CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203858Orig1s000

SUMMARY REVIEW

Summary Basis for Regulatory Action

Date	December 21, 2012
From	Christine P. Nguyen, MD Acting Deputy Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA #	203-858
Applicant Name	Aegerion Pharmaceuticals, Inc.
Date of Submission	2/29/12
PDUFA Goal Date	12/29/12
Proprietary Name / Established (USAN) Name	Juxtapid/lomitapide
Dosage Forms / Strength	5, 10, 20 mg oral capsules (immediate release) Recommended starting dose of 5 mg daily at bedtime. After 2 weeks the daily dose may be increased, based on acceptable safety and tolerability, to 10 mg and then, at a minimum of 4-week intervals, to 20 mg, 40 mg, and the maximum recommended dose of 60 mg.
Proposed Indication	An adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B) and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH)
Regulatory Action:	Approval

Material Reviewed/Consulted **Reviews from the following disciplines:**	**Names of discipline reviewers**
Clinical	James Smith/ Eric Colman
Statistics	Cynthia Liu/ Jon Todd Sahlroot
Pharmacology Toxicology	Brian (Tim) Hummer/ Karen Davis-Bruno
CMC Biopharmaceutics	Xavier Ysern/ Ali H Al Hakim Elsbeth Chikhale/ John Duan
Clinical Pharmacology	Sze (Johnny) Lau/ Immo Zadezensky
Office of Scientific Investigations	Susan Leibenhaut/ Janice Pohlman
OSE/DEPI	Patricia Bright/ Diane Wysowski
OSE/DRISK	Amarilys Vega/ Cynthia LaCivita
Pediatric and Maternal Health Staff	Jeanine Best/ Melissa Tassinari

OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

1. Introduction and Background

This memo summarizes the basis for the regulatory action for lomitapide. This oral drug is being proposed for the orphan indication of the treatment of homozygous familial hypercholesteremia (HoFH). In-depth review and analyses of specific issues can be found in the primary reviews of the respective disciplines. This memo contains my summary, assessments, and conclusions concerning the major issues identified during the review of this application.

Lomitapide is a first-in-class small molecule inhibitor of the microsomal triglyceride protein (MTP) that transfers lipids to apolipoprotein B to form the apo B-containing lipoprotein complex. Inhibition of MTP prevents the assembly and secretion of apo B-containing lipoproteins, which include VLDL-C (the precursor of LDL-C), and chylomicrons from the liver and intestine, respectively.

Homozygous familial hypercholesteremia (HoFH) results from loss of function mutations in both alleles of the LDL receptor (LDL-R). These mutations render the LDL-Rs absent or non-functional leading to reduced clearance of LDL particles from circulation, resulting in marked elevation in plasma LDL-C levels. Untreated LDL-C levels in individuals with HoFH usually range from 500 to 1000 mg/dL. If left untreated, HoFH patients die prematurely from accelerated atherosclerotic cardiovascular disease by the second or third decade of life. In the U.S., the prevalence of HoFH is approximately 1 per million persons.

Treatment options for HoFH are limited in number and in scope. High potency HMG-CoA reductase inhibitors (statins), with or without a cholesterol absorption inhibitor, and LDL apheresis are the mainstay of therapy (see Table 1). Statin therapy depends on functional LDL-Rs for most of its lipid lowering effects and, therefore, has limited efficacy in HoFH. Similar to dialysis, LDL apheresis is an extracorporal procedure that selectively removes apo-B containing lipoproteins (VLDL-C, LDL-C, lipoprotein (a), and triglycerides). The procedure, however, needs to be performed on a chronic, repetitive basis of every one to two weeks, and there are currently only 35 apheresis centers in the U.S. Liver transplantation has been employed rarely as a last resort.

Table 1: Non-surgical therapies for HoFH

Therapy	Mechanism of action	LDC-C lowering response in HoFH
HMG-CoA reductase inhibitors	LDLR activity	< 10 – 25%
Cholesterol absorption inhibitors	LDLR activity, inhibits cholesterol absorption	< 10%
LDL-apheresis*	LDL-C removal	~30 – 40%[1]

*Response based on time averaged LDL-C levels; acutely, apheresis lowers LDL-C by 50-75%

Drug therapy in combination with LDL apheresis can typically reduce LDL-C by 45% to 55%.[2] Because HoFH patients have such elevated LDL-C levels at baseline (> 500 mg/dL),

[1] Pfohl M, Naoumova RP, Klass C, Knisel W, Jakober B, Risler T, Thompson GR. Acute and chronic effects on cholesterol biosynthesis of LDL-apheresis with or without concomitant HMG-CoA reductase inhibitor therapy. J Lipid Res. 1994;35(11):1946.
[2] Gilbert R. Thompson, M. Barbir, D. Davies, et al. Efficacy criteria and cholesterol targets for LDL apheresis. Atherosclerosis 208 (2010) 317–321.

combining multiple treatment modalities still fails to provide adequate control of LDL-C, and HoFH patients remain at high-risk for serious adverse cardiovascular events and premature death. There is a clear need for additional therapies to help HoFH patients either approach or reach LDL-C treatment goals.

This NDA submission supports the use of lomitapide at a starting daily dose of 5 mg titrated to a maximum of 60 mg, based on safety and tolerability, as an adjunct to diet and lipid lowering therapies to reduce LDL-C in HoFH patients.

