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:[25] 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.[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),[29–31] 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,[33–35] 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 Q2W 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 Q2W 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).


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## Supplementary Files

**Supplementary File 1**

**Inclusion/Exclusion criteria**

**Supplementary File 2**

**Table S1.** Baseline lipid-lowering therapy

**Table S2.** Efficacy at 12 weeks

**Table S3.** Efficacy: mean of weeks 10 and 12

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-14-0130

ORIGINAL ARTICLE

# Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease

The STABILITY Investigators*


## ABSTRACT

### BACKGROUND

Elevated lipoprotein-associated phospholipase $A_2$ activity promotes the development of vulnerable atherosclerotic plaques, and elevated plasma levels of this enzyme are associated with an increased risk of coronary events. Darapladib is a selective oral inhibitor of lipoprotein-associated phospholipase $A_2$.

### METHODS

In a double-blind trial, we randomly assigned 15,828 patients with stable coronary heart disease to receive either once-daily darapladib (at a dose of 160 mg) or placebo. The primary end point was a composite of cardiovascular death, myocardial infarction, or stroke. Secondary end points included the components of the primary end point as well as major coronary events (death from coronary heart disease, myocardial infarction, or urgent coronary revascularization for myocardial ischemia) and total coronary events (death from coronary heart disease, myocardial infarction, hospitalization for unstable angina, or any coronary revascularization).

### RESULTS

During a median follow-up period of 3.7 years, the primary end point occurred in 769 of 7924 patients (9.7%) in the darapladib group and 819 of 7904 patients (10.4%) in the placebo group (hazard ratio in the darapladib group, 0.94; 95% confidence interval [CI], 0.85 to 1.03; P=0.20). There were also no significant between-group differences in the rates of the individual components of the primary end point or in all-cause mortality. Darapladib, as compared with placebo, reduced the rate of major coronary events (9.3% vs. 10.3%; hazard ratio, 0.90; 95% CI, 0.82 to 1.00; P=0.045) and total coronary events (14.6% vs. 16.1%; hazard ratio, 0.91; 95% CI, 0.84 to 0.98; P=0.02).

### CONCLUSIONS

In patients with stable coronary heart disease, darapladib did not significantly reduce the risk of the primary composite end point of cardiovascular death, myocardial infarction, or stroke. (Funded by GlaxoSmithKline; STABILITY ClinicalTrials.gov number, NCT00799903.)


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*The investigators in the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) trial are listed in the Supplementary Appendix, available at NEJM.org.

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Atherosclerotic lesions in humans — in particular, vulnerable[1] and ruptured plaques — are characterized by inflammatory activity and a high expression of lipoprotein-associated phospholipase $A_2$.[2,3] In atherosclerotic plaques, lipoprotein-associated phospholipase $A_2$ increases the production of proinflammatory and proapoptotic mediators.[4-8] In a meta-analysis of individual records from 79,036 participants in 32 prospective studies, there was a continuous association between lipoprotein-associated phospholipase $A_2$ activity and the risk of coronary heart disease, with a relative increase in risk of 1.10 (95% confidence interval [CI], 1.05 to 1.16) for each 1-SD increase in lipoprotein-associated phospholipase $A_2$ activity, after adjustment for conventional risk factors.[9]

Darapladib is a potent and reversible oral inhibitor of lipoprotein-associated phospholipase $A_2$.[10] In a swine model of atherosclerosis, darapladib reduced levels of lipoprotein-associated phospholipase $A_2$ in plaque, reduced the necrotic core area, and inhibited the development of lesions in coronary arteries.[11] Darapladib has also been shown to reduce lipoprotein-associated phospholipase $A_2$ activity in human carotid plaque.[12] In the Integrated Biomarker and Imaging Study 2 (IBIS-2) involving patients with coronary heart disease, darapladib, as compared with placebo, halted the progression in the volume of the necrotic core of coronary-artery plaques (a secondary end point), as determined by intravascular ultrasonographic virtual histologic analysis during a 12-month period.[13] These findings suggest that darapladib could reduce the risk of events associated with coronary heart disease by altering the composition of atherosclerotic plaques to a less vulnerable state.[1] In the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy (STABILITY) trial, we evaluated the clinical efficacy and safety of darapladib in patients with chronic coronary heart disease.

## METHODS

### STUDY DESIGN AND OVERSIGHT

The study design has been described previously.[14] The trial was sponsored by GlaxoSmithKline. The executive and steering committees designed the study and supervised its conduct. (A complete list of committee members is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) In each country, the study was approved by national regulatory authorities and by local ethics committees or institutional review boards, according to local regulations.

Data were collected and managed by GlaxoSmithKline. Unblinded interim analyses of the ongoing trial, including four efficacy analyses (two prespecified and two unplanned) and semiannual safety analyses, were conducted at the University of Wisconsin–Madison and reviewed by an independent data and safety monitoring committee. The final analyses of trial data were performed by GlaxoSmithKline. Final statistical analyses of key efficacy and safety measures, including those presented in this article, were independently verified by the Duke Clinical Research Institute.

The first draft of the manuscript was written by the first author. The executive and steering committees contributed to subsequent drafts of the manuscript and approved the submission of the final manuscript for publication. The study's cochairs had full access to all data, verified their accuracy, and vouch for the fidelity of the study to the protocol, available at NEJM.org.

### STUDY POPULATION

Patients were eligible to participate in the study if they had coronary heart disease, as documented by at least one of the following: previous myocardial infarction, previous percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG), or multivessel coronary artery disease. In addition, at least one of the following additional predictors of cardiovascular risk was required: an age of 60 years or older, diabetes requiring pharmacotherapy, a high-density lipoprotein (HDL) cholesterol level of less than 40 mg per deciliter (1.03 mmol per liter), status as a smoker of five or more cigarettes per day at study entry or within 3 months before screening, moderate renal dysfunction, or polyvascular arterial disease. Exclusion criteria were planned PCI or CABG or another major surgical procedure, current liver disease, severe renal impairment, a history of nephrectomy or kidney transplantation, current New York Heart Association class III or IV heart failure, or severe asthma that was poorly controlled with standard medical therapy. Details of the inclusion and exclusion criteria are provided in the Supplementary Appendix. All patients provided written informed consent.

### STUDY PROCEDURES AND FOLLOW-UP

After baseline assessments were performed, patients were randomly assigned, with the use of an interactive voice-response system, to receive either a once-daily oral dose of darapladib (160 mg) or matching placebo to be taken with food and swallowed whole. The assigned dose of darapladib was expected to lower plasma levels of lipoprotein-associated phospholipase $A_2$ by approximately 60%.[13]

Patients were instructed to return for clinic visits 1, 3, and 6 months after randomization and thereafter every 6 months for the duration of the study. In addition, patients were followed up by telephone beginning at 9 months and then every 6 months thereafter until the end of the study.

Investigators were strongly encouraged to treat patients according to international guidelines for secondary prevention of coronary heart disease. All patients were to receive long-term treatment with platelet-inhibitor therapy and statin therapy unless such therapy was not indicated according to guidelines, was contraindicated, or resulted in unacceptable side effects. Metrics of standard of care were monitored by the study leaders and provided to all investigators every 6 months, which allowed the investigators to compare the standard of care at their sites with national and international standards at other sites participating in this study. In addition, the importance of adherence to standard-of-care medications was reinforced over the duration of the trial and at periodic meetings with investigators.

Patients were instructed to continue taking the study drug until the day before their end-of-treatment visit. Patients who permanently discontinued a study drug before the end of the study were contacted by telephone for an assessment of clinical outcomes. At the end of the study, all patients were asked to return to the clinic within a 3-month period for their final study visit. Final survival status was sought for patients who were lost to follow-up or withdrew consent.

### STUDY END POINTS

The primary end point was a composite of cardiovascular death, myocardial infarction, or stroke. Secondary end points included major coronary events (a composite of death from coronary heart disease, myocardial infarction, or urgent coronary revascularization for myocardial ischemia); total coronary events (a composite of death from coronary heart disease, myocardial infarction, hospitalization for unstable angina, or any coronary revascularization procedure); the individual components of the primary end point; a composite of all-cause mortality, myocardial infarction, or stroke; and all-cause mortality. Definitions of the primary and secondary end points are provided in the Supplementary Appendix.

### LABORATORY TESTING

All laboratory tests were performed at central laboratories (Quest Diagnostics Clinical Laboratories). The estimated glomerular filtration rate (GFR) was calculated with the use of the Modification of Diet in Renal Disease method.[15]

### SAFETY MONITORING AND ADJUDICATION

Investigators were responsible for detecting, documenting, and reporting adverse events and serious adverse events. Information on adverse events was collected from the time the randomized regimens were started until 35 days after the last dose of a study drug was taken or at the next follow-up visit, whichever occurred later. Serious adverse events that were assessed as being related to a study drug or related to study participation were recorded up to and including any follow-up contact. The occurrence of cancers and of gastrointestinal polyps or neoplasms was recorded until the end of the study, including during the period after discontinuation of the study drug, since 2-year carcinogenicity studies in rodents had suggested that darapladib was associated with the development of jejunal adenomas or adenocarcinomas in male mice and rats. Other adverse events of special interest included asthma, anaphylaxis, diarrhea, and odor-related events, because in previous studies,[13] darapladib had been associated with an unpleasant odor of skin, urine, or feces.

Suspected primary and secondary end points were evaluated by an independent clinical-events committee whose members were unaware of the study-group assignments. Gastrointestinal neoplasms and cancers were adjudicated by a separate committee in a blinded fashion.

### STATISTICAL ANALYSIS

We anticipated an annual event rate for the primary end point of 4% in the placebo group. We then estimated that 1500 events would be required for the study to have a power of 90% to

detect a relative-risk reduction of 15.5% in the rate of the primary end point in the darapladib group, as compared with the placebo group.

All patients who underwent randomization were included in the intention-to-treat analyses. Time-to-event analyses were performed with the use of Kaplan–Meier estimates for the primary and secondary end points. Hazard ratios and 95% confidence intervals were estimated with the use of Cox proportional-hazards models. The effect of treatment on the primary end point was estimated with the use of hazard ratios and adjusted 95.1% confidence intervals, with a two-sided P value of 0.049 indicating statistical significance after adjustment for the four interim analyses conducted by the data and safety monitoring committee. For secondary and other end points, no adjustments were made for multiple testing. Nominal significance refers to an unadjusted P value of less than 0.05 in which the type I error was not controlled at the 5% level.

