Introduction

- Lomitapide is an orally active inhibitor of microsomal triglyceride transfer protein that has been developed specifically for the treatment of homozygous familial hypercholesterolemia (HoFH), a rare genetic disease characterized by markedly elevated plasma levels of low-density lipoprotein cholesterol (LDL-C) and prematurely cardiovascular disease.1
- Based on the results of a pivotal Phase 3 study, lomitapide has been approved in the United States, the European Union, Canada, and Mexico as an adjunct to other lipid-lowering therapies, including apheresis, to reduce LDL-C in patients with HoFH.2

Aims

- The primary objective of this Phase 1 study (AERGEPH-733-023, NCT01761877) was to compare the pharmacology (PK/PD) of lomitapide between Japanese and Caucasian subjects with elevated LDL-C after single and multiple doses, across the dose range studied (10–60 mg). Secondary objectives were to compare the pharmacodynamics (PD), safety, and tolerability between ethnicities across the dose range studied.

Methods

Subjects

- 36 Japanese and 36 Caucasian healthy male subjects (aged 20–45 years) with LDL-C level ≥110 mg/dL were enrolled in the study and were randomly assigned to receive a single or multiple ascending doses of lomitapide.
- Cohort 1 (10 mg): 20 Japanese and 20 Caucasian subjects treated with lomitapide; 10 Japanese and 10 Caucasian subjects treated with placebo.
- Cohorts 2, 3, and 4 (20, 40, and 60 mg): six Japanese and six Caucasian subjects treated with lomitapide; two Japanese and two Caucasian subjects treated with placebo.
- Japanese and 35 Caucasian subjects completed the study (see Safety Analysis for details of subjects who did not complete the study).

Study Design

- A randomized, double-blind, placebo-controlled, single- and multiple ascending dose study.
- No prescription or nonprescription drugs were permitted while the subjects participated in the study, except when necessary to treat an adverse event (AE) or in case of rescue medication.
- An overview of the study design is shown in Figure 1.

PK/PD

- The majority of treatment-related adverse events (TEAEs) were gastrointestinal (GI) disorders.
- The incidence of treatment-related TEAEs was gastrointestinal (GI) disorders.

Outcome measures

- PK parameters were LDL-C, very low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and apolipoprotein B (Apo B) and triglycerides (TG).
- PD parameters were derived for lomitapide and the metabolites M1 and M2 by noncompartmental analysis using Phoenix WinNonlin (version 6.2.1).
- Single-dose PK (Day 7): maximum plasma concentration (Cmax, tmax) were used for calculations (AUC from zero to last quantifiable concentration, AUC0-τ).
- Multiple-dose PK (Day 27): Cmax, AUC0-τ, AUC over the dosing interval (AUC0-τ).
- On Days 1, 14, 20, 22, 24, and 27, predose plasma samples were taken in order to determine the minimum plasma concentration.
- Safety assessments included standard laboratory safety tests, vital signs, 12-lead electrocardiogram, and physical examination.

Pharmacokinetic analyses

- The ratio of AUC0-τ (Japanese/Caucasian subjects) ranged from 94% to 110% with no consistent pattern across doses (Figure 3).
- The ratio of Cmax also failed to demonstrate a consistent pattern across doses (range: 52–143%). Ratios for Cmax were similar across dose cohorts.
- There were no remarkable differences in mean Cmax or AUC0-τ values for metabolites M1 and M2 between Japanese and Caucasian subjects across dose levels (data not shown).

Pharmacodynamics

- The ratio of placebo-subtracted mean percent change from baseline in LDL-C was dose-dependent and similar across both ethnic groups.
- Similar changes were observed for other lipoproteins. Lowest mean value and corresponding percentage change (P% change) in FPD parameters are summarized in Table 1.
- Linear regression analysis of the steady-state lomitapide AUC0-τ versus predose trough concentration (C0) showed that adjusted R² was 0.70 for both Japanese and Caucasian subjects at the 10, 20, 40, and 60 mg dose levels, indicating the relationship between AUC0-τ and C0 was linear (data not shown).
- The incidence of treatment-related TEAEs was gastrointestinal (GI) disorders.
- There were no serious AEs.
- Three subjects died outside of the study: two Japanese subjects (one with increased hepatic enzymes and one with viral cranial paraesthesia), and one Caucasian subject (myocardial).
- The abnormalities seen in the liver function tests (ALT, AST) were in line with expectations.
- The occurrence of abnormal ALT did not seem to be dose or race dependent.

Safety profile

- The safety profile of lomitapide appeared similar in Japanese and Caucasian subjects, with no evidence of a greater incidence of hepatic or renal abnormalities in either ethnic group, and no suggestion of an increased comparative incidence of GI or other TEAEs.

Conclusion

- The safety profile of lomitapide was similar in Japanese and Caucasian subjects. Single and multiple oral doses of lomitapide were well tolerated in both groups.
- These findings suggest that a different dose range for lomitapide in Japanese subjects compared with Caucasian subjects is unnecessary.

References


Acknowledgments

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Table 1. Lowest mean value and corresponding percent change in FPD parameters if LDL-C levels

<table>
<thead>
<tr>
<th>PD parameter</th>
<th>Cochort 1 (10 mg)</th>
<th>Cochort 2 (20 mg)</th>
<th>Cochort 3 (40 mg)</th>
<th>Cochort 4 (60 mg)</th>
<th>Japanese subjects</th>
<th>Caucasian subjects</th>
</tr>
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<tbody>
<tr>
<td>Cmax (ng/mL)</td>
<td>140.5</td>
<td>10.4</td>
<td>140.8</td>
<td>4.4</td>
<td>72.9</td>
<td>60.6</td>
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<tr>
<td>AUC0-τ (mg*h)</td>
<td>37.4</td>
<td>37.4</td>
<td>37.4</td>
<td>37.4</td>
<td>37.4</td>
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</table>

Table 2. Number of Japanese (J) and Caucasian (C) subjects with treatment-emergent TEAEs by treatment group

<table>
<thead>
<tr>
<th>Group</th>
<th>J (n)</th>
<th>C (n)</th>
<th>J (n)</th>
<th>C (n)</th>
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<td>T007</td>
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<tr>
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<tr>
<td>T016</td>
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<td>1</td>
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Table 3. Ratios of least squares (LS) means Japanese/Caucasian subjects (%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cohort</th>
<th>J/C ratio</th>
<th>J/C ratio</th>
<th>J/C ratio</th>
<th>J/C ratio</th>
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<td></td>
<td>Cohort 2 (20 mg)</td>
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<td>100</td>
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<td></td>
<td>Cohort 3 (40 mg)</td>
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<td></td>
<td>Cohort 4 (60 mg)</td>
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