The clinical trial information provided in this public disclosure synopsis is supplied for informational purposes only.

Please note that the results reported in any single trial may not reflect the overall potential risks or benefits of a product which are based on an evaluation of an entire research program.

Before prescribing any Takeda products, healthcare professionals should consult prescribing information for the product approved in their country.

SYNOPSIS

Title of Study:

A Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of Lapaquistat Acetate 100 mg or Placebo When Coadministered With High-Dose Statin Therapy in Subjects With Primary Hypercholesterolemia

Name of Sponsor:

Takeda Global Research & Development Center, Inc.

Name of Active Ingredient:

Lapaquistat acetate

Name of Finished Product:

Not applicable

Investigators/Study Centers:

46 sites in the United States, Canada, Europe, South Africa, and Israel

Publication:

None

Study Period:	**Phase of Development:**
15 November 2005 to 06 March 2007	Phase 3

OBJECTIVES

Primary:

The primary objective of this study was to evaluate the change in direct fasting plasma low-density lipoprotein cholesterol (LDL-C) in subjects with primary hypercholesterolemia treated with lapaquistat acetate 100 mg once daily (QD) or placebo QD when coadministered with high-dose atorvastatin, rosuvastatin, or simvastatin for 24 weeks.

Secondary:

The secondary objectives of this study were:

- To evaluate safety and tolerability (adverse events, safety laboratory tests, physical examination, vital signs, electrocardiogram [ECG] assessments, and best corrected visual acuity [BCVA] results).
- To evaluate changes in calculated LDL-C, non–high-density lipoprotein cholesterol (HDL-C) (total cholesterol [TC] minus HDL-C), TC, apolipoprotein B (Apo B), triglycerides (TG), HDL-C, apolipoprotein A1 (Apo A1), very-low-density lipoprotein cholesterol (VLDL-C), and derived ratio variables LDL-C/HDL-C, TC/HDL-C, and Apo B/Apo A1.
- To evaluate change in high-sensitivity C-reactive protein (hs-CRP).
- To evaluate the percentage of subjects who achieve LDL-C concentrations of <3.37, <2.59, and <1.81 mmol/L (<130, <100, and <70 mg/dL) at Final Visit.
- To evaluate the long-term safety of lapaquistat acetate treatment in this population during the open-label extension period. (Results of the open-label extension will be addressed in a separate report.)

METHODOLOGY

This was a phase 3, double-blind, placebo-controlled, parallel-group, randomized, multicenter study designed to evaluate the efficacy and safety of lapaquistat acetate 100 mg or placebo when coadministered with a stable dose of atorvastatin 80 mg, rosuvastatin 40 mg, or simvastatin 80 mg QD for 24 weeks in subjects with primary hypercholesterolemia. Subjects who had been taking the highest recommended dose of a statin once daily for at least 4 weeks prior to Screening and who initially met study eligibility criteria entered a 4- to 6-week diet stabilization period (therapeutic lifestyle change diet or equivalent). Subjects already being treated with atorvastatin 80 mg QD, rosuvastatin 40 mg QD, or simvastatin 80 mg QD continued this regimen for a 4-week run-in period; all others

Title of Study:

A Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of Lapaquistat Acetate 100 mg or Placebo When Coadministered With High-Dose Statin Therapy in Subjects With Primary Hypercholesterolemia

discontinued their statin treatment at Visit 1 and initiated rosuvastatin 20 mg QD for 2 weeks, then rosuvastatin 40 mg QD for 4 weeks (in countries with a valid marketing authorization for rosuvastatin). Subjects on a stable ezetimibe regimen were allowed to continue it during the study. All subjects returned to the site at Weeks -2 and -1 for repeat qualifying lipid tests.

Qualifying subjects were randomized to treatment after stratification on the basis of the subject's statin treatment (atorvastatin, rosuvastatin, or simvastatin) and baseline TG level (≤1.70 mmol/L or >1.70 mmol/L [≤150 mg/dL or >150 mg/dL]). Subjects self-administered study drug (lapaquistat acetate 100 mg QD or placebo QD) in combination with high-dose statin treatment for 24 weeks and returned to the site at Weeks 2, 4, 8, 12, 16, 20, and 24 for study procedures.

Number of Subjects:

Planned: 600 subjects (300 per treatment group).