2. Recommendations of Review Disciplines regarding Approvability

This section summarizes key recommendations from the review disciplines.

CMC: In his review signed on October 18, 2012, the primary reviewer (Xavier Ysern) recommended approval of lomitapide from a CMC perspective.

Biopharmaceutics (ONDQA): In her review signed October 26, 2012, the primary reviewer (Elsbeth Chikhale) recommended approval of lomitapide from a biopharmaceutics perspective. A waiver for the requirement to conduct a BA/BE study for the 10 mg capsule strength was granted.

Pharmacology Toxicology: In his review signed November 5, 2012, the primary reviewer (Brian [Tim] Hummer) recommended approval of lomitapide from a pharmacology-toxicology perspective. Safety concerns based on preclinical findings are discussed in Section 4 (Safety). The team recommended a juvenile toxicology study, as a postmarket requirement, to be conducted prior to evaluating lomitapide in pediatric HoFH patients.

Clinical Pharmacology: In his review signed November 5, 2012, the primary reviewer (Sze [Johnny] Lau) recommended approval from a clinical pharmacology perspective. Recommended dosing modifications based on drug-drug interactions, food effect, and hepatic/renal impairment that will be incorporated into labeling are discussed in Section 4 (Safety).

Statistics: In her review signed November 30, 2012, the primary reviewer (Cynthia Liu) concluded that lomitapide was effective in reducing LDL-C and the pre-specified secondary lipid parameters and recommended approval from a statistical perspective.

Clinical: In his review signed November 27, 2012, the primary reviewer (James Smith) recommended approval from a clinical perspective. Important clinical findings and assessments are discussed in Sections 3 (Efficacy) and 4 (Safety) below.

I concur with the recommendation of approval from the review disciplines.

3. Efficacy

Efficacy of lomitapide in HoFH patients was demonstrated in one Phase 3 trial (HoFH-pivotal, 29 HoFH patients); with supportive evidence from one Phase 2 study (HoFH-pilot, 6 HoFH

patients). The primary efficacy endpoint in both trials was the percent change from baseline to endpoint in directly measured serum LDL-C; each subject served as his or her own control.

The surrogate endpoint of serum LDL-C has been an accepted primary efficacy measure in marketing applications for lipid-lowering therapies in the U.S. The relationship between reductions in LDL-C levels and decreased risk of adverse cardiovascular outcomes has been well established for statin therapy. Although there are no data correlating LDL-C reduction and improved cardiovascular outcomes for MTP inhibitors, there is no reason to believe that LDL-C would not be an acceptable efficacy endpoint for HoFH patients treated with lomitapide. Moreover, a definitive cardiovascular outcomes trial in HoFH patients would be infeasible because of the rarity of the disease, and LDL-C is the most appropriate surrogate measure available.

The HoFH-pivotal trial was a multinational, open-label, single-arm trial in 29 HoFH patients on stable diet and maximally tolerated LDL lowering drugs, with or without apheresis, at baseline. Patients received lomitapide as add-on therapy at an individually defined maximum tolerated dose between 5 and 60 mg once daily for 78 weeks (weeks 0 to 26 was the efficacy phase, weeks 26 to 78 was the safety phase). Patients could enroll in the extension study (HoFH-extension) after completing the 78 weeks of treatment; the extension study is ongoing.

The primary efficacy endpoint, % change in LDL-C levels from baseline to Week 26/end of treatment, was analyzed using paired t-test performed on the intent to treat population (all 29 patients) with last-observation-carried-forward (LOCF) imputation of missing data. Primary efficacy results are shown in Table 2. It should be noted that the observed LDL-C reduction from lomitapide treatment was in addition to the lipid lowering effects of baseline therapies.

Table 2: Primary Endpoint – Percent change in LDL-C from baseline to Week 26 (HoFH-pivotal)

N = 29	Baseline LDL-C (mg/dL)	Week 26/ITT/LOCF LDL-C (mg/dL)	Absolute Change from Baseline (mg/dL)	Relative Change from Baseline (%)	P*
Mean (SD) 95% CI	337 (114)	191 (107)	-147 (127)	**-40** (32) -52 to -27	<0.001
Median Min, Max	357 152, 565	169 28, 443	-107 -351, +49	**-50** -93, +21	

Source: Adapted from primary statistical review (Cynthia Liu), Table 2
* P-value based on paired t-test for mean % change

Maximum LDL-C reduction reached plateau at Week 18 and was maintained at approximately 45% reduction at Week 56; the mean maximum tolerated dose at Week 26 and at Week 56 was approximately 40 mg.

Categorical LDL-C response: 19 of the 29 patients (66%) had LDL-C reductions ≥ 25%, with 8 (28%) having LDL-C levels < 100 mg/dL. Four of these 8 patients were receiving apheresis. The fact that HoFH patients treated with adjunctive lomitapide could attain the National Cholesterol Education Program's target LDL-C treatment goal is noteworthy.

Apheresis: Of the 29 patients, 18 (62%) were receiving apheresis treatment at the beginning of the trial. Because the acute reduction and ensuing rebounds in plasma lipid levels could confound efficacy measurements, the protocol specified that the timing of on-treatment LDL-C measurements relative to the preceding apheresis was to be the same as that established at baseline. In general, patients on apheresis experienced a mean LDL-C reduction at Week 26/LOCF of smaller magnitude compared to patients not on apheresis (-35% versus -49%). This observation may be confounded by the fact that a greater proportion of patients on apheresis discontinued drug treatment in the efficacy phase and the mean drug dose at Week 26/LOCF was higher for patients not on apheresis. Taken altogether, there is no compelling reason to believe that apheresis negatively impacts the efficacy of lomitapide.

