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 –

Atsushi Hirayama; Narimon Honarpour; Masayuki Yoshida; Shizuya Yamashita; Fannie Huang; Scott M. Wasserman; Tamio Teramoto

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 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.3–14 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...
against PCSK9 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, and combination therapy with statins resulted in reductions of up to 66% vs. placebo. Studies in patients with familial hypercholesterolemia and statin intolerance have shown similar efficacy. YUKAWA (Study of LDL-Cholesterol Reduction Using a Monoclonal PCSK9 Antibody in Japanese Patients With Advanced 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). 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 Populationa

| Demographics | Placebo | Evolocumab | All patients |
|--------------|---------|------------|-------------|
| Q2W (n=52)   | QM (n=50) | Total (n=102) | 70 mg Q2W (n=49) | Q2W (n=52) | QM (n=51) | Total (n=103) |
| 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 (%) | 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) |
| CAD          | 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) |
| PAD or CVD   | 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) |
| T2DM         | 40 (76.9) | 36 (72.0) | 76 (74.5) | 40 (81.6) | 34 (65.4) | 35 (66.8) | 41 (77.4) | 150 (73.2) | 226 (73.6) |
| Hypertension | 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) |
| Elevated WCb | 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 syndromei | 17 (32.7) | 12 (24.0) | 29 (28.4) | 13 (26.5) | 11 (21.6) | 16 (30.2) | 11 (21.6) | 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) | 150 (55.4) |
| High-intensity statin use | 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) |

All percentages based on n. aStudy population includes all randomized patients who received ≥1 dose of investigational product. bElevated waist circumference (WC) defined as ≥85 cm for men, ≥90 cm for women. cJAS 2012 criteria. dDaily simvastatin 80 mg, atorvastatin ≥40 mg, rosuvastatin ≥20 mg, or any statin plus ezetimibe. eDaily 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. fMedian (Q1, Q3).

Table of Demographics and Baseline Characteristics of the Study Populationa

| Baseline lipids (mean [SD]) | Placebo | Evolocumab | All patients |
|----------------------------|---------|------------|-------------|
| UC LDL-C, mmol/L          | 3.7 (0.5) | 3.7 (0.6) | 3.7 (0.5) |
| Calculated LDL-C, mmol/L  | 3.7 (0.5) | 3.6 (0.6) | 3.7 (0.5) |
| Lp(a), mmol/L             | 17.5 (65.5) | 10.3 (66.0) | 16.0 (66.0) |
| TC, mmol/L                | 5.8 (0.6) | 5.8 (0.6) | 5.8 (0.6) |
| HDL-C, mmol/L             | 1.4 (0.3) | 1.4 (0.3) | 1.4 (0.3) |
| TG, mmol/L                | 1.6 (0.6) | 1.6 (0.6) | 1.6 (0.6) |
| VLDL-C, mmol/L            | 0.7 | 0.7 | 0.6 |
| Non-HDL-C, mmol/L         | 4.4 (0.6) | 4.4 (0.7) | 4.4 (0.6) |
| ApoB, g/L                 | 1.2 | 0.9 | 1.0 |
| ApoA1, g/L                | 1.6 | 0.6 | 1.4 |
| TC:HDL-C                  | 4.4 | 4.3 | 4.3 |
| ApoB:ApoA                 | 0.8 | 0.8 | 0.8 |
| PCSK9, ng/ml              | 389.4 | 411.3 | 400.1 |

Results

Patient disposition is summarized in Figure 1. Of the 452

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.
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 (2.7)% in all placebo patients (total), −68.6 (3.0)% 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

