

Efficacy and Safety of Alirocumab in Japanese Patients with Diabetes Mellitus: Post-hoc Subanalysis of ODYSSEY Japan

Tamio Teramoto¹, Makiko Usami², Yoshiharu Takagi³ and Marie T. Baccara-Dinet⁴,
for the ODYSSEY Japan Investigators

¹Teikyo Academic Research Center, Teikyo University, Tokyo, Japan

²Cardiovascular Medical, Sanofi, Tokyo, Japan

³Clinical Sciences and Operations, Sanofi, Tokyo, Japan

⁴PCSK9 Development and Launch Unit, Sanofi, Montpellier, France

Aim: To examine the efficacy and safety of alirocumab in Japanese patients with dyslipidemia with or without diabetes mellitus (DM).

Methods: Patients ($n=216$) with heterozygous familial hypercholesterolemia (heFH), non-FH at high cardiovascular risk with coronary artery disease (CAD), or category III (primary prevention) were enrolled; 148 (68.5%) patients had a diagnosis of DM at baseline. Patients were randomized (2:1), with stratification factor (heFH, non-FH), to alirocumab (75 mg every 2 weeks [Q2W] with increase to 150 mg if week 8 LDL-C was above pre-defined limits) or placebo subcutaneously for 52 weeks on top of stable statin therapy.

Results: At Week 24, least square (LS) mean $\pm$ standard error changes in low-density lipoprotein cholesterol (LDL-C) concentration from baseline in alirocumab-treated patients were $-63.1 \pm 1.6\%$ and $-60.8 \pm 2.7\%$ in those with and without DM. These LDL-C reductions were maintained to Week 52: $-63.0 \pm 1.6\%$ (LS mean difference vs placebo $-62.4 \pm 3.0\%$; $P < 0.0001$) with DM and $-61.3 \pm 2.8\%$ (LS mean difference vs placebo $-53.4 \pm 4.0\%$; $P < 0.0001$) without DM. The most common adverse events in the alirocumab group were nasopharyngitis, back pain, injection site reaction, and fall. No particular safety signals or concerns were noted between DM and non-DM groups at 52 weeks. A dose-increase in alirocumab from 75 to 150 mg Q2W was necessary in two heFH patients, neither of whom had DM.

Conclusions: In high-cardiovascular-risk Japanese patients with hypercholesterolemia on stable statin therapy, alirocumab produced substantial and sustained LDL-C reductions throughout the 52-week study regardless of DM status at baseline, with a similar safety profile to placebo.

Key words: Alirocumab, Low-density lipoprotein cholesterol, Coronary artery disease, Diabetes mellitus

Abbreviations: Apo: apolipoprotein, CAD: coronary artery disease, DM: diabetes mellitus, FH: familial hypercholesterolemia, FPG: fasting plasma glucose, HbA_{1c}: glycated hemoglobin, HDL-C: high-density lipoprotein cholesterol, JAS: Japan Atherosclerosis Society, LDL-C: low-density lipoprotein cholesterol, heFH: heterozygous familial hypercholesterolemia, ITT: intention to treat, LDL-C: low-density lipoprotein cholesterol, LLT: lipid-lowering therapy, Lp(a): lipoprotein(a), LS: least square, PCSK9: proprotein convertase subtilisin/kexin 9, Q2W: every 2 weeks, SC: subcutaneous, SE: standard error, SD: standard deviation, TG: triglycerides

Introduction

Diabetes mellitus (DM) is an independent risk

factor for cardiovascular disease¹⁾, and is considered equivalent to having a history of coronary artery disease (CAD)²⁾. Patients with both DM and CAD are at

Address for correspondence: Tamio Teramoto, Teikyo Academic Research Center, 2-11-1, Kaga, Itabashi-ku, Tokyo, 173-8605, Japan
E-mail: tera@med.teikyo-u.ac.jp

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substantially higher risk of cardiovascular events than patients with one or neither condition³). DM is also associated with mixed dyslipidemia, characterized by high levels of plasma triglycerides (TG) and low levels of high-density lipoprotein cholesterol (HDL-C)⁴.

Guidelines recommend lipid-lowering therapy (LLT) for patients with DM and/or CAD to lower concentrations of atherogenic cholesterol⁵⁻⁸). In the 2012 Japan Atherosclerosis Society (JAS) guidelines, the target low-density lipoprotein cholesterol (LDL-C) value was <3.1 mmol/L (120 mg/dL) for primary prevention of CAD in patients with a high-risk condition (e.g. DM, chronic kidney disease, peripheral artery disease, ischemic stroke) and <2.6 mmol/L (100 mg/dL) for secondary prevention regardless of the presence of DM⁸). The 2017 JAS guidelines⁷) recommend to lower the LDL-C target to <1.8 mmol/L (70 mg/dL) in diabetic patients with other high-cardiovascular-risk disease for secondary prevention of CAD, similar to the European recommendations⁹). However, the LDL-C target for diabetic patients in primary prevention is still 3.1 mmol/L (120 mg/dL), which is less strict than the European target, as DM is not considered by the JAS as a high-risk equivalent to CAD. As non-HDL-C is an indicator of cardiovascular risk, non-HDL-C lowering is recommended as a co-primary treatment target, along with LDL-C^{6,7}). In diabetic patients with high elevated TG, non-HDL-C is a secondary target of lipid management for the prevention of atherosclerotic cardiovascular disease^{6,7}).

Statins are the preferred pharmacological therapy for lowering LDL-C and are generally well tolerated^{5,10}), but concerns have been raised about statin intolerance and an increased risk of new-onset DM associated with statin treatment. The risk of incident DM is higher with the more potent statins, in the elderly, and in the presence of other risk factors for DM^{11, 12}). However, the benefits of statins in terms of lowering cardiovascular events in high-cardiovascular-risk patients greatly outweigh concerns over the small increase in incidence of known adverse events⁵).

