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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 –

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Background: YUKAWA is a 12-week, randomized, double-blind, placebo-controlled, phase 2 study evaluating the efficacy and safety of evolocumab (AMG 145) in statin-treated Japanese patients at high cardiovascular risk.

Methods and Results: 310 eligible patients receiving stable statin (±ezetimibe) therapy were randomized to 1 of 6 treatments: placebo every 2 weeks (Q2W) or monthly (QM), evolocumab 70 mg or 140 mg Q2W, or evolocumab 280 mg or 420 mg QM. The primary endpoint was the percentage change from baseline in low-density lipoprotein cholesterol (LDL-C) measured by preparative ultracentrifugation (UC). Secondary endpoints included percentage changes in other lipid parameters and the proportion of patients with LDL-C <1.8 mmol/L. Mean (SD) age was 62 (10) years; 37% were female; and the mean (SD) baseline LDL-C was 3.7 (0.5) mmol/L (by UC). Mean (SE) changes vs. placebo in LDL-C were greatest in the high-dose groups: −68.6 (3.0) % and −63.9 (3.2) % with 140 mg Q2W and 420 mg QM dosing, respectively. Up to 96% of evolocumab-treated patients achieved LDL-C <1.8 mmol/L. Adverse events (AEs) were more frequent in evolocumab (51%) vs. placebo (38%) patients; 4 patients taking evolocumab discontinued treatment because of an AE. There were no significant differences in AE rates based on dose or dose frequency.

Conclusions: In Japanese patients at high cardiovascular risk with hypercholesterolemia on stable statin therapy, evolocumab significantly reduced LDL-C and was well tolerated during this 12-week study. (*Circ J* 2014; **78:** 1073–1082)

Key Words: Dyslipidemia; Hypercholesterolemia; Low-density lipoprotein cholesterol; PCSK9 antibody

Cardiovascular disease (CVD) remains the leading cause of death globally, with over 17 million deaths per year.[1] In Japan, CVD-associated deaths from heart disease and stroke are the second and third highest causes of death, respectively.[2] The incidence of coronary artery disease (CAD), a leading contributor to CVD incidence, increases in Japanese patients as low-density lipoprotein cholesterol (LDL-C) levels rise.[3,4] Although treatment with statins lowers the risk of CVD events,[5–10] high-risk patients may still fail to reach LDL-C goals,[1] leaving them vulnerable to subsequent cardiovascular events. Nearly half of the high-risk Japanese patients have not reached their Japan Atherosclerosis Society (JAS)-guideline LDL-C goal.[11,12]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secreted protein that binds to the LDL receptor (LDLR), preventing it from recycling to the cell surface.[13] This results in less available LDLR and higher circulating LDL-C levels.[13] Inhibition of PCSK9 with anti-PCSK9 antibodies increases hepatic LDLR recycling, which enhances LDL-C clearance from the serum.[14,15] Evolocumab is a fully human monoclonal antibody

