Lomitapide single-and multiple-dose exposure in Japanese and Caucasian subjects: results of a Phase 1 pharmacokinetic and pharmacodynamic study

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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 premature cardiovascular disease.[1]
- Based on the results of a pivotal Phase 3 study,[2] 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.[3,4]

Aims

- The primary objective of this Phase 1 study (AEGR-733-023; NCT01760187) was to compare the pharmacokinetics (PK) of lomitapide between Japanese and Caucasian subjects with elevated LDL-C after single and multiple doses, across the dose range studied (10–60mg). Secondary objectives were to compare the pharmacodynamics (PD), safety, and tolerability between ethnicities across the dose range studied.

Methods

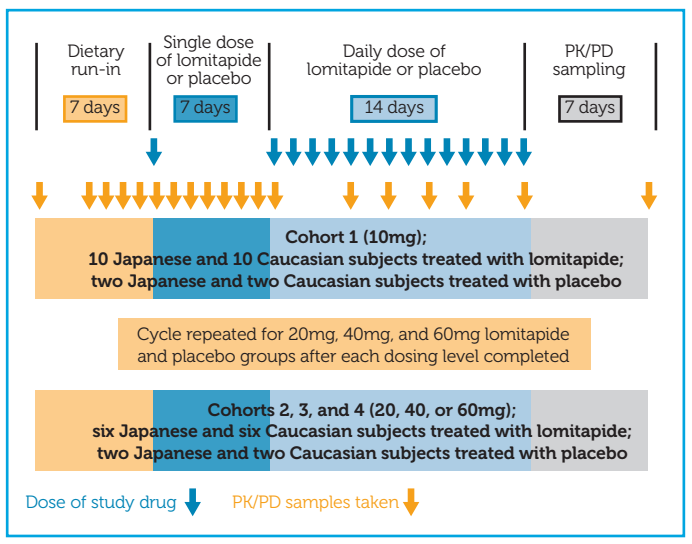
Subjects

- 36 Japanese and 36 Caucasian healthy male subjects (aged 20–45 years) with LDL-C level ≥110mg/dL entered the study and were analysed for safety and PD.
  - Four randomized cohorts:
    - Cohort 1 (10mg): 10 Japanese and 10 Caucasian subjects treated with lomitapide; two Japanese and two Caucasian subjects treated with placebo.
    - Cohorts 2, 3, and 4 (20, 40, and 60mg): six Japanese and six Caucasian subjects treated with lomitapide; two Japanese and two Caucasian subjects treated with placebo.
  - 34 Japanese and 35 Caucasian subjects completed the study (see Safety analysis for details of three 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.

Figure 1. *Study design*



Outcome measures

- PD parameters were LDL-C, very low density lipoprotein (VLDL), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), lipoprotein (a), apolipoprotein B (Apo B), and triglycerides (TG).
- PK parameters were derived for lomitapide and the metabolites M1 and M3 by noncompartmental analysis using Phoenix WinNonlin (version 6.2.1).
  - Single-dose PK (Day 7): maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration time curve (AUC) from zero to infinity, AUC from zero to last quantifiable concentration (AUC_{0-t}), and half-life ($t_{1/2}$).
  - Multiple-dose PK (Day 27): C_{max}, t_{max}, AUC over the dosing interval (τ=24 h) on Day 27 ($AUC_{0-\tau}$), $t_{1/2}$.
  - On Days 14, 18, 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.

Results

Pharmacodynamic analyses

- Lomitapide dose-dependent reductions in lipid parameters (LDL-C, VLDL, TC, Apo B, and TG) were observed in similar levels across ethnic groups.
  - The placebo-subtracted mean percent change from baseline in LDL-C at Day 28 (end of multiple dosing phase) is shown in Figure 2.
  - Similar changes were observed for other lipoproteins. Lowest mean value and corresponding percentage (%) change in PD parameters are summarized in Table 1.