Of the 13 apheresis-treated patients remaining in the HoFH-pivotal study at Week 26, three discontinued apheresis and three reduced the frequency of the procedure by Week 78. All but one patient either maintained the LDL reduction achieved during the efficacy phase or experienced slight rise in LDL-C levels, but these levels remained ≥ 50% below baseline. I consider these favorable alterations in apheresis to be significant in reducing the burden of the treatment for HoFH patients. Although decreasing the frequency of or discontinuing apheresis while on lomitapide may lead to less than optimal LDL-C reduction than if the apheresis regimen was not altered, the quality of life benefits of forgoing each apheresis procedure can be immediately appreciated, given the avoidance of time, cost, inconvenience, and risks that are incurred each time the procedure is performed.

Supportive data from the HoFH-pilot study for the primary endpoint of mean % change in LDL-C from baseline to the end of the dosing intervals (approximately 4 weeks each) are shown below. This study enrolled 6 adult HoFH patients who received lomitapide once daily according to a prespecified dosing scheme that called for dose escalation every 4 weeks (starting at 0.03 mg/kg and ending at 1.0 mg/kg). LDL-C levels were measured at the end of every 4 weeks at a certain dose. These findings demonstrate a dose response indicating a drug effect of lomitapide.

Table 3: Supportive Evidence of LDL-C reduction (HoFH-pilot)

Study Visit	Mean Daily Dose (mg)	LDL-C (mg/dL)	Absolute Change from Baseline (mg/dL)	Relative Change from Baseline (%)
Baseline	0	614 (106)		
End of 0.03 mg/kg	2.0	591 (110)	-23 (46)	-3.7 (8.3)
End of 0.1 mg/kg	6.7	566 (141)	-48 (121)	-7.1 (20.0)
End of 0.3 mg/kg	20.1	465 (103)	-149 (30)	-24.7 (5.3)
End of 1.0 mg/kg	67.0	303 (81)	-311 (70)	-50.9 (9.3)

Source: HoFH-pilot CSR, Appendix 7L.
Values are means (SD).

Results for the secondary endpoints from the HoFH-pivotal trial are shown in Table 4. These findings are reassuring in that the changes in these lipid parameters are consistent with LDL-C reduction, but it would be premature to conclude that these changes are adequate evidence of additional cardiovascular benefits beyond lowering of LDL-C. I agree with Dr. Smith's recommendation that only the secondary endpoints of total cholesterol, apoB, and non-HDL-C should be included in the indication for lomitapide. These endpoints are reflected in changes

in LDL-C and could potentially inform drug benefit in a manner similar to LDL-C. Hypertriglyceridemia is not a feature of HoFH disease, and the clinical relevance of triglyceride reduction in a population that has normal triglyceride levels is questionable.

Table 4: Secondary endpoints (HoFH-pivotal)

Lipid Parameters	Relative Change from Baseline to Week 26/LOCF N=29 Mean change % (SD)
Total cholesterol	-36 (28)*
ApoB	-40 (30)*
Triglycerides	-29 (56)*
Non-HDL-C	-40 (30)*
VLDL-C	-29 (58)
Lp (a)	-11(34)

Source: Adapted from primary clinical review (James Smith), Table 71
*P < 0.01 based on paired t-test for mean % change

HDL-C: Serum HDL-C levels declined from Week 0 to Week 26 (mean reduction of 7% [using LOCF] or 12% [using completer analysis]) but subsequently returned to baseline levels by Week 56. Serum levels of apoA1 followed a similar pattern. The reason for these lipid changes is unknown. Given the magnitude of reduction of HDL-C, the spontaneous return of HDL levels to baseline with continued treatment, and the uncertain effect of drug-induced changes in HDL-C on cardiovascular risk, I do not believe these HDL-C changes would significantly offset the benefit anticipated from lomitapide's favorable effect on LDL-C.

Efficacy conclusion

Lomitapide was efficacious in reducing serum LDL-C in HoFH patients on a low-fat diet and maximally tolerated lipid lowering treatment. Drug benefit was also observed for other lipid parameters, such as total cholesterol, apo B, and non-HDL-C. In some patients, lomitapide led to beneficial alterations in apheresis regimen or the attainment of NCEP's LDL-C target treatment goal. I consider these drug benefits to be clinically important.

4. Safety

The clinical safety findings of lomitapide have been thoroughly discussed in Dr. Smith's review. This safety assessment focuses on safety findings in the HoFH population, and is limited to significant safety issues of interest identified by the review teams. Although 915 individuals (most were healthy volunteers, patients with renal/hepatic impairment, or non-HoFH patients with hypercholesteremia) received at least one dose of lomitapide in the 24 studies provided in the NDA, the phase 3 safety database to support the intended use for lomitapide only consists of 29 HoFH patients enrolled in the HoFH-pivotal trial and its extension. Such a small safety database could only provide assurance that the true incidence of an adverse outcome is no greater than 10% when the outcome is not observed in the trial.