The consistency of effects on efficacy end points was prespecified to be explored in 35 subgroups, without adjustment for multiple comparisons. The analyses of safety data focused on adverse events, laboratory data, and vital signs and included all patients who received at least one dose of a study drug. Baseline and on-treatment lipoprotein-associated phospholipase $A_2$ levels are not yet available and thus are not reported here.

## RESULTS

### STUDY PATIENTS

From December 2008 through April 2010, we enrolled 15,828 patients at 663 centers in 39 countries (Fig. 1). A total of 7924 patients were randomly assigned to the darapladib group, and 7904 were assigned to the placebo group. The median age of the patients was 65 years; 81% were men, 78% were white, 20% were current or recent smokers, and 34% had diabetes mellitus requiring pharmacotherapy (Table 1, and Table S1 in the Supplementary Appendix). The median low-density lipoprotein (LDL) cholesterol level at baseline was 79.9 mg per deciliter (2.07 mmol per liter).

### FOLLOW-UP, ADHERENCE, AND BACKGROUND THERAPY

The median duration of follow-up for the primary end point was 3.7 years (interquartile range, 3.5 to 3.8). The median duration of study-drug exposure was 3.5 years in the darapladib group and 3.6 years in the placebo group. We were able to ascertain vital status for 99.3% of the patients (15,722 of 15,828) and for 99.6% of the total possible follow-up time. For the analysis of the primary end point, complete follow-up was obtained in 96.5% of patients and for 97.7% of total follow-up time (Fig. S1 in the Supplementary Appendix). The percentage of patients with at least 80% adherence to treatment, as determined on the basis of pill counts, was 89.3% in the darapladib group and 91.3% in the placebo group.

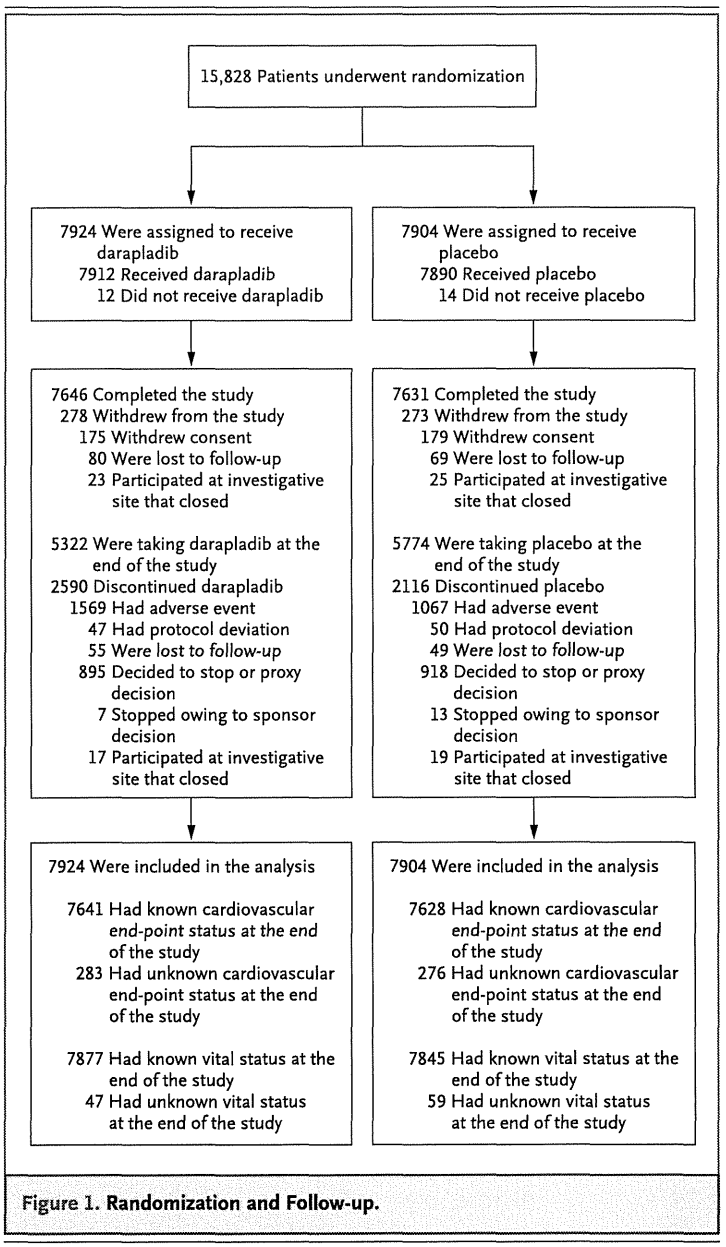


**Figure 1. Randomization and Follow-up.**

**Table 1. Characteristics of the Patients at Baseline.***

| Characteristic | Placebo (N=7904) | Darapladib (N=7924) |
|---|---|---|
| Age | | |
| Median (IQR) — yr | 65.0 (59.0–71.0) | 65.0 (59.0–71.0) |
| <65 yr — no. (%) | 3893 (49.3) | 3808 (48.1) |
| 65–74 yr — no. (%) | 2938 (37.2) | 3022 (38.1) |
| ≥75 yr — no. (%) | 1073 (13.6) | 1094 (13.8) |
| Female sex — no. (%) | 1506 (19.1) | 1461 (18.4) |
| Race or ethnic group — no. (%)† | | |
| White | 6174 (78.1) | 6232 (78.6) |
| Black | 191 (2.4) | 175 (2.2) |
| Central, South, or Southeast Asian | 598 (7.6) | 592 (7.5) |
| East Asian or Japanese | 766 (9.7) | 758 (9.6) |
| Other | 175 (2.2) | 167 (2.1) |
| Region of enrollment — no. (%) | | |
| North America | | |
| All | 2016 (25.5) | 2007 (25.3) |
| United States | 1555 (19.7) | 1547 (19.5) |
| South America | 597 (7.6) | 602 (7.6) |
| Western Europe | 1980 (25.1) | 2006 (25.3) |
| Eastern Europe | 1764 (22.3) | 1767 (22.3) |
| Asia or Pacific Rim | 1547 (19.6) | 1542 (19.5) |
| Cardiovascular risk factors | | |
| Diabetes requiring pharmacotherapy — no. (%) | 2687 (34.0) | 2664 (33.6) |
| High-density lipoprotein cholesterol | | |
| Median (IQR) — mg/dl | 44.4 (38.6–52.9) | 44.8 (38.6–53.7) |
| <40 mg/dl — no. (%) | 2786 (35.2) | 2646 (33.4) |
| Smoker — no. (%)‡ | 1656 (21.0) | 1572 (19.8) |
| Renal dysfunction — no. (%)§ | 2374 (30.0) | 2410 (30.4) |
| Polyvascular disease — no. (%) | 1187 (15.0) | 1185 (15.0) |
| Qualifying diagnosis of coronary heart disease — no. (%) | | |
| Previous myocardial infarction | 4642 (58.7) | 4681 (59.1) |
| Previous coronary revascularization | 5911 (74.8) | 5952 (75.1) |
| Percutaneous coronary intervention | 3978 (50.3) | 3987 (50.3) |
| Coronary-artery bypass grafting | 2592 (32.8) | 2644 (33.4) |
| Multivessel disease | 1191 (15.1) | 1199 (15.1) |

* There was no significant difference between the two groups, except among patients who had a high-density lipoprotein cholesterol level of less than 40 mg per deciliter (P=0.01). Percentages may not total 100 because of rounding. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. IQR denotes interquartile range.

† Race or ethnic group was self-reported.

‡ Smokers included both current smokers of five or more cigarettes per day and those who were smokers within 3 months before screening.

§ Renal dysfunction was defined as an estimated glomerular filtration rate of 30 to 59 ml per minute per 1.73 $m^2$ of body-surface area (moderate kidney disease) or a urine albumin-to-creatinine ratio of 30 or more (as measured in milligrams of albumin and grams of creatinine).

The use of guideline-recommended treatments for secondary prevention was high. At trial close-out, 90% of the patients were taking aspirin, 96% statins, 79% beta-blockers, 54% angiotensin-converting–enzyme inhibitors, and 26% angiotensin II–receptor blockers. The median LDL cholesterol level at the end of the study was 78.0 mg per deciliter (2.02 mmol per liter) in the darap-

ladib group and 78.8 mg per deciliter (2.04 mmol per liter) in the placebo group. The mean blood pressure at the end of the study was 132/77 mm Hg in the darapladib group and 131/77 mm Hg in the placebo group.

### EFFICACY OUTCOMES

#### *Primary End Point*

The primary end point occurred in 769 of 7924 patients (9.7%) in the darapladib group and in 819 of 7904 patients (10.4%) in the placebo group (hazard ratio in the darapladib group, 0.94; 95% CI, 0.85 to 1.03; P=0.20) (Table 2 and Fig. 2). There were no significant effects of darapladib on any of the components of the primary end point (cardiovascular death, myocardial infarction, or stroke) or on all-cause mortality. The hazard ratio for the effect of darapladib on myocardial infarction was 0.89 (95% CI, 0.77 to 1.03; P=0.11). The effects on different types of myocardial infarction are shown in the Table S2 in the Supplementary Appendix.