Table 2. Efficacy at 12 Weeks

|                         | Evolocumab Q2W | Placebo Q2W | Evolocumab QM | Placebo QM |
|-------------------------|----------------|-------------|---------------|------------|
| **LDL-C**               | 70 mg (n=49)  | 140 mg (n=52) | 280 mg (n=51) | 420 mg (n=53) |
| Mean (SE) percentage change vs. placebo | −52.9 (3.0); <0.001 | −68.6 (3.0); <0.001 | N/A | −58.2 (3.2); <0.001 |
| Change in UC LDL-C vs. placebo (mmol/L; SE); P value | −2.0 (0.1); <0.001 | −2.5 (0.1); <0.001 | NA | −2.1 (0.1); <0.001 |
| Achieved LDL-C (mmol/L; mean [SD]) | 1.5 (0.8) | 0.9 (0.5) | 3.6 (0.5) | 1.5 (0.5) |
| LDL-C <2.6 mmol/L at week 12 (n [%]) | 44 (94) | 49 (98) | 2 (4) | 48 (94) |
| LDL-C <1.8 mmol/L at week 12 (n [%]; P value) | 31 (66); <0.001 | 48 (96); <0.001 | 0 (–) | 41 (80); <0.001 |

Other lipid parameters

|                         | Evolocumab Q2W | Placebo Q2W | Evolocumab QM | Placebo QM |
|-------------------------|----------------|-------------|---------------|------------|
| Lp(a), mean (SE) % change vs. placebo; P value | −41.5 (4.9); <0.001 | −50.6 (4.9); <0.001 | NA | −39.6 (4.9); <0.001 |
| ApoB:ApoA1, mean (SD), g/L | 0.4 (0.2) | 0.2 (0.1) | 0.7 (0.2) | 0.4 (0.1) |
| TC:HDL-C, mean (SE) % change vs. placebo; P value | −36.2 (2.2); <0.001 | −45.3 (2.1); <0.001 | NA | −36.3 (2.3); <0.001 |
| HDL-C, mean (SE) % change vs. placebo; P value | 4.4 (3.2); 0.17 | 9.1 (3.1); 0.04 | NA | 16.3 (3.1); <0.001 |
| HDL-D, mean (SD), mmol/L | 1.6 (0.4) | 1.6 (0.4) | 1.5 (0.4) | 1.6 (0.4) |
| TG, mean (SE) percentage change vs. placebo; P value | −14.3 (6.3); 0.025 | −16.6 (6.2); 0.009 | NA | −17.1 (6.5); 0.009 |
| Lp(a), mean (SD), nmol/L | 30.8 (42.5) | 30.9 (42.3) | 53.4 (58.5) | 29.4 (41.9) |
| ApoB, mean (SE) % change vs. placebo; P value | −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 |
| Non-HDL-C, mean (SE) % change vs. placebo; P value | −49.5 (–46.4, –1.8); 0.001 | −52.2 (–47.8, –2.4); 0.001 | NA | −58.1 (–54.3, –2.8); 0.001 |
| ApoA1, mean (SE) % change vs. placebo; P value | −40.2 (–36.3, –0.1); 0.001 | −53.4 (–49.5, –0.6); 0.001 | NA | −58.1 (–54.3, –2.8); 0.001 |
| ApoB:ApoA1, mean (SE) % change vs. placebo; P value | −40.2 (–36.3, –0.1); 0.001 | −53.4 (–49.5, –0.6); 0.001 | NA | −58.1 (–54.3, –2.8); 0.001 |

*For least-squares mean percentage change from baseline in lipid parameters for each treatment group, see Supplementary File 1. Least-squares mean difference within each dose frequency vs. matching placebo. Calculated LDL-C. Percentage calculated from n at week 12. NA, not applicable; SE, standard error. Other abbreviations as in Table 1.*
Figure 2. Mean percentage change in LDL-C measured by ultracentrifugation in the main subgroups given evolocumab either 140 mg SC Q2 W (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.
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, efficacy and safety results are expected to be similar to those seen in patients without familial hypercholesterolemia.\textsuperscript{16,17,20}

Therapeutic monoclonal antibodies such as evolocumab demonstrate non-linear pharmacokinetics. Dosing evolocumab at QM intervals compared with Q2 W can provide similar time-averaged reductions in PCSK9. In assessing PCSK9 suppression for this study, the evolocumab 140 mg Q2 W 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 Q2 W). 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-

![Figure 3](image_url)