Death: One death (myocardial infarction) occurred in the entire drug development program (54 year-old man with factor V Leiden, a history of deep vein thrombosis, morbid obesity (BMI 42 kg/m^2)). Although a potential drug association could not be completely excluded, I believe it is unlikely that lomitapide caused the event.

Non-fatal serious adverse events (SAEs): All narratives were reviewed by Dr. Smith. I agree with Dr. Smith's assessment that lomitapide may have contributed to the SAEs experienced by the following 2 patients:

1. Subject 11-004: This case of "hepatoxicity" occurred in a 54 year-old man with elevated liver enzyme tests at baseline and throughout the phase 3 trial (1.5X to 5X ULN). His liver biopsy, obtained at baseline as workup for elevated liver enzymes, showed mild steatosis. At the scheduled Week 138 visit, his ALT was 24X ULN, AST 13X ULN, and alkaline phosphatase 2.5X ULN, with normal bilirubin levels. Prior to this visit, he was treated with clarithromycin (a strong CYP3A4 inhibitor) and the antidepressant agomelatine (known to increase hepatic aminotransferases), and had increased his alcohol intake. He was otherwise asymptomatic. His liver enzymes normalized several months after all drugs were discontinued. His follow-up liver biopsy showed simple steatosis that had increased from his previous biopsy, without histologic evidence of inflammation or fibrosis.

   I concur with Dr. Smith's assessment that this was a case of (multi) drug-induced hepatoxicity, given all the culprits involved. This case illustrates the need to emphasize through labeling the potential serious sequelae of drug-drug interactions (DDI) of lomitapide with CYP3A4 inhibitors or with hepatotoxic drugs or substances.

2. Subject 01-1003: This patient experienced multiple SAE's related to over-anticoagulation that may have resulted from the now known drug-drug interaction between lomitapide and warfarin. Labeling will address this DDI and recommend monitoring for INR levels when warfarin is administered concomitantly with lomitapide.

Drug discontinuation due to adverse events: In the HoFH-pivotal trial, 6 of 29 patients (21%) discontinued drug treatment prior to Week 26: 3 discontinued for gastrointestinal symptoms; 2 withdrew consent with AEs of headaches, unstable INR, and gastrointestinal symptoms; and 1 discontinued because of anxiety about gastrointestinal side effects. In the ongoing HoFH-extension study, 2 of 18 patients discontinued due to AE's (hepatotoxicity, aminotransferase elevations).

Common adverse events of interest: Gastrointestinal side effects, such as diarrhea, nausea, vomiting, dyspepsia, abdominal pain, were nearly universal, occurring in > 90% of HoFH patients. The most common severe AEs were also GI related. A decrease in weight was reported as an adverse event in 7 (24%) of the 29 HoFH patients. The largest change in mean weight was observed at Week 26 (-5% relative to baseline), with attenuation of weight decrease thereafter. It is, however, reassuring that the incidence of these AEs declined after the initial 26 weeks, despite the fact that no patients withdrew between Week 26 and Week 78 in the pivotal study. This pattern suggests possible tolerance or adaptation to these AEs.

Special Safety Issues

- Liver abnormalities

Hepatic transaminase elevations:
The incidence of peak ALT elevations at various thresholds in the 78-week HoFH-pivotal (Week 0 – 26 efficacy phase and Week 26 – 78 safety phase) trial and its ongoing extension (HoFH-extension) is shown below:

Table 4: Peak ALT elevations (HoFH)

Peak ALT During Period	Efficacy Phase (N=29)	Safety Phase (N=23)	All HoFH-pivotal (N=29)	HoFH-extension (N=18)	All HoFH (N=29)
≥2x, <3x ULN	3 (10%)	4 (17%)	4 (14%)	0	3 (10%)
≥3x, <5x ULN	4 (14%)	3 (13%)	6 (21%)*	2 (11%)	4 (14%)*
≥5x, <10x ULN	3 (10%)	2 (9%)	3 (10%)	1 (6%)	4 (14%)
≥10x, <20x ULN	1 (3%)	0	1 (3%)	2 (11%)	2 (7%)
≥20x ULN	0	0	0	1 (6%)	1 (3%)

Source: Primary clinical review (James Smith), Table 86
*Although 6 patients had peak ALT between 3-5X ULN, two of those experienced higher peak ALT elevations (5-10X ULN, >20X ULN) during the extension study, leaving 4 subjects in the 3-5X ULN category when the pivotal and extension studies are combined.