The treatment effect with respect to the primary end point was consistent in almost all prespecified subgroups. The only interactions below the P=0.10 level were among smokers (P=0.04

**Table 2. Primary and Secondary Efficacy End Points.***

| End Point | Placebo (N=7904) | | Darapladib (N=7924) | | Hazard Ratio (95% CI)† | P Value |
|---|---|---|---|---|---|---|
| | Patients with Events | Event Rate | Patients with Events | Event Rate | | |
| | *no. (%)* | *no. of events/ 100 person-yr* | *no. (%)* | *no. of events/ 100 person-yr* | | |
| Primary end point | 819 (10.4) | 3.04 | 769 (9.7) | 2.85 | 0.94 (0.85–1.03) | 0.20 |
| Cardiovascular death | 315 (4.0) | 1.13 | 308 (3.9) | 1.11 | | |
| Nonfatal myocardial infarction | 369 (4.7) | 1.36 | 329 (4.2) | 1.21 | | |
| Nonfatal stroke | 135 (1.7) | 0.49 | 132 (1.7) | 0.48 | | |
| Secondary end point | | | | | | |
| Major coronary event | 814 (10.3) | 3.03 | 737 (9.3) | 2.74 | 0.90 (0.82–1.00) | 0.045 |
| Death from coronary heart disease | 303 (3.8) | 1.09 | 284 (3.6) | 1.02 | | |
| Nonfatal myocardial infarction | 368 (4.7) | 1.36 | 325 (4.1) | 1.20 | | |
| Urgent coronary revascularization for myocardial ischemia | 143 (1.8) | 0.52 | 128 (1.6) | 0.46 | | |
| Total coronary events | 1269 (16.1) | 4.90 | 1159 (14.6) | 4.45 | 0.91 (0.84–0.98) | 0.02 |
| Death from coronary heart disease | 293 (3.7) | 1.06 | 270 (3.4) | 0.97 | | |
| Nonfatal myocardial infarction | 320 (4.0) | 1.18 | 281 (3.5) | 1.03 | | |
| Hospitalization for unstable angina | 145 (1.8) | 0.53 | 129 (1.6) | 0.47 | | |
| Any coronary revascularization procedure | 511 (6.5) | 1.91 | 479 (6.0) | 1.78 | | |
| Cardiovascular death | 373 (4.7) | 1.34 | 359 (4.5) | 1.29 | 0.96 (0.83–1.11) | 0.59 |
| Myocardial infarction | 405 (5.1) | 1.49 | 361 (4.6) | 1.33 | 0.89 (0.77–1.03) | 0.11 |
| Stroke | 152 (1.9) | 0.55 | 154 (1.9) | 0.56 | 1.01 (0.81–1.27) | 0.92 |
| All-cause mortality, nonfatal myocardial infarction, or nonfatal stroke | 962 (12.2) | 3.57 | 926 (11.7) | 3.43 | 0.96 (0.88–1.05) | 0.40 |
| All-cause mortality | 458 (5.8) | 1.65 | 465 (5.9) | 1.67 | | |
| Nonfatal myocardial infarction | 369 (4.7) | 1.36 | 329 (4.2) | 1.21 | | |
| Nonfatal stroke | 135 (1.7) | 0.49 | 132 (1.7) | 0.48 | | |
| Total all-cause mortality | 577 (7.3) | 2.00 | 582 (7.3) | 2.02 | 1.01 (0.90–1.13) | 0.87 |

* The components of each of the composite end points have been summarized as mutually exclusive components without hazard ratios, confidence intervals, or P values. A mutually exclusive component is the first occurrence of any event in the composite. All other categories represent time-to-event end points and are specified as primary or secondary end points in the protocol.

† Hazard ratios are for the darapladib group, as compared with the placebo group.

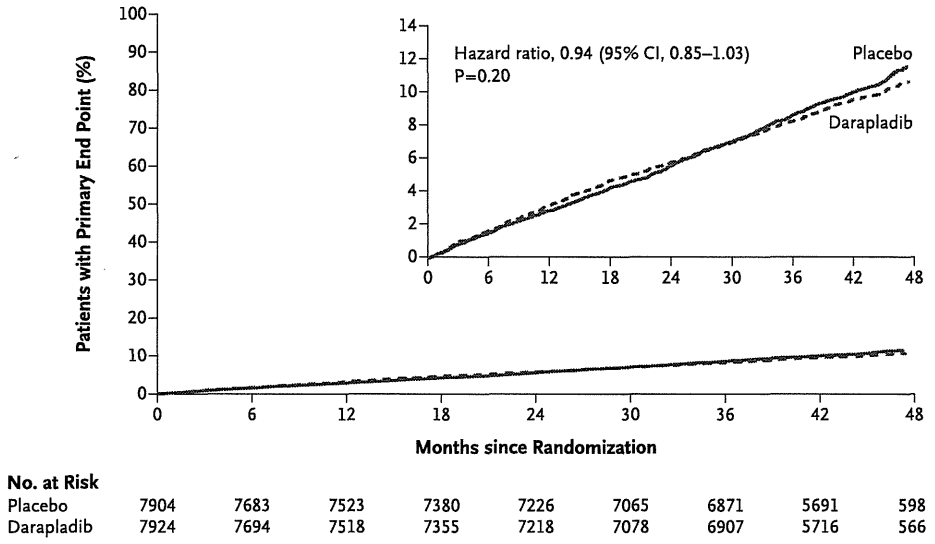


**Figure 2. Kaplan–Meier Curves for the Primary End Point of Death from Cardiovascular Causes, Myocardial Infarction, or Stroke.**

The inset shows the same data on an enlarged y axis.

for interaction) and white patients (P=0.08 for interaction) (Fig. S2 in the Supplementary Appendix).

*Secondary End Points*

Among patients receiving darapladib, there was a nominally significant reduction in the first prespecified secondary end point of a composite of major coronary events, which occurred in 737 patients (9.3%) in the darapladib group and in 814 patients (10.3%) in the placebo group (hazard ratio, 0.90; 95% CI, 0.82 to 1.00; P=0.045) (Table 2, and Fig. S3 in the Supplementary Appendix). Similar effects were observed for the composite of total coronary events (hazard ratio, 0.91; 95% CI, 0.84 to 0.98; P=0.02).

### ADVERSE EVENTS

More patients in the darapladib group than in the placebo group discontinued the study drug (32.7% vs. 26.8%; hazard ratio, 1.29; 95% CI, 1.22 to 1.37) (Fig. S4 in the Supplementary Appendix). Any adverse event leading to discontinuation of a study drug occurred in 19.8% of the patients in the darapladib group and in 13.5% of those in the placebo group (hazard ratio, 1.55; 95% CI, 1.43 to 1.67) (Table 3). More patients in the darapladib group than in the placebo group discontinued the study drug because of diarrhea (3.2% vs. 0.8%), feces odor (2.2% vs. 0.1%), urine odor (1.4% vs. <0.1%), and skin odor (2.2% vs. 0.1%).

There were more serious adverse events of renal failure in the darapladib group than in the placebo group (1.5% vs. 1.1%; hazard ratio, 1.35; 95% CI, 1.03 to 1.78). At 3 months, the mean estimated GFR was lower by 2 ml per minute per 1.73 $m^2$ of body-surface area in the darapladib group than in the placebo group, with a similar between-group difference observed during the entire treatment period. There was no significant between-group difference in the subgroup of 2650 patients in whom the estimated GFR was measured approximately 1 month after the end of treatment, with a change from baseline in the estimated GFR in the darapladib group, as compared with the placebo group, of −0.12 ml per minute per 1.73 $m^2$ (95% CI, −1.35 to 1.12; P=0.85). No significant between-group difference in the number of overall cancers or gastrointestinal cancers was observed.

## DISCUSSION

In this large, multicenter, randomized trial involving patients with stable chronic coronary heart

disease who were followed for a median of 3.7 years, darapladib did not significantly reduce the incidence of the primary end point of cardiovascular death, myocardial infarction, or stroke. There were no significant reductions in the incidence of the components of the primary end point, as assessed individually, or in the rate of all-cause mortality. There was a nominally significant reduction in the secondary end points of major and total coronary events, which is a signal of possible efficacy. The lack of effect of the administered dose of darapladib on the primary end point may relate to a smaller effect on vulnerable coronary plaque than was anticipated on the basis of previous studies.[12,13]

It is possible that the coronary risk among patients in our study may already have been minimized by concurrent therapy. The trial was designed to test the incremental effect of a new treatment administered in patients who were receiving a high level of standard of care for secondary prevention at baseline. Thus, more than a third of the patients had an LDL cholesterol level of less than 70 mg per deciliter (1.81 mmol per liter) at baseline, and revascularization had been performed in 75% of the patients before randomization. High rates of the use of evidence-based medications were maintained throughout the trial. These standards of care are consistently higher than those that were observed in patients with stable chronic coronary heart disease who were included in previous large international registries.[16-18] These factors probably reduced event rates in the two study groups and may have reduced the proportion of events that were modifiable.

Another consideration is that 96% of the patients at trial closeout were taking statins, which have been shown to reduce levels of lipoprotein-associated phospholipase $A_2$ by up to 35%.[19-21] In addition, in the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) study, among patients with stable chronic coronary heart disease, more than half the treatment effect of pravastatin in reducing rates of death from coronary heart disease or myocardial infarction was estimated to be due to an association with a reduction in levels of lipoprotein-associated phospholipase $A_2$.[22] Incremental benefits of inhibiting lipoprotein-associated phospholipase $A_2$ activity, if present, could be less in patients treated with statins.

**Table 3. Adverse Events.**

| Event | Placebo (N=7890) | Darapladib (N=7912) |
|---|---|---|
| | *no. of patients (%)* | |
| Any serious adverse event* | 3448 (43.7) | 3369 (42.6) |
| Any adverse event leading to study-drug discontinuation | 1067 (13.5) | 1569 (19.8) |
| Diarrhea | | |
| Any | 495 (6.3) | 965 (12.2) |
| Leading to study-drug discontinuation | 60 (0.8) | 254 (3.2) |
| Abnormal feces odor | | |
| Any | 63 (0.8) | 728 (9.2) |
| Leading to study-drug discontinuation | 5 (0.1) | 177 (2.2) |
| Abnormal skin odor | | |
| Any | 34 (0.4) | 383 (4.8) |
| Leading to study-drug discontinuation | 4 (0.1) | 174 (2.2) |
| Abnormal urine odor | | |
| Any | 81 (1.0) | 473 (6.0) |
| Leading to study-drug discontinuation | 1 (<0.1) | 113 (1.4) |
| Asthma | 64 (0.8) | 43 (0.5) |
| Renal failure† | 89 (1.1) | 120 (1.5) |
| Newly diagnosed cancer | | |
| Any | 529 (6.7) | 508 (6.4) |
| Adjudicated gastrointestinal | 105 (1.3) | 102 (1.3) |
| Liver events‡ | 52 (0.7) | 54 (0.7) |
| Anaphylaxis‡ | 7 (0.1) | 9 (0.1) |

* Serious adverse events include cardiovascular events. A complete list of adverse events according to system organ class is provided in Table S3 in the Supplementary Appendix.

† Patients listed in this category include all those with serious renal adverse events according to the *Medical Dictionary for Regulatory Activities* preferred terms of acute renal failure, renal failure, and chronic renal failure. The mean (±SD) change from baseline in the estimated glomerular filtration rate at the end of the treatment period was a reduction of 0.8±14.1 ml per minute per 1.73 $m^2$ among 7322 patients who were evaluated in the darapladib group and an increase of 1.7±14.4 ml per minute per 1.73 $m^2$ among 7498 patients who were evaluated in the placebo group, for a between-group difference (darapladib group minus placebo group) of −2.5 ml per minute per 1.73 $m^2$ (95% confidence interval, −3.0 to −2.1).