Proprotein convertase subtilisin/kexin 9 (PCSK9) is a key regulator of serum cholesterol levels¹³) and is closely linked to atherosclerosis¹⁴); as such, it presents a novel pharmacological target for hypercholesterolemia. Alirocumab is a fully human monoclonal antibody that inhibits PCSK9. The ODYSSEY phase 3 clinical trial program, encompassing dyslipidemic patients at increased risk of atherosclerotic cardiovascular disease, showed that alirocumab, as monotherapy or in combination with other LLT, reduces LDL-C concentrations by 40% to 73%¹⁵⁻²⁶). In a sub-analysis of the COMBO II study (NCT01644188), alirocumab provided consistently greater reductions in

LDL-C versus ezetimibe throughout the 104-week study, with similar reductions in LDL-C in patients with and without DM²⁷). ODYSSEY Japan (NCT 02107898), a phase 3 study targeting high-cardiovascular-risk Japanese patients with heterozygous familial hypercholesterolemia (heFH) or non-FH on stable statin therapy, reported a 62.5% reduction from baseline in LDL-C with alirocumab²⁸).

Aim

The aim of this post-hoc subanalysis from the ODYSSEY Japan study was to examine the efficacy and safety of alirocumab over 52 weeks in Japanese patients with and without DM.

Methods

ODYSSEY Japan study (ClinicalTrials.gov identifier: NCT02107898) was a randomized double-blind study that enrolled adults with heFH (diagnosed by genotyping or clinical criteria) with or without a history of documented CAD, or patients with non-FH at high cardiovascular risk with a history of documented CAD or who were classified as JAS category III⁸) (i.e. high-risk primary prevention⁷). Documented CAD was defined as myocardial infarction, unstable angina, coronary revascularization procedure, or clinically significant CAD diagnosed by invasive or non-invasive testing. Enrollment and follow-up took place at 31 Japanese sites between March 2014 and September 2015. Eligible patients had hypercholesterolemia that was not adequately controlled on a stable daily dose of statin therapy with or without other LLT (i.e. LDL-C $\geq$ 2.6 mmol/L [$\geq$ 100 mg/dL] in heFH or non-FH patients with CAD, and $\geq$ 3.1 mmol/L [120 mg/dL] in category III patients, per the JAS 2012 guidelines⁸)). The trial methods have been reported elsewhere²⁸).

The study was performed according to the 18th World Medical Assembly and all applicable amendments laid down by the World Medical Assemblies, and the International Conference on Harmonization guidelines for good clinical practice, all applicable laws, rules and regulations. The protocol was approved by the institutional review boards of participating centers. Patients gave written informed consent.

Study Design

Patients were randomized (2:1) to receive subcutaneous (SC) alirocumab 75 mg or placebo (in 1-mL injection volumes) every 2 weeks (Q2W) for 52 weeks on top of stable statin treatment (type and dose of statin were not prespecified) with or without other

LLT. The study drug was administered using an auto-injector. Per protocol, the alirocumab dose was increased automatically at Week 12 to 150 mg Q2W (in a 1-mL injection volume) if the Week-8 LDL-C value was ≥ 2.6 mmol/L (≥ 100 mg/dL) in heFH patients or non-FH patients with a history of CAD, or ≥ 3.1 mmol/L (≥ 120 mg/dL) in category III patients. Investigators and patients were blinded to any dose increase. Patients were instructed to remain on a stable diet, as recommended in the JAS guidelines⁸⁾ or equivalent, and were not permitted to take fibrates (other than fenofibrate) or red yeast rice products. Lipid variables were measured by a central laboratory and LDL-C level was calculated using the Friedewald formula²⁹⁾.

Endpoints

The present study investigated alirocumab efficacy and safety in high-cardiovascular-risk Japanese patients with or without DM over a period of 52 weeks, and was a subanalysis of the ODYSSEY Japan study²⁸⁾. The primary efficacy endpoint was percent change in calculated LDL-C from baseline to Week 24, analyzed using an intent-to-treat (ITT) approach using all lipid data. Secondary efficacy endpoints included percent change in LDL-C from baseline to Week 52, and percent change in apolipoprotein B (apoB), non-HDL-C, fasting TG, lipoprotein(a) (Lp(a)), HDL-C, and apolipoprotein A-1 (apoA-1) from baseline to Weeks 24 and 52. Safety was assessed through analysis of adverse event reports and laboratory analyses (including mean change in fasting glucose and glycated hemoglobin [HbA_{1c}]), from the first to the last double-blind dose of study treatment, with a 70-day follow-up period.

Statistical Analysis

Efficacy endpoints were analyzed using a mixed effect model with a repeated measures approach to account for missing data for the lipid parameters, with the exception of Lp(a), TG, and achievement of LDL-C goals. These three variables were analyzed using a multiple imputation approach for handling of missing values, followed by robust regression for Lp(a) and TG, and by logistic regression for achievement of LDL-C goals. The significance level of the treatment-by-DM subgroup factor interaction term at Week 52 was also derived from the mixed effect model with repeated measures. Safety data were analyzed using descriptive statistics. Analyses were performed using SAS version 9.2 software (SAS Institute Inc., Cary, North Carolina).