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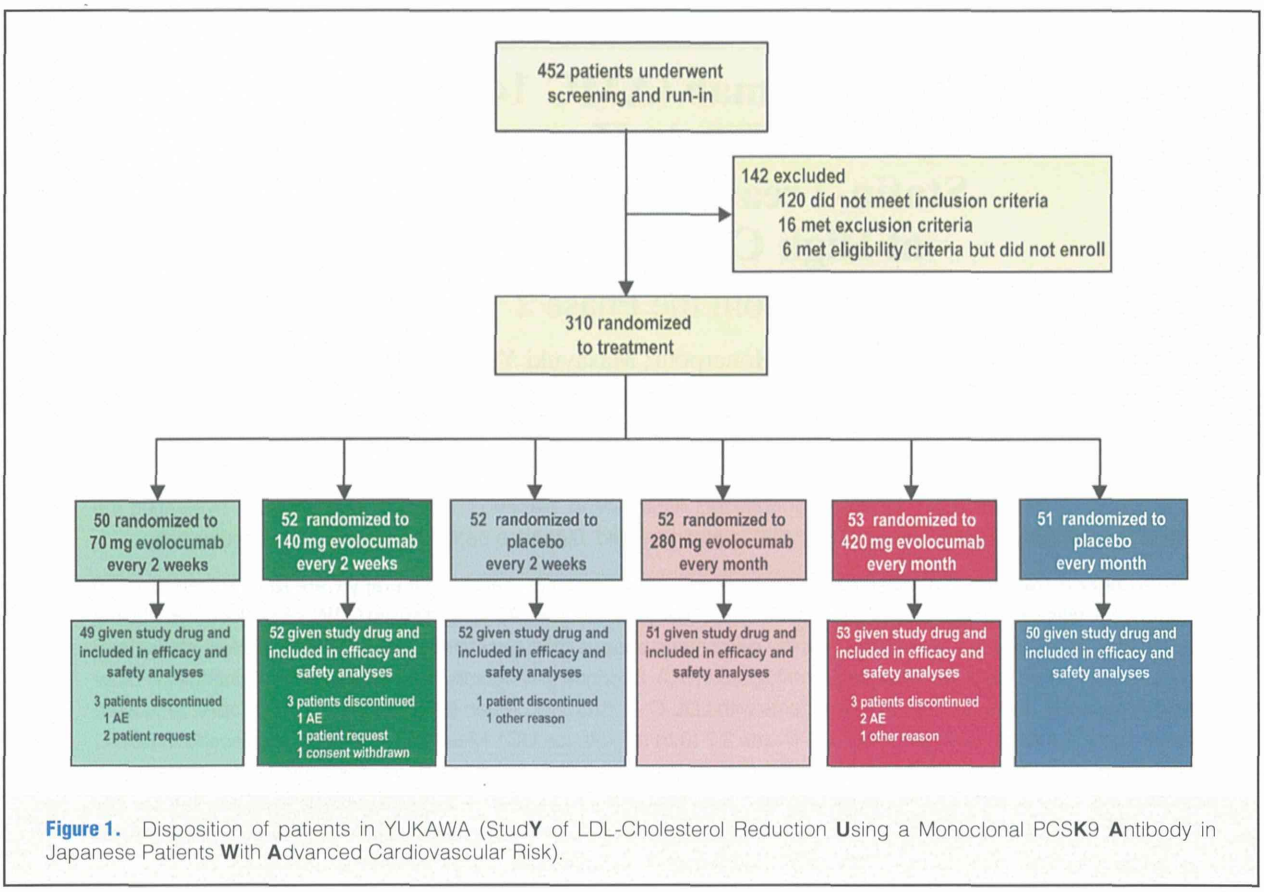

Figure 1. Disposition of patients in YUKAWA (Stud**Y** of LDL-Cholesterol Reduction **U**sing a Monoclonal PCS**K**9 **A**ntibody in Japanese Patients **W**ith **A**dvanced Cardiovascular Risk).

against PCSK9[14] that inhibits the binding of PCSK9 to LDLRs. In global phase 2 studies, evolocumab monotherapy reduced LDL-C measured by preparative ultracentrifugation (UC) by up to 53% vs. placebo,[16] and combination therapy with statins resulted in reductions of up to 66% vs. placebo.[17] Studies in patients with familial hypercholesterolemia[18,19] and statin intolerance[20] have shown similar efficacy. YUKAWA (Stud**Y** of LDL-Cholesterol Reduction **U**sing a Monoclonal PCS**K**9 **A**ntibody in Japanese Patients **W**ith **A**dvanced Cardiovascular Risk) is the first study to examine the efficacy and tolerability of evolocumab in hypercholesterolemic Japanese patients at high cardiovascular risk and on baseline statin therapy.

Methods

Patient Population and Study Design

YUKAWA is a 12-week, phase 2, randomized, multicenter, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy and safety of every 2 weeks (Q2W) or monthly (QM) evolocumab when used in combination with a statin in Japanese patients (NCT01652703). The study was carried out in 42 study centers in Japan. Briefly, patients were eligible if they were 20–80 years of age (inclusive) and classified as high risk for cardiovascular events. Patients were considered high risk if they had any of the following: history of CAD or cerebral infarction; a diagnosis of heterozygous familial hypercholesterolemia, arteriosclerosis obliterans/peripheral artery disease, or type 2 diabetes mellitus ≥3 months prior to randomization; a fasting plasma glucose >6.1 mmol/L ≥3 months prior to randomization; or the presence of ≥3 additional risk factors relating to age, smoking history, family history of CAD, and past diagnosis of hypertension or reduced high-density lipoprotein (HDL).[12,21] Inclusion/exclusion criteria are summarized in **Supplementary File 1**. Patients were required to be on stable statin therapy for ≥4 weeks prior to LDL-C screening. Baseline lipid requirements at screening were fasting LDL-C ≥3.0 mmol/L and fasting triglycerides ≤4.5 mmol/L.