Figure 2. *Placebo-subtracted mean percent change from baseline in LDL-C across dose cohorts in Japanese and Caucasian subjects, shown with 95% confidence interval (CI)*

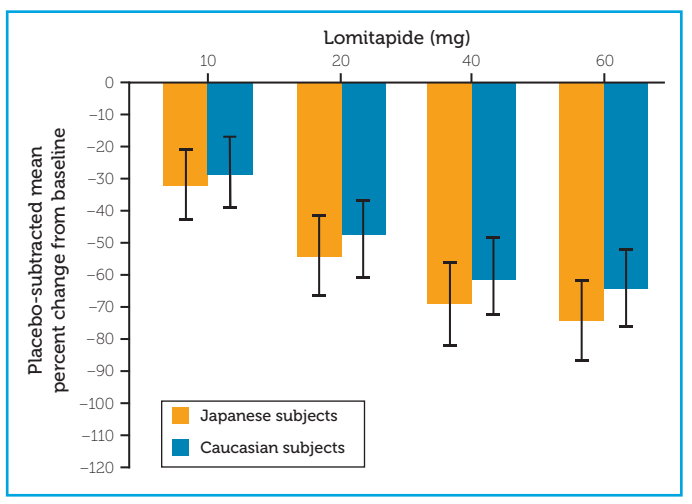


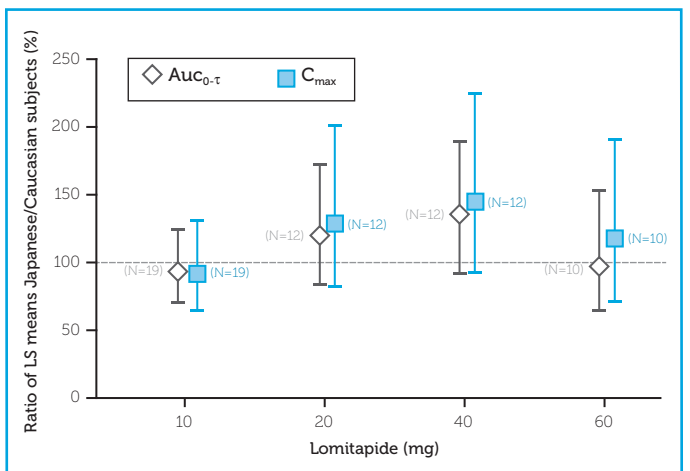
Table 1. *Lowest mean value and corresponding percent change in PD parameters*

PD parameter	Cohort	Japanese subjects		Caucasian subjects	
		Lowest mean value (mg/dL)	Change (%)	Lowest mean value (mg/dL)	Change (%)
LDL-C	Placebo	140.3	1.0	142.8	−4.4
	1 (10mg)	72.9	−49.6	74.9	−52.8
	2 (20mg)	31.7	−75.4	32.3	−76.5
	3 (40mg)	7.2	−94.4	12.0	−92.1
	4 (60mg)	5.8	−95.7	6.0	−96.0
HDL-C	Placebo	41.1	−8.0	34.5	−8.1
	1 (10mg)	33.3	−17.9	27.2	−26.4
	2 (20mg)	36.2	−19.8	29.8	−24.1
	3 (40mg)	31.8	−26.8	22.0	−37.7
	4 (60mg)	32.8	−25.1	27.3	−32.1
VLDL	Placebo	33.9	9.4	35.8	−0.8
	1 (10mg)	16.0	−54.8	15.5	−52.7
	2 (20mg)	9.9	−74.1	7.9	−76.2
	3 (40mg)	3.4	−90.6	3.7	−85.5
	4 (60mg)	2.2	−94.5	3.0	−92.6
TC	Placebo	215.8	2.9	216.1	−1.0
	1 (10mg)	130.2	−39.1	127.0	−43.5
	2 (20mg)	84.8	−57.8	78.7	−61.0
	3 (40mg)	48.3	−76.5	44.8	−78.3
	4 (60mg)	43.6	−79.2	42.4	−81.2
Lipoprotein (a)	Placebo	19.0	−37.0	27.4	−24.0
	1 (10mg)	27.1	−36.1	26.9	−27.1
	2 (20mg)	7.8	−63.1	25.8	−42.5
	3 (40mg)	12.5	−53.3	8.6	−48.3
	4 (60mg)	11.9	−54.3	16.8	−53.5
Apo B	Placebo	109.5	1.7	115.2	−4.0
	1 (10mg)	63.5	−44.1	64.6	−16.1
	2 (20mg)	29.7	−70.9	29.9	−71.8
	3 (40mg)	11.1	−89.4	13.3	−88.3
	4 (60mg)	10.0	−90.7	10.0	−91.7
Total TG	Placebo	169.2	9.4	179.1	−0.7
	1 (10mg)	80.1	−54.8	77.4	−52.7
	2 (20mg)	49.6	−74.1	39.4	−76.3
	3 (40mg)	15.4	−90.4	15.1	−88.0
	4 (60mg)	9.7	−93.7	12.6	−92.9

