One-Year Efficacy and Safety of Evolocumab in Japanese Patients

— A Pooled Analysis From the Open-Label Extension OSLER Studies —

Atsushi Hirayama, MD, PhD; Shizuya Yamashita, MD, PhD; Hyoe Inomata, MD, PhD; Helina Kassahun, MD; Marcoli Cyrille, MD; Andrea Ruzza, MD, PhD; Masayuki Yoshida, MD; Arihiro Kiyosue, MD, PhD; Yuhui Ma, PhD; Tamio Teramoto, MD, PhD

Background: Evolocumab, a fully human monoclonal antibody against PCSK9, significantly reduced low-density lipoprotein-cholesterol (LDL-C) levels in Japanese patients by up to 76% when administered with a statin. We evaluated the efficacy and safety of 1 year of evolocumab in a pooled analysis of patients from the 12-week YUKAWA studies who continued into the open-label extension (OLE) OSLER studies.

Methods and Results: YUKAWA-1 and YUKAWA-2 were conducted in hypercholesterolemic, high-cardiovascular-risk Japanese patients who were receiving statin therapy. Patients completing these studies were eligible for an OLE study. At OLE entry, patients were re-randomized 2:1 to evolocumab+standard of care (SOC) or SOC alone (OSLER-1: evolocumab 420 mg monthly; OSLER-2: evolocumab 140 mg biweekly or 420 mg monthly). A 1-year analysis was performed on patients enrolled from the YUKAWA studies into OSLER. At parent-study baseline (YUKAWA-1 or YUKAWA-2 patients continuing into OSLER), mean (SD) age was 61 (10) years; 39% were female; mean (SD) baseline LDL-C (on statin) was 119.7 (33.0) mg/dL. Overall rates of adverse events were comparable between evolocumab+SOC and SOC alone. In YUKAWA patients receiving evolocumab+SOC, mean (SE) reductions in LDL-C from parent-study baseline to OLE 1 year were 69.1% (1.2%; OSLER-1) and 65.1% (2.2%; OSLER-2).

Conclusions: In a pooled 1-year analysis of Japanese patients in the ongoing OSLER studies, treatment with evolocumab+SOC was well tolerated and resulted in sustained LDL-C reductions at 1 year.

Key Words: Dyslipidemia; Hyperlipidemia; Lipid-lowering therapy; LDL-C; PCSK9 inhibition

Cardiovascular (CV) disease-related deaths from heart disease and stroke are the second and third highest causes of death in Japan.¹ Reductions in low-density lipoprotein cholesterol (LDL-C) correlate with a decrease in the incidence of CV disease.^{2–4} Despite available therapies, over 30% of patients in Japan with atherosclerotic CV disease (ASCVD) are unable to achieve desired LDL-C levels.⁵

Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) is a new therapeutic strategy for lowering LDL-C. The binding of PCSK9 to the LDL receptor (LDLR) leads to a reduction in LDLR recycling and a decrease in the number of LDLRs on the cell surface. Inhibiting

PCSK9 leads to an increase in recycling of LDLR and more receptors on the cell surface; the result of this is greater clearance of LDL-C and therefore lower LDL-C levels.

Evolocumab, a monoclonal antibody to PCSK9, reduced mean LDL-C levels by up to 76% (vs. placebo) at 12 weeks when administered together with a statin in Japan-specific clinical trials.^{6,7} Here, we report 1-year efficacy and safety data from an analysis of Japanese patients who completed a 12-week phase 2 or 3 evolocumab clinical trial in Japan (YUKAWA-1 or YUKAWA-2, respectively), and continued into 1 of 2 ongoing evolocumab open-label extension (OLE) studies (OSLER-1 and OSLER-2).

Received October 6, 2016; revised manuscript received February 5, 2017; accepted February 15, 2017; released online March 29, 2017 Time for primary review: 22 days

Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo (A.H.); Departments of Community Medicine and Cardiovascular Medicine, Osaka University Graduate School of Medicine, Osaka (S.Y.); Rinku General Medical Center, Osaka (S.Y.); Amgen Astellas BioPharma K.K., Tokyo (H.I.), Japan; Amgen Inc., Thousand Oaks, CA (H.K., M.C., A.R., Y.M.), USA; Life Science and Bioethics Research Center, Tokyo Medical and Dental University, Tokyo (M.Y.); Department of Cardiovascular Medicine, The University of Tokyo Hospital, Tokyo (A.K.); and Teikyo Academic Research Center, Teikyo University, Tokyo (T.T.), Japan