Results

Of the 216 patients who were randomly allocated to receive alirocumab ($n=144$) or placebo ($n=72$), 148 (68.5%) had a diagnosis of DM reported in their medical history at baseline. Of those randomized to alirocumab, 72.9% (105/144) had DM compared with 59.7% (43/72) on placebo. Across the treatment groups and DM subgroups, the mean age ranged from 60.1 to 62.4 years and mean body mass index from 23.5 to 26.4 kg/m², and 57.1% to 69.0% were men (Table 1). Less than 10% of patients with heFH were part of the DM group. Mean HbA_{1c} was 7.2% (alirocumab) and 7.0% (placebo) in patients with DM, and 5.8% and 5.7%, respectively, in patients without DM. Calculated levels of LDL-C and Lp(a) were numerically lower among the patients with DM. The use of high-intensity statin treatment (atorvastatin 40 mg/day or rosuvastatin 20 mg/day) or non-statin LLT was higher in the patients without DM.

The mean duration of disease in the DM cohort was 8.5 ± 7.7 years in the alirocumab group and 9.9 ± 8.2 years in the placebo group. Most patients with DM ($n=118$, 79.7%) were receiving antihyperglycemic medication. Twenty percent of patients on alirocumab were receiving insulin compared with 9.3% of those on placebo.

The dose of alirocumab was increased, per protocol, from 75 to 150 mg Q2W at Week 12 in two patients (both with heFH), neither of whom had DM.

Efficacy

At Week 24, least square (LS) mean $\pm$ SE change in LDL-C concentration from baseline in alirocumab-treated patients was $-63.1 \pm 1.6\%$ in those with DM and $-60.8 \pm 2.7\%$ in those without DM (Fig. 1). These reductions in LDL-C were maintained to Week 52: $-63.0 \pm 1.6\%$ (LS mean difference vs placebo $-62.4 \pm 3.0\%$; $P < 0.0001$) with DM and $-61.3 \pm 2.8\%$ (LS mean difference vs placebo $-53.4 \pm 4.0\%$; $P < 0.0001$) without DM.

At Week 24 in the alirocumab cohort, 97.1% of patients with DM and 95.8% without DM achieved the LDL-C goal of < 2.6 mmol/L (100 mg/dL) for heFH patients or non-FH patients with a history of CAD, or < 3.1 mmol/L (120 mg/dL) for category III patients (Fig. 2). Corresponding data at Week 52 were 98.0% and 88.2%, respectively. Most patients (96.1%) on alirocumab achieved an LDL-C level of < 2.6 mmol/L (100 mg/dL) at Week 24, and a slightly lower percentage (79.8% in DM, 63.2% in non-DM) met the < 1.8 mmol/L (70 mg/dL) value (Fig. 2). These achievements in LDL-C reduction were main-

Table 1. Baseline characteristics according to presence of DM at baseline (randomized population)

Characteristic	With DM at baseline		Without DM at baseline	
	Alirocumab (<i>n</i> = 105)	Placebo (<i>n</i> = 43)	Alirocumab (<i>n</i> = 39)	Placebo (<i>n</i> = 29)
Age (years)	60.1 ± 9.0	61.5 ± 8.7	60.9 ± 11.6	62.4 ± 9.6
Men	60 (57.1)	27 (62.8)	24 (61.5)	20 (69.0)
Body mass index (kg/m ²)	26.4 ± 4.4	25.6 ± 3.2	23.5 ± 3.1	25.1 ± 3.2
heFH	6 (5.7)	4 (9.3)	21 (53.8)	10 (34.5)
CAD	10 (9.5)	6 (14.0)	14 (35.9)	10 (34.5)
Ischemic stroke	2 (1.9)	1 (2.3)	0	0
Chronic kidney disease	6 (5.7)	1 (2.3)	2 (5.1)	4 (13.8)
HbA _{1c} (%)	7.2 (0.8)*	7.0 (0.7)	5.8 (0.4)	5.7 (0.3)
Fasting plasma glucose (mmol/L)	7.6 ± 1.4*	7.5 ± 1.7	5.6 ± 0.6	5.5 ± 0.7
Duration of DM (years)	8.5 ± 7.7	9.9 ± 8.2	–	–
Lipid profile				
Calculated LDL-C (mmol/L)	3.6 ± 0.62	3.6 ± 0.65	3.7 ± 0.87	3.8 ± 0.73
(mg/dL)	139.9 ± 23.9	137.2 ± 25.0	143.8 ± 33.5	148.1 ± 28.2
Non-HDL-C (mmol/L)	4.4 ± 0.69	4.3 ± 0.82	4.3 ± 0.91	4.6 ± 0.72
(mg/dL)	168.8 ± 26.8	166.7 ± 31.6	166.8 ± 35.1	177.6 ± 27.8
Apolipoprotein B (mg/dL)	111.0 ± 17.4	110.8 ± 18.6	109.2 ± 19.3	117.8 ± 15.8
Lipoprotein(a) (mg/dL)	14.3 (8.8:32.4)	12.7 (7.7:33.3)	23.0 (13.6:42.8)	16.8 (11.6:36.8)
Triglycerides (mmol/L)	1.5 (1.1:2.1)	1.4 (0.84:1.9)	1.2 (0.84:1.7)	1.7 (1.1:2.1)
(mg/dL)	132.0 (100.0:182.0)	126.0 (74.0:172.0)	105.0 (74.0:154.0)	147.0 (95.0:186.0)
HDL-C (mmol/L)	1.4 ± 0.29	1.5 ± 0.44	1.5 ± 0.34	1.4 ± 0.36
(mg/dL)	53.8 ± 11.2	56.4 ± 16.8	56.9 ± 13.1	52.7 ± 13.8
Apolipoprotein A1 (mmol/L)	1.6 ± 0.24	1.6 ± 0.32	1.6 ± 0.28	1.6 ± 0.30
(mg/dL)	157.5 ± 23.5	161.9 ± 31.8	158.5 ± 27.6	157.1 ± 30.0
Total cholesterol (mmol/L)	5.8 ± 0.71	5.8 ± 0.90	5.8 ± 0.93	6.0 ± 0.87
(mg/dL)	222.6 ± 27.5	222.8 ± 34.7	223.7 ± 35.8	230.4 ± 33.8
Oral antihyperglycemic drug	85 (81.0)	33 (76.7)	–	–
Insulin	21 (20.0)	4 (9.3)	–	–
Taking high-intensity statin [†]	2 (1.9)	1 (2.3)	5 (12.8)	2 (6.9)
Statin dose				
Pravastatin (5–20 mg/day)	49 (46.7)	20 (46.5)	11 (28.2)	17 (58.6)
Rosuvastatin (2.5–20 mg/day)	18 (17.1)	4 (9.3)	13 (33.3)	5 (17.2)
Atorvastatin (5–40 mg/day)	14 (13.3)	10 (23.3)	7 (17.9)	4 (13.8)
Pitavastatin (0.5–4 mg/day)	16 (15.2)	9 (20.9)	6 (15.4)	1 (3.4)
Simvastatin (5–10 mg/day)	5 (4.8)	0	2 (5.1)	1 (3.4)
Fluvastatin (20–30 mg/day)	3 (2.9)	0	0	1 (3.4)
Any lipid-lowering therapy other than statin	5 (4.8)	6 (14.0)	14 (35.9)	6 (20.7)

