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RESEARCH**

APPLICATION NUMBER:

203858Orig1s000

MEDICAL REVIEW(S)

Memo to the File

NDA: 203858
Drug name: lomitapide
Reviewer: James P. Smith, MD, MS
Date: 07 December 2012

RE: Amendment to Clinical Review

On page 175 of my clinical review, signed 27 November 2012, I provided brief narratives for five subjects in HoFH-pivotal who had at least one peak ALT $\geq 3x$ but $< 5x$ ULN. As enumerated in Table 86, however, six patients had a peak ALT in this range during HoFH-pivotal. A brief summary of the additional subject's ALT elevation follows:

Subject 02-001 (U.S.) had one isolated ALT 3.6x ULN on study day 202, detected at an unscheduled visit at a local laboratory between weeks 26 and 31. The subject was taking lomitapide 40 mg at the time. This resolved with continued dosing when next measured 8 days later (ALT 23 IU/L on study day 210 at the week 31 visit). A reason for the unscheduled visit is not provided in the narrative, and the case report forms do not mention this visit. The only labs drawn on day 202 were ALT, AST, alkaline phosphatase, albumin, bilirubin, and total protein. No changes to lomitapide dose or concomitant medications were recorded.

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/s/

JAMES P SMITH
12/07/2012

ERIC C COLMAN
12/07/2012

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203858
Priority or Standard	Standard
Submit Date(s)	28 February 2012
Received Date(s)	29 February 2012
PDUFA Goal Date	29 December 2012
Division / Office	DMEP / ODE II / OND
Reviewer Name(s)	James P. Smith, MD, MS
Review Completion Date	13 November 2012
Established Name	lomitapide mesylate
(Proposed) Trade Name	TRADENAME
Therapeutic Class	Microsomal triglyceride transfer protein (MTP) inhibitor
Applicant	Aegerion, Inc.
Formulation(s)	Capsules (5, 10, and 20 mg)
Dosing Regimen	Daily oral dose
Indication(s)	Reduce LDL-C, total cholesterol, apo B, and TG
Intended Population(s)	Homozygous familial hypercholesterolemia

Template Version: [March 6, 2009](#)

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Lomitapide mesylate should be approved for use as 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), pending agreements with labeling and a revised Risk Evaluation and Mitigation Strategy (REMS) to address the risk for hepatotoxicity.

The applicant also requested that lomitapide be approved for the reduction of triglycerides (TG). I recommend that a TG-lowering effect be omitted from this claim in the HoFH population.

The applicant did not request that lomitapide be approved for the reduction of non-HDL-C, but I recommend adding this effect to the indication.

1.2 Risk Benefit Assessment

HoFH is a rare (~ 1 in 10^6), autosomal recessive disease caused by mutations in the gene coding the LDL receptor (LDL-R) or an adaptor protein critical for LDL-R function. Because the LDL-R removes LDL particles from plasma via endocytosis, absent or defective LDL-R substantially reduces cellular uptake of LDL-C, leading to abnormally high levels of LDL-C in the systemic circulation. Extremely high levels of LDL-C put these individuals at high risk for early and severe cardiovascular disease. The clinical consequences include cutaneous and tendinous xanthomata, corneal arcus, and diffuse and accelerated atherosclerotic disease. These manifestations typically present before the age of 20 years, and cardiovascular death is not uncommon in childhood.

Statins are the pharmacological agents of choice for HoFH, but unfortunately, this class of drugs is not particularly effective in reducing LDL-C in this population because they act primarily by upregulating LDL-R, which is defective or absent in these individuals. Other non-statin lipid-lowering drugs, such as ezetimibe, produce reductions in LDL-C that are usually insufficient to reach LDL-C goals. LDL apheresis is an extracorporeal therapy that selectively removes LDL particles from plasma and achieves significant reductions of LDL-C through repeated sessions, typically weekly or biweekly. Although time-averaged LDL-C reductions of approximately 50% can result, the procedure is accompanied by its own set of challenges and complications, and LDL-C typically remain far above the LDL-C goal for high-risk individuals in the general population. Thus, there is certainly an unmet medical need for this life-threatening, rare disease, and this requires a net risk/benefit assessment that is distinct from the general population with hypercholesterolemia.

The phase 3 program for lomitapide mesylate comprises a single, uncontrolled, 29-subject pivotal trial in the HoFH population and its ongoing extension study. For the pivotal trial, subjects were stabilized on their background lipid-lowering regimens, a low-fat diet, and LDL apheresis (if applicable) during a 6-week run-in period. The dosage of lomitapide was escalated from 5 mg daily to 60 mg daily during an 18-week period if safety (transaminases) and tolerability (primarily gastrointestinal symptoms) allowed. Among the 29 subjects who received lomitapide, 23 completed the 26-week efficacy period, during which time background lipid-lowering therapies could not be altered. After the efficacy period, all 23 subjects continued taking lomitapide and completed the 52-week safety phase; the dose of lomitapide could not be increased beyond the maximum tolerated dose determined for each subject during the efficacy period. Nineteen subjects subsequently enrolled in the optional extension study. Combining the pivotal trial and its extension, 23 subjects were exposed to lomitapide for at least one year, 15 for at least two years, and only 5 for at least three years.

Benefit

The primary efficacy parameter for the phase 3 pivotal trial was % change in LDL-C from baseline to week 26, with each subject serving as their own control in this single-arm trial. Although one might debate the validity of LDL-C as a surrogate for cardiovascular outcomes when evaluating non-statin drugs, I believe that this is a reasonable and appropriate endpoint for the HoFH population. Unlike dyslipidemia in the general population, in which multiple genetic and environmental factors contribute to its pathophysiology, the HoFH phenotype is essentially a monogenic disorder of deranged LDL metabolism. Thus, lowering LDL-C is certainly a reasonable therapeutic goal. Having said this, LDL-C remains a surrogate; attempting to estimate to what degree the risk for cardiovascular morbidity and mortality is reduced for a given change in LDL-C requires extrapolation to LDL-C levels far above the experience of clinical trials in the general population. The often-quoted quantitative relationships between cardiovascular risk reduction and LDL-C reduction may not apply to this situation.

Mean LDL-C was 336 mg/dL at baseline in the HoFH pivotal trial despite subjects taking maximally tolerated lipid-lowering therapy. At week 26/LOCF, the mean LDL-C was 190 mg/dL, representing a -40.1% change from baseline ($P < 0.0001$). Although one cannot definitively determine a dose-response relationship from a study that employs a forced-titration regimen, there was a positive correlation between mean dosage prescribed and LDL-C reduction observed. Of the 29 subjects who started the trial, 20 (69%) achieved $\geq 15\%$ reduction in LDL-C from baseline to week 26/LOCF, 19 (66%) achieved $\geq 25\%$, and 14 (48%) achieved $\geq 50\%$. Eight (35%) of the 23 subjects who completed the efficacy period had an LDL-C level < 100 mg/dL at week 26, with one subject having a level < 70 mg/dL.

The secondary efficacy parameters for the HoFH pivotal trial were % changes from baseline to week 26/LOCF in TC, apoB, TG, non-HDL-C, VLDL-C, and Lp(a). With the exception of Lp(a), statistically significant reductions were observed in these parameters. As mentioned previously, HoFH is a genetic disorder of *LDL metabolism*;

therefore, the therapeutic approach to this disease ought to target the reduction of LDL. Given that changes in LDL are reflected in TC, apoB, and non-HDL-C, it seems reasonable that changes in these parameters would be expected to predict clinical outcomes as well, although I'm not certain that they have clinical utility distinct from LDL-C in the HoFH population. I do not, however, believe that changes in triglycerides can be expected to contribute to the potential benefit of lomitapide. Hypertriglyceridemia is *not* a feature of HoFH (median 92 mg/dL at baseline in the pivotal trial), so the clinical benefit of modifying TG in this population is dubious.

Risk

Before summarizing the known risks of lomitapide, I will emphasize that the absence of a given risk should not be reassuring. The only clinical experience using doses in the range intended for marketing, for sufficient duration, comes from the phase 3 HoFH pivotal trial and its extension. As stated above, the 78-week pivotal trial only enrolled 29 subjects. Although this number of subjects was sufficient to support efficacy of lomitapide in reducing LDL-C, it is entirely plausible that adverse events that occur with a true incidence of approximately 10% may not have been observed in this trial at all. In addition to the limitations imposed by the sample size, the pivotal trial lacked a control group, which limits the ability to interpret many of the safety findings with confidence.

The primary risks of lomitapide identified during the clinical review include (1) potential for hepatotoxicity, suggested by transaminase elevations and the accumulation of hepatic fat; (2) near-universal gastrointestinal adverse events; (3) decreases in levels of fat-soluble vitamins and essential fatty acids; (4) drug-drug interactions; (5) preclinical signal of malignancy; and (6) preclinical signal of teratogenicity.

The risk of greatest concern with lomitapide is the potential for hepatotoxicity. In the HoFH phase 3 program (pivotal trial and its extension), 11 (38%) of the 29 subjects ever experienced ALT $\geq 3x$ ULN, and 7 (24%) had a peak $\geq 5x$ ULN. These elevations were not associated with impaired liver function (e.g., elevated INR or total bilirubin), but this is not too reassuring given the size of the study population. Although it is plausible that these transaminase elevations are a result of lomitapide-induced hepatic steatosis (steatohepatitis cannot be diagnosed without liver biopsy, which were not performed), a direct effect of lomitapide on hepatocellular injury remains possible. Review of narratives and longitudinal profiles of transaminases over time revealed that transaminase abnormalities $\geq 5x$ ULN were reversible, with improvements typically noted within 2-4 weeks of dose modification. Because dose reduction was not mandated for ALT values in the 3-5xULN range in the pivotal trial, these profiles also demonstrated that transaminases sometimes decrease despite continued dosing.

Accumulation of hepatic fat was expected based on lomitapide's mechanism of action. Lomitapide inhibits the transfer of triglycerides onto apo B, decreasing the synthesis of VLDL in the liver. Because the liver cannot export TG as VLDL, fat accumulates in the liver. In the pivotal trial, the mean absolute change in % hepatic fat from baseline to week 26 was +8.1% and to week 78 was +7.4%. Thus, hepatic fat seems to accumulate

early and then, in general, plateau. Eighteen (78%) of 23 subjects with available data demonstrated a maximum absolute increase in hepatic fat >5%, and three (13%) had an absolute increase >20%. What is unknown, however, is whether lomitapide-induced hepatic steatosis will promote the development of steatohepatitis. Simple steatosis (i.e., without inflammatory features or ballooning degeneration of hepatocytes) has a benign prognosis, but steatohepatitis can progress to cirrhosis over several years. Liver biopsy is required to distinguish these disorders, and liver biopsies were not performed during the pivotal trial. Data from a phase 2 study, in addition to limited data from the HoFH program, suggest that the accumulation of hepatic fat is reversible following discontinuation of lomitapide, but whether histological sequelae (e.g., fibrosis) would remain after long-term exposure is unknown.

Taken together, the hepatic risk for lomitapide is distinct from most other drugs with a liver-related signal. I am not most concerned about idiosyncratic acute hepatic failure, but rather a chronic, somewhat insidious process that could lead to advanced liver disease over the course of years. Because one might expect a patient with HoFH to take lomitapide for life, the potential for such a long-term risk must be strongly considered.

The most common adverse events in the HoFH pivotal trial were gastrointestinal in nature, with 27 (93%) of 29 subjects reported at least one adverse event in the Gastrointestinal Disorders Systems Organ Class (SOC). Diarrhea, nausea, vomiting, dyspepsia, and abdominal pain all occurred in >25% of subjects. Lomitapide inhibits the formation of chylomicrons, reducing absorption of dietary fat, and leading to steatorrhea and its associated symptoms. Gastrointestinal symptoms contributed to four of the six premature discontinuations before the efficacy endpoint (week 26). The applicant suggests that adherence to a strict low-fat diet (<20% total energy as fat) reduces the incidence and severity of these symptoms, citing differences between dietary fat restriction in the HoFH pilot and pivotal trials compared with phase 2 trials in the general hypercholesterolemic population. Narratives from the pivotal trial suggest that these symptoms improve when lomitapide is temporarily held or the dose is reduced. In addition, the applicant states that initiating therapy with a low dose of lomitapide and slowly titrating to higher doses also improves gastrointestinal tolerability. I do find it reassuring that despite the high incidence of these symptoms, all 23 subjects who completed the week 26 visit remained in the pivotal trial for an additional year, with fewer subjects reporting gastrointestinal AEs during this time (e.g., diarrhea reported by 79% and 35% of subjects during the efficacy and safety phases, respectively).

Malabsorption of fat-soluble vitamins and essential fatty acids was recognized as a potential risk of lomitapide, and serum levels of these fat-soluble nutrients were assessed in the HoFH pilot and pivotal trials. In the 6-subject pilot study, in which subjects took a standard multivitamin daily, mean decreases from baseline to the end of treatment were observed in several fatty acid parameters (alpha-linolenic acid [ALA], gamma-linolenic acid, linoleic acid [LA], arachidonic acid [AA], eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA], and docosapentaenoic acid), with statistically significant reductions at the highest two doses tested. Thus, in the pivotal trial, subjects

were provided dietary supplements containing vitamin E, the essential fatty acids, and the omega-3 fatty acids EPA and DHA. Measures of central tendency revealed reductions from baseline to week 26, followed by relative stability to week 78, for beta-carotene, ALA, LA, EPA, DHA, and AA. Longitudinal patient profiles show that excursions beyond the established reference ranges for fat-soluble vitamins were, for the most part, transient. In addition, subject-level profiles for the fatty acids showed substantial intra-subject variability for several of the analytes, and there were only occasional and transient excursions below the reference range for most fatty acids measured. ALA was most commonly measured below the reference range. Clinical consequences of these changes were not reported. Overall, the clinical importance of the observed reductions in fat-soluble nutrients is unclear, but it seems to be a risk that could be mitigated with dietary supplementation. I will note, however, that the optimal doses of the supplement's components have not been established, and the possibility that lomitapide inhibits their absorption if both are administered simultaneously has not been investigated.

Drug-drug interactions have been identified with lomitapide. First, the strong CYP3A inhibitor ketoconazole increased the exposure of lomitapide 27-fold; moderate and weak CYP3A inhibitors have not been studied *in vivo*. In the HoFH extension study, one subject was found to have an ALT ~24x ULN (with normal bilirubin and INR) within days of starting the strong CYP3A inhibitor clarithromycin; although there were other potential causes for elevated transaminases in this case, the temporal relationship between the CYP3A inhibitor and the elevated ALT raises concern for clarithromycin playing a role. Second, lomitapide interacts with warfarin, resulting in a 22% increase in INR. Last, regarding the effects of lomitapide on other lipid-lowering drugs, lomitapide approximately doubles simvastatin exposure with concomitant use, which could increase the risk for simvastatin-associated myopathy.

Two 2-year carcinogenicity studies were conducted in mice and rats, revealing a statistically significant increase in hepatocellular neoplasms and small intestinal adenomas/carcinomas in mice. The no-observed effect levels for drug-related neoplasms in male and female mice confer clinical safety margins of 0.4 to 2x the exposures expected from lomitapide 60 mg daily in humans. No drug-related neoplasms were observed in the rat at any dose tested, giving clinical safety margins of at least 6-8x. To date, no neoplasms have been observed in the lomitapide development program, but the absence of neoplasms is not reassuring given the extremely limited size and duration of the clinical trials.

Nonclinical data also suggest the lomitapide is a teratogen. Lomitapide was associated with significant fetal malformations in rats and ferrets at less than clinical exposure (based on 60 mg dose) when administered during organogenesis. In rabbits, adverse effects were not observed at 3x clinical dose, but embryo-fetal lethality was observed $\geq 6x$ clinical dose. There have been no reports of pregnancy among women taking lomitapide.

Conclusion

HoFH is a life-threatening disease of LDL metabolism that is in need of additional treatment options. The magnitude of the LDL-lowering effect of lomitapide is unprecedented for a pharmacological agent in the HoFH population and, although it will never be proven because of the rarity of the disease, it would be expected to reduce the risk for cardiovascular morbidity and mortality. The risks of lomitapide are concerning, however, especially since they are riddled with adjectives such as “potential” and “unknown.” I have the greatest concern for the potential risk for hepatotoxicity. Although it is straightforward to measure transaminases and other liver-related laboratories, it is currently not known what these elevated levels, which occur with impressive frequency, are signaling. Are these patients developing steatohepatitis? If so, what degree of transaminase elevation should raise alarm? How often would the putative lomitapide-associated steatohepatitis be present in the absence of transaminase elevations? Or, is the hepatic steatosis caused by lomitapide relatively benign? We do not have answers to these questions, especially given the absence of liver histology from lomitapide-treated patients.

Regarding the other risks associated with lomitapide, I believe that most can be mitigated in some manner. Gastrointestinal adverse reactions affect tolerability, but they do not seem to have long-term adverse consequences. The reductions in fat-soluble nutrients should be manageable with dietary supplementation, and we do not have evidence that the observed changes in these nutrients are clinically important in adults. Drug-drug interactions, especially with CYP3A inhibitors, are concerning but shouldn't preclude approval for this population. The preclinical signal for neoplasms is modest, and trials to rule out this risk in humans would be infeasible; therefore, post-marketing surveillance through an observational study proposed by the applicant and through enhanced pharmacovigilance seems reasonable. Last, the teratogenic potential of lomitapide should be able to be mitigated through labeling and a medication guide. Women with HoFH should have close relationships with their healthcare providers and are taking other drugs (e.g., statins) that are contraindicated in pregnancy; therefore, they ought to be aware of the issues surrounding family planning.

I should note that lomitapide has not been studied in any pediatric patients. Since patients with HoFH can present with cutaneous xanthomas within the first year of life, and clinically apparent vascular disease within the first decade, it is unfortunate that we do not have any data to support the safety or effectiveness, or even dosing recommendations, of lomitapide in the pediatric population.

On balance, although approval could potentially lead to trading one disease (cardiovascular) for another (liver), the former is a certainty and the latter is a “maybe” for patients with HoFH. For this reason, I believe that the net risk/benefit analysis favors benefit for the HoFH population. The probability of cardiovascular disease would not have to fall much at all (e.g., off-label use) before risk/benefit would be dominated by risk. Thus, to support approval, which should benefit this orphan population with an unmet

medical need, I believe that Risk Evaluation and Mitigation Strategies (REMS) are necessary to both educate prescribers and limit access to patients with HoFH.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

See Dr. Amarilys Vega's review of the applicant's proposed REMS. Briefly, I concur that a REMS is required to ensure that benefit would be expected to exceed risk if lomitapide is approved. The primary safety concern, as discussed above, is the risk for hepatotoxicity.

Although liver dysfunction has not been observed in the development program, the incidence of elevated transaminases is substantial and the phase 3 pivotal trial only involved 29 subjects. Thus, the lack of cases of typical drug-induced liver injury is not reassuring; using the "rule of 3" as a rough estimate, adverse events with incidences as high as 10-15% with broader use could have escaped detection in this trial. Although 915 subjects were exposed to oral lomitapide during the development program, the doses and durations for the vast majority of these subjects are irrelevant to the target population and the proposed dosing regimen. Furthermore, unlike most drugs with a hepatic safety signal, acute hepatic failure is *not* the primary liver-related concern for lomitapide. Lomitapide induces hepatic steatosis, by limiting the liver's ability to export triglycerides via VLDL particles; the long-term consequences of the accumulation of hepatic fat are unknown. Whether lomitapide-induced hepatic steatosis will behave similarly to simple steatosis with a benign clinical course, or whether it will induce inflammation (steatohepatitis) and progress to cirrhosis over many years, is unknown. Although it seems reasonable to expect the benefit of LDL-C reduction to exceed this risk in the setting of life-threatening HoFH, I would expect this risk and the limited size of the current safety database to preclude approval for the general population with hypercholesterolemia (e.g., "statin-intolerant" patients). The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) also emphasized that a "strong" or "tight" REMS should be required to limit use to the HoFH population if lomitapide is approved.

As Dr. Vega outlines in her review, FDA proposes that the REMS would have the following goals:

- To educate prescribers about the approved indication for use of lomitapide, 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;
- To limit access to therapy with lomitapide to patients with a clinical or laboratory diagnosis consistent with HoFH.

The REMS would include elements to assure safe use (ETASU), an implementation system, and a timetable for submission of assessments. The ETASU would include prescriber certification (requires training), pharmacy certification, and assurance that lomitapide will only be dispensed to patients with evidence or other documentation of safe use conditions. The proposed safe use condition consists of a "Prescription

Authorization” form integrated with each *new* prescription that would require the provider to attest to the following statements (draft):

- I understand that TRADENAME is indicated . . . (final indication text)
- I certify that this patient has a clinical or laboratory diagnosis consistent with HoFH.
- I understand that lomitapide has not been studied in pediatric patients less than 18 years.
- I attest that I have obtained the liver-related laboratory tests for this patient as directed in TRADENAME’s prescribing information.
- I certify that the TRADENAME is medically necessary for this patient and that the information provided above is accurate to the best of my knowledge.

It will not be required to submit laboratory evidence of HoFH. Genetic testing is not available to all patients, all genetic mutations defining HoFH are not known, and commercial tests are not available for all genetic mutations. In addition, the published literature demonstrates that the clinical diagnosis of HoFH varies among lipid experts; therefore, requiring a patient to meet a specific definition of HoFH may restrict therapy from patients for whom it is medically appropriate.

Off-label use of lomitapide in the pediatric population is expected given the extent of lipid-related comorbidities often observed in childhood among patients with HoFH. There are no data to support the safety or efficacy of lomitapide in the pediatric population. Although I would not support encouraging pediatric patients to take lomitapide at this time, I recognize that some parents, patients, and their healthcare providers may make an informed decision to assume the unknown risks. Although labeling will state that lomitapide has not been studied in pediatric patients, adding this limitation to the attestation will help ensure that providers are aware.

A medication guide will be developed to inform patients of the risk for hepatotoxicity and potential for teratogenicity based on nonclinical data. The medication guide would not be included as part of the REMS.

Similarly, the applicant has proposed a postmarket observational study to follow approximately (b) (4) HoFH patients over time. This study would not be part of the REMS. See Dr. Patricia Bright’s review for additional information.

1.4 Recommendations for Postmarket Requirements and Commitments

With respect to the clinical discipline, I have no recommendations for postmarket requirements or commitments.

2 Introduction and Regulatory Background

Homozygous Familial Hypercholesterolemia

Homozygous familial hypercholesterolemia (HoFH) is a rare, autosomal-recessive disease characterized by marked elevations in LDL-C. The prevalence is estimated to be 1 in 1,000,000, which yields estimates of approximately 300 individuals in the United States. Individuals with this disease have mutations in the gene coding the LDL-receptor (LDL-R) or an adaptor protein critical for LDL-R function; more than 600 genetic variants have been described. LDL-R activity may be undetectable (receptor-negative) or may be detectable but low (receptor-defective) when assessed *ex vivo*. Because the LDL-R removes LDL particles from plasma via endocytosis, absent or defective LDL-R substantially reduces cellular uptake of LDL-C, leading to abnormally high levels of LDL-C in the systemic circulation. Extremely high levels of LDL-C put these individuals at high risk for early and severe cardiovascular disease. An individual may carry two different mutations in each LDL-R allele (i.e., compound heterozygote) or the same mutation in both alleles (i.e., true homozygote), but both results in the clinical phenotype designated “homozygous familial hypercholesterolemia.”¹⁻³

De novo intracellular synthesis of cholesterol is adequate for normal fetal and childhood growth and development even with a complete lack of LDL-R activity. With time, however, the clinical consequences of persistent severe elevations in LDL-C include cutaneous and tendinous xanthomata, corneal arcus, and diffuse and accelerated atherosclerotic disease. The aggressive atherosclerotic process often affects the aortic root and valve in addition to the coronary arteries and other segments of the arterial tree. These manifestations typically present before the age of 20 years, with nearly all children presenting with cutaneous xanthomata. Untreated, individuals with HoFH typically have LDL-C levels of 650 mg/dL and cardiovascular death is not uncommon in childhood.³

Statins are the pharmacological agents of choice for HoFH, but unfortunately, this class of drugs is not particularly effective in reducing LDL-C in this population because they act primarily by upregulating LDL-R, which is defective or absent in these individuals. For example, among 40 patients with HoFH who received rosuvastatin 20 mg daily for 6 weeks followed by 40 mg daily for 6 weeks, the achieved reduction in LDL-C was 22%; in contrast, LDL-C reductions of $\geq 50\%$ were observed for similar doses in non-familial hyperlipidemia (CRESTOR PI; Feb 2012). Similarly, among 29 patients with HoFH who received atorvastatin at maximum doses of 20 to 80 mg, the mean LDL-C reduction was 18%; in contrast, LDL-C reductions of approximately 40% would be typical even at the 20 mg dose in non-familial hyperlipidemia (LIPITOR PI; Feb 2012).

The non-statin lipid-lowering drug ezetimibe is indicated to reduce total cholesterol and LDL-C in patients with HoFH, in combination with atorvastatin or simvastatin. As described in labeling, LDL-C was reduced by 27% among individuals with HoFH treated with ezetimibe plus either atorvastatin 80 mg or simvastatin 80 mg (ZETIA PI; Jan

2012). Given the extremely high LDL-C levels in this population, reductions of this magnitude are usually insufficient to reach LDL-C goals.

Non-pharmacologic therapy for HoFH includes extracorporeal modalities (LDL apheresis, plasmapheresis), portacaval shunting, partial ileal bypass surgery, and liver transplantation. Except for the extracorporeal treatments, these procedures are uncommonly employed. Portacaval shunting and partial ileal bypass lower LDL-C, but the effect is variable and often transient. In a 2011 publication that describes a retrospective cohort of 149 patients with HoFH in South Africa, 21 patients had been treated with a portacaval shunt, all prior to 2000, and only 7 had been treated with partial ileal bypass surgery, all prior to 1985.⁴ Liver transplantation is effective given the replacement of defective hepatic LDL-R with normal LDL-R from the donor, but this therapy is limited by a lack of donor organs and complications associated with chronic immunosuppression.⁵

LDL apheresis selectively removes LDL particles from plasma and achieves significant reductions of LDL-C through repeated sessions, typically weekly or biweekly.⁶ It has not been shown definitively to reduce cardiovascular events in well-controlled, prospective trials. There are multiple different systems and methods of LDL apheresis, but these comparisons are beyond the scope of this document. This therapy is FDA approved and covered by most insurance companies if the LDL-C is >500 mg/dL among patients with HoFH, >300 mg/dL among patients without coronary artery disease (CAD), or >200 mg/dL among patients with CAD despite 6-months treatment with maximal drug and dietary therapy.⁷ The procedure is generally well tolerated but can pose challenges with regard to vascular access, often requiring the creation of an arteriovenous fistula similar to those used by end-stage renal disease patients treated with hemodialysis. LDL-C concentrations fall 60-70% acutely but immediately begin to rise again, necessitating repeat procedures as mentioned above, with time-averaged LDL-C reductions of ~50%. In combination with a high-dose statin and an inhibitor of cholesterol absorption, one expert notes that LDL-C “can be brought down to an acceptable level in most patients (6-8 mmol/L [~230-310 mg/dL]).”⁸ These “acceptable” values remain far above the LDL-C goal for high-risk individuals in the general population, highlighting the need for additional therapeutic possibilities in this orphan population.

Microsomal Triglyceride Transfer Protein

In 1950, Bassen and Kornzweig reported a clinical syndrome of peripheral blood acanthocytosis, atypical retinitis pigmentosa, and ataxia. During the next decade, others observed that affected individuals had extreme hypocholesterolemia and the absence of serum beta-lipoprotein, leading to the name “abetalipoproteinemia” (ABL). The fundamental defect was later found to be the complete absence of plasma apolipoprotein B (apoB)-containing lipoproteins, which include VLDL, chylomicrons, and LDL. In 1992, deficiency of microsomal triglyceride transfer protein (MTP) was suggested to be the proximal cause. MTP is a heterodimeric protein that resides in the lumen of the endoplasmic reticulum, primarily of hepatocytes and enterocytes, and acts as a chaperone to facilitate the transfer of lipids onto apoB. This failure to deliver lipid

leads to the proteolytic destruction of nascent apoB. In 1993, mutations in the gene encoding the larger ~97-kDa M subunit of MTP were reported in patients with ABL.^{9, 10}

The identification of MTP as a protein critical to the formation of apoB-containing lipoproteins suggested that MTP inhibitors might have therapeutic potential to inhibit the production of VLDL and chylomicrons, which ultimately give rise to atherogenic lipoproteins such as LDL. In the mid-1990s, the compound now known as lomitapide was found to be a potent small-molecule inhibitor of MTP.¹¹

Differentiated epithelial cells of the small intestine and hepatocytes are the primary sites of MTP expression in mammals. MTP activity is maximal in the duodenum and proximal jejunum and decreases in the distal jejunum and ileum until it is virtually absent in the colon.¹² In mouse liver, MTP protein expression is higher in cells proximal to the central vein and decreases toward the periphery of the lobule.¹³ MTP has also been detected in tubular epithelial cells of mouse kidney and human cardiac myocytes, but levels are far lower than liver and intestine.¹⁴⁻¹⁶ Both MTP mRNA and protein have also been detected in human retina.¹⁷

The clinical features of individuals with ABL represent the multi-system effects that can result from *complete* MTP deficiency. All reported patients have had fat malabsorption, acanthocytosis, hypocholesterolemia, and serum apoB deficiency. Other common features include retinitis pigmentosa, spinocerebellar ataxia, and myopathy. The presentation is heterogeneous, however, potentially affecting multiple body systems:⁹

- *Gastrointestinal*: diarrhea (malabsorption) and fat-soluble vitamin deficiency;
- *Hepatic*: elevated serum transaminases and hepatomegaly resulting from hepatic steatosis; cirrhosis has been reported in a few cases, although dietary supplementation with medium-chain triglycerides was implicated in each of these cases;¹⁸
- *Hematologic*: acanthocytosis, and occasionally anemia, elevated PT/INR;
- *Neurologic*: upper or lower motor neuron findings, or both, resulting from demyelination; typical onset is in the first or second decade of life; treatment with vitamin E appears to prevent and/or improve neurologic dysfunction;
- *Muscle*: myopathy involving both striated and smooth muscle of unclear etiology, although ceroid pigment deposition may play a role;
- *Ophthalmic*: pigmentary retinal degeneration is most prominent, with early loss of night or color vision. Retinopathy is often insidious with patients unaware of progression but complete loss of vision can ultimately occur. Anecdotally, early supplementation with both vitamins A and E may attenuate this degeneration in some cases, but lack of MTP activity in the retina has also been implicated as a direct cause.¹⁷

Parents of affected individuals (i.e., obligate heterozygotes) do not develop neurological symptoms, retinitis, or acanthocytosis, and have a fairly normal plasma lipid and lipoprotein pattern.^{10, 19, 20}

MTP and Nonalcoholic Fatty Liver Disease

Inhibition of MTP can lead to the development of hepatic steatosis, but the risk for progression to cirrhosis is unknown. Among those affected by abetalipoproteinemia, rare reports of cirrhosis have attributed the liver disease to supplementation with medium-chain triglycerides. Similarly, hepatic steatosis accompanies the rare disorder familial hypobetalipoproteinemia (FHBL), an autosomal co-dominant disorder resulting from *APOB* mutations. Even FHBL heterozygotes have increased levels of hepatic fat compared with controls, but its clinical consequences are not well described.^{9, 21}

In the general population, nonalcoholic fatty liver disease (NAFLD) refers to a spectrum characterized by hepatic steatosis, either by imaging or histology, without known causes for secondary accumulation of hepatic fat. Causes of secondary hepatic steatosis include excessive alcohol use, hepatitis C (genotype 3), inherited disorders including those described above, and steatogenic medications. NAFLD can be further divided into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH), the latter consisting of inflammation and hepatocyte injury in addition to steatosis. NASH is the entity that raises the greatest concern for progression to cirrhosis and end-stage liver disease. Estimates vary widely based on population and method of assessment, but the prevalence of NAFLD in the general population is likely ~20%, whereas the prevalence of NASH is ~3-5%.²² The factors that cause the minority of individuals with NAFLD to progress to NASH are not well understood.

In an effort to describe “normal” levels of hepatic fat, Szczepaniak *et al.* evaluated 345 subjects from the Dallas Heart Study who had low alcohol consumption, normal BMI, normal fasting glucose values, normal transaminases, and did not have a history of diabetes or liver disease. They used localized proton nuclear magnetic resonance spectroscopy (NMRS) to measure hepatic triglyceride content, considered to be the optimal noninvasive method given its strong correlation with biopsy results. In this low-risk group, the distribution of hepatic fat was skewed with a median 1.9% and a 95th percentile of 5.56%. Applying this 5.56% cutoff to the entire 2,287-subject cohort, which is notable for a higher prevalence of obesity (~43%) and moderate-to-excessive alcohol intake (~69%), the prevalence of hepatic steatosis was approximately 31%. In the overall cohort, the median level of hepatic fat was 4.7% with 75th and 95th percentiles of 8.6% and 22.9%, respectively.²³

NAFLD is associated with obesity, dyslipidemia, metabolic syndrome, and type 2 diabetes mellitus.²² The mechanisms underlying the development of NAFLD in these disorders are not entirely understood, but hepatic insulin resistance is thought to play a role by promoting lipolysis, which increases the influx of free fatty acids (FFAs) from peripheral fat stores, enhancing de novo hepatic lipogenesis, and reducing fat export from the liver by inhibiting apoB production.^{24, 25} Some have proposed that elevated levels of proinflammatory cytokines (e.g., IL-6, TNF- α), which often accompany obesity, may suppress insulin signaling in the liver and contribute to accumulation of hepatic fat. Others have suggested that the converse may be true: increased expression of genes normally found abundantly in adipose tissue, including the chemokines MCP-1 and

MIP-1 α , has been described among subjects with hepatic steatosis, suggesting the possibility that chronic hepatic inflammation secondary to triglyceride accumulation could promote systemic insulin resistance.^{26, 27}

Several studies have suggested that patients with NAFLD have higher overall mortality compared with matched controls. Although patients with NASH are at increased risk for liver-related mortality, the major cause of death among patients with NAFLD is cardiovascular disease.²² Although many of the comorbidities associated with NAFLD are cardiovascular risk factors themselves, some have proposed that NAFLD independently contributes to the increased risk. For example, Targher *et al.* reported that among 2,103 patients with type 2 diabetes followed prospectively for 6.5 years, the presence of NAFLD was associated with a statistically significant 2-fold risk for incident cardiovascular events even after adjustment for age, sex, smoking, duration of diabetes, HbA1c, LDL-C, and medications (hypoglycemic, antihypertensive, lipid-lowering, or antiplatelet drugs) (HR 1.96 [95% CI, 1.4-2.7; P<0.0001]).²⁸ Similar observations have been made in community-based cohorts and type 1 diabetics.²⁹ Wong *et al.* found that among 612 patients undergoing coronary angiography, fatty liver was associated with 2.3-fold higher odds of coronary artery disease in a final multivariable model adjusted for age, sex, diabetes, waist circumference, fasting glucose, HDL-C, and ALT.³⁰

Given the shared risk factors between NAFLD and CVD, residual confounding is a near-certainty when attempting to draw conclusions regarding whether NAFLD itself promotes CVD. Thus, the identification of biologically plausible mechanisms that could mediate a cause-and-effect relationship would be useful. To complicate matters further, simple hepatic steatosis (i.e., NAFL), which does not exhibit an inflammatory component by definition, may confer a risk distinct from the inflammatory NASH. As mentioned previously, visceral adiposity can serve as a source of a proinflammatory milieu, activating intracellular signaling such as the NF- κ B and JNK pathways. In fact, selective deletion of *Jnk1* in adipose tissue suppresses hepatic insulin resistance induced by a high-fat diet in mice, supporting a link between adipocytes and the liver.³¹ Within the liver itself, hepatic steatosis is associated with increased production of proinflammatory cytokines (e.g., IL-6) by hepatocytes, Kupffer cells, and hepatic stellate cells, which may contribute to the progression of NAFLD and CVD. Furthermore, graded associations have been demonstrated for inflammatory markers, procoagulant factors (e.g., fibrinogen, PAI-1), and markers of oxidative stress as one compares subjects without steatosis, with simple steatosis, and with NASH.²⁹ Last, it has been suggested that NAFLD contributes to CVD by modulating lipoprotein metabolism, especially during the post-prandial period.³² Although these data remain insufficient to conclude that hepatic steatosis itself contributes to the pathogenesis of CVD, the emerging data at least appear consistent with the hypothesis.

LDL-C as an Endpoint

The percent change in LDL-C from baseline to week 26 was the primary efficacy parameter in the HoFH phase 3 pivotal trial. Lomitapide was added to a background of

stable lipid-lowering treatment, which may have included LDL apheresis, prescribed by the subjects' lipid specialists.

Hypercholesterolemia, specifically an increase in LDL-C levels, is a major risk factor for the development of atherosclerosis and coronary heart disease (CHD). Many large-scale, randomized trials have shown that reducing LDL-C levels with statins reduces the risk of CHD, with a direct relationship between LDL-C levels and CHD events. One meta-analysis concluded that lowering LDL-C by 1 mmol/L (~40 mg/dL) for 4 to 5 years reduces the risk of coronary events and strokes by 22%.³³ Several recent trials have shown that statin regimens using higher doses or more-potent agents, which both yield greater reductions in LDL-C, reduce the risk of vascular events more than less-intensive statin regimens in patients at very high cardiovascular risk.³⁴⁻³⁷ The Third Report of the National Cholesterol Education Program (NCEP) Adult Treatment Panel in 2001 recommended an LDL-C goal of less than 100 mg/dL for patients at high risk for CHD.³⁸ In 2004, based on accumulating trial data, the NCEP, the American Heart Association, and the American College of Cardiology recommended an optional more-aggressive LDL-C goal of less than 70 mg/dL for patients at very high risk for CHD, even if baseline LDL-C levels were below 100 mg/dL.³⁹

The goal of lipid-lowering therapy is to reduce the risk for cardiovascular disease. In the past, reduction of LDL-C alone has been viewed favorably as a surrogate outcome if the reduction was sufficiently robust and if the investigational product did not have safety signals raising concern that risk exceeded benefit. Within the last few years, however, several controlled clinical trials have demonstrated that favorable changes in lipid parameters do not always translate into the expected cardiovascular benefit. One example is the ILLUMINATE trial, which showed that treatment with torcetrapib decreased LDL-C and increased HDL-C levels but also increased the risk for death and CVD.⁴⁰ Although the hypothesized reasons for these "failures" are varied, this experience challenges previous assumptions about lipid-related surrogate endpoints. Future data from Improved Reduction of Outcomes: Vytarin Efficacy International Trial (IMPROVE-IT)⁴¹ will provide important information regarding the validity of LDL-C lowering with a non-statin drug. Thus, in the absence of cardiovascular outcomes data, contemporary decisions to approve novel LDL-lowering therapies are not only influenced by the direction and magnitude of drug-induced changes in LDL-C, but also by the effects of the drug on other lipid parameters and markers of cardiometabolic risk, as well as evidence for off-target toxicity.

Given the rarity of HoFH, it is not feasible to require the demonstration of benefit on cardiovascular outcomes for investigational products in this population specifically. Ideally, the cardiovascular outcome efficacy and safety of a novel investigational lipid-altering product would be evaluated in a broader hyperlipidemic population before, or in

* IMPROVE-IT is evaluating ezetimibe/simvastatin combination 10/40mg compared to simvastatin 40 mg monotherapy in subjects with stabilized high-risk acute coronary syndrome with a composite primary outcome of cardiovascular death, myocardial infarction, nonfatal stroke, rehospitalization for acute coronary syndrome, or revascularization. The trial started in October 2005 and the estimated completion date is June 2013.

parallel with, the HoFH population. However, for lomitapide, significant concern of potential harm from hepatic steatosis has limited its use to narrow populations of patients at very high risk for CAD.

2.1 Product Information

The non-proprietary name of this product is lomitapide mesylate. Proposed tradenames at the time of this review have included (b) (4)

Lomitapide is a new molecular entity. Its pharmacological categories include (1) microsomal triglyceride transfer protein (MTP) inhibitor and (2) lipid-altering agent.

The applicant proposes the following indication:

TRADENAME is indicated as an adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and triglycerides (TG) in patients with homozygous familial hypercholesterolemia (HoFH).

Reviewer Comment: Although the proposed indication reads “patients” instead of “adults with...” or “adult patients with...,” the applicant has stated that they only intend to market lomitapide to adults given the absence of pediatric data.

Proposed dosage and administration instructions follow:

- Patients should follow a low-fat diet supplying less than 20% of energy from fat prior to initiating TRADENAME treatment, and should continue this diet during treatment;
- TRADENAME should be administered once daily at bedtime, with a glass of water and without food;
- The recommended starting dose is 5 mg. After 2 weeks, the 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.
- Patients should take daily dietary supplements that provide approximately 400 IU vitamin E, 200 mg linoleic acid, 110 mg EPA, 220 mg ALA, and 80 mg DHA per day, throughout treatment with TRADENAME.

TRADENAME would be available in 5 mg, 10 mg, and 20 mg capsules.

2.2 Tables of Currently Available Treatments for Proposed Indications

The following drugs are currently approved for the reduction of elevated total cholesterol and LDL-C specifically for patients with HoFH: simvastatin, atorvastatin, rosuvastatin, ezetimibe, and simvastatin/ezetimibe. Rosuvastatin is also approved for the reduction of apolipoprotein B in the HoFH population.

2.3 Availability of Proposed Active Ingredient in the United States

Lomitapide is not currently available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Lomitapide is first-in-class.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The lomitapide development program spans more than 16 years. The initial IND (IND 50820) was submitted on 18 June 1996 by Bristol-Myers Squibb (BMS) with an aim to develop the drug for mixed dyslipidemia. BMS abandoned development in 2000 as a result of concerns regarding gastrointestinal tolerability, hepatic steatosis, and preclinical pulmonary phospholipidosis. On 21 August 2002, this IND was transferred to Daniel Rader, MD (University of Pennsylvania) with the anticipation that the drug would be developed for patients with HoFH, a population for whom the benefits of the drug might outweigh the risks.

Dr. Rader conducted a six-subject pilot study in the HoFH population from June 2003 to February 2004. The division held an end-of-phase 2 (EOP2) teleconference on 20 July 2004. The potential for significant drug-drug interactions, given that lomitapide appeared to be a CYP3A4 inhibitor, was noted, and the division requested that at least one PK interaction study with a known CYP3A4 substrate (simvastatin or atorvastatin) be conducted prior to the initiation of a phase 3 trial. The division also noted that any expanded use of lomitapide beyond the HoFH population would shift the risk/benefit profile of the development program.