**Figure 3.** Mean percentage change in calculated LDL-C concentration from baseline by visit Q2 W (A) or QM (B). Error bars indicate standard error (SE). Results are based on observed data. LDL-C, low-density lipoprotein cholesterol; Q2 W, every 2 weeks; QM, monthly.
Evolocumab in Statin-Treated Japanese Patients

protein B (ApoB), lipoprotein a (Lp[a]), the ApoB:ApoA1 ratio, and the TC:HDL-C ratio, and in all but the evolocumab 70mg Q2W group for HDL-C and ApoA1 at week 12 (Table 2, Table S2). Favorable changes were also seen in other lipids for the mean of weeks 10 and 12 (Table S3).

The majority (94% to 98%) of patients in the evolocumab treatment groups achieved the most stringent JAS-recommended LDL-C goal of <2.6 mmol/L at week 12. Goal achievement was highest in the 140 mg Q2W and 420 mg QM groups (98% and 96%, respectively, vs. 3% placebo; Figure 4A). The majority of evolocumab-treated patients also achieved LDL-C levels <1.8 mmol/L (Figure 4B).

Although more AEs were reported in evolocumab-treated (51%) vs. placebo-treated (38%) patients (Table 3), most were Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 (mild or moderate), and no imbalances in AEs were observed with respect to dose or dose frequency. Nasopharyngitis was the most frequent AE; 4 (2%) patients in the evolocumab treatment group reported serious AEs (Table 3), none of which was considered related to the study drug. These AEs were carcinoid tumor of the cecum with a pre-randomization history of anal bleeding (drug was withdrawn); fracture of left clavicle, ribs, and ankle (dose was altered or withheld); prostate cancer (dose was unchanged); and worsening of arteriosclerosis (dose was unchanged). In total, 4 evolocumab-treated patients discontinued treatment because of any AE.
Results from YUKAWA suggest that evolocumab dosed Q2 W or QM yields significant reductions in LDL-C and other lipids (Table 2). Concomitant with global evolocumab phase 2 results,16–18,20 the greatest and most sustained LDL-C reductions were seen in the highest dose groups (140 mg Q2 W and 420 mg QM; Table 2, Table S2). As mentioned before, time-averaged reductions in LDL-C can be estimated using the mean of weeks 10 and 12. When comparing the mean reduction at weeks 10 and 12 between the 140 mg Q2 W and 420 mg QM groups, results were also similar (Table S3). Favorable changes were seen in additional lipid parameters at both week 12 and the mean of weeks 10 and 12, with the 140 mg Q2 W and 420 mg QM doses resulting in the greatest changes. Most (94–98%) of the YUKAWA patients on evolocumab Q2 W or QM achieved the JAS-recommended lipid target of <2.6 mmol/L. In this study, the mean (SD) baseline LDL-C was 3.7 (0.5) mmol/L, with no patients having an LDL-C <2.6 mmol/L. At 12 weeks, up to 98% of patients receiving evolocumab achieved an LDL-C <2.6 mmol/L. (Figure 4). Because of the less potent and lower doses of statins used in Japan, fewer patients in YUKAWA were on high-intensity statin therapy compared with the LAPLACE-TIMI-57 or RUTHERFORD global phase 2 studies, in which evolocumab was administered with a background of statin therapy (Table 1). Compared with LAPLACE-TIMI 57, the prevalence of diabetes, hypertension, and smoking were higher in Japanese patients.24 Changes in LDL-C and other lipid parameters in the YUKAWA patients were comparable to those seen in the other evolocumab phase 2 studies at week 12.17,18 Additionally, reductions in LDL-C did not appear to be significantly affected by factors such as age, weight, baseline lipid concentrations, or
CV risk factors (Figure 2).