Pharmacokinetics

- The ratio of $AUC_{0-\tau}$ (Japanese/Caucasian subjects) ranged from 94% to 133% with no consistent pattern across doses (Figure 3). Ratios for C_{max} also failed to demonstrate a consistent pattern across doses (range 92–145%). Exposures in both ethnic groups were similar (Figure 3).
- There was no remarkable difference in mean C_{max} or $AUC_{0-\tau}$ values for metabolites M1 and M3 between Japanese and Caucasian subjects across dose levels (data not shown).

Figure 3. *Ratios of least squares (LS) means Japanese/Caucasian subjects (%) for C_{max} and $AUC_{0-\tau}$ following multiple ascending doses of lomitapide, demonstrating that exposures were similar in the two ethnic groups. Ratios are shown with 90% CIs*



n, total number of subjects (Japanese and Caucasian); LS mean from analysis of variance, calculated by transforming the natural log means back to the linear scale (i.e., geometric LS mean)

- Linear regression analysis of the steady-state lomitapide $AUC_{0-\tau}$ versus predose trough concentration (C_{trough}) showed that adjusted R^2 was >70% for both Japanese and Caucasian subjects at the 10, 20, 40, and 60mg dose levels, indicating that the relationship between $AUC_{0-\tau}$ and C_{trough} was linear (data not shown).

Safety analysis

- Overall, safety results showed good tolerability of lomitapide.
  - The number of Japanese and Caucasian subjects with treatment-related treatment-emergent AEs (TEAEs), by treatment group, is summarized in Table 2.
    - The majority of treatment-related TEAEs were gastrointestinal (GI) disorders.
    - The incidence of TEAEs, including GI TEAEs, appeared to increase with raising the lomitapide dose.
    - There were no serious AEs.
    - Three subjects discontinued due to AEs: two Japanese subjects (one with increased hepatic enzymes and one with VII cranial nerve paralysis), and one Caucasian suject (diarrhea).
- The abnormalities seen in the liver function tests (LFTs) were in line with expectations.
  - The occurrence of abnormal LFTs did not seem to be dose or race dependent.