Grant 1R01 FD003098-01 was awarded from the agency's Office of Orphan Products Development (OOPD) for a phase 3 trial in the HoFH population. Subsequently, the sponsor proposed to expand the patient population to "severe refractory hypercholesterolemia," but the division noted that this change would dictate a pivotal trial of more than the 36 subjects initially proposed. The sponsor chose to remain with the HoFH population, and a face-to-face meeting was held on 07 February 2007 to discuss the phase 3 pivotal trial for this orphan indication. Since the sponsor would not be pursuing an adequately sized phase 3 trial for a broader population, the division suggested a single-arm trial design to increase the safety database in the orphan population, as long as there was an adequate run-in period to stabilize concomitant lipid-lowering therapy. The sponsor accepted this design and proposed to include 25

subjects diagnosed with HoFH who would all receive lomitapide at the maximum tolerated dose for a minimum of 52 weeks. The division queried why the proposed sample size had been decreased, and the sponsor responded that they anticipated difficulty finding the patients within the United States; power for efficacy would not be compromised based on the revised design in which each subject would serve as his/her own control. The division did encourage the sponsor to include sufficient numbers of women and Asians given that “the behavior and potential toxicity of the drug is likely to be enhanced in these populations.” Last, the division concurred with the dose-titration scheme to enhance tolerability but had concerns regarding adequate safety margins for pulmonary phospholipidosis, which had been observed in preclinical studies. It was recognized, however, that the potential benefit to the HoFH population may outweigh the risks; therefore, the proposed dosing scheme was allowed to proceed with appropriate disclosure during informed consent.

The division clearly articulated that departure from the HoFH population would affect the development program. “We would like to reiterate our position that while the study of BMS-201038 [*i.e.*, *lomitapide*] in high-risk patients such as those with homozygous FH is acceptable despite significant potential risk associated with drug-induced fat accumulation in the liver and lung (and perhaps the intestine), the use of BMS-201038 in a lower-risk population (e.g., heterozygous FH, type IIa and IIb patients) may not be justified in light of the documented preclinical toxicities observed at low multiple of the proposed clinical doses.”

On 13 April 2007, IND 50820 was transferred from Dr. Rader to Aegerion Pharmaceuticals for the development of lomitapide for “moderate hypercholesterolemia,” which included severe refractory hypercholesterolemia. On 16 May 2007, Dr. Rader submitted IND 77775 for the development of lomitapide for HoFH.

On 07 June 2007, IND 50820 was placed on partial clinical hold (PCH) for studies >6 months duration because of insufficient information to assess the risk for pulmonary phospholipidosis with long-term use of the drug. Sponsors of MTP inhibitors, with the exception of Dr. Rader (IND 77775), were asked to submit a final report from a completed 3-month, repeat-dose rat toxicology study that included a recovery group and a sufficient number of active doses to establish a NOAEL for pulmonary phospholipidosis. IND 77775 was not placed on PCH because the risk-benefit ratio was considered distinct for the HoFH population. See the pharm/tox briefing document for additional information.

On 23 October 2007, orphan drug designation was granted for the treatment of HoFH (designation 07-2459). The HoFH phase 3 pivotal trial was initiated on 18 December 2007, and its IND was transferred from Dr. Rader to Aegerion on 28 February 2008 to facilitate the conduct of multi-site trials.

The division held a face-to-face EOP2 meeting with Aegerion on 09 November 2009 to discuss the lomitapide development program, as Aegerion expressed interest in the refractory HeFH population. Topics of discussion included: (1) concern over pulmonary

phospholipidosis had lessened given the identification of a number of approved products that were associated with pulmonary phospholipidosis in animals but had not been associated with pulmonary toxicity in humans; (2) recently submitted mouse carcinogenicity study results showed malignant tumors in the small intestine and liver, with a rat carcinogenicity study ongoing; (3) uncertainty regarding the long-term consequences of lomitapide-associated hepatic steatosis; (4) concern regarding the potential for increased fecal fat excretion and associated long-term risks. The agency agreed that a trial could be initiated in the refractory HeFH population, but this would need to be accompanied by a second trial in high-risk HeFH patients as well; furthermore, the agency noted that it would be possible that a clinical outcomes trial would be required. These trials have not been pursued to date.

On 18 February 2010, the partial clinical hold for pulmonary phospholipidosis was lifted (see pharm/tox briefing document for further information), but during a face-to-face meeting on 17 May 2010, Aegerion informed the division that they would only be pursuing the HoFH indication as a result of financial constraints. Aegerion stated that they were amenable to “whatever post-approval supply constraints were necessary to ensure that the drug was available only to the HoFH population.” In a follow-up teleconference on 28 July 2010 to discuss a potential NDA limited to HoFH, the agency accepted that at the time of submission, all patients would have been treated for a minimum of 56 weeks.

A pre-NDA meeting was held on 15 June 2011. Clinical topics addressed during this meeting included:

- Regarding CYP3A4 drug-drug interactions, the sponsor “proposed to address the CYP3A4 interaction in labeling; the package insert will indicate to avoid taking lomitapide with moderate CYP3A4 inhibitors in addition to strong CYP3A4 inhibitors and labeling will caution about the use of lomitapide with mild CYP3A4 inhibitors. The agency agreed with this approach.” (This quote reflects the sponsor’s correction of the meeting minutes, received 21 July 2011.) “The firm was encouraged to use simulations to evaluate the effect of mild and moderate CYP3A4 inhibitors on lomitapide. The labeling language will be a review issue. It was also strongly recommended that the sponsor address the in-vitro induction potential of lomitapide and its major metabolites on major CYP enzymes.”
- The Agency agreed to the sponsor’s proposal to conduct a population PK analysis later in development by combining data from pediatric studies.
- The Agency confirmed that a single, pivotal phase 3 study lacking a placebo control arm would not preclude filing or approval of the lomitapide NDA for the HoFH population.
- The Agency agreed that the available exposure data from the single pivotal phase 3 study (UP1002/733-005) are sufficient to support an NDA for HoFH. Briefly, the sponsor stated that data would be available for 18 patients who had been exposed for at least 1.5 years and 10 who had been exposed for at least 2 years; maximum tolerated dose for patients receiving treatment for at least 2 years would range from 20 mg to 60 mg.

- The Agency noted that including a “functional HoFH” definition of average fasting LDL > 300 mg/dL on maximally tolerated lipid-lowering therapy closely resembles the severe refractory HeFH population, which would shift the risk-benefit ratio. “Dr. Rader recognized that the treatment indication for lomitapide will need to align with the inclusion criteria of the Phase 3 trial. Additionally, Dr. Rader understood that inclusion of patients on maximal tolerated therapy with LDL >300 mg/dL for treatment with lomitapide (which was not an inclusion criterion in the Phase 3 trial) is a REMS issue that will be addressed as part of the NDA review process.”
- Regarding a potential REMS, the sponsor was encouraged to submit all planned materials that would be necessary to implement their proposal and to provide detailed plans of how distribution would be restricted to the HoFH population studied in the Phase 3 trial, including how documentation of HoFH status would be collected and confirmed, how distribution would be accomplished, and how the system would be monitored for compliance.
- The sponsor stated that the primary data to support the effectiveness and safety would come from the phase 3 study UP1002/733-005 with supportive data from UP1001 (HoFH, phase 2) and 5 other phase 2 studies that involved subjects with elevated LDL-C. The Agency agreed with the general approach.
- The Agency accepted the proposed dates of database locks as long as adverse events of special interest that occurred afterward would be included in the safety update prior to filing the NDA.

NDA 203858 was received by the agency on 29 February 2012.

Table 1 presents a more extensive synopsis of the regulatory history.

Table 1. Lomitapide – Regulatory History

Date	Event / Notes
18 Jun 1996	IND 50820 submitted by Bristol-Myers Squibb (BMS) • <i>BMS-201038 for treatment of mixed dyslipidemia.</i>
08 Jan 1997	EOP1 Meeting
18 Feb 1998	Meeting to discuss safety issues and clinical development plan
21 Aug 2002	IND 50820 transferred to Daniel J. Rader, MD, University of Pennsylvania • <i>Anticipated for treatment of HoFH</i>
20 July 2004	EOP2 Teleconference • <i>Potential for DDI noted by the Division given that BMS-201038 appeared to be a potent CYP3A4 inhibitor. Given the potential for combination with other lipid-altering drugs in clinical practice, DDI studies with simvastatin, atorvastatin, rosuvastatin, and ezetimibe were considered necessary.</i> • <i>Concern about pulmonary phospholipidosis (PL) in chronic rodent toxicity studies without an established NOAEL. Dr. Rader noted that pulmonary function tests were performed in clinical studies and function was reported as normal.</i> • <i>DMEP asked for information about the metabolic enzyme responsible for the test drug.</i> • <i>DMEP noted that any expanded use of the product beyond HoFH would shift the risk-benefit profile of the development program.</i>
27 Jan 2006	OOPD Grant 1R01 FD003098-01 awarded for MTP Inhibitor for Familial Hypercholesterolemia (PI: Marina Cuchel, MD, PhD)

Date	Event / Notes
28 Aug 2006	Division provided comments regarding pivotal Phase 3 trial, "A phase III study of the MTP inhibitor BMS-201038 in patients with severe refractory hypercholesterolemia on current lipid lowering therapy." • <i>PK/PD DDI studies with warfarin and a CYP2D6 substrate were highly recommended.</i>
07 Feb 2007	EOP2 teleconference to discuss pivotal trial for HoFH indication • <i>DMEP agreed that a proposed sample size of 25 subjects diagnosed with HoFH, all of whom would receive BMS-201038 at the maximum tolerated dose for a minimum of 52 weeks, should be adequate for the assessment of efficacy in the proposed population.</i> • <i>DMEP encouraged the sponsor to include "sufficient numbers of women and Asians in the study population given that the behavior and potential toxicity of the drug is likely [to] be enhanced in these populations."</i> • <i>DMEP agreed with a dose-titration scheme to enhance tolerability, but the proposed dosages did not provide adequate safety margins for pulmonary phospholipidosis, which remained a concern.</i> • <i>Discussion of DDI PK study designs</i> • <i>DMEP agreed that no placebo arm would be required given a proposed design that included a minimum 6-week run-in period for all subjects where concomitant lipid-lowering treatment must remain stable. The sponsor stated that the concomitant treatment was to remain stable for the first 26 weeks of the study. In addition, a 6-week follow-up period was added following the last dose of BMS-201038 when concomitant lipid-lowering therapy should remain stable. "In addition, the absence of the placebo group allows that all subjects will be exposed to a minimum of 52 weeks at the maximum tolerated dose of study drug."</i> • <i>DMEP: "The dose titration scheme allows for patients to be treated at their maximum tolerated dose for 8.5-17 months, depending on the duration of their individualized titration. The sponsor is urged to follow patients for one year after their maximum tolerated dose has been achieved." The sponsor concurred.</i> • <i>DMEP and the sponsor agreed to CK monitoring, measurement of beta-carotene, vitamin K levels (via carboxylation of serum osteocalcin), major metabolites, alpha-tocopherol (reported as Vitamin E/LDL or Vitamin E/HDL ratios, and further testing such as adipose-tissue sampling with abnormal ratios), and hepatic fat (¹H MRS instead of MRI). Vitamin E supplementation would be increased to 400 IU daily.</i> • <i>The sponsor agreed to remove diabetes as an exclusion criterion.</i> • <i>Requirements for carcinogenicity, genotoxicity, and reproductive toxicology studies were discussed.</i> • <i>DMEP suggested several pulmonary and hepatobiliary exclusions and prohibited concomitant medications (corticosteroids, betaine).</i>
13 Apr 2007	IND 50820 transferred to Aegerion for development of AEGR-733 (formerly known as BMS-210038) for "moderate hypercholesterolemia," which included severe refractory hypercholesterolemia
16 May 2007	IND 77775 submitted by Daniel J. Rader, MD, University of Pennsylvania, for HoFH
07 June 2007	Partial clinical hold (PCH) for IND 50820 (studies >6 months duration) • <i>In October 2006, after consultation with the Division of Gastroenterology Products, the Division of Pulmonary and Allergy Products, and consideration of the pharm/tox review of the pre-clinical data, all MTP inhibitors – with the exception of IND 77775 – were placed on PCH for clinical protocols >6 months duration because "insufficient information is available to assess the risk for pulmonary phospholipidosis with long-term use of the drug." Sponsors were asked to submit a final report from a completed 3-month, repeat-dose rat toxicology study that included a recovery group and a sufficient number of active doses to establish a NOAEL for pulmonary PL. The protocols were to include electron microscopy. IND</i>

Date	Event / Notes
	<i>77775 was not placed on PCH because the risk-benefit ratio was considered distinct for the HoFH population.</i>
23 Oct 2007	Orphan drug designation for the treatment of HoFH (Designation 07-2459)
28 Feb 2008	IND 77775 transferred to Aegerion from Dr. Rader to facilitate conducting multi-site trials
10 Aug 2009	Teleconference with Aegerion in lieu of premature EOP2 meeting • <i>At an 05 Aug 2009 internal meeting preceding a scheduled 12 Aug 2009 EOP2 teleconference, DMEP determined that lingering concerns regarding PL and the failure to study lomitapide in combination with an optimal statin dose in severe refractory hypercholestermia precluded an EOP2 meeting.</i> • <i>Dr. Eric Colman informed representatives from Aegerion that the mouse carcinogenicity study results, which would include data on pulmonary PL, would need to be submitted before a discussion of phase 3 studies in the severe refractory hypercholesterolemic population.</i>
09 Nov 2009	Type B Face-to-face EOP2 Meeting with Aegerion • <i>Mouse carcinogenicity data: malignant tumors in the small intestine and liver at high doses. Data had not been reviewed in detail by the Agency (submitted 26 Oct 2009). The rat carcinogenicity study was ongoing, but reportedly no tumors had been observed. DMEP stated that the rat results would be important in determining the overall safety implications for humans; <u>“At minimum, the carcinogenicity findings with the respective systemic exposure multiples would be included in the label, if the drug is eventually approved.”</u></i> • <i>Pulmonary PL: DMEP had less concern given that a number of approved compounds (e.g., fluoxetine) were identified that were associated with pulmonary PL in animal studies without known pulmonary dysfunction in humans. However, Aegerion was encouraged to resolve this issue from a pre-clinical perspective.</i> • <i>Hepatic steatosis: DMEP recommended a 6-month safety study to observe lomitapide’s effect on hepatic fat, hepatic structure/function, and insulin sensitivity. Exploratory endpoints such as IL-6, CRP, CK18 fragments, and enhanced liver fibrosis (ELF) panel were suggested. The sponsor cited results from study 733-004 to answer safety questions regarding hepatic fat accumulation with lomitapide use; in this 12-week study in ~250 patients, hepatic fat was measured four times and the company stored samples that could be used to measure biomarkers.</i> • <i>The sponsor stated their intent to submit an NDA if the rat carci study was negative and the Agency allowed them to focus on the refractor HeFH population, with appropriate liver monitoring. DMEP replied that additional information would be needed in the broader dyslipidemic population given that the drug would invariably be used by this population, even if approved for a very limited indication. The sponsor was encouraged to submit an updated development plan; this was submitted 18 Nov 2009.</i> • <i>In response to pre-clinical questions about fecal fat, the sponsor submitted human study CV145002 report on 18 Dec 2009; on 29 Dec 2009, the agency told the firm that these data were insufficient to address the question of fecal fat excretion with lomitapide because the study was not adequately conducted.</i>
18 Feb 2010	Partial clinical hold lifted
17 May 2010	Type B Face-to-face EOP2 Meeting • <i>Several clinical pharmacology comments were relayed to the sponsor prior to this meeting, including clarification of the dosing of lomitapide with respect to meals, requiring a DDI study with warfarin, requiring an investigation of the inhibition/induction potential of the major metabolites (such as M1 and M3) on major CYP enzymes in in vitro and possibly in vivo systems, and a renal impairment study. The sponsor was asked to justify why only the metabolites M1, M2, and M3 were to be monitored given that M8 was the most abundant metabolite.</i> • <i>At this meeting, Aegerion informed DMEP that they were only pursuing the HoFH</i>

Date	Event / Notes
	<i>indication as a result of financial constraints. Aegerion was amenable to “whatever post-approval supply constraints were necessary to ensure that the drug was available only to the HoFH population.”</i> •  (b) (4)
28 Jul 2010	Follow-up teleconference to discuss NDA limited to HoFH • <i>“At the time of submission, all patients will have been treated for a minimum of 56 weeks. This was found acceptable by the Agency.”</i> • <i>Clinical pharmacology concerns were still outstanding. In addition to those mentioned previously, it was also a concern that lomitapide exposure was higher in women than in men. Furthermore, since the DDI study with simvastatin did not use the maximum dose of lomitapide, a separate DDI study with simvastatin and 60-mg lomitapide was recommended.</i>
03 Mar 2011	Orphan drug designation for the treatment of familial chylomicronemia
05 Apr 2011	Type B pre-NDA CMC meeting
14 Apr 2011	Fast-track designation request submitted
14 Jun 2011	Fast-track designation denied, as the development program was not designed to determine whether the product will reduce cardiovascular morbidity or mortality in the HoFH population or lower-risk populations
15 Jun 2011	Type B Face-to-face pre-NDA Meeting (Clinical questions only) • <i>The sponsor was encouraged to characterize all metabolites.</i> • <i>Regarding CYP3A4 DDIs, the sponsor “proposed to address the CYP3A4 interaction in labeling; the package insert will indicate to avoid taking lomitapide with moderate or mild CYP3A4 inhibitors in addition to strong CYP3A4 inhibitors. The agency agreed with this approach. The firm was encouraged to use simulations to evaluate the effect of mild and moderate CYP3A4 inhibitors on lomitapide. The labeling language will be a review issue. It was also strongly recommended that the sponsor address the in-vitro induction potential of lomitapide and its major metabolites on major CYP enzymes.” Note: The sponsor submitted a correction to these minutes on 21 July 2011, stating that moderate and strong CYP3A4 inhibitors should be avoided and that labeling would “caution about the use of lomitapide with mild CYP3A4 inhibitors.”</i> • <i>The Agency agreed to the sponsor’s proposal to conduct a population PK analysis later in development by combining data from pediatric studies.</i> • <i>The Agency confirmed that a single, pivotal phase 3 study lacking a placebo control arm would not preclude filing or approval of the lomitapide NDA for the HoFH population.</i> • <i>The Agency agreed that the available exposure data from the single pivotal phase 3 study (UP1002/733-005) are sufficient to support an NDA for HoFH. Briefly, the sponsor stated that data would be available for 18 patients who had been exposed for at least 1.5 years and 10 who had been exposed for at least 2 years; maximum tolerated dose for patients receiving treatment for at least 2 years would range from 20 mg to 60 mg.</i> • <i>The Agency noted that including a “functional HoFH” definition of average fasting LDL > 300 mg/dL on maximally tolerated lipid-lowering therapy closely resembles the severe refractory HeFH population, which would shift the risk-benefit ratio. “Dr. Rader recognized that the treatment indication for lomitapide will need to align with the inclusion criteria of the Phase 3 trial. Additionally, Dr. Rader understood that inclusion of patients on maximal tolerated therapy with LDL >300 mg/dL for treatment with lomitapide (which was not an inclusion criterion in the Phase 3 trial) is a REMS issue that will be addressed as part of the NDA review process.”</i>

Date	Event / Notes
	• <i>Regarding a potential REMS, the sponsor was encouraged to submit all planned materials that would be necessary to implement their proposal and to provide detailed plans of how distribution would be restricted to the HoFH population studied in the Phase 3 trial, including how documentation of HoFH status would be collected and confirmed, how distribution would be accomplished, and how the system would be monitored for compliance.</i> • <i>CDISC SDTM and ADaM datasets would be submitted</i> • <i>The sponsor stated that the primary data to support the effectiveness and safety would come from the phase 3 study UP1002/733-005 with supportive data from UP1001 (HoFH, phase 2) and 5 other phase 2 studies that involved subjects with elevated LDL-C. The Agency agreed with the general approach.</i> • <i>The Agency accepted the proposed dates of database locks as long as adverse events of special interest that occurred afterward would be included in the safety update prior to filing the NDA.</i> • <i>Analyses and tables to facilitate the clinical review were requested (e.g., Hy's Law cases, categorical laboratory-related analyses, review of reasons for dropout/discontinuation, analyses of changes in concomitant medications, correlations between compliance with dietary fat and adverse events, analyses regarding the number and frequency of adverse events depending on dose of concomitant statin, analyses comparing efficacy with and without LDL apheresis, data presentation to facilitate site selection for inspection).</i>

2.6 Other Relevant Background Information

Not applicable.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This NDA was submitted in eCTD format. The submission quality and integrity was acceptable. The initial NDA submission received 29 February 2012 included all safety and efficacy data from the HoFH pivotal trial through study week 56 and its extension study through 12 April 2011. The data cut-off for serious adverse events, adverse events leading to discontinuation, and adverse events of special interest was 08 September 2011. On 27 June 2012, the applicant submitted a 120-day safety update that included *safety* data through the remainder of the HoFH pivotal trial (78 weeks total) and its extension study through 31 December 2011. The applicant's analyses of supportive efficacy data from week 56 through 78 of the pivotal trial, or during the extension study, have not been submitted to date.

3.2 Compliance with Good Clinical Practices

The applicant provides a statement of Good Clinical Practice (Module 2.7.3, Section 1.3). All clinical studies were conducted under the supervision of an IRB with adequate informed consent procedures.

The sponsor (Aegerion Pharmaceuticals) and three sites from the phase 3 HoFH pivotal trial were inspected by the Office of Scientific Investigation: University of Pennsylvania; University of Capetown Health Science (S. Africa), and Netcare Private Hospital (S. Africa). No concerns regarding data integrity were identified. See Dr. Susan Leibenhaut's clinical inspection summary for additional information (31 October 2012).

3.3 Financial Disclosures

No investigator reported disclosable financial interests or arrangements with the applicant. For study CV145-009, which was conducted in 1999, the applicant could not reach 23 investigators (4 sites); evidence of due diligence was submitted (Module 1.3.4).

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See Dr. Xavier Ysern's review.

The dosage form of lomitapide mesylate is hard-gelatin capsules, which the applicant proposes to market in 5, 10, and 20-mg strengths. The molecular formula is $C_{39}H_{37}F_6N_3O_2 \cdot CH_4O_3S$ with a molecular weight of 789.8 amu (693.7 + 96.1). The chemical name is *N*-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)]][1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9*H*-fluorene-9-carboxamide, methanesulfonate salt. The chemical structure is shown in Figure 1.

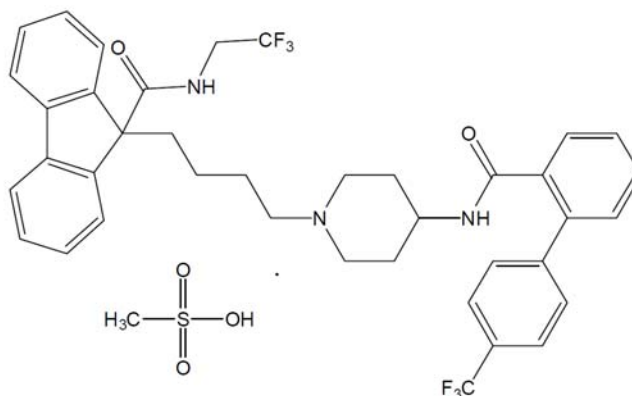


Figure 1. Chemical Structure of Lomitapide

Source: Dr. Ysern's review.

From a CMC point-of-view, Dr. Ysern recommends approval pending (1) completion of the submission of the Method Validation Package and (2) satisfactory recommendation of the dissolution specification by the Biopharm review team. In addition, the

recommendation from the Office of Compliance for the acceptability of the manufacturing sites is pending at the time of this review.

Furthermore, Dr. Ysern notes that based on the stability data submitted, “an expiry of 24 months for drug product (b) (4) packaged in (b) (4) high-density polyethylene bottles sealed with an induction seal and closed with a (b) (4) child-resistant twist-off closure is granted under the recommended storage conditions: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Protect from moisture.”

Reviewer Comment: CMC review states that “the CMC-pertinent sections of the package insert, Sections 11 (Description) and 16 (How Supplied/Storage and Handling), are adequately provided.”

4.3 Preclinical Pharmacology/Toxicology

See Dr. B. Timothy Hummer’s review for full details. References to clinical exposure in the text below are based on a 60 mg daily human dosage.

Neutral Lipid Accumulation

- Lipid accumulation in small intestine occurred at clinically relevant exposures in mice, rats, and dogs and was shown to be reversible in mice after a 2-year exposure. This was not associated with signs of toxicity or inflammation. The safety implications for humans are unknown.
- Lipid accumulation in hepatocytes occurred at or near clinically relevant exposures in mice, rats, and dogs. In rats treated for 6 months, lipid vacuolation had reversed after a 6-month treatment-free period. Slight increases in ALT and/or AST were noted in rats and dogs; slightly larger increases in mean serum alkaline phosphatase were also observed in rats. In rats, minimal single cell necrosis and minimal subacute inflammation was seen in the liver after 3 and 6 months of treatment at clinically relevant exposures. After 2 years of dosing in rats, an increase in the incidence and severity (minimal to moderate) of focal/multifocal fibrosis and centrilobular hepatocyte vacuolation were observed at clinically relevant exposures. These changes were not associated with an increased incidence of hepatocellular tumors.
- In the 2-year rat carcinogenicity study, hepatic fibrosis was observed, which appeared to correlate with the presence of hepatocyte vacuolation. After 2 years of treatment in mice and 1 year of treatment in dogs, however, hepatocellular vacuolation was not observed even though it was observed in shorter duration studies.
- There was an increased incidence of the presence of foamy alveolar macrophages (histiocytes) in rats at clinically relevant exposures and in mice at slightly greater than clinical exposure. The severity of histiocytosis was generally minimal in mice and minimal to mild in rats, and appeared to be reversible after a 6-month recovery period in rats. In dogs, treatment-related histiocytosis was not observed. Early in lomitapide’s development, this was thought to be a mixture of neutral lipid and phospholipid vacuoles, but the most recent ultrastructural

evaluations suggest that the vacuolation is consistent with neutral lipid vacuoles. Whether this has any different safety implications, however, is unknown.

Reviewer Comment: One subject in the HoFH extension study has undergone esophagogastroduodenoscopy. Similar to the nonclinical observations, the duodenal mucosa had a white, velvety appearance, and biopsy demonstrated preserved villous morphology but several foci of diffuse cytoplasmic vacuolation of the villous enterocytes without intestinal lymphangiectasia.

Lung

- See description of alveolar histiocytosis above.
- After 1 year of treatment in dogs, there was a low incidence of minimal to mild pleural fibrosis as well as minimal focal mineralization, mild chronic active inflammation, and minimal to mild alveolar edema. With the exception of pleural fibrosis, which was observed in both genders at the mid- and high-dose levels, these findings were only observed in a single gender (1 or 2 animals out of 4) at the high-dose level.
- In the 2-year rat study, there were increases in the incidence of alveolar spicules, lymphocyte infiltration with macrophage accumulation, thickened alveolar septa with macrophage infiltrates, septal cell mineralization, and pleural/subpleural fibrosis. The incidence and severity of these findings generally increased in a dose-related manner.

Carcinogenicity

- Treatment for 2 years in mice resulted in an increased incidence of hepatocellular tumors at clinically relevant exposures in males and at approximately 9-fold higher than clinical exposures in females. Evaluation of liver tissue did not reveal an increase in liver toxicity or chronic inflammation, which are potential mechanisms for tumor development. Some liver fibrosis was observed in the rat carcinogenicity study but an increase in hepatocellular tumors was *not* observed in rats.
- A small but statistically significant increase in small intestinal tumors was observed in mice at approximately 25-fold higher than clinical exposures. The high clinical exposure margin in conjunction with the fact that this tumor type was only observed in a single species lowers the overall concern for human safety with regard to small intestinal tumors.
- In mice, the NOELs for drug-related neoplasms were 0.3 mg/kg/day for males and 15 mg/kg/day for females, representing clinical exposure margins of 0.4x and 2x, respectively. In rats, the NOELs were the highest doages tested, 7.5 mg/kg/day for males and 2 mg/kg/day for females, representing clinical exposure margins of 6x and 8x, respectively.
- It is the opinion of Pharm/Tox that the possible tumor risk with lomitapide treatment in humans can be adequately addressed through labeling.

Teratogenic Potential

- Treatment with lomitapide during the period of organogenesis resulted in embryonic death and fetal malformations of the abdomen, limbs, tail, and head in rats and ferrets at clinically relevant exposures. Treatment with lomitapide in pregnant rabbits resulted in embryonic loss at doses that are approximately 6.5-fold higher than the clinical dose of 60 mg (based on body surface area extrapolation).

Fat-Soluble Vitamin Deficiencies

- Deficiencies in fat-soluble vitamins (e.g., vitamins A, D, E, K) were observed in animal studies, which led to systemic hemorrhage in rats at exposures that were approximately 17-fold higher than clinical exposure, resulting in death at higher exposure (~70-fold clinical exposure). When supplemental vitamin K was provided or lower doses were administered, systemic bleeding was not observed.
- Vitamin supplementation was not provided for the 1-year toxicology study in dogs or for any of the pivotal developmental and reproductive toxicology studies.

Table 2, excerpted from Dr. Hummer's review, summarizes noteworthy treatment-related effects from nonclinical studies.

Table 2. Summary of Noteworthy Treatment-Related Effects from Nonclinical Studies

Observed Effect	Species	Study Duration	NOEL (mg/kg/d)	Safety Margin*
Liver - lipid vacuolation	Mouse	3 months	<1.5	<2X
		2 years	45 [†]	~75X
	Rat	3 months	<1	<2X
		6 months	<0.02	<0.4X
		2 years	M: <0.25 F: <0.03	M: <0.25X F: <0.1X
	Dog	6 months	0.1	M: 1X F: 2X
12 months		5 ^{††}	60X	
Liver - fibrosis, focal/multifocal	Rat	2 years	M: <0.25 F: 0.03	M: <0.25X F: 0.1X
Small intestine - lipid vacuolation	Mouse	3 months	<1.5	<2X
		2 years	<0.3	<0.4X
	Rat	3 months	<1	<2X
		6 months	0.02	0.4X
		2 years	M: <0.25 F: <0.03	M: <0.25X F: <0.1X
	Dog	6 months	<0.01	M: <0.2X F: <1X
12 months		0.05	0.2X	
Lung - histiocytosis/ foamy macrophages	Mouse	3 months	1.5	2X
		2 years	45 ^{†††}	~75X
	Rat	3 months	<1	<2X
		3 months	<0.01	<0.1X
		6 months	0.02	0.4X
		2 years	M: 7.5 [†] F: 2 [†]	M: 6X F: 8X
	Dog	6 months	10 [†]	200X
		12 months	5 [†]	60X
Lung - pleural fibrosis	Rat	2 years	M: 7.5 [†] F: 0.03	M: 6X F: 0.1X
	Dog	12 months	0.05	0.2X
Lung - thickened alveolar septa with macrophage infiltrates	Rat	2 years	M: 0.25 F: 0.03	M: 0.25X F: 0.1X
Lung - septal cell mineralization	Rat	2 years	M: 0.25 F: 2.0 [†]	M: 0.25X F: 8X
Lung - alveolar spicules	Mouse	2 years	7.5	10X
	Rat	2 years	M: 0.25 F: 0.03	M: 0.25X F: 0.1X

NOEL = no observed effect level

*Safety margins were calculated using a mean AUC_{0-24h} value of 69.5 ng·h/mL for humans at 60 mg.

[†]Finding not observed.

^{††}Lipid vacuolation was not observed in hepatocytes from the 12-month dog study; however, mean liver weights were statistically significantly increased at 5 mg/kg/d compared with control values.

^{†††}Lipid vacuoles were not observed in lung macrophages or type 2 pneumocytes by light microscopy but were noted in some animals by electron microscopy at ≥0.3 mg/kg/d for males and ≥15 mg/kg/d for females.

Source: Pharmacology/Toxicology Review (Dr. B. Timothy Hummer).

4.4 Clinical Pharmacology

See Dr. Lau's review for full details.

4.4.1 Mechanism of Action

Lomitapide directly binds and inhibits microsomal triglyceride transfer protein (MTP), which resides in the lumen of the endoplasmic reticulum, thereby preventing the assembly of apoB-containing lipoproteins in enterocytes and hepatocytes. This inhibits the synthesis of chylomicrons and VLDL, respectively, which ultimately give rise to the atherogenic LDL.

4.4.2 Pharmacodynamics

The first-in-human study CV145-001 tested single doses of oral lomitapide ranging from 1 to 200 mg. A dose-response was observed for LDL reduction at doses ≥ 50 mg; total cholesterol and apoB were similar. Dose-related decreases in triglycerides were also observed at doses ≥ 25 mg, with peak reductions occurring 8 hours after the dose. The first multiple-dose study, CV145-002, was a double-blind, randomized, placebo-controlled study in which 4 groups of 9 men each received daily doses of lomitapide 10, 25, 50, or 100 mg or matched placebo for 14 days. The 100-mg group was stopped on day 8 as a result of gastrointestinal adverse events (e.g., loose stools, abdominal discomfort, nausea), and a planned 200-mg dose was not investigated. The results of the lipid parameters assessed in this trial are summarized in Table 3, and the effects on LDL-C are depicted in Figure 2. Dose-dependent reductions in LDL-C were observed, with maximal effect between days 8-11.

Table 3. CV145-002 – Lomitapide Pharmacodynamics

Geometric Mean (95% C.I.) Percent Change in Lipids from Baseline					
Lipid Study Day†	Dose of BMS-201038				
	Placebo (n=12)	10 mg (n=6)	25 mg (n=6*)	50 mg (n=6)	100 mg (n=6)
T-C					
Day 4	-7 (-13, -1)	-10 (-16, -3)	-25 (-29, -21)	-33 (-40, -24)	-42 (-60, -16)
Day 8	-0 (-6, +6)	-18 (-35, +4)	-41 (-50, -30)	-60 (-71, -46)	-71 (-77, -63)
Day 11	+4 (-4, +13)	-16 (-34, +6)	-40 (-46, -34)	-63 (-80, -33)	-56 (-62, -49)
Day 14 or 15	+5 (-2, +13)	-14 (-26, -0)	-37 (-49, -23)	-63 (-80, -30)	-37 (-45, -27)
LDL-C					
Day 4	-10 (-15, -4)	-21 (-37, -1)	-32 (-37, -27)	-37 (-46, -26)	-45 (-65, -13)
Day 8	-8 (-16, -0)	-26 (-46, +3)	-54 (-65, -39)	-71 (-78, -61)	-86 (-95, -63)
Day 11	-2 (-11, 8)	-20 (-38, +3)	-57 (-67, -44)	-80 (-91, -54)	-71 (-77, -62)
Day 14 or 15	+6 (-4, 17)	-17 (-30, -0)	-46 (-58, -31)	-79 (-92, -47)	-49 (-54, -44)
HDL-C					
Day 4	-6 (-14, +2)	-10 (-18, -0)	-22 (-30, -13)	-28 (-42, -12)	-15 (-33, +9)
Day 8	-9 (-15, -3)	-13 (-24, -1)	-24 (-29, -18)	-32 (-45, -16)	-26 (-39, -9)
Day 11	-6 (-12, -0)	-7 (-13, +1)	-25 (-33, -17)	-13 (-29, +7)	-27 (-38, -13)
Day 14 or 15	-4 (-13, +6)	-3 (-15, +11)	-25 (-36, -12)	-9 (-26, +12)	-27 (-37, -17)
TG					
Day 4	-1 (-30, +40)	+19(-13,+64)	+11(-38,102)	-23 (-56,+32)	-77 (-95,+14)
Day 8	+40 (+8, +82)	+13(-27,+74)	+9 (-37, +89)	-52 (-81,+24)	-68 (-85, -33)
Day 11	+43(+17,+75)	-7(-38,+39)	+31(-34,160)	-57 (-83, +9)	-26 (-37, -12)
Day 14 or 15	+7 (-8, +23)	-22(-47, +15)	+1 (-16, +22)	-60 (-81, -16)	+18(-17,+67)
VLDL-C					
Day 4	-1 (-30, +42)	+18(-16,+64)	+12 (-38,102)	-24(-55, +30)	-77 (-95,+13)
Day 8	+40 (+9, +82)	+13(-27,+74)	+11 (-36, 92)	-54(-83, +25)	-69 (-86, -34)
Day 11	+44(+18,+76)	-7(-38,+39)	+31 (-34,163)	-57(-83, +9)	-26 (-37, -13)
Day 14 or 15	+7 (-8, +23)	-22(-47, +16)	+2 (-17, +28)	-60 (-81, -17)	+17(-17,+65)
apoB					
Day 4	-5 (-15, +6)	-3 (-13, +8)	-20 (-31, -7)	-34 (-44, -23)	-58 (-78,-18)
Day 8	+6 (-4, +17)	-16 (-30, +2)	-37 (-52, -19)	-73 (-83, -57)	-84 (-92, -67)
Day 11	+13 (+3, +23)	-17 (-37, +8)	-31 (-41, -18)	-83 (-96, -30)	-55 (-61, -49)
Day 14 or 15	+7 (-1, +15)	-16 (-31, +2)	-35 (-52, -11)	-83 (-97, -12)	-27 (-39, -13)

†Note: For the 10 mg, 25 mg, and 50 mg groups and the placebo subjects associated with these groups, the lipid data is from Day 15. For the 100 mg group and the placebo subjects associated with this group, the lipid data is from Day 14. Also note that the dosing regimen was discontinued on either Day 6 or 7, in the 100 mg group.

*Note: n=5 in the 25 mg group on Days 8, 11, & 15.

Abbreviations: C.I., confidence interval; n, number of subjects

Source: CV145-002 clinical study report (CSR).

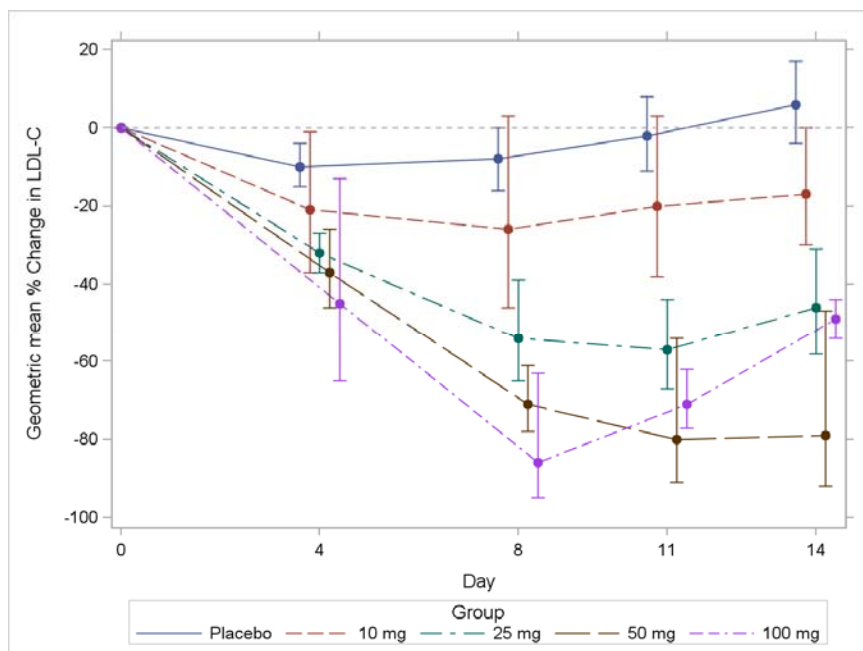


Figure 2. CV145-002 – Lomitapide Dose-Response for LDL-C

Source: FDA clinical reviewer’s depiction of data in Table 3, above.

Error bars represent 95% CI of the geometric mean % changes.

Note that dosing was discontinued for all subjects on day 6 or 7 in the 100-mg group.

In the similarly designed study CV145-010, 18 women were randomly assigned to daily doses of lomitapide 10 mg, 25 mg, or matched placebo for 14 days. The geometric mean (SD) % reductions in LDL-C on day 15 were +1.9% (8.8), -34.3% (13.0), and -76.7% (13.9) for the placebo, lomitapide 10 mg, and lomitapide 25 mg groups, respectively. Maximal reduction of LDL-C occurred between days 11 and 14.

4.4.3 Pharmacokinetics

Throughout development, 15 clinical studies examined the clinical pharmacology of lomitapide. Six of these studies were sponsored by BMS in 1996-1997 (1 single-dose and 2 multiple-dose PK studies; 1 absolute bioavailability study; 1 food-effect study; 1 mass-balance study). Aegerion conducted an additional mass-balance study, 2 PK studies in special populations (hepatic and renal impairment), 5 drug-drug interaction studies, and a thorough QT study (Table 4). Except for the special populations, all of these studies were conducted in volunteers who were essentially healthy (some required total cholesterol $\geq$ 195-200 mg/dL).

Table 4. Clinical Pharmacology Studies

Study Identifier	Year	Description
CV145-001	1996	Single-dose PK; 1, 5, 25, 50, 100, 200 mg *
CV145-002	1996	Multiple-dose PK; 10, 25, 50, 100 mg daily x 14 days; <i>100 mg stopped on day 8 (GI tolerability)</i>
CV145-003	1996	Single-dose absolute bioavailability study; 7.5, 15, 30, or 60 mg IV, or 50 mg PO
CV145-005	1997	Food-effect bioavailability study (single 50 mg dose)
CV145-006	1997	ADME; single-dose [^{14} C] 50 mg (100 μ Ci) solution

Study Identifier	Year	Description
CV145-010	1997	Multiple-dose PK; 10 or 25 mg daily x 14 days (women only)
AEGR-733-010	2010	ADME; single-dose [¹⁴ C] 50 mg solution
AEGR-733-017	2011	Hepatic impairment PK; single-dose 60 mg
AEGR-733-021	2011	End-stage renal disease PK; single-dose 60 mg
AEGR-733-002	2006	DDI: atorvastatin, simvastatin, rosuvastatin, fenofibrate, ezetimibe, extended-release niacin (PK)
AEGR-733-013	2010	DDI: warfarin (PK/PD)
AEGR-733-018	2010	DDI: ethinyl estradiol/norgestimate (PK)
AEGR-733-019	2010	DDI: ketoconazole (PK)
AEGR-733-015	2011	DDI: simvastatin
AEGR-733-011	2011	Thorough QT Study

Source: Module 2.7.6.

* Unless otherwise indicated, all doses are oral.

Although sparse PK sampling was conducted in the HoFH phase 3 trial, no analyses have been conducted with these data to date. At the pre-NDA meeting, the agency agreed to the sponsor's proposal to conduct a population PK analysis later in development by combining data from pediatric studies.

ADME Summary

The following summary of the PK of lomitapide is excerpted from Dr. Lau's Clinical Pharmacology review:

Absorption

Upon oral administration of a single 60 mg dose (3 x 20 mg) of lomitapide, the lomitapide C_{max} , AUC_{0-inf} , and t_{max} are 1.2 ng/mL, 65 ng•hr/mL, and 6 hours, respectively, in healthy volunteers. Mean lomitapide absolute oral bioavailability is 7.1% between an oral 50 mg lomitapide capsule of an early formulation and intravenous 30 mg lomitapide solution. Of the same 50 mg lomitapide capsule, a high fat meal increases lomitapide C_{max} and AUC 77% and 58%, respectively, as compared to fasting, whereas a low fat meal increases lomitapide C_{max} and AUC 70% and 52%, respectively, as compared to fasting. Lomitapide PK is approximately dose-proportional for oral single doses from 10-100 mg.