Although AEs were more frequent in patients receiving evolocumab vs. placebo, the majority were CTCAE grade 1 or 2 (mild or moderate), and showed no appreciable relationship to dose or dose frequency. Serious AEs were infrequent (2% evolocumab vs. 0% placebo), and none was considered to be treatment related. In addition, elevations in CK (0.5% evolocumab; 1.0% placebo) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT; 0.5% evolocumab, 0% placebo) were rare. As evolocumab is a monoclonal antibody, patients were actively monitored for hypersensitivity- and immunogenicity-related side effects, such as injection-site reactions and antidrug antibodies:26 4 patients in the evolocumab group reported potential injection-site reactions, and none of the evolocumab-treated patients was found to have antidrug antibodies (binding or neutralizing). One patient in the placebo group was reported to have a positive evolocumab-binding antibody titer at the week 12 visit. This finding likely reflects non-specific evolocumab-binding antibodies that were detected by a highly sensitive assay. This case was not associated with any reported AE or alteration in patient treatment.

Intracerebral hemorrhage and cognitive impairment have been reported as potential causes of concern in the context of lipid reduction with statins.26 27 A recent longer term study of evolocumab in approximately 1,100 subjects did not identify a difference in the incidence of either hemorrhagic stroke or cognitive impairment between the evolocumab (plus standard of care) arm vs. standard of care alone, irrespective of achieved LDL-C levels.28 Similarly, in YUKAWA, there were no reported cases of hemorrhagic stroke or cognitive impairment over the study period. Rates of other AEs, serious AEs, myalgia, and CK and AST/ALT elevations were comparable between patients who achieved low (<1.04 mmol/L) or very low (<0.65 mmol/L) LDL-C levels. These results suggest that evolocumab can be used effectively and safely to reduce LDL-C in Japanese patients. As YUKAWA was a 12-week study, the long-term safety of achieving low and very low LDL-C will be better understood once longer term data are available for Japanese patients.

Current guidelines for lipid management recommend targeting either specific LDL-C concentrations (<2.6 mmol/L) or <1.8 mmol/L),28 31 or a percentage reduction in LDL-C (≥50%) for high-risk patients.32 However, patients receiving statin therapy may not be able to achieve these goals,33 34 and patient risk for CVD could be lowered with additional LDL-C reduction using other therapies.30 31 33 In this study, the baseline LDL-C for high-risk patients was 3.7 mmol/L, despite stable use of background statin therapy. After 12 weeks of treatment with evolocumab, patients showed LDL-C reductions of up to 69%, and most (up to 96%) of the evolocumab-treated patients achieved LDL-C levels <1.8 mmol/L. Stable LDL-C reductions of the magnitude described here have not been seen with other classes of non-statin therapies.36 37

Close to half of high-risk Japanese patients are not at recommended LDL-C levels.11 12 Thus, long-term use of evolocumab is poised to become an important treatment option for patients at high cardiovascular risk and/or unable to achieve their lipid goal. The YUKAWA study results suggest that novel, antibody-based therapies such as evolocumab may be used effectively and safely to reduce LDL-C in Japanese patients. Results from a large, ongoing cardiovascular outcomes trial will help elucidate whether the additional LDL-C lowering seen with evolocumab is associated with a reduction in cardiovascular events.38

Conclusions

Evolocumab Q2 W or QM in combination with background statin therapy demonstrated robust efficacy and was well tolerated in a 12-week study in high-cardiovascular-risk Japanese patients with hypercholesterolemia. The greatest LDL-C reductions from baseline were observed with the 140 mg Q2 W and 420 mg QM dosages. These findings support the continued investigation of evolocumab treatment in Japanese patients in a similarly designed phase 3 study currently underway (NCT01953328).

Acknowledgments

Statistical programming support was provided by Wei Cui, MS, of Amgen Inc and Qingwen Zhao, MS, on behalf of Amgen Inc. Editorial support was provided by Annalise M. Nawrocki, PhD, of Amgen Inc.

Disclosures

This study was funded by Amgen, Inc.