Randomization and Study Blinding

Prior to randomization, all patients received a placebo injection to assess tolerance and acceptability of subcutaneous (SC) administration. Eligible patients who tolerated placebo injections were assigned equally to 1 of 6 treatment arms: SC placebo, evolocumab 70 mg, or evolocumab 140 mg Q2W; or SC placebo, evolocumab 280 mg, or evolocumab 420 mg QM (**Figure 1**). Baseline stratification factors included screening LDL-C (<3.4 mmol/L vs. ≥3.4 mmol/L) and a diagnosis of heterozygous familial hypercholesterolemia (yes vs. no). Treatment assignment and on-treatment laboratory lipid-panel values were blinded; dosing frequency was not blinded.

Study Endpoints

The primary efficacy endpoint was percentage change from baseline in LDL-C at week 12. Secondary endpoints assessed at week 12 were absolute change in LDL-C, percentage changes from baseline in other lipid parameters, and the proportion of patients who reached LDL-C <1.8 mmol/L. For endpoint assessments, LDL-C was measured by UC. Safety endpoints included the incidence of adverse events (AEs), laboratory values and vital signs, electrocardiography (ECG) parameters,

Table 1. Demographics and Baseline Characteristics of the Study Population[a]

	Placebo			Evolocumab					All patients
	Q2W (n=52)	QM (n=50)	Total (n=102)	70 mg Q2W (n=49)	140 mg Q2W (n=52)	280 mg QM (n=51)	420 mg QM (n=53)	Total (n=205)	Total (n=307)
Demographics									
Age, years, mean (SD)	60.2 (10.1)	60.9 (9.8)	60.5 (9.9)	64.1 (9.7)	60.8 (9.2)	61.6 (9.6)	61.3 (9.9)	61.9 (9.6)	61.5 (9.7)
Female, n (%)	16 (30.8)	14 (28.0)	30 (29.4)	24 (49.0)	20 (38.5)	23 (45.1)	17 (32.1)	84 (41.0)	114 (37.1)
Cardiac risk factors, n (%)									
CAD	15 (28.8)	15 (30.0)	30 (29.4)	12 (24.5)	13 (25.0)	9 (17.6)	13 (24.5)	47 (22.9)	77 (25.1)
PAD or CVD	7 (13.5)	7 (14.0)	14 (13.7)	8 (16.3)	4 (7.7)	7 (13.7)	9 (17.0)	28 (13.7)	42 (13.7)
T2DM	16 (30.8)	18 (36.0)	34 (33.3)	19 (38.8)	21 (40.4)	25 (49.0)	18 (34.0)	83 (40.5)	117 (38.1)
Hypertension	40 (76.9)	36 (72.0)	76 (74.5)	40 (81.6)	34 (65.4)	35 (68.6)	41 (77.4)	150 (73.2)	226 (73.6)
Elevated WC[b]	33 (63.5)	34 (68.0)	67 (65.7)	34 (69.4)	33 (63.5)	34 (66.7)	34 (64.2)	135 (65.9)	202 (65.8)
Current smoker	11 (21.2)	16 (32.0)	27 (26.5)	11 (22.4)	12 (23.1)	15 (29.4)	14 (26.4)	52 (25.4)	79 (25.7)
Metabolic syndrome[c]	17 (32.7)	12 (24.0)	29 (28.4)	13 (26.5)	14 (26.9)	11 (21.6)	16 (30.2)	54 (26.3)	83 (27.0)
≥2 cardiovascular risk factors	24 (46.2)	26 (52.0)	50 (49.0)	32 (65.3)	25 (48.1)	30 (58.8)	33 (62.3)	120 (58.5)	170 (55.4)
High-intensity statin use (global definition)[d]	2 (3.8)	3 (6.0)	5 (4.9)	6 (12.2)	2 (3.8)	3 (5.9)	3 (5.7)	14 (6.8)	19 (6.2)
High-intensity statin use (Japan-specific definition)[e]	14 (26.9)	14 (28.0)	28 (27.5)	14 (28.6)	11 (21.2)	10 (19.6)	10 (18.9)	45 (22.0)	73 (23.8)
Baseline lipids (mean [SD])									
UC LDL-C, mmol/L	3.7 (0.5)	3.7 (0.6)	3.7 (0.5)	3.7 (0.5)	3.6 (0.6)	3.6 (0.5)	3.6 (0.5)	3.7 (0.5)	3.7 (0.5)
Calculated LDL-C, mmol/L	3.7 (0.5)	3.6 (0.6)	3.7 (0.5)	3.7 (0.6)	3.6 (0.6)	3.6 (0.5)	3.6 (0.5)	3.6 (0.6)	3.6 (0.6)
Lp(a), nmol/L[f]	32.0 (17.5, 65.5)	35.0 (13.0, 66.0)	33.5 (16.0, 66.0)	29.0 (14.0, 56.0)	32.0 (11.0, 67.0)	27.0 (12.0, 53.0)	48.0 (20.0, 82.0)	33.5 (12.0, 66.0)	33.5 (13.0, 66.0)
TC, mmol/L	5.8 (0.6)	5.8 (0.6)	5.8 (0.6)	5.8 (0.7)	5.7 (0.7)	5.7 (0.7)	5.7 (0.6)	5.7 (0.7)	5.8 (0.6)
HDL-C, mmol/L	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)	1.4 (0.4)	1.4 (0.3)	1.4 (0.4)	1.4 (0.4)	1.4 (0.3)	1.4 (0.3)
TG, mmol/L	1.6 (0.6)	1.6 (0.6)	1.6 (0.6)	1.6 (0.7)	1.5 (0.5)	1.4 (0.5)	1.6 (0.7)	1.5 (0.6)	1.5 (0.6)
VLDL-C, mmol/L[f]	0.7 (0.5, 0.9)	0.7 (0.5, 0.9)	0.7 (0.5, 0.9)	0.7 (0.4, 0.9)	0.6 (0.5, 0.8)	0.6 (0.5, 0.7)	0.7 (0.5, 0.9)	0.6 (0.5, 0.8)	0.6 (0.5, 0.9)
Non-HDL-C, mmol/L	4.4 (0.6)	4.4 (0.7)	4.4 (0.6)	4.4 (0.7)	4.3 (0.7)	4.3 (0.6)	4.3 (0.6)	4.3 (0.7)	4.3 (0.6)
ApoB, g/L	1.2 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)
ApoA1, g/L	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)	1.6 (0.3)	1.6 (0.2)	1.6 (0.2)	1.6 (0.3)
TC:HDL-C	4.4 (0.9)	4.3 (1.1)	4.3 (1.0)	4.4 (1.2)	4.3 (1.0)	4.2 (1.0)	4.2 (1.0)	4.3 (1.0)	4.3 (1.0)
ApoB:ApoA1	0.8 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)
PCSK9, ng/ml	389.4 (121.2)	411.3 (101.1)	400.1 (111.8)	402.6 (129.1)	392.6 (125.8)	411.5 (137.9)	416.6 (143.9)	405.9 (133.8)	404.0 (126.8)