Distribution

The mean lomitapide volume of distribution at steady state is 985-1292 L. Lomitapide is 99.8% plasma protein bound. Lomitapide is not a P-gp substrate. Lomitapide inhibits P-gp but does not inhibit BCRP.

Metabolism

Liver extensively metabolizes lomitapide. The metabolic pathways include oxidation, oxidative N-dealkylation, glucuronide conjugation, and piperidine ring opening. Cytochrome P450 (CYP) 3A4 metabolizes lomitapide to its major metabolites, M1 and M3, as detected in plasma. CYPs 1A2, 2B6, 2C8, and 2C19 may metabolize lomitapide to a small extent to M1. M1 and M3 do not have the microsomal triglyceride transfer protein inhibition activity. Lomitapide does not induce CYPs 1A2, 3A4, and 2B6. Lomitapide is a weak in vivo CYP3A inhibitor. Lomitapide does not inhibit CYPs 1A2, 2B6, 2C9, 2C19, 2D6, and 2E1. M1 and M3 do not induce CYPs 1A2, 3A4, and 2B6. M1 and M3 do not inhibit CYPs 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4.

Excretion

In a mass-balance study, a mean of 59.5% and 33.4% of the dose was excreted in the urine and feces, respectively. In another mass-balance study, a mean of 52.9% and 35.1% of the dose was excreted in the urine and feces, respectively. M1 is the major urinary metabolite. Lomitapide is the major component in the feces. The mean lomitapide terminal half-life is 39.7 hours.

Dose-Response Relationships

Per Pharmacometrics, a dose-response analysis for effectiveness (% change from baseline in LDL-C) in Phase 3 study was not performed because doses were escalated from 5 mg to an individually determined maximum tolerated dose up to 60 mg. Per Pharmacometrics, a dose-response analysis for safety in Phase 3 study was not performed because doses were escalated from 5 mg to an individually determined maximum tolerated dose up to 60 mg.

5 Sources of Clinical Data

The original NDA submission, the 120-day safety update, and the applicant's responses to the agency's information requests provided the clinical data for this review. The NDA includes results of investigations performed by Bristol-Myers Squibb, the University of Pennsylvania, and Aegerion. The data cutoff for the 120-day safety update was 31 December 2011 for the ongoing HoFH extension study.

5.1 Tables of Studies/Clinical Trials

The efficacy and safety of lomitapide in the HoFH population was evaluated in one, single-arm, 78-week, phase 3 trial involving 29 subjects (hereafter, "HoFH-pivotal"). The primary efficacy endpoint was at 26 weeks, and the NDA was submitted when all subjects had completed their 56-week visit. The 120-day safety update included safety data for HoFH-pivotal through week 78. Supportive efficacy data for the HoFH population derive from the one, single-arm, 16-week, phase 2 pilot trial involving 6 subjects ("HoFH-pilot"). Supportive safety data for the HoFH population come from an open-label extension study that followed the phase 3 trial ("HoFH-extension") and from HoFH-pilot. Combined, these two HoFH trials enrolled 31 unique subjects, as 4 subjects who participated in HoFH-pilot also participated in HoFH-pivotal. The remaining two subjects in HoFH-pilot had traveled from Lebanon to the University of Pennsylvania for the phase 2 trial; therefore, their participation in the longer HoFH-pivotal was not feasible. Table 5 summarizes the trials involving the HoFH population.

The remainder of lomitapide's clinical development program was performed in subjects who were healthy volunteers (although some were required to have elevated levels of total cholesterol) or hyperlipidemic subjects who may have had other cardiac risk factors. Lomitapide has not been studied in subjects with HeFH, severe refractory HeFH, or other populations of high cardiovascular risk.

Table 6 summarizes the phase 2 trials in non-HoFH populations that were submitted to support the efficacy of lomitapide. As expected from a phase 2 program, these trials were short duration (4, 8, 8, 12, and 12 weeks). In addition, however, the dosages of lomitapide in the phase 2 database are far lower than those proposed for the HoFH population (max 60 mg daily): the 4-week trial studied lomitapide 25 mg daily; one 8-week trial studied a max dosage of 5 mg daily; the remaining three trials studied a max dosage of 10 mg daily. As described later in the review, the logic underlying the progression of the lomitapide phase 2 program arose from the applicant's exploration of the potential use of lomitapide in a broader population. During phase 2, the applicant

seems to have been studying successively lower doses of lomitapide in an attempt to find a tolerable dose that retained sufficient efficacy for potential approval in a broader dyslipidemic population.

Results from trial AEGR-733-003a were not reviewed. The original AEGR-733-003 trial was stopped prematurely because of an unexpectedly high incidence of GI adverse events; the sponsor reports to have identified *Bacillus cereus* in the drug product used during this trial, with consistent clinical symptoms. The trial was reinitiated after changing the lot of drug product. Data obtained after resuming the protocol is referred to as trial AEGR-733-003b.

Table 7 summarizes one phase 2 and five phase 1 trials that investigated the effects of lomitapide on the PK of concomitant lipid-lowering therapies, the 2D6 substrate dextromethorphan, warfarin, and an oral contraceptive. In addition, the effect of ketoconazole on the PK of lomitapide was assessed. The primary results from these studies are presented in Section 7.5.5 (p. 242).

Table 8 summarizes six phase 1 trials that describe the initial PK, safety, and tolerability experience in the lomitapide development program. With the exception of one mass-balance study conducted by Aegerion in 2010, the remaining studies were conducted by BMS between 1996 and 1998. The applicant includes the two 14-day, multiple-dose, PK/PD phase 1 studies, which enrolled hypercholesterolemic but otherwise healthy men (CV145-002) and women (CV145-010), in their safety pool of subjects with “elevated LDL-C and other cardiac risk factors.”

Last, Table 9 summarizes the investigations of lomitapide PK in special populations (hepatic impairment; end-stage renal disease) and the thorough QTc (TQT) study.

Table 5. Efficacy & Safety Trials in HoFH

Study Identifier (Dates)	Study Type	Objective(s)	Population	Design	Duration of Treatment Period	Dosage Regimen	N
UP1002/AEGR-733-005 (2007-2011)	HoFH (Efficacy & Safety)	Efficacy & long-term safety at individually identified MTD (add-on to standard-of-care LLT)	HoFH	Phase 3, single-arm, open-label, dose-escalation	78 wks*	lomit 5, 10, 20, 40, 60 mg as tolerated	29
AEGR-733-012* (2009-ongoing)	HoFH*	Long-term safety, efficacy	HoFH	Extension for AEGR-733-005	Ongoing	MTD from 733-005	18**
UP1001 (2003-2004)	HoFH (Efficacy & Safety)	Safety, tolerability, efficacy	HoFH	Phase 2, single-arm, open-label, dose-escalation	16 wks	lomit 0.03 – 1.0 mg/kg	6

Source: Modified from applicant's Module 2.7.6 (Table 1).

LLT = lipid-lowering therapy; MTD = maximum-tolerated dose. All dosage regimens used daily doses.

* Initial NDA submission included all efficacy and safety data through week 56 of UP1002/AEGR-733-005 and serious adverse events, adverse events leading to discontinuation, and adverse events of special interest through 08 September 2011. The 120-day safety update, received 27 June 2012, included safety data through week 78 of this trial as well as safety data through 31 December 2011 of the ongoing extension study, 733-012.

** One additional subject (total n=19) enrolled in the extension study prior to the 31 December 2011 data cutoff, but did not yet have an on-study follow-up visit.

Table 6. Phase 2 Efficacy & Safety Trials in Non-HoFH

Study Identifier (Dates)	Study Type	Objectives	Population	Design	Duration of Treatment Period	Dosage Regimen	N
CV145-009 (1999)	Elevated LDL-C (Efficacy & Safety)	Effect on hepatic fat & reversibility; safety; PD	LDL-C $\geq$ 160 TG $\leq$ 500	Phase 2, randomized, double-blind, placebo-control	4 wks	lomit 25 mg	lomit: 38 pbo: 38 (Total N=76)
AEGR-733-001 (2006)	Elevated LDL-C (Efficacy & Safety)	Efficacy of monotherapy or add-on to ezetimibe; safety	LDL-C $\geq$ 130 ($\geq$ 2 risk factors) or $\geq$ 160 ($\leq$ 1 risk factor) and $<$ 250 TG $\leq$ 400	Phase 2, randomized, double-blind, active-control, dose-escalation	12 wks	lomit 5, 7.5, 10 mg eze 10 mg	lomit + pbo: 28 pbo + eze: 29 lomit + eze: 28 (Total N=85)
AEGR-733-003b (2007-2008)	Elevated LDL-C (Efficacy & Safety)	Efficacy of monotherapy or add-on to atorvastatin; safety	LDL-C $\geq$ 130 ($\geq$ 2 risk factors) or $\geq$ 160 ($\leq$ 1 risk factor) and $<$ 250 TG $\leq$ 400	Phase 2, randomized, double-blind, placebo- and active-control, fixed dose	8 wks	lomit 5, 10 mg atorva 20mg	pbo: 27 atorva: 26 lomit 5mg: 26 lomit 10mg: 26 lomit 5 + atorva: 26 lomit 10 + atorva: 26 (Total N=157)
AEGR-733-004 (2007-2008)	Elevated LDL-C (Efficacy & Safety)	Effect on hepatic fat in combination with LLT; safety; PD	LDL-C 100-190 Hep fat $<$ 6.2% (MRS)	Phase 2, randomized, double-blind, placebo-control, fixed dose	12 wks	lomit 2.5, 5, 7.5, 10 mg alone; 5 mg in combination feno 145 mg atorva 20 mg eze 10 mg	pbo: 33 lomit 2.5mg: 34 lomit 5mg: 34 lomit 7.5mg: 34 lomit 10mg: 35 lomit 5 + atorva: 28 lomit 5 + feno: 33 lomit 5 + eze: 29 (Total N=260)
AEGR-733-006 (2008)	Elevated LDL-C (Efficacy & Safety)	Efficacy of add-on to atorvastatin; safety	LDL-C $\geq$ 130 ($\geq$ 2 risk factors) or $\geq$ 160 ($\leq$ 1 risk factor) and $<$ 250 TG $\leq$ 400	Phase 2, randomized, double-blind, active-control, dose-escalation	8 wks	lomit 2.5, 5 mg atorva 20 mg	atorva: 23 lomit + atorva: 21 (Total N=44)

Source: Modified from applicant's Module 2.7.6 (Table 1).

All LDL-C and TG values are presented as mg/dL. All dosage regimens used daily doses.

PD = pharmacodynamics; lomit = lomitapide; pbo = placebo; eze = ezetimibe; atorva = atorvastatin; feno = micronized fenofibrate
Lomitapide was administered orally.

Table 7. Drug Interaction Trials

Study Identifier (Dates)	Objectives	Population	Design	Interaction Tested	Duration of Lomitapide Treatment	Dosage Regimen	N
CV145-005 (1997)	Effect of food (fasted, low- and high-fat breakfast) on bioavailability	Healthy volunteers	Phase 1, randomized, open-label, 3-way crossover	Food	6 single-dose treatment sequences	lomit 50 mg single dose	25
AEGR-733-002 (2006-2007)	DDI (CYP 3A4 and 2D6; LLT)	Healthy volunteers	Phase 2, fixed-sequence (i.e., not randomized), open-label	Atorvastatin Simvastatin Ezetimibe Rosuvastatin Fenofibrate Dextromethorphan Niacin ER	7 days	lomit 10, 60 mg QD atorva 20mg simva 20mg eze 10mg rosuva 20mg feno 145mg dextro 30mg niacin ER 1g	Total N=129 (127 received lomitapide) in 9 groups (10-20 per group)
AEGR-733-013 (2010)	DDI	Healthy men	Phase 1, open-label, 2-period sequential	Warfarin	12 days	lomit 60 mg QD warfarin 10mg	16
AEGR-733-015 (2011)	DDI	Healthy women	Phase 1, randomized, double-blind, placebo-controlled, 3-period, 2-way crossover	Ortho Cyclen® (ethinyl estradiol and norgestimate)	8 days	lomit 50 mg QD	Total N=28 (28, 27, and 23 completed periods 1, 2, 3, respectively)
AEGR-733-018 (2010)	DDI (CYP3A4)	Healthy volunteers	Phase 1, open-label, 2-period sequential	Ketoconazole	Single dose x 2	lomit 60 mg keto 200 mg BID	30
AEGR-733-019 (2010)	DDI (CYP3A4)	Healthy volunteers	Phase 1, open-label, 2-period sequential	Simvastatin	7 days	lomit 60 mg QD simva 40 mg	16

Source: Modified from applicant's Module 2.7.6 (Table 1).

LLT = lipid-lowering therapy; lomit = lomitapide; atorva = atorvastatin; simva = simvastatin; eze = ezetimibe; rosuva = rosuvastatin; feno = micronized fenofibrate; dextro = dextromethorphan; ER = extended-release; keto = ketoconazole

Lomitapide was administered orally.

Table 8. Dose-Finding, Bioavailability, Mass Balance

Study Identifier (Dates)	Study Type	Objectives	Population	Design	Duration of Treatment Period	Dosage Regimen	N
CV145-001 (1996)	Single-dose PK/PD	Safety, PK, PD	Healthy men*, total chol $\geq$ 196	Randomized, double-blind, placebo-control	Single doses	lomit 1, 5, 25, 50, 100, 200 mg	lomit 1: 6 lomit 5: 6 lomit 25: 6 lomit 50: 6 lomit 100: 7 lomit 200: 6 pbo: 18 (Total N=55)
CV145-003 (1996)	Single-dose PK/PD/BA	Safety, PK, PD, BA	Healthy men*, total chol $\geq$ 200	Randomized, double-blind, placebo-control	Single doses	lomit 7.5, 15, 30, 60 mg IV lomit 50 mg PO	lomit 7.5 IV: 6 lomit 15 IV: 6 lomit 30 IV, 50 PO: 6 lomit 60 IV: 6 pbo: 8
CV145-006 (1997)	Mass balance	ADME	Healthy men*	Open-label	Single dose	lomit ~50 mg radiolabeled solution	6
AEGR-733-010 (2010)	Mass balance	ADME	Healthy men	Open-label	Single dose	lomit ~50 mg radiolabeled solution	6
CV145-002 (1996)	Multiple-dose PK/PD	Safety, PK, PD	Healthy men*, total chol $\geq$ 200	Randomized, double-blind, placebo-control	14 days (8 days in 100 mg group 2° GI AEs)	lomit 10, 25, 50, 100 mg QD	lomit 10: 6 lomit 25: 6 lomit 50: 6 lomit 100: 6 pbo: 12 (Total N=36)
CV145-010 (1997-1998)	Multiple-dose PK/PD	PK, PD	Healthy women, total chol $\geq$ 200	Randomized, double-blind, placebo-control	14 days	lomit 10, 25 mg QD	lomit 10: 6 lomit 25: 6 pbo: 6

Source: Modified from applicant's Module 2.7.6 (Table 1).

Total cholesterol levels are presented as mg/dL. PK = pharmacokinetics; PD = pharmacodynamics; BA = bioavailability; lomit = lomitapide; pbo = placebo; ADME = absorption, distribution, metabolism, excretion

* Although women were not excluded per protocol, only men were studied.

Unless otherwise indicated, lomitapide was administered orally.

Table 9. Special Safety / Special Populations

Study Identifier (Dates)	Study Type	Objectives	Population	Design	Duration of Treatment Period	Dosage Regimen	N
AEGR-733-017 (2011)	PK / Special population	PK and safety in mild-mod hepatic impairment	Mild-mod hepatic impairment & matched healthy volunteers	Open-label	Single dose	60 mg	Child-Pugh 5-6: 8 Child-Pugh 7-9: 8 Controls for mild: 8 Controls for mod: 8
AEGR-733-021 (2011)	PK / Special population	PK and safety in renal impairment (ESRD)	ESRD & matched healthy volunteers	Open-label	Single dose	60 mg	ESRD on HD: 7 Matched controls: 7
AEGR-733-011 (2011)	Special safety	Thorough QTc Study	Healthy volunteers	Randomized, placebo-control, 5-period crossover	Single dose	75, 200 mg keto 200 mg BID moxi 400 mg (single-dose)	56

Source: Modified from applicant's Module 2.7.6 (Table 1).

PK = pharmacokinetics; ESRD = end-stage renal disease; HD = hemodialysis

5.2 Review Strategy

I conducted an independent review of both the efficacy and safety of lomitapide. Tables and figures in this review that are marked “FDA clinical reviewer’s analysis” are the result of my analyses using primarily the SDTM datasets submitted with the NDA. The specific datasets used for each analysis are provided. SAS v9.2 was used for all analyses.

Given the population under consideration for approval, the primary focus of this review was the single HoFH-pivotal trial.

Cynthia Liu, Office of Biometrics, conducted an independent review of the efficacy of lomitapide.

5.3 Discussion of Individual Studies/Clinical Trials

Table 10 presents a summary of the number of subjects ever exposed to oral lomitapide during its development, categorized by the phase and type of study. Overall, a total of 915 subjects ever received an oral dose of lomitapide, either as monotherapy or combined with other lipid-lowering drugs. Of these, 307 (34%) were enrolled in phase 1 protocols, 446 (49%) in controlled phase 2 protocols (4-12 weeks), 133 (15%) in uncontrolled phase 2 protocols (drug-drug interaction study and HoFH-pilot), and 29 (3%) in the HoFH-pivotal trial.

Table 10. Enumeration of Subjects in Lomitapide Development

Phase / Study Type	Treatment			TOTAL
	Lomitapide	Active Control	Placebo	
(Studies included in applicant’s safety pools)				
Phase 1				
Single-dose ^a	87	0	26	113
Multiple-dose ^b	150	16	44	168
Total Phase 1	237	16	70	281
Phase 2				
Controlled	446	78	98	622
Fixed-dose ^c	369	26	98	493
Escalated-dose ^d	77	52	0	129
Uncontrolled	133	0	0	133
Fixed-dose ^e	127	0	0	127
Escalated-dose ^f	6	0	0	6
Total Phase 2	579	78	98	755
Phase 3 ^g	29	0	0	29
Subtotal in Applicant’s Safety Pools	845	94	168	1065
(Studies summarized separately in applicant’s safety summary)				
Phase 1				
Single-dose ^h	14	0	0	14
Multiple-dose ⁱ	56	53	56	56

Phase / Study Type	Treatment			TOTAL
	Lomitapide	Active Control	Placebo	
Total Phase 1	70	53	56	80
Phase 3^j	18	0	0	18
GRAND TOTAL	915	147	224	1145

Source: Derived from Integrated Summary of Safety (ISS), Table 2.

^a CV145-001, -003, -006; AEGR-733-010 and -017.

^b CV145-002, -005 (6 single-dose treatment sequences), -010; AEGR-733-013, -015, -018 (single dose x 2), and -019.

^c CV145-009, AEGR-733-003b and -004.

^d AEGR-733-001 and -006.

^e AEGR-733-002 (excludes 2 subjects who received statins alone and did not receive lomitapide)

^f HoFH-pilot (UP1001)

^g HoFH-pivotal (UP1002/AEGR-733-005)

^h AEGR-733-021 (Special population: ESRD)

ⁱ AEGR-733-011 (TQT study) includes data from 53 and 56 subjects who also received ketoconazole or moxifloxacin in this cross-over study; these subjects are not double-counted in the total column.

^j HoFH-extension (AEGR-733-012) not counted in overall totals since subjects rolled over from HoFH-pivotal.

Phase 1

A total of 361 subjects, 317 of whom received lomitapide, participated in 14 phase 1 clinical trials, spanning 1996-2011. These trials are summarized in Table 7, Table 8, and Table 9. Five phase 1 studies included multiple daily doses of oral lomitapide:

- CV145-002 (six subjects per cohort of 10 mg, 25 mg, 50 mg, or 100 mg daily x 14 days)
- CV145-010 (six women per cohort of 10 mg or 25 mg daily x 14 days)
- AEGR-733-013 (16 subjects in warfarin DDI study received 60 mg daily x 12 days)
- AEGR-733-015 (27 subjects in Ortho Cyclen[®] DDI study received 50 mg daily x 8 days)
- AEGR-733-019 (16 subjects in simvastatin DDI study received 60 mg daily x 7 days)

Subjects in the remaining phase 1 studies either received a single dose or more than one single dose separated in time (e.g., six single-dose treatment sequences in the food-effect study CV145-005).

Phase 2 Program (excluding HoFH-pilot)

A total of 755 subjects, 579 of whom received lomitapide, participated in 7 phase 2 clinical trials, spanning 1999-2008. These trials included AEGR-733-002 (a drug-drug interaction study briefly described in Section 7.5.5, p. 242), the six-subject HoFH-pilot, and the five phase 2 studies listed in Table 6, which were conducted in hyperlipidemic non-HoFH subjects.

Because there is only one 29-subject phase 3 trial, each of the five non-HoFH phase 2 studies proposed to support efficacy were reviewed individually. In this section, I will review the major design features and results from each of these five trials. The trial designs are described in greater detail in the Appendix (p. 258).

Study CV145-009

Study CV145-009 (“C-009”) was conducted by BMS in 1999 to compare the effects of lomitapide 25 mg daily x 4 weeks with matched placebo on the reversibility of hepatic fat content as measured by MRI/NMRS in healthy subjects with hypercholesterolemia (fasting LDL-C $\geq$ 160 mg/dL and TG $\leq$ 500 mg/dL, obtained off lipid-lowering agents after a lipid-stabilization period). Following a 4-week lipid stabilization period and institution of a NCEP Step 1 diet ($\leq$ 30% of total calories from fat) and a 4-week placebo lead-in during which qualifying LDL-C values were obtained, 76 subjects were randomly assigned to lomitapide 25 mg daily or matched placebo for 4 weeks followed by a 6-week off-treatment period.

C-009 Demographics & Disposition

The lomitapide and placebo arms were balanced well with respect to demographic and baseline characteristics. Of the 76 subjects enrolled, 48 (63%) were men; 69 (91%) were white, 6 (8%) were black, and 1 (1%) was Asian/Pacific islander. The mean (SD) age was 52 (10) years with a range of 24 to 65 years. The mean (SD) BMI was 28.0 (4.1) kg/m². Mean LDL-C at baseline was 190 mg/dL.

Table 11 summarizes the disposition of subjects in study C-009. There was a substantially higher drop-out rate in the lomitapide group (31.6%) compared with the placebo group (2.6%).

Table 11. C-009 – Subject Disposition

	BMS-201038 N=38 n (%)	Placebo N=38 n (%)	All Subjects N=76 n (%)
Subjects randomized	38	38	76
Subjects treated	38 (100.0)	38 (100.0)	76 (100.0)
Subjects completed	26 (68.4)	37 (97.4)	63 (82.9)
Subjects discontinued	12 (31.6)	1 (2.6)	13 (17.1)
Reason for discontinuation			
Adverse event	10 (26.3)	0 (0.0)	10 (13.2)
Other	2 (5.3)	1 (2.6)	3 (3.9)

Data Source: [Table 14.1](#)

Source: C-009 CSR, Table 3.

The “other” reasons for discontinuation in the BMS-201038 (lomitapide) group were (1) not having the baseline MRI archived (Subject 002-001, who took drug for 3 days before discontinuation), and (2) increased transaminases (not reported as AE) (subject 002-022, who took drug for 20 days before discontinuation). The only subject in the placebo

group who discontinued early was because of a conflict between the subject's personal schedule and the end-of-study visit.

C-009 Efficacy Results

Table 12 summarizes the baseline values and % changes in lipid parameters after 4 weeks of treatment (lomitapide 25 mg daily or matched placebo) and 6 weeks after drug discontinuation (weeks B5 and B11, respectively). The placebo-subtracted % change in LDL-C from baseline to week 4 was -57.7% among completers (P<0.0001). After six weeks off-treatment, LDL-C had largely returned to baseline (-5.8% placebo-subtracted change from baseline). Note that these values only include subjects with available data (i.e., no imputation). The longitudinal profiles of these parameters, expressed as placebo-subtracted % change from baseline, are depicted in the subsequent figure.

Table 12. C-009 – Mean (SD) % Changes in Lipid Parameters at 4 weeks & Off-treatment

	Lomitapide 25 mg			Placebo		
	Mean (SD) at Baseline (mg/dL) (n=37)	% change (SD) from BL to Week B5 (n=24)	% change (SD) from BL to Week B11 (n=19)	Mean (SD) at Baseline (mg/dL) (n=38)	% change (SD) from BL to Week B5 (n=31)	% change (SD) from BL to Week B11 (n=19)
LDL-C	189 (30)	-64.0 (22.3)	-11.2 (21.2)	190 (30)	-6.3 (12.5)	-5.4 (10.2)
TC	271 (37)	-51.6 (18.5)	-6.8 (18.8)	276 (32)	-2.7 (10.4)	-1.7 (8.2)
Apo B	160 (28)	-58.5 (17.8)*	-21.7 (18.1)	162 (38)	-4.8 (14.3)	-14.5 (12.5)
TG	160 (71)	-26.0 (39.2)	-4.2 (33.8)	180 (106)	+9.3 (35.8)	+4.4 (32.8)
VLDL-C	32 (14)	-25.3 (39.7)	-3.7 (34.0)	36 (21)	+9.3 (35.9)	+4.3 (32.6)
Lp(a)	41 (32)	-27.9 (15.4)	-8.6 (21.3)	38 (30)	-4.8 (15.1)	-5.6 (14.2)
HDL-C	50 (13)	-13.6 (22.3)	+12.7 (26.0)	51 (14)	+5.4 (16.9)	+15.4 (17.3)

Source: C-009 CSR, Table 14.4.

BL = Baseline. Week B5 = After 4 weeks on treatment. Week B11 = Six weeks after drug discontinuation.

* n=23.

The P-values for between-group differences based on one-way ANOVA for % change from baseline to week B5 were <0.0001 for LDL-C, TC, Apo B, and Lp(a); p=0.001 for TG; p=0.0014 for VLDL-C; and p=0.0007 for HDL-C.

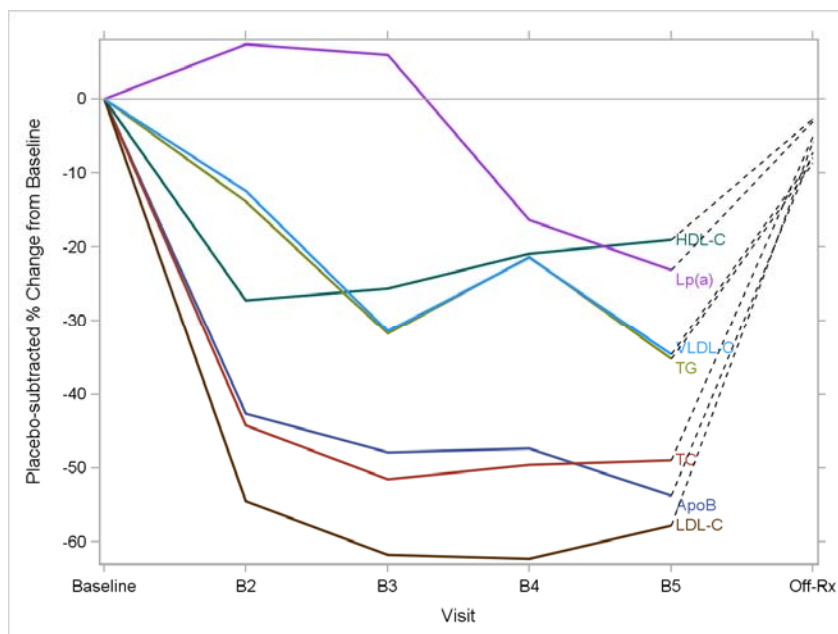


Figure 3. C-009 – Lipid Parameters Over Time

Source: FDA clinical reviewer’s depiction of data derived from C-009 CSR, Table 14.4. Approximately 1 week separates each on-treatment visit (Baseline through B5), with ~6 weeks elapsing between B5 and the off-treatment follow-up visit.

C-009 Safety Results

The extent of exposure to study drug in study C-009 is summarized in Table 13. The majority of subjects in both groups took study drug between 15 and 30 days. The mean duration of exposure was similar in the two groups.

Table 13. C-009 – Extent of Exposure

Treatment	Number of Subjects (%)				Total Subjects	Mean Total Dose (mg)	Range Total Dose (mg)	Mean Duration of Exposure (Days)
	<7 Days	7-14 Days	15-30 Days	>30 Days				
BMS-201038	5 (13.2)	2 (5.3)	21 (55.3)	10 (26.3)	38	636.8	75-750 ^a	25.5
Placebo	1 (2.6)	0 (0.0)	24 (63.2)	13 (34.2)	38	0.0	0-0	30.6

^a Subject 007-020 received 750 mg of BMS-201038 (25 mg x 30 days, 23-Jun-1999 to 22-Jul-1999 [last dose]); however, as reported on Table 14.5, the BMS exposure database incorrectly calculated 1750 mg (25 mg x 70 days, 23-Jun-1999 to 31-Aug-1999 [incorrect date of last dose as reported in the BMS exposure dataset]).

Data Source: [Table 14.5](#)

Source: C-009 CSR, Table 7.

Adverse Events

There were no SAEs or deaths in this study. Treatment-emergent AEs (TEAEs) occurred in 35 (92%) and 17 (45%) of the lomitapide and placebo groups, respectively (Table 14). The AE profile was qualitatively similar to that observed among subjects with HoFH, i.e., primarily dominated by gastrointestinal events (Table 15). The AEs contributing to premature discontinuation of lomitapide included at least one gastrointestinal AE in 8 (21%) subjects (diarrhea [n=7]; nausea/vomiting [n=4];

abdominal pain [n=2]; and decreased appetite, distension abdomen, eructation, and flatulence [n=1 each]), general AE in 3 (8%) subjects (fatigue [n=2]; malaise, volume depletion, weakness, and weight loss [n=1 each]), hepatic/biliary AE in 3 (8%) subjects (liver function test increase [n=2]; ALAT increased, ASAT increased, and hepatomegaly [n=1 each]); and nervous system AE in 1 (3%) (headache). No subjects assigned to placebo discontinued prematurely because of an AE.

Table 14. C-009 – Adverse Event Summary

Category	BMS-201038 25mg N=38 n(%)	Placebo N=38 n(%)	All Subjects N=76 n(%)
Any AE	37 (97.4)	22 (57.9)	59 (77.6)
Pre-treatment AE	14 (36.8)	17 (44.7)	31 (40.8)
Treatment-emergent AE	35 (92.1)	17 (44.7)	52 (68.4)
Treatment-related AE	34 (89.5)	12 (31.6)	46 (60.5)
Serious AE	0 (0.0)	0 (0.0)	0 (0.0)
Severe AE	8 (21.1)	2 (5.3)	10 (13.2)
Discontinued due to AE	10 (26.3)	0 (0.0)	10 (13.2)

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Source: C-009 CSR, Table 14.6.1.

Reviewer Comment: Although the AE tables report that 3 subjects discontinued because of transaminase abnormalities (subjects 001-003, 007-002, 007-003), a fourth subject also discontinued because of increased liver enzymes that was not reported as an AE (subject 002-022; see below).

Table 15. C-009 – Selected Common Treatment-Emergent Adverse Events

System Organ Class Preferred Term	Lomitapide 25 mg (N=38)	Placebo (N=38)
Gastrointestinal	33 (87%)	4 (11%)
Diarrhea	31 (82%)	3 (8%)
Nausea/vomiting	13 (34%)	0
Abdominal pain	6 (16%)	1 (3%)
Distention abdomen	5 (13%)	0
Flatulence	5 (13%)	0
Decreased appetite	4 (11%)	0
Dyspepsia/heartburn	3 (8%)	0
General	11 (29%)	2 (5%)
Fatigue	4 (11%)	0
Weakness	3 (8%)	0
Weight loss	2 (5%)	0
Nervous System	5 (13%)	4 (11%)
Dizziness	2 (5%)	1 (3%)
Hepatic/biliary	5 (13%)	0
Liver function test increase	3 (8%)	0
ALAT increased	2 (5%)	0
ASAT increased	2 (5%)	0

Source: Derived from C-009 CSR, Table 14.6.2.

Only TEAEs that were more common in the lomitapide than placebo group and were reported by ≥5% of subjects (i.e., ≥2 subjects) in the lomitapide group are listed.

Although adverse event severity assessments are subjective, among the 35 subjects assigned to lomitapide who experienced a TEAE, 25 (71%) reported that the event was

either moderate (n=17) or severe (n=8) in intensity. Among the 17 subjects assigned to placebo who experienced a TEAE, 6 (35%) reported that the event was moderate intensity and none reported severe intensity.

As shown in Table 15, diarrhea was the most frequently reported TEAE. Among lomitapide-treated subjects, the severity of diarrhea was mild in 8 (26%) of the 31 who reported this symptom, moderate in 16 (52%), and severe in 7 (23%). Often, the diarrhea was accompanied by nausea/vomiting, abdominal pain, and/or abdominal distension.

Liver-related Laboratory Values

In C-009, 4 (11%) of 38 lomitapide-treated subjects discontinued because of abnormal transaminases. The mean absolute change from baseline in ALT increased during lomitapide treatment at weeks B2, B3, B4, and B5 (+9.09, 30.84, 51.90, and 62.3 U/L, respectively), but decreased 6 weeks after drug discontinuation at week B11 (+28.74 U/L compared with baseline). The placebo mean absolute changes from baseline were minor (-0.14, -0.11, +0.97, 1.11, and 4.05 U/L). AST tracked with ALT but changes were of lower magnitude.

Based on my analysis of the submitted C-009 laboratory dataset, 12 (32%) subjects assigned to lomitapide and no subjects assigned to placebo had a peak ALT $\geq 3x$ ULN (Table 16). Peak transaminase values typically occurred after drug discontinuation, in three cases approximately 2 weeks later, but this was generally followed by resolution. One subject, however, was followed out to day 451 with continued elevation in transaminases. This subject also had a value above the normal range at baseline (60 U/L; 1.3x ULN). Longitudinal profiles of ALT for subjects who ever experienced ALT $\geq 3x$ ULN are shown in Figure 4.

Table 16. C-009 – Peak ALT Abnormalities

Peak ALT	Lomitapide 25 mg (n=37)*	Placebo (n=38)
$\geq 2x, < 3x$ ULN	5 (14%)	0
$\geq 3x, < 5x$ ULN	9 (24%)	0
$\geq 5x, < 10x$ ULN	2 (5%)	0
$\geq 10x$ ULN	1 (3%)	0

Source: FDA clinical reviewer's analysis of submitted C-009 laboratory dataset (LB.xpt)

* One subject (002-001) was discontinued after 3 days of lomitapide because the baseline MRI "was not archived." This subject did not have a full panel of baseline laboratories, either.

The CSR reports 11 subjects with peak ALT $> 3x$ ULN. I identified an additional subject (007-022) with peak ALT 3.8xULN at day 30.

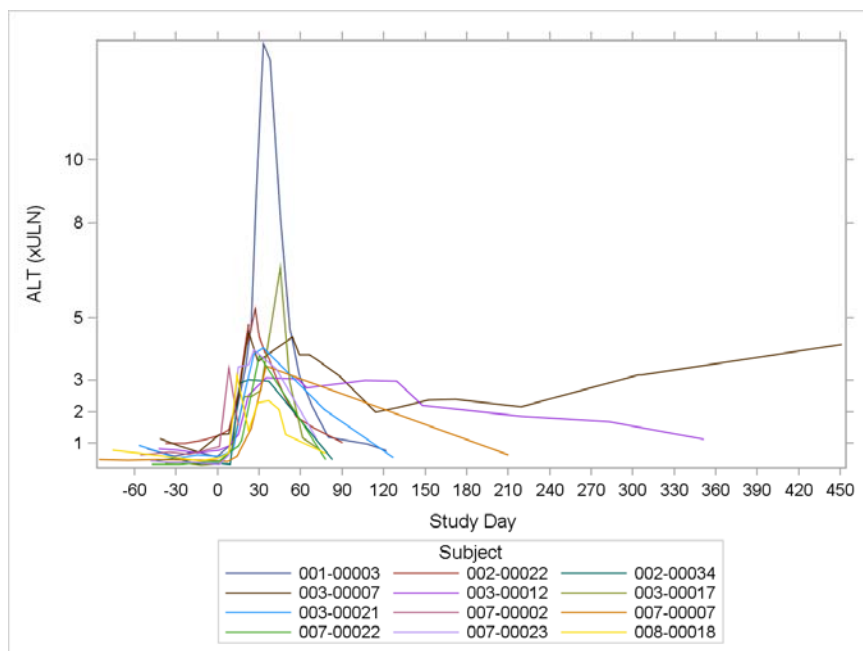


Figure 4. C-009 – ALT Profiles for Subjects with Peak ALT $\geq$ 3x ULN

Source: FDA clinical reviewer's analysis of submitted C-009 laboratory dataset (*LB.xpt*). First dose of lomitapide = study day 1 (i.e., Period B). Recall that the expected dosing duration was approximately 28 days followed by a 42-day off-drug follow-up period (i.e., to approximately day 70).

Hepatic Fat

In C-009, each subject had MRI/NMRS performed at baseline, after 4 weeks of treatment (lomitapide 25 mg daily or matched placebo), and 6 weeks after drug discontinuation (weeks A4, B5, and B11, respectively). If the % hepatic fat content at the end-of-study visit did not decrease by a pre-specified amount, which depended on the baseline and end-of-treatment values, a fourth NMRS was performed 12 weeks after drug discontinuation (week B17).

Subjects treated with lomitapide 25 mg daily for 4 weeks had a mean 20.88% (absolute percentage points) increase in % hepatic fat from baseline to the end of treatment; those treated with placebo had a 0.56% increase, yielding a difference of 20.32% (95% CI 17.08-23.56; $p < 0.0001$). Six weeks after discontinuation, subjects treated with lomitapide had a mean 4.02% hepatic fat, which was not statistically significantly different than placebo (mean difference between groups 3.11% [95% CI, -0.98 to 7.20; $p = 0.13$]) (Table 17).

Table 17. C-009 – Absolute Changes in % Hepatic Fat

	Mean ± (SD)					
	BMS-201038			Placebo		
	Baseline	Week B5	Week B11	Baseline	Week B5	Week B11
% hepatic fat content	11.03 (9.235)	31.65 (13.314)	14.57 (14.216)	7.50 (7.611)	8.06 (7.153)	8.94 (9.240)
Change from baseline		20.88 (8.910)	4.02 (8.676)		0.56 (3.721)	0.91 (7.428)
Difference		20.32	3.11			
95% CI		17.08-23.56	-0.98-7.20			
P value		<.0001	0.1340			

CI=Confidence interval; SD=Standard deviation
Data Source: Table 14.3

Source: C-009 CSR, Table 5.

Among the 28 lomitapide subjects with available data at baseline and end-of-treatment, 24 (86%) had an increase in % hepatic fat $\geq 10\%$ absolute percentage points from baseline; no subjects in the placebo group exhibited a similar increase (Table 18).

Table 18. C-009 – Categorical Changes in % Hepatic Fat at End-of-Treatment

Change from Baseline to End-of-Treatment (Absolute % points)	Lomitapide 25 mg x 4 weeks (n=28)*	Placebo (n=37)
Less than baseline	0	15 (41%)
> Baseline but < +5%	1 (4%)	16 (43%)
$\geq +5\%$ but < +10%	3 (11%)	6 (16%)
$\geq +10\%$ but < +20%	10 (36%)	0
$\geq +20\%$	14 (50%)	0

Source: FDA clinical reviewer's analysis of C-009 submitted dataset (OM.xpt).

* Ten and one subjects with missing data in the lomitapide and placebo groups, respectively.

Five subjects in the lomitapide group and two subjects in the placebo group had more than one off-treatment hepatic fat value measured because of an insufficient fall in hepatic fat at the scheduled off-treatment visit. These subjects and their hepatic fat measurements assessments are summarized in Table 19.

Table 19. C-009 – Hepatic Fat in Subjects with Insufficient Resolution at Follow-up

Subject	Baseline	End-of-Rx (Day)	Off-Rx #1 (Day)	Off-Rx #2 (Day)	Off-Rx #3 (Day)	Off-Rx #4 (Day)
Lomitapide						
001-00003	11.8%	(Early D/C on Day 18)*	45.6% (Day 24)	20.8% (Day 39)	20.8% (Day 59)	15.2% (Day 108)
003-00007	24.8%	36.0% (Day 29)	36.7% (Day 72)	43.2% (Day 114)	42.0% (Day 172)	
003-00012	35.2%	62.2% (Day 24)**	51.6% (Day 64)	49.0% (Day 106)	46.5% (Day 148)	
007-00020	17.0%	47.4% (Day 29)	33.8% (Day 71)	33.4% (Day 143)		

Subject	Baseline	End-of-Rx (Day)	Off-Rx #1 (Day)	Off-Rx #2 (Day)	Off-Rx #3 (Day)	Off-Rx #4 (Day)
008-00001	9.3%	26.6% (Day 29)	18.0% (Day 71)	12.6% (Day 112)		
Placebo						
002-00032	2.1%	3.4% (Day 25)	24.4% (Day 74)	1.1% (Day 88)		
003-00009	7.3%	15.0% (Day 28)	36.2% (Day 71)	19.3% (Day 113)		

Source: FDA clinical reviewer's analysis of C-009 submitted datasets (OM.xpt)

The day listed for end-of-treatment is not necessarily the day that treatment was stopped; it is the study day corresponding to the end-of-treatment % hepatic fat assessment.

* 001-00003 discontinued after 18 days of lomitapide because of increased ALT, AST, and hepatomegaly. The ALT peaked at 643 IU/L (13.7x ULN) on day 33, approximately 2 weeks after discontinuing drug. It fell to 387 IU/L at day 45 and ultimately to 46 IU/L on day 108.

** 003-00012 discontinued after 21 days of lomitapide because of decreased appetite, diarrhea, fatigue, and weight loss, but this subject also had increased ALT and AST. The ALT was 141 IU/L (2.5x ULN) at day 22 and peaked at 173 IU/L (3.1x ULN) on day 35. It appears the subject was followed for at least 351 days, with an ALT of 64 IU/L at the time.

Reviewer Comment: Lomitapide-induced increases in hepatic fat appear largely reversible (although not universally) within weeks, at least after short-term (4-week) use.

I explored the association between baseline % hepatic fat and peak ALT observed on study among lomitapide-treated subjects only. Among the 8 lomitapide-treated subjects with baseline hepatic fat >15%, 6 had a peak ALT $\geq 3x$ ULN, 1 had a peak ALT 2.5x ULN, and 1 remained within the normal range throughout. Simple linear regression did not suggest a statistically significant relationship between these variables ($p=0.10$), although the sample size is small. The point estimate for the slope was positive, however, which would be consistent with higher % hepatic fat at baseline being associated with higher peak transaminase values, on average (Figure 5).