Values are mean ± SD, *n* (%), or median (Q1:Q3). CAD, coronary artery disease; DM, diabetes mellitus; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; heFH, heterozygous familial hypercholesterolemia; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; Q, quartile; SD, standard deviation.

**n* = 104 patients (ITT). One patient was randomized twice and did not have a required LDL-C value and was therefore excluded from the safety and ITT populations.

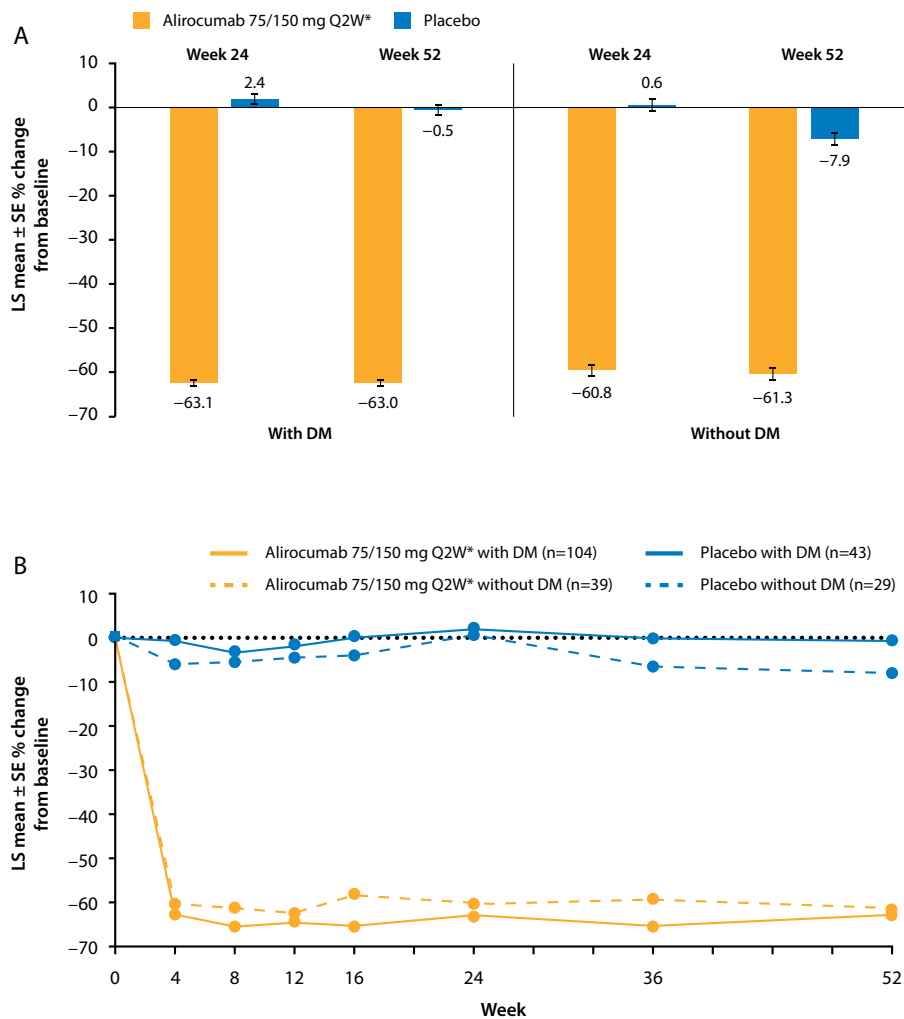
[†] Atorvastatin 40 mg daily or rosuvastatin 20 mg daily.

tained through Week 52.

Similar reductions from baseline to Week 52 in apoB, non-HDL-C, and Lp(a) were observed in alirocumab-treated patients with and without DM (Fig. 3). In the alirocumab group, fasting TG decreased by 9.9% in patients with DM and by

17.7% in those without DM. HDL-C and apoA-1 both increased in the alirocumab-treated patients, irrespective of DM status, with similar increases relative to placebo.

The mean ± SD rate of adherence to treatment (defined as percentage of days that patients received

**Fig. 1.**

LS mean $\pm$ SE percent change from baseline in calculated LDL-C according to baseline diabetic status (ITT):

A: at Week 24 and at Week 52

B: over time.