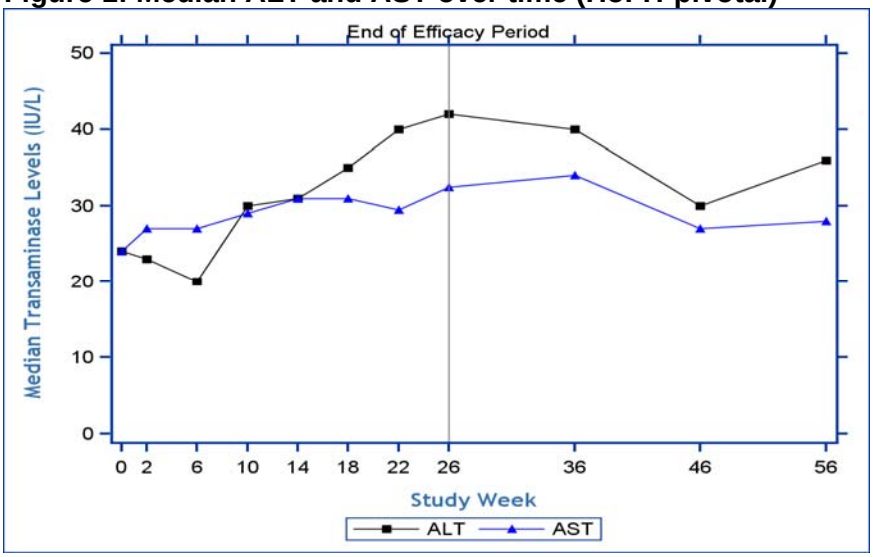
In the combined HoFH-pivotal and extension trials, 38% (11 of 29) of HoFH patients experienced at least one ALT value ≥ 3X ULN. These changes were not accompanied by laboratory changes indicating liver dysfunction, such as elevations in total bilirubin or INR. The median time to first ALT elevation was 126 days ([IQR 43, 155] for the 10 patients who had a peak ALT value ≥ 3X ULN during HoFH-pivotal. The remaining patient had her first ALT elevation during the HoFH-extension when she was found to have ALT elevations 10X ULN found on routine testing. She had been taking cold medications for the preceding several weeks. Her transaminase values decreased to near normal levels with dose interruption, and lomitapide was restarted at a lower dose 5 weeks later.

The single patient with ALT elevation > 20X ULN in the HoFH-extension trial was discussed earlier in the "Non-fatal SAE" section. Increased ALT ≥ 5X ULN was observed in 4 patients during the HoFH-pivotal trial and occurred across a wide range of lomitapide doses (10 mg, 10 mg, 20 mg, and 60 mg). Liver enzyme levels improved with dose modifications, and all four patients completed Week 78, with three of them ultimately tolerating doses equal to or exceeding the dose being taken at the time of their first ALT exceeding 5x ULN. One of the four patients subsequently experienced an ALT elevation > 10X ULN in the HoFH-extension trial and permanently discontinued lomitapide.

Of the six patients with peak ALT ≥ 3X ULN < 5X ULN, five had resolution to <3x ULN without dose reduction or interruption.

The temporal trend in median ALT and AST values up to Week 56 in the HoFH-pivotal trial is shown below. The shifts in aminotransferases are evident but there were no cases of "Hy's Law." One must be mindful, however, of the very small safety database when interpreting these findings.

Figure 1: Median ALT and AST over time (HoFH-pivotal)



Source: Primary clinical review (James Smith), Figure 34

In the 16-week HoFH-pilot trial, 3 of 6 patients experienced on-treatment ALT/AST elevations ≥ 5X ULN. Liver enzymes declined between dose titration, and all patients eventually received the highest daily dose of 1.0 mg/kg. All aminotransferase elevations normalized after drug discontinuation. There were no changes in other liver laboratory parameters, including total bilirubin, outside the normal range.

In summary, lomitapide increases aminotransferases at a high frequency. The mechanism of action responsible for this adverse outcome is not well understood and may or may not be entirely related to hepatic fat accumulation; however,

- Extreme transaminase elevations > 10X ULN occurred in the presence of other factors known to increase the risk of hepatic injury (drug-drug interactions, exposure to other hepatotoxins).
- Hepatic enzyme elevations, even those of substantial magnitude, were reversible within weeks of drug interruption or dose reduction. Rechallenges were usually successful in patients who required drug interruption.
- More modest elevations of < 5X ULN can resolve despite continued dosing, suggesting possible adaptation.
- The serum aminotransferase elevations were not accompanied by evidence of impaired liver function, and there were no cases of Hy's law, albeit the available safety data are very limited.

For the reasons listed above, I believe that this significant risk of lomitapide can be appropriately managed in clinical practice, with available risk management strategies of labeling and REMS. That said, the risk of serious liver injury with lomitapide is undefined at this time due to a very small safety database, and will need to be further characterized in the postmarket long-term observational study.

Hepatic steatosis

Hepatic fat accumulation is an expected pharmacodynamic effect of lomitapide by virtue of its mechanism of action. Measurement of hepatic fat was performed using nuclear magnetic resonance spectroscopy (NMRS)/MRI in the HoFH-pivotal trial (at weeks 0, 26, 56, and 78) and in the ongoing HoFH-extension trial (every 6 months). The table below shows the temporal trend of hepatic fat accumulation observed in the HoFH-pivotal and HoFH-extension trials. In general, hepatic steatosis persisted, or increased modestly, with continued lomitapide treatment.

Table 5: Hepatic fat accumulation over time (HoFH-pivotal, HoFH-extension)

	N	Absolute Δ in Hepatic Fat from Baseline		
		Mean (SD)	Median [IQR]	Range
Baseline	*23*	*0.9 (1.0)*	*0.7 [0.3, 1.0]*	*0.0 to 3.8*
Week 26	22	+8.1 (7.5)	+5.9 [2.7, 11.5]	+0.4 to 29.9
Week 56	21	+6.4 (8.0)	+5.3 [1.0, 8.5]	-0.5 to +35.1
Week 78	21	+7.4 (5.4)	+5.9 [3.8, 11.5]	+0.01 to 18.3
Week 102 / Week 24*	14	+8.4 (6.8)	+6.8 [3.0, 15.4]	+0.2 to 22.5
Week 126 / Week 48*	9	+7.8 (6.8)	+7.0 [3.5, 7.7]	+1.2 to 22.0
Week 150 / Week 72*	5	+9.0 (8.2)	+11.0 [4.2, 13.5]	-0.2 to +21.0

Source: Primary clinical review (James Smith), Table 89

Categorical maximum changes in hepatic fat observed in the HoFH-pivotal and HoFH-extension trials are shown below. Overall, 11 (48%) of 23 patients with hepatic fat data had a peak increase in hepatic fat content > 10%.