Mailing address: Atsushi Hirayama, MD, PhD, Division of Cardiology, Department of Medicine, Nihon University School of Medicine, 30-1 Oyaguchikamicho, Itabashi-ku, Tokyo 173-8610, Japan. E-mail: hirayama.atsushi@nihon-u.ac.jp

ISSN-1346-9843 All rights are reserved to the Japanese Circulation Society. For permissions, please e-mail: cj@j-circ.or.jp

Methods

Study Design

We analyzed the 1-year data from Japanese patients enrolled in the ongoing OLE OSLER-1 (NCT01439880) and OSLER-2 (NCT01854918) studies who had previously completed a 12-week parent-study, YUKAWA-1 (NCT01652703) or YUKAWA-2 (NCT01953328) (**Figure 1**). YUKAWA-1 was a 12-week, randomized, double-blind, placebo-controlled, phase 2 study evaluating the efficacy and safety of evolocumab in statin-treated Japanese patients at high CV risk.⁶ YUKAWA-2 was a 12-week, phase 3 study evaluating the efficacy and safety of evolocumab along with low-dose or high-dose atorvastatin in Japanese patients with hyperlipidemia or mixed dyslipidemia and high CV risk.⁷ Patients eligible for the YUKAWA studies were ≥ 20 years old, had stable statin therapy prior to screening, and triglycerides ≤ 400 mg/dL. Additionally, YUKAWA-1 patients were required to have LDL-C ≥ 115 mg/dL plus any statin at screening, while patients in YUKAWA-2 were required to have LDL-C ≥ 100 mg/dL and were also required to be on atorvastatin 5 or 20 mg daily. In both studies, high CV risk was defined using the Japan Atherosclerosis Society criteria.⁸

Patients, Randomization, Study Treatment and Follow-up

Patients who completed the 12-week YUKAWA-1 (n=307) or YUKAWA-2 (n=404) study could choose to participate in the ongoing OLE studies OSLER-1 or OSLER-2, respec-

tively (**Figure 1**). In YUKAWA-1, patients entered the study on stable background statin therapy, while in YUKAWA-2 the patients were randomized to and stabilized on background atorvastatin 5 or 20 mg/day prior to randomization to the study drug. At the end of each parent study, all patients entering an OLE study were randomized to receive either evolocumab+standard of care (SOC) or SOC alone in a 2:1 ratio. Evolocumab was administered subcutaneously at a dose of 420 mg once a month in OSLER-1 and, based on patient choice, at a dose of either 140 mg every 2 weeks or 420 mg once a month in OSLER-2. The 2 regimens have been shown to be clinically equivalent to each other. All patients, investigators, and study care providers were aware of the randomized treatment assignments in the OLE studies. In OSLER, background SOC was based on local guidelines. In Japan, SOC background therapy was based on the Japanese Atherosclerosis Society guidelines for the diagnosis and prevention of ASCVD.⁸ The study visit schedules were similar in OSLER-1 and -2. All patients had in-person clinic visits on day 1 and then quarterly visits at weeks 12, 24, 36, and 48. Year 1 of treatment concluded at week 52 in OSLER-1 and at week 48 in OSLER-2; after year 1, all patients receive evolocumab therapy plus SOC. The studies are still ongoing. Study protocols were approved by the independent ethics committee at each study site. Amgen Inc. sponsored and designed the YUKAWA and OSLER trials and was responsible for data collection and analysis. All patients provided written informed consent before study enrollment.