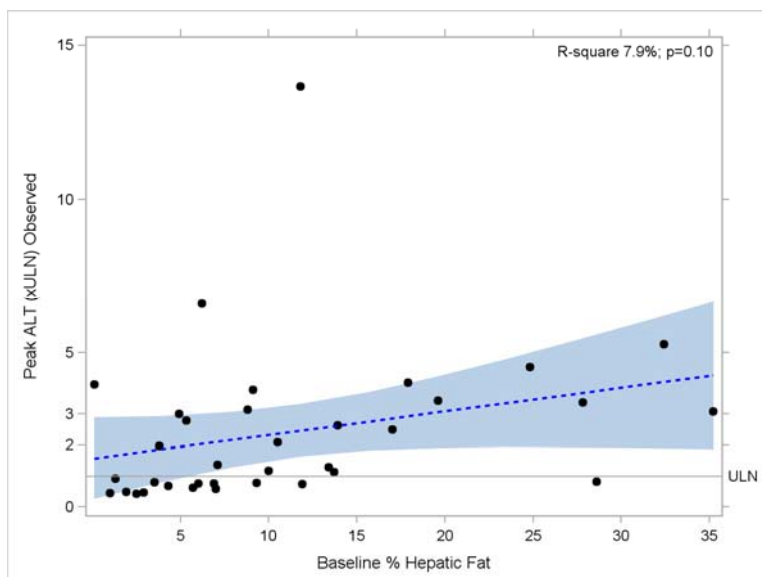
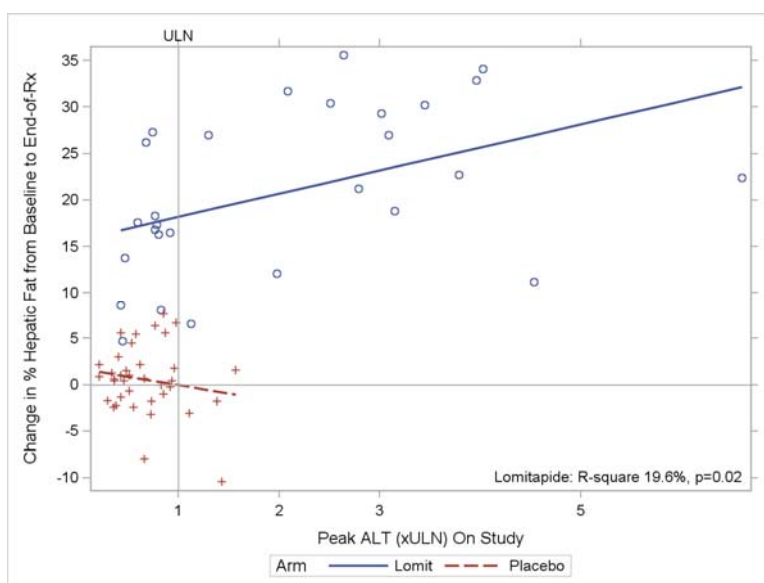


Figure 5. C-009 – Baseline Hepatic Fat vs. Peak ALT Observed

Source: FDA clinical reviewer's analysis of C-009 submitted datasets (*OM, LB xpt*).
This figure only includes data from the lomitapide arm.
Regression line (simple linear regression) with shaded 95% confidence limits for predicted mean values.

Last, I explored the relationship between peak ALT during the study, expressed as multiples above the ULN, with absolute % change in hepatic fat (from baseline to end-of-treatment). There was a statistically significant association between these observations among lomitapide-treated subjects, with the peak ALT observed explaining nearly the 20% of the variation in the change in hepatic fat ($p=0.02$) (Figure 6). The association between peak ALT expressed relative to baseline ALT (i.e., on the day of study drug initiation for this analysis) and change in hepatic fat was similar (not shown).



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Figure 6. C-009 – Peak ALT (x ULN) vs. Change in Hepatic Fat

Source: FDA clinical reviewer's analysis of submitted C-009 datasets (*LB, OM xpt*).

Reviewer Comment: *These exploratory analyses do not establish a causal relationship between hepatic fat and the changes in transaminases observed. Clinically, however, there would be greater concern for increases in hepatic fat associated with ALT elevations.*

Vitamin E

Mean levels of total vitamin E decreased during lomitapide treatment (-49.5% placebo-subtracted; $P<0.0001$) but returned to near-baseline levels 6 weeks after drug discontinuation. This was largely the result of a reduction in plasma lipids, which carry vitamin E; between-group differences in changes in the vitamin E:lipid (TC+TG) ratio, however, were not detected (-0.3% placebo-subtracted; $P=0.49$) (Table 20). Other fat-soluble nutrients were not assessed.

Table 20. C-009 – Changes in Vitamin E

	Lomitapide 25 mg		Placebo		P
	Mean (SD)	% Change from Baseline	Mean (SD)	% Change from Baseline	
Vit E (µg/dL)					
Baseline	21.2 (9.4)		21.0 (10.3)		
Week B5	9.6 (5.0)	-50.2%	19.4 (9.5)	-0.7%	<0.0001
Week B11	17.4 (6.3)	-7.4%	18.6 (8.4)	-8.0%	0.94
Vit E:Lipid (TC+TG)					
Baseline	4.83 (1.71)		4.75 (2.07)		
Week B5	4.16 (1.55)	-0.5%	4.53 (2.18)	-0.2%	0.49
Week B11	4.89 (2.08)	+0.4%	4.54 (2.27)	-0.4%	0.54

Source: Derived from C-009 CSR, Table 12.

Laboratory Results

Measures of central tendency of hematology, serum chemistry, urinalysis, and coagulation test results did not suggest clinically significant differences between lomitapide and placebo with the exception of ALT and AST, which are discussed elsewhere. The relevant data in the C-009 CSR are Tables 14.7.1, *.2, *.4, *.5, and *.8.

Vital Signs

Mean systolic blood pressure, diastolic blood pressure, and pulse were similar between subjects treated with lomitapide and placebo. After four weeks of treatment (Week B5), the between-group difference (lomitapide – placebo) in mean SBP was -3.1 mmHg, in mean DBP was -1.6 mmHg, and in mean pulse was +0.1 bpm. Additional data are summarized in the C-009 CSR in Table 14.8.1.

Weight Change

Among completers, the mean change in weight from baseline was -1.9% in the lomitapide group and +0.1% in the placebo group (P<0.0001), a between-group difference of -2.1% change from baseline (95% CI, -2.9 to -1.2; P<0.0001).

Pulmonary Function Tests

Table 21 describes results from PFTs conducted at baseline, end-of-treatment (week B5) and at off-treatment follow-up (week B11). The values presented are the % predicted values for the observed measurements.

Table 21. C-009 – Absolute Changes in Pulmonary Function Parameters

	Lomitapide 25 mg		Placebo	
	Mean (SD)	Change from Baseline	Mean (SD)	Change from Baseline
DLCO (% predicted)				
Baseline	97.7 (19.0) n=37		98.6 (19.5) n=37	
Week B5	100.1 (20.3) n=28	+1.3 (9.4) n=27	98.2 (17.1) n=36	-1.7 (10.5) n=35
Week B11	100.0 (18.9) n=31	+0.9 (12.6) n=30	98.2 (20.4) n=37	-0.7 (11.6) n=36

	Lomitapide 25 mg		Placebo	
	Mean (SD)	Change from Baseline	Mean (SD)	Change from Baseline
FEF₂₅₋₇₅ (% predicted)				
Baseline	87.9 (25.2) n=37		85.6 (22.7) n=37	
Week B5	82.5 (24.6) n=28	-2.1 (13.0) n=27	84.1 (23.4) n=37	-0.2 (11.1) n=36
Week B11	83.9 (22.5) n=31	-2.7 (11.9) n=31	85.3 (20.1) n=37	-0.9 (11.9) n=36
FEV₁ (% predicted)				
Baseline	103.4 (13.3) n=37		101.4 (13.5) n=36	
Week B5	100.7 (14.1) n=28	-0.3 (6.2) n=27	100.9 (11.3) n=37	-1.0 (7.2) n=35
Week B11	101.5 (13.6) n=30	-1.0 (6.1) n=29	102.3 (10.8) n=37	-0.2 (5.7) n=35
FVC (% predicted)				
Baseline	103.6 (12.7) n=37		103.6 (13.9) n=36	
Week B5	101.8 (13.0) n=28	-0.5 (6.3) n=27	101.9 (12.4) n=38	-1.9 (6.9) n=37
Week B11	101.3 (12.5) n=31	-1.3 (5.8) n=30	103.5 (11.1) n=37	-1.3 (6.1) n=36

Source: C-009 CSR, Table 14.10.

Week B5 = end of 4-week treatment period; Week B11 = six weeks after drug discontinuation.

Reviewer Comments:

1. *Subjects who may be at greater risk of developing hepatic steatosis (diabetes, alcohol consumption) were excluded from this study.*
2. *Protocol amendment #3 added a discontinuation criterion for ALT >3x ULN as a result of 4 (10%) of 41 subjects randomized at the time having been discontinued because of abnormal transaminases as high as 643 IU/L. This may have reduced the incidence of transaminase abnormalities of greater magnitude.*
3. *Given the rather large proportion of missing data in the lomitapide group (26%) and the fact that these data are likely not missing at random, these results may be biased. It is plausible that the missing subjects may have had larger amounts of hepatic fat at follow-up or may have been at higher risk for other adverse effects.*
4. *Lomitapide-induced increases in hepatic fat appear largely reversible (although not universally) within weeks, at least after short-term (4-week) use.*

Study AEGR-733-001

Because dosages of lomitapide 25-100 mg/day in previous phase 1 and 2 studies were associated with hepatic and gastrointestinal adverse events, Aegerion sought to determine whether dosages lower than 25 mg/day could provide clinically significant

reductions in LDL-C with an improved AE profile. Study AEGR-733-001 (“A-001”) was conducted in 2006 to evaluate whether 12 weeks of lomitapide in combination with ezetimibe 10 mg daily was superior to monotherapy with either agent in adult subjects with fasting LDL-C ≥ 160 mg/dL (0-1 NCEP risk factors) or ≥ 130 mg/dL (≥ 2 NCEP risk factors or prior CHD), obtained after a 4-week washout period of lipid-lowering agents. Lomitapide was force-titrated from 5 mg to 7.5 mg to 10 mg daily at 4-week intervals. Subjects were counseled to implement a low-fat diet (<20% calories from fat).

A-001 Demographics & Disposition

Of the 85 subjects enrolled, 40 (47%) were men; 62 (73%) were white, 22 (26%) were black, and 1 (1%) was Hispanic. The mean (SD) age was 55 (7) years with a range of 37 to 71 years. The mean (SD) BMI was 29.2 (6.0) kg/m². Mean (SD) LDL-C at baseline was 167 (28) mg/dL with a range of 113 to 260 mg/dL.

This trial enrolled a relatively healthy population. The minority of subjects were taking lipid-lowering medications prior to wash-out, ranging from 29% to 39% across groups. Similarly, the minority had BP >140/90 or were on antihypertensive therapy at baseline, ranging from 28% to 43% across groups. Only one subject in the trial (randomized to ezetimibe monotherapy) had a history of atherosclerotic heart disease.

Table 22 summarizes the disposition of subjects in study A-001. The drop-out rate was high for a 12-week study, with the highest incidence of premature discontinuation in the lomitapide monotherapy arm (32.1%). With the exception of a single loss to follow-up, all drop-outs were the result of adverse effects, which will be described subsequently.

Table 22. A-001 – Subject Disposition

	Lomitapide Monotherapy (n=28)	Ezetimibe Monotherapy (n=29)	Lomitapide + Ezetimibe (n=28)
Randomized (= ITT)	28	29	28
Treated	28 (100%)	29 (100%)	28 (100%)
Completed	19 (67.9%)	24 (82.8%)	24 (85.7%)
Discontinued	9 (32.1%)	5 (17.2%)	4 (14.3%)
Reason for D/C			
Adverse event	9 (32.1%)	4 (13.8%)	4 (14.3%)
Lost to follow-up	0	1 (3.4%)	0

Source: A-001 CSR, Table 4.

A-001 Efficacy Results

Table 23 summarizes the mean baseline values for lipid parameters in trial A-001, and Table 24 summarizes the % changes in lipid parameters after 12 weeks of treatment. Recall that subjects receiving active lomitapide were initiated at 5 mg daily x 4 weeks and then force-titrated to 7.5 mg x 4 weeks followed by 10 mg x 4 weeks. These values only include subjects with available data (i.e., no imputation), and the proportion of each group with missing data because of premature discontinuation is substantial (14% to 32%).

Table 23. A-001 – Mean (SD) Baseline Lipid Parameters

	Lomitapide Monotherapy (n=28)	Ezetimibe Monotherapy (n=29)	Combination (n=28)
LDL-C	169 (32)	164 (26)	168 (26)
TC	254 (37)	245 (29)	251 (33)
TG (median)	168.5	124	128.5
Non-HDL-C	202 (33)	192 (28)	197 (28)
Apo B	158 (26)	151 (18)	154 (20)
Lp(a)	45 (46)	36 (31)	39 (37)
HDL-C	52 (13)	54 (11)	55 (14)
Apo AI	169 (26)	174 (27)	175 (33)

Source: A-001 CSR Table 14.1.9.

All values are mg/dL.

Table 24. A-001 – Mean (SD) % Changes in Lipid Parameters at 12 weeks

	Lomitapide Monotherapy (L) (n=19)*	Ezetimibe Monotherapy (E) (n=24)*	Combination (C) (n=24)*	P (E vs. C)	P (L vs. C)	P (L vs. E)
LDL-C	-29.9% (15.3)	-19.6% (9.9)	-46.2% (23.8)	<0.001	0.013	0.016
TC	-22.8% (12.3)	-12.0% (8.7)	-34.4% (18.8)	<0.001	0.026	0.002
TG	-5.8% (33.6)	+2.8% (35.1)	-7.0% (36.0)	0.35	0.91	0.43
Non-HDL-C	-26.9% (14.6)	-17.0% (10.5)	-41.3% (22.7)	<0.001	0.022	0.013
Apo B	-23.7% (14.2)	-14.5% (10.6)	-36.6% (21.7)	<0.001	0.035	0.021
Lp(a)	-11.4% (29.1)	+7.5% (24.1)	-12.0% (23.7)	0.013	0.94	0.033
HDL-C	-6.2% (10.8)	+5.9% (9.6)	-9.2% (14.4)	<0.001	0.47	<0.001
Apo AI	-8.0% (12.3)	+2.3% (9.5)	-10.7% (15.8)	0.001	0.55	0.004

Source: A-001 CSR Tables 14.2.1-8.

* For apo B and apo AI, n = 18 (L), 23 (E), and 24 (C); for Lp(a), n = 18 (L), 21 (E), and 20 (C).

The absolute difference between ezetimibe monotherapy and combination therapy with regard to % change in LDL-C at week 12 was -26.6% with 95% CI -37.2% to -16.1%.

Reviewer Comments:

1. The effects of lomitapide and ezetimibe appear additive, when used in combination, with regard to LDL-C, TC, Non-HDL-C, and apo B.
2. The effect of the lomitapide regimen itself can be estimated from the comparison of combination therapy vs. ezetimibe alone. The nominal P values indicate robust statistical significance with regard to lomitapide contributing to the lowering of LDL-C, TC, non-HDL-C, HDL-C, apo B, apo A1, and perhaps Lp(a) (the latter being less robust in the setting of multiple comparisons).
3. This lomitapide regimen did not demonstrate a convincing effect on lowering TG, at least using the studied doses for this duration of therapy.
4. The effect of lomitapide-induced reductions in HDL-C (and apo AI) on clinical outcomes is unknown.

The observed effects on LDL-C at week 4 (i.e., after lomitapide 5 mg) and week 8 (i.e., after lomitapide 7.5 mg) are shown in Table 25.

Table 25. A-001 – Mean (SD) % Changes in Lipid Parameters at Interim Visits

	Lomitapide Monotherapy (L) (n=28)	Ezetimibe Monotherapy (E) (n=29)	Combination (C) (n=28)	P (E vs. C)	P (L vs. C)	P (L vs. E)
Week 4 (after 5 mg)	-18.6% (16.5) n=24	-19.9% (8.3) n=26	-34.5% (11.6) n=27	<0.001	<0.001	0.73
Week 8 (after 7.5 mg)	-26.4% (13.9) n=21	-21.6% (11.2) n=24	-38.0% (16.9) n=26	<0.001	0.015	0.21
Week 12 (after 10 mg)	-29.9% (15.3) n=19	-19.6% (9.9) n=24	-46.2% (23.8) n=24	<0.001	0.013	0.016

Source: A-001 CSR, Tables 14.2.1, 14.2.11, 14.2.19

A-001 Safety Results

I used the applicant's submitted drug exposure dataset to describe the duration of exposure to active lomitapide at the various dosages used during this trial (Table 26).

Table 26. A-001 – Extent of Exposure (Duration by Dose)

Active Lomitapide Dose (All Groups)	# Subjects who Received Dose	Median [IQR] Days on Dose	Min, Max Days on Dose
5 mg	55	28 [27, 28]	3, 32
7.5 mg	51	28 [28, 29]	2, 35
10 mg	47	28 [26, 29]	4, 32

Source: FDA clinical reviewer's analysis of submitted A-001 drug exposure dataset (EX.xpt).

Adverse Events

Table 27 presents an overall summary of the TEAEs in the ITT population. There was one SAE in this trial, which was fatal, in the lomitapide monotherapy arm (described below). Nine (32%) of the 28 subjects assigned to lomitapide monotherapy discontinued because of an AE compared with 4 (14%) in each of the other two arms (lomitapide+ezetimibe and ezetimibe monotherapy). TEAEs occurred in 24 (86%), 24 (86%), and 16 (55%) subjects of the lomitapide monotherapy, lomitapide+ezetimibe combination therapy, and ezetimibe monotherapy groups, respectively.

Table 27. A-001 – Adverse Event Summary

	Combination Therapy (n=28)	AEGR-733 Monotherapy (n=28)	Ezetimibe Monotherapy (n=29)
Number (%) of Subjects With Any Treatment-Emergent AE	24 (85.7)	24 (85.7)	16 (55.2)
Number (%) of Subjects With Any Serious Treatment-Emergent AE	0	1 (3.6)	0
Number (%) of Subjects Who Died	0	1 (3.6)	0
Number (%) of Subjects With Any TEAE Possibly Related to Study Treatment	15 (53.6)	21 (75.0)	12 (41.4)
Number (%) of Subjects Who Discontinued Due to Treatment-Emergent AEs	4 (14.3)	9 (32.1)	4 (13.8)

AE = adverse event

Source Data: [End-of-Text Tables 14.3.1.1, 14.3.1.4.1–14.3.1.4.3, 14.3.1.6, 14.3.2.1, and 14.3.2.3.](#)

Source: A-001 CSR, Table 18.

The only fatal SAE in the lomitapide development program (myocardial infarction) occurred in this trial. This event is described in Section 7.3.1 (p. 158). There were no other SAEs.

In study A-001, abnormal transaminases were the most common reason for premature discontinuation of study drug among subjects who received lomitapide. Among the nine (32%) subjects who discontinued lomitapide monotherapy, the AEs responsible for discontinuation included increased ALT (n=5), increased AST (n=2), and one event each of “increased hepatic enzyme,” abdominal discomfort, diarrhea, and deep vein thrombosis. Among the four (14%) subjects who discontinued lomitapide+ezetimibe combination therapy, the AEs responsible for discontinuation included “liver function test abnormal” (n=2) and one event each of increased ALT, diarrhea, and muscle spasms. Last, among the four subjects (14%) who discontinued ezetimibe monotherapy, the AEs responsible for discontinuation included one event each of increased creatinine, constipation, nausea, myalgia, and dizziness.

Given that this was an active-controlled trial without a placebo group, I have not tabulated common adverse events. In general, observed non-serious AEs were consistent with other trials in the lomitapide development program. The most commonly observed TEAEs by preferred term in the combination therapy group were diarrhea (36%), increased ALT (18%), vomiting (14%), increased AST, and abnormal liver function test and upper respiratory tract infection (11% each). The most commonly observed in the lomitapide monotherapy group were diarrhea (39%); increased ALT (29%); increased AST (25%); dyspepsia, flatulence, and nausea (14% each); and abdominal pain, constipation, and eructation (11% each). The most commonly observed in the ezetimibe monotherapy group were abdominal distension, abdominal pain, back pain, diarrhea, dizziness, dyspepsia, and nasopharyngitis, each reported by 2 subjects (i.e., 7% each).

Liver-related Laboratory Values

In A-001, adverse events of elevated transaminases were reported for 6 (21%) of 28 subjects in the lomitapide+ezetimibe combination arm, 10 (36%) of 28 subjects in the lomitapide monotherapy arm, and no subjects in the ezetimibe monotherapy arm. Included among these, 3 (11%) subjects in the combination arm and 6 (21%) in the lomitapide monotherapy arm were withdrawn from the study because of elevated transaminases.

Ten (36%) of the 28 subjects assigned to lomitapide monotherapy and seven (25%) of the 28 subjects assigned to lomitapide+ezetimibe combination therapy had a peak ALT $\geq 3x$ ULN after randomization; no subject assigned to ezetimibe monotherapy had an ALT elevation to this degree (Table 28). All 17 of these subjects had bilirubin levels $< 1.2x$ ULN and normal INR.

Table 28. A-001 – Peak ALT Abnormalities

Peak ALT	Lomitapide Monotherapy (n=28)	Ezetimibe Monotherapy (n=29)	Combination (n=28)
$\geq 2x, < 3x$ ULN	1 (4%)	1 (3%)	3 (11%)
$\geq 3x, < 5x$ ULN	5 (18%)	0	4 (14%)
$\geq 5x, < 10x$ ULN	5 (18%)	0	3 (11%)
$\geq 10x$ ULN	0	0	0

Source: FDA clinical reviewer’s analysis of submitted A-001 laboratory dataset (LB xpt)

Reviewer Comments:

1. *The clinical study report states that 4 subjects in the combination therapy group and 5 subjects in the lomitapide monotherapy group had confirmed ALT values $> 3xULN$, where confirmation was defined as an elevation found on 2 consecutive tests. What the report does not mention, however, is that 3 of the “unconfirmed” elevations in each of the lomitapide monotherapy group and combination therapy group – which I have included in the table above – occurred at the week 12 end-of-treatment visit; therefore, these subjects discontinued therapy per protocol at the time of the elevation $> 3xULN$ and their levels fell below $3xULN$ when they returned for unscheduled follow-up visits. Regarding the other two “unconfirmed” elevations, subject 04-1062 had an ALT of $3.8xULN$ on study day 42, which led to discontinuation of lomitapide 7.5 mg monotherapy two days later; the next ALT value, obtained 8 days after drug discontinuation, was $2.0xULN$. The last “unconfirmed” elevation occurred in subject 01-1061 three days after discontinuing lomitapide+ezetimibe combination therapy at week 12 per protocol. At this subject’s end-of-treatment visit (day 86), ALT was $1.3x$ ULN. It was rechecked on day 99 and found to be $7.1xULN$, which fell to $2xULN$ by day 113. This last subject’s ALT elevation is the least likely to have been induced by lomitapide simply based on the relationship to last dose, but additional data to support an alternative cause were not provided.*
2. *These data demonstrate that escalating the dose of lomitapide even more slowly than performed in the HoFH-pivotal trial does not prevent the elevation of*

transaminases, which occurred in 30% of all subjects who received lomitapide in a 12-week period.

Figure 7 shows the longitudinal profiles of ALT (relative to ULN) for only the 17 subjects who ever had ALT $\geq 3x$ ULN (treatment arms are not distinguished). Colored lines indicate days during which the subject was on-treatment according to the submitted exposure dataset (compliance not considered); black dashed lines continue the profiles across any off-treatment follow-up visits. Recall that all of these subjects would be expected to be taking regimens including lomitapide 5 mg between baseline and week 4, 7.5 mg between weeks 4 and 8, and 10 mg between weeks 8 and 12.

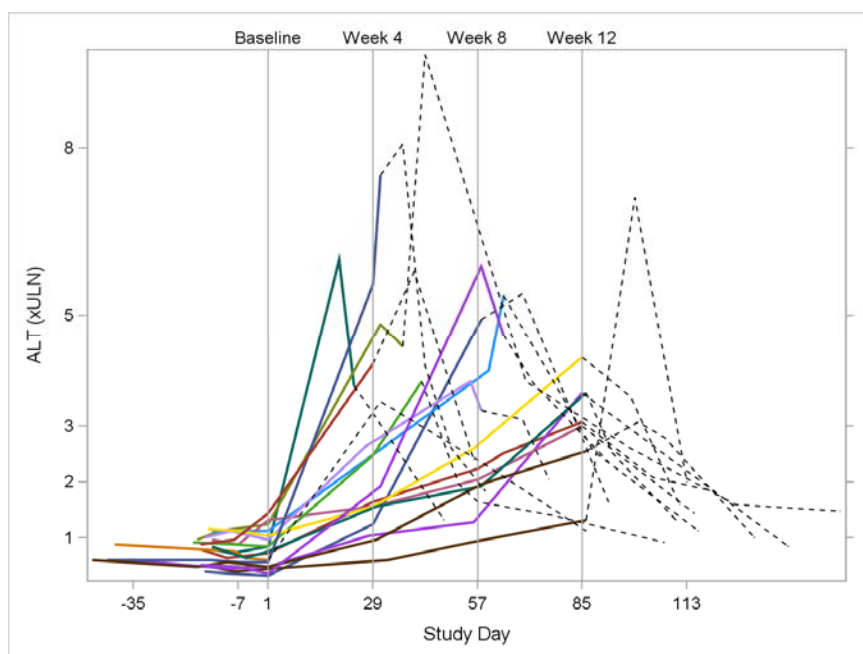


Figure 7. A-001 – ALT Profiles for Subjects with Peak ALT $\geq 3x$ ULN

Source: FDA clinical reviewer's analysis of submitted A-001 datasets (LB and EX.xpt). Black, dashed lines indicate values following treatment discontinuation. Lomitapide monotherapy and combination therapy groups are combined.

Reviewer Comments:

1. *This figure shows that this study cannot contribute information regarding how ALT responds with continued dosing, since study drug was universally discontinued among subjects who had ALT $\geq 3x$ ULN.*
2. *ALT typically fell substantially within 2-4 weeks of discontinuing study drug.*
3. *Elevations in ALT were observed early in the trial, when subjects were taking lomitapide 5 mg daily.*

Hepatic Fat

Hepatic fat was not measured in study A-001.

Vitamin E

Fat-soluble nutrients were not measured in study A-001.

Laboratory Results

Measures of central tendency of hematology, serum chemistry, urinalysis, and coagulation test results did not suggest clinically significant differences between treatment groups with the exception of transaminases, which are discussed above. The relevant data in the A-001 CSR are Tables 14.3.3.1-3.

Other than transaminases, post-baseline laboratory values marked as “clinically significant” by investigators included increased creatinine (1 subject in combination therapy arm and 1 subject in ezetimibe monotherapy arm), increased glucose in 2 subjects in the lomitapide monotherapy arm, and increased WBC in 1 subject in the ezetimibe monotherapy arm.

Vital Signs

The clinical study report states “There were no differences between the 3 groups and no clinically meaningful changes between baseline and the last visit in vital sign measurements,” but no tables of descriptive statistics for vital signs across study visit were submitted for this trial.

Weight Change

Among the 19 subjects in the lomitapide monotherapy arm who completed the week 12 visit, the mean (SD) change in weight from baseline was -0.7 (2.0) kg, or -1.0% from baseline. Among the 24 subjects in the ezetimibe monotherapy arm, the mean change in weight was -0.2 (1.8) kg, or -0.1% from baseline. Among the 24 subjects in the lomitapide+ezetimibe combination arm, the mean change in weight was -1.4 (2.6) kg, or -1.4% from baseline. None of the between-group comparisons were statistically significant (all $P \geq 0.077$).

Pulmonary Function Tests

Pulmonary function was not assessed in study A-001.

Study AEGR-733-003b

In 2007, Aegerion sponsored study AEGR-733-003b (“A-003b”) to compare 8 weeks of fixed-dose lomitapide (5 or 10 mg daily) in combination with atorvastatin 20 mg daily with both placebo and monotherapy of each agent in adult subjects with hyperlipidemia as described above for study A-001. Subjects were counseled to implement a low-fat diet (<30% calories from fat).

Reviewer Comments:

1. *Comparing effect sizes of lomitapide to atorvastatin, or even comparing the incremental effect of lomitapide on background atorvastatin, is not generalizable to the HoFH population because of the attenuated effect of statins in patients with dysfunctional LDL receptors.*
2. *Initially, this study was initiated as AEGR-733-003 on 17 May 2007 and new enrollment was stopped prematurely on 28 June 2007 because of GI AEs that*

were more severe than expected based on previous studies. The sponsor identified contamination with Bacillus cereus in the AEGR-733 capsules. After correcting this issue of contamination, the protocol was re-initiated as A-003b, described below. Other than confirming that there were no SAEs or deaths reported, I did not review the details of the prematurely terminated trial.

A-003b Demographics & Disposition

Of the 157 subjects enrolled, 70 (45%) were men; 127 (81%) were white and 23 (15%) were black. The mean (SD) age was 54 (10) years with a range of 22 to 70 years. The mean (SD) BMI was 28.8 (4.6) kg/m². Mean (SD) LDL-C at baseline was 173 (28) mg/dL with a range of 104 to 280 mg/dL.

This trial enrolled a relatively healthy population. The sum of the number of NCEP risk factors (see inclusion criteria above), subtracting one for HDL-C ≥60 mg/dL, was 0 for 18%, 1 for 29%, 2 for 35%, 3 for 12%, 4 for 1%, and 5 for 1%. Only 4 (2.5%) of the 157 subjects reported a prior history of atherosclerotic cardiovascular disease.

The minority of subjects were taking lipid-lowering medications prior to wash-out. My analysis of the submitted concomitant medications dataset (*CM.xpt*), for example, showed that only 25% of subjects had been on statins (6 or 7 subjects in each group had a history of statin use). Similarly, the minority had BP >140/90 or were on antihypertensive therapy at baseline, ranging from 27% to 46% across groups.

Table 29 summarizes the disposition of subjects in study A-003b. The drop-out rate was very high for an 8-week study, with the highest incidence of premature discontinuation in the groups that included lomitapide 10 mg daily (62% and 69% drop-out for monotherapy and combination therapy, respectively). Premature discontinuation was largely the result of adverse events (predominantly diarrhea).

Table 29. A-003b – Subject Disposition

	P	L5	L10	A20	L5+A20	L10+A20	All
Enrolled	27	26	26	26	26	26	157
Completed	26 (96%)	17 (65%)	10 (39%)	25 (96%)	18 (69%)	8 (31%)	104 (66%)
Discontinued	1 (4%)	9 (35%)	16 (62%)	1 (4%)	8 (31%)	18 (69%)	53 (34%)
Reason for D/C							
Adverse event	0	9 (35%)	14 (54%)	0	5 (19%)	17* (65%)	45* (29%)
Consent withdrawn	1 (4%)	0	2 (8%)	1 (4%)	3 (12%)	0*	7* (4%)
Other	0	0	0	0	0	1 (4%)	1 (1%)

Source: A-003b CSR, Table 10-1.

P = placebo; A20 = atorvastatin 20 mg; L5 = lomitapide 5 mg; L10 = lomitapide 10 mg

* Differs from Table 10-1 in CSR; the AE database indicates 45 subjects withdrew for adverse events (instead of 44); subject 05115 in L10+A20 “withdrew consent due to AEs.”

Reviewer Comments:

1. According to the submitted line listings, the “other” discontinuation was “Subject (05123) removed from the study due to lab values.” A review of the laboratory dataset shows that this subject had ALT values of 32, 213, and 233 IU/L at weeks 2, 4, and 6, respectively. The subject discontinued study drug the day after the week 6 visit and was withdrawn from the study approximately 2 weeks later when the ALT was 272 IU/L. An off-study followup visit 43 days later documented resolution of ALT to 32 IU/L.
2. Reasons for withdrawal of consent were not collected.

A-003b Efficacy Results

Table 30 summarizes the mean baseline values for lipid parameters in trial A-003b, and Table 31 summarizes the least squares means of % changes in lipid parameters after 8 weeks of treatment. These values only include subjects with available data (i.e., no imputation), and the proportion of each group with missing data because of premature discontinuation is substantial (e.g., 65% missing in L10+A20 group).

Table 30. A-003b – Mean (SD) Baseline Lipid Parameters

	P (n=27)	L5 (n=26)	L10 (n=26)	A20 (n=26)	L5+A20 (n=26)	L10+A20 (n=26)	All (n=157)
LDL-C	166 (25)	177 (38)	172 (29)	174 (24)	169 (17)	179 (33)	173 (28)
TC	251 (29)	265 (37)	261 (37)	262 (28)	248 (24)	259 (38)	257 (33)
TG*	176 (111)	178 (186)	171 (92)	173 (83)	161 (57)	131 (67)	165 (107)
ApoB	149 (22)	153 (24)	155 (28)	152 (22)	150 (16)	148 (25)	151 (23)
HDL-C	50 (14)	55 (18)	54 (15)	53 (12)	47 (11)	54 (13)	52 (14)
ApoAI	161 (31)	165 (29)	165 (28)	167 (28)	153 (29)	164 (28)	163 (29)

Source: FDA clinical reviewer’s analysis of submitted A-003b laboratory dataset (LB.xpt)

Baseline = Visit 3 (VISITNUM=4). All values are mean (SD) in mg/dL.

* Because the sponsor performed t tests to compare all efficacy endpoints between groups, the mean (SD) is presented for TG despite its skewed distribution. Median values for the P through L10+A20 groups were 128, 156, 127, 139, 165, and 109 mg/dL, respectively.

The clinical study report presents P values for all 15 pairwise comparisons between groups at week 8, but the most relevant supportive data for the HoFH indication are the comparisons between placebo and lomitapide monotherapy. I have, however, included the atorvastatin monotherapy vs. lomitapide+atorvastatin combinations for completeness.

Table 31. A-003b – Mean % Changes in Lipid Parameters at Week 8

	P (n=27)	L5 (n=26)	L10 (n=26)	A20 (n=26)	L5+A20 (n=26)	L10+A20 (n=26)
N^s	25 (93%)	18 (69%)	10 (38%)	24 (92%)	18 (69%)	9 (35%)
LDL-C	+1.9%	-15.8%**	-36.8% [‡]	-41.6%	-47.2%	-49.9%
TC	+2.0%	-18.4% [‡]	-33.2% [‡]	-30.0%	-37.2%	-39.6%
TG	-1.1%	-9.8%	-11.7%	-13.5%	-30.9%	-25.7%
Non-HDL-C	+1.8%	-19.3% [‡]	-36.2% [‡]	-38.5%	-45.2%	-47.9%
ApoB	+0.2%	-16.7% [†]	-35.9% [‡]	-34.1%	-41.1%	-46.3%*
HDL-C	+3.3%	-8.7%*	-15.8%**	+3.6%	-1.6%	-3.5%
ApoAI	-0.6%	-10.0%*	-20.0% [‡]	-0.7%	-5.8%	-9.4%

Source: A-003b CSR, Tables 11-6

The sponsor did not perform pairwise t-test comparisons between groups for TG since the overall one-way ANOVA $P=0.48$, suggesting that the null hypothesis of no difference between groups in mean % change in TG could not be rejected.

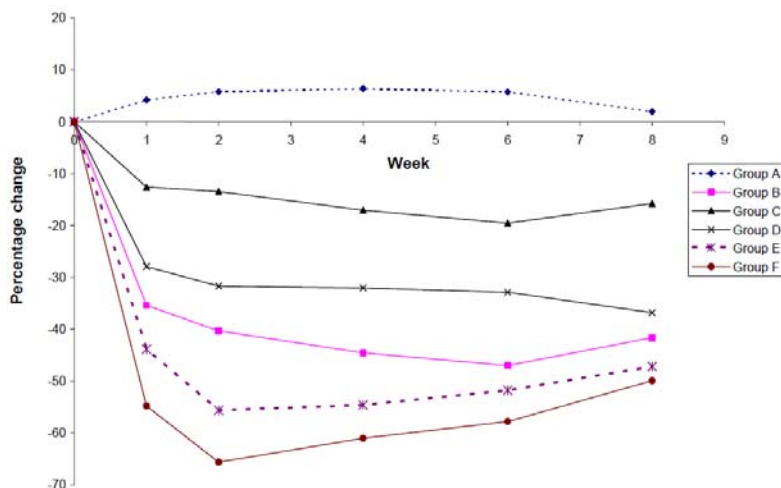
* $P<0.05$; ** $P<0.01$; † $P<0.001$; ‡ $P<0.0001$ with the P group being the referent for L5 and L10, and the A20 group being the referent for L5+A20 and L10+A20.

§ For TC, TG, ApoB, HDL-C, and ApoAI, $n=26$ for P, $n=19$ for L5, and $n=25$ for A20.

Reviewer Comments:

1. *At least among subjects who were able to stay on drug for the duration of the 8-week trial, lomitapide caused statistically significant reductions in LDL-C, TC, non-HDL-C, apoB, HDL-C, and apoAI. Furthermore, in this fixed-dose study, there appears to be a dose-response from 5 mg to 10 mg among completers.*
2. *These results are akin to a per-protocol analysis, as the clinical study report states that “blood draws for lipid and other efficacy measures (not safety) were only drawn if the study subject had received study medication in the past 3 days.” This has the potential to introduce bias in favor of lomitapide.*
3. *This study does not provide evidence for an effect of lomitapide on TG, at least at the doses and duration studied.*
4. *Note that the placebo-subtracted change in HDL-C from baseline to week 8 is -12% and -19.1% for lomitapide 5 mg and 10 mg, respectively, which could plausibly increase CV risk.*
5. *At least at the low doses of lomitapide studied, this phase 2 study does not provide convincing evidence of benefit for lomitapide when added to atorvastatin 20 mg daily among non-HoFH hyperlipidemic subjects. These comparisons are not relevant for HoFH patients, however, since patients with LDLR dysfunction would not be expected to achieve a mean 40% reduction in LDL-C with moderate-dose atorvastatin.*

The mean % change in LDL-C over time for each group is shown in Figure 8. Recall that no imputation was performed and there was substantial dropout in lomitapide-treated groups.



Best Available Copy

Groups: A=Placebo, B=Atorvastatin 20 mg, C=AEGR-733 5 mg, D=AEGR-733 10 mg, E=AEGR-733 5 mg + atorvastatin 20 mg, F=AEGR-733 10 mg + atorvastatin 20 mg
Reference: Table 14.2.3-1

Figure 8. A-003b – Mean % Change in LDL-C Over Time
Source: A-003b CSR, Figure 11-1.

A-003b Safety Results

The sponsor did not summarize exposure data for A-003b in the clinical study report. I used the submitted drug exposure dataset to describe the exposure to active lomitapide or placebo by group (Table 32).

Table 32. A-003b – Extent of Exposure

Days on Study Drug	P (n=27)	L5 (n=25*)	L10 (n=26)	A20 (n=26)	L5+A20 (n=26)	L10+A20 (n=26)
Median [IQR]	56 [55, 57]	55 [28, 57]	34 [5, 56]	56 [56, 58]	56 [39, 56]	16 [7, 56]
Min, Max	7, 62	3, 64	1, 65	28, 70	5, 64	3, 67

Source: FDA clinical reviewer’s analysis of submitted A-003b exposure dataset (EX.xpt)
* One subject in the L5 group did not have an end date recorded.

Reviewer Comment: Note the high incidence of early discontinuation in lomitapide-treated groups, especially at the 10 mg dose (e.g., 7 [27%] of the 26 subjects in the L10 group stopped study drug on or before study day 5). Thus, the incidence of any AEs that are associated with longer exposure to study drug may be underestimated in these groups.

Adverse Events

Table 33 presents an overall summary of the treatment-emergent adverse events in the ITT population. There were two SAEs in this trial (one myocardial infarction in each of the lomitapide monotherapy arms), described in Section 7.3.2 (p. 159), and there were no deaths.

Among the 52 subjects assigned to a treatment arm that included lomitapide 5 mg, 14 (27%) discontinued because of an AE. Among the 52 subjects assigned to an arm that included lomitapide 10 mg, 31 (60%) discontinued because of an AE. In contrast, no subject assigned to either placebo or atorvastatin monotherapy discontinued because of an AE.

Table 33. A-003b – Adverse Event Summary

	P (n=27)	L5 (n=26)	L10 (n=26)	A20 (n=26)	L5+A20 (n=26)	L10+A20 (n=26)
Any TEAE	17 (63%)	23 (88%)	23 (88%)	15 (58%)	21 (81%)	24 (92%)
“Severe”	1 (4%)	8 (31%)	8 (31%)	2 (8%)	5 (19%)	12 (46%)
SAE	0	1 (4%)	1 (4%)	0	0	0
Deaths	0	0	0	0	0	0
D/C Due to TEAE	0	9 (35%)	14 (54%)	0	5 (19%)	17 (65%)

Source: Derived from A-003b CSR, Table 12-1.

TEAE = treatment-emergent adverse event; “Severe” intensity of AE was assigned by the investigator; SAE = serious adverse events

Reviewer Comment: Even at low doses (5-10 mg) for short-term therapy (8 weeks), lomitapide is not well tolerated in the general population, with discontinuation rates of ~20-65% observed in this phase 2 trial. Furthermore, even though severity of AEs is subjective, the incidence of severe AEs is quite high.

Table 123 (Appendix) summarizes the adverse events that led to study discontinuation in A-003b by system organ class and preferred term. The most common causes for premature discontinuation were gastrointestinal symptoms (predominantly diarrhea). Subject counts of treatment-emergent AEs that were more reported by ≥5% of subjects (i.e., ≥2 subjects) and were more common in a lomitapide (with or without atorvastatin) group than a control (placebo or atorvastatin) group are listed in Table 124 (Appendix).

Reviewer Comments:

1. Consistent with other studies, the most common lomitapide-associated AEs are gastrointestinal symptoms and abnormalities of hepatic transaminases.
2. There is no further information available for 3 cases of “chest pain” in the lomitapide 5 mg monotherapy group. There were no cases of “chest pain” in any of the three other lomitapide groups. The investigators classified these events as mild/possibly related, mild/unrelated, and moderate/unlikely related.

Liver-related Laboratory Values

In contrast to the preceding clinical trials that discontinued study drug for transaminases >3x ULN, this trial implemented the following liver-related safety criteria:

- ALT and/or AST >10x ULN and/or bilirubin >2x ULN: discontinue and follow until resolution or stabilization;
- ALT and/or AST >5x ULN, alkaline phosphatase >3x ULN, or bilirubin 1.5x ULN (unless evidence of underlying Gilbert’s syndrome): confirm result within 7-14 days and discontinue study medication if repeat values exceed these thresholds

until ALT or AST <2x ULN, alkaline phosphatase <1.5x ULN, or bilirubin <1.0x ULN, at which point the drug could be restarted;

- ALT and/or AST >2x but <5x ULN and otherwise asymptomatic, and/or bilirubin >1.0x but <1.5x ULN (with normal pre-treatment levels): carefully follow for further evaluation but continue on study drug.