All percentages based on n. [a]Study population includes all randomized patients who received ≥1 dose of investigational product. [b]Elevated waist circumference (WC) defined as ≥85 cm for men, ≥90 cm for women. [c]JAS 2012 criteria. [d]Daily simvastatin 80 mg, atorvastatin ≥40 mg, rosuvastatin ≥20 mg, or any statin plus ezetimibe. [e]Daily atorvastatin ≥10 mg, pitavastatin ≥2 mg, rosuvastatin ≥5 mg, simvastatin ≥20 mg, lovastatin ≥40 mg, fluvastatin ≥80 mg, pravastatin ≥40 mg, or any statin plus ezetimibe. [f]Median (Q1, Q3).
Apo, apolipoprotein; CAD, coronary artery disease; CVD, cerebrovascular disease; HDL-C, high-density lipoprotein cholesterol; JAS, Japanese Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein A; PAD, peripheral arterial disease; PCSK9, proprotein convertase subtilisin/kexin type 9; Q1, first quartile; Q2W, every 2 weeks; Q3, second quartile; QM, monthly; SD, standard deviation; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; UC, ultracentrifugation; VLDL-C, very low-density lipoprotein cholesterol.

and incidence of anti-evolocumab antibodies.

Statistical Analysis

Analyses were conducted on data for randomized patients who received ≥1 dose of evolocumab or placebo. The primary endpoint was analyzed using an analysis of covariance model, including treatment group and the stratification factor of screening LDL-C. A last observation carried forward approach was used to impute missing values. Secondary endpoints were evaluated similarly to the primary endpoint; LDL-C response was assessed using a logistic regression, which included terms for treatment group and screening LDL-C. Secondary endpoint analyses were not adjusted for multiple comparisons. Analysis of the percentage change from baseline to the average of weeks 10 and 12 for lipid parameters of interest was performed using a repeated measures model and observed data, which included treatment group, the stratification factor of screening LDL-C, scheduled visit, and the interaction of treatment with scheduled visit.