Atsushi Hirayama received honoraria from Bayer Pharmaceutical Co, Astellas Pharma Inc, Daiichi-Sankyo Pharmaceutical Co, Sanofi K.K., Sanwa Drugaku Kenkyusho Co, Boehringer Ingelheim Japan, Kyowa Hakko Kirin Co Ltd, Takeda Pharmaceutical Co Ltd, Kowa Co Ltd, Kissei Pharmaceutical Co Ltd, MSD K.K., Shionogi Pharmaceutical Co, Eizai Co Ltd, Chugai Pharmaceutical Co, Pfizer Japan, Otsuka Pharmaceutical Co, Tanabe Mitsubishi Pharmaceutical Co, Novartis Pharma K.K., and Astra Zeneca Co and received research support to institution from Astellas Pharmaceuticals Co, Astra-Zeneca K.K., Eisai Co, Ltd. MSD, Otsuka Pharmaceutical Co Ltd, ONO Pharmaceutical Co Ltd, Kissei Pharmaceutical Co Ltd, Kyowa Hakko Kirin Co Ltd, Goodman Co Ltd, KOWA Pharmaceutical Co Ltd, Sanofi K.K., Shionogi & Co Ltd, Genzyme Japan K.K., Zeon Medical Inc, Daiichi Sankyo Co Ltd, Dainippon Sumitomo Pharma Co Ltd, Takeda Pharmaceutical Co Ltd, Mitsubishi Tanabe Pharma Corporation, Chugai Pharmaceutical Co Ltd, Toa Eiyu Ltd, Nippon Boehringer Ingelheim Co Ltd, Nihon Medi-Physics Co Ltd, Medtronic Japan Co Ltd, Novartis Pharma K.K., Pfizer Japan Inc, and Mochida Pharmaceutical Co Ltd. Shizuya Yamashita received honoraria from MSD, Bayer, and Kowa; served on advisory boards for Skylight Biotech, Kowa, Otsuka, and Amgen; received research support from MSD, Bayer, Astellas, Kowa, Shionogi, Otsuka Pharmaceutical Co, Kissei, and Boehringer. Tamio Teramoto received support from Astellas K.K., MSD K.K., Kowa K.K., Kissei K.K., Daiichi Sankyo K.K., Pfizer K.K., Bayer K.K., Otsuka K.K., and KOBAYASHI K.K., NARIMON HONAPOUR, FANNIE HUANG, and SCOTT M. WASSERMAN are employees of Amgen Inc and own Amgen stock/stock options. Masayuki Yoshida has no disclosures to report.

References

1. Global Atlas on Cardiovascular Disease Prevention and Control 2011. http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=21049&Itemid=(accessed 9 December, 2013).
2. Iso H. Lifestyle and cardiovascular disease in Japan. J Atheroscler Thrombol 2011; 18: 83 – 88.
3. Imano H, Noda H, Kitamura A, Sato S, Kiyama M, Sankai T, et al. Low-density lipoprotein cholesterol and risk of coronary heart disease among Japanese men and women: The Circulatory Risk in Communities Study (CIRCS). Prev Med 2011; 52: 381 – 386.
4. Saito I, Folsom AR, Aono H, Ozawa H, Ikbeke T, Yamashita T. Comparison of fatal coronary heart disease occurrence based on population surveys in Japan and the USA. Int J Epidemiol 2000; 29: 837 – 844.
5. Downs JR, Clearfield M, Tyrodel HA, Whitney EJ, Kruyer W, Langendorfer A, et al. Air Force/Texas Coronary Atherosclerosis Prevention study (AFCAPS/TEXCAPS): Additional perspectives on tolerability of long-term treatment with lovastatin. Am J Cardiol 2001; 87: 1074 – 1079.
6. Ridker PM, MacFadyen J, Fonseca F, Genest J, Gotto A, Kastelein J, et al. Number needed to treat with rosuvastatin to prevent first cardiovascular events and death among men and women with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: Justification for the use of statins in prevention: An intervention trial evaluating rosuvastatin (JUPITER). Circ Cardiovasc Qual Outcomes 2009; 2: 616 – 623.
7. Sever PS, Chang CL, Gupta AK, Whitehead C, Poulter NR, ASCOT Investigators. The Anglo-Scandinavian Cardiac Outcomes Trial: Circulation Journal Vol.78, May 2014