*75 mg Q2W increased to 150 mg Q2W at Week 12 if LDL-C levels at Week 8 were ≥ 2.6 mmol/L (100 mg/dL) or ≥ 3.1 mmol/L (120 mg/dL).

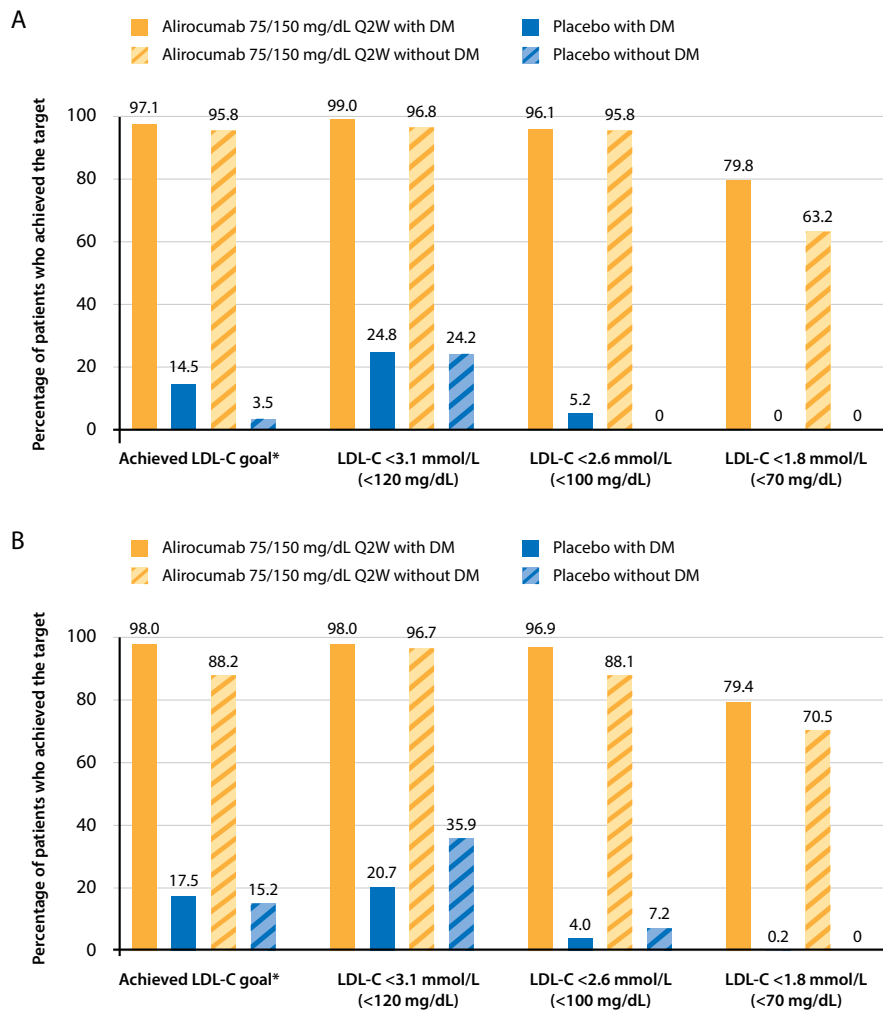
DM, diabetes mellitus; ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; LS, least square; Q2W, every 2 weeks; SE, standard error.

treatment per planned dosing schedule) was high in both treatment groups. In alirocumab-treated patients, adherence was $95.8 \pm 4.0\%$ for patients with DM and $95.8 \pm 4.9\%$ for those without DM. Corresponding data for the placebo-treated group were $95.0 \pm 4.4\%$ and $96.0 \pm 2.8\%$, respectively.

Safety

HbA_{1c} and mean fasting glucose levels in the patients with and without DM remained largely unchanged throughout the study (Fig. 4A and 4B, respectively). The overall rate of any treatment-related

adverse event up to Week 52 was similar across patient subgroups, regardless of DM status or treatment group, ranging from 89.4% to 94.9% in alirocumab-treated patients and from 82.8% to 83.7% in placebo-treated patients (Table 2). No deaths were reported in the study. The most common adverse events occurring in the alirocumab-treated patients were nasopharyngitis, back pain, injection site reaction, and fall. In addition, 21 patients (14.7%) in the alirocumab group and 7 patients (9.7%) in the placebo group had adverse events identified as “diabetes and diabetes complications” (i.e. worsening of pre-existing DM).

**Fig. 2.**

Achievement of LDL-C targets at:

A: 24 weeks

B: 52 weeks.

* <2.6 mmol/L (100 mg/dL) for heFH patients or non-FH patients who have a history of documented CAD, or <3.1 mmol/L (120 mg/dL) for non-FH patients who have a history of documented diseases or other risk factors as categorized in category III patients.