AEs and serious AEs were recorded throughout the study and were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA v16.0). Laboratory parameters were summarized using descriptive statistics for each treatment group at each scheduled visit. Rates of anti-evolocumab antibody formation were tabulated by treatment group.

Results

Patient disposition is summarized in **Figure 1**. Of the 452

Table 2. Efficacy at 12 Weeks

	Evolocumab Q2W		Placebo Q2W	Evolocumab QM		Placebo QM
	70 mg (n=49)	140 mg (n=52)	(n=52)	280 mg (n=51)	420 mg (n=53)	(n=50)
LDL-C						
Mean (SE) percentage change vs. placebo in UC LDL-C; P value[a,b]	−52.9 (3.0); <0.001	−68.6 (3.0); <0.001	N/A	−58.2 (3.2); <0.001	−63.9 (3.2); <0.001	NA
Change in UC LDL-C vs. placebo (mmol/L; SE); P value[b]	−2.0 (0.1); <0.001	−2.5 (0.1); <0.001	NA	−2.1 (0.1); <0.001	−2.3 (0.1); <0.001	NA
Achieved LDL-C (mmol/L; mean [SD])[c]	1.5 (0.8)	0.9 (0.5)	3.6 (0.5)	1.5 (0.5)	1.2 (0.7)	3.6 (0.8)
LDL-C <2.6 mmol/L at week 12 (n [%])[d]	44 (94)	49 (98)	2 (4)	48 (94)	49 (96)	1 (2)
LDL-C <1.8 mmol/L at week 12 (n [%]; P value)[d]	31 (66); <0.001	48 (96); <0.001	0 (–)	41 (80); <0.001	42 (82); <0.001	0 (–)
Other lipid parameters						
Lp(a), mean (SE) % change vs. placebo; P value[a,b]	−41.5 (4.9); <0.001	−50.6 (4.9); <0.001	NA	−39.6 (4.9); <0.001	−32.3 (4.9); <0.001	NA
Achieved Lp(a), mean (SD), nmol/L	30.8 (42.5)	30.9 (42.3)	53.4 (58.5)	29.4 (41.9)	52.1 (68.1)	67.7 (87.0)
TC, mean (SE) % change vs. placebo; P value[a,b]	−36.2 (2.2); <0.001	−45.3 (2.1); <0.001	NA	−36.3 (2.3); <0.001	−40.2 (2.3); <0.001	NA
Achieved TC mean (SD), mmol/L	3.7 (0.9)	3.1 (0.6)	5.8 (0.7)	3.7 (0.7)	3.5 (0.8)	5.8 (0.8)
HDL-C, mean (SE) % change vs. placebo; P value[a,b]	4.4 (3.2); 0.17	9.1 (3.1); 0.004	NA	16.3 (3.1); <0.001	13.2 (3.1); <0.001	NA
Achieved HDL-C, mean (SD), mmol/L	1.6 (0.4)	1.6 (0.4)	1.5 (0.4)	1.6 (0.4)	1.6 (0.4)	1.4 (0.3)
TG, mean (SE) percentage change vs. placebo; P value[a,b]	−14.3 (6.3); 0.025	−16.6 (6.2); 0.009	NA	−17.1 (6.5); 0.009	−20.2 (6.4); 0.002	NA
Achieved TG, mean (SD), mmol/L	1.4 (0.6)	1.3 (0.6)	1.6 (0.9)	1.3 (0.5)	1.4 (0.7)	1.7 (0.8)
VLDL-C, median (Q1, Q3) % change vs. placebo; P value[a,b]	−22.2 (−42.4, −1.9); 0.002	−21.2 (−40.6, −1.7); 0.002	NA	−25.1 (−47.8, −2.4); 0.015	−24.1 (−46.4, −1.8); 0.004	NA
Achieved VLDL-C, median (Q1, Q3), mmol/L	0.5 (0.3, 0.6)	0.4 (0.3, 0.5)	0.6 (0.4, 1.0)	0.4 (0.3, 0.6)	0.5 (0.3, 0.6)	0.7 (0.4, 0.9)
Non-HDL-C, mean (SE) % change vs. placebo; P value[a,b]	−49.5 (2.7); <0.001	−62.6 (2.7); <0.001	NA	−53.5 (3.0); <0.001	−58.1 (3.0); <0.001	NA
Achieved Non-HDL-C, mean (SD), mmol/L	2.2 (0.9)	1.5 (0.5)	4.3 (0.7)	2.0 (0.6)	1.9 (0.8)	4.4 (0.9)
ApoB, mean (SE) % change vs. placebo; P value[a,b]	−46.8 (2.6); <0.001	−60.7 (2.5); <0.001	NA	−47.4 (2.8); <0.001	−53.4 (2.8); <0.001	NA
Achieved ApoB, mean (SD), g/L	0.6 (0.2)	0.4 (0.1)	1.1 (0.2)	0.6 (0.2)	0.5 (0.2)	1.1 (0.2)
ApoA1, mean (SE) % change vs. placebo; P value[a,b]	4.0 (2.4); 0.100	6.3 (2.4); 0.009	NA	9.3 (2.2); <0.001	9.6 (2.2); <0.001	NA
Achieved ApoA1, mean (SD), g/L	1.7 (0.3)	1.7 (0.3)	1.6 (0.3)	1.7 (0.3)	1.7 (0.3)	1.5 (0.2)
TC:HDL-C, mean (SE) % change vs. placebo; P value[a,b]	−37.2 (2.7); <0.001	−47.0 (2.6); <0.001	NA	−45.3 (2.9); <0.001	−46.7 (2.9); <0.001	NA
Achieved TCmean (SD), mmol/L	2.5 (0.8)	2.0 (0.4)	4.2 (1.1)	2.3 (0.5)	2.3 (0.9)	4.3 (1.2)
ApoB:ApoA1, mean (SE) % change vs. placebo; P value[a,b]	−47.5 (3.0); <0.001	−61.4 (2.9); <0.001	NA	−52.2 (3.1); <0.001	−57.8 (3.0); <0.001	NA
Achieved ApoB:ApoA1, mean (SD), g/L	0.4 (0.2)	0.2 (0.1)	0.7 (0.2)	0.4 (0.1)	0.3 (0.2)	0.7 (0.2)

