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 50 mg versus Placebo in Subjects with Hypercholesterolemia, With an Optional Open-Label Extension

Name of Sponsor:

Takeda Global Research & Development Centre (Europe) Ltd.

Name of Active Ingredient:

Lapaquistat acetate

Name of Finished Product:

Not applicable

Investigators/Study Centers:

51 sites in Europe, including Russia and Israel

Publication (reference):

None

Study Period (years):	**Phase of Development:**
10 September 2007 to 07 May 2008	Phase 3b

OBJECTIVES

Double-Blind Period:

Primary

The primary objective of this study was to evaluate the reduction in low-density lipoprotein cholesterol (LDL-C) in subjects with hypercholesterolemia treated with lapaquistat acetate 50 mg once daily (QD) or placebo QD for 12 weeks.

Secondary

The secondary objectives of this study were to evaluate after 12 weeks of treatment:

1. Safety and tolerability (adverse events, safety laboratory tests, physical examination, vital signs, and electrocardiograms [ECG]).
2. Changes in lipid variables (high-density lipoprotein cholesterol [HDL-C], non–high-density lipoprotein cholesterol [non–HDL-C], total cholesterol [TC], triglycerides [TG], apolipoprotein A1 [Apo A1], apolipoprotein B [Apo B], and very-low-density lipoprotein cholesterol [VLDL-C]).
3. Changes in derived ratios (LDL-C/HDL-C, TC/HDL-C, Apo B/Apo A1).
4. Changes in high-sensitivity C-reactive protein (hs-CRP).

Open-Label Extension:

An optional 48-week open-label extension (OLE) followed the 12-week double-blind (DB) Period, and the objective of the OLE was to evaluate the long-term safety of lapaquistat acetate 50 mg QD after 48 weeks of open-label treatment. Efficacy analysis was also done during the OLE Period, as a secondary evaluation.

The safety results of both the DB Period and the OLE are summarized in this abbreviated study report.

METHODOLOGY

This multicenter study was a phase 3b, DB, placebo-controlled, parallel-group, randomized study designed to evaluate the safety and efficacy of lapaquistat acetate 50 mg QD administered orally in subjects with hypercholesterolemia, followed by an OLE designed to evaluate the long-term safety of lapaquistat acetate 50 mg QD administered orally.

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Number of Subjects:

Planned: 600 to 660 subjects (450-495 lapaquistat acetate, 150-165 placebo)

Analyzed: DB Full Analysis Set — 653 subjects (488 lapaquistat acetate, 165 placebo)

DB Safety Analysis Set — 654 subjects (489 lapaquistat acetate, 165 placebo)

OLE Safety Analysis Set — 207 subjects

Diagnosis and Main Criteria for Inclusion:

To qualify for study participation, subjects must have been men or women at least 18 years of age; have been able to understand and willing to sign an informed consent form; have been willing and able to comply with a standardized diet (therapeutic lifestyle changes or equivalent); and have had, prior to Randomization, a mean LDL-C ≥130 mg/dL (3.37 mmol/L) and ≤190 mg/dL (4.92 mmol/L) for 2 consecutive samples at least 7 days apart (with the difference between the 2 individual LDL-C values having been <15% of the higher value), and a mean TG level ≤400 mg/dL (4.52 mmol/L) for 2 consecutive samples at least 1 week apart (with each of the 2 individual values having been ≤450 mg/dL [5.08 mmol/L]). Women of childbearing potential who were sexually active must have agreed to use adequate contraception from screening throughout the duration of the study and for 30 days following the last dose.

Test Product, Dose and Mode of Administration, Lot Number:

Lapaquistat acetate, 50 mg tablet, oral Z553B043, Z553B061

Duration of Treatment:

After a 6-week Dietary Run-In Period, the total duration of treatment was to be a maximum of 60 weeks, including a 12-week DB Period and an optional 48-week OLE.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Placebo, tablet, oral Z5335112

Criteria for Evaluation:

The primary efficacy variable for this study was fasting plasma LDL-C.

The secondary efficacy variables were non–HDL-C; TC; Apo B; TG; HDL-C; Apo A1; VLDL-C; the derived ratios LDL-C/HDL-C, TC/HDL-C, and Apo B/Apo A1; and hs-CRP.

Safety:

Safety variables were adverse events, clinical laboratory test results, vital signs measurements, ECG results, and physical examination findings.