Analyzed: Full analysis set: 647 subjects (325 placebo and 322 lapaquistat acetate 100 mg).
Safety analysis set: 647 subjects (325 placebo and 322 lapaquistat acetate 100 mg).

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, a subject must have been a man or woman, aged at least 18 years, who had taken the highest recommended dose of a statin for at least 4 weeks prior to Screening and met the following lipid criteria prior to randomization: (1) mean LDL-C values ≥2.59 mmol/L (≥100 mg/dL) from 2 consecutive samples taken no less than 1 week apart, with the difference between the 2 values not exceeding 15% of the higher value; and (2) mean TG value of ≤4.52 mmol/L (≤400 mg/dL) from 2 consecutive samples taken no less than 1 week apart, with the upper value for either sample ≤5.1 mmol/L (≤450 mg/dL).

Test Product	Dose and Mode of Administration	Lot Numbers
Lapaquistat acetate	100 mg tablet, oral, QD	See Appendix 16.1.6
Matching placebo	Tablet, oral, QD	

All subjects also took atorvastatin 80 mg QD, rosuvastatin 40 mg QD (or 20 mg QD during Screening), or simvastatin 80 mg QD throughout the study (see Appendix 16.1.6).

Duration of Treatment:

The treatment duration was 24 weeks, which followed a 4- to 6-week run-in period. (An optional 96-week open-label lapaquistat acetate treatment period followed the 24-week double-blind period; the open-label results are not reported herein.)

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was fasting plasma LDL-C concentration based on direct measurement.

The secondary efficacy variables were fasting plasma concentrations of calculated LDL-C, non–HDL-C (derived as TC minus HDL-C), TC, Apo B, TG, HDL-C, Apo A1, VLDL-C, derived lipid ratios (TC/HDL-C, LDL-C/HDL-C, and Apo B/Apo A1), hs-CRP, and the proportion of subjects who achieved direct fasting plasma LDL-C concentrations of less than 1.81, 2.59, and 3.37 mmol/L (70, 100, and 130 mg/dL) at Final Visit.

At Baseline, the median hs-CRP value was 0.90 mg/L in both treatment groups. At Week 24, the median change from Baseline was -9.52% in the placebo group and -25.00% for lapaquistat acetate (P=0.001).

Safety:

Safety variables included adverse events, clinical laboratory results (chemistry, hematology, urinalysis, and serum pregnancy tests), physical examination findings, ECG assessments, BCVA results, and vital signs.

Title of Study:

A Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of Lapaquistat Acetate 100 mg or Placebo When Coadministered With High-Dose Statin Therapy in Subjects With Primary Hypercholesterolemia

Statistical Methods:

All statistical analyses were based on the statistical analysis plan, which was finalized before unblinding.

The primary efficacy analysis was based on the percent change from Baseline to Week 24 (or time of early withdrawal) in direct fasting plasma LDL-C value. Treatment groups were compared using an analysis of covariance (ANCOVA) model with treatment as factor and baseline value as covariate. Secondary variables were analyzed using the same model as the primary analysis. For time-effect displays, primary and secondary variables were summarized and analyzed by study visit, using ANCOVA models similar to the model used in the primary analysis. For TG, the assumption of normality was assessed using the Shapiro-Wilk statistic. For both TG and hs-CRP, the estimates of difference in medians and 95% confidence intervals (CIs) were calculated based on the Hodges-Lehmann method and the distribution-free CI, respectively. Proportions of subjects who achieved LDL-C concentrations of less than 1.81, 2.59, and 3.37 mmol/L (70, 100, and 130 mg/dL) at Week 24 (or time of early withdrawal) were summarized in a shift table; no formal statistical analysis was performed. Numbers of subjects reaching LDL-C goals determined with a risk-based algorithm devised by the National Cholesterol Education Program (NCEP) were also analyzed using a logistic regression model with terms for treatment, risk category, and Baseline LDL-C.

In the safety analyses, adverse events were coded using the Medical Dictionary for Regulatory Activities (Version 8.1) and summarized using descriptive statistics. Clinical laboratory test results were summarized descriptively by treatment. Markedly abnormal laboratory values were summarized by treatment group, including the number and percentage of subjects in each laboratory parameter group. Shift tables were produced that included the number of subjects per group with low, normal, or high values with respect to the reference ranges, and the number and percentage of subjects in each shift combination. Descriptive statistics of vital signs, ECG intervals, and BCVA evaluations were produced for each treatment group.