Table 1. Baseline Demographics and Characteristics at Parent Safety Baseline

	OSLER-1 (YUKAWA-1)		OSLER-2 (YUKAWA-2)	
	SOC (n=73)	Evolocumab+SOC (n=146)	SOC (n=113)	Evolocumab+SOC (n=224)
Demographics				
Female, n (%)	32 (44)	55 (38)	47 (42)	85 (38)
Age, years, mean (SD)	62 (10)	61 (9)	61 (11)	61 (10)
Cardiovascular risk factors, n (%)				
Hypertension	53 (73)	113 (77)	80 (71)	166 (74)
T2DM	21 (29)	60 (41)	51 (45)	116 (52)
MetS*	19 (26)	44 (30)	36 (32)	57 (25)
Impaired fasting glucose (FPG $\geq$ 100 mg/dL)	40 (55)	105 (72)	82 (73)	162 (72)
Current smoker	16 (22)	45 (31)	26 (23)	55 (25)
Cerebrovascular disease or PAD, n (%)				
Any	12 (16)	19 (13)	15 (13)	25 (11)
Carotid- or vertebral-artery disease	4 (5)	1 (1)	8 (7)	15 (7)
Stroke	9 (12)	17 (12)	8 (7)	11 (5)
PAD	5 (7)	2 (1)	0	3 (1)
HeFH, n (%)	10 (14)	3 (2)	8 (7)	14 (6)
CAD, n (%)				
Any	19 (26)	32 (22)	12 (11)	21 (9)
MI	9 (12)	11 (8)	7 (6)	12 (5)
PCI	11 (15)	24 (16)	8 (7)	7 (3)
Background statin,[†] n (%)				
Intensive	21 (29)	32 (22)	59 (52)	108 (48)
Nonintensive	52 (71)	114 (78)	54 (48)	116 (52)
Baseline lipids				
LDL-C, mg/dL, mean (SD)	146.0 (22.7)	138.7 (22.0)	105.3 (29.4)	106.0 (32.1)
TC, mg/dL, mean (SD)	228.5 (25.8)	220.7 (26.0)	190.4 (34.5)	189.3 (36.1)
HDL-C, mg/dL, mean (SD)	56.5 (13.8)	54.2 (12.7)	57.1 (14.9)	57.1 (12.9)
Lp(a), nmol/L, median (Q1, Q3)	35 (13, 67)	33 (13, 61)	34 (13, 57)	33 (13, 58)
Triglycerides, mg/dL, median (Q1, Q3)	123 (97, 158)	129 (102, 166)	129 (101, 171)	117 (91, 160)
NonHDL-C, mg/dL, mean (SD)	172.0 (24.9)	166.4 (25.5)	133.3 (33.0)	132.2 (36.1)
ApoB, mg/dL, mean (SD)	113.5 (16.5)	110.3 (16.9)	93.6 (20.7)	93.8 (23.0)
ApoA1, mg/dL, mean (SD)	158.9 (22.6)	156.9 (23.4)	163.0 (27.4)	161.9 (24.7)
Glycemic background				
FPG, mg/dL, mean (SD)	112.0 (29.3)	113.8 (22.9)	116.1 (28.4)	115.6 (24.5)
HbA _{1c} , %, mean (SD)	6.1 (0.8)	6.3 (0.7)	6.2 (0.7)	6.2 (0.8)

*Metabolic syndrome is defined as having no T2DM, as well as $\geq$ 3 of the following risk factors: elevated waist circumference, triglycerides $\geq$ 1.7 mmol/L, low HDL-C, systolic blood pressure $\geq$ 130 mmHg or diastolic blood pressure $\geq$ 85 mmHg, hypertension, or FPG $\geq$ 100 mg/dL.

[†]Japan-specific definition: intensive if atorvastatin $\geq$ 10 mg QD, rosuvastatin $\geq$ 5 mg QD, simvastatin $\geq$ 20 mg QD, fluvastatin $\geq$ 80 mg QD, lovastatin $\geq$ 40 mg QD, pitavastatin $\geq$ 2 mg QD, pravastatin $\geq$ 40 mg QD or any statin use with concurrent ezetimibe use, and nonintensive is any statin use not classified as intensive. In YUKAWA-2, patients were randomized to background statin. Apo, apolipoprotein; CAD, coronary artery disease; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein-cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein-cholesterol; Lp(a), lipoprotein(a); MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; Q, quartile; QD, daily; SD, standard deviation; SOC, standard of care; T2DM, type 2 diabetes mellitus; TC, total cholesterol.

Efficacy and Safety Endpoints

The primary endpoint in both OSLER-1 and OSLER-2 was the incidence of adverse events (AEs). Additional safety endpoints included serious AEs, AEs leading to the discontinuation of study drug (evolocumab), abnormalities in creatine kinase levels and liver function test levels, and the development of binding or neutralizing antibodies against evolocumab, which were assayed as reported previously.^{9,10} The secondary endpoint was the percentage change in LDL-C level from study baseline. Other efficacy measures included non-high-density lipoprotein-cholesterol (non-HDL-C), total cholesterol (TC), triglycerides, HDL-C, apolipoproteins A1 and B (ApoA1 and ApoB, respec-

tively), and lipoprotein(a) (Lp(a)). Lipids were measured at a central laboratory (Medpace Reference Laboratories, Cincinnati, and Leuven, Belgium) after a fast of at least 9 h. The LDL-C level was calculated with the Friedewald formula.¹¹