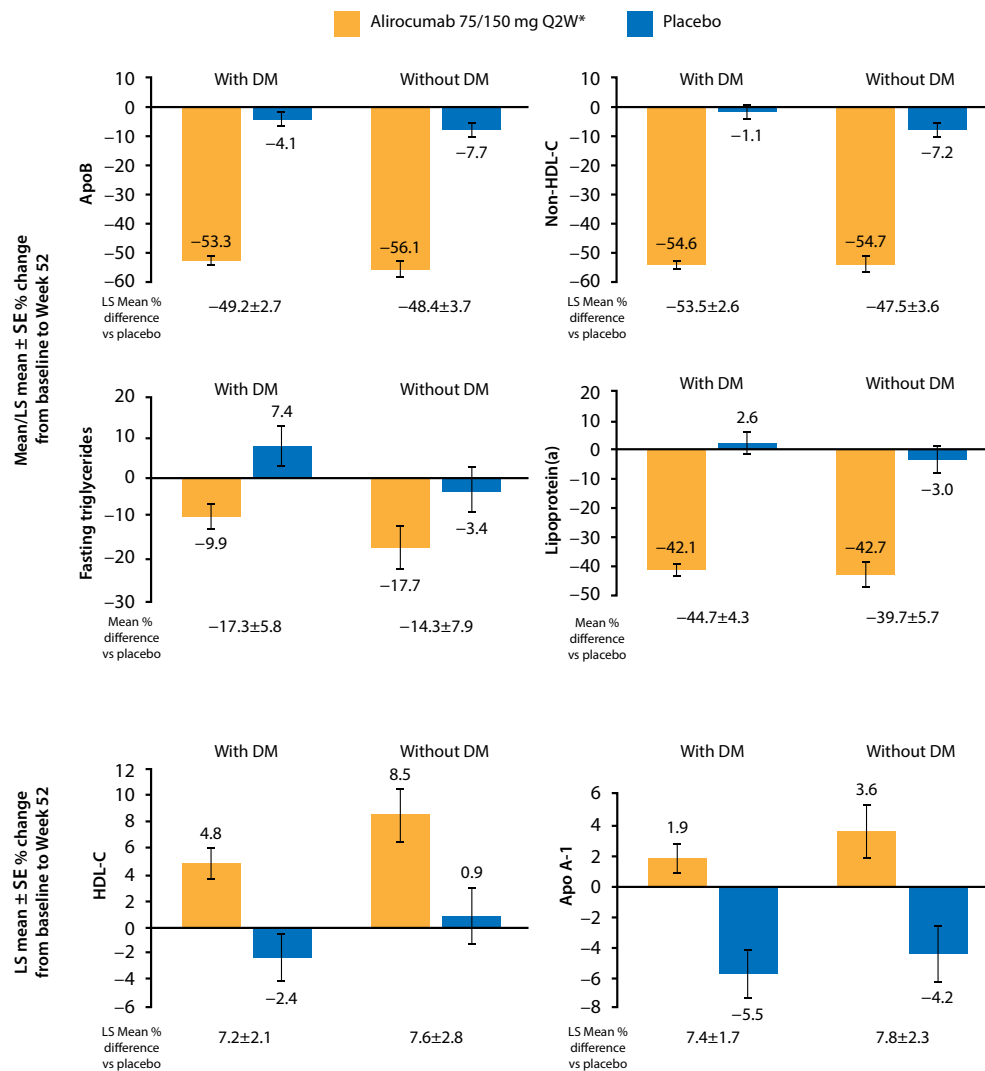
CAD, coronary artery disease; DM, diabetes mellitus; heFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks.

All of these patients had DM at baseline except for one in the placebo group who had newly diagnosed type 2 DM during the treatment period. None of the DM events was considered to be serious.

Discussion

This post-hoc subanalysis from the ODYSSEY Japan trial was performed in the 216 high-cardiovascular-risk Japanese patients with dyslipidemia. Owing to the inclusion of high-risk category III patients, a large percentage (i.e. 68.5%) had DM at baseline; the

prevalence of FH was lower among the patients with versus those without DM. Treatment with alirocumab resulted in a substantial and sustained reduction in LDL-C to Week 52 in patients with or without DM, with a similar safety profile and no emerging safety signals. Alirocumab did not affect glycemic parameters, as assessed by HbA_{1c} and fasting plasma glucose, the levels of which remained constant throughout the 52-week trial. Alirocumab was generally well-tolerated and the rates of adverse events were similar in diabetic and non-diabetic subgroups. Injection site reactions were more frequent among the alirocumab-treated

**Fig. 3.**

Percent change from baseline to Week 52 in apoB, non-HDL-C, fasting triglycerides, lipoprotein(a), HDL-C and apoA-1 by diabetic status (ITT). Values for difference versus placebo are presented as the LS mean $\pm$ SE for ApoB and non-HDL-C and as combined estimate for adjusted mean $\pm$ SE for triglyceride and lipoprotein(a).

Alirocumab with DM ($n=103$ -104); alirocumab without DM ($n=38$ -39); placebo with DM ($n=42$ -43); placebo without DM ($n=29$).

*75 mg Q2W increased to 150 mg Q2W at Week 12 if LDL-C levels at Week 8 were ≥ 2.6 mmol/L (100 mg/dL) or ≥ 3.1 mmol/L (120 mg/dL).

Apo, apolipoprotein; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; ITT, intent-to-treat; LS, least square; SE, standard error; Q2W, every 2 weeks.

patients, but the rates in patients with versus without DM were similar. The alirocumab 75 mg Q2W dose was sufficient to achieve the risk-based LDL-C targets in all except 2 of the 144 patients, neither of whom had DM.

In a Japanese database analysis³⁰⁾, more than 20% of patients did not meet the 2012 JAS⁸⁾ target of 120 mg/dL for DM, and statin treatment was under-

utilized in high-risk populations including patients with DM. In our subanalysis, 80% of the alirocumab-treated patients with DM achieved an LDL-C value of 70 mg/dL, the target recommended in the 2017 JAS guideline⁷⁾ for this population with other high-cardiovascular-risk disease.