Statistical Methods:

The safety data were summarized using descriptive summary statistics.

DB Period

The primary efficacy analysis was based on the percent change in LDL-C from Baseline to the Week 12 (or Early Termination [ET]) on-treatment value during the DB period. The treatment groups were compared using an analysis of covariance (ANCOVA) model with terms for treatment group and baseline value (as a covariate). The P-value, least squares (LS) means, difference between the LS treatment means, and 95% confidence intervals for the treatment difference were displayed in the summary tables. Also for the primary efficacy variable, subgroup analyses by TG level (≤150, >150mg/dL, classified by baseline value), age (<65, ≥65 years), gender, race (White, non-White), and body mass index (≤30, >30 kg/m^2) were performed. To display time effects, the primary variable was also summarized and analyzed by study visit using the ANCOVA described above. These ANCOVA analyses were also repeated using observed data at each study visit individually (without last observation carried forward). At Baseline, analysis of variance was used with treatment group as a fixed effect. LS means, differences between LS treatment means, and P-values were presented. In addition, subjects achieving prespecified LDL-C concentrations of

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<160, <130, and <100 mg/dL (4.1, 3.37, and 2.59 mmol/L, respectively) at Week 12 (or ET) were summarized in a shift table (from Baseline to Week 12 [or ET]).

To display time effects, the secondary variables (non-HDL-C, TC, Apo B, TG, HDL-C, Apo A1, VLDL-C, LDL-C/HDL-C, TC/HDL-C, Apo B/Apo A1, and hs-CRP) were summarized by study visit and at Final Visit using last observation carried forward. For the derived ratios, change from Baseline was summarized; for the other variables, percent change from Baseline was summarized.

OLE

The efficacy variables (LDL-C, non-HDL-C, TC, Apo B, TG, HDL-C, Apo A1, VLDL-C, LDL-C/HDL-C, TC/HDL-C, Apo B/Apo A1, and hs-CRP) were summarized by study visit and at Final Visit using last observation carried forward. For the derived ratios, change from Baseline was summarized; for the other variables, percent change from Baseline was summarized.

SUMMARY OF RESULTS

Subject Disposition:

A total of 1163 subjects were screened in 51 centers in Europe, including Russia and Israel. Of these, 507 subjects were not randomized to treatment; however, 1 subject who was not randomized to treatment received lapaquistat acetate. The most common reasons that subjects were not randomized were LDL-C criterion not met, other entrance criteria not met, and voluntary withdrawal.

Of the 656 subjects randomized to treatment in the DB Period, 3 (0.5%) were not treated; 247 (37.7%) completed the study; and 406 (61.9%) prematurely discontinued from the study, including 106 of 165 subjects in the placebo group (64.2%) and 300 of 491 subjects in the lapaquistat acetate group (61.1%). The most common reason for premature discontinuation was study termination.

A total of 209 subjects from the DB Period were enrolled in the OLE, including 49 subjects who had received placebo and 160 subjects who had received lapaquistat acetate 50 mg. Of the 209 subjects enrolled in the OLE, 2 (1.0%) were not treated; 3 (1.4%) completed the study; and 204 (97.6%) prematurely discontinued from the study. The most common reason for premature discontinuation was premature study termination by the sponsor.

Demographics:

Of the subjects included in the full analysis set for the DB Period, 261 (40.0%) were male and 392 (60.0%) were female, and nearly all (99.5%) were White. The mean age was 56.7 years. No important differences in demographic or baseline characteristics were observed between the treatment groups.

Of the subjects included in the safety set for the OLE, 73 (35.3%) were male and 134 (64.7%) were female, and nearly all (99.5%) were White. The mean age was 58.3 years.

Efficacy Results:

Because this study was prematurely terminated, efficacy results are not presented in the text of this abbreviated report. Tabular results for efficacy are provided in Tables 15.1.7.2-15.1.7.3, 15.2.1.1-15.2.13.1, 15.1.5.2OLE-15.1.5.3OLE, and 15.2.1.1OLE-15.2.12.2OLE.

Safety Results:

DB Period

During the DB Period, adverse events were reported for 24.8% of subjects in the placebo group (41/165) and 24.1% of subjects in the lapaquistat acetate group (118/489). The most frequently reported adverse events were nasopharyngitis (4.2% in the placebo group and 3.7% in the lapaquistat acetate group) and headache (4.2% in the placebo group and 2.2% in the lapaquistat acetate group). Most adverse events in both treatment groups were mild or moderate in intensity; adverse events of severe intensity were experienced by 0.6% of subjects in the placebo group and 1.0% of subjects in the lapaquistat acetate group.