Statistical Analysis

The data from OSLER-1 (YUKAWA-1 subset) and OSLER-2 (YUKAWA-2 subset) were combined into a single analysis set. Lipid measurements were summarized by study and treatment with the use of descriptive statistics. Safety data were pooled and described according to the incidence of AEs. Statistical analyses for efficacy and

Table 2. Adverse Events (Pooled YUKAWA-1/OSLER-1 and YUKAWA-2/OSLER-2)

Adverse events, n (%)	SOC* (n=186)	Evolocumab+SOC (n=370)
Any	134 (72.0)	277 (74.9)
Serious	18 (9.7)	27 (7.3)
Leading to discontinuation of study drug*	NA	3 (0.8)
Most common ($\geq 1\%$)		
Nasopharyngitis	53 (28.4)	95 (25.7)
Diabetes mellitus	6 (3.2)	27 (7.3)
Back pain	2 (1.1)	20 (5.4)
Muscle-related†	0	0
Injection-site reactions*	NA	10 (2.7)
Post-baseline binding antibody‡	0	1 (0.3)
Laboratory results		
AST/ALT $>3\times$ ULN at any post-baseline visit	2 (1.1)	6 (1.6)
CK $>5\times$ ULN at any post-baseline visit	0	2 (0.5)

*SOC-alone group did not receive placebo injections, so could not stop study drug or have injection site reactions.

†Potential muscle-related events were identified using the rhabdomyolysis-myopathy standardized MedDRA Query (SMQ). ‡No neutralizing antibodies were detected. ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; SOC, standard of care; ULN, upper limit of normal.

safety data were performed with SAS, version 9.3 (Cary, NC, USA).

Results

Patients

A total of 719 Japanese patients were enrolled in YUKAWA-1 (310) and YUKAWA-2 (409); a total of 556 patients, 219 from YUKAWA-1 and 337 from YUKAWA-2, were enrolled in the OSLER program. Of the 219 patients enrolled in YUKAWA-1, 146 were randomly assigned to receive evolocumab+SOC and 73 to receive SOC alone at OSLER-1 entry. Of the 337 patients enrolled in YUKAWA-2, 224 were randomly assigned to receive evolocumab+SOC and 113 to receive SOC alone at OSLER-2 entry. Baseline demographic characteristics (12-week parent-study baseline) for YUKAWA-1 and YUKAWA-2 patients continuing into OSLER-1 or OSLER-2 are shown in **Table 1**. The mean (SD) age of the patients was 61 (10) years. Neither the YUKAWA studies nor the OSLER studies were designed to address glycemic control; hence, randomization was not stratified by baseline diabetes risk factors. Thus, there was an imbalance in impaired fasting glucose (IFG) and type 2 diabetes mellitus (T2DM) between the evolocumab+SOC and the SOC-alone treatment groups in both parent YUKAWA studies, and there were also differences between the YUKAWA-1 and YUKAWA-2 study populations with respect to parent-study baseline lipid levels and CV risk. At YUKAWA-1 and YUKAWA-2 baseline, 72% of those in the evolocumab+SOC treatment group had IFG (fasting plasma glucose (FPG) ≥ 100 mg/dL), while 66% of patients in the SOC-alone treatment group had IFG. Furthermore, at the time of enrollment into the YUKAWA studies, 48% of patients randomized to evolocumab+SOC compared with 39% of patients randomized to SOC alone had diabetes.

OSLER statin assignment is described in the **Methods**; changes in open-label statin therapy were infrequent (3.8% in the evolocumab+SOC group and 4.3% in the SOC-alone group).