The findings from this subanalysis are consistent with the results of other ODYSSEY studies, showing

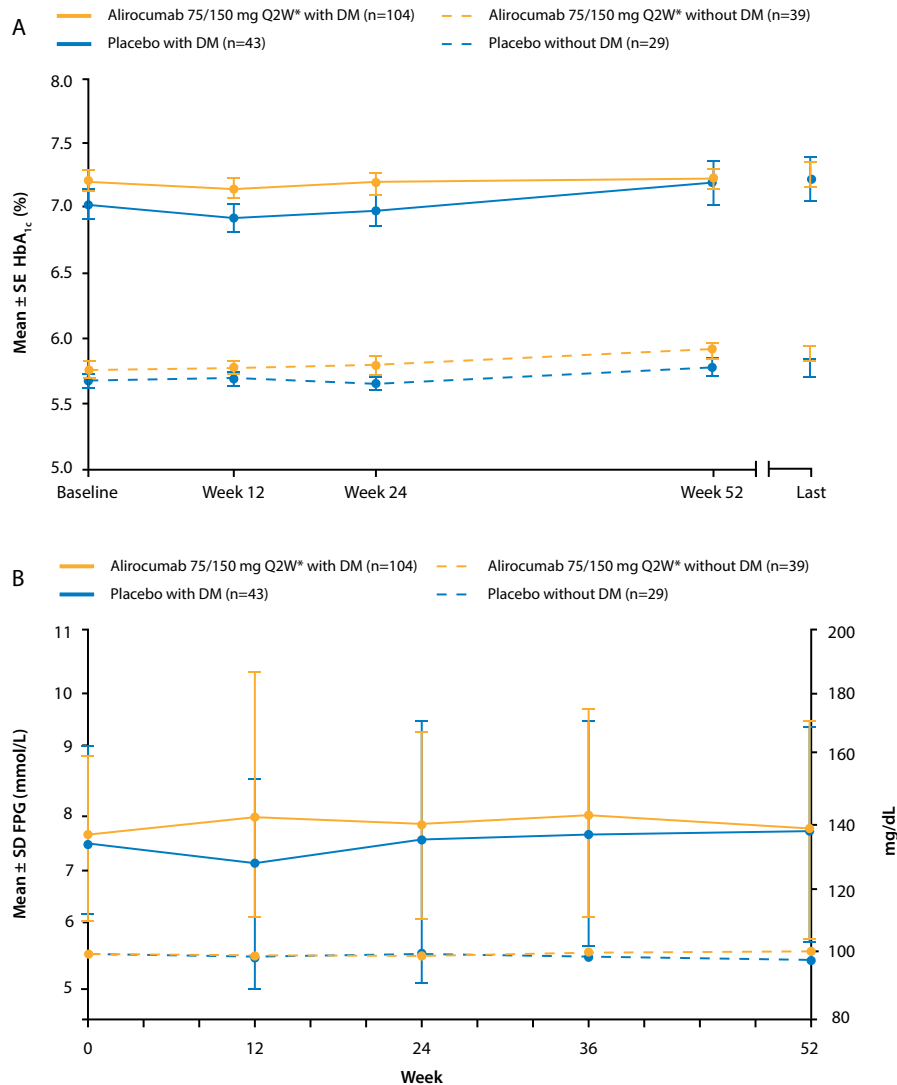


Fig. 4.

Mean HbA_{1c} and FPG over time, according to diabetic status at baseline (safety population):

A: HbA_{1c}

B: FPG.

DM, diabetes mellitus; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; SE, standard error; Q2W, every 2 weeks.

*75 mg Q2W increased to 150 mg Q2W at Week 12 if LDL-C levels at Week 8 were ≥ 2.6 mmol/L (100 mg/dL) or ≥ 3.1 mmol/L (120 mg/dL).

no difference in efficacy between patients with versus those without diabetes or prediabetes^{24, 25, 27, 31, 32}. The ODYSSEY LONG TERM trial (NCT01507831) reported that alirocumab, on a background of a maximally tolerated dose of statin therapy, reduced LDL-C levels significantly over 78 weeks in 2,341 high-cardiovascular-risk patients, one third of whom had DM at baseline²⁵. The reduction from baseline in LDL-C was similar in patients with and without DM ($60.0 \pm 1.3\%$ and $61.6 \pm 0.9\%$, respectively). Similar findings have been reported for the PCSK9 inhibitor evoloc-

umab in a meta-analysis of individual patient data, which reported similar mean reductions in LDL-C versus placebo (60% vs 66% in patients with vs without type 2 DM) over 12 weeks³³.

Patients with versus those without DM are on average at twice the risk of cardiovascular disease¹. Consequently, optimal management of diabetic patients, and adherence to evidence-based recommendations for meeting lifestyle, blood pressure, lipid and glycemic targets, is essential to reduce the risk of developing cardiovascular disease or having a recurrent

Table 2. Treatment-emergent adverse events up to Week 52 by diabetic status at baseline (safety population)

Preferred term	With DM		Without DM	
	Alirocumab (<i>n</i> = 104)	Placebo (<i>n</i> = 43)	Alirocumab (<i>n</i> = 39)	Placebo (<i>n</i> = 29)
Any class	93 (89.4)	36 (83.7)	37 (94.9)	24 (82.8)
Adverse events in >5% of alirocumab-treated patients (listed in descending order of number of events in alirocumab-treated patients with DM)				
Nasopharyngitis	47 (45.2)	15 (34.9)	18 (46.2)	11 (37.9)
Back pain	15 (14.4)	3 (7.0)	3 (7.7)	1 (3.4)
DM*	12 (11.5) [†]	4 (9.3) [†]	0	0
DM (type 2)	7 (6.7) [†]	0	0	1 (3.4)
Injection site reaction	12 (11.5)	2 (4.7)	6 (15.4)	1 (3.4)
Fall	10 (9.6)	3 (7.0)	1 (2.6)	2 (6.9)
Contusion	7 (6.7)	2 (4.7)	1 (2.6)	1 (3.4)
Periodontitis	7 (6.7)	1 (2.3)	0	0
Dental caries	7 (6.7)	1 (2.3)	2 (5.1)	0
Pharyngitis	6 (5.8)	2 (4.7)	3 (7.7)	2 (6.9)
Hypertension	5 (4.8)	5 (11.6)	4 (10.3)	0
Blood creatine phosphokinase increased [‡]	3 (2.9)	0	2 (5.1)	0
Gastroenteritis	3 (2.9)	1 (2.3)	2 (5.1)	2 (6.9)
Neck pain	3 (2.9)	1 (2.3)	2 (5.1)	1 (3.4)
Gastritis	2 (1.9)	0	2 (5.1)	0
Spinal osteoarthritis	2 (1.9)	0	3 (7.7)	0
Hematuria	1 (1.0)	0	2 (5.1)	0
Hypoaesthesia	1 (1.0)	1 (2.3)	2 (5.1)	0
Gout	0	0	2 (5.1)	0
Myalgia	0	3 (7.0)	2 (5.1)	0
Prostatitis	0	1 (2.3)	2 (5.1)	0