Table 6: Categorical maximum hepatic fat changes (HoFH-pivotal, HoFH-extension)

Maximum Absolute Increase in % Hepatic Fat	All HoFH (Pivotal + Extension) (N=29)	HoFH-Pivotal			HoFH-Extension (N=18)
		Efficacy Phase Wk 0-26 (N=29)	Safety Phase Wk 26-78 (N=23)	Entire Trial Wk 0-78 (N=29)	
# of Evaluable Subjects*	**23**	**22**	**22**	**23**	**18**
≤5%	4 (17%)	9 (41%)	6 (27%)	5 (22%)	4 (22%)
>5% to ≤10%	8 (35%)	6 (27%)	8 (36%)	8 (35%)	8 (44%)
>10% to ≤15%	4 (17%)	4 (18%)	3 (14%)	4 (17%)	2 (11%)
>15% to ≤20%	3 (13%)	1 (5%)	4 (18%)	3 (13%)	2 (11%)
>20% to ≤25%	2 (9%)	1 (5%)	0	1 (4%)	2 (11%)
>25%	2 (9%)	1 (5%)	1 (5%)	2 (9%)	0

Source: Primary clinical review (James Smith), Table 90

Multiple analyses conducted by Dr. Smith indicated that neither the magnitude of LDL-C reduction nor aminotransferase elevations could reliably predict the presence or severity of hepatic steatosis. Dr. Smith's analysis of the temporal trend of hepatic fat accumulation in affected individuals showed a general trend of initial increase in the first 26 weeks with stabilization thereafter in most, but not all, patients. Dr. Smith also concluded that the "plateaus or observed reductions in hepatic fat cannot often be explained by a decrease in dose." Off-treatment imaging data available for the 7 HoFH patients who discontinued lomitapide indicate reversibility of fat accumulation on imaging weeks to months after drug discontinuation.

All 6 HoFH patients enrolled in the 16-week HoFH-pilot trial had increased hepatic fat on imaging, with peak values ranging from 9% to 44%. These imaging changes returned to baseline 4 to 14 weeks after drug discontinuation. In a non-HoFH phase 2 trial evaluating the reversibility of fat accumulation, lomitapide treatment (25 mg daily) resulted in a placebo-adjusted mean ~20% increase in hepatic fat after 4 weeks of treatment. These imaging changes were reversible 6 weeks after drug discontinuation. There were no data on reversibility based on histopathology in the lomitapide safety database.

Liver biopsies were not protocol-mandated in lomitapide trials. In the entire clinical safety database, "for-cause" liver biopsy results from two patients treated with lomitapide for an extended duration were available for review. Biopsy from the patient with the SAE of "hepatoxicity" at Week 138 in the HoFH-extension trial showed worsening of simple steatosis, but without evidence of inflammation or fibrosis, compared to his biopsy obtained at baseline. A 2012 biopsy from a patient with familial chylomicronemia treated with lomitapide for 13 years in a compassionate care program showed progression of inflammation and fibrosis compared to biopsy results obtained in 2008. The role of lomitapide in the patient's worsening liver histopathology could not be discerned in light of her underlying disease.

Our understanding of non-alcoholic fatty liver disease (NAFLD), a primary disease not secondary to other known causes of hepatic fat accumulation, sheds some light on the natural history of chronic liver injury from hepatic fat accumulation. Simple steatosis of NAFLD generally has a benign course, whereas steatosis associated with inflammation and necrosis (non-alcoholic steatohepatitis, or NASH) can progress to cirrhosis in up to 10 to 20% of the cases. There are no non-invasive biomarkers that could reliably predict the progression from simple steatosis to NASH or allow for early detection of NASH.

The risk of chronic liver injury, including steatohepatitis, from lomitapide-induced hepatic steatosis is unknown at this time. Whether the clinical course of hepatic steatosis caused by lomitapide follows a similar path as NAFLD is uncertain. Published literature on marketed drugs implicated in chronic steatosis and steatohepatitis (e.g., amiodarone) is not likely to be generalizable, as the risks may be drug-, patient-, or disease-specific. No evidence currently exists to inform the routine use of biomarkers or imaging studies to screen for drug-induced steatohepatitis or to guide treatment decisions, such as when to contraindicate or discontinue treatment.

Regardless of the aforementioned informational gaps, for lomitapide-treated patients, hepatic fat could be monitored by imaging studies, and a liver biopsy could be performed to inform histopathological changes and provide an opportunity to discontinue treatment prior to the development of more serious liver injury. Lomitapide-induced fat accumulation measured by imaging study appears to be reversible with drug discontinuation.

- Dietary fat malabsorption

Lomitapide interferes with dietary fat absorption from the intestine by virtue of its mechanism of action. The HoFH-pilot trial showed statistically significant reduction in systemic levels of fatty acid nutrients at lomitapide doses ≥ 0.3 mg/kg. Subsequently, all patients in the HoFH-

pivotal trial received dietary supplements containing vitamin E (400 IU), linoleic acid (200 mg), alpha-linolenic acid (220 mg), EPA (110 mg), and DHA (80 mg). With supplementation, the median levels of serum vitamin E, beta-carotene, ALA, linoleic acid, EPA, DHA, and arachidonic acid decreased from baseline to Week 26, but remained above the lower limit of the reference range, with subsequent stabilization or trends toward baseline.