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Adverse events of increased alanine aminotransferase/aspartate aminotransferase (ALT/AST) were reported for 4 subjects in the lapaquistat acetate group; none of the events were considered related to study drug. An adverse event of increased creatine kinase (CK) was reported for 1 subject in the lapaquistat acetate group; the event was considered possibly related to study drug. No adverse events of increased ALT/AST or increased CK were reported in the placebo group. In addition, mean increases in ALT, AST, and CK were observed from Baseline to Final Visit in the lapaquistat acetate group but not in the placebo group. No other clinically significant abnormal laboratory values were observed.

One subject had ECG results that were categorized as abnormal but not clinically significant at Baseline and as abnormal and clinically significant at Final Visit. No other clinically significant ECG abnormalities were observed. No changes in vital signs or physical examination findings were reported as adverse events during the DB Period.

A total of 20 subjects experienced adverse events leading to temporary or permanent discontinuation of study drug (4/165 subjects in the placebo group [2.4%] and 16/489 subjects in the lapaquistat acetate group [3.3%]). Two subjects in the placebo group and 3 subjects in the lapaquistat acetate group had adverse events leading to temporary discontinuation of study drug. Of the 2 subjects in the placebo group, 1 had an adverse event considered not related to study drug, and 1 had an adverse event considered possibly related to study drug. Of the 3 subjects in the lapaquistat acetate group, 1 had an adverse event considered not related to study drug, and 2 had adverse events considered possibly or probably related to study drug. Two subjects in the placebo group (1.2%) and 13 subjects in the lapaquistat acetate group (2.6%) experienced adverse events leading to permanent discontinuation of study drug. Both subjects in the placebo group had adverse events considered possibly related to study drug. Of the 13 subjects in the lapaquistat acetate group, 3 had adverse events considered not related to study drug, and 10 had adverse events considered possibly or probably related to study drug.

A total of 6 serious adverse events (SAEs), including 1 death, were reported for 6 subjects (1/165 subjects in the placebo group [0.6%] and 5/489 subjects in the lapaquistat acetate group [1.0%]). One SAE was considered possibly related to study drug (syncope in a subject in the lapaquistat acetate group); all other SAEs were considered not related to study drug.

One subject in the lapaquistat acetate group died (acute coronary insufficiency); the death was considered not related to study drug.

OLE

In the OLE, adverse events were reported for 27.1% of subjects (56/207). The most frequently reported adverse events were respiratory tract infection viral (5.8%), hypertension (2.9%), and bronchitis and nasopharyngitis (2.4% each). Most adverse events were mild or moderate in intensity; adverse events of severe intensity were experienced by 1.9% of subjects.

Adverse events of increased ALT/AST were reported for 4 subjects; these events were considered possibly related to study drug in 2 subjects and not related to study drug in 2 subjects. Adverse events of increased CK were reported for 2 subjects; these events were considered possibly related to study drug. Mean changes in ALT, AST, and CK from Baseline to Final Visit were small and not clinically meaningful. No other clinically significant abnormal laboratory values and no changes in vital signs, ECGs, or physical examination findings were reported as adverse events in the OLE.

A total of 4 subjects experienced adverse events leading to temporary or permanent discontinuation of study drug (1.9%). Three subjects who received lapaquistat acetate during the DB Period had adverse events leading to temporary discontinuation of study drug; all of these events were considered not related to study drug. One subject who received placebo during the DB Period had an adverse event leading to permanent discontinuation of study drug; this event was considered not related to study drug.

A total of 4 SAEs were reported for 3 of 207 subjects (1.4%) during the OLE. None of these SAEs were considered by the investigator to be related to study drug.

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No deaths occurred in the OLE.
CONCLUSIONS: • The study was prematurely terminated. • One death was reported during the DB Period; the death was considered not related to study drug. No deaths were reported in the OLE. • SAEs were reported for 6 subjects during the DB Period and 3 subjects in the OLE. • Laboratory abnormalities of ALT and AST elevations were infrequent and seen only in the lapaquistat acetate treatment groups.
Date of Report: 13 May 2009