‡ All the patients included in this category met the criteria for discontinuing the study on the basis of these events, as specified in the protocol.

There was a nominally significant reduction of approximately 10% in the rate of the prespecified secondary composite end points of major and total coronary events. The effects on these end points were consistent across the components of these composite end points, including death from coronary heart disease, myocardial infarction, coronary revascularization,

and hospitalization for unstable angina, and it is possible that the inhibition of lipoprotein-associated phospholipase $A_2$ may reduce these measures of coronary disease risk. However, these findings should be considered exploratory and of uncertain importance in light of the lack of effect on the primary end point.

In accordance with previous findings, there was an increase in the rate of diarrhea among patients receiving darapladib, as compared with those receiving placebo, along with increases in the rates of odor (in skin, feces, and urine), an effect that is thought to be related to the sulfhydryl group in the darapladib molecule. Because of the occurrence of these events, there were more study-drug discontinuations in the darapladib group than in the placebo group, with most discontinuations occurring during the first year. The mechanisms and clinical significance of the changes in renal laboratory measures and of the renal serious adverse events are uncertain.

In conclusion, we evaluated a novel mechanism for reducing plaque vulnerability by inhibition of lipoprotein-associated phospholipase $A_2$ with darapladib in patients with stable coronary heart disease who were receiving guideline-based background medical therapy. Darapladib did not significantly reduce the rate of the primary end point of cardiovascular death, myocardial infarction, or stroke.

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## APPENDIX

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# Efficacy, Safety, Tolerability, and Pharmacokinetic Profile of *Evacetrapib* Administered as Monotherapy or in Combination With *Atorvastatin* in Japanese Patients With Dyslipidemia☆

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**The cholesteryl ester transfer protein (CETP) inhibitor evacetrapib has been previously shown to increase high-density lipoprotein cholesterol (HDL-C) and decrease low-density lipoprotein cholesterol (LDL-C) levels, as monotherapy or in combination with statins. In this study, 165 Japanese patients with elevated LDL-C or low HDL-C levels were randomly assigned to receive placebo, evacetrapib monotherapy 30 mg, 100 mg, or 500 mg, atorvastatin 10 mg, or evacetrapib 100 mg in combination with atorvastatin 10 mg. After 12 weeks, evacetrapib monotherapy increased HDL-C levels by 74%, 115%, and 136% and decreased LDL-C levels by 15%, 23%, and 22% and CETP activity by 50%, 83%, and 95% (for the 30-mg, 100-mg, and 500-mg dose groups, respectively) versus placebo. In combination with atorvastatin 10 mg, evacetrapib 100 mg increased HDL-C levels by 103% and decreased LDL-C levels by 15% and CETP activity by 68% versus atorvastatin alone. After a 4- to 6-week washout, HDL-C, LDL-C, and CETP mass and activity returned to baseline levels in the evacetrapib-treated groups, and most patients had evacetrapib concentrations below the quantitation limit. Evacetrapib monotherapy or in combination with atorvastatin was not likely to be associated with any significant change in blood pressure and did not have any adverse effects on mineralocorticoid or glucocorticoid measures. Notably, plasma evacetrapib concentrations were mostly undetectable, and all pharmacodynamic biomarkers (HDL-C and LDL-C levels and CETP mass and activity) returned to baseline after a 4- to 6-week washout. In conclusion, evacetrapib as monotherapy or in combination with atorvastatin effectively decreased CETP activity and LDL-C levels and increased HDL-C levels after 12 weeks in Japanese patients with dyslipidemia.** © 2014 The Authors. Published by Elsevier Inc. All rights reserved. **(Am J Cardiol 2014;113:2021–2029)**

Although pharmacologic inhibition of cholesteryl ester transfer protein (CETP) leads to substantial increase in high-density lipoprotein cholesterol (HDL-C) and significant decrease in low-density lipoprotein cholesterol (LDL-C) levels, torcetrapib resulted in an increased risk of cardiovascular (CV) morbidity and mortality, and dalcetrapib was not different from placebo in reducing CV events. Treatment with torcetrapib, but not with other CETP inhibitors, was also associated with significant increase in blood pressure (BP) and plasma sodium, bicarbonate, and aldosterone levels and decrease in potassium levels.[1] Moreover, recent data show that persistent effects on lipids and residual plasma levels of anacetrapib were observed 12 weeks after cessation of treatment with anacetrapib in the Determining the Efficacy and Tolerability of CETP Inhibition With Anacetrapib (DEFINE) trial,[2] and similar findings were also reported during a Japanese phase 2b study (8-week treatment with anacetrapib followed by an 8-week off-drug reversal period).[3] Evacetrapib has been shown to inhibit CETP activity both in human plasma and in a human CETP transgenic mouse model, without increases in aldosterone or BP.[4] In a phase 1 study conducted in healthy Japanese subjects, evacetrapib was well tolerated when administered for 14 days over the dose range of 30 to 600 mg and significantly increased HDL-C and decreased LDL-C levels.[5] In a 12-week phase 2 study conducted in the United States and Europe, evacetrapib raised HDL-C levels up to 129% and lowered LDL-C up to 36% in nearly 400 patients with dyslipidemia and was also well tolerated without showing any adverse effect on either BP or mineralocorticoid levels.[6] The present study evaluated efficacy, safety, tolerability, and pharmacokinetic profile of evacetrapib monotherapy at doses up to 500 mg and evacetrapib 100 mg in combination with 10 mg of atorvastatin in Japanese patients with dyslipidemia.

## Methods

This study was a multicenter, randomized, double-blind, parallel group, placebo- and active-controlled, phase 2, dose-response study (*ClinicalTrials.gov* identifier is NCT01375075). The institutional review boards of all

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See page 2029 for disclosure information.

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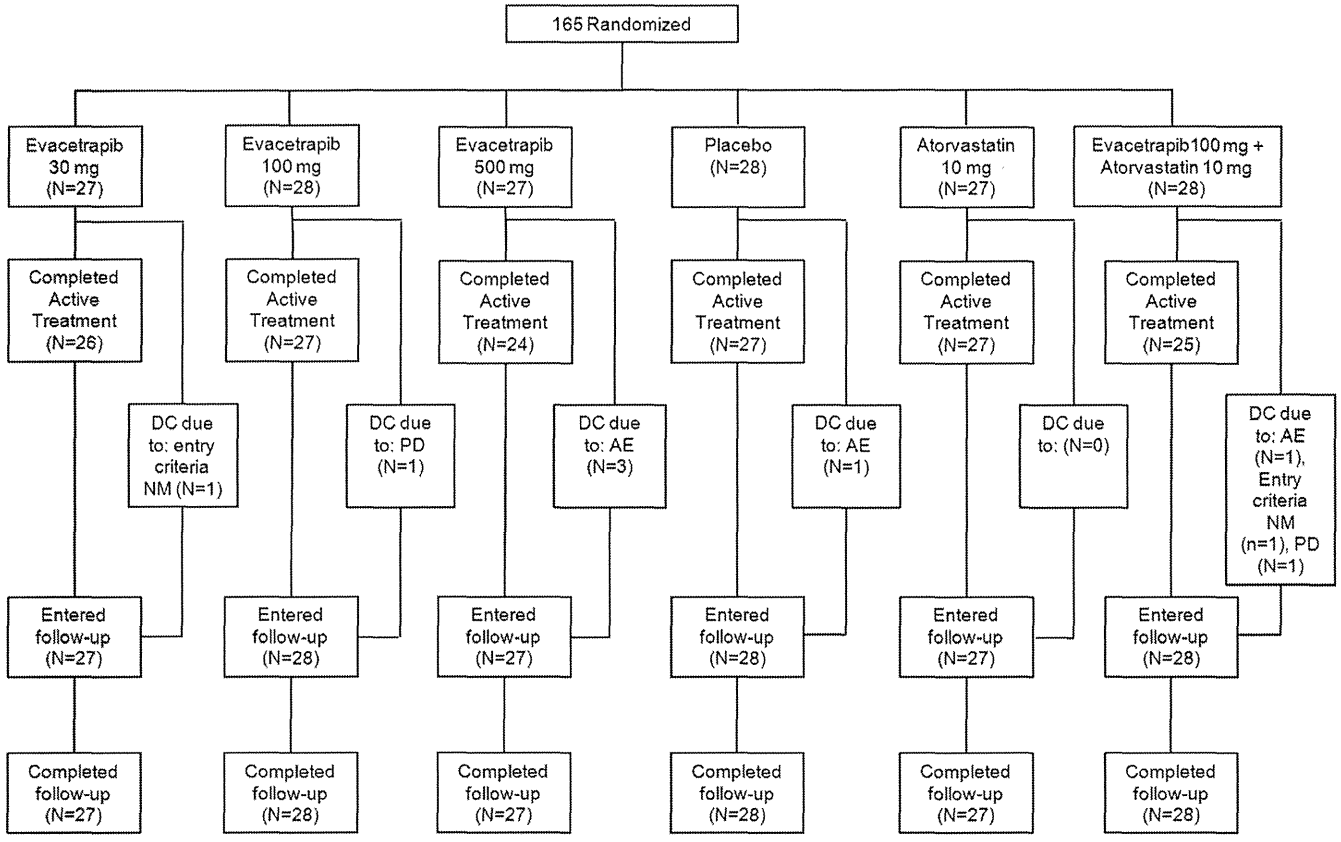


Figure 1. Patient disposition. AE = adverse events; DC = discontinued; NM = not met; PD = patient decision.