It appears that dietary supplements, which are available over the counter, provided adequate coverage for lomitapide-induced reduced absorption of fat-soluble nutrients in adults, although no information is available in pediatric HoFH patients.

- Preclinical safety signals

Teratogenicity: Embryo-fetal developmental studies in rats and ferrets showed major teratogenic effects during the organogenesis period at clinically relevant exposures. Fetal malformations affecting the eye, brain, and limb, and increased perinatal mortality were also observed at relevant human exposure in the peri-and post-natal development toxicity study in the rat. The review teams, OSE, and the Pediatric and Maternal Health Team all concluded that this risk could be managed with labeling (Pregnancy Category X, and Medication Guide to advise patients of this risk with an emphasis on the use of effective contraception) and the recommendation that pregnancy should be excluded prior to initiating lomitapide treatment.

I agree with this approach. The most important risk management strategy lies in the *prevention* of an unintended pregnancy, as 50% of pregnancies in the US are unplanned and the teratogenic effects in the preclinical studies occurred during organogenesis, a period where most women are often not aware that they are pregnant. Because lomitapide will be used in a small at-risk population managed primarily by healthcare providers familiar with prescribing products with similar teratogenic profile, requirements such as ongoing pregnancy testing or a patient's attestation of compliance with effective contraception are not warranted at this time.

Neoplasms: A two-year carcinogenicity study in mice showed a statistically significant increase in hepatocellular and small intestinal neoplasms at clinically relevant exposures. A two-year carcinogenicity study in rats did not demonstrate any drug-related neoplastic findings. No malignancies were reported in the small clinical safety database of lomitapide.

Important Clinical Pharmacology findings affecting dosing recommendations

- *Liver Impairment*:

Lomitapide exposure is increased up to 50% and (b) (4) in patients with mild and moderate hepatic impairment, respectively, as measured by the Child-Pugh scoring system. Patients with severe hepatic impairment were not evaluated. Lomitapide will be contraindicated in patients with moderate or severe hepatic impairment. The clinical pharmacology team recommends a maximum daily dose of 40 mg in patients with mild hepatic impairment.

- *Renal Impairment*:

Lomitapide exposure is increased by 50% in patients with end stage renal disease on dialysis. The clinical pharmacology team recommends a maximum daily dose of 40 mg in patients with end stage renal disease receiving hemodialysis.

- *Drug-drug interactions*:

When co-administered with ketoconazole, a potent CYP3A4 inhibitor, lomitapide Cmax and AUCinf increased by 15- and 27-fold, respectively. The concomitant use of lomitaptide and moderate or strong CYP3A4 inhibitors is contraindicated. Concomitant use of lomitapide and weak CPY3A4 inhibitor resulted in doubling of lomitapide exposure. The clinical pharmacology team recommends a maximum daily dose of 30 mg when lomitapide is given with a weak CYP3A4 inhibitor.

Co-administration of lomitapide 60 mg and warfarin resulted in increased exposure of warfarin by approximately 30%, and prolongation of INR by 22%. Labeling recommends routine monitoring of INR when lomitapide is used concomitantly with warfarin.

Co-administration of the highest dose of lomitapide (60 mg) and simvastatin 40 mg resulted in an approximate doubling of simvastatin exposure. Because the risk of myopathy, including rhabdomyolysis, with simvastatin is dose-related, the clinical pharmacology team recommends reducing the simvastatin dose by 50% when use concomitantly with lomitapide.

- *Food effect*:

In a food effect study conducted in 1997 using a formulation that was qualitatively, but not quantitatively, similar to the to-be-marketed formulation, exposure of lomitapide (Cmax, AUC) was increased by approximately 50-75% with food intake compared to fasting. Gastrointestinal adverse reactions were also more common in the fed state. In the HoFH-pivotal trial, patients were instructed to take drug at least 2 hours after dinner. Labeling for lomitapide administration will instruct patients to take lomitapide without food at least 2 hours after the evening meal.

Safety conclusion

The most concerning safety issues are elevations in serum aminotransferases and induction of hepatic steatosis at frequent rates. These liver abnormalities can be monitored by available laboratory and radiographic studies, and are usually reversible with dose reduction, interruption, or discontinuation. There has been no evidence of liver function impairment in the very small safety database. The risks of serious acute and/or chronic clinical liver injury with lomitapide remain unknown at this time.

Malabsorption of essential fatty acid and vitamins appears to be adequately addressed with vitamin supplementation provided in the HoFH-pivotal trials for adults, although information is lacking in pediatric HoFH patients.

Finally, preclinical drug-related safety findings observed at clinically relevant exposures include teratogenicity and hepatic and small intestinal neoplasms.

These risks can be managed with labeling and a risk management and evaluation program (REMS) (hepatic risks). The safety of lomitapide will be further elucidated by the required postmarket requirements (PMRs).