In A-003b, adverse events of elevated transaminases (i.e., combined preferred terms of ALT increased, AST increased, hepatic enzymes increased, liver function test abnormal, and transaminases increased) were reported for 1 subject (4%) in each of the placebo and atorvastatin monotherapy groups; 2 (8%) and 5 (19%) subjects in the lomitapide 5 mg and 10 mg monotherapy groups, respectively; and 2 (8%) and 1 (4%) subject in the lomitapide 5 mg and 10 mg in combination with atorvastatin groups, respectively. Included among these, 4 (15%) of 26 subjects in the lomitapide 10 mg monotherapy group and 1 (4%) subject in each of the lomitapide + atorvastatin groups were withdrawn for elevated transaminases.

There was one case of ALT ≥3x ULN in the placebo group in a subject who had normal transaminases through the week 6 study visit (range, 9-14 IU/L) and then had an ALT 75 IU/L (3.0x ULN) at the final study visit at week 8. There were no cases of ALT ≥3x ULN in the atorvastatin monotherapy group. In contrast, 24% of subjects treated with lomitapide monotherapy 10 mg daily had a peak ALT ≥3x ULN during the 8 week trial, even given the high proportion of early discontinuations in this group (Table 34). Longitudinal ALT profiles for these subjects are shown in Figure 9.

Concomitant total bilirubin levels, alkaline phosphatase, and INR levels were normal for all subjects with ALT ≥3x ULN.

Table 34. A-003b – Peak ALT Abnormalities

Peak ALT	P (n=27)	L5 (n=26)	L10 (n=26)	A20 (n=26)	L5+A20 (n=26)	L10+A20 (n=26)
≥2x, <3x ULN	1 (4%)	3 (12%)	2 (8%)	1 (4%)	3 (12%)	0
≥3x, <5x ULN	1 (4%)	1 (4%)	3 (12%)	0	1 (4%)	2 (8%)
≥5x, <10x ULN	0	0	2 (8%)	0	1 (4%)	0
≥10x ULN	0	0	1 (4%)	0	1 (4%)	1 (4%)

Source: FDA clinical reviewer's analysis of submitted A-003b laboratory dataset (LB.xpt).

Reviewer Comment: The substantially lower exposure to lomitapide 10 mg as a result of premature discontinuations, especially in combination with atorvastatin, likely produced underestimates of the incidence of transaminase elevations in these groups.

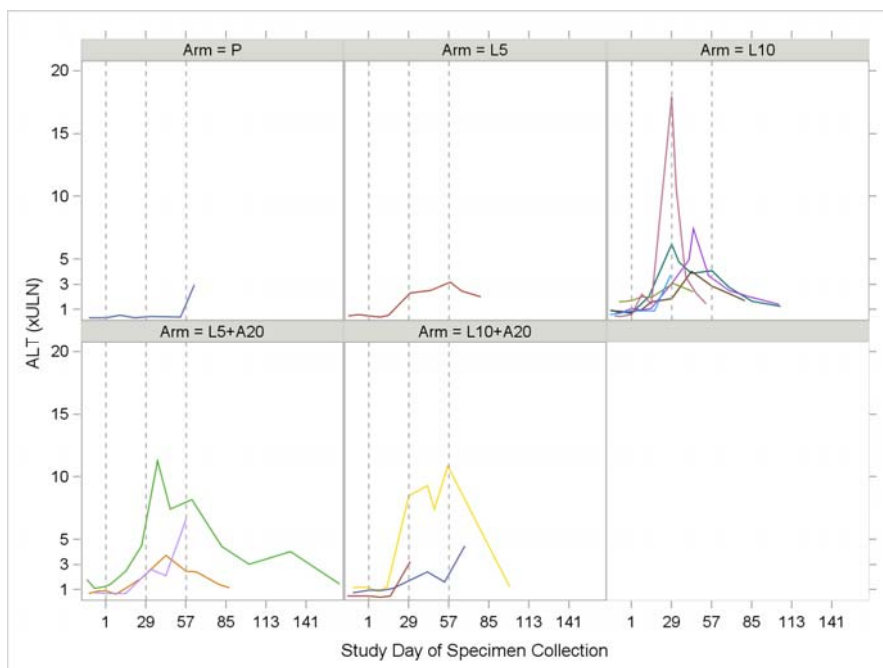


Figure 9. A-003b – ALT Profiles for Subjects with Peak ALT $\geq 3x$ ULN

Source: FDA clinical reviewer’s analysis of A-003b laboratory dataset (*LB.xpt*)

Dashed lines are the approximate times of the week 4 and week 8 visits for reference. Only subjects with peak ALT $\geq 3x$ ULN after baseline are included in this figure.

Hepatic Fat

Hepatic fat was not measured in study A-003b.

Vitamin A & E

Vitamins A and E were measured at screening, baseline, and at each study visit during trial A-003b. Summary statistics for these values were not submitted in the clinical study report, so the following analyses are derived directly from the laboratory datasets (Table 35 and Table 36). For vitamin A, the LLN ranged from 1.12 to 1.33 $\mu\text{mol/L}$, and for vitamin E, the LLN was 11.61 $\mu\text{mol/L}$. I did not identify any post-baseline values that were below the LLN for any subject.

Table 35. A-003b – Mean (SD) Vitamin A Levels Over 8 Weeks

Vitamin A ($\mu\text{mol/L}$)	P (n=27)	L5 (n=26)	L10 (n=26)	A20 (n=26)	L5+A20 (n=26)	L10+A20 (n=26)
Baseline	2.3 (0.5) n=25	2.1 (0.4) n=25	2.1 (0.5) n=26	2.4 (0.7) n=23	2.3 (0.5) n=26	2.0 (0.5) n=25
Week 1	2.4 (0.6) n=27	2.4 (0.4) n=23	2.3 (0.6) n=18	2.3 (0.8) n=25	2.4 (0.5) n=22	2.0 (0.5) n=19
Week 2	2.4 (0.6) n=25	2.4 (0.5) n=21	2.3 (0.6) n=17	2.3 (0.8) n=26	2.2 (0.5) n=21	2.2 (0.5) n=13
Week 4	2.4 (0.5) n=26	2.4 (0.6) n=19	2.0 (0.4) n=16	2.3 (0.7) n=25	2.3 (0.5) n=20	2.0 (0.5) n=10
Week 6	2.4 (0.6) n=26	2.4 (0.5) n=17	2.0 (0.5) n=11	2.2 (0.6) n=25	2.3 (0.6) n=19	2.1 (0.6) n=9
Week 8	2.3 (0.6) n=26	2.4 (0.6) n=19	2.1 (0.6) n=10	2.3 (0.7) n=25	2.3 (0.5) n=17	2.1 (0.7) n=9

Source: FDA clinical reviewer’s analysis of submitted A-003b laboratory dataset (*LB.xpt*).

Table 36. A-003b – Mean (SD) Total Vitamin E Levels Over 8 Weeks

Vitamin E (µmol/L)	P (n=27)	L5 (n=26)	L10 (n=26)	A20 (n=26)	L5+A20 (n=26)	L10+A20 (n=26)
Baseline	42.0 (14.6)	45.2 (12.9)	43.0 (13.6)	45.6 (21.7)	44.9 (19.8)	38.4 (9.2)
Week 1	43.4 (14.1)	39.6 (12.2)	34.0 (15.1)	36.5 (13.8)	31.6 (18.5)	23.5 (7.2)
Week 2	42.0 (13.7)	37.1 (11.4)	31.9 (14.3)	34.6 (14.7)	27.7 (20.8)	21.3 (8.1)
Week 4	41.9 (13.1)	37.2 (13.0)	28.3 (13.1)	33.6 (15.2)	25.5 (12.8)	21.5 (11.8)
Week 6	43.2 (15.4)	36.9 (11.1)	27.2 (8.3)	33.5 (12.7)	28.2 (23.6)	23.4 (13.7)
Week 8	42.6 (16.9)	36.9 (13.0)	23.2 (5.0)	34.4 (15.6)	26.0 (6.5)	26.8 (12.5)

Source: FDA clinical reviewer's analysis of submitted A-003b laboratory dataset (LB.xpt).
For n at each time point, see Table 35 above.

Reviewer Comment: Consistent with other trials in the development program, lomitapide induced a dose-related decrease in total vitamin E, but not vitamin A, in this 8-week study. Although it's possible that the subjects who discontinued prematurely may have been more likely to have shown decreases in vitamin A, the fact that there does not even appear to be a modest decrease in mean vitamin A levels among completers is reassuring, although this study used low doses of lomitapide for a relatively short duration.

Laboratory Results

Laboratory results from the 8-week A-003b study were not analyzed in detail other than to note that there were no substantial differences observed between groups at week 8 with regard to measures of central tendency of hematology, serum chemistry (excluding liver-related tests discussed elsewhere), urinalysis, and coagulation test results among completers (Table 37).

Table 37. A-003b – Mean (SD) Safety Laboratory Values at Week 8

	P (n=27)	L5 (n=26)	L10 (n=26)	A20 (n=26)	L5+A20 (n=26)	L10+A20 (n=26)
# values at week 8:	26	19	10	25	18	9
Sodium (mEq/L)	140 (1)	141 (2)	139 (4)	141 (3)	140 (2)	140 (2)
Potassium (mEq/L)	4.2 (0.5)	4.3 (0.3)	4.3 (0.5)	4.3 (0.3)	4.0 (0.1)	4.4 (0.2)
Chloride (mEq/L)	103 (2)	104 (2)	103 (5)	103 (3)	103 (2)	104 (1)
Bicarbonate (mEq/L)	26 (2)	26 (2)	25 (2)	26 (2)	26 (4)	26 (3)
BUN (mg/dL)	14 (4)	14 (5)	12 (3)	13 (4)	14 (5)	15 (5)
Creatinine (mg/dL)	1.0 (0.2)	1.0 (0.1)	0.9 (0.2)	1.0 (0.2)	1.1 (0.2)	0.9 (0.2)
Glucose (mg/dL)	91 (9)	91 (8)	94 (11)	91 (10)	92 (13)	86 (17)
Calcium (mg/dL)	9.7 (0.3)	10.0 (0.4)	9.7 (0.4)	10.0 (0.4)	9.8 (0.3)	9.7 (0.3)
Total Protein (g/dL)	6.9 (0.5)	6.8 (0.4)	6.7 (0.5)	7.0 (0.4)	6.9 (0.5)	6.7 (0.4)
Albumin (g/dL)	4.2 (0.3)	4.3 (0.3)	4.3 (0.3)	4.3 (0.4)	4.3 (0.2)	4.3 (0.2)
WBC (10 ³ /mL)	5.6 (1.0)	5.6 (1.4)	7.2 (2.6)	6.4 (1.9)	6.3 (1.5)	6.2 (2.5)
Hemoglobin (g/dL)	14.4 (1.2)	14.6 (1.5)	14.2 (1.6)	13.8 (1.3)	14.6 (1.2)	14.1 (0.6)
Hematocrit (%)	42.5 (3.5)	43.0 (4.0)	41.9 (4.5)	41.0 (3.7)	42.9 (3.8)	41.8 (1.7)
Platelets (10 ³ /mL)	250 (61)	247 (62)	260 (87)	280 (71)	270 (46)	235 (54)
INR*	1.0 (0.2)	0.9 (0.1)	1.0 (0.2)	1.2 (1.1)	1.2 (0.9)	0.9 (0.1)
aPTT (sec)*	20.3 (1.6)	20.2 (2.1)	21.0 (2.6)	20.5 (2.1)	20.9 (2.4)	21.0 (2.6)
C-peptide (ng/mL)	2.2 (1.1)	2.0 (1.0)	2.4 (1.4)	2.1 (0.9)	2.4 (1.3)	2.1 (1.0)
Insulin (µIU/mL)	12.0 (7.5)	8.5 (5.8)	13.8 (14.3)	10.0 (5.2)	13.5 (11.4)	11.9 (6.2)

	P (n=27)	L5 (n=26)	L10 (n=26)	A20 (n=26)	L5+A20 (n=26)	L10+A20 (n=26)
Median hsCRP (mg/L)	2.1	1.9	1.5	1.5	2.2	0.7

Source: A-003b CSR, Tables 14.3-2b, -2c, -2d, -2e, -3a, -3b, and -3c.

* For INR and aPTT: n=25 (P), n=23 (A20), and n=15 (L5+A20).

Vital Signs

Descriptive statistics of vital signs in study A-003b were not submitted with the clinical study report (neither measures of central tendency nor shift tables). I calculated the mean (SD) for heart rate, systolic BP, and diastolic BP at baseline (visit 3) and week 8 (visit 8) in the submitted laboratory dataset (Table 38). No hypothesis testing was performed.

Table 38. A-003b – Mean (SD) Vital Sign Measurements

	P	L5	L10	A20	L5+A20	L10+A20
N at Baseline	27	26	26	26	26	26
N at Week 8	26	19	10	25	18	9
Heart rate						
Baseline	66.9 (11.6)	66.2 (8.7)	70.6 (12.4)	72.4 (6.7)	69.1 (9.8)	68.0 (9.2)
Week 8	68.1 (12.3)	67.1 (9.1)	70.7 (9.5)	72.4 (9.1)	69.7 (10.1)	73.2 (8.7)
Systolic BP						
Baseline	123.0 (14.6)	121.4 (14.2)	122.8 (9.6)	125.8 (14.5)	122.2 (13.1)	123.0 (13.4)
Week 8	124.2 (10.8)	119.9 (12.3)	120.1 (19.8)	127.1 (12.9)	121.4 (14.9)	118.2 (14.3)
Diastolic BP						
Baseline	76.7 (6.0)	75.9 (7.4)	77.2 (8.5)	77.5 (8.2)	78.8 (10.3)	77.5 (8.7)
Week 8	76.9 (6.9)	76.2 (10.1)	74.1 (11.0)	78.7 (6.0)	78.2 (10.0)	78.7 (7.5)

Source: FDA clinical reviewer's analysis of submitted A-003b vital signs dataset (VS xpt).

Reviewer Comment: The completer population does not demonstrate any concerning lomitapide-associated trends with regard to changes in heart rate or blood pressure during 8 weeks of treatment.

Weight Change

Among completers, the % changes in body weight from baseline to week 8 were -0.01% for placebo (n=26), -2.5% for lomitapide 5 mg monotherapy (n=19), and -3.5% for lomitapide 10 mg monotherapy (n=10) ($P \leq 0.0005$ for both comparisons). Regarding the atorvastatin-containing groups, the % changes in body weight were -0.4% for atorvastatin 20 mg monotherapy (n=25), -1.8% for lomitapide 5 mg + atorvastatin 20 mg (n=18), and -2.8% for lomitapide 10 mg + atorvastatin 20 mg (n=10) ($P=0.04$ and $P=0.008$ for L5+A20 and L10+A20 vs. atorvastatin monotherapy, respectively).

Pulmonary Function Tests

Pulmonary function was not assessed in study A-003b.

Study AEGR-733-004

Pursuing these lower doses of lomitapide, Aegerion conducted study AEGR-733-004 (“A-004”) in 2007-2008 to better characterize hepatic fat accumulation and to explore whether the use of concomitant medications (atorvastatin, fenofibrate, or ezetimibe) may attenuate this accumulation. This 12-week study was the longest-duration *placebo-controlled* trial in the lomitapide development program.

Study A-004 enrolled 260 adults with LDL-C $\geq$ 100 and $<$ 190 mg/dL (after a 4-week washout of lipid-lowering agents) who had hepatic fat $<$ 6.2% by NMRS at screening. Similar to study C-009 described above, which also assessed lomitapide-induced hepatic fat, there were multiple exclusion criteria; these included a history of diabetes mellitus, regular alcohol use ($>$ 1 drink per day), liver disease or transaminases $>$ ULN at screening, and BMI $>$ 35 kg/m². Following the screening and washout period, during which a low-fat ($<$ 30% total calories from fat) was implemented, subjects were randomly assigned to one of 8 treatment arms for 12 weeks: placebo; fixed-dose lomitapide monotherapy at either 2.5, 5, 7.5, or 10 mg daily; or lomitapide 5 mg daily in combination with daily doses of either atorvastatin 20 mg, micronized fenofibrate 145 mg, or ezetimibe 10 mg. There was no scheduled off-treatment follow-up visit. Hepatic fat was evaluated with MRS/MRI at baseline and weeks 4, 8, and 12.

A-004 Demographics & Disposition

Of the 260 subjects enrolled, 124 (48%) were men; 182 (70%) were white, 55 (21%) were black, 19 (7%) were Hispanic, and 3 (1%) were Asian. The mean (SD) age was 51 (11) years with a range of 20 to 70 years. The mean (SD) BMI was 27.3 (3.7) kg/m². Mean (SD) waist circumference was 92 (11) cm. Mean (SD) LDL-C at baseline was 143 (28) mg/dL with a range of 85 to 317 mg/dL.

This trial enrolled a relatively healthy population. Based on NCEP risk stratification, the majority of subjects in each group had 0 or 1 CHD risk factor (67 to 91%). Five subjects had a history of prior CHD or atherosclerotic disease.

The minority of subjects were taking lipid-lowering medications prior to wash-out. The clinical study report does not report previous statin use, but my analysis of the submitted concomitant medications dataset (*CM.xpt*) showed that only 28 (11%) of the 260 subjects had been on statins (1 to 6 subjects in each group had a history of statin use). Similarly, the minority had a history of hypertension (12% to 24% across groups).

Table 39 summarizes the disposition of subjects in study A-004. Similar to other phase 2 studies for lomitapide, premature discontinuation was relatively common among lomitapide-treated subjects, primarily because of adverse events (predominantly diarrhea).

Table 39. A-004 – Subject Disposition

	Pbo	Lomitapide (mg daily)				Lomitapide 5 mg daily +			All
		2.5	5	7.5	10	Atv	Feno	Eze	
Enrolled	33	34	34	34	35	28	33	29	260
Completed	31 (94%)	25 (74%)	24 (71%)	29 (85%)	21 (60%)	23 (82%)	28 (85%)	25 (86%)	206 (79%)

	Pbo	Lomitapide (mg daily)				Lomitapide 5 mg daily +			All
		2.5	5	7.5	10	Atv	Feno	Eze	
Discontinued	2 (6%)	9 (27%)	10 (29%)	5 (15%)	14 (40%)	5 (18%)	5 (15%)	4 (14%)	54 (21%)
Reason for D/C									
Adverse event	1 (3%)	7 (21%)	8 (24%)	5 (15%)	11 (31%)	4 (14%)	4 (12%)	2 (7%)	42 (16%)
Subject Request	1 (3%)	1 (3%)	2* (6%)	0	2 (6%)	1 (4%)	0	2 (7%)	9 (4%)
Lost to Follow-up	0	1 (3%)	0	0	0	0	0	0	1 (0.4%)
Other**	0	0	0	0	1 (3%)	0	1 (3%)	0	2 (0.8%)

Source: A-004 CSR, Table 10-1.

Pbo = placebo; Atv = atorvastatin 20 mg daily; Feno = micronized fenofibrate 145 mg daily; Eze = ezetimibe 10 mg daily.

* The reasons provided for these subject requests suggest that AEs contributed: one subject (03017) “revoked consent to participate in the study due to frustration with side effects” and the other (13017) “had stomach pain x1 day,” reportedly stopped study drug on his own, and contacted the site 10 days later. The remaining subject requests to discontinue referenced changes in employment precluding continued participation, discomfort with MRI, and moving out of town.

** The “Other” causes were “Withdrew consent” in the lomitapide 10 mg group after 4 days on study drug) and an out-of-range AST at baseline in the lomitapide+fenofibrate group (sponsor contacted site after 7 days on study drug).

Reviewer Comments: This was a fixed-dose trial, which may have affected tolerability for the higher doses of lomitapide (i.e., 10 mg daily) according to the sponsor.

A-004 Efficacy Results

Hepatic Fat

The primary endpoint for trial A-004 was the absolute change in % hepatic fat from baseline to week 12 for lomitapide 5 mg daily vs. placebo. The placebo-subtracted change from baseline was a 4.7% (95% CI, 2.3% to 7.1%) absolute percentage point increase in % hepatic fat (p<0.001); the placebo group showed no change during the 12 weeks (mean +0.03%). Table 40 summarizes the mean and median changes from baseline to week 12 across lomitapide monotherapy groups compared with placebo.

Table 40. A-004 – Absolute Change in % Hepatic Fat at Week 12

Group	n / N	Absolute Change in % Hepatic Fat from Baseline to Week 12			Placebo-subtracted difference (95% CI)	P (vs. pbo)
		Mean (SD)	Median	Min, Max		
Placebo	31 / 33	0.03 (1.8)	-0.2	-5.3, 6.4	-	
Lomitapide 2.5 mg	27 / 34	4.95 (7.1)	1.2	-0.9, 30.2	4.92 (2.27, 7.07)	<0.001
Lomitapide 5 mg	24 / 34	4.72 (6.3)	1.3	-1.4, 19.4	4.68 (2.30, 7.07)	<0.001
Lomitapide 7.5 mg	27 / 34	3.94 (5.8)	2.3	-4.3, 18.2	3.91 (1.73, 6.10)	<0.001
Lomitapide 10 mg	20 / 35	7.86 (9.5)	4.2	-0.6, 29.0	7.82	<0.001

Group	n / N	Absolute Change in % Hepatic Fat from Baseline to Week 12			Placebo-subtracted difference (95% CI)	P (vs. pbo)
		Mean (SD)	Median	Min, Max		
					(4.31, 11.33)	

Source: A-004 CSR, Table 11-4.
n / N = # with data (completers) / # enrolled

To explore the rate of accumulation of hepatic fat over time, I plotted the placebo-subtracted mean change (absolute) in % hepatic fat using available data at each study visit (Figure 10). Imputing week 12 missing data using LOCF modestly attenuated the observed increases in hepatic fat (not shown). Because of the skewed distributions of changes in hepatic fat, I have also presented the median absolute values for % hepatic fat at each visit in Figure 11.

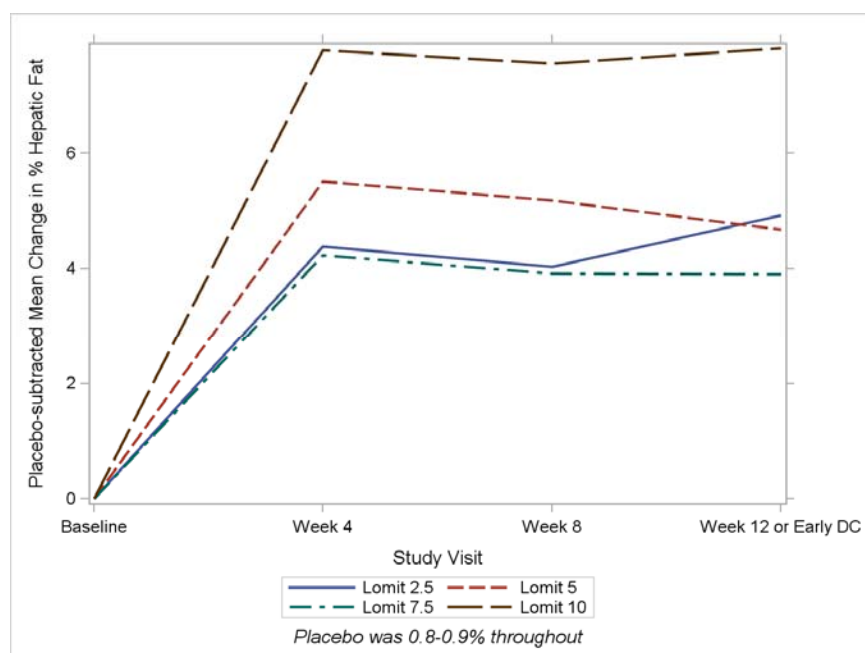


Figure 10. A-004 – Placebo-subtracted Mean Changes in % Hepatic Fat

Source: FDA clinical reviewer's depiction of data in A-004 CSR Tables 14.2.1.1 through 14.2.3.1.3.

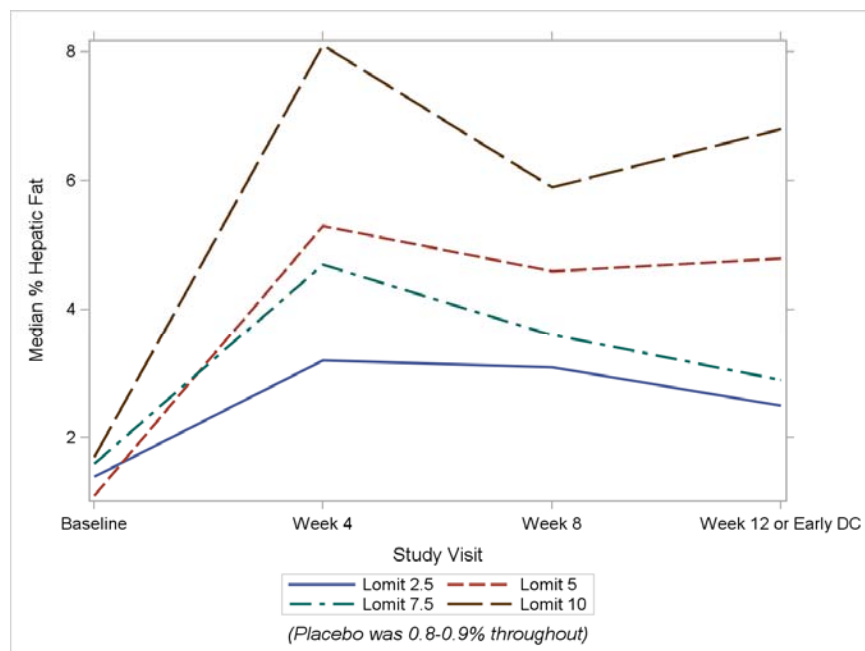


Figure 11. A-004 – Median % Hepatic Fat at Each Visit

Source: FDA clinical reviewer’s depiction of data in A-004 CSR Tables 14.2.1.1 through 14.2.3.1.3.

The trial did not provide evidence that concomitant treatment with atorvastatin, micronized fenofibrate, or ezetimibe attenuates hepatic fat accumulation induced by lomitapide 5 mg daily over 12 weeks (Table 41).

Table 41. A-004 – Effect of Concomitant Lipid-lowering Therapy on Hepatic Fat

Group	n / N	Absolute Change in % Hepatic Fat from Baseline to Week 12			Lomit 5mg-subtracted difference (95% CI)	P (vs. lomit 5 mg)
		Mean (SD)	Median	Min, Max		
Lomitapide 5 mg	24 / 34	4.72 (6.3)	1.3	-1.4, 19.4	-	
Lomitapide 5 mg + atorvastatin 20 mg	23 / 28	3.68 (5.4)	1.3	-2.9, 17.3	1.03 (-2.41, 4.48)	0.55
Lomitapide 5 mg + micronized fenofibrate 145 mg	26 / 33	7.70 (9.4)	4.5	-1.0, 37.5	-2.98 (-7.57, 1.61)	0.20
Lomitapide 5 mg + ezetimibe 10 mg	26 / 29	7.55 (6.2)	6.4	-0.3, 20.0	-2.83 (-6.39, 0.73)	0.12

Source: A-004 CSR, Table 11-6.

n / N = # with data (completers) / # enrolled

Pearson correlations between absolute change in ALT (or AST) and change in % hepatic fat were generally positive, but the strength of these correlations (and their statistical significance) varied. In Table 42, I have summarized these cross-sectional correlations at weeks 4, 8, and 12.

Table 42. A-004 – Correlations Between Changes in ALT and Change in % Hepatic Fat

Group	Week 4			Week 8			Week 12		
	n	r	P	n	r	P	n	r	P
Placebo	30	0.02	0.92	29	-0.06	0.77	31	-0.07	0.72
Lomit 2.5 mg	28	0.54	0.003	26	0.79	<0.001	27	0.65	<0.001
Lomit 5 mg	28	0.58	0.001	24	0.69	<0.001	24	0.78	<0.001
Lomit 7.5 mg	28	0.15	0.44	28	0.19	0.33	27	0.46	0.02
Lomit 10 mg	27	0.73	<0.001	25	0.34	0.10	20	0.33	0.15
Lomit 5 mg + atorva	24	0.75	<0.001	21	0.65	0.001	23	0.73	<0.001
Lomit 5 mg + feno	31	-0.05	0.78	26	0.46	0.02	26	0.72	<0.001
Lomit 5 mg + eze	25	0.13	0.54	28	0.43	0.02	26	0.46	0.02

Source: A-004 CSR, Table 14.2.6.1

The sponsor investigated associations between % changes in various lipid parameters and % changes in hepatic fat in all lomitapide monotherapy groups at all post-baseline time points combined (Table 43). P values for the linear regression models that generated these R² values were not provided.

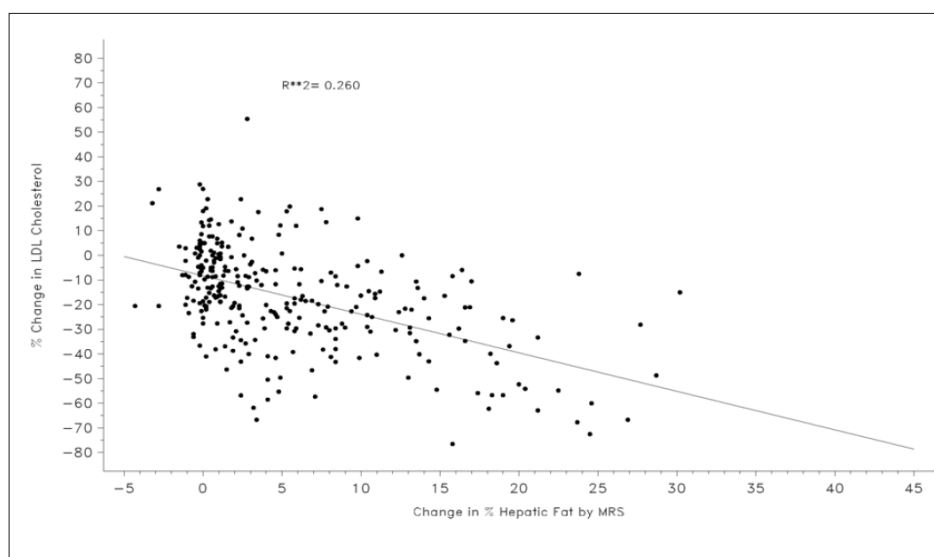
Table 43. A-004 – Associations Between Changes in Lipids and Hepatic Fat

Linear association between change in % hepatic fat (absolute) and % change in . . .	R ²
LDL-C	26.0%
TG	1.6%
HDL-C	3.5%
Non-HDL-C	26.2%
ApoB	22.4%

Source: A-004 CSR, Figures 5-9.

Analyses limited to post-baseline visits for lomitapide monotherapy arms.

A scatterplot describing the relationship of changes in % hepatic fat and LDL-C is shown in Figure 12.



Data source: Section 14.2, Figure 15.3.1

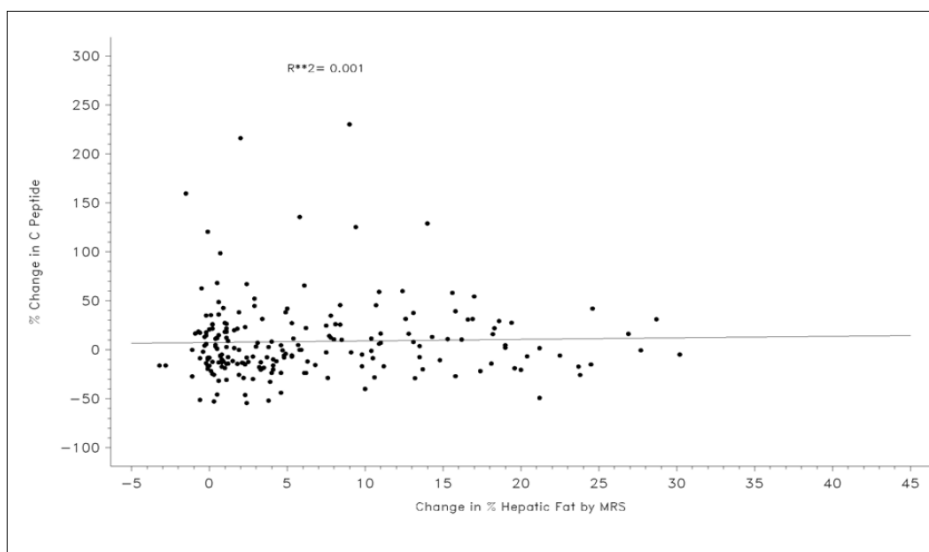
Figure 12. A-004 – Change in % Hepatic Fat vs. % Change in LDL-C

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Source: A-004 CSR, Figure 5.

Reviewer Comment: *Although the sponsor suggests that the correlation between change in LDL-C and hepatic fat in the monotherapy treatment groups was “weak,” these data do show that the subjects who have the greatest increases in hepatic fat also have the greatest reductions in LDL-C, in general. The long-term consequence of this hepatic fat accumulation is the unanswerable question with the currently available data.*

One concern regarding the accumulation of hepatic fat is the association between insulin resistance and hepatic fat. It is generally believed that, in the general population, the accumulation of hepatic fat is a *consequence* of insulin resistance. Some have suggested, however, that hepatic fat itself might induce insulin resistance. Regarding this possibility, I note that the sponsor has examined cross-sectional associations between % change in C-peptide and change in % hepatic fat. Combining all lomitapide-monotherapy groups and all post-baseline visits, there was no evidence for an association between these measures ($R^2 = 0.1\%$) (Figure 13).



Data source: Section 14.2, [Figure 15.3.6](#)

Figure 13. A-004 – Change in % Hepatic Fat vs. % Change in C-peptide

Source: A-004 CSR, Figure 10.

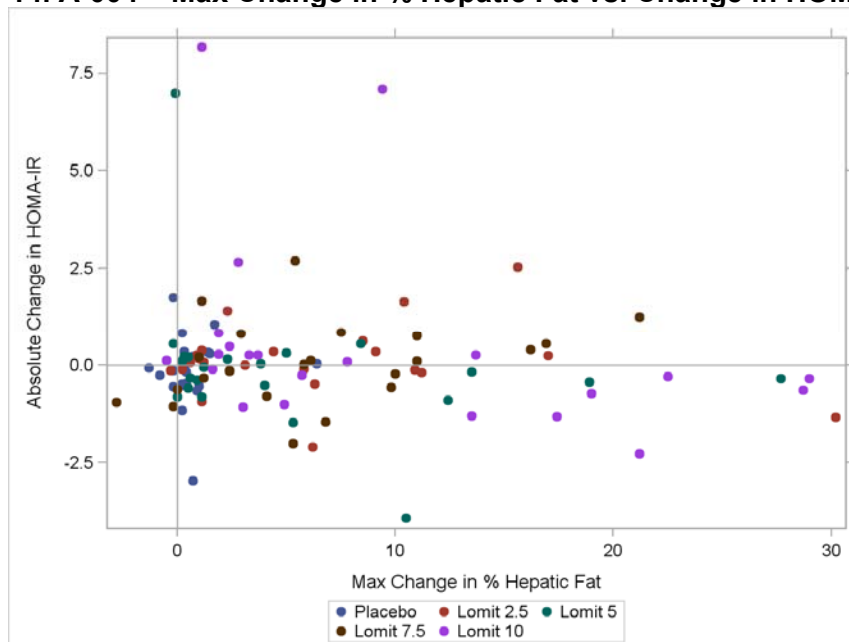
Reviewer Comment: *Although a repeated-measures model would have been more appropriate given that within-subject observations are not independent over time, I agree that data from this trial do not seem to suggest an association between lomitapide-induced hepatic fat accumulation and changes in C-peptide, providing some reassurance that endogenous insulin levels do not increase substantially with the development of hepatic fat, at least with the use of low-dose lomitapide (≤ 10 mg daily) for ≤ 12 weeks.*

In an additional exploratory analysis, I examined the association between maximum change in % hepatic fat during the study in the lomitapide monotherapy groups with

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absolute change in HOMA-IR as a measure of insulin resistance. Subjects without baseline insulin values were excluded from the analysis (~25% in each group). Although I did not apply any statistical tests, it's apparent that those with the largest increases in hepatic fat did not typically exhibit increases in insulin resistance, at least as measured by the HOMA-IR score (Figure 14).

Figure 14. A-004 – Max Change in % Hepatic Fat vs. Change in HOMA-IR



Source: FDA clinical reviewer's analysis of submitted A-004 datasets (OM and LB xpt).
N=22-23 per group with available data.

Effects on Lipid Profile

Changes in the lipid profile were secondary efficacy outcomes in trial A-004. Table 44 summarizes the baseline values for lipid parameters in this trial for the placebo and lomitapide monotherapy groups.

Table 44. A-004 – Mean (SD) Baseline Lipid Parameters

Parameter	Placebo (n=33)	Lomit 2.5 mg (n=34)	Lomit 5 mg (n=33)	Lomit 7.5 mg (n=34)	Lomit 10 mg (n=34)
LDL-C	137 (26)	143 (30)	138 (24)	145 (26)	147 (23)
TC	216 (33)	224 (41)	213 (29)	228 (28)	228 (31)
TG	119 (58)	118 (59)	108 (63)	148 (85)	130 (66)
ApoB	116 (18)	122 (24)	117 (24)	131 (26)	128 (19)
HDL-C	55 (14)	57 (14)	54 (12)	53 (15)	55 (16)
ApoAI	163 (28)	165 (30)	160 (24)	164 (27)	162 (30)

Source: A-004 CSR, Table 14.2.8.1.
All values are mean (SD) in mg/dL at the baseline visit.

Table 45 summarizes the placebo-subtracted % changes from baseline to week 12/LOCF for the lomitapide monotherapy groups. Because this is the longest-duration placebo-controlled trial in the lomitapide development program, I examined values both

with and without LOCF imputation as a sensitivity analysis. I have not shown the without-imputation values (i.e., the completers population) for brevity because the differences between analyses were modest and did not affect interpretation of the results.

Table 45. A-004 – Mean (SD) Placebo-subtracted % Changes in Lipids at Week 12/LOCF

Parameter	Lomit 2.5 mg (n=34)	Lomit 5 mg (n=33)	Lomit 7.5 mg (n=34)	Lomit 10 mg (n=34)
LDL-C	-12.6 (-24.6, -0.5)*	-15.3 (-27.3, -3.2)**	-16.0 (-28.1, -3.9)**	-32.4 (-44.4, -20.4)†
TC	-9.3 (-18.6, 0.0)	-11.4 (-20.7, -2.1)**	-14.3 (-23.6, -5.0)†	-27.1 (-36.3, -17.8)†
TG	-5.5 (-30.0, 19.0)	-4.9 (-29.4, 19.6)	-20.33 (-44.8, 4.2)	-20.6 (-44.9, 3.7)
ApoB	-10.5 (-21.5, 0.6)	-12.6 (-23.7, -1.5)*	-18.4 (-29.4, -7.3)†	-33.3 (-44.3, -22.2)†
HDL-C	-6.0 (-15.0, 3.0)	-3.1 (-12.0, 5.9)	-5.0 (-13.9, 4.0)	-17.0 (-26.1, -7.8)†
ApoAI	-4.1 (-12.1, 3.8)	-4.3 (-12.3, 3.8)	-9.2 (-17.2, -1.2)*	-15.5 (-23.5, -7.5)†

Source: A-004 CSR, Table 14.2.8.1

* P<0.05; ** P<0.01; † P<0.001 for between-group comparisons with placebo as the referent. 95% CIs are noted in parentheses.

Reviewer Comments:

1. *These data support a dose-dependent effect of lomitapide on the reduction of LDL-C, total cholesterol, and apoB.*
2. *This trial failed to detect a statistically significant effect of lomitapide on TG compared with placebo. The mean and median % changes from baseline to week 12/LOCF in the placebo group were +11.0% and +3%, respectively, corresponding to mean and median absolute changes of +4.6 and 3 mg/dL. For the lomitapide monotherapy groups, the median absolute within-group changes from baseline to week 12/LOCF were -5, +1, -18, and -13 mg/dL for the lomitapide 2.5, 5, 7.5, and 10 mg daily groups, respectively. Thus, the effect of lomitapide on fasting TG is modest at these doses, at best, and highly variable.*

HDL-C values dropped rather abruptly after the initiation of lomitapide with a return toward baseline over time (Figure 15). A similar profile was *not* observed for LDL-C, which decreased during the first 2 weeks and remained reasonably stable through week 12, with the most variability noted in the lomitapide 10 mg group (Figure 16).

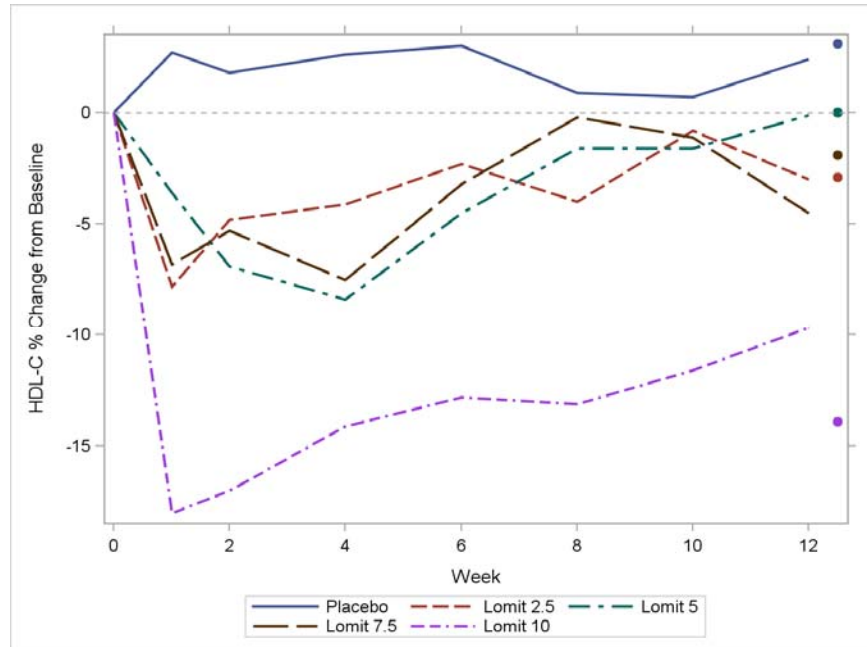


Figure 15. A-004 – % Change in HDL-C from Baseline Over 12 Weeks
Source: FDA clinical reviewer’s depiction of data in A-004 CSR, Table 14.2.8.1.
All available data at each time point were used. Dots indicate Week 12/LOCF value.

Reviewer Comment: The comparison between the week 12 and week 12/LOCF values suggest that this attenuation was not entirely the result of early discontinuations.