Table 1
Baseline characteristics

| Variable | Placebo (n = 28) | EVA 30 mg (n = 27) | EVA 100 mg (n = 28) | EVA 500 mg (n = 27) | ATO 10 mg (n = 27) | ATO 10 mg plus EVA 100 mg (n = 28) |
|---|---|---|---|---|---|---|
| Age (years), mean ± SD | 50 ± 9.6 | 49 ± 11 | 48 ± 12 | 49 ± 8.1 | 49 ± 8.8 | 50 ± 10 |
| Female | 10 (36%) | 8 (30%) | 10 (36%) | 9 (33%) | 8 (30%) | 10 (36%) |
| Height (cm), mean ± SD | 166 ± 8.6 | 165 ± 9.5 | 165 ± 10 | 167 ± 9.3 | 167 ± 6.8 | 165 ± 8.3 |
| Weight (kg), mean ± SD | 69 ± 14 | 69 ± 14 | 66 ± 12 | 69 ± 16 | 67 ± 13 | 70 ± 18 |
| Body mass index (kg/m$^2$), mean ± SD | 25 ± 3.7 | 25 ± 3.4 | 24 ± 3.2 | 24 ± 4.1 | 24 ± 3.3 | 26 ± 5.5 |
| LDL-C (mg/dL), mean ± SD | 140 ± 27 | 144 ± 24 | 144 ± 23 | 143 ± 30 | 134 ± 32 | 140 ± 20 |
| HDL-C (mg/dL), mean ± SD | 51 ± 14 | 50 ± 13 | 52 ± 16 | 49 ± 11 | 49 ± 14 | 52 ± 14 |
| Triglycerides (mg/dL), median (range) | 119 (47, 303) | 142 (50, 380) | 124 (52, 355) | 134 (55, 379) | 147 (49, 322) | 118 (50, 296) |

ATO = atorvastatin; EVA = evacetrapib; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; n = number of patients; SD = standard deviation.

participating centers approved the protocol, and all patients provided written informed consent. This 12-week study included placebo, evacetrapib monotherapy (30 mg, 100 mg, or 500 mg), atorvastatin 10 mg monotherapy, or evacetrapib 100 mg in combination with atorvastatin 10 mg, administered orally once daily.

The study included 4 consecutive phases: screening, diet lead-in/washout, treatment, and follow-up. After screening, eligible patients were instructed to discontinue lipid-related medications and begin a diet therapy in accordance with the Japan Atherosclerosis Society guidelines for diagnosis and prevention of atherosclerotic CV disease.[7] The diet lead-in/washout phase was either 2 weeks (for patients not taking any lipid-modifying medication) or 4 weeks (for those undergoing washout of statins, ezetimibe, bile acid sequestrants, ethyl icosapentate, or over-the-counter medications or health foods used to treat lipids).

Patients who remained eligible after following the diet lead-in/washout phase were equally randomized into 1 of the 6 treatment groups: placebo, evacetrapib monotherapy (30 mg, 100 mg, or 500 mg), atorvastatin 10 mg monotherapy, or evacetrapib 100 mg in combination with atorvastatin 10 mg. Randomization was performed by an interactive voice response system and was stratified by baseline levels of

Table 2
Change from baseline to week 12 in serum lipid measurements

| Measures | Placebo (n = 28) | EVA 30 mg (n = 27) | EVA 100 mg (n = 27) | EVA 500 mg (n = 27) | ATO 10 mg (n = 27) | ATO 10 mg plus EVA 100 mg (n = 28) |
|---|---|---|---|---|---|---|
| LDL-C (mg/dL) | | | | | | |
| Baseline | 140 ± 27 | 144 ± 24 | 145 ± 22 | 143 ± 30 | 134 ± 32 | 140 ± 20 |
| Week 12 | 141 ± 30 | 122 ± 28 | 111 ± 24 | 108 ± 36 | 84 ± 28 | 61 ± 17 |
| Percentage change | 1.2 ± 3.4 | −14 ± 3.5 | −22 ± 3.4 | −21 ± 3.6 | −38 ± 3.4 | −52 ± 3.5 |
| Relative change | | −15 (−24, 7.4)* | −23 (−31, 15)** | −22 (−30, −14)** | | −15 (−23, −6.6)*** |
| HDL-C (mg/dL) | | | | | | |
| Baseline | 51 ± 14 | 50 ± 13 | 53 ± 16 | 49 ± 11 | 49 ± 14 | 52 ± 14 |
| Week 12 | 54 ± 16 | 91 ± 27 | 111 ± 30 | 125 ± 34 | 57 ± 14 | 109 ± 30 |
| Percentage change | 8.0 ± 8.8 | 82 ± 8.9 | 123 ± 8.9 | 144 ± 9.2 | 17 ± 8.9 | 121 ± 8.9 |
| Relative change | | 74 (53, 95)** | 115 (95, 136)** | 136 (115, 157)** | | 103 (82, 124)** |
| Triglycerides (mg/dL) | | | | | | |
| Baseline | 119 (47, 303) | 142 (50, 380) | 124 (52, 355) | 134 (55, 379) | 147 (49, 322) | 118 (50, 296) |
| Week 12 | 115 (54, 324) | 123 (59, 392) | 100 (58, 390) | 115 (46, 797) | 88 (50, 231) | 95 (38, 199) |
| Percentage change | 5.1 ± 9.7 | 3.7 ± 9.9 | 12 ± 9.7 | 12 ± 10 | −25 ± 9.7 | −21 ± 10 |
| Relative change | | −1.3 (−24, 22) | 6.8 (−16, 30) | 7.0 (−16, 30) | | 3.5 (−20, 27) |

Baseline and week 12 values for LDL-C and HDL-C are mean ± SD. Baseline and week 12 values for triglycerides are median (range). Percentage changes are LS mean ± SE in percentage changes from baseline. Relative changes are differences of LS mean with 90% CI in percentage changes from baseline between evacetrapib monotherapy groups vs. placebo or between atorvastatin + evacetrapib combination therapy group vs. atorvastatin monotherapy, based on MMRM analysis.

ATO = atorvastatin; CI = confidence interval; EVA = evacetrapib; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LS = least square; MMRM = mixed-effect model repeated measure; n = number of patients; SD = standard deviation; SE = standard error.

*p-value = .002; **p-value <.001; ***p-value = .003.

Table 3
Change from baseline to week 12 in corrected cholesteryl ester transfer protein activity and cholesteryl ester transfer protein mass

| Measures | Placebo (n = 28) | EVA 30 mg (n = 27) | EVA 100 mg (n = 27) | EVA 500 mg (n = 27) | ATO 10 mg (n = 27) | ATO 10 mg plus EVA 100 mg (n = 28) |
|---|---|---|---|---|---|---|
| CETP activity (pmol/mL/min) | | | | | | |
| Baseline | 22 ± 4.6 | 21 ± 4.3 | 23 ± 4.8 | 23 ± 6.4 | 23 ± 6.2 | 23 ± 6.9 |
| Week 12 | 24 ± 6.1 | 12 ± 4.1 | 5.7 ± 3.3 | 3.1 ± 3.2 | 21 ± 6.7 | 5.7 ± 4.7 |
| Percentage change | 9.2 ± 3.5 | −41 ± 3.6 | −74 ± 3.6 | −85 ± 3.7 | −5.7 ± 3.5 | −73 ± 3.7 |
| Relative change | | −50 (−59, −42)* | −83 (−91, −75)* | −95 (−103, −86)* | | −68 (−76, −59)* |
| CETP mass (μg/mL) | | | | | | |
| Baseline | 2.3 ± 0.5 | 2.2 ± 0.5 | 2.3 ± 0.4 | 2.3 ± 0.5 | 2.2 ± 0.4 | 2.4 ± 0.5 |
| Week 12 | 2.4 ± 0.5 | 4.2 ± 1.1 | 5.3 ± 1.7 | 5.7 ± 1.7 | 2.0 ± 0.4 | 4.6 ± 1.5 |
| Percentage change | 5.8 ± 11 | 87 ± 31 | 127 ± 55 | 152 ± 71 | −8.6 ± 12 | 93 ± 41 |
| Relative change | | 1.8 (1.3, 2.3)* | 2.8 (2.3, 3.3)* | 3.2 (2.7, 3.7)* | | 2.1 (1.7, 2.6)* |

CETP activity results are corrected for the maximum inhibitable CETP activity with evacetrapib by visit. Baseline and week 12 values for CETP activity and CETP mass are mean ± SD. Percentage change for CETP activity is LS mean ± SE in percentage change from baseline. Percentage change for CETP mass is mean ± SD. Relative changes are differences of LS mean with 90% CI in percentage changes (CETP activity) or absolute changes (CETP mass) from baseline between evacetrapib monotherapy groups vs. placebo or between atorvastatin + evacetrapib combination therapy group vs. atorvastatin monotherapy, based on MMRM analysis.

ATO = atorvastatin; CETP = cholesteryl ester transfer protein; CI = confidence interval; EVA = evacetrapib; LS = least square; MMRM = mixed-effect model repeated measure; n = number of patients; SD = standard deviation; SE = standard error.

*p-value <.001.

serum triglycerides (<150 or ≥150 mg/dl) and HDL-C (<45 or ≥45 mg/dl for men; <50 or ≥50 mg/dl for women). A follow-up visit was conducted 4 weeks (+2-week allowance) after cessation of the study drug.

Men and women aged ≥20 years were included in this study. Eligible patients were required to meet either low HDL-C or high LDL-C lipid criteria. Patients meeting the low HDL-C criteria had an HDL-C level of <45 mg/dl for men or <50 mg/dl for women, plus LDL-C <190 mg/dl (and 0 to 1 risk factors), <160 mg/dl (and 2 risk factors), or <130 mg/dl (and ≥3 risk factors). Patients meeting the high LDL-C criteria had an LDL-C level of >100 mg/dl but <190 mg/dl (and 0 to 1 risk factors), <160 mg/dl (and 2 risk factors), or <130 mg/dl (and ≥3 risk factors). Risk factors were defined as age (men ≥45 years, women ≥55 years), hypertension, diabetes (including impaired glucose tolerance), smoking, family history of coronary artery disease (assessed by the clinical investigator), and low HDL-C (<40 mg/dl).[7] All patients were required to have a fasting triglyceride level of <400 mg/dl.

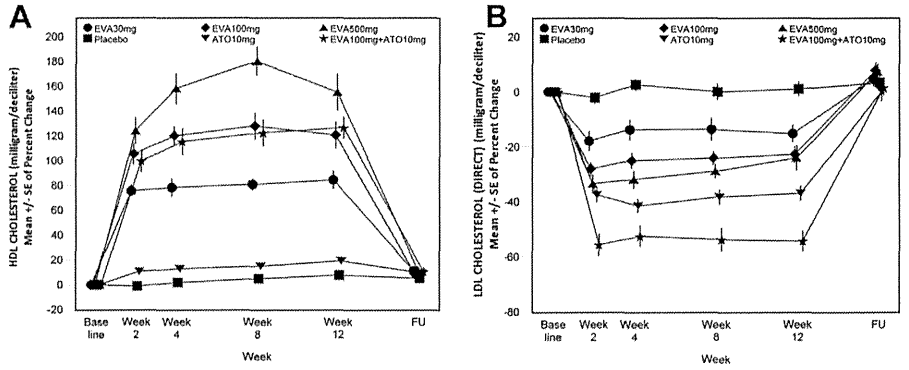


Figure 2. Change over time from baseline through follow-up in *(A)* HDL-C and *(B)* LDL-C results. The follow-up visit was conducted 4 to 6 weeks after cessation of the study drug. ATO = atorvastatin; DIRECT = LDL-C determined using the direct method; EVA = evacetrapib; FU = follow-up; SE = standard error.

