultimate mechanism of increasing hepatic LDLR activity.[32,35] In this subgroup analysis of ODYSSEY KT study, alirocumab significantly reduced LDL-C by 51%, which is highly comparable to the LDL-C reduction in ODYSSEY series studies.[36] Showing no evidence of ethnic difference, the treatment outcomes of alirocumab in Taiwanese patients align well with the results of previous ODYSSEY phase 3 trials enrolling Caucasian, African American, Japanese, and Korean populations.[17,19,20,29,36] Similar to previous trials, 89.1% of alirocumab-treated patients in this subgroup analysis maintained the alirocumab regimen of 75 mg Q2W (83.2% in COMBO I; 86% in OPTIONS I; 81.5% in OPTIONS II), providing insight into the suggested dose regimen of alirocumab for Taiwanese patients.[16,30,37] Furthermore, favorable effects of alirocumab on other lipid parameters were also observed in Taiwanese patients. Notably, both lipoprotein (a) and high-density lipoprotein cholesterol were previously reported as independent risk factors for coronary artery disease.[5,38] Among all currently approved PCSK9 inhibitors (ie, alirocumab and evolocumab), this subgroup analysis is the first dedicated study to report complete clinical data of a PCSK9 inhibitor in the Taiwanese population.

An acceptable safety profile of alirocumab was demonstrated in the Taiwanese population. Consistent with the findings in ODYSSEY KT and ODYSSEY Japan trials, no significant differences between the alirocumab and placebo groups were found regarding the incidence of TEAEs in Taiwanese population (68.4% with alirocumab vs 69.5% with placebo).[19,20] The rates of treatment-emergent serious adverse events in both groups were low but numerically higher in the active treatment group. This finding is dissimilar to that of ODYSSEY LONG TERM, ODYSSEY Japan, and a pooled analysis of four alirocumab clinical trials in Asia with larger sample size and longer follow-up duration, and may require further evaluation.[17,19,20] As for other adverse events of interest, it should be noticed that alirocumab did not lead to a higher incidence rate of liver-related adverse events (hepatic disorders) in this study, which is different from what we have observed from statin use.[39,40] Both the present study and other global trials showed the comparable adverse event rates between alirocumab and control groups. Alirocumab is considered generally well-tolerated across ODYSSEY series trials. The numerically different adverse event or drug discontinuation rates among studies would be due to the different study duration and populations. In addition, 5.3% of alirocumab-treated patients experienced treatment-emergent ADA positive response but all of these cases were transient and not associated with an impact on the effect of LDL-C lowering. This observation was confirmed by ODYSSEY LONG TERM study and a metaanalysis of eight ODYSSEY studies, showing sustained LDL-C reduction despite the development of ADA in 5.1% of patients.[41] Nonetheless, 21.1% of patients in the treatment group with alirocumab in the current study showed two consecutive LDL-C <25 mg/dL within 24 weeks. Concerns regarding too low LDL-C level were not borne out and no specific safety signals (eg, cataracts and neurocognitive disorders) were identified in patients with two consecutive LDL-C < 25 mg/dL.

Several limitations should be noted when interpreting our findings. First, the number of participants in this study is relatively small. Second, the 6-month follow-up duration of this study is relatively short. In light of the significant association of LDL-C concentration and CV events[25] and the role of PCSK9 in both

Table 3

Adverse events and safety laboratory values (safety population)

	ODYSSEY KT		KT-TW	
	Placebo (n = 102)	Alirocumab (n = 97)	Placebo (n = 59)	Alirocumab (n = 57)
TEAEs, n, %	63 (61.8)	57 (58.8)	41 (69.5)	39 (68.4)
Treatment-emergent SAEs, n, %	10 (9.8)	17 (17.5)	5 (8.5)	12 (21.1)
TEAEs leading to death, n, %	0	1 (1.0)	0	1 (1.8)
TEAEs leading to treatment discontinuation, n, %	1 (1.0)	2 (2.1)	1 (1.7)	2 (3.5)
AEs of interest, n, %				
Injection site reactions	3 (2.9)	2 (2.1)	1 (1.7)	1 (1.8)
General allergic reactions	4 (3.9)	4 (4.1)	4 (6.8)	2 (3.5)
Hepatic disorders	5 (4.9)	3 (3.1)	3 (5.1)	2 (3.5)
Neurological event	3 (2.9)	0	2 (3.4)	0
Neurocognitive disorders	1 (1.0)	0	0	0
Ophthalmologic disorders[a]	0	1 (1.0)	0	1 (1.0)
Nasopharyngitis	4 (3.9)	6 (6.2)	2 (3.4)	3 (5.3)
Upper respiratory infection	6 (5.9)	3 (3.1)	6 (10.2)	2 (3.5)
Headache	3 (2.9)	5 (5.2)	3 (5.1)	1 (1.8)
Diarrhea	1 (1.0)	5 (5.2)	1 (1.7)	5 (8.8)
Dizziness	3 (2.9)	6 (6.2)	3 (5.1)	5 (8.8)
Cough	4 (3.9)	1 (1.0)	4 (6.8)	1 (1.8)
Cardiac disorders, n, %	9 (8.8)	9 (9.3)	6 (10.2)	7 (12.3)
Vascular disorders, n, %	1 (1.0)	1 (1.0)	0	1 (1.8)
Laboratory values, n, %				
Alanine aminotransferase > 3 times ULN	1/102 (1.0)	1/97 (1.0)	1/59 (1.7)	1/57 (1.8)
Aspartate aminotransferase > 3 times ULN	1/102 (1.0)	1/96 (1.0)	1/59 (1.7)	0/56 (0)
Creatinine kinase > 3 times ULN and ≤10 ULN	6/100 (6.0)	2/96 (2.1)	3/58 (5.2)	0

AE = adverse event; TEAEs = treatment-emergent adverse events; ULN = upper limit of normal.
[a]Ophthalmologic disorders only include cataract reactions.

lipid homeostasis and atherosclerosis,[42–44] a reduction in LDL-C level by inhibition of PCSK9 might have a prognostic impact. With regard to the limitations of current evidence, a large-scale and long-term clinical trial of alirocumab is demanded. ODYSSEY OUTCOMES trial (NCT01663402), a phase 3 randomized controlled trial that enrolled approximately 19,000 patients worldwide (including Taiwan) for 5 years, was completed.[45] The study results were presented in the 67th American College of Cardiology annual congress scientific session first and recently published online.[46] On a background of maximally tolerated statin therapy, patients with recent ACS were randomized to receive alirocumab or placebo, targeting LDL-C levels of 25 to 50 mg/dL and allowing levels as low as 15 mg/dL. Compared with placebo, alirocumab reduced the risk of CV events and was associated with a lower rate of all-cause mortality with no new safety issues observed. The final publication provides complete study results and complement long-term effects on outcome events and safety of alirocumab.[46]

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A23.

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