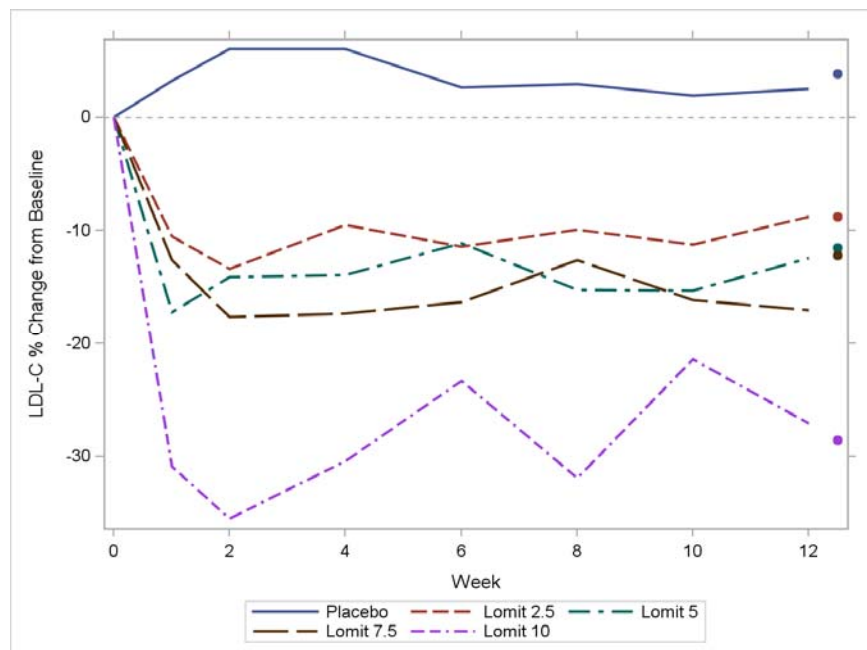


Figure 16. A-004 – % Change in LDL-C from Baseline Over 12 Weeks
Source: FDA clinical reviewer’s depiction of data in A-004 CSR, Table 14.2.8.1.
All available data at each time point were used. Dots indicate Week 12/LOCF value.

A-004 Safety Results

Table 46 summarizes exposure to study drug across groups in trial A-004.

Table 46. A-004 – Extent of Exposure

Days on Study Drug	Pbo (n=33)	Lomitapide (mg daily)				Lomitapide 5 mg daily +		
		2.5 (n=34)	5 (n=34)	7.5 (n=34)	10 (n=35)	Atv (n=28)	Feno (n=33)	Eze (n=29)
Mean (SD)	81 (12)	71 (26)	69 (25)	75 (22)	62 (33)	72 (29)	73 (25)	79 (15)
Median	84	83	83	84	83	84	84	84
Min, Max	26, 91	2, 90	4, 86	7, 89	4, 99	6, 89	4, 90	16, 91

Source: A-004 CSR, Table 14.1.8.

Adverse Events

Table 47 presents an overall summary of the treatment-emergent adverse events in the ITT population. There were three SAEs in this trial, described in Section 7.3.2 (p. 159). There were no deaths.

Table 47. A-004 – Adverse Event Summary

	Pbo (n=33)	Lomitapide (mg daily)				Lomitapide 5 mg daily +		
		2.5 (n=34)	5 (n=34)	7.5 (n=34)	10 (n=35)	Atv (n=28)	Feno (n=33)	Eze (n=29)
Any TEAE	20 (61%)	31 (91%)	30 (88%)	29 (85%)	32 (91%)	24 (86%)	29 (88%)	25 (86%)
SAE*	0	1 (3%)	0	0	2 (6%)	0	0	0
Deaths	0	0	0	0	0	0	0	0
D/C Due to TEAE	1 (3%)	7 (21%)	8 (24%)	5 (15%)	11 (31%)	4 (14%)	4 (12%)	2 (7%)

Source: A-004 CSR, Table 12-1.

TEAE = treatment-emergent adverse event.

* SAE = serious adverse event. For this table, these events are limited to those occurring after first dose of lomitapide. Two additional subjects had SAEs after enrollment but prior to first dose of study drug.

Among the 227 subjects who received any dose of lomitapide, 41 (18%) discontinued because of an AE. In contrast, one (3%) of the 33 subjects assigned to placebo discontinued because of an AE. The majority of discontinuations (41 of 42) occurred in subjects who received lomitapide (monotherapy or in combination). Similar to other studies, adverse events in the Gastrointestinal Disorders SOC contributed the most to premature discontinuation. Diarrhea contributed to 26 of 42 subjects discontinuing prematurely. Other GI disorders leading to discontinuation included nausea (n=7), upper abdominal pain (n=6), abdominal pain (n=5), abdominal distension (n=2), and stomach discomfort (n=2). Three subjects discontinued as a result of arthralgia and three subjects as a result of fatigue. One subject in the lomitapide 10 mg monotherapy group and one in the lomitapide 5 mg + fenofibrate group discontinued because of elevated transaminases. Discontinuations as a result of AEs occurred most frequently in the lomitapide 10 mg group (31%).

Because this is the longest placebo-controlled trial in the lomitapide development program, I have presented the subject counts of TEAEs that were reported by ≥5% of subjects (i.e., ≥2 subjects) in a lomitapide monotherapy group *and* were more frequent

than placebo (Table 48). I have not included arms of combination therapy in this table for brevity and because of the lack of an active-control group.

Table 48. A-004 – Selected Common Treatment-Emergent Adverse Events

SOC / Preferred Term	Pbo (n=33)	Lomitapide (mg daily)			
		2.5 (n=34)	5 (n=34)	7.5 (n=34)	10 (n=35)
Gastrointestinal Disorders	14 (42%)	23 (68%)	23 (68%)	22 (65%)	30 (86%)
Diarrhea	4 (12%)	16 (47%)	15 (44%)	16 (47%)	23 (66%)
Nausea	1 (3%)	2 (6%)	8 (24%)	8 (24%)	13 (37%)
Abdominal distension	2 (6%)	3 (9%)	3 (9%)	4 (12%)	2 (6%)
Abdominal pain upper	2 (6%)	2 (6%)	2 (6%)	4 (12%)	4 (11%)
Flatulence	2 (6%)	5 (15%)	3 (9%)	1 (3%)	2 (6%)
Abdominal pain	2 (6%)	2 (6%)	3 (9%)	1 (3%)	3 (9%)
Vomiting	1 (3%)	2 (6%)	3 (9%)	1 (3%)	4 (11%)
Dyspepsia	1 (3%)	4 (12%)	1 (3%)	1 (3%)	2 (6%)
Eructation	0	1 (3%)	0	0	2 (6%)
Stomach discomfort	0	0	1 (3%)	0	2 (6%)
Infections & Infestations	4 (12%)	6 (18%)	5 (15%)	9 (26%)	5 (14%)
Influenza	0	1 (3%)	2 (6%)	0	1 (3%)
Upper respiratory infection	1 (3%)	1 (3%)	0	2 (6%)	0
Investigations	3 (9%)	7 (21%)	7 (21%)	4 (12%)	8 (23%)
ALT increased	0	3 (9%)	2 (6%)	1 (3%)	1 (3%)
AST increased	0	2 (6%)	1 (3%)	1 (3%)	1 (3%)
WBC count decreased	1 (3%)	2 (6%)	1 (3%)	0	0
Nervous System	5 (15%)	3 (9%)	9 (26%)	9 (26%)	2 (6%)
Headache	4 (12%)	2 (6%)	6 (18%)	8 (24%)	1 (3%)
Dizziness	1 (3%)	1 (3%)	2 (6%)	0	1 (3%)
General Disorders	3 (9%)	4 (12%)	8 (24%)	6 (18%)	5 (15%)
Fatigue	2 (6%)	3 (9%)	5 (15%)	3 (9%)	3 (9%)
Oedema peripheral	0	0	0	2 (6%)	0
Musculoskeletal	6 (18%)	3 (9%)	10 (29%)	3 (9%)	2 (6%)
Arthralgia	0	0	4 (12%)	0	1 (3%)
Musculoskeletal pain	0	0	2 (6%)	0	0
Pain in extremity	1 (3%)	0	2 (6%)	0	0
Respiratory, Thoracic, Mediastinal	1 (3%)	5 (15%)	2 (6%)	4 (12%)	2 (6%)
Cough	0	2 (6%)	0	1 (3%)	2 (6%)
Skin & Subcutaneous	1 (3%)	2 (6%)	3 (9%)	0	0
Metabolism & Nutrition Disorders	0	1 (3%)	0	1 (3%)	2 (6%)
Anorexia	0	0	0	0	2 (6%)
Immune System Disorders	0	0	1 (3%)	2 (6%)	1 (3%)
Seasonal allergy	0	0	1 (3%)	2 (6%)	1 (3%)
Reproductive System / Breast	0	0	2 (6%)	1 (3%)	0
Dysmenorrhoea	0	0	2 (6%)	0	0

Source: FDA clinical reviewer's analysis of submitted A-004 AE dataset (AE xpt).

Events with a non-missing start date prior to first dose are excluded.

A preferred term is listed only if it was reported by ≥5% of subjects (i.e., ≥2 subjects) and by more subjects in a lomitapide group than the placebo group.

Reviewer Comment: The AE profile in this trial is generally consistent with other phase 2 trials in the development program.

Liver-related Laboratory Values

In A-004, 11 (5%) of 227 subjects treated with any dose of lomitapide (monotherapy and combination therapy groups combined) had at least one AE reported of increased ALT and/or increased AST: 3 (9%) of the lomitapide 2.5 mg group, 2 (6%) of the lomitapide 5 mg group, 1 (3%) of the lomitapide 7.5 mg group, 1 (3%) of the lomitapide 10 mg group, and 4 (12%) of the lomitapide 5 mg + fenofibrate group. There were no AEs of increased transaminases reported for the placebo group or the lomitapide 5 mg in combination with either atorvastatin or ezetimibe groups.

Using the laboratory dataset, I identified peak ALT values for each subject and categorized them relative to the laboratory's ULN (Table 49). No subjects in the placebo group had an ALT $\geq 2x$ ULN. Use of lomitapide was associated with elevated transaminases, and although there wasn't a definite dose-response across the range of 2.5 to 10 mg doses, the lomitapide 10 mg daily group had the highest proportion of markedly elevated transaminases (3 [9%] of 35 subjects with peak ALT values of 10.8x, 11.6x, and 11.7x ULN).

Concomitant total bilirubin, alkaline phosphatase, and INR levels were $<1.5x$ ULN for all except 2 subjects with ALT $\geq 3x$ ULN:

- Subject 10013 (lomitapide 10 mg) had an ALT 290 IU/L (11.6x ULN) at the final study visit at week 12 (at the preceding week 10 visit, ALT was 22 IU/L). At week 12, alkaline phosphatase was 132 U/L (1.8x ULN) but total bilirubin was 0.3 mg/dL and INR 0.9.
- Subject 04016 (lomitapide 5 mg + fenofibrate) had an ALT 112 IU/L (4.5x ULN) at week 4 with an alkaline phosphatase 125 U/L (1.7x ULN), but total bilirubin 0.6 mg/dL and INR 0.9.

Table 49. A-004 – Peak ALT Abnormalities

Peak ALT	Pbo (n=33)	Lomitapide (mg daily)				Lomitapide 5 mg daily +		
		2.5 (n=34)	5 (n=34)	7.5 (n=34)	10 (n=35)	Atv (n=28)	Feno (n=33)	Eze (n=29)
$\geq 2x, <3x$ ULN	0	0	3 (9%)	2 (6%)	4 (11%)	0	4 (12%)	3 (10%)
$\geq 3x, <5x$ ULN	0	1 (3%)	1 (3%)	0	2 (6%)	1 (4%)	2 (6%)	0
$\geq 5x, <10x$ ULN	0	1 (3%)	0	1 (3%)	0	0	0	0
$\geq 10x, <20x$ ULN	0	0	0	0	3 (9%)	0	1 (3%)	0

Source: FDA clinical reviewer's analysis of submitted A-004 laboratory dataset (LB xpt).

Vitamins A & E

In trial A-004, Vitamins A and E were measured at every study visit from baseline through week 12 (end-of-study) or early termination.

There were no statistically significant changes in Vitamin A from baseline to week 12 (with or without LOCF), compared with placebo. Although the large variability and small sample size limited power to detect differences, the point estimates for the mean absolute changes from baseline were modest and did not show a convincing dose-response. Baseline mean Vitamin A levels among the placebo and lomitapide monotherapy groups ranged from 59.6 to 62.4 $\mu\text{g/dL}$; at week 12/LOCF, the absolute

mean (SD) change from baseline was +1.8 (12.0) µg/dL in the placebo group and +0.2 (11.3), +2.6 (8.03), -2.0 (12.1), and +1.7 (9.7) µg/dL in the lomitapide 2.5, 5, 7.5, and 10 mg monotherapy groups, respectively.

There were statistically significant reductions in total Vitamin E from baseline to week 12 (with or without LOCF) in the lomitapide 5, 7.5, and 10 mg monotherapy groups compared with placebo. (The groups with lomitapide 5 mg in combination with atorvastatin, fenofibrate, and ezetimibe also demonstrated statistically significant reductions compared with placebo, but these groups will not be discussed further.) Baseline mean Vitamin E levels among the placebo and lomitapide monotherapy groups ranged from 1.4 to 1.6 mg/dL; at week 12/LOCF, the absolute mean (SD) change from baseline was +0.1 (0.32) mg/dL in the placebo group and -0.1 (0.36), -0.2 (0.27), -0.2 (0.33), and -0.3 (0.39) mg/dL in the lomitapide 2.5, 5, 7.5, and 10 mg monotherapy groups, respectively. No subject decreased below the LLN (0.50 mg/dL) during the study.

The sponsor performed a post hoc analysis of the change in the ratio between Vitamin E and lipids (Vitamin E:TC+TG). Baseline mean ratios among the placebo and lomitapide monotherapy groups ranged from 4.22 to 4.68; at week 12/LOCF, the absolute mean (SD) change from baseline was +0.31 (0.93) in the placebo group and +0.04 (0.62), -0.24 (0.85), +0.04 (0.68), and -0.18 (1.16) in the lomitapide 2.5, 5, 7.5, and 10 mg monotherapy groups, respectively.

Reviewer Comment: The longitudinal profile of vitamin E mirrors those of the lipid profiles – a reduction during the first 4 weeks followed by relatively stability or slight return toward baseline. This is consistent with the association between vitamin E and lipids, especially those containing apoB, which are necessary for its transport. It is reassuring both that vitamin E did not fall below the LLN despite its decrease and that the vitamin E:lipid ratio remained stable.

Laboratory Results

Table 50 summarizes the mean (SD) values for safety laboratories at week 12/LOCF in the placebo and lomitapide monotherapy groups. Baseline mean values were similar between groups (not shown). I have not presented the lomitapide combination groups because of a lack of active controls; I did review results from these groups, however, and they did not raise safety concerns. Furthermore, the differences between the mean values with and without LOCF were modest and did not change the interpretation of these results.

Table 50. A-004 – Mean (SD) Safety Laboratory Values at Week 12/LOCF

Parameter at Week 12/LOCF	Pbo (n=33)	Lomitapide (mg daily)			
		2.5 (n=34)	5 (n=34)	7.5 (n=34)	10 (n=35)
Sodium (mEq/L)	140 (2)	140 (2)	139 (2)	140 (2)	140 (2)
Potassium (mEq/L)	4.2 (0.3)	4.2 (0.3)	4.2 (0.3)	4.4 (0.4)	4.3 (0.4)
Chloride (mEq/L)	103 (2)	104 (2)	104 (2)	103 (2)	104 (2)
Bicarbonate (mEq/L)	25.7 (2.3)	25.6 (1.9)	25.3 (2.6)	26.1 (1.5)	25.7 (2.6)

Parameter at Week 12/LOCF	Pbo (n=33)	Lomitapide (mg daily)			
		2.5 (n=34)	5 (n=34)	7.5 (n=34)	10 (n=35)
BUN (mg/dL)	13.6 (3.9)	13.4 (4.1)	12.9 (4.3)	14.1 (3.2)	13.3 (3.6)
Creatinine (mg/dL)	1.0 (0.2)	1.0 (0.2)	1.0 (0.1)	1.0 (0.1)	1.0 (0.2)
Glucose (mg/dL)	89 (9)	88 (8)	87 (7)	90 (7)	90 (9)
Calcium (mg/dL)	9.6 (0.4)	9.6 (0.4)	9.6 (0.3)	9.7 (0.4)	9.7 (0.4)
Total Protein (g/dL)	6.8 (0.5)	6.7 (0.5)	6.8 (0.4)	6.8 (0.5)	6.9 (0.4)
Albumin (g/dL)	4.2 (0.3)	4.2 (0.3)	4.3 (0.3)	4.2 (0.3)	4.3 (0.3)
WBC (10 ³ /mL)	5.8 (1.9)	5.3 (1.4)	5.8 (1.5)	5.8 (1.8)	5.9 (1.6)
Hemoglobin (g/dL)	14.0 (1.2)	13.5 (1.4)	14.0 (1.3)	13.8 (1.3)	13.9 (1.6)
Hematocrit (%)	41.7 (3.4)	40.3 (3.8)	41.5 (3.7)	41.2 (3.9)	41.2 (4.7)
Platelets (10 ³ /mL)	266 (74)	259 (86)	274 (57)	252 (69)	254 (62)
INR	1.0 (0.2)	1.0 (0.2)	1.0 (0.2)	0.9 (0.2)	0.9 (0.2)
aPTT (sec)	20.6 (1.9)	21.1 (1.8)	21.2 (2.2)	20.3 (1.5)	20.7 (1.7)
C-peptide (ng/mL)	1.8 (1.6)	1.7 (0.7)	1.6 (0.7)	1.8 (0.7)	1.8 (0.9)
Insulin (μIU/mL)	7.0 (2.5)	8.6 (4.9)	7.7 (5.5)	8.9 (5.6)	8.8 (8.2)
Median hsCRP (mg/L)	1.3	1.3	1.4	1.4	1.1

Source: A-004 CSR, Table 14.3.8.2.

Vital Signs

Table 51 describes the mean (SD) heart rate and blood pressure at baseline and week 12 (or end-of-study) for the placebo and lomitapide monotherapy groups.

Table 51. A-004 – Mean (SD) Vital Sign Measurements

	Pbo (n=33)	Lomitapide (mg daily)			
		2.5 (n=34)	5 (n=34)	7.5 (n=34)	10 (n=35)
Heart rate					
Baseline	69.5 (9.5)	67.6 (11.1)	69.8 (8.6)	71.7 (10.1)	69.2 (7.9)
Week 12/LOCF	67.1 (11.1)	68.2 (10.6)	68.7 (8.7)	71.6 (11.1)	71.1 (10.4)
Systolic BP					
Baseline	119.5 (13.9)	122.9 (11.4)	122.0 (14.4)	120.7 (13.7)	123.4 (15.1)
Week 12/LOCF	119.5 (14.4)	120.8 (16.6)	119.0 (12.5)	117.1 (12.3)	122.2 (15.2)
Diastolic BP					
Baseline	76.0 (6.8)	78.3 (8.5)	75.2 (10.2)	77.3 (9.8)	75.4 (10.3)
Week 12/LOCF	73.5 (9.2)	76.0 (10.6)	74.8 (8.6)	74.6 (8.6)	75.6 (9.2)

Source: A-004 CSR, Table 14.3.12

Reviewer Comment: No concerning signals based on central tendency of vital signs were detected in this trial. Although the mean heart rate increased 1.9 bpm from baseline to Week 12/LOCF (placebo-subtracted, +4.3 bpm) in the lomitapide 10 mg group, there is no suggestion of dose-response and a similar observation has not been made in other trials. Furthermore, in this trial, the ECG ventricular rate did not change from baseline to end-of-study in the lomitapide 10 mg group (66.4 bpm and 66.3 bpm, respectively, which was actually a -1.0 bpm placebo-subtracted change).

Weight Change

A summary of the % changes in body weight from baseline to week 12/LOCF for the lomitapide monotherapy (and placebo) groups is presented in Table 52. The two highest lomitapide dosages led to a statistically significant but modest reduction in average weight by week 12.

Table 52. A-004 – Mean (SD) % Change in Body Weight at Week 12/LOCF

Group	% Change in Body Weight from Baseline to Week 12/LOCF			Placebo-subtracted difference (95% CI)	P (vs. pbo)
	Mean (SD)	Median	Min, Max		
Placebo	0.11 (2.42)	0.4	-5.9, 7.2	-	
Lomitapide 2.5 mg	-1.59 (2.94)	-1.3	-8.0, 3.4	-1.70 (-3.5, 0.1)	0.09
Lomitapide 5 mg	-1.00 (1.98)	-1.4	-4.7, 3.2	-1.11 (-3.0, 0.7)	0.45
Lomitapide 7.5 mg	-1.81 (2.77)	-2.2	-7.2, 5.1	-1.92 (-3.8, -0.1)	0.04
Lomitapide 10 mg	-2.53 (2.59)	-1.9	-10.5, 2.2	-2.64 (-4.5, -0.8)	0.001

Source: A-004 CSR, Table 14.2.9.

Pulmonary Function

Pulmonary function was assessed by spirometry and DL_{CO} at baseline and week 12 (or end-of-study for those who discontinued early). The sponsor submitted results for FEV₁, FVC, DL_{CO}, and FEF₂₅₋₇₅ (Table 53).

Table 53. A-004 – Mean (SD) Values for Pulmonary Function Parameters at Week 12/LOCF

	Pbo	Lomitapide (mg daily)			
		2.5	5	7.5	10
N at Baseline	33	34	34	34	35
N at Week 12/LOCF	30	30	31	31	30
FEV₁ (L)					
Baseline	3.11 (0.76)	2.88 (0.77)	3.13 (0.74)	3.11 (1.02)	2.78 (0.69)
Week 12/LOCF	3.09 (0.74)	2.82 (0.79)	3.18 (0.78)	3.08 (0.94)	2.85 (0.76)
FVC (L)					
Baseline	3.96 (1.09)	3.76 (0.93)	3.97 (0.97)	3.87 (1.02)	3.57 (0.86)
Week 12/LOCF	3.94 (1.01)	3.76 (0.93)	4.03 (1.02)	3.98 (1.08)	3.68 (0.90)
DLCO (mL/min/mmHg)					
Baseline	24.0 (5.6)	22.7 (6.3)	25.3 (5.5)	23.9 (6.5)	22.2 (6.3)
Week 12/LOCF	24.1 (5.7)	22.3 (6.4)	25.6 (5.9)	23.8 (5.8)	23.1 (6.2)
FEF₂₅₋₇₅ (L/sec)					
Baseline	3.03 (0.84)	2.64 (1.20)	2.98 (0.93)	2.85 (1.14)	2.65 (0.99)
Week 12/LOCF	2.97 (0.84)	2.53 (1.12)	3.01 (1.01)	2.83 (1.33)	3.05 (2.45)

Source: A-004 CSR, Table 14.3.15

Reviewer Comment: These data do not suggest a lomitapide-associated change in pulmonary function, at least as measured by spirometry and DLCO after 12 weeks of exposure at dosages ≤10 mg daily.

Study AEGR-733-006

The last phase 2 trial in Aegerion’s development program for lomitapide aimed to investigate whether adding a low dose of lomitapide to atorvastatin 20 mg daily would reduce LDL-C more than atorvastatin alone. Trial A-003b had studied fixed-dose lomitapide 5 mg or 10 mg in combination with atorvastatin 20 mg daily for 8 weeks. In study AEGR-733-006 (“A-006”), they used a dose-escalation strategy of 2.5 mg daily x 4 weeks followed by 5 mg daily x 4 weeks.

Given that this study was short-duration, active-controlled, and used doses that are largely irrelevant to the HoFH indication under review, only a brief summary follows.

A-006 Summary of Results

This 8-week trial enrolled 44 subjects (23 atorvastatin monotherapy; 21 atorvastatin + lomitapide) and 41 completed the study. The three premature discontinuations were for AEs: two in the combination group and one in the atorvastatin monotherapy group (see below).

Overall, the mean (SD) age was 59 (7) years, 46% were men, and 42 (96%) of 44 were white. The median sum of NCEP cardiac risk factors was 2. The mean (SD) LDL-C at baseline was 178 (29) mg/dL, with a range of 109 to 227 mg/dL.

Table 54 summarizes the changes in lipid parameters for each group from baseline to weeks 4 and 8, along with the P values for the between-group comparisons.

Table 54. A-006 – Summary of Effect on Lipids

Parameter	Week 4			Week 8		
	A20 (n=23)	A20+L* (n=19)	P	A20 (n=22)	A20+L* (n=19)	P
LDL-C	-42.5 (12.7)	-51.0 (18.3)	0.004	-39.6 (14.4)	-49.9 (26.8)	<0.001
TC	-31.3 (9.2)	-38.1 (15.4)	0.003	-27.8 (12.0)	-37.8 (22.9)	<0.001
TG	-21.5 (18.3)	-17.8 (28.3)	0.99	-23.3 (21.2)	-18.9 (36.2)	0.70
Non-HDL-C	-39.6 (10.8)	-45.8 (17.7)	0.011	-36.9 (13.9)	-45.3 (26.4)	<0.001
ApoB	-33.6 (10.2)	-37.7 (17.1)	0.07	-30.6 (13.0)	-37.2 (27.2)	0.009
HDL-C	+6.7 (8.1)	-1.9 (10.7)	0.005	+13.6 (10.4)	-1.0 (13.4)	<0.001
ApoAI	+4.8 (7.5)	-7.8 (8.9)	<0.001	+0.2 (10.6)	-12.6 (10.7)	<0.001

Source: A-006 CSR, Tables 11.5-1 through 11.5-7.

Primary efficacy comparison is in ***bolded italics***.

* A20 = atorvastatin 20 mg daily; L = lomitapide 2.5 mg daily (at week 4) followed by force titration to 5 mg daily for an additional 4 weeks (week 8).

Reviewer Comments:

1. *These comparisons cannot be extrapolated to the HoFH population, as the incremental effect of lomitapide to a statin in the general population may be distinct from the incremental effect in the HoFH population where statins are less effective as a result of LDLR mutations.*

2. *Add-on lomitapide did not lower TG more than atorvastatin alone, at the doses and duration studied.*
3. *Similar to other studies, reductions in HDL-C and apoA1 were observed with the addition of low-dose lomitapide.*

With regard to safety, there were no treatment-emergent SAEs or deaths in this study. There was one SAE of diverticulitis in the atorvastatin group, but this was for an operation scheduled for abdominal symptoms that preceded study drug (and did not worsen on study drug). This SAE led to early discontinuation. The AEs leading to early discontinuation for 2 subjects in the combination therapy group were elevated ALT for Subject 03-009 (64 IU/L on day 0, 67 IU/L at week 1, and 82 IU/L at early termination visit), and gastrointestinal symptoms for Subject 05-009 (diarrhea, worsening heartburn, gas, stomach ache began on day 2, leading to discontinuation on day 8).

Adverse events that occurred in at least 2 subjects and with greater frequency in the combination therapy group compared with atorvastatin alone were diarrhea (10 vs. 3 subjects), dyspepsia (3 vs. 0), flatulence (4 vs. 2), nausea (3 vs. 2); urinary tract infection (3 vs. 0); ALT increased (4 vs. 0); headache (3 vs. 2); and dermal cyst (2 vs. 0).

Given the low doses of lomitapide used in this study, its short duration, and the fact that a clinically significant lomitapide-atorvastatin interaction is not expected at the doses studied (see Section 7.5.5, p. 242), I did not review all laboratories, vital signs, and ECGs in detail. Shift tables and measures of central tendency did reveal increases in ALT and AST, however, similar to other studies. There were 3 subjects in the combination therapy group with peak ALT levels $\geq 3x$ ULN (4.5x, 4.7x, and 4.8x); two occurred at week 8 (final visit) and one at week 6. There were no concomitant increases in total bilirubin, alkaline phosphatase, or INR. No subjects in the atorvastatin monotherapy group had ALT levels $\geq 3x$ ULN.

Phase 2 and 3 HoFH Trial Designs

This section describes the study designs of the phase 3 pivotal trial and the phase 2 pilot trial of lomitapide in HoFH. The information herein was primarily derived from the study protocols themselves and not from the final clinical study reports. Efficacy and safety results from the HoFH trials are presented in Sections 6 and 7, respectively.

Study UP1002/AEGR-733-005 (“HoFH-pivotal”)

Title: “A phase III study of microsomal triglyceride transfer protein (MTP) inhibitor AEGR-733 in patients with homozygous familial hypercholesterolemia on current lipid-lowering therapy”

Study Centers and Study Period

Eleven study centers in United States (2), South Africa (3), Canada (2), and Italy (4).
First informed consent: 18 December 2007
Data cut-off for initial NDA submission (all had completed week 56): 12 April 2011
Data cut-off for SAEs and other AEs of interest (on submission): 08 September 2011
Data cut-off for 120-day safety update (all had completed week 78): 31 December 2011

Trial Objectives & Design

Primary Objective

- Evaluate the efficacy of lomitapide as defined by % change in LDL-C at the maximum tolerated dose (MTD) compared with baseline after 26 weeks of treatment in combination with other lipid-lowering therapy in patients with HoFH

Secondary Objectives

- To evaluate other lipid parameters, long-term safety, % change in hepatic fat, and PK of lomitapide in combination with other lipid-lowering agents in patients with HoFH as assessed by
 - % change in TC, non-HDL-C, HDL-C, TG, VLDL, Lp(a), and apolipoproteins B (apoB) and AI (apoAI)
 - Changes in liver-associated enzymes (AST, ALT, total bilirubin, alkaline phosphatase)
 - Number of subjects developing biopsy-proven evidence of steatohepatitis or other liver pathologies
 - Changes in safety laboratories, reported AEs, physical exam, QT or QTc, serum levels of fat-soluble vitamins, serum levels of fatty acids, weight, hsCRP, hepatic fat, pulmonary function tests
 - PK parameters

Study Design

- Phase 3 clinical trial to evaluate both the efficacy and long-term safety of lomitapide at the MTD
- Single-arm multicenter trial involving 29 subjects with HoFH who received lomitapide following a protocol-specified escalation of dose to the MTD
- Duration: ~6-week run-in period to stabilize current lipid-lowering therapy (including apheresis if applicable) + 78 weeks treatment, comprising a 26-week efficacy phase and a 52-week safety phase
 - Note: At original NDA submission, complete data were presented through the week 56 assessment.
- Dose-escalation: Daily doses of 5 mg x 2 weeks followed by 10, 20, 40, and 60 mg at 4-week intervals as tolerated; further titration to 80 mg was an option if certain safety and efficacy criteria were met
- During the safety phase, the dose of lomitapide was not to be increased above the MTD established during the efficacy phase

- Lipid-lowering therapy and LDL apheresis schedule were to remain constant during the efficacy phase (through week 26) but could be changed during the safety phase (week 26 onward).
- Criteria with regard to measuring LDL-C in relation to LDL apheresis schedule were established.
- Off-drug follow-up visit at week 84 (6 weeks post-treatment) for subjects who did not enroll in the optional extension study (AEGR-733-012; hereafter, "HoFH-extension").

Reviewer Comment: During the development program for lomitapide, the Agency agreed to the plausibility of a single-arm trial serving as the only pivotal phase 3 trial to support an indication in the HoFH population. The six-week run-in period, which was intended to stabilize concomitant lipid-lowering therapy, should reduce the magnitude of regression to the mean when assessing efficacy. Furthermore, placebo groups in other parallel-group randomized trials of lipid-lowering agents have generally exhibited very little change in LDL-C from baseline over time.

Trial Population

The protocol anticipated the enrollment of 25 adult subjects with HoFH.

Inclusion Criteria (selected)

- Males and females ≥ 18 years of age
- Diagnosis of functional homozygous FH by at least one of the following clinical criteria:
 - documented functional mutation(s) in both LDL receptor alleles or alleles known to affect LDL receptor functionality, OR
 - skin fibroblast LDL receptor activity $<20\%$ normal, OR
 - untreated TC >500 mg/dL and TG <300 mg/dL AND both parents with documented untreated TC >250 mg/dL
- Body weight ≥ 40 kg and <136 kg (due to MRI weight limit)
- Negative screening pregnancy test if female of child-bearing potential

Exclusion Criteria (selected)

- Uncontrolled hypertension: SBP >180 mmHg, DBP >95 mmHg on medication
- History of chronic renal insufficiency (serum creatinine >2.5 mg/dL)
- History of biopsy-proven cirrhosis or abnormal LFTs at screening (AST or ALT $>2x$ ULN and/or total bilirubin >1.5 mg/dL unless patient has unconjugated hyperbilirubinemia due to Gilbert's syndrome)
- Chronic hepatitis B or hepatitis C (positive for HBsAg or HepC Ab)
- Male subjects reporting >2 drinks/day or females reporting >1 drink/day (1 drink = 12 oz beer, 1 oz hard liquor, 5 oz wine)
- Any major surgical procedure <3 months prior to screening visit
- Cardiac insufficiency defined by NYHA Class III or IV
- Previous organ transplantation
- History of non-skin malignancy within previous 3 years

- Known significant gastrointestinal bowel disease or malabsorption (e.g., inflammatory bowel disease or chronic pancreatitis requiring use of daily pancreatic enzymes)
- Certain medications known to be potentially hepatotoxic, especially those that can induce microvesicular or macrovesicular steatosis. These include, but are not limited to, Accutane, amiodarone, heavy acetaminophen use (4g/day >3x/week), methotrexate, tetracyclines, and tamoxifen
- Documented diagnosis of any of the following pulmonary conditions: asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis
- Documented diagnosis of any of the following liver diseases: nonalcoholic steatohepatitis, alcoholic liver disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, Wilson's disease, hemochromatosis, α_1 -anti-trypsin deficiency.
- Current use of corticosteroids or betaine

Study Conduct & Schedule

Study Schedule Highlights

At visit 1 (screening), potential subjects signed informed consent and underwent a history and physical, ECG, and blood/urine samples for laboratory testing. In addition, a dietician met with subjects at visit 1 to instruct them to follow a *diet supplying <20% energy from fat*; the dietician was to review current eating habits, point out needed changes, address potential adherence problems, and review detailed diet instructions. Subjects were provided information to call or schedule a meeting with the dietician on an as-needed basis during the study.

Eligible subjects were contacted and instructed not to change concomitant lipid-lowering therapy for ≥ 6 weeks before baseline (and through week 26). After a minimum of 4 weeks from the start of this run-in period, subjects returned for visit 2 (week -2), at which time they were instructed to start taking *dietary supplements of vitamin E and fatty acids*.

After completing at least 6 weeks of a run-in period, subjects returned for visit 3 (week 0), where they underwent the baseline physical examination, vital signs, ECG, laboratories, Gastrointestinal Symptom Rating Scale (GSRS) questionnaire, liver imaging (MRI/NMRS), and PFTs with DLCO. Two-day diet records were to be returned. Lomitapide 5 mg daily was initiated at this visit.

Visits 4 through 10 occurred at weeks 2, 6, 10, 14, 18, 22, and 26 (± 3 days). The lomitapide dose was escalated at each visit, as tolerated (see below), through 5, 10, 20, 40, and 60 mg daily. *Although LDL-C values were available to investigators, the protocol did not specify LDL-C criteria that would preclude dose escalation.* The increase to 60 mg (intended maximum dose) was scheduled to occur at week 14 (visit 7) if the escalation occurred without complication, and primary efficacy was assessed at week 26 (visit 10). Each visit included a physical examination, vital signs, ECG, laboratory evaluation, GSRS, recording of alcohol consumption, pill count, and AE

monitoring. Diet records were returned at each of these visits 4-7 and 10. Liver imaging and PFTs were performed at the primary efficacy endpoint.

The safety phase began after the efficacy endpoint at week 26. At safety-phase visits 11 through 15 (weeks 36, 46, 56, 66, and 78 ± 2 weeks), subjects underwent physical exam, vital signs, ECG, laboratory evaluation, GSRS, recording of alcohol consumption, pill count, and AE monitoring. Diet records were returned at weeks 36 and 78. Liver imaging and PFTs were performed at weeks 56 and 78.

On the recommendation of the DSMB, additional time points only for liver monitoring were implemented in February 2009. In addition to the time points described above, ALT, AST, total bilirubin, and alkaline phosphatase were measured at weeks 31, 41, and 51; therefore, in the final protocol, liver-related laboratory tests were obtained at a minimum of every 4-5 weeks until week 56.

Visit 15 (week 78) was the final visit for subjects who proceeded into the optional HoFH-extension study. Patients who did not enroll into the extension were asked to return for visit 16 (week 84), six weeks after discontinuing study drug. This visit included a physical examination, vital signs, ECG, laboratory evaluation, GSRS, liver imaging, PFTs, and AE monitoring. Subjects who discontinued early were also asked to return for an early-termination visit that included these assessments.

Table 55 summarizes the schedule of selected assessments.

Table 55. Timing of Selected Assessments in HoFH-pivotal

Assessment	Baseline or Prior	Efficacy Phase	Safety Phase	Follow-up
Liver imaging	0	26	56, 78	84
PFTs with DLCO	0	26	56, 78	84
ECG	0	2, 6, 10, 14, 18, 22, 26	36, 46, 56, 66, 78	84
Liver labs	Screening, 0	2, 6, 10, 14, 18, 22, 26	31, 36, 41, 46, 51, 56, 66, 78	84
ADEK assessment	-2, 0	2, 6, 10, 14, 18, 22, 26	36, 46, 56, 66, 78	84
Fatty acid profile	-2, 0	2, 6, 10, 14, 18, 22, 26	36, 46, 56, 66, 78	84
Fasting lipid panel	-2, 0	2, 6, 10, 14, 18, 22, 26	36, 46, 56, 66, 78	84
GSRS	0	2, 6, 10, 14, 18, 22, 26	36, 46, 56, 66, 78	84
EtOH consumption	Screening, 0	2, 6, 10, 14, 18, 22, 26	36, 46, 56, 66, 78	84
Diet records	0	2, 6, 10, 14, 26	36, 78	

Source: Derived from UP1002 protocol v9.0 (03 June 2011), Appendix A.

ADEK assessment: Serum concentrations of the individual vitamins and β-carotene. Vit K included indirect (PT/INR) and direct (carboxylation of serum osteocalcin) measurement.

Fatty acid profile: linoleic acid and alpha-linolenic acid, EPA, DHA, arachidonic acid, eicosatrienoic acid
GSRS = Gastrointestinal Symptoms Rating Scale

A schematic of the post-baseline study design is shown in Figure 17.

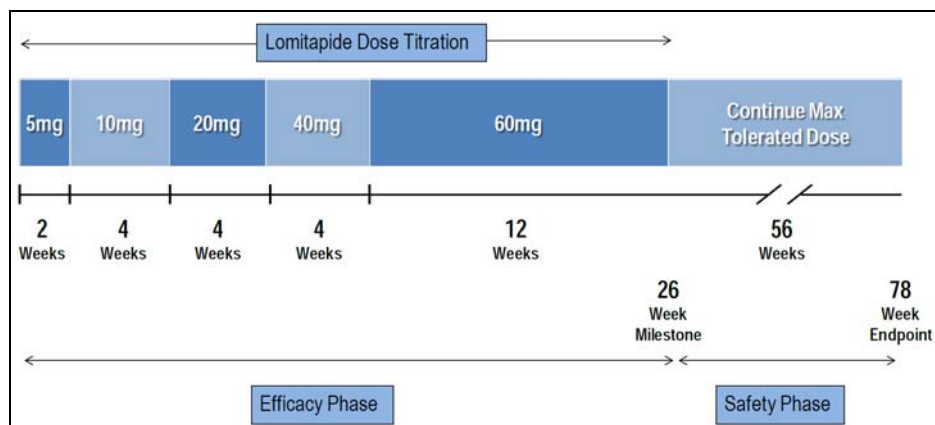


Figure 17. Study Schematic (Post-Baseline)

Source: UP1002/AEGR-733-005 CSR, Figure 1.

Treatment

The phase 2 HoFH study (UP1001) was the first to employ a dose-escalation algorithm, which led to improved tolerability with regard to GI adverse effects (notably, diarrhea); therefore, a dose-escalation scheme was used in the pivotal phase 3 trial as well.

Beginning at visit 2, *approximately two weeks before starting study drug*, subjects were instructed to begin taking daily, sponsor-provided dietary supplements to supply approximately 400 IU vitamin E, 200 mg linoleic acid (LA), 110 mg eicosapentaenoic acid (EPA), 220 mg alpha-linolenic acid (ALA), and 80 mg docosahexaenoic acid (DHA). They were told to continue this supplement throughout the study.

Criteria for Dose Escalations up to 60 mg Daily

At visits where study drug dosage was scheduled for escalation (visits 4, 5, 6, 7; for visit 8, see below), liver-related tests must have been reviewed to confirm the subject did not meet “level 3” or “level 4” hepatotoxicity (see below for definitions). Once confirmed, the study site would contact the subject to notify him/her to escalate the dosage. *If the subject met level 3 or level 4 hepatotoxicity, the subject was to be notified to continue to take the current dose and come back for repeat measurements at least 7 days after the date of the last visit.*

Criteria for Dose Escalation from 60 mg to 80 mg Daily

If a subject met the following three criteria, they would be eligible to titrate to a lomitapide dosage of 80 mg daily:

1. ALT, AST, and total bilirubin within normal range at visit 8 (i.e., after 4 weeks of 60 mg daily). Exception could be given if total bilirubin was due to unconjugated bilirubin from confirmed Gilbert’s syndrome or hemolysis with a subsequent normal value;
2. Subjects of normal or below-normal body weight ($BMI \leq 24.9 \text{ kg/m}^2$) could not have weight loss $\geq 3\%$ based on body weight measured at any visit during weeks 2 through 18 (visits 4-8) compared to baseline (visit 3);
3. LDL-C $\geq 200 \text{ mg/dL}$ at visit 8

Guidelines for Dosage Modification or Interruption

The principal investigator and/or DSMB had authority to reduce study drug dosage or discontinue study drug for safety concerns. Actions for liver-related events during the trial are summarized in Table 56.

Table 56. HoFH-pivotal – Protocol Actions in Response to Potential Liver-related Events

Event	Description	Action
Liver biopsy with type 3 or type 4 NASH	N/A	Permanent study drug discontinuation
Liver dysfunction with asterixis	Grade 3 hepatic AE	
Liver dysfunction with encephalopathy or coma	Grade 4 hepatic AE	
<i>Confirmed*</i> ALT/AST ≥ 10 x ULN (or ≥ 200 IU/L above an abnormal baseline value)	Level 4 hepatotoxicity	Immediate discontinuation, report to DSMB, weekly visit until resolution. (See footnote for Canada-specific actions.**)
ALT/AST ≥ 20.0 x ULN on any single measurement		
ALT/AST > 5 xULN <i>and</i> total bilirubin > 2 x ULN <i>without symptoms</i>		
<i>Confirmed</i> alkaline phosphatase > 5 x ULN		
Total bilirubin ≥ 3.0 mg/dL in the absence of Gilbert's syndrome or hemolysis		
ALT/AST 5.0-9.9x ULN (or > 100 but < 200 IU/L above abnormal baseline)	Level 3 hepatotoxicity	If confirmed, reduction in dose to previous tolerated dose followed by repeat assessment after being on the reduced dose 7 days. If still level 3 but abnormal measurements falling by $\geq 20\%$, dose kept the same with weekly reassessments until resolution of level 3. If falling by $< 20\%$, dose reduced further to the previous tolerated dose.
Resolution of level 3 hepatotoxicity during efficacy phase (weeks 0-26)	N/A	Dose could be escalated again per original protocol with ALT/AST drawn at 1 and 2 weeks after reaching the dose at which the level 3 abnormality occurred.
Resolution of level 3 hepatotoxicity during safety phase (weeks 26-78)	N/A	Dose could be escalated again per original protocol but not beyond MTD established during efficacy period.
ALT/AST 2.0-4.9x ULN (or > 50 but ≤ 100 IU/L above abnormal baseline)	Level 2 hepatotoxicity	No action necessary
ALT/AST 1.1-1.9x ULN (or ≤ 50 IU/L above abnormal baseline)	Level 1 hepatotoxicity	No action necessary
Any change in hepatic fat	N/A	No action necessary

Source: FDA reviewer's summary of HoFH-pivotal protocol.