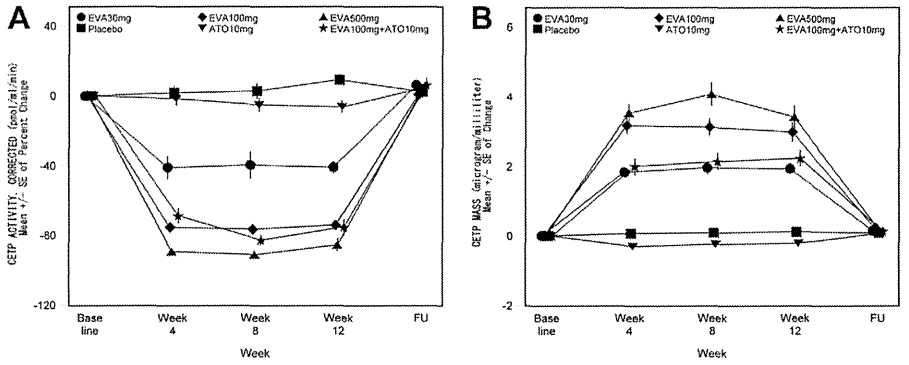


Figure 3. Change over time from baseline through follow-up in *(A)* CETP activity and *(B)* CETP mass results. The follow-up visit was conducted 4 to 6 weeks after cessation of the study drug. ATO = atorvastatin; EVA = evacetrapib; FU = follow-up; SE = standard error.

Patients were excluded if they had any clinical manifestations of coronary heart disease (stable or unstable angina pectoris, acute coronary syndrome, or myocardial infarction) or a coronary revascularization procedure including stent placement, symptomatic carotid artery disease, or symptomatic peripheral arterial disease. Patients were also excluded if they had a systolic blood pressure (SBP) of >140 mm Hg or diastolic blood pressure (DBP) >90 mm Hg, had symptoms consistent with moderate or severe heart failure, or had an electrocardiographic abnormality consistent with QTc prolongation, wide QRS complexes, atrial fibrillation, congenital long QT syndrome, or history of ventricular tachycardia. Other exclusion criteria were recent history of a rash, chronic skin disorder (psoriasis, eczema, or urticaria), or history of any drug-related rash; patients expected to start, or were unwilling to undergo adequate washout of, lipid-modifying therapies (as described previously); and patients taking probucol, fibrate, or nicotinic agents within 8 weeks before screening.

Patients were examined during scheduled visits at weeks 2, 4, 8, and 12 (during the treatment phase), and at the follow-up visit, and were required to fast for at least 8 hours before sample collections. Serum lipid parameters (including total cholesterol, LDL-C, HDL-C, and triglyceride levels) were measured at all visits, and CETP activity and mass were measured at weeks 4, 8, and 12 and at the follow-up visit. Plasma evacetrapib concentrations were also measured before and after dose at weeks 2, 4, 8, and 12 and at the follow-up visit.

Screening laboratory tests were performed locally; all other laboratory tests were performed at a central laboratory (Covance Central Laboratory Services, Indianapolis, Indiana). Plasma concentrations of evacetrapib were measured at Bioanalytical Systems, Inc. (West Lafayette, Indiana) and were assayed using a validated liquid chromatography-tandem mass spectrometry method. Measurement of CETP mass in serum samples was performed by enzyme-linked immunosorbent assay. Serum CETP activity was measured by fluorometric assay and expressed after correction for the maximum inhibitable CETP activity with evacetrapib.

Safety was evaluated by means of adverse event assessment, clinical laboratory tests, vital signs (BP and pulse in sitting position), electrocardiograms, and rash assessment. Rash evaluation included history and examination, rash photography, laboratory assessments, and rash punch biopsy for nonlocalized, clinically significant rashes. Skin biopsies were read by a central dermatopathologist. Rash cases were adjudicated by a central dermatologist blinded to study treatment.

Assuming SDs of 30% and 25% for percent changes in HDL-C and LDL-C, respectively, Pearson correlation coefficient of 0.4 between changes, and a 15% dropout rate of enrolled patients, a sample size of 25 patients randomized to each treatment group (22 completers per treatment group) was calculated to provide 83% power to simultaneously detect a 40% increase from baseline in HDL-C and a 20% decrease from baseline in LDL-C in patients treated with

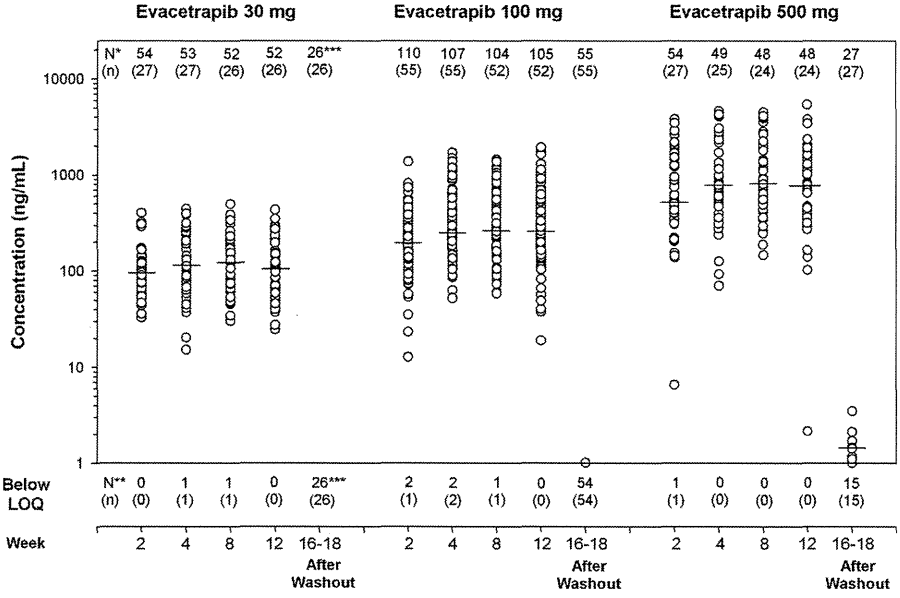


Figure 4. Drug exposure on treatment and after a 4-week washout. The *horizontal lines* show the median of concentrations by week and treatment group. The evacetrapib 100-mg group includes patients receiving monotherapy and patients receiving combination therapy with atorvastatin. *N and n displayed at the *top* of the plot indicate the numbers of all pharmacokinetic observations (N, including observations below the LOQ) and patients (n) who had pharmacokinetic observations. **N and n displayed at the *bottom* of the plot indicate the number of observations (N) below the LOQ and the number of patients (n) who had observations below the LOQ. ***A concentration value of approximately 91 ng/ml at week 16 to 18 at 30 mg was excluded as an outlier as the log-transformed value was greater than the arithmetic mean + 3 times the SD of the remaining log-transformed values at week 16 to 18. LOQ = limit of quantitation (1 ng/ml); N = number of observations; n = number of patients.

Table 4
Safety data

| Variable | Placebo (n = 28) | EVA 30 mg (n = 27) | EVA 100 mg (n = 28) | EVA 500 mg (n = 27) | ATO 10 mg (n = 27) | ATO 10 mg plus EVA 100 mg (n = 28) |
|---|---|---|---|---|---|---|
| TEAEs | 9 (32%) | 12 (44%) | 12 (43%) | 11 (41%) | 10 (37%) | 11 (39%) |
| Study drug-related TEAEs | 1 (3.6%) | 4 (15%) | 2 (7.1%) | 3 (11%) | 3 (11%) | 3 (11%) |
| Adverse events leading to discontinuation | 1 (3.6%) | 0 | 0 | 3 (11%) | 0 | 1 (3.6%) |
| Serious adverse events | 1 (3.6%) | 0 | 0 | 1 (3.6%) | 0 | 0 |
| ALT > 3x ULN | 0 | 0 | 0 | 1 (3.7%) | 1 (3.7%) | 1 (3.6%) |
| AST > 3x ULN | 0 | 0 | 0 | 0 | 1 (3.7%) | 1 (3.6%) |
| Creatine kinase >5x ULN | 1 (3.6%) | 1 (3.7%) | 1 (3.6%) | 0 | 1 (3.7%) | 0 |
| Elevation in SBP ≥15 mm Hg | 4 (14%) | 6 (22%) | 5 (18%) | 7 (26%) | 6 (22%) | 5 (18%) |
| Elevation in DBP ≥10 mm Hg | 10 (36%) | 13 (48%) | 7 (25%) | 12 (44%) | 7 (26%) | 9 (32%) |

Treatment-emergent adverse events (TEAEs) are defined as an adverse event beginning after the first dose of study drug or an adverse event that increases in severity after the first dose of study drug.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ATO = atorvastatin; DBP = diastolic blood pressure; EVA = evacetrapib; n = number of patients; SBP = systolic blood pressure; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.

evacetrapib compared with placebo (2-sided *t* test, significance level 0.1).

The intent-to-treat (ITT) population was defined as randomized patients who received at least 1 dose of study treatment. The modified ITT population consisted of ITT patients who had at least 1 baseline measurement and 1 postbaseline HDL-C measurement. Efficacy analyses were conducted for the active treatment phase on the modified ITT population. Safety analyses were conducted on the ITT population.

The primary efficacy analysis of the primary variables was restricted maximum likelihood–based mixed-effects model for repeated measures with baseline measurement as covariate; treatment, visit (weeks 2, 4, 8, or 12), and treatment-by-visit interaction as fixed effects; and patient as a random effect. Least squares (LS) means, LS mean differences, 90% confidence intervals, and p values were reported by treatment and by visit.