[a]For least-squares mean percentage change from baseline in lipid parameters for each treatment group, see Supplementary File 1. [b]Least-squares mean difference within each dose frequency vs. matching placebo. [c]Calculated LDL-C. [d]Percentage calculated from n at week 12. NA, not applicable; SE, standard error. Other abbreviations as in Table 1.

patients screened for YUKAWA, 310 (69%) were randomized to treatment (2:1 evolocumab:placebo) (**Figure 1**). Baseline characteristics of the study population are reported in **Table 1**. Briefly, 37% were female; mean (standard deviation; SD) age was 62 (10) years; 55% were identified as having 2 or more cardiovascular risk factors, 38% had type 2 diabetes mellitus, and 25% had CAD. The mean (SD) baseline LDL-C values were 3.7 (0.5) mmol/L for placebo patients (total), 3.6 (0.6) mmol/L for evolocumab 140 mg Q2W, and 3.6 (0.5) mmol/L for evolocumab 420 mg QM. Baseline statin use was consistent with contemporary Japanese practice (**Table S1**).

All evolocumab treatment groups showed statistically significant ($P < 0.001$) mean changes from baseline in LDL-C vs. placebo at week 12, with the highest evolocumab doses within each dose frequency (140 mg Q2W and 420 mg QM) providing the greatest efficacy (**Table 2**). Mean (standard error; SE) percentage changes vs. placebo at week 12 were −68.6 (3.0) % 140 mg Q2W and −63.9 (3.2) % 420 mg QM (both $P<0.001$; **Table 2**), reflecting mean (SE) changes from baseline of −71.3 (2.2) % and −63.9 (2.3) %, respectively (**Table S2**). Subgroup efficacy results were consistent with these findings (**Figure 2**). Reductions in calculated LDL-C were apparent by week 2 in the evolocumab treatment groups and continued through the end of study (**Figure 3**). The most robust and sustained reductions were seen in the 140 mg Q2W and 420 mg QM groups.