Safety

This was a smaller, population-based pooled analysis of ongoing studies, and the safety analyses focused on overall safety. AEs were mostly mild (grade 1 or 2). Over the first year of the ongoing OSLER-1 and OSLER-2 studies, AEs occurred in a comparable proportion of patients in the evolocumab+SOC (74.9%) and SOC-alone (72.0%) treatment groups (**Table 2**). Rates of serious AEs were also comparable between the evolocumab+SOC (7.3%) and SOC-alone (9.7%) treatment groups. Serious AEs leading to premature study discontinuation occurred in 3 (0.8%) evolocumab+SOC patients. Injection-site reactions were reported in 10 (2.7%) patients in the evolocumab+SOC group (SOC-alone group did not receive injections), and all were mild (grade 1 or 2). Post-baseline binding antibodies to evolocumab were detected in 1 patient (0.3%) in the evolocumab+SOC group. No neutralizing antibodies against evolocumab were detected. Elevations in aminotransferases (>3 -fold of the upper limit of normal [ULN]) or creatine kinase >5 -fold of the ULN were rare and occurred at a similar rate in the SOC-alone and evolocumab+SOC treatment groups. The incidence of diabetes AEs was 7.3% in the evolocumab+SOC treatment group and 3.2% in the SOC-alone treatment group (**Table 2**). These AEs were not new-onset diabetes, but were diabetes-related events. Of the 27 in the evolocumab+SOC arm reporting an AE of diabetes, 22 had diabetes at OSLER baseline. Of the 5 evolocumab+SOC patients who were not classified as having diabetes at OSLER baseline, all 5 had FPG and/or glycated hemoglobin (HbA_{1c}) measurements at baseline consistent with diabetes or IFG. Of the 6 patients in the SOC-alone arm reporting a diabetes AE, all 6 had diabetes at OSLER baseline. No notable changes from baseline to end of study were reported for FPG or HbA_{1c} levels over the 1-year period in patients with type 2 diabetes (T2DM), metabolic syndrome (MetS), or neither (**Tables S1,S2**).

Lipid Parameters

In YUKAWA-1 patients rolling over into OSLER-1, the mean baseline LDL-C on statin (at 12-week parent-study

Percentage change from baseline in lipids	OSLER-1 (YUKAWA-1)		OSLER-2 (YUKAWA-2)	
	SOC (n=73)	Evolocumab+SOC (n=146)	SOC (n=113)	Evolocumab+SOC (n=224)
LDL-C				
Week 12	-1.9 (1.5)	-70.1 (0.9)	11.3 (3.2)	-70.0 (1.4)
1 year*	0.1 (1.8)	-69.1 (1.2)	18.7 (3.0)	-65.1 (2.2)
HDL-C				
Week 12	-2.1 (1.5)	7.3 (1.3)	-5.8 (1.1)	3.8 (1.0)
1 year*	6.0 (1.6)	14.0 (1.4)	-0.9 (1.4)	8.1 (1.0)
NonHDL-C				
Week 12	-1.3 (1.3)	-61.7 (0.9)	9.3 (2.4)	-59.73 (1.2)
1 year*	0.2 (1.7)	-60.3 (1.1)	17.3 (2.5)	-55.13 (1.8)
Lp(a)				
Week 12	0 (-10.6, 15.3)	-47.7 (-62.0, -29.2)	-3.9 (-25.3, 12.8)	-47.8 (-66.7, -28.0)
1 year*	16.3 (0, 29.6)	-40.4 (-60.0, -14.3)	0 (-18.8, 27.3)	-44.1 (-62.9, -13.1)
Triglycerides				
Week 12	-2.2 (-17.6, 26.6)	-21.0 (-35.5, -1.7)	1.3 (-16.5, 34.3)	-15.2 (-32.1, 5.0)
1 year*	-0.9 (-18.0, 21.1)	-21.3 (-33.7, -2.7)	10.0 (-10.6, 39.2)	-13.2 (-29.8, 8.6)
ApoB				
Week 12	-2.1 (1.3)	-57.9 (0.9)	6.4 (2.0)	-57.5 (1.1)
1 year*	4.4 (1.6)	-54.3 (1.1)	8.6 (2.3)	-53.9 (1.5)
ApoA1				
Week 12	-1.0 (1.2)	5.3 (0.9)	-1.9 (1.1)	4.7 (0.8)
1 year*	8.7 (1.2)	13.7 (1.1)	-1.1 (1.2)	3.9 (0.8)

Data are mean (SE) or median (Q1, Q3). *Week 52 for OSLER-1 and week 48 for OSLER-2. SE, standard error. Other abbreviations as in Table 1.

baseline) was 146.0 mg/dL in the SOC-alone treatment group and 138.7 mg/dL in the evolocumab+SOC treatment group. In YUKAWA-2 patients rolling over into OSLER-2, the mean baseline LDL-C on statin (at 12-week parent-study baseline) was 105.3 mg/dL in the SOC-alone group and 106.0 mg/dL in the evolocumab+SOC treatment group (Table 1). At the end of year 1 of OSLER-1, evolocumab+SOC reduced LDL-C by a mean (SE) of 69.1% (1.2%) from the 12-week parent-study baseline (Table 3), for a mean absolute reduction from 138.7 to 42.7 mg/dL (Table S3; Figure 2). In OSLER-2, evolocumab+SOC reduced LDL-C by a mean (SE) of 65.1% (2.2%) from 12-week parent-study baseline (Table 3), for a mean absolute reduction from parent-study baseline of 106.0 to 35.4 mg/dL (Table S3; Figure 2). The reduction in LDL-C levels with evolocumab was robust and persistent throughout the study period (Figure 2).