Values are *n* (%).

*Reported as DM by the investigators (includes type 1 and type 2 DM).

[†]Worsening of pre-existing DM.

[‡]> 3 × upper limit of normal.

DM, diabetes mellitus.

event. Statins are the preferred treatment for lowering LDL-C^{5, 10}, but are associated with transition to diabetes^{11, 12}. In a meta-analysis involving 91,140 patients followed for at least 1 year, statins were associated with a 9% increased risk for incident DM¹². The number needed to treat for one additional case of DM was estimated at 255 over 4 years of treatment¹². The risk was higher with the more potent statins at high doses, in the elderly, and in the presence of risk factors for DM^{11, 12}. Only one patient – in the placebo-treated group – in our present study (in which all patients were receiving stable statin therapy) developed new-onset DM. The levels of HbA_{1c} and fasting glucose levels remained constant during our 52-week study. No apparent increase in the occurrence of new-onset DM or in adverse metabolic effects was reported in a pooled analysis of 10 ODYSSEY trials involving 3,448 patients without DM at baseline who were followed for 6–18 months³¹. Additional data with longer-term follow-up are needed to definitively rule out any asso-

ciation between alirocumab and transition to diabetes, but to date there is no evidence of such an association.

The ODYSSEY DM-INSULIN study (NCT 02585778)³⁴ showed that alirocumab met its primary efficacy endpoints of reducing LDL-C from baseline to 24 weeks in insulin-treated diabetic patients, by 49.0 ± 2.7% versus placebo in type 1 DM and by 47.8 ± 6.5% versus placebo in type 2 DM (both *P* < 0.0001). The results from the ODYSSEY DM-INSULIN study confirm that alirocumab produces significant LDL-C reductions in patients with type 2 or type 1 DM receiving insulin treatment. Data from DM-DYSLIPIDEMA (NCT02642159) showed consistent results in patients with type 2 DM and mixed dyslipidemia (LS mean difference in LDL-C reduction of 32.5% [97.5% confidence interval 27.0–38.1%] versus usual care in type 2 DM)³⁵.

Fisher *et al.*³⁶ illustrated the benefit of LLT on the combined endpoint of cardiovascular death or non-fatal myocardial infarction in patients with versus

without DM, based on the results from the older statin trials. The FOURIER trial (NCT01764633)³⁷ reported recently that treatment with evolocumab reduced the rate of cardiovascular events in patients with atherosclerotic cardiovascular disease and LDL-C levels ≥ 1.8 mmol/L (70 mg/dL) who were receiving statin therapy, and lowered LDL-C levels to a median of 0.78 mmol/L (30 mg/dL). A prespecified analysis from FOURIER also reported significantly reduced cardiovascular risk in patients with and without diabetes, and no increase in risk of new-onset diabetes or worsening of glycaemia³⁸. In a post-hoc analysis from the ODYSSEY LONG TERM trial, there was evidence of a reduction in the rate of cardiovascular events with alirocumab (hazard ratio 0.52; 95% confidence interval, 0.31 to 0.90; nominal $P=0.02$) in patients at high risk for cardiovascular events²⁵. The ongoing ODYSSEY OUTCOMES trial (NCT 01663402)³⁹ should shed light on the effect of alirocumab on clinical outcomes in patients after an acute coronary syndrome as well as on the glycemic effect. Combined, these data should provide evidence for the potential role of the PCSK9 inhibitors in addition, or as an alternative, to statins in everyday practice.

Limitations

At randomization, patients were stratified according to heFH status but not for DM status. In this post-hoc analysis, heFH was more prevalent among the patients without DM, consistent with the higher rate of CAD and the higher levels of LDL-C in this group. Otherwise, treatment groups were well balanced in terms of patient demographics, presenting characteristics, and medical history.

Conclusion

In this subgroup analysis of ODYSSEY Japan in high-cardiovascular-risk Japanese patients with dyslipidemia despite stable statin therapy, alirocumab produced substantial and sustained LDL-C reductions throughout the 52-week study regardless of DM status at baseline, with a similar long-term safety profile to placebo. A dose-increase in alirocumab from 75 to 150 mg Q2W was necessary in only two heFH patients, neither of whom had DM. No effect on glycemic parameters was apparent.

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Conflicts of Interest

TT: honoraria and scholarship grants from Sanofi, Daiichi-Sankyo, Bayer, Takeda Pharmaceutical, Astellas Pharma, Amgen Astellas BioPharma, Pfizer, Shionogi, Eli Lilly, Kissei Pharmaceutical, Mochida Pharmaceutical, MSD and Kowa. Courses endowed at his affiliation by Bayer, Shionogi, Mochida Pharmaceutical, MSD, Aska Pharmaceutical and Kowa.

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