SUMMARY OF RESULTS

Subject Disposition:

There were 649 subjects randomized to placebo or lapaquistat acetate 100 mg treatment. Two subjects (1 in each treatment group) failed to receive study drug; thus, 647 received at least 1 dose of lapaquistat acetate or placebo and were included in the safety analysis set. A total of 606 subjects completed the study, and 43 subjects were prematurely withdrawn: 17 (5.2%) receiving placebo and 26 (8.0%) receiving lapaquistat acetate 100 mg. The most common reason for withdrawal was an adverse event. The study population was predominantly White (92.9%) and male (60.7%), with a mean age of 51.8 years. There were no important differences between treatment groups in any of the baseline demographic characteristics or baseline efficacy parameters.

Title of Study:

A Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of Lapaquistat Acetate 100 mg or Placebo When Coadministered With High-Dose Statin Therapy in Subjects With Primary Hypercholesterolemia

Efficacy Results:

Summary of Primary and Secondary Lipid Variables: Percent Change From Baseline at Week 24

	% Change From Baseline, Least Squares Mean (SE)		
Variable	**Placebo (n=325)**	**Lapaquistat Acetate 100 mg (n=322)**	**% Difference From Placebo (95% CI)**
Direct LDL-C	1.32 (0.835)	-14.57 (0.837)	-15.89 (-18.21, -13.57), P<0.001
Calculated LDL-C	2.09 (0.884)	-14.90 (0.887)	-16.99 (-19.45, -14.53), P<0.001
Non–HDL-C	2.09 (0.820)	-12.96 (0.821)	-15.05 (-17.33, -12.77), P<0.001
TC	1.80 (0.655)	-10.09 (0.656)	-11.89 (-13.71, -10.07), P<0.001
Apo B	5.42 (0.772)	-6.52 (0.771)	-11.93 (-14.08, -9.79), P<0.001
TG (a)	1.28	-6.25	-6.49 (-10.31, -2.63), P<0.001
HDL-C	0.80 (0.673)	-0.04 (0.674)	-0.84 (-2.71, 1.03), P=0.377
Apo A1	2.25 (0.688)	0.78 (0.687)	-1.47 (-3.38, 0.44), P=0.131
VLDL-C	4.37 (1.646)	-0.66 (1.652)	-5.03 (-9.61, -0.45), P=0.031

(a) For TG, changes from Baseline are medians, not means.

The efficacy results for the primary and main secondary variables are presented in the above table. In addition, statistically significant LDL-C reductions were first observed at Week 2 in the lapaquistat acetate group and were maintained throughout the 24-week treatment period. Of subjects with a baseline direct LDL-C value ≥3.37 mmol/L, 48.6% of lapaquistat acetate subjects achieved levels below 3.37 mmol/L by Final Visit, compared with 12.4% of subjects receiving placebo. Of subjects above their target LDL-C level at Baseline based on risk-modified NCEP criteria, 34.0% of those receiving lapaquistat acetate were below the goal at Final Visit, compared with 11.1% of placebo subjects.

Statistically significant and consistent LDL-C reductions were observed for lapaquistat acetate (ranging from 10.97% to 18.42%) in all subgroups based on statin type, baseline TG value, age, gender, race, body mass index, ezetimibe use, and mutated LDL receptor gene status.

Clinically meaningful and statistically significant reductions were observed in all lipid ratios with lapaquistat acetate compared with placebo. The Apo B/Apo A1 ratio was reduced by 0.06 with lapaquistat acetate, compared with an increase of 0.03 with placebo.

Safety Results:

Of the 649 subjects enrolled in this study, 647 received at least 1 dose of lapaquistat acetate or placebo and were included in the safety analysis set. A total of 471 subjects (72.8%) experienced 1 or more adverse events during the study: 71.4% of placebo subjects and 74.2% of lapaquistat acetate subjects. There were 176 subjects who experienced an adverse event that was considered possibly, probably, or definitely related to study drug: 22.2% of placebo subjects and 32.3% of lapaquistat acetate subjects. Most adverse events were judged by the investigator as mild or moderate in intensity; 26 subjects (4.0%) experienced a severe event (4.6% and 3.4% of subjects in the placebo and lapaquistat acetate groups, respectively). Adverse events that occurred in at least 5% of subjects in any treatment group were nasopharyngitis, headache, influenza, upper respiratory tract infection, and diarrhea.