5. Risk Management and Assessment

The review teams and the Office of Surveillance and Epidemiology (OSE) will require the following risk management (REMS) and assessment (PMRs) strategies:

Risk Management:

1. Risk Evaluation and Mitigation Strategies (REMS) program: The REMS program consisting of elements to assure safe use (ETASUs) was discussed with the REMS Oversight Committee and the Office of Chief Counsel. The goals of the REMS are to educate prescribers about the potential risk of hepatotoxicity associated with the use of lomitapide and the need to monitor patients during treatment with lomitapide as per product labeling. A further goal is to restrict access to therapy with lomitapide to patients with a clinical or laboratory diagnosis consistent with HoFH. The ETASU includes prescriber certification, dispensing pharmacy certification, and documentation of safe-use conditions, consisting of a prescriber authorization form affirming that the patient has a clinical or laboratory diagnosis consistent with HoFH. The clinical database supporting the approval of lomitapide is very limited and serious safety concerns have been identified already. Therefore, at this time, the benefit/risk of drug treatment is expected to be favorable only in patients with severe familial disease consistent with HoFH. Such physician affirmation balances the need to have lomitapide available to patients with the most severe familial disease while preventing its use in patients with a very different risk/benefit context, such as those who are intolerant to statin therapy. The REMS program may be modified as we learn more about the safety of lomitapide in the postmarket setting. I agree with the content of the REMS program.

2. Labeling, which includes a Medication Guide outside of the REMS, will have a Boxed Warning for the risk of hepatotoxicity. Labeling will include recommendations for screening and monitoring with liver tests. Because of the lack of data correlating hepatic fat findings on imaging study to outcomes to inform clinical management decisions, no specific recommendations can be made in labeling regarding the use of imaging in the surveillance and management of hepatic steatosis. At this time, whether to follow and how to manage changes in hepatic steatosis should be left to clinicians as they continually reassess risk and benefit for individual patients.

Risk Assessment:

3. Postmarket requirement (PMR): As a condition of approval, the applicant is required to conduct the following PMRs to better define the long-term risks of lomitapide:
    - A 10-year, prospective observational cohort study (a product exposure registry) of patients with HoFH treated with lomitapide to obtain information on the occurrence, and outcomes when possible, of hepatic adverse events, hepatic and small bowel malignancies, teratogenicity, major adverse cardiovascular events, and death (including cause of death). I believe that this study is the most

feasible and efficient mechanism to obtain long-term safety information for lomitapide.

- Implementation of an enhanced pharmacovigilance program for reports of adverse events of interest (e.g., malignancy, teratogenicity, hepatic adverse outcomes) for 10 years from the date of approval. Interim analyses and summaries of safety information will be submitted annually.
- A juvenile toxicology study to asses the effects of lomitapide on neurological development (learning, memory, behavior and coordination), growth, and long bone development with and without vitamin and essential fatty acid supplementation.

6. Advisory Committee Meeting

This application was discussed at the Endocrinologic and Metabolic Drug Advisory Committee on October 17, 2012. The pertinent discussions are provided in Dr. Smith's review. Regarding whether there is sufficient evidence of efficacy and safety to support the marketing approval of lomitapide, the vote was 13 versus 2 in favor of approval.

7. Conclusions and Recommended Regulatory Action

HoFH is a life-threatening disease associated with premature death from accelerated atherosclerosis secondary to severely elevated LDL-C. Available therapies are suboptimal due to limited efficacy, availability, and/or unacceptable morbidity, and there is a clear unmet medical need for treatment of this rare disease.

Lomitapide is a first in class, new molecular entity, small drug molecule targeted at blocking the synthesis of lipoproteins that give rise to LDL-C. Titrated to tolerability and safety, lomitapide effectively decreased LDL-C by approximately 40% to 50% from baseline in HoFH patients already on low-fat diet and maximally tolerated lipid lowering therapy, with or without apheresis. By providing such incremental LDL-C lowering effects beyond existing lipid lowering modalities, lomitapide is a meaningful therapeutic option for HoFH patients.

The principal safety concerns are the frequent and significant increases in hepatic aminotransferase levels and liver fat content. These hepatic abnormalities can be monitored in clinical practice and appear to be reversible with dosing modifications or discontinuation. The risk of serious acute or chronic liver injury is unknown at this time. Other safety concerns are the preclinical findings of teratogenicity and hepatic and small intestinal neoplasms at clinically relevant exposure.

Risk management includes a REMS program to ensure that access to lomitapide is limited to patients with a clinical phenotype consistent with HoFH, where the benefits would likely outweigh the serious risks, and that the hepatic risks are understood by the prescribers. Although not as part of the REMS, a Medication Guide will be available to inform patients of the risks of hepatotoxicity and teratogenicity. The postmarketing requirements of a long-term observational study and enhanced pharmacovigilance will help to better define the safety profile of lomitapide when used outside of the confines of clinical trials.

The risk-benefit consideration for lomitapide is distinct from that of other lipid lowering drugs, given the serious nature of HoFH, the lack of adequate treatment options, and the demonstrated drug efficacy in a treatment-resistant population. Because the risk tolerance for HoFH patients is unique and HoFH is a rare disease, I can justify accepting the very limited clinical database as the basis of approval of lomitapide for this population. Overall, I believe that the benefit and risk balance is favorable for the use of lomitapide in the intended population, and agree with the review teams that lomitapide should be approved as an adjunct to low-fat diet and maximally tolerated lipid lowering therapies to reduce LDL-C in patients with HoFH.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHRISTINE P NGUYEN
12/21/2012