The least-squares mean percentage change in LDL-C was

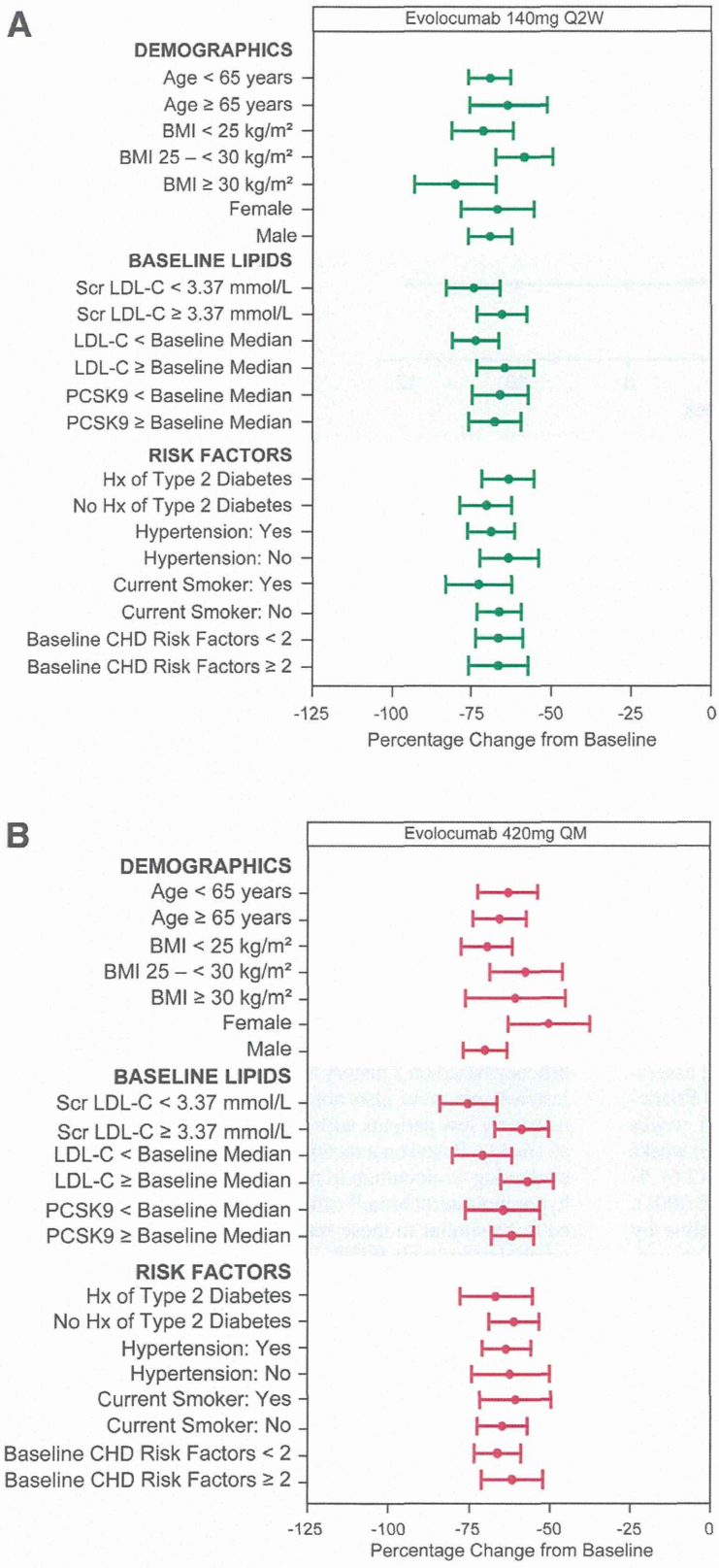

Figure 2. Mean percentage change in LDL-C measured by ultracentrifugation in the main subgroups given evolocumab either 140 mg SC Q2W (**A**) or 420 mg SC QM (**B**). Values reported are least-squares mean differences (95% CI) compared with matching placebo. Values less than 0 favor evolocumab, whereas those greater than 0 favor placebo. BMI, body mass index; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly; SC, subcutaneous; Scr, screening; Hx, history.