Two subjects died during the study; 1 placebo subject died of an accidental fall, and 1 lapaquistat acetate subject died of a skeletal metastasis of an unknown primary tumor that predated the first dose of study drug. Eight lapaquistat acetate–treated subjects experienced a total of 11 treatment-emergent SAEs, and all but 1 of these events were judged by the investigator to be not related to study drug. Ten placebo subjects experienced SAEs. Twenty-eight subjects (10 [3.1%] of placebo subjects and 18 [5.6%] of lapaquistat acetate subjects) either withdrew from the study (22 subjects) or had study drug interrupted (6 subjects) because of an adverse event.

Title of Study:

A Double-Blind, Randomized Study to Evaluate the Efficacy and Safety of Lapaquistat Acetate 100 mg or Placebo When Coadministered With High-Dose Statin Therapy in Subjects With Primary Hypercholesterolemia

Elevations in liver function values, and adverse events representing such elevations, occurred at higher incidences with lapaquistat acetate 100 mg than with placebo.

No subjects were withdrawn because of protocol-specified alanine aminotransferase (ALT)/aspartate aminotransferase elevation criteria for removal of subjects from study, although 1 subject on lapaquistat acetate who was withdrawn owing to an SAE of acute hepatitis B also had ALT elevations above 10 times the upper limit of normal (xULN). Excluding this subject, ALT elevations to >3xULN at consecutive visits occurred in 5 (1.5%) subjects receiving lapaquistat acetate and 1 (0.3%) subject receiving placebo. None of the elevations was accompanied by symptoms or increases in bilirubin to >2xULN. In all cases where subsequent values were available, the elevations either resolved to within normal limits or to below 3xULN. Four of those receiving lapaquistat acetate were receiving triple therapy, taking rosuvastatin as their companion statin as well as ezetimibe 10 mg. One of the 4 experiencing such elevations withdrew from the study. The fifth subject experiencing such consecutive ALT elevations to > 3xULN was on combination therapy of lapaquistat acetate plus a statin but without ezetimibe. Notably, the rate of consecutive ALT elevations greater than or equal to 3xULN occurring in lapaquistat subjects taking a companion statin without ezetimibe was equal to that in the placebo group taking companion statin without ezetimibe. Specifically, without ezetimibe, only one such subject in each group experienced consecutive ALT elevations to >3xULN.

Creatine kinase (CK) elevations to >10xULN occurred in 4 subjects (1 placebo and 3 lapaquistat acetate). All of these elevations were asymptomatic, 3 of them were considered adverse events, and 1 of the subjects was withdrawn from the study as a result of the elevation. A total of 12 subjects (3 placebo and 9 lapaquistat acetate) had muscle-related adverse events that led to withdrawal from the study or temporary study drug interruption. Two lapaquistat acetate–treated subjects had muscle spasms or myalgia considered related to study drug and at least 1 elevated CK value (>3xULN) during the study.

There were no major findings in hematology, urinalysis, vital signs, ECGs, physical examination, or BCVA results.

CONCLUSIONS:

Administration of lapaquistat acetate 100 mg QD for 24 weeks was effective in reducing LDL-C levels in subjects with primary hypercholesterolemia receiving a stable, high-dose regimen of atorvastatin, rosuvastatin, or simvastatin. This effect was consistent irrespective of whether ezetimibe 10 mg QD was also taken. Categorical analyses of numbers of subjects reaching target LDL-C values showed a substantial and significant benefit of lapaquistat acetate over continuation of the lipid-lowering regimen alone. Subgroup analyses showed a consistent response; differences between lapaquistat acetate and placebo were highly statistically significant within all subgroups. Statistically significant and clinically meaningful reductions were also observed in mean direct and calculated LDL-C, non–HDL-C, TC, and Apo B, in median TG and hs-CRP values, and in the lipid ratios Apo B/Apo A1, LDL-C/HDL-C, and TC/HDL-C. The addition of lapaquistat acetate to high-dose statin therapy was also shown to be effective in reducing LDL-C values in the subpopulation of subjects with genetically confirmed heterozygous familial hypercholesterolemia.

In this study, treatment with lapaquistat acetate 100 mg QD was safe and well tolerated in combination with high-dose statin therapy.

The addition of lapaquistat acetate to maximum approved doses of 3 commonly used statins provides important incremental reductions in LDL-C in a population with elevated LDL-C at high risk of coronary heart disease.