Consistent changes in other lipid parameters were also observed throughout the 1-year study period. Evolocumab+SOC reduced Lp(a) by a median (Q1, Q3) of 40.4% (60.0%, 14.3%) (OSLER-1) and 44.1% (62.9%, 13.1%) (OSLER-2), reduced triglycerides by a median (Q1, Q3) of 21.3% (33.7%, 2.7%) (OSLER-1) and 13.2% (29.8%, 8.6%) (OSLER-2), reduced ApoB by a mean (SE) of 54.3% (1.1%) (OSLER-1) and 53.9% (1.5%) (OSLER-2), increased ApoA1 by a mean (SE) of 13.7% (1.1%) (OSLER-1) and 3.9% (0.8%) (OSLER-2), increased HDL-C levels by a mean (SE) of 14.0% (1.4%) (OSLER-1) and 8.1% (1.0%) (OSLER-2) and reduced nonHDL-C by a mean (SE) of 60.3% (1.1%) (OSLER-1) and 55.1% (1.8%) (OSLER-2) (Table 3; Figure S1). Absolute achieved lipid levels for week 12 and end of study (week 52 OSLER-1; week 48 OSLER-2) are reported in Table S3.

Discussion

In patients from YUKAWA-1 and YUKAWA-2 who completed 1 year of treatment in OSLER-1 or OSLER-2, evolocumab+SOC reduced LDL-C levels by 69.1% and 65.1%, respectively. LDL-C reductions were overall consistent with those previously reported from the 12-week YUKAWA-1 and YUKAWA-2 trials (63% and 69%, respectively).^{6,7} Reductions in LDL-C in the evolocumab treatment group were also consistent with those reported in an overall OSLER-1/OSLER-2 1-year analysis.⁹ This was despite differences in parent-study baseline LDL-C levels because of differences in study entry criteria and study design (baseline LDL-C higher in YUKAWA-1 and lower in YUKAWA-2 vs. levels reported in the overall OSLER-1/OSLER-2 1-year dataset).⁹ In YUKAWA-1, LDL-C was required to be ≥ 115 mg/dL at baseline, while in YUKAWA-2 LDL-C was required to be ≥ 100 mg/dL. Furthermore, baseline LDL-C in YUKAWA-2 was measured after the completion of the lipid-stabilization period.

Here, we show that the LDL-C reductions seen in YUKAWA-1 and YUKAWA-2 persisted up to 1 year in these patients following open-label treatment. In contrast, LDL-C levels in patients receiving SOC alone showed no change in OSLER-1 and incremental increases in OSLER-2. The reason for the increase in LDL-C seen in OSLER-2 patients receiving SOC alone is unclear but does not appear to be related to a change in background statin therapy, as the rate of change in background statin therapy was low (4%).

At 1 year, evolocumab+SOC treatment resulted in ben-

eficial changes in other lipids (Tables 3, S3; Figure S1), which was also reported in other studies.^{6,7,12} HDL-C increased by 14.0% in OSLER-1 and 8.1% in OSLER-2. The reason for the greater increase in the percentage change in HDL-C in OSLER-1 is unclear; however, HDL-C levels in the OSLER-1 SOC-alone treatment group increased by 6.0%, suggesting a treatment difference for the evolocumab+SOC treatment group (vs. SOC alone) of 8%, which was similar to that observed in the OSLER-2 subgroup. Increases in HDL-C levels in the OLE SOC-alone treatment groups may have been related to background SOC treatment, which was based on local guidelines and may have included background statin therapy (see Methods).

Lp(a) reductions (40.4% OSLER-1 subgroup and 44.1% OSLER-2 subgroup) are consistent with those reported in other published evolocumab studies.¹²⁻¹⁴ The mechanism of Lp(a) reduction by evolocumab is still not fully understood; however, this effect, a unique feature of PCSK9 inhibition, may be important as elevations in Lp(a) are associated with coronary heart disease risk independent of LDL-C levels.¹⁵