* "Confirmed" indicates two measurements ≥ 7 days apart.

** In Canada, ALT/AST ≥ 10 x ULN prompted a repeat blood draw *within 3 days* of the first value meeting this criterion to ensure the elevation had not exceeded 20xULN. If this occurred, study drug was to be withdrawn immediately. If the day +3 measurement showed value(s) < 10 x ULN, then the day +7 confirmation was not required; otherwise, the day +7 draw was used to guide further testing, dose modification/interruption, etc.

In addition, subjects with below-normal body weight (BMI <18.5 kg/m²) at anytime during the study who continued to lose weight, despite appropriate attempts at corrective measures, and who were deemed at clinical risk in the judgment of the treating investigator were to be discontinued and followed until an acceptable stable weight was reached.

Stopping Rules of Entire Study

The protocol specified that the entire study would be terminated if any subject developed fulminant hepatitis thought related to study drug, regardless of clinical outcome, or if at least three patients developed “clinically important drug-induced liver disease, defined as any elevation of ALT, AST, or alkaline phosphatase with increased serum total bilirubin ≥3.0 mg/dL in the absence of Gilbert’s syndrome and hemolysis, or type 4 NASH.”

Diet

Subjects met with a nutritionist/registered dietician at the screening visit (visit 1) for instruction on how to consume <20% energy from fat and the possible relationship between dietary fat intake and gastrointestinal side effects (steatorrhea). In addition, subjects were told about the effects of lomitapide on the liver and that alcohol may exacerbate liver abnormalities. They were encouraged to avoid alcohol completely, but at least limit to ≤1 drink/day (women) or ≤2 drinks/day (men). Diet records were periodically collected (Table 55).

Assessment of Compliance

A protocol deviation was defined as any time that >2 consecutive doses are missed given the relatively long half-life of lomitapide. Study medication was provided as capsules in bottles; the pharmacist would dispense the appropriate bottle or combination of bottles from the following three selections: 25 count of 5 mg; 65 count of 20 mg; 100 count of 20 mg. The subjects were instructed to bring their bottles of study drug to every clinical visit after enrollment.

Gastrointestinal Symptom Rating Scale

According to the sponsor, the GSRS was originally constructed for measuring changes in psychopathology. On the basis of “clinical experience and reports in the literature on gastrointestinal symptoms of patients with irritable bowel syndrome and peptic ulcer disease, a selection of relevant items was made. The original questionnaire is an interview-based rating scale but has been modified to become a self-administered questionnaire.” Regarding scoring, the questionnaire contains 15 items and uses a 7-item Likert scale, where 1 represents the most positive option and 7 the most negative. A mean value for the items in each dimension is calculated: diarrhea (3 questions), indigestion (4), constipation (3), abdominal pain (3), reflux (2). These data will not be presented in this review.

Safety Considerations

Safety was monitored with

- physical examinations, including vital signs and weight/BMI measurement
- laboratory assessments (hematology, clinical chemistry, urinalysis)
- fat-soluble vitamin levels
 - Serum concentrations of vitamins A, D, and E, with vitamin E also expressed as the ratio of vitamin E/lipids (TC+TG)
 - Indirect assessment of vitamin K via PT/INR
 - Direct assessment of vitamin K via carboxylation of serum osteocalcin
- β -carotene levels
- fatty acid profile: LA, ALA, EPA, DHA, arachidonic acid (AA), and eicosatrienoic (Mead) acid
- pulmonary function testing (see below)
- measurement of hepatic fat (see below)
- electrocardiograms (see below)
- AE monitoring

Adverse Events – Definitions

- *AE*: untoward medical occurrence in a subject participating in a clinical trial regardless of causal relationship with the study drug
- *Serious AE (SAE)*: any AE that results in death; is life-threatening (at immediate risk of death from the event as it occurred); requires inpatient hospitalization (overnight stay) or prolongs a current hospitalization; causes a persistent or significant disability/incapacity; or is a congenital anomaly/birth defect in the offspring of a subject who received study drug. Furthermore, it may be an event that requires intervention to prevent one of these outcomes.
- *Intensity*: CTCAE was used for hepatic or gastrointestinal AEs. Otherwise, the investigator assigned intensity as mild (no limitation of usual activities or only slight discomfort), moderate (limitation of usual activities or significant discomfort), or severe (inability to carry out usual activities or very marked discomfort).
- *Relationship to Study Drug*: Assigned by the investigator: definite, probable, possible, unlikely, none. Each is defined in the protocol.

Vital Signs

Vital signs included blood pressure and heart rate after sitting for 5 minutes, temperature, and respiration rate.

Laboratory Measurements

Except for urine pregnancy tests, laboratory measurements were performed by central facilities: lipids, chemistry, hematology, and urinalysis samples were analyzed by PPD (Highland Heights, KY for US/Canada; Zaventem, Belgium for Italy/South Africa); fatty acid levels were subcontracted to Mayo Medical Laboratories by the Cleveland Clinic (Cleveland, OH); osteocalcin levels were determined at CCB-R-Synarc (Lyon, France).

ECG – Local & Central

The ECG was evaluated locally at the site, including an assessment of the overall ECG (normal, abnormal, clinical significance of any abnormalities), heart rate, and the PR, QRS, QT, and machine-determined QTc intervals. In addition, the sponsor used a core ECG laboratory to review copies of the paper ECGs obtained at each study site, blinded with respect to patient identifiers and visit. Interval durations (RR, PR, QRS, QT) were determined by one trained analyst using manual caliper placement on three consecutive beats. A cardiologist verified the interval durations and performed a morphology analysis. Heart rate and the corrected QT interval based on Fridericia's formula (QTcF) were calculated.

Hepatic Fat

Hepatic lipid content was assessed by MRI/NMRS at weeks 0, 26, 56, and 78. In addition, for subjects who did not enter the optional extension study, an evaluation was to be performed 6 weeks after stopping study drug. The NMRS results were primary; the MRI results were to be compared with NMRS to assess the viability of using MRI alone in future studies. For patients with contraindications to MRI/NMRS, a CT scan or ultrasound could be considered, but quantitative data were not obtained from CT/ultrasound.

Pulmonary Function

Spirometry was performed based on preclinical data that raised a concern for pulmonary phospholipidosis. This included forced vital capacity (FVC), forced expiratory volume during 1 second (FEV₁), forced expiratory flow 25-75% (FEF₂₅₋₇₅), and carbon monoxide lung diffusion (DLCO).

Weight

Weight was measured at each visit, and subjects of normal or below-normal body weight (≤ 24.9 kg/m²) with weight loss ≥ 1.5 kg since the preceding visit would be instructed by the dietician on how to increase caloric intake.

Data Safety Monitoring Board

An independent DSMB was established for this trial: Michael Davidson, MD (Chair; lipidologist), David Waters, MD (cardiologist), James Lewis, MD (hepatologist), and Robert McCarter, PhD (biostatistician) replaced by Michael Szarek, PhD (biostatistician). The DSMB was to review safety data on an ongoing basis and to convene after a minimum of 2 patients completed 6 weeks of treatment as well as after all patients had completed week 26 and week 56.

Reviewer Comments: The DSMB reviewed patient-level data regularly and provided feedback regarding dose adjustments, patient counseling (e.g., reducing alcohol intake), etc. Essentially, every patient that participated in this protocol who had a liver-related abnormality had a virtual consultation with hepatologist Dr. James Lewis through laboratory and narrative review on a regular basis.

Review of the DSMB minutes reveals that even late in the trial, the DSMB had concerns regarding liver safety; during meetings in May and July 2010, the DSMB suggested institution of an LDL-C cutoff at which dose escalation would not occur. At

that time, Aegerion noted that there were only 4 subjects in the trial who had not yet completed the efficacy phase, and those subjects were scheduled to complete visit 10 by September 2010. Because a protocol amendment might not have received IRB/EC approval for implementation before that time, the DSMB recommended distributing a protocol amendment to the sites with a letter indicating that IRB/EC approval had not yet been received, but that requests for a protocol waiver/deviation from the medical officer were possible. Aegerion reviewed LDL-C levels from the four subjects who could still potentially undergo dose titration and determined that the recommended protocol amendment would be unlikely to affect study conduct; therefore, this suggestion was not implemented.

Endpoints & Assessments

As previously mentioned, subjects were expected to be treated with concomitant lipid-lowering therapy, including LDL apheresis in many cases, during this study. All lipid-lowering therapies were to remain stable during the six-week run-in period and throughout the efficacy phase (through week 26). Only after week 26, if LDL-C levels dropped below 100 mg/dL, could a subject's concomitant lipid-lowering therapies be decreased upon consultation with the physician who managed the subject's dyslipidemia.

Definition of Baseline Lipid/Lipoprotein Parameters

Baseline values of the lipid and lipoprotein parameters were the mean of the measurements at visits 2 and 3 (4 weeks into the 6-wk run-in period and initiation of study drug, respectively).

Apheresis Considerations for Evaluation of Efficacy

For patients receiving apheresis, efficacy was to be evaluated on the basis of pre-apheresis lipid levels. Once the apheresis schedule is established during the run-in, the time point for lipid assessment was to be maintained relative to the previous apheresis treatment in order to perform all measurements at the same point on the LDL-rebound curve. For visits 2, 3, 8, and 10 (4 wks into the 6-wk run-in, drug initiation, week 18 [anticipated on 60 mg x 4 wks], and week 26 [efficacy endpoint]), fasting lipids were to be "drawn just prior to the apheresis treatment and apheresis must occur +/- 1 day from the regimen established during the run-in period."

Primary Efficacy Endpoint: % change from baseline in LDL-C at 26 weeks (visit 10)

Secondary Efficacy Parameters: % change from baseline to 26 weeks (visit 10) in total cholesterol (TC), apolipoprotein B (apoB), triglycerides (TG), non-HDL-C, VLDL-C, and Lp(a).

Exploratory Efficacy Parameters: Included changes in calculated LDL-C, TC/HDL-C ratio, C-reactive protein, HDL-C, and apoA-I.

Pharmacokinetic Assessments: Sparse blood sampling of plasma levels of lopitamide were collected at baseline, all visits during the efficacy phase, and at weeks 36, 46, 56,

66, and 78 during the safety phase. Two PK blood samples were drawn at week 26, 56, and 78; at other time points, one sample was drawn.

Statistical Considerations

The clinical study report states that the final statistical analysis plan (SAP) is dated 09 August 2010 (version 1.0). The final SAP submitted in the NDA, however, is version 1.6 and dated 17 May 2011 with an amendment dated 18 November 2011.

Selected analytical considerations drawn from the SAP follow. For a comprehensive review of the statistical considerations relevant to this study and application, see Cynthia Liu's review (Office of Biometrics).

Sample Size & Power Considerations

The sample size was calculated to detect a 25% change in LDL-C, assuming a 30% standard deviation and 15% drop-out, with 90% power and a type I error of 5%. Under these assumptions, the sponsor calculated that 20 subjects would be needed. "In order to adequately assess safety, up to 26 subjects were planned for enrollment [~9% of the US population of homozygous FH]."

Populations for Analysis

The applicant defined four patient populations for analysis:

- *Intent-to-treat (ITT)*: all patients who received at least one dose of lomitapide and had a baseline and post-baseline LDL-C value. This was the primary population for efficacy analyses.
- *Safety*: all patients who took at least one dose of lomitapide. This was the primary population for safety analyses; this turned out to be identical to the ITT population for this trial.
- *Completers*: all patients in ITT who completed specific study phases
 - *Week 26 Completers*: patients who completed the 26-week efficacy phase
 - *Week 56 Completers*: patients who completed through week 56
 - *Safety Completers*: patients who completed the safety phase of the study; these subjects must have participated through the week 78 visit
- *Per-protocol (PP)*: subset of ITT, which *excluded* those that met the following criteria:
 - Baseline LDL-C values (visits 2 and 3) that differed >20%
 - Average compliance <80% or >120% during the entire efficacy phase
 - Changes in lipid-lowering therapy during the last 12 weeks of the efficacy phase
 - Changes in apheresis frequency (> ±6 days from the regimen established during run-in) for at least 2 treatments
 - Increase of 200% or decrease of 75% of dose of a lipid-lowering medication for 4 weeks or more

Primary Efficacy Analysis

The null hypothesis for the primary endpoint was that the mean % change from baseline in directly measured LDL-C at 26 weeks was 0 mg/dL (ITT population); the alternative

was that the change was not equal to 0 mg/dL. A paired t-test was to be used to analyze change from baseline unless the data were not normally distributed, in which case the Wilcoxon Signed Rank test was to be used.

For subjects with missing values at the efficacy endpoint, the LOCF method of imputation was pre-specified. In addition, a sensitivity analysis using an area-under-the-curve (AUC) approach to LDL-C outcomes was described.

Secondary Efficacy Analysis

The key secondary efficacy parameters were considered to be total cholesterol, apolipoprotein B, and triglycerides. This group of secondary endpoints was to be statistically evaluated in a sequential fashion in the order listed, each at $\alpha = 0.05$, and where significance would be claimed for an endpoint only when the previous parameter was also significant. The additional secondary parameters (non-HDL-C, VLDL-C, and Lp(a)) were to be analyzed in a similar fashion, separately from the first three parameters.

Exploratory Efficacy Analyses

Changes in calculated LDL-C were to be assessed in exploratory analyses (calculated LDL-C = total cholesterol – HDL-C – (TG/5) if TG < 400 mg/dL, otherwise missing).

Missing Data

For the primary and secondary endpoints, missing data at the week 26 (visit 10) visit were to be replaced by the last available value (LOCF). If there were missing values in the baseline determination (mean of visits 2 and 3 for lipids/lipoproteins; visit 3 for others), the last non-missing value before the date of first dose of study drug was to be used. For safety-phase analyses that calculate change from the end of efficacy (visit 10), the last non-missing value before visit 10 was to be used in the case of a missing value at visit 10.

Protocol Amendments

The original protocol under which the first patients were enrolled in 2007 at US study sites was protocol UP1002 version 5.0 (26 February 2007; first informed consent was obtained on 18 December 2007 according to submitted raw data). The protocol underwent 4 subsequent protocol amendments: v7.0 (20 May 2008), v8.0 (09 February 2009), and v9.0 (03 June 2011).

The first protocol used for sites outside of the United States was UP1002 version 7.0 (20 May 2008), also known as AEGR-733-005 version 2.0.

Reviewer Comment: All protocol amendments were reviewed. The majority of changes were additions to safety monitoring or clarifications. The three additional visits during the safety phase to measure transaminases more frequently (at weeks 31, 41, and 51) were added in the 09 February 2009 amendment. This amendment also added the requirement for retesting AST and ALT levels 1-2 weeks after rechallenge at the dose level that originally led to a level 3 hepatotoxicity event.

Study AEGR-733-012 (“HoFH-extension”)

Briefly, the protocol of the HoFH extension study largely mirrors that of the pivotal trial. Study visits occur every 12 weeks. At each visit, safety assessments include vital signs, safety laboratories (comprehensive metabolic panel, CBC, coagulation parameters, vitamin A, vitamin E, β -carotene), fasting lipids, hsCRP, urinalysis, and a urine pregnancy test. Additional assessments performed every 24 weeks include physical examination, ECG, liver NMRS/MRI, and pulmonary function tests.

Study UP1001 (“HoFH-pilot”)

Title: “A phase II open-label, dose-escalation study to determine the safety, tolerability, and efficacy of microsomal triglyceride transfer protein (MTP) inhibitor BMS-201038 in patients with homozygous familial hypercholesterolemia.”

Study Center and Study Period

Single study center: University of Pennsylvania Medical Center

First subject enrolled: 05 June 2003

Last patient last visit: 16 February 2004

Trial Objectives & Design

Primary Objective

- To determine the safety and tolerability of four doses of lomitapide given as an initial dose and then force-titrated for an additional three doses over a 16-week period.

Secondary Objectives

- % change in LDL-C, TC, TG, and VLDL-C at the end of each 4-week dose period compared with the baseline value and with the end of the previous dose phase(s)
- changes in other plasma apolipoproteins (A-I, A-II, B, C-III, E) and Lp(a)

Study Design

- Phase 2 clinical trial to evaluate the safety, tolerability, and pharmacodynamics of lomitapide
- Single-arm, single site trial involving a minimum of 6 subjects with HoFH who received lomitapide following a protocol-specified dose-escalation regimen (ranging 0.03 mg/kg/d to 1.0 mg/kg/d)
- Concomitant lipid-lowering therapy and LDL apheresis was *not allowed*
- Duration: 22 weeks (comprising 15 visits)

Trial Population

The protocol anticipated the enrollment of a minimum of six subjects with HoFH.

Inclusion Criteria (selected)

- Males and females $\geq$ 13 years of age
- Clinical diagnosis of HoFH and one of the following:
 - documented functional mutation in both LDL receptor alleles, *or*
 - skin fibroblast LDL receptor activity $<20\%$ normal, *or*
 - TC >500 mg/dL and TG <300 mg/dL and both parents have documented TC >250 mg/dL
- Body weight ≥ 40 kg
- Negative screening pregnancy test if female of child-bearing potential
- *Subjects must be willing and able to go off all lipid-lowering medications, dietary supplements (psyllium preparations) and LDL apheresis within 4 weeks prior to the baseline visit until the end of the study.*

Reviewer Comment: *The last inclusion criterion listed distinguishes the pilot and pivotal HoFH trials.*

Exclusion Criteria (selected)

- Uncontrolled hypertension defined as SBP >180 mmHg, DBP >95 mmHg
- History of chronic renal insufficiency (serum creatinine >2.5 mg/dL)
- History of liver disease or abnormal "LFTs" at screening ($>3x$ ULN)
- Any major surgical procedure occurring <3 months prior to the screening visit
- Cardiac insufficiency defined by NYHA Class III or IV
- History of a non-skin malignancy within the previous 5 years
- History of alcohol or drug abuse

Study Conduct & Schedule

Study Schedule Highlights

After an initial screening by telephone, potentially eligible patients were invited to a screening visit. At the screening visit, they signed informed consent and underwent a medical history, physical examination, ECG, weight, height, waist circumference, sitting BP, heart rate, fasting laboratory assessment, and urine pregnancy test if applicable. Subjects received dietary counseling at the screening visit and were instructed to begin taking the sponsor-supplied multivitamin (see below).

All lipid-lowering therapies (medications and LDL apheresis, if applicable) were to be stopped within 4 weeks prior to the subsequent baseline visit and throughout the study.

Subjects returned for a baseline visit (day 0) 1-2 weeks after the screening visit. They were instructed to begin taking a once-daily dosage of 0.03 mg/kg with follow-up visits at day 7, 14, and 28 (± 3 days). Dose escalation occurred every 4 weeks with similar follow-up visits after each change in dose. If none of the stopping rules applied, the study days corresponding to each dose escalation were day 28 (0.1 mg/kg/d), day 56 (0.3 mg/kg/d), and day 84 (1.0 mg/kg/d). Research personnel were to call the subjects 24-72 hours following each change in dose to monitor for AEs.

Each study visit included a physical exam, vital signs (BP, HR, weight, height), laboratory assessment (comprehensive metabolic lab panel, TSH, INR, and CBC), urinalysis, AE monitoring, urine pregnancy test, and assessment of drug adherence.

In addition, the following were performed at Days 0, 28, 56, 84, and 112: ECG, dietary counseling and dietary records, fat-soluble vitamin levels, fatty acid profile, full fasting lipid profile, liver NMRS, and pulmonary function tests.

The last day of treatment was Day 112. The end-of-study visit followed a 28-day off-treatment period (Day 140). This visit included a physical exam, ECG, vital signs, laboratory assessment, fat-soluble vitamin levels, fatty acid profile, fasting lipid profile, urinalysis, AE monitoring, liver NMRS, and pulmonary function tests.

Treatment

Lomitapide (“BMS-201038”) was supplied as a powder from Bristol Myers Squibb. The investigational pharmacist weighed study drug, based on the subject’s weight and assigned dose, and packaged standard gelatin capsules. Study drug was to be taken with water once daily in the morning.

A weight-based dosing strategy was used since the study was designed to include adolescents. The dose-escalation design was hypothesized to improve tolerability with regard to steatorrhea and accumulation of hepatic fat.

Subjects were also provided a standard multivitamin intended to supply 100% of the current dietary reference intake (DRI) based on age and gender for all essential vitamins and minerals, including fat-soluble vitamins. They were instructed to begin taking this multivitamin at the screening visit.

Reviewer Comment: HoFH-pilot used a standard multivitamin in contrast to HoFH-pivotal, which used vitamin E and a supplement containing the essential fatty acids (LA and ALA), EPA, and DHA. The only dietary supplement common to these two protocols was vitamin E, which was supplemented at exceedingly different doses (400 IU/day in HoFH-pivotal compared to ~22 IU/day in HoFH-pilot).

Criteria for Dose Escalation: Dose escalation could occur if the subject tolerated therapy without evidence of grade 3 toxicity defined by the NCI’s CTCAE (see below). Among the CTCAE grade 3 laboratory abnormalities are ALT or AST >5.0 to 20.0x ULN and bilirubin >3.0 to 10.0x ULN.

Guidelines for Dosage Modification, Interruption, or Discontinuation

If an individual had evidence of grade 3 toxicity, they were to return for a repeat lab test as soon as possible. Upon confirmation, dosage was decreased to 1.5x the previous dose for an additional four weeks following the visit schedule per standard protocol. If grade 3 toxicity was still present at 7, 14, or 28 days after the reduction in dose, the dose was further decreased to the previous pre-escalated dose (i.e., 0.03, 0.1, or 0.3 mg/kg/d) for an additional four weeks. If grade 3 toxicity persisted at any visit (7, 14, or

28 days) following this reduction, study drug was to be discontinued. The subject would return 4 weeks after discontinuation for a final safety visit. Otherwise, the subject could escalate to the next dose per standard protocol after four weeks on the reduced dose.

With regard to hepatotoxicity, if a subject had confirmed grade 4 toxicity, study drug was to be discontinued and the subject was to return for a final study visit after four weeks. Confirmed grade 4 hepatotoxicity was defined as any of the following occurring on two separate occasions at least 24 hours apart:

- ALT or AST >20.0x ULN
- alkaline phosphatase >20.0x ULN
- total bilirubin >10.0x ULN

Diet

Subjects met with a registered dietician at the screening visit for initial dietary instruction and then at each subsequent visit to monitor dietary compliance and weight maintenance. Subjects were instructed to minimize dietary fat (<10% of energy from fat) and to include 2% of total calories from essential fatty acids to prevent dietary deficiencies. Furthermore, the dietician would call subjects 3-5 days after the screening visit to assess compliance and assist with potential problems regarding diet adherence.

In addition, subjects received a standard multivitamin as noted above.

Assessment of Compliance

Study drug compliance was monitored by pill count.

Safety Considerations

Safety was assessed by physical examination, ECGs, pulmonary function tests, liver NMRS, laboratory parameters, vital signs, and any signs/symptoms reported. In addition to study visits, research personnel called each subject 24-72 hours following the initiation of each dose to ask about any short-term adverse effects.

Adverse Events – Definitions

- *AE*: all observed or volunteered adverse events regardless of suspected causal relationship to study drug, including adverse drug reactions; illnesses with onset during the study; exacerbations of pre-existing illnesses; abnormal objective test findings that result in a change in study drug dosage, discontinuation, or require intervention or diagnostic evaluation to assess the risk to the subject; and clinically significant changes in physical examination findings.
- *SAE*: Any AE that results in death, is life-threatening, results in inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or results in congenital anomaly/birth defect.
- All AEs were to be graded using the NCI's CTCAE v3.0 (10 June 2003). For subjects receiving anti-coagulation, AEs regarding PT and INR were graded using the American College of Cardiology's criteria for administering vitamin K based on INR: INR ≥ 5 but < 10 was a non-serious AE, and INR ≥ 10 was an SAE.

Vital Signs: Standardized methods for collecting vital sign data were not specified in the protocol.

Laboratory Measurements

Comprehensive metabolic panel included sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, TSH (baseline and end-of-study), INR, and total bilirubin. CBC included WBC, hemoglobin, hematocrit, platelet count, red cell distribution width, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration.

Fat-soluble vitamin assessment included measuring serum concentrations of vitamins A, D, and E. Levels of vitamin K were assessed indirectly with the INR.

Fatty acid profile included blood levels of LA, ALA, gamma-linolenic acid (GLA), AA, EPA, and DHA.

For subjects on anti-coagulation therapy, INR was to be checked 3 days after each drug escalation and weekly throughout the study.

ECG: Methodology for ECG measurement and evaluation was not specified in the protocol.

Hepatic Fat: NMRS was used to assess hepatic fat at baseline, days 28, 56, 84, 112, and end-of-study (day 140).

Pulmonary Function: Assessment of pulmonary function included FVC, FEV₁, FEF₂₅₋₇₅, and DLCO.

Data Safety Monitoring Board: A DSMB was established to review laboratory data and adverse events on an ongoing basis.

Endpoints & Assessments

Primary Endpoint: “to establish safety and tolerability . . . in this population with regards to laboratory and clinical parameters.”

Primary Efficacy Endpoint (Secondary Objective): % reduction in LDL-C (directly measured), comparing the effect of each dose to baseline and LDL-C values at the end of previous dose phases

Secondary Efficacy Outcomes: Changes in TC, VLDL-C, HDL-C, TG, apoAI, apoAII, apoB, apoCIII, apoE, and Lp(a) at visits 1, 2, 5, 8, 11, 14, and 15 (Screening, Baseline, Days 28, 56, 84, 112, and 140).

Pharmacokinetic Assessments: Neither the collection nor analysis of pharmacokinetic data is mentioned in the protocol.

Statistical Considerations

“A formal statistical analysis plan was not developed for this Phase 2 study. Analyses were based on protocol-defined procedures,” according to the HoFH-pilot CSR.

Sample Size & Power Considerations

Formal sample size calculations were not performed; however, the sponsor anticipated that enrolling 8 subjects would allow detection of LDL-C reductions of at least 30%.

Populations for Analysis: Not defined in the protocol.

Primary Analysis: “The primary endpoint of this study is to establish safety and tolerability . . . in this population with regards to laboratory and clinical parameters. This will be done using paired Student’s t-tests for continuous variables and Fisher’s Exact tests for proportions.”

Primary Efficacy Analysis: “Our primary efficacy variable will be percent reduction in LDL-C, comparing the effect of each dose to baseline and LDL-C values at the end of previous dose phases. This will again be done using a paired Student’s t-test. Because we will be making multiple time point comparisons, all t-tests will be adjusted using Bonferroni methods.”

Missing Data: Handling of missing data is not specified in the protocol.

Protocol Amendments

The original protocol (14 November 2002) was amended seven times; five of the amendments were implemented after the first subject was enrolled. Based on my review of these amendments, the most substantive included a modification of the grading criteria for AEs (amendment 5 [29 August 2003] updated CTCAE version 2 to version 3; amendment 6 [09 October 2003] established the ACC-based grading of PT/INR-related AEs) and a reduction in the planned sample size from eight to six subjects (amendment 7 [23 January 2004]).

Reviewer Comment: These protocol amendments are not expected to influence the interpretation of this pilot trial.

6 Review of Efficacy

Efficacy Summary

Exposure to Lomitapide

The overall phase 3 HoFH database (pivotal trial and its extension) includes 29 subjects ever exposed to lomitapide, with 23 exposed for at least one year, 15 for at least two years, and 5 for at least three years. Notably, all subjects who completed the first 26 weeks of the pivotal trial (efficacy endpoint) remained in the trial to its completion at

week 78. The dose-escalation regimen used in the pivotal trial is the same that the applicant proposes for labeling: 5 mg daily for 2 weeks followed by increases to daily doses of 10 mg, 20 mg, 40 mg, and 60 mg at 4-week intervals as tolerated. Titration was to be based on safety/tolerability only and not on achieved LDL-C levels. In the pivotal trial, the maximally tolerated doses at week 26 were 5 mg (n=3), 10 mg (n=2), 20 mg (n=6), 40 mg (n=7), 60 mg (n=10), and 80 mg (n=1; see protocol). Beyond week 26, subjects were not allowed to escalate beyond their individually determined maximum tolerated dose established during the efficacy period.

Primary Endpoint: LDL-C Reduction at Week 26

The primary efficacy parameter for the phase 3 pivotal trial was % change in LDL-C from baseline to week 26 (using last observation carried forward [LOCF] imputation), with each subject serving as their own control. To minimize the contribution of regression to the mean in this single-arm trial, subjects were required to be on a stable lipid-lowering regimen for 6 weeks prior to the first dose of lomitapide, and baseline values were determined from the mean of two measurements at 4 weeks into the 6-week run-in period and at initiation of study drug. Concomitant lipid-lowering regimens and LDL apheresis schedules were not to be altered during the first 26 weeks of the trial. For those receiving LDL apheresis, efficacy was to be evaluated on the basis of pre-apheresis lipid levels.

Mean LDL-C was 336 mg/dL at baseline in the pivotal trial despite subjects taking maximally tolerated lipid-lowering therapy. At week 26/LOCF, the mean LDL-C was 190 mg/dL, representing a -40.1% change from baseline ($P < 0.0001$). Although one cannot definitively determine a dose-response relationship from a study that employs a force-titration regimen, there at least was a positive correlation between mean dosage prescribed and observed LDL-C reduction at the population level (Figure 18).

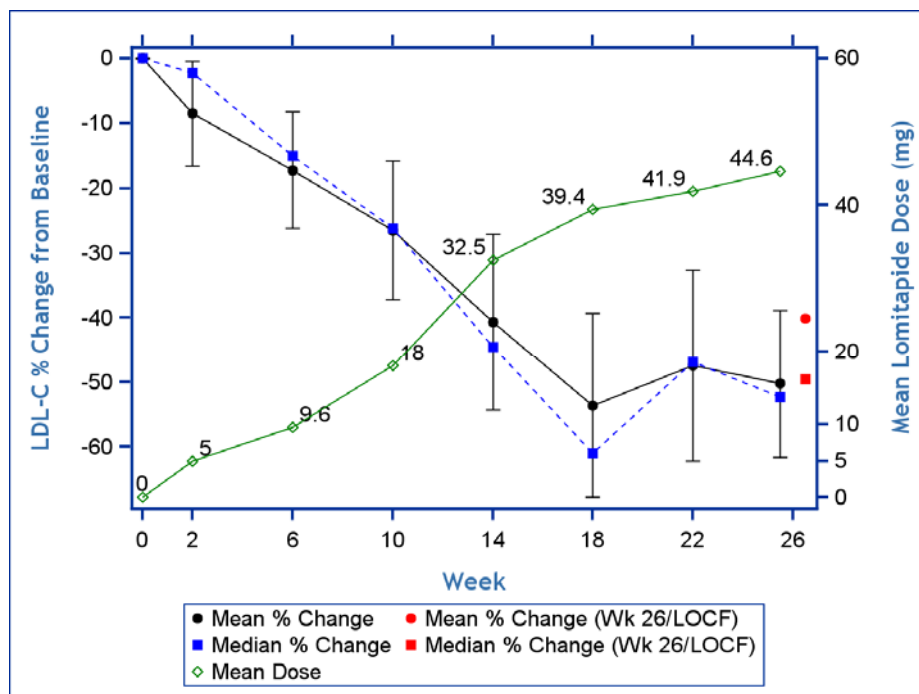


Figure 18. HoFH-pivotal – % Change in LDL-C

Of the 29 subjects who started the trial, 20 (69%) achieved $\geq 15\%$ reduction in LDL-C from baseline to week 26/LOCF, 19 (66%) achieved $\geq 25\%$, and 14 (48%) achieved $\geq 50\%$. Eight (35%) of the 23 subjects who completed the efficacy period had an LDL-C level < 100 mg/dL at week 26, with one subject having a level < 70 mg/dL.

Secondary Efficacy Parameters

The secondary efficacy parameters for the HoFH pivotal trial were % changes from baseline to week 26/LOCF in TC, apoB, TG, non-HDL-C, VLDL-C, and Lp(a). With the exception of Lp(a), statistically significant reductions were observed in these parameters.

Effect on HDL-C and Apolipoprotein AI

In the HoFH pivotal trial, mean baseline values for HDL-C and apoAI were 41 mg/dL and 105 mg/dL, respectively. The relative change in HDL-C from baseline to week 26/LOCF was -6.9% ($P=0.072$), although it was -12.3% ($P=0.004$) among the 23 subjects who completed the efficacy period. The corresponding relative changes in apoAI were -6.5% ($P=0.038$) and -10.7% ($P=0.003$) for the ITT/LOCF and completers populations, respectively. These reductions waned over time, with changes from baseline to week 56 of $+0.7\%$ for HDL-C and $+1.0\%$ for apoAI. The clinical consequences, if any, of these changes are unknown.

6.1 Indication

The applicant proposes the following indication:

TRADENAME is indicated as an adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and triglycerides (TG) in patients with homozygous familial hypercholesterolemia (HoFH).

Proposed dosage and administration instructions follow:

- Patients should follow a low-fat diet supplying less than 20% of energy from fat prior to initiating TRADENAME treatment, and should continue this diet during treatment;
- TRADENAME should be administered once daily at bedtime, with a glass of water and without food;
- The recommended starting dose is 5 mg. After 2 weeks, the 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.
- Patients should take daily dietary supplements that provide approximately 400 IU vitamin E, 200 mg linoleic acid, 110 mg EPA, 220 mg ALA, and 80 mg DHA per day, throughout treatment with TRADENAME.

TRADENAME would be available in 5 mg, 10 mg, and 20 mg capsules.

6.1.1 Methods

My review of efficacy focuses on the one pivotal phase 3 trial conducted in the HoFH population (HoFH-pivotal), with supportive data from the HoFH phase 2 study (HoFH-pilot). In addition, please see Cynthia Liu's statistical review for further analysis of the efficacy results.

Section 5.3 briefly describes efficacy results (reduction of LDL-C) for each of the five phase 2 trials conducted in non-HoFH subjects with hyperlipidemia, but as stated previously, these trials were 4-12 weeks in duration and used far lower doses than used and proposed for HoFH; therefore, they will not be discussed further in this section.

The protocol for HoFH-pivotal is summarized in Section 5.3 (p. 95). Briefly, the primary efficacy endpoint was % change from baseline in directly measured LDL-C at 26 weeks, with each subject serving as their own control in this single-arm trial. Subjects were expected to be treated with concomitant lipid-lowering therapy, including LDL apheresis in many cases, during this trial; therefore, all lipid-lowering therapies were to remain stable during a six-week run-in period and throughout the efficacy phase (through week 26). Only after week 26, if LDL-C levels dropped below 100 mg/dL, could a subject's concomitant lipid-lowering therapies be decreased upon consultation with the physician who managed the subject's dyslipidemia.

Baseline values of the lipid and lipoprotein parameters were the mean of the measurements at visits 2 and 3 (4 weeks into the 6-wk run-in period and initiation of study drug, respectively).

For patients receiving apheresis, efficacy was to be evaluated on the basis of pre-apheresis lipid levels. Once the apheresis schedule was established during the run-in, the time point for lipid assessment was to be maintained relative to the previous apheresis treatment in order to perform all measurements at the same point on the LDL-rebound curve. For visits 2, 3, 8, and 10 (4 wks into the 6-wk run-in, drug initiation, week 18 [anticipated on 60 mg x 4 wks], and week 26 [efficacy endpoint]), fasting lipids were to be “drawn just prior to the apheresis treatment and apheresis must occur +/- 1 day from the regimen established during the run-in period.”

The primary analysis used the “ITT” population, defined by the applicant as all subjects who ever received a dose of lomitapide and who had LDL-C levels at baseline and at least one post-baseline time point. The LDL-C requirement did not exclude any subjects from analysis. Missing data at the week-26 efficacy endpoint were imputed using LOCF.

6.1.2 Demographics

Selected demographic and baseline characteristics of the subjects in the HoFH pilot, pivotal, and extension studies are summarized in Table 57 and Table 60. Four of the subjects who participated in HoFH-pilot also participated in HoFH-pivotal (corresponding equivalent subject identifiers: AROD85 = 01-001; MANJ85 = 01-002; EMEN64 = 01-003; DWOL68 = 01-004). The remaining two subjects in HoFH-pilot had traveled to the University of Pennsylvania from Lebanon for the phase 2 trial; therefore, these subjects did not participate in the phase 3 trial.

In HoFH-pivotal, all 29 subjects who entered the efficacy phase received at least one dose of lomitapide; therefore, the safety population and the ITT population are identical. The mean age at baseline was 30 years with a range of 18 to 55 years, 16 (55%) were men, and the majority (26 [86%]) were white. The mean BMI was 25.8 kg/m², with only four subjects meeting criteria for obesity. One subject had type 2 diabetes.

In HoFH-pilot, the mean age at baseline was 25 years with a range of 17 to 39 years; the 17 year-old subject received her first dose of lomitapide four days prior to her 18th birthday.

Table 57. Baseline Characteristics of HoFH Trials

Characteristic	HoFH Pilot (N=6)	HoFH Pivotal (N=29)	HoFH Extension (N=19)*
Age (y)	25.0 (9.2)	30.7 (10.6)	31.9 (11.8)
<18	1 (17%)	0	0
≥18, <30	3 (50%)	14 (48%)	10 (53%)
≥30, <40	2 (33%)	9 (31%)	4 (21%)
≥40, <50	0	4 (14%)	3 (16%)
≥50	0	2 (7%)	2 (11%)

Characteristic	HoFH Pilot (N=6)	HoFH Pivotal (N=29)	HoFH Extension (N=19)*
Male	3 (50%)	16 (55%)	10 (53%)
Race			
Caucasian	5 (83%)	25 (86%)	17 (89%)
Asian	1 (17%)	2 (7%)	1 (5%)
African American	0	1 (3%)	0
Other	0	1 (3%)	1 (5%)
Weight (kg)	67.0 (11.7)	73.5 (18.1)	67.0 (12.3)
BMI (kg/m²)	24.9 (3.8)	25.8 (5.4)	24.3 (5.2)
≤25	3 (50%)	16 (55%)	12 (63%)
>25, ≤30	3 (50%)	9 (31%)	5 (26%)
≥30	0	4 (14%)	2 (11%)
Diabetes mellitus	0	1 (3%)	1 (5%)

Source: HoFH-pilot CSR Table 3, HoFH-pivotal CSR Table 8; FDA clinical reviewer's analysis of raw data

Values are mean (SD) or n (%). Ages were used as integer values and were not rounded up.

* As of the data cutoff date 31 Dec 2011, 19 subjects had been enrolled in the extension study but one subject (35-001) had not yet attended his first follow-up visit. Therefore, the applicant included subject 35-001 in the demographics table but not in others.

Table 58 summarizes the evidence for HoFH diagnosis among the 29 subjects in HoFH-pivotal. All had genetic information available: 28 had documented defects in the LDLR gene and 1 had a defect in the LDLR adaptor protein ARH. Of those with LDLR defects, 25 were documented true or compound homozygotes (mutations in each of 2 alleles; 7 subjects exhibited the same mutation in each *LDLR* allele), 1 was missing information for the second allele, and the remaining 2 subjects only had a single mutant allele (the second allele may have carried the same mutation, but this is speculation). In addition, 7 of the 29 subjects also had documentation of skin fibroblast LDLR activity <20% of normal, and 11 subjects also had untreated TC >500 mg/dL and TG <300 mg/dL with both parents having documented untreated TC >250 mg/dL.

Table 58. HoFH-pivotal – Evidence for HoFH

Diagnostic Criteria	HoFH-pivotal
Genetic	16
Genetic + Ex vivo LDLR	2
Genetic + Family history	6
Genetic + Ex vivo LDLR + Family history	5
TOTAL	29

Source: HoFH-pivotal CSR, Listing 16.2.3

Genetic = documented functional mutation(s) in both *LDLR* alleles or alleles known to affect LDLR functionality; Ex vivo LDLR = Skin fibroblast LDLR activity <20% normal; Family history = untreated TC >500 mg/dL and TG <300 mg/dL and both parents have documented untreated TC >250 mg/dL.

In HoFH-pilot, four subjects were receptor-negative based on known homozygosity for loss-of-function LDLR mutations, one was receptor-negative based on phenotype and LDLR activity in skin fibroblasts, and one was found to have a defective LDLR based on her LDLR mutation.

Of the 29 subjects in HoFH-pivotal, 27 (93%) had a history of cardiovascular or cerebrovascular disease at study entry. Consistent with the clinical characteristics of HoFH, many had undergone invasive cardiac procedures at young ages. Ten (34%) of the subjects had a history of CABG with a median age of 21 years at first operation. Three subjects underwent CABG at the ages of 4, 5, and 8. One subject had a history of three CABG operations by age 29. Several subjects also had a history of multiple coronary catheterizations at early ages (e.g., one underwent the procedure 4 times between age 15 and 39; another subject had 3 procedures at ages 19, 20, and 21). The study population also demonstrated the high incidence of valvular disease with HoFH; for example, three subjects had a history of aortic valve replacement (ages 26, 35, and 37) and several others carried a diagnosis of aortic stenosis of varying degrees. Cerebrovascular disease was evidence in three subjects with a history of transient ischemic attack and one subject with a history of carotid endarterectomy. Other medical and surgical history included xanthoma (48%), arcus lipoides (24%), and hypertension (21%).

Concomitant lipid-lowering therapy was not allowed in HoFH-pilot. In HoFH-pivotal, 18 (62%) of the 29 subjects were receiving extracorporeal LDL-lowering therapy at baseline: 10 with LDL apheresis, 6 with plasmapheresis, and 2 with unreported type. Among patients receiving extracorporeal therapy (generically referred to as “apheresis” hereafter), the frequency established during the baseline period was q7 days for 4 subjects, q14 days for 12 subjects, q28 days for 1 subject, and q42 days for 1 subject (Source: 20 April 2012 response to FDA information request).

