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APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	203-858/N-000
Drug Name:	Lomitapide mesylate capsules
Indication(s):	Treatment of homozygous familial hypercholesterolemia
Applicant:	Aegerion Pharmaceuticals, Inc.
Date(s):	Received 02/29/12; user fee (10 months) 12/29/12
Review Priority:	Standard
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical Reviewer:	Cynthia Liu, MA
Concurring Reviewer(s):	Todd Sahlroot, Ph.D., Statistical Team Leader and Deputy Director of Biometrics II
Medical Division:	Division of Metabolic and Endocrine Products (HFD-510)
Clinical Team:	James Smith, M.D., Medical Reviewer
	Eric Colman, M.D., Medical Team Leader and Deputy Director of DMEP
Project manager:	Kati Johnson
Keywords:	NDA review, clinical studies

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Data from the pivotal Phase 3 trial have demonstrated that lomitapide was effective in reducing LDL-C, total cholesterol (TC), Apo B, triglycerides (TRIG), non-HDL-C, and VLDL-C in patients with HoFH after 26 weeks of treatment when used as an adjunct to a low-fat diet and other lipid-lowering therapies with or without LDL apheresis. The reductions seemed to be maintained through Week 56 for LDL-C, TC, ApoB, and non-HDL-C. Lomitapide was also shown to lower HDL-C during the 26-week dose-titration efficacy phase. However, the mean HDL-C at Week 56 was returned to its baseline level.

Evaluation of the data after Week 56 may be important for TRIG, VLDL-C, and especially HDL-C since the long-term effect of lomitapide on these parameters remains to be seen.

Labeling Comments: The following bullets summarize this reviewer's comments for the sponsor's proposed labeling in the Clinical Studies section.

- The sponsor stated the primary efficacy endpoint as "mean" percent change in LDL-C from baseline at Week 26. The "mean" should be omitted since it is not an endpoint; rather, it is an average of the endpoint values of the treated subjects in the study.

- Figure 1 is currently based on the ITT population with LOCF. This reviewer thinks that the graph should be based on the completers over time, with Week 26/LOCF values alongside.

- Table 5 presents the results for Week 26/LOCF (N = 29) and Week 56 (N = 23). It may be informative to include Week 26 (N = 23) results also so that there is a direct comparison between the 2 time points.

- The parameters listed in Table 5 should be clearly identified as the primary, key secondary, and other efficacy variables in the text. An asterisk (*) may be used to indicate a significant p-value for the primary and key secondary variables since their statistical analyses were prioritized.

1.2 Brief Overview of Clinical Studies

Aegerion Pharmaceuticals, Inc. has submitted an original NDA seeking approval of lomitapide mesylate capsules for the treatment of homozygous familial hypercholesterolemia (HoFH) when used as an adjunct to a low-fat diet and other lipid-lowering therapies with or without LDL apheresis. Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor. It has received an orphan drug designation for this indication on 10/23/2007. In

this NDA, the sponsor included the results from 24 clinical trials, ranging from Phase 1 to Phase 3, that were conducted in healthy subjects, adults with elevated LDL-C and other risk factors for CVD (without HoFH), adults with hepatic impairment, adults with end stage renal disease on dialysis, and adults with HoFH. The efficacy of lomitapide in patients with HoFH would be determined primarily based on the results from a pivotal Phase 3 study UP1002/AEGR-733-005 (29 patients) and a supportive Proof-of-Concept Phase 2 study UP1001 (6 patients) since the other trials were conducted in different populations.

The pivotal Phase 3 study was a 78-week, open-label, single-arm, dose-escalation (5, 10, 20, 40, 60 mg/day), multicenter, multinational trial, conducted at 11 sites located in US, Canada, South Africa, and Italy. The supportive Phase 2 study was a 16-week, open-label, single-arm, dose-escalation (0.03, 0.1, 0.3, 1.0 mg/kg/day), single-center (in US) trial. In the pivotal study, subjects were required to continue their concomitant lipid-lowering therapies through Week 26 (efficacy phase) and follow a diet with < 20% energy from fat; while in the supportive study, subjects were asked to stop all the lipid-lowering therapies prior to the Baseline visit but follow a rigorous low-fat diet with < 10% energy from fat.

At the time of the NDA submission, the pivotal trial was still ongoing. Therefore, the sponsor's clinical study report covers only the data and results through Week 56 based on the data cut-off date of 04/12/2011.

1.3 Statistical Issues and Findings

For Study UP1002/AEGR-733-005, a total of 29 subjects were enrolled and treated with lomitapide. As of 04/12/2011 the data cut-off date, 6 patients discontinued from the trial prior to Week 26; 23 of the 29 enrolled patients completed Week 56; and 18 of the 23 patients completed the entire 78-week trial. For Study UP1001, all the 6 enrolled subjects completed the trial.

As shown in Table 6 in the main body of this review, for the pivotal Phase 3 trial (Study UP1002/AEGR-733-005), the mean % decrease in LDL-C from baseline to Week 26 was about 40% for the ITT/LOCF population (N = 29) and 50% for the completers (N = 23). In addition, a total of 20 patients had a > 15% decrease in LDL-C at Week 26. Although the study was not designed as a dose-response trial, it was noted that the mean % reductions in LDL-C were increasing as doses were increased over the titration period (see Table 7 in the main body of this review). The reduction, however, reached a plateau at Week 18, but was sustained around 40-45% between Weeks 36 and 56 with the mean maximum tolerated dose (MTD) about 40 mg.

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