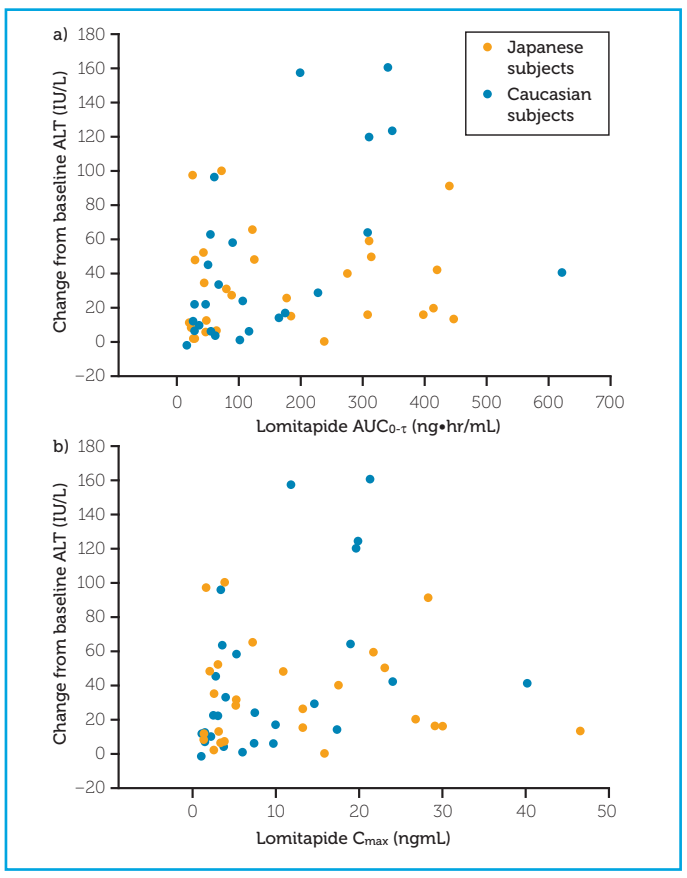
Safety relationships

- There was no apparent relationship between ALT levels and lomitapide $AUC_{0-\tau}$ and C_{max} values (Figure 4).

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

System organ class preferred term	Lomitapide								Pooled placebo	
	10mg		20mg		40mg		60mg			
	J n=10	C n=10	J n=6	C n=6	J n=6	C n=6	J n=6	C n=6	J n=8	C n=8
GI disorders	2	4	–	1	3	5	5	6	2	1
General disorders and administration site conditions	2	–	–	–	–	1	–	–	–	1
Metabolism and nutrition disorders	–	1	–	–	–	–	–	2	–	–
Investigations	1	–	–	–	–	–	–	–	–	–
Musculoskeletal and connective tissue disorders	1	1	–	–	–	–	–	2	–	2
Nervous system disorders	1	1	1	1	–	–	1	2	1	–
Renal and urinary disorders	–	–	–	–	–	1	–	–	–	–
Psychiatric disorders	1	–	–	–	–	–	–	–	–	–
Respiratory, thoracic, and mediastinal disorders	–	–	–	1	–	1	–	–	–	2
Vascular disorders	–	–	1	–	2	–	–	–	–	–

Figure 4. *Scatter plots of change from baseline in ALT versus (a) lomitapide $AUC_{0-\tau}$ and (b) lomitapide C_{max} following multiple dose administration of lomitapide on Day 27*



Discussion

- There were no clinically relevant differences in multiple dose exposure, PK, or PD of lomitapide between Japanese and Caucasian subjects with elevated LDL-C levels.
  - The ratio (Japanese/Caucasian subjects) of $AUC_{0-\tau}$ (94–133%) and C_{max} (92–145%) showed no consistent pattern across doses, suggesting no greater exposure in either ethnic group.
  - Mean percent change from baseline in LDL-C was dose dependent and similar across dose cohorts in Japanese and Caucasian subjects.
- The safety profile of lomitapide appeared similar in Japanese and Caucasian subjects, with no evidence of a greater incidence of hepatic aminotransferase elevations in either ethnic group, and no suggestion of an increased comparative incidence of GI (or other) TEAEs.
  - The absence of any difference in the incidence of adverse events suggests that no clinically relevant difference in exposure occurred during the study.
  - The lack of relationship between lomitapide exposure and peak aminotransferase level or cumulative aminotransferase release suggests that this adverse effect would not be sensitive to any ethnic differences in exposure.

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

1. Marais AD, Firth JD, Blom DJ. Semin Vasc Med 2004;4:43–50.
2. Cuchel M, Meagher EA, du Toit Theron H, Blom DJ, Marais AD, Hegele RA, Averna MR, Sirtori CR, Shah PK, Gaudet D, Stefanutti C, Vigna GB, Du Plessis AM, Propert KJ, Sasiela WJ, Bloedon LT, Rader DJ; Phase 3 HoFH Lomitapide Study investigators. Lancet 2013;381:40–6.
3. Aegerion Pharmaceuticals Inc. Juxtapid prescribing information 2013. Available from: http://www.juxtapidremsprogram.com/_pdf/012187_JuxtapidPI_8.5x11_FIN.PDF
4. Aegerion Pharmaceuticals Inc. Lojuxta summary of product characteristics 2013. Available from: http://www.medicines.org.uk/emc/medicine/28321/SPC/Lojuxta+hard+capsules/.

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