CETP activity and percent change from baseline, as well as CETP mass and change from baseline, were analyzed using a similar mixed-effects model for repeated measures with treatment, visit (weeks 4, 8, or 12), and treatment-by-visit interaction as fixed effects; baseline measurement as a covariate; and patient as a random effect with LS means, LS mean differences, 90% confidence intervals, and p values being reported by treatment and by visit. A mixed-effects model for repeated measures with baseline measurement,

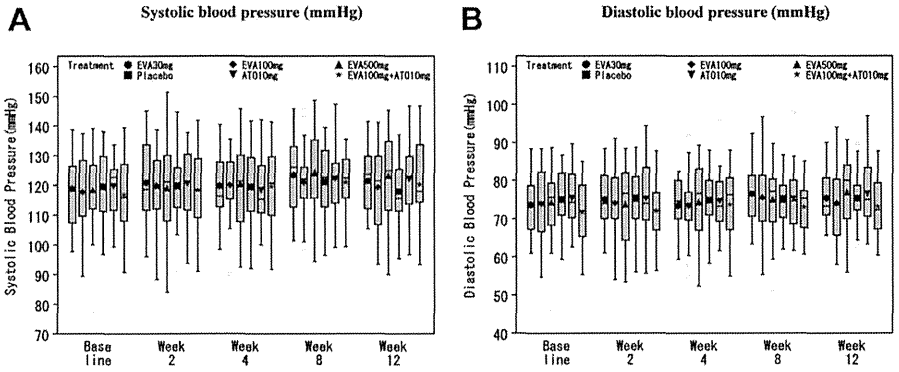


Figure 5. Box-and-whisker plot of BP from baseline through week 12: *(A)* SBP (mm Hg) and *(B)* DBP (mm Hg). The *symbol* in the box interior represents the mean. The *horizontal line* in the box interior represents the median. The length of the box represents the interquartile range. The *whiskers* are drawn to the most extreme points that lie within the fences. The *upper fence* is defined as the third quartile plus 1.5 times the interquartile range. The *lower fence* is defined as the first quartile minus 1.5 times the interquartile range. ATO = atorvastatin; EVA = evacetrapib.

treatment, visit, and treatment by visit as independent variables was used to analyze vital signs and laboratory parameters (i.e., mineralocorticoid and electrolytes).

No formal adjustment for multiplicity was made for all planned efficacy and safety analyses. Unless otherwise specified, data were analyzed with a 2-sided significance level of 0.1. Statistical analyses were carried out using SAS (SAS Institute, Cary, North Carolina).

## Results

From June 2011 to November 2011, a total of 225 patients were screened at 15 sites in Japan. A total of 165 patients were randomized and a total of 156 patients completed the study by March 2012. The disposition of these patients is shown in Figure 1. Baseline characteristics of the patients were similar among the different treatment groups studied and are listed in Table 1. The mean age of patients was 49 years, and 67% of the patients were male. The baseline lipid profile was characterized by mean LDL-C, HDL-C, and triglycerides of 141 mg/dl, 51 mg/dl, and 143 mg/dl, respectively. Sixty-seven of 165 patients (41%) met the low HDL-C criteria (<45 mg/dl for men or <50 mg/dl for women).

Evacetrapib treatment for 12 weeks in Japanese patients with hypercholesterolemia or low HDL-C resulted in statistically significant dose-related increases in HDL-C and decreases in LDL-C. Percent changes in HDL-C, LDL-C, and triglycerides are summarized in Table 2. The relative changes in HDL-C between evacetrapib monotherapy and placebo were 74%, 115%, and 136% for the 30-mg, 100-mg, and 500-mg treatment groups, respectively. The relative changes in LDL-C between monotherapy and placebo were −15%, −23%, and −22% for the 30-mg, 100-mg, and 500-mg dose groups, respectively. When evacetrapib 100 mg was administered in combination with atorvastatin 10 mg, the magnitude of change in HDL-C (+103%) and LDL-C (−15%) levels relative to atorvastatin alone was similar to that of evacetrapib 100 mg as monotherapy.

No statistically significant difference was observed in percent change in fasting triglycerides with evacetrapib monotherapy compared with placebo or with evacetrapib in combination with atorvastatin compared with atorvastatin alone.

Percent changes in CETP activity and CETP mass are summarized in Table 3. The relative changes in corrected CETP activity between evacetrapib monotherapy and placebo were −50%, −83%, and −95% for the 30-mg, 100-mg, and 500-mg dose groups, respectively. When evacetrapib 100 mg was administered in combination with atorvastatin 10 mg, the decrease in CETP activity relative to atorvastatin alone was −68%. The mean baseline CETP mass was from 2.2 to 2.4 μg/ml for all groups. At 12 weeks, CETP mass decreased (9% on average) in the atorvastatin 10-mg group, whereas it significantly increased in a dose-dependent manner (between 82% and 139% on average) on evacetrapib monotherapy. CETP mass also significantly increased (88% on average) when evacetrapib 100 mg was administered in combination with atorvastatin 10 mg.

At the follow-up visit, HDL-C and LDL-C levels (Figure 2) as well as CETP activity and mass (Figure 3) returned to baseline in all evacetrapib monotherapy and evacetrapib-plus-atorvastatin groups. Most of the patients (87%) across all dose groups had evacetrapib concentrations that were below the quantitation limit of the assay (<1.00 ng/ml) at the follow-up visit, while the remaining patients had a concentration near the quantitation limit (from 1.0 to 3.5 ng/ml; 12 of them in the 500-mg and 1 in the 100-mg group; Figure 4).

Adverse event rates and important laboratory and BP measurements are summarized in Table 4. Overall, 65 patients (39%) experienced at least 1 treatment-emergent adverse event (TEAE), but there was no statistically significant difference in the incidence of these TEAEs across the treatment groups. Sixteen patients (9.7%) experienced at least 1 TEAE considered possibly related to study drug, and 5 patients (3.0%) discontinued from the study because of an adverse event. Frequently observed TEAEs were nasopharyngitis (n = 22, 13%), hepatic function abnormality (n = 5, 3.0%), back pain (n = 4, 2.4%), gastroenteritis (n = 3, 1.8%), and headache (n = 3, 1.8%), but there was no statistically significant difference in the incidence of these TEAEs across the treatment groups. During the course of the study, 2 patients

Table 5
Baseline, week 12, and relative change from baseline to week 12 in blood pressure, mineralocorticoids, and electrolytes

| Variable | Placebo (n = 28) | EVA 30 mg (n = 27) | EVA 100 mg (n = 28) | EVA 500 mg (n = 27) | ATO 10 mg (n = 27) | ATO 10 mg plus EVA 100 mg (n = 28) |
|---|---|---|---|---|---|---|
| SBP (mm Hg) | | | | | | |
| Baseline | 119 ± 12 | 119 ± 12 | 118 ± 13 | 118 ± 13 | 120 ± 9.8 | 117 ± 13 |
| Week 12 | 118 ± 10 | 121 ± 11 | 119 ± 13 | 123 ± 14 | 122 ± 12 | 120 ± 14 |
| Absolute change | −1.4 ± 1.8 | 2.4 ± 1.8 | 1.4 ± 1.8 | 4.5 ± 1.8 | 2.6 ± 1.8 | 2.0 ± 1.8 |
| Relative change | — | 3.7 (−0.4, 7.9) | 2.8 (−1.3, 6.9) | 5.9 (1.7, 10)* | — | −0.5 (−4.7, 3.6) |
| DBP (mm Hg) | | | | | | |
| Baseline | 75 ± 7.3 | 74 ± 7.3 | 74 ± 9.7 | 74 ± 9.8 | 75 ± 7.6 | 72 ± 8.5 |
| Week 12 | 75 ± 6.4 | 75 ± 7.2 | 74 ± 9.4 | 77 ± 9.9 | 77 ± 8.2 | 73 ± 8.2 |
| Absolute Change | 0.7 ± 1.1 | 1.5 ± 1.1 | 0.0 ± 1.1 | 2.5 ± 1.1 | 1.5 ± 1.1 | 0.5 ± 1.1 |
| Relative change | — | 0.8 (−1.7, 3.2) | −0.7 (−3.1, 1.8) | 1.8 (−0.7, 4.3) | — | −1.0 (−3.5, 1.5) |
| Aldosterone (ng/dL) | | | | | | |
| Baseline | 6.5 ± 4. 1 | 7.0 ± 8.1 | 3.7 ± 2.4 | 3.9 ± 3.0 | 3.9 ± 2.3 | 4.4 ± 3.2 |
| Week 12 | 5.6 ± 3.5 | 5.2 ± 3.3 | 5.0 ± 3.3 | 5.2 ± 4.7 | 5.6 ± 6.0 | 5.5 ± 3.1 |
| Absolute change | 0.3 ± 0.8 | −0.4 ± 0.8 | 0.4 ± 0.8 | 0.6 ± 0.8 | 1.0 ± 0.8 | 0.6 ± 0.8 |
| Relative change | — | −0.7 (−2.6, 1.1) | 0.04 (−1.8, 1.9) | 0.26 (−1.7, 2.2) | — | −0.3 (−2.2, 1.5) |
| Salivary cortisol (μg/dL) | | | | | | |
| Baseline | 0.05 ± 0.03 | 0.10 ± 0.12 | 0.09 ± 0.11 | 0.05 ± 0.02 | 0.08 ± 0.08 | 0.08 ± 0.1 |
| Week 12 | 0.06 ± 0.04 | 0.06 ± 0.02 | 0.09 ± 0.15 | 0.06 ± 0.05 | 0.08 ± 0.09 | 0.06 ± 0.04 |
| Absolute change | −0.01 ± 0.02 | −0.02 ± 0.02 | 0.01 ± 0.02 | −0.01 ± 0.02 | 0.00 ± 0.02 | −0.00 ± 0.02 |
| Relative change | — | −0.00 (−0.04, 0.03) | 0.02 (−0.01, 0.06) | 0.00 (−0.03, 0.04) | — | −0.01 (−0.05, 0.03) |
| Sodium (mEq/L) | | | | | | |
| Baseline | 140 ± 1.7 | 140 ± 1.8 | 141 ± 2.1 | 141 ± 1.9 | 141 ± 1.4 | 141 ± 1.6 |
| Week 12 | 140 ± 2.3 | 140 ± 1.5 | 140 ± 1.3 | 141 ± 1.8 | 141 ± 2.0 | 141 ± 2.0 |
| Absolute change | −0.3 ± 0.3 | −0.2 ± 0.3 | −0.3 ± 0.3 | −0.1 ± 0.3 | 0.4 ± 0.3 | 0.5 ± 0.3 |
| Relative change | — | 0.1 (−0.6, 0.8) | −0.01 (−0.7, 0.7) | 0.3 (−0.5, 1.0) | — | 0.2 (−0.5, 0.9) |
| Potassium (mEq/L) | | | | | | |
| Baseline | 3.8 ± 0.2 | 3.9 ± 0.2 | 3.8 ± 0.3 | 3.9 ± 0.3 | 3.7 ± 0.3 | 3.8 ± 0.2 |
| Week 12 | 3.8 ± 0.2 | 3.9 ± 0.2 | 3.9 ± 0.3 | 3.9 ± 0.3 | 3.8 ± 0.2 | 3.9 ± 0.3 |
| Absolute change | 0.01 ± 0.1 | 0.02 ± 0.1 | 0.1 ± 0.1 | 0.1 ± 0.1 | 0.01 ± 0.1 | 0.1 ± 0.1 |
| Relative change | — | 0.01 (−0.1, 0.1) | 0.1 (−0.02, 0.2) | 0.1 (−0.01, 0.2) | — | 0.1 (−0.03, 0.2) |
| Bicarbonate (mEq/L) | | | | | | |
| Baseline | 23 ± 2.1 | 24 ± 2.7 | 24 ± 2.4 | 24 ± 1.9 | 23 ± 2.2 | 23 ± 2.6 |
| Week 12 | 24 ± 2.1 | 24 ± 2.9 | 25 ± 2.3 | 24 ± 2.4 | 24 ± 2.7 | 25 ± 2.9 |
| Absolute change | 0.5 ± 0.4 | 0.6 ± 0.43 | 0.6 ± 0.4 | 0.6 ± 0.5 | 0.6 ± 0.4 | 1.2 ± 0.4 |
| Relative change | — | 0.1 (−0.9, 1.1) | 0.1 (−0.9, 1.1) | 0.1 (−0.9, 1.1) | — | 0.6 (−0.4, 1.6) |