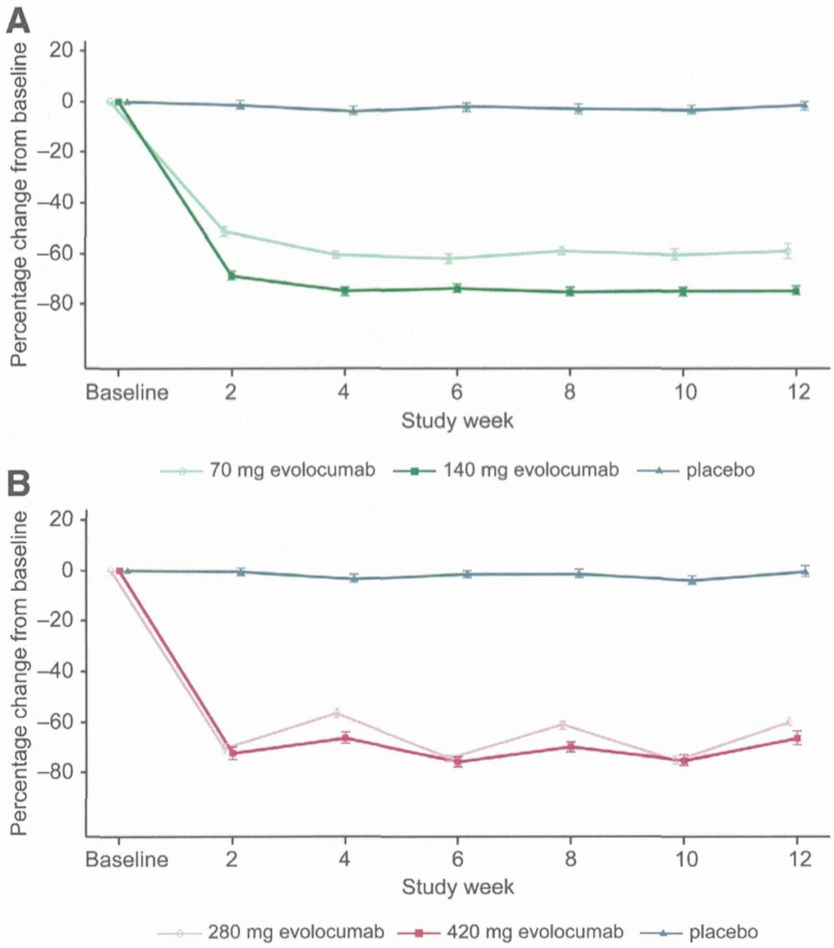

Figure 3. Mean percentage change in calculated LDL-C concentration from baseline by visit Q2W (**A**) or QM (**B**). Error bars indicate standard error (SE). Results are based on observed data. LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly.

also calculated for the mean of weeks 10 and 12, as this measure can be more reflective of the time-averaged reduction in LDL-C than the week 12 assessment alone.[22] LDL-C assessments at study visits between day 1 and week 12 used Friedewald's calculation. As a result, the mean LDL-C at weeks 10/12 reflects the average calculated LDL-C. Mean (SE) weeks 10/12 percentage changes vs. placebo were −71.7 (2.6) % 140 mg Q2W and −68.7 (2.6) % 420 mg QM (both P<0.0001), reflecting mean (SE) percentage changes from baseline by treatment group of −74.9 (1.8) % and −70.9 (1.9) %, respectively (**Table S3**).

Comparable LDL-C reductions were achieved with these doses in patients receiving intensive and non-intensive statin therapy. In patients receiving intensive statin therapy (global definition, see **Table 1**, footnote), mean (SE) changes in LDL-C of −63.8% (11.3) and −66.0% (10.8) were observed at week 12 with 140 mg Q2W and 420 mg QM dose groups, respectively. In those receiving non-intensive statin therapy, mean (SE) changes in LDL-C were −71% (2.2) and −63.7% (2.3) at week 12 for the 140 mg Q2W and 420 mg QM dose groups, respectively. Although the sample size for intensive statin use (global definition) was small (n=14 on evolocumab), similar results were seen when using the Japan-specific definition of intensive statin use (see **Table 1**, footnote), which classified more patients as receiving intensive statin therapy (n=45 on evolocumab). This suggests that the effect of evolocumab 140 mg Q2W and 420 mg QM does not change substantially with the intensity of background statin therapy. Appreciable differences in efficacy based on a history of heterozygous familial hypercholesterolemia were also not observed in this study; however, relatively few patients with this diagnosis received evolocumab (n=11). Based on a recently completed global phase 2 study evaluating evolocumab in patients with heterozygous familial hypercholesterolemia,[18] efficacy and safety results are expected to be similar to those seen in patients without familial hypercholesterolemia.[16,17,20]

Therapeutic monoclonal antibodies such as evolocumab demonstrate non-linear pharmacokinetics. Dosing evolocumab at QM intervals compared with Q2W can provide similar time-averaged reductions in PCSK9. In assessing PCSK9 suppression for this study, the evolocumab 140 mg Q2W group demonstrated mean (SE) unbound PCSK9 reductions of 83.2% (2.2) at week 2, 77.8% (2.7) at week 10, and 77.0% (3.0) at week 12 (2 weeks after the last dose of evolocumab 140 mg Q2W). In the evolocumab 420 mg QM group, mean reductions of unbound PCSK9 from baseline were 98.8% (0.3) at week 2, 94.2% (2.5) at week 10, and 50.6% (4.4) by week 12 (4 weeks after the last dose of 420 mg evolocumab QM).

Statistically significant improvements ($P < 0.05$) were also seen in all evolocumab treatment groups for total cholesterol (TC), triglycerides, very low-density lipoprotein cholesterol (VLDL-C), non-HDL cholesterol (non-HDL-C), apolipopro-