One year of open-label treatment with evolocumab+SOC was well tolerated in Japanese patients, and safety data were consistent overall with reports from global long-term studies of evolocumab, including the DESCARTES study as well as analyses of the overall OSLER-1 and OSLER-2 1-year datasets.^{9,16} In this smaller pooled analysis, we did note a numerically higher incidence of diabetes-related AEs in the evolocumab+SOC treatment arm vs. SOC-alone. However, these AEs did not represent new-onset diabetes; rather, they were diabetes events occurring in patients with pre-existing diabetes or IFG. Indeed, there was an imbalance of more YUKAWA patients with T2DM or at risk for developing T2DM in the evolocumab+SOC arm vs. SOC alone at OSLER baseline because of unequal randomization into OSLER. Importantly, FPG and HbA_{1c} levels did not change notably during the study period among patients with or without diabetes mellitus or MetS. Thus far, there have been no concerns regarding diabetes in the larger, global, clinical trials of evolocumab, including in the DESCARTES study and the published 1-year data from the overall OSLER studies.^{9,10,16} In an integrated safety analysis of patients from the OSLER studies treated with evolocumab+SOC or SOC alone for a median of 11.1 months of exposure, the rate of new-onset diabetes in those with baseline FPG < 126 mg/dL were 3.2% in the evolocumab+SOC treatment group and 3.2% in the SOC alone group.¹⁷ In a recent subanalysis of DESCARTES (n=901), the overall rate of new-onset diabetes was 5.6% in the evolocumab treatment group and 6.6% in the placebo group; in patients with baseline FPG < 100 mg/dL, rates were 2.7% and 1.9%, respectively.¹⁸ No notable changes were observed in FPG, HbA_{1c}, insulin, C-peptide, or HOMA indices between evolocumab or placebo after 1 year of treatment.¹⁸ The larger, ongoing FOURIER study will provide even longer-term safety data, including independent adjudication of new-onset diabetes cases, and will thus be able to more definitively address whether PCSK9 inhibitors have any effect on the incidence of diabetes.

The FOURIER study (NCT01764633) is designed to evaluate whether a reduction in LDL-C levels through PCSK9 inhibition leads to a corresponding reduction in CV events. The recent IMPROVE-IT trial⁴ showed that the addition of ezetimibe, a cholesterol-absorption inhibitor, to a statin, significantly reduced CV events as compared with

statin monotherapy. Although the reduction in such events with statins, and now the addition of ezetimibe, is well established,^{2,3} it is unknown whether the addition of a PCSK9 inhibitor will lead to a further reduction in CV events. A post-hoc exploratory analysis of all patients from the first year of OSLER-1 and OSLER-2 showed a statistically significant reduction in prespecified major cardiac AEs with evolocumab vs. SOC.¹⁹ A similar observation was reported in a post-hoc analysis of an alirocumab study.²⁰ However, these analyses were post-hoc and the studies were shorter term than the planned outcome studies, FOURIER and ODYSSEY Outcomes, and it remains unclear whether the robust LDL-C reductions with PCSK9 inhibitors shown in previous clinical studies lead to additional benefit through CV risk reduction. The FOURIER study also includes EBBINGHAUS (NCT02207634), a dedicated and structured neurocognitive study, which will provide safety data on long-term treatment with evolocumab in a large randomized cohort, including in Japanese patients.

In conclusion, 1-year of treatment with evolocumab, administered biweekly or monthly, demonstrated marked and persistent LDL-C reductions and was well tolerated in high-CV-risk patients with hypercholesterolemia.

Acknowledgments

Amgen Inc. funded this study. The authors acknowledge Annalise M. Nawrocki, PhD, of Amgen Inc. and Katherine Hsu, PharmD, on behalf of Amgen Inc. for providing medical writing support for the manuscript.

Conflict of Interest

A.H. has received research grants from Daiichi-Sankyo Pharma, Bayer, Bristol-Myers Squibb, Pfizer Japan, Boston Scientific Japan, Astellas, Astra Zeneca, MSD, Otsuka, Kyowa Kirin Hakko, Sanofi, Takeda, Tanabe Mitsubishi, Dainihon Sumitomo, Nihon Boehringer Ingelheim and Nihon Medipharma. A.H. has also served on speakers, bureaus for Daiichi-Sankyo, Bayer, Bristol-Myers Squibb, and AstraZeneca. S.Y. has received a consulting fee from and served on speakers, bureau for Amgen. H.I. is an employee of Amgen Astellas and holds Amgen stock/stock options. H.K., M.C., and A.R. are Amgen employees and hold Amgen stock/stock options. Y.M. has served as a consultant for Amgen. M.Y. has no disclosures to report. A.K. has no disclosures to report. T.T. has received research grants from Daiichi-Sankyo, Kowa, Eli Lilly, Takeda, and Shionogi. T.T. has also served on speakers bureaus for Bayer, Pfizer, Daiichi-Sankyo, Kowa, Takeda, Astellas, Kissei, Sanofi, and Amgen Astellas BP.