Lipid-lowering medications at baseline in HoFH-pivotal included statins for 27 (93%) subjects, and these were typically prescribed at maximum dose (rosuvastatin: 11 at 40 mg daily, 1 at 30 mg daily, 1 at 10 mg daily; atorvastatin: 8 at 80 mg daily, 1 at 40 mg daily; simvastatin: 1 subject each at 160 mg daily, 40 mg twice daily, and 40 mg daily; and 2 subjects at 20 mg daily). Ezetimibe was prescribed for 22 (76%), all at 10 mg daily. Nicotinic acid, bile acid sequestrants, and fibrates were prescribed in the minority (Table 59).

Table 59. HoFH-pivotal – Baseline Lipid-Lowering Therapy

Therapy	HoFH-pivotal (N=29)
Current apheresis	18 (62%)
<i>LDL apheresis</i>	10
<i>Plasmapheresis</i>	6
<i>Type not reported</i>	2
Lipid-lowering therapy	
Statin	27 (93%)
<i>rosuvastatin</i>	13
<i>atorvastatin</i>	9
<i>simvastatin</i>	5
Ezetimibe	22 (76%)
Nicotinic acid	3 (10%)
Bile acid sequestrant	1 (3%)
Fibrate	1 (3%)

Source: FDA clinical reviewer's analysis of submitted raw data (CM.xpt)

Despite these intensive regimens, on-treatment lipid and lipoprotein values remained high at baseline among the subjects enrolled in HoFH-pivotal (Table 60). Mean LDL-C was 336 mg/dL, with a range of 152 to 564 mg/dL. Twenty (69%) of the 29 subjects had a baseline LDL-C exceeding 250 mg/dL, and approximately half (51%) had values exceeding 350 mg/dL. On their baseline lipid-lowering regimens, mean total cholesterol was 430 mg/dL.

Table 60. HoFH – Baseline Lipid, Lipoprotein, hsCRP Values

Parameter	HoFH-pilot (N=6)	HoFH-pivotal (N=29)
Total cholesterol (mg/dL)	851 (195) 684 – 1212	430 (135) 191 – 720
LDL-C (mg/dL)	614 (106) 480 – 789	336 (114) 152 – 564
HDL-C (mg/dL)	26 (5) 20 – 35	44 (11) 29 – 69
Triglycerides (mg/dL)	259 [130, 362] 82 – 605	92 [72, 128] 32 – 253
Non-HDL-C (mg/dL)	824 (195) 649 – 1185	386 (132) 158 – 660
VLDL-C (mg/dL)	210 (199) 21 – 549	21 (10) 6 – 51
ApoB (mg/dL)	310 (52) 240 – 387	260 (80) 124 – 432
ApoAI (mg/dL)	66 (19) 30 – 83	115 (28) 58 – 187
hsCRP (mg/L)		2.0 [0.7, 5.1] 0.2 – 50.6

Source: HoFH-pivotal CSR Table 9; FDA clinical reviewer's analysis of raw data
Values are mean (SD), median [25th, 75thiles], or Min – Max.

Reviewer Comments: *The marked differences in these parameters between HoFH-pilot and HoFH-pivotal reflects the fact that subjects had to be withdrawn from concomitant lipid-lowering therapies, including LDL apheresis, at least 4 weeks prior to the baseline visit in HoFH-pilot.*

Baseline values for other laboratory parameters of interest (fat-soluble vitamin assessments, fatty acid levels, etc.) are presented with the relevant safety analyses in Section 7.

Enrollment by Site

Eleven sites participated in the HoFH-pivotal trial: 2 sites in the United States (7 subjects), 3 sites in South Africa (11 subjects), 4 sites in Italy (6 subjects), and 2 sites in Canada (5 subjects) (Table 61).

Table 61. HoFH-pivotal – Enrollment by Site

Country / Site	# Subjects
United States	7 (24%)

Country / Site	# Subjects
University of Pennsylvania	5
Cedars-Sinai Medical Center	2
South Africa	11 (38%)
University of Capetown Health Science Faculty	4
Netcare Private Hospital (Bloemfontein)	5
Prinshof Campus (Pretoria)	2
Italy	6 (21%)
Azienda Ospedaliera Universitaria "P. Giaccone" (Palermo)	2
Azienda Ospedaliera Ospedale Niguarda Ca'Granda (Milano)	2
Azienda Ospedaliera Universitaria di Ferrara – Arcispedale Sant' Anna (Ferrara)	1
Azienda Policlinico Umberto I (Roma)	1
Canada	5 (17%)
ECOGENE-21 (Chicoutimi, Quebec)	2
Robarts Research Institute (London, Ontario)	3

Source: HoFH-pivotal CSR.

6.1.3 Subject Disposition

Table 62 summarizes the disposition of subjects through week 78 of the HoFH-pivotal trial. Of the 32 subjects screened, 31 entered the run-in period (one subject apparently did not meet entry criteria). Two subjects who entered the run-in period withdrew consent before the baseline visit.

All 29 subjects who completed the run-in phase proceeded to the efficacy phase, and all received at least one dose of study drug. Six (21%) subjects discontinued the study during the efficacy phase (week 0 through 26), as described below. Of the 23 subjects who completed the week-26 efficacy assessment, all remained in the study through the end-of-study visit at week 78.

Reviewer Comment: Five subjects received protocol waivers for inclusion/exclusion criteria: 22-003 (weight 142.5 kg and reported >2 drinks/day on weekends); 22-004 (documented diagnosis of NASH); 23-002 (history of asthma in childhood, no longer active); 13-001 and 13-002 could not undergo MRI (metal prosthetic valves). Regarding the subject with a history of "NASH," the verbatim term in the medical history database was "slight hepatic steatosis" apparently diagnosed ~10 months before the baseline visit; a supplemental dataset suggests that ultrasonography – not a liver biopsy – led to this presumed diagnosis.

Table 62. HoFH-pivotal – Subject Disposition

Disposition	HoFH-pivotal
Screened	32
Entered run-in	31
Discontinued during run-in	2
Completed run-in	29
Entered efficacy phase	29
Completed efficacy	23
Entered safety phase	23
Completed week 78	23

Source: HoFH-pivotal CSR, Table 6 and 120-day safety update report.

Of the 23 subjects who completed HoFH-pivotal, 19 enrolled in the extension study. One subject (01-002) had reportedly been dishonest with investigators with regard to the doses that she was taking during the pivotal trial; therefore, she was not allowed to participate in the extension. Three subjects did not continue into the extension for reasons that were not specified, although I note that one subject had multiple gastrointestinal side effects throughout the pivotal trial (01-001); one had an AE of “severe hepatic steatosis,” mild hepatomegaly, and transaminase elevations that led to dose interruptions (02-002); and one had an increase in hepatic fat from 2.7% at baseline to 44.3% at approximately week 63, then refused further MRI evaluations because of pain at the site of sternal wires (32-001).

Table 63 describes the reported reasons that led to early withdrawal from the HoFH-pivotal trial and its extension. No subjects withdrew prematurely from the phase 2 HoFH-pilot trial.

Table 63. Reasons for Early Withdrawal from HoFH-pivotal and Extension

Reason for Early Withdrawal from Trial	HoFH-pivotal (N=29)	HoFH-extension (N=19)
Withdrew consent	3 (10%)*	0
Adverse event	4 (7%)	1 (6%)**
Non-compliance	1 (3%)	0
Physician decision	0	1 (6%)
Other	0	2 (11%)†
TOTAL	6 (21%)*	3 (17%)

Source: HoFH-pivotal CSR, Table 6, and 120-day safety update report, Table 2.

* Two patients who withdrew consent also had AEs listed as leading to treatment discontinuation according to the applicant; the third also had an AE contribute to treatment discontinuation (unstable INR) per my review.

** One subject (11-004) discontinued from the extension study because of an SAE (hepatotoxicity), although the applicant reports that this subject was placed back on treatment after the data cutoff.

† Other reasons included discontinuation to plan a pregnancy (Subject 12-001) and sponsor termination of the subject because of elevated transaminases (Subject 01-004).

The adverse events and descriptions of the subjects who withdrew consent are reviewed in Section 7.3.3 (p. 167).

The numbers of patients in each analysis dataset for HoFH-pivotal (described in the protocol above, p. 106) are shown in Table 64.

Table 64. HoFH-pivotal – Analysis Populations

HoFH-pivotal Analysis Data Sets	N (%)
ITT Population	29 (100%)
Safety Population	29 (100%)
Per Protocol Population	19 (66%)
Completers Population	
Week 26	23 (79%)
Week 78	23 (79%)

Source: HoFH-pivotal CSR, Table 7.

Reviewing the list of protocol deviations, it appears that study medication compliance, based on pill count, was responsible for 7 of the 10 exclusions from the per-protocol population. This review will focus on the ITT/Safety population with sensitivity analyses as appropriate.

Achieved Maximum Tolerated Doses

Table 65 describes the distribution of maximum tolerated dose (MTD) at week 26 among the 29 subjects in HoFH-pivotal. In addition, the MTD for the 23 subjects who completed the efficacy period are described along with the same subjects' doses at the end of the trial (week 78). Among the 12 subjects who completed the efficacy period at doses less than the intended maximum of 60 mg daily, GI symptoms limited further dose escalation for 10 subjects. Typical symptoms included nausea, vomiting, diarrhea, abdominal pain or discomfort, urgency to have a bowel movement, and weight loss. Two subjects stopped escalating their dose because of abnormal transaminases: the 5-mg subject had ALT 10xULN at 10 mg, and a 40-mg subject had 2 episodes of ALT >7x ULN during the efficacy period.

Table 65. HoFH-pivotal – Distribution of Achieved Doses

Dose	Efficacy Period (Week 0-26 Max Tolerated Dose)		End of Trial (Week 78) (n=23)
	ITT (n=29)	Completers (n=23)	
5 mg	3 (10%)	1 (4%)	1 (4%)
10 mg	2 (7%)	0	0
20 mg	6 (21%)	5 (22%)	7 (30%)
40 mg	7 (24%)	6 (26%)	6 (26%)
60 mg	10 (34%)	10 (43%)	9 (39%)
80 mg	1 (3%)	1 (4%)	0

Source: HoFH-pivotal CSR, Table 8, and exposure dataset (EX xpt).

Reviewer Comments:

1. Although 6 (21%) of the 29 subjects discontinued early, it is notable that all discontinuations occurred within the first 6 months of dosing (during the titration period) and that all remaining subjects tolerated at least a year of additional dosing.
2. Although the distribution of doses shifts downward slightly between week 26 and the end of the trial, recall that subjects were not allowed to increase their dose beyond their week 26 dose; therefore, a downward shift is the only shift possible. Thus, one should not conclude that subjects receiving doses <60 mg at week 26 could not have tolerated higher doses later in the trial; this simply wasn't tested.

In HoFH-pilot, all six subjects completed the study and escalated their weight-based doses per protocol. The maximum dose of 1.0 mg/kg was administered for a range of 25 to 32 days for each subject. Based on subject weights recorded at visit 11 when the escalation to 1.0 mg/kg was scheduled to occur, the highest dosages should have been approximately 55, 58, 60, 66, 75, and 96 mg/day.

6.1.4 Analysis of Primary Endpoint(s)

For HoFH-pivotal, the primary efficacy analysis was % change in directly measured LDL-C from baseline to week 26 in the ITT population using LOCF imputation. In this section, results for the primary endpoint are presented along with supportive LDL-C-related analyses for completeness.

The mean LDL-C decreased from 336 mg/dL at baseline to 190 mg/dL at the end of the 26-week efficacy phase, yielding a -40% change from baseline ($p < 0.001$; paired t-test). The descriptive statistics for the primary endpoint are shown in Table 66.

Table 66. HoFH-pivotal – Direct LDL-C (Primary Endpoint) at Week 26

	Direct LDL-C (mg/dL)	Absolute Change from Baseline (mg/dL)	Relative Change from Baseline (%)	P*
Baseline				
Mean (SD)	336 (114)	-	-	-
95% CI	293-380			
Median	357			
Min, Max	152, 564			
Week 26/LOCF				
Mean (SD)	190 (104)	-147 (127)	-40.1 (31.3)	<0.001
95% CI	150-229	-195, -98	-51.9 to -28.2	
Median	169	-107	-49.5	
Min, Max	28, 442	-351, +49	-92.6, +20.4	

Source: HoFH-pivotal CSR, Table 12.

* P-value based on paired t-test for mean % change.

Mean absolute changes and mean relative changes from baseline to week 26 were highly statistically significant (all $P < 0.001$) regardless of population analyzed: completers (i.e., ITT without LOCF), ITT with LOCF imputation, or per-protocol with or without LOCF imputation. For the 6 subjects in the ITT population who discontinued early, note that the last on-study lipid evaluation was used in the applicant's analysis, including assessments conducted at the off-treatment follow-up visit, which could have occurred up to 4 weeks after the last dose of lomitapide. Table 67 shows the mean and median absolute and relative changes from baseline to week 26 in these populations; LOCF imputation attenuates the magnitude of the changes observed in the completer population. Note also that the elimination of subjects with major protocol deviations does not affect the overall results.

Table 67. HoFH-pivotal – LDL-C Changes from Baseline to Week 26 (Sensitivity Analyses)

Changes from Baseline to Week 26	ITT/Safety		Per-Protocol*	
	With LOCF (n=29)	Without LOCF (n=23)	With LOCF (n=19)	Without LOCF (n=15)
Mean (SD) (mg/dL)	-147 (127)	-185 (115)	-144 (121)	-183 (105)
Median (mg/dL)	-107	-203	-107	-183

Changes from Baseline to Week 26	ITT/Safety		Per-Protocol*	
	With LOCF (n=29)	Without LOCF (n=23)	With LOCF (n=19)	Without LOCF (n=15)
Mean %	-40.1%	-50.2%	-40.9%	-51.9%
Median %	-49.5%	-52.3%	-51.2%	-52.3%

Source: HoFH-pivotal CSR, Tables 14.2.1.1.1-3, 14.2.3.1.1.1-2

* Per-protocol population is a subset of the ITT population that excludes subjects with baseline LDL-C values (visits 2 and 3) that differed >20%; average compliance <80% or >120% during the entire efficacy phase; or changes in lipid-lowering therapy during the last 12 weeks of the efficacy phase, which included changes in apheresis frequency (> ±6 days from the regimen established during run-in) for at least 2 treatments or an increase of 200% or decrease of 75% of dose of a lipid-lowering medication for 4 weeks or more.

As another sensitivity analysis, the sponsor analyzed LDL-C profiles using a trapezoidal area-under-the-curve (AUC) method, limited to measured values only (i.e., no LOCF). The sponsor reported a mean (SD) AUC of change from baseline of -2606 (2239) mg/dL*weeks. Perhaps more interpretable, this corresponds to a time-averaged mean (SD) LDL-C reduction of -104 (86) mg/dL (95% CI, -137 to -71 mg/dL; p<0.001).

Table 68 presents the applicant’s analysis of mean LDL-C over time without imputation, along with the respective changes from baseline and P-values determined from paired t-tests.

Table 68. HoFH-pivotal – LDL-C by Study Visit

TIME POINT (N)	OBSERVED VALUE (MG/DL)	OBSERVED CHANGE (MG/DL)	P-VALUE ¹	PERCENT CHANGE (%)	P-VALUE ²
Baseline (29)	336.4 (113.54)	NA	NA	NA	NA
Week 2 (28)	308.5 (125.17)	-32.3 (77.03)	0.035	-8.5 (20.84)	0.040
Week 6 (29)	277.8 (124.85)	-58.6 (85.77)	< 0.001	-17.2 (23.74)	< 0.001
Week 10 (27)	244.7 (128.04)	-90.2 (102.96)	< 0.001	-26.5 (26.93)	< 0.001
Week 14 (27)	198.7 (128.17)	-136.2 (122.02)	< 0.001	-40.6 (34.56)	< 0.001
Week 18 (23)	162.8 (109.81)	-187.0 (119.56)	< 0.001	-53.6 (33.02)	< 0.001
Week 22 (24)	180.3 (126.40)	-166.6 (132.48)	< 0.001	-47.4 (35.12)	< 0.001
Week 26 (23)	167.5 (96.09)	-184.5 (115.26)	< 0.001	-50.2 (26.47)	< 0.001

Source: Table 14.2.1.1.1

1 p-value on the mean observed change from Baseline based on paired t-test

2 p-value on the mean percent change from Baseline based on paired t-test

Source: HoFH-pivotal CSR, Table 13. No imputation.

The LDL-C results from the efficacy period of HoFH-pivotal are depicted graphically in the following figures. Figure 19 shows the mean (with 95% CI) and median values of LDL-C over time. Figure 20 shows the mean (with 95% CI) and median absolute changes from baseline over time. Each figure also includes the week 26/LOCF values for comparison.

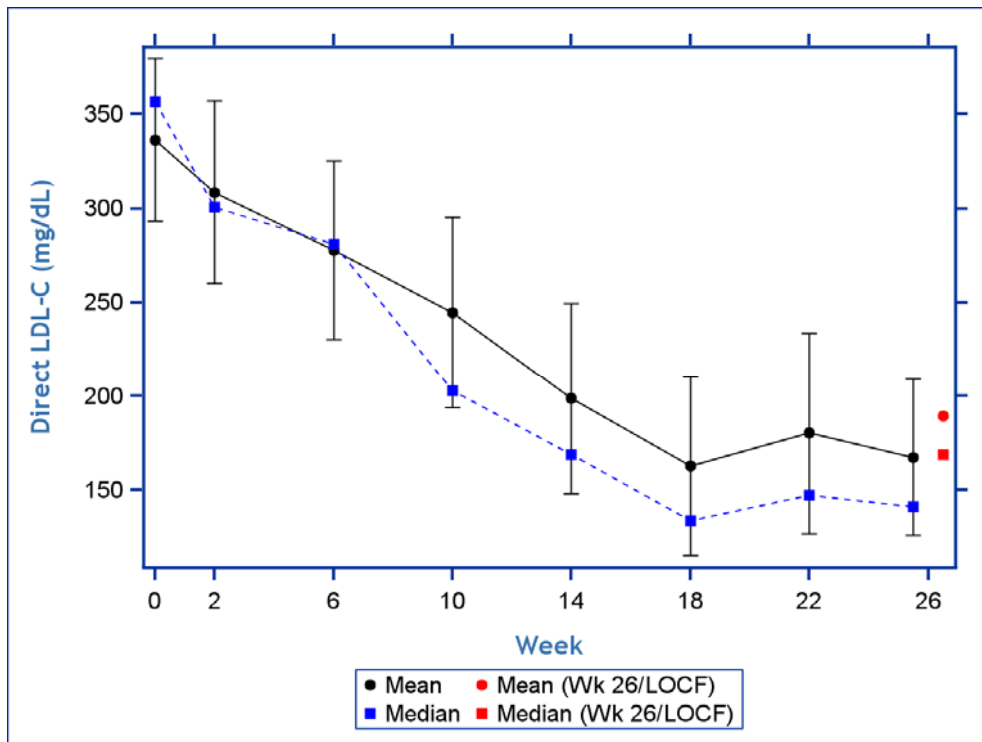


Figure 19. HoFH-pivotal – Mean and Median LDL-C Over Time

Source: HoFH-pivotal CSR, Table 14.2.1.1.1.
Error bars represent 95% CI of the mean.

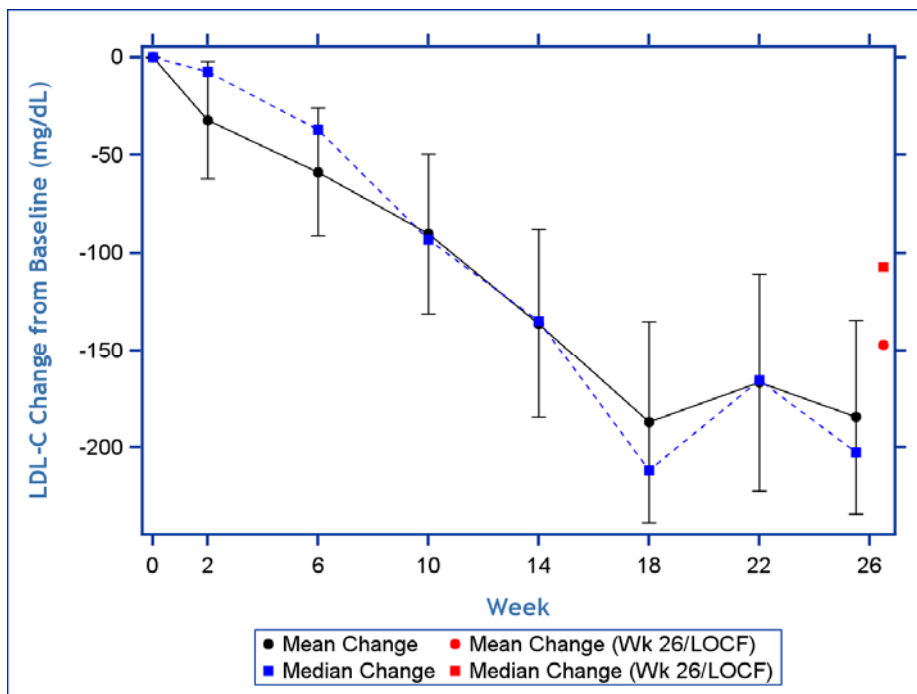


Figure 20. HoFH-pivotal – Absolute Changes in LDL-C from Baseline Over Time

Source: HoFH-pivotal CSR, Table 14.2.1.1.1.
Error bars represent 95% CI of the mean.

Figure 21 shows the relative changes in LDL-C from baseline over time as well as the average dose being taken at each time point.

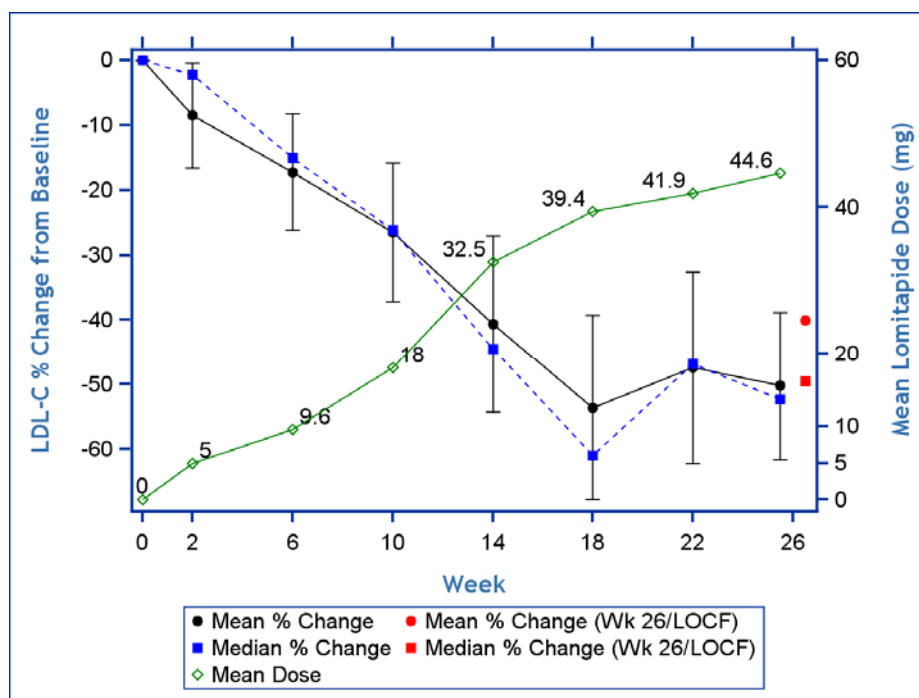


Figure 21. HoFH-pivotal – Relative Changes in LDL-C from Baseline Over Time

Source: FDA clinical reviewer’s depiction of data in HoFH-pivotal CSR Tables 14.2.1.1.1 and 14.1.2.8.1.

Error bars represent 95% CI of the mean only.

Reviewer Comment: According to the protocol-specified regimen, the last titration (to 60 mg) would occur at week 18 if a subject escalated their dosage without need for interruption/reduction. Although one cannot definitively determine a dose-response relationship from a study that employs a force-titration regimen, there is at least a positive correlation between mean dosage prescribed and observed LDL-C reduction at the population level.

Figure 22 presents % reduction in direct LDL-C from baseline to week 26 categorized by maximum tolerated dose, with and without LOCF imputation. Note that the mean LDL reduction among subjects who tolerated 40 mg was greater than that observed among those who could only tolerate 20 mg (-46% vs. -33%, respectively, with LOCF), but the differences between 40 mg and 60 mg were modest. Furthermore, because of a 40-mg MTD subject who had nearly a 20% increase from baseline at last measurement, the mean decrease among 40-mg completers was 57% compared with 55% among the 60-mg completers.

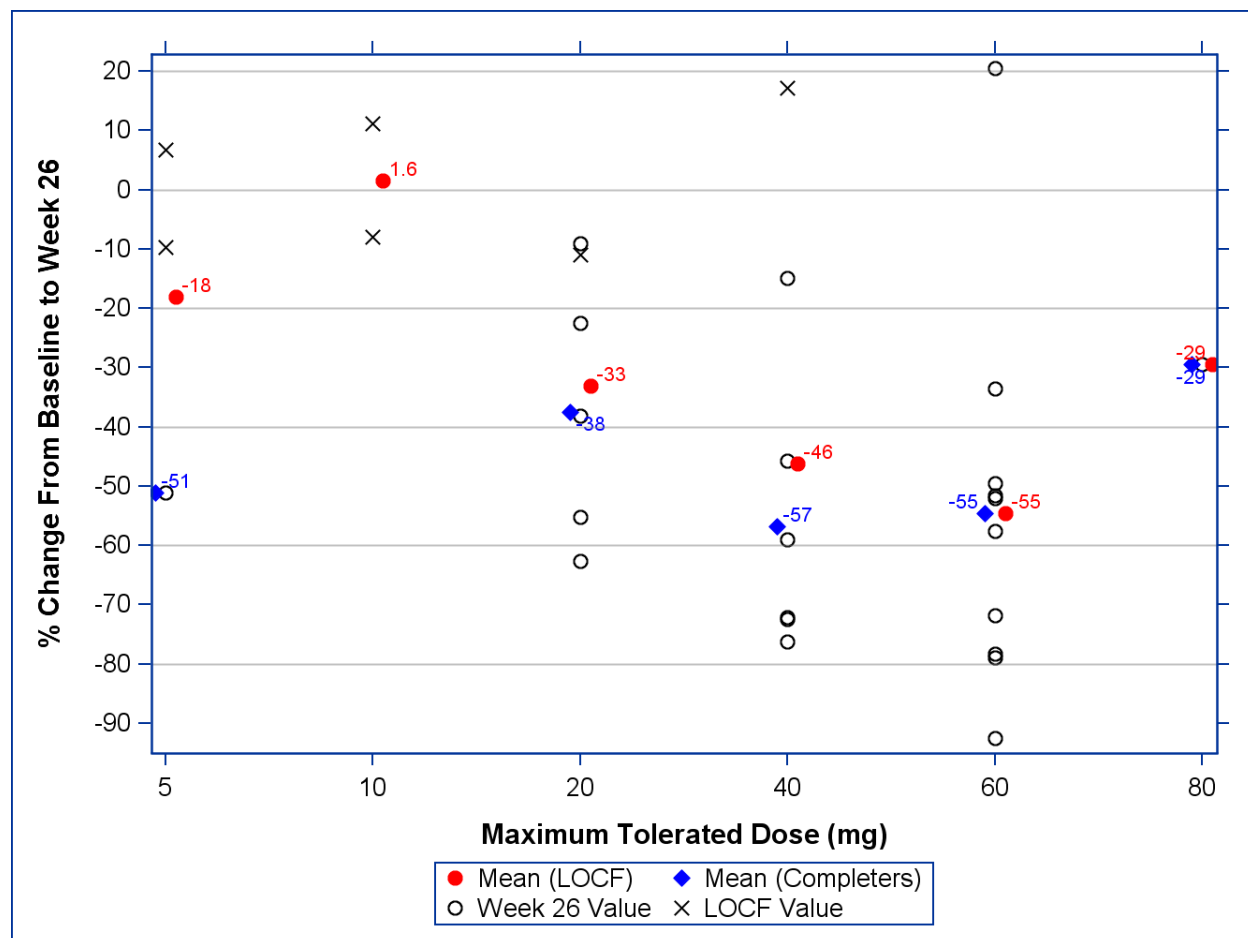


Figure 22. HoFH-pivotal – LDL-C % Change at Week 26 by Maximum Tolerated Dose

Source: FDA clinical reviewer’s analysis of submitted analysis dataset *ADLB.xpt*. The one subject with an 80-mg maximum tolerated dose is included with the 60-mg group; this subject had a 29% reduction in LDL-C at week 26.

Reviewer Comment: Unlike a parallel-group randomized trial, groups defined based on MTD are not independent in a dose-escalation design. Essentially, MTD is an outcome of the trial itself, and using one outcome to predict another outcome (LDL reduction) carries substantial possibilities for introducing bias into the interpretation of these values as dose-response data. For example, MTD depends on safety and tolerability, and the incidence of adverse effects limiting tolerability could correlate with LDL reduction; thus, the relationship between MTD and LDL reduction could be confounded. Given this limitation, it is at least somewhat reassuring that there is a qualitative positive correlation between MTD and mean (or median, not shown) % LDL-C reduction from baseline to week 26.

One could hypothesize that for an individual subject, higher doses could even have the potential to be less effective than lower doses, in clinical practice, if dose-related adverse effects contributed to more nonadherence at higher doses. To explore this, I compared the nadir LDL-C during the efficacy period with the week 26 LDL-C for each of the 23 completers:

- For 6 subjects, the end of the efficacy period (week 26) was also the subject's nadir LDL-C. The remaining 17 subjects had a nadir LDL-C prior to week 26.
- Of those who had a nadir *prior* to week 26, 13 were reported to be taking the same dose of lomitapide at both their nadir LDL-C visit and their week 26 visit. One subject was taking a higher dose of lomitapide at the nadir. Three subjects were taking a lower dose of lomitapide at the nadir compared with week 26:
 - Subject 01-002. Nadir at week 10 (LDL 326 mg/dL; -24% from baseline) after lomitapide 10 mg period. At week 26, LDL 388 mg/dL (-9% from baseline) while taking lomitapide 20 mg.
 - Subject 11-001. Nadir at week 2 (LDL 256 mg/dL; +7% above baseline) after lomitapide 5 mg period. At week 26, LDL 290 mg/dL (+21% above baseline) while taking lomitapide 60 mg.
 - Subject 12-004. Nadir at week 14 (LDL 112 mg/dL; -55% from baseline) on lomitapide 40 mg. At week 26, LDL 164 mg/dL (-34% from baseline) while taking lomitapide 60 mg.

Reviewer Comment: For the majority of subjects who completed the efficacy period (19 of 23), the dose at nadir LDL-C was the same as the maximum tolerated dose, even if the nadir preceded the week 26 efficacy endpoint. One subject did have an interesting LDL-C profile (nadir LDL-C during the efficacy period was 7% above baseline, with a week-26 value 21% above baseline despite lomitapide 60 mg). This subject had several interruptions in LDL apheresis, GI adverse events leading to multiple dose interruptions, and three SAEs (acute coronary syndrome, angina pectoris, lower respiratory infection) during the efficacy period; presumably, these events collectively led to substantial nonadherence.

Categorical Changes in LDL-C in HoFH-pivotal

Of the 29 subjects who started the trial, 20 (69%) achieved $\geq 15\%$ reduction in LDL-C from baseline to week 26/LOCF, 19 (66%) achieved $\geq 25\%$, and 14 (48%) achieved $\geq 50\%$. Eight (35%) of the 23 subjects who completed the efficacy period had an LDL-C level < 100 mg/dL at week 26, with one subject having a level < 70 mg/dL. Four of these subjects were receiving apheresis.

Apheresis Considerations

For subjects receiving LDL apheresis, the timing of the LDL-C measurements at baseline (week -2 and week 0) in relation to the preceding apheresis treatment should be the same as the timing of future measurements. The protocol specified that for weeks -2, 0, 18, and 26, fasting lipids were to be “drawn just prior to the apheresis treatment and apheresis must occur +/- 1 day from the regimen established during the run-in period.” Using the concomitant medication dataset (*CM.xpt*), I created dot plots showing the spacing of apheresis treatments for each subject during HoFH-pivotal to visually note changes in apheresis frequency (Figure 23).

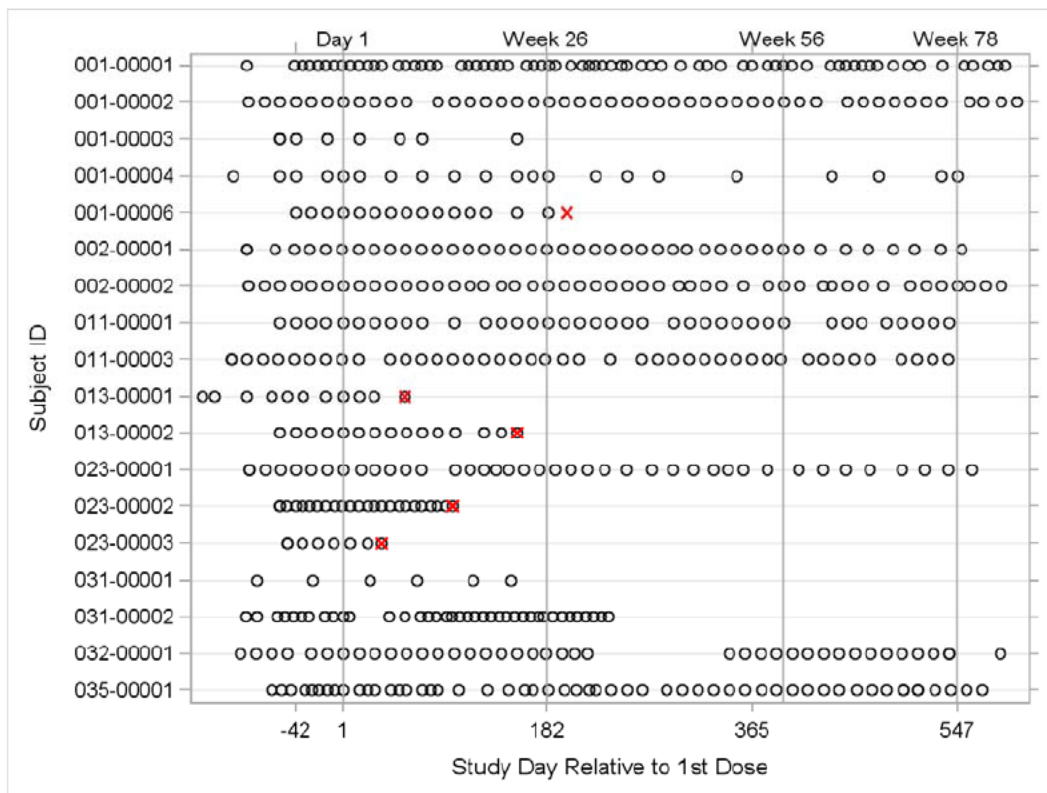


Figure 23. HoFH-pivotal – Apheresis Frequency by Subject

Source: FDA clinical reviewer’s analysis of HoFH-pivotal dataset (*CM.xpt*)

Open circles represent apheresis treatments; red Xs denote early termination visits for the 5 apheresis subjects who permanently discontinued study drug prematurely. Reference lines at weeks 26, 56, and 78 are approximations (i.e., individual subjects may have had study visits slightly before or after these lines).

The time between an apheresis treatment and the week 26/LOCF visit would have the greatest potential to introduce bias to the primary assessment of efficacy in HoFH-pivotal. In response to a 09 April 2012 information request, the sponsor provided subject-level data regarding the timing of direct LDL-C measurements in relation to apheresis (Table 69). I have highlighted rows with timing discrepancies.

Table 69. HoFH-pivotal – Days from Apheresis to LDL-C Assessment

Subject	Regimen Established During Run-in	Week -2	Week 0	Week 26/LOCF
01-001	7	7	7	7
01-002	14	No direct LDL-C	14	14
01-003	28	28	14	28
01-004	14	17	14	14
01-006	14	14	14	14
02-001	14	14	14	14
02-002	14	14	14	14
11-001	14	13	15	14
11-003	14	14	14	12
13-001	14	20	15	27

Subject	Regimen Established During Run-in	Week -2	Week 0	Week 26/LOCF
13-002	14	14	14	14
23-001	14	14	14	14
23-002	7	6	6	6
23-003	14	14	14	13
31-001	42	8	26	35
31-002	7	14	9	5
32-001	14	14	14	5
35-001	7	7	7	14
Mean (SD)		13.5 (5.2)	13.3 (4.4)	13.2 (8.0)
Median		14	14	14

Source: 20 April 2012 response to FDA information request.

Numbers are days from most recent apheresis to the corresponding direct LDL-C measurement.

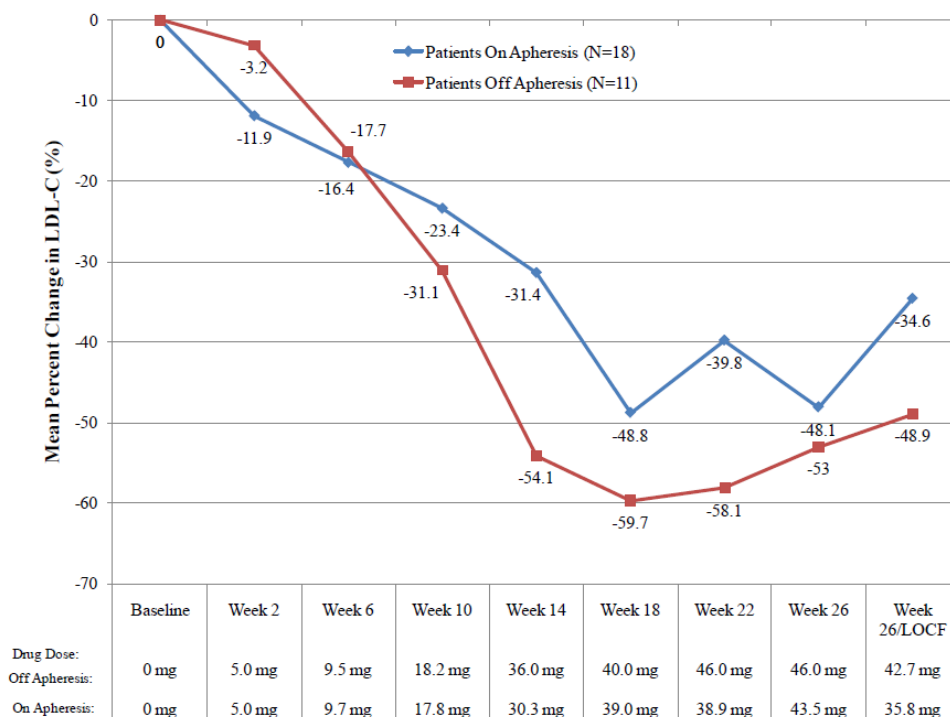
Shaded, bolded rows indicate timing discrepancies (see text).

A shorter time between apheresis to LDL-C measurement at week 26/LOCF, compared with the corresponding time at week -2 and 0, would be most likely to bias in favor of the drug. Of the 8 subjects I highlighted with more than ± 1 day discrepancy, this occurred in 4: 01-004, 11-003, 31-002, and 32-001.

- Subject 01-004 had week -2, 0, and 26 direct LDL-C values of 580, 501, and 272 mg/dL, respectively. The latter 2 values were both drawn 14 days after the preceding apheresis. The sponsor appears to have excluded the week -2 value in their baseline calculation for this subject, which is a conservative approach.
- Subject 11-003 had week -2, 0, and 26 direct LDL-C values of 359, 298, and 91 mg/dL, respectively. Drawing LDL-C two days early (12 vs. 14 days after apheresis) would not be expected to have this degree of impact (-72% change from baseline).
- Subject 31-002 had week -2, 0, and 26 direct LDL-C values of 433, 360, and 148 mg/dL, respectively. Although assessing LDL-C at 5 days after apheresis compared with 9 and 14 days is concerning, I note that this subject had an LDL-C value of 103 mg/dL at week 6, 35 days after apheresis; the subject had just finished 10 mg x 4 weeks. At the week 26 assessment, the dose was 20 mg. I believe it is unlikely that the apheresis timing substantially biased the efficacy assessment in this subject.
- Subject 32-001 had week -2, 0, and 26 direct LDL-C values of 341, 374, and 174 mg/dL, respectively. At the week 18 and week 22 assessments, which occurred 14 days after apheresis (similar to the baseline assessments), LDL-C was 123 mg/dL and 214 mg/dL, respectively. This subject took 5 mg from approximately week 7 onward as a result of level 3 hepatotoxicity, so the dose was constant across these visits. Therefore, it seems unlikely that the apheresis timing substantially biased the efficacy assessment in this subject.

Reviewer Comment: In conclusion, the apheresis timing discrepancies noted above do not alter my interpretation of the effect of lomitapide on LDL-C in this trial.

Among the 18 patients who were treated with apheresis during the efficacy period, mean baseline LDL-C was 325 mg/dL; among the 11 who were not being treated with apheresis, the mean baseline LDL-C was 355 mg/dL. Those who were *not* treated with apheresis had a larger mean % change in LDL-C from baseline to week 26/LOCF (-49% vs. -35%). Figure 24 depicts mean % change in LDL-C from baseline over time during the efficacy period.



Source: Table 14.1.2.8.3 and Table 14.2.2.13

Figure 24. HoFH-pivotal – Mean % Change in LDL-C During Efficacy Period by Apheresis

Source: HoFH-pivotal CSR, Figure 7.

Note that the applicant presented data available at each time point for this figure but that the last two “time points” are both week 26, just with and without LOCF imputation.

Notably, a larger proportion of subjects receiving apheresis discontinued the study during the efficacy phase compared with subjects not receiving apheresis (5 of 18 [28%] vs. 1 of 11 [9%]). Possibly related to this, the mean dose of study drug at week 26/LOCF was higher among those who were not receiving apheresis (43 mg vs. 36 mg). This may explain, or at least contribute to, the observed differences in LDL-C lowering between these subgroups.

Reviewer Comment: Taken together, these data suggest that lomitapide is effective in lowering LDL-C for both patients treated with and not treated with apheresis. In addition, apheresis-related factors were unlikely to have biased the assessment of the efficacy of lomitapide.

Individual LDL-C Profiles in HoFH-pivotal

Figure 25 presents the HoFH-pivotal subject-level direct LDL-C measurements available at the time of initial NDA submission (from ISE dataset *ADLP.xpt*). For the six subjects who discontinued early, the last LDL-C value recorded may have been drawn off treatment. As pertinent examples, subjects 13-002 and 22-003 each show a decrease in LDL-C with a return to near-baseline. The final LDL-C values were obtained approximately 2 weeks and 1 month after stopping drug, respectively.

Reviewer Comments: Although one could attempt to explain each upturn and downturn in LDL-C, this is difficult to do objectively since it's quite natural to seek supportive information retrospectively. As an example, subject 01-006 had a nadir LDL-C of 301 mg/dL (-2.0% from baseline) after 4 weeks at the 40 mg dose, which one may wish to attribute to the sponsor's statement, "Lomitapide compliance [during the efficacy phase] was only 52.5% for this subject." However, subject 02-002 had a -52% LDL-C reduction at week 