Baseline and week 12 values are mean ± SD. Absolute changes are LS mean ± SE in changes from baseline. Relative changes are differences of LS mean with 90% CI in changes from baseline between evacetrapib monotherapy groups vs. placebo or between atorvastatin + evacetrapib combination therapy group vs. atorvastatin monotherapy, based on MMRM analysis.

ATO = atorvastatin; CI = confidence interval; DBP = diastolic blood pressure; EVA = evacetrapib; LS = least squares; MMRM = mixed-effect model repeated measures; n = number of patients; SBP = systolic blood pressure; SD = standard deviation; SE = standard error.

*p-value = 0.021.

experienced treatment-emergent serious adverse events (SAEs). In 1 patient in the evacetrapib 500-mg treatment group, the treatment-emergent SAEs (toxic skin eruption and pyrexia) were judged to be related to the study drug. However, this patient had undergone a tooth extraction and had been treated with several medications, including a cephalosporin, before developing the symptoms. This patient was discontinued from the study as a result of the event. The other patient (in the placebo treatment group) experienced multiple unrelated SAEs caused by a car accident, including sternal fracture, traumatic lung injury, and lumbar vertebral fracture.

Skin and subcutaneous tissue adverse reactions were reported in 5 patients during the active treatment phase: 3 patients in the evacetrapib 500-mg treatment group, 1 patient in the evacetrapib 30-mg treatment group, and 1 patient in the evacetrapib 100 mg plus atorvastatin 10 mg combination treatment group. Of these 5 events, 1 event was adjudicated to be high-risk rash (the SAE described previously), 2 events were adjudicated to be low-risk rashes, and 2 events were adjudicated to be unrelated dermatoses.

Evacetrapib as monotherapy and in combination with atorvastatin did not produce a clinically important adverse effect to any of the clinical chemistry analytes or hematology parameters. Overall, elevations of alanine aminotransferase and aspartate aminotransferase (>3 times the upper limit of normal [ULN]) occurred in 3 and 2 patients, respectively (Table 4). One of 3 patients with alanine aminotransferase elevation and 1 of 2 patients with aspartate aminotransferase elevation were in the atorvastatin 10-mg treatment group. However, these increases were transient and recovered during the study period, and no patient had

concomitant increase in alanine aminotransferase (>3 times ULN) and total bilirubin (>2 times ULN). Creatine kinase levels were elevated (>5 times ULN) in 4 patients (Table 4). However, 2 of these events (1 occurring in the evacetrapib 30-mg treatment group and 1 in the placebo group) were observed only at baseline, before administration of study medication. The other 2 events (1 occurring in the evacetrapib 100-mg treatment group and 1 occurring in the atorvastatin 10-mg treatment group) were also transient.

Figure 5 illustrates box-and-whisker plots for SBP and DBP from baseline through the end of treatment. There was no clinically relevant change in either SBP or DBP during the study period in any of the treatment groups. SBP significantly increased in the evacetrapib 500-mg treatment group compared with placebo (evacetrapib 500-mg treatment group 4.5 ± 1.8 mm Hg, placebo group −1.4 ± 1.8 mm Hg, LS mean difference 5.9 ± 2.5 mm Hg, $p = 0.021$; Table 5). Considerable variability was observed in the different treatment groups independent of evacetrapib administration, as demonstrated by an average decrease of 1.4 ± 1.8 mm Hg in the placebo group and increase of 2.6 ± 1.8 mm Hg in the atorvastatin monotherapy group. Additionally, no dose-dependent effect of evacetrapib on SBP was observed. DBP was not statistically different among the 6 treatment groups. Moreover, the proportion of patients experiencing significant BP elevation (SBP ≥15 mm Hg or DBP ≥10 mm Hg) was not significantly different between treatment groups (Table 4). Follow-up results indicated that, for those patients whose BP increased from normotensive or prehypertensive to hypertensive during the course of the study, these observed BP increases were transient in nature and returned to baseline levels at the follow-up visit.

Last, evacetrapib did not have any adverse effect on mineralocorticoid or glucocorticoid measures, which included serum aldosterone and salivary cortisol, and serum electrolytes such as sodium, bicarbonate, and potassium (Table 5).

## Discussion

The present study confirmed the efficacy of evacetrapib in significantly increasing HDL-C and decreasing LDL-C levels in Japanese patients with dyslipidemia characterized by either high LDL-C or low HDL-C levels. The significant changes in HDL-C and LDL-C levels were observed with evacetrapib as monotherapy at all dose levels (30 mg, 100 mg, and 500 mg) as well as in combination with atorvastatin. In this 12-week study, the administration of evacetrapib 500 mg as monotherapy increased HDL-C by as much as 136% and decreased LDL-C by as much as 22% relative to placebo. Significant changes persisted when evacetrapib 100 mg was given in combination with atorvastatin 10 mg, suggesting an additive and pharmacologically independent effect of evacetrapib on both HDL-C and LDL-C response.

These results are comparable to those of the phase 2 study of evacetrapib in patients with dyslipidemia from the United States and Europe.[6] Baseline LDL-C levels were similar in the Japanese and United States/Europe studies (141 mg/dl vs 144 mg/dl, respectively), whereas baseline HDL-C levels were lower in the present study of Japanese patients with dyslipidemia (51 mg/dl vs 55 mg/dl). The lower mean baseline HDL-C levels could actually explain the relatively higher magnitude of HDL-C increase observed with evacetrapib in the present study, because treatment response was found to correlate with baseline HDL-C in this study and in the global study.[6]

Although neither torcetrapib nor dalcetrapib demonstrated reductions in the risk of CV events in the Investigation of Lipid Level Management to Understand its Impact in Atherosclerotic Events to (ILLUMINATE) trial and dalcetrapib-OUTCOMES studies, respectively, CV risk reduction might be shown by more potent CETP inhibitors. HDL-C increases were only 31% by dalcetrapib and 61% by torcetrapib in the phase 2 studies, in comparison with >130% by evacetrapib and anacetrapib.[8] Further support in favor of positive effects of pharmacologic CETP inhibition on atherosclerosis comes from the post hoc analysis of the Investigation of Lipid Level Management Using Coronary Ultrasound to Assess Reduction of Atherosclerosis by CETP Inhibition and HDL Elevation (ILLUSTRATE) intravascular ultrasound study with torcetrapib.[9] Although treatment with torcetrapib did not result in any significant effect on percent atheroma volume,[10] an inverse relation was observed between changes in levels of HDL-C and percent atheroma volume. Atherosclerosis regression was observed in the highest quartile of HDL-C levels achieved with torcetrapib, thus indirectly suggesting that these HDL particles are functional. Indeed, experiments using HDL samples isolated from patients after treatment with a CETP inhibitor, such as anacetrapib and torcetrapib, indicate that HDL particles retain both their ability to promote cholesterol transport and their anti-inflammatory effects.[11–13] In addition, treatment with anacetrapib and torcetrapib were shown to promote macrophage-to-feces reverse cholesterol transport and to increase fecal excretion of bile acid and/or cholesterol in the rodent models of dyslipidemia.[14,15] In these experiments in human and rodent models, an increase of reverse cholesterol transport by CETP inhibition has been suggested to be associated with increases of both HDL-C concentration and cholesterol efflux capacity per HDL particle.[11,12,15] All together, these results support the hypothesis that HDL particles are still functional after treatment with strong CETP inhibitors.

The present study also showed that almost complete washout of evacetrapib occurred within the 4- to 6-week reversal period after 12 weeks of evacetrapib monotherapy as well as in combination with atorvastatin. The effects on lipids (HDL-C and LDL-C) and CETP mass and activity were no longer apparent after 4 to 6 weeks of drug cessation, consistent with evacetrapib blood levels that were near or below the quantitation limit of the assay. These observations are consistent with the terminal half-life of evacetrapib.[16] In contrast, persistent plasma anacetrapib concentrations and significant lipid changes (LDL-C and HDL-C) were observed 8 weeks after the last dose of anacetrapib (given for 8 weeks at 100 or 300 mg/day dose).[3] Approximately 20% of the plasma anacetrapib concentrations remained at each anacetrapib dose as monotherapy or in coadministration with atorvastatin. Approximately 1/3 to 1/2 of the effect on LDL-C and approximately 1/5 to 1/2 of the effect on HDL-C with anacetrapib at week 8 were still observed 8 weeks after anacetrapib cessation. Moreover, Gotto et al[2] have also recently shown that significant concentrations of anacetrapib are still measurable in plasma 12 weeks after cessation of treatment in the 76-week DEFINE study, strongly suggesting that evacetrapib and anacetrapib differ in the way they are distributed and/or eliminated.