References

1. Iso H. Lifestyle and cardiovascular disease in Japan. *J Atheroscler Thromb* 2011; **18**: 83–88.
2. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalra N, 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.
3. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005; **366**: 1267–1278.
4. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015; **372**: 2387–2397.
5. Teramoto T, Uno K, Miyoshi I, Khan I, Gorczyca K, Sanchez RJ, et al. Low-density lipoprotein cholesterol levels and lipid-modifying therapy prescription patterns in the real world: An analysis of more than 33,000 high cardiovascular risk patients in Japan. *Atherosclerosis* 2016; **251**: 248–254.
6. Hirayama A, Honarpour N, Yoshida M, Yamashita S, Huang F, Wasserman SM, et al. Effects of evolocumab (AMG 145), a monoclonal antibody to PCSK9, in hypercholesterolemic, statin-treated Japanese patients at high cardiovascular risk: Primary results from the phase 2 YUKAWA study. *Circ J* 2014; **78**: 1073–1082.

7. Kiyosue A, Honarpour N, Kurtz C, Xue A, Wasserman SM, Hirayama A. A phase 3 study of evolocumab (AMG 145) in statin-treated Japanese patients at high cardiovascular risk. *Am J Cardiol* 2016; **117**: 40–47.
8. Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi 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.
9. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; **372**: 1500–1509.
10. Koren MJ, Giugliano RP, Raal FJ, Sullivan D, Bolognese M, Langslet G, et al. Efficacy and safety of longer-term administration of evolocumab (AMG 145) in patients with hypercholesterolemia: 52-week results from the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) randomized trial. *Circulation* 2014; **129**: 234–243.
11. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18**: 499–502.
12. Robinson JG, Nedergaard BS, Rogers WJ, Fialkow J, Neutel JM, Ramstad D, et al. Effect of evolocumab or ezetimibe added to moderate- or high-intensity statin therapy on LDL-C lowering in patients with hypercholesterolemia: The LAPLACE-2 randomized clinical trial. *JAMA* 2014; **311**: 1870–1882.
13. Raal FJ, Giugliano RP, Sabatine MS, Koren MJ, Langslet G, Bays H, et al. Reduction in lipoprotein(a) with PCSK9 monoclonal antibody evolocumab (AMG 145): A pooled analysis of more than 1,300 patients in 4 phase II trials. *J Am Coll Cardiol* 2014; **63**: 1278–1288.
14. Raal FJ, Giugliano RP, Sabatine MS, Koren MJ, Blom D, Seidah NG, et al. PCSK9 inhibition-mediated reduction in Lp(a) with evolocumab: An analysis of 10 clinical trials and the LDL receptor's role. *J Lipid Res* 2016; **57**: 1086–1096.
15. Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. *Circulation* 2001; **104**: 1108–1113.
16. Blom DJ, Hala T, Bolognese M, Lillestol MJ, Toth PD, Burgess L, et al. A 52-week placebo-controlled trial of evolocumab in hyperlipidemia. *N Engl J Med* 2014; **370**: 1809–1819.
17. Toth PP, Descamps O, Genest J, Sattar N, Preiss D, Dent-Acosta RE, et al. A pooled safety analysis of over 6000 patients from double-blind and open-label extension studies with evolocumab. In: Proceedings of the Scientific Sessions of the American College of Cardiology. Chicago, IL: ACC, 2016.
18. Blom DJ, Koren MJ, Roth E, Monsalvo ML, Djedjos CS, Nelson P, et al. Evaluation of the efficacy, safety, and glycaemic effects of evolocumab (AMG 145) in hypercholesterolaemic patients stratified by glycaemic status and metabolic syndrome. *Diabetes Obes Metab* 2017; **19**: 98–107.
19. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, Robinson J, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; **372**: 1500–1509.
20. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; **372**: 1489–1499.

Supplementary Files

Supplementary File 1

Figure S1. Percentage change from baseline in LDL-C and other lipids at year 1 in patients from YUKAWA continuing into the OSLER program.

Table S1. Glycemic parameters of patients

Table S2. Glycemic measures by study week and glycemic status of patients

Table S3. Lipid levels by study week

Please find supplementary file(s);
<http://dx.doi.org/10.1253/circj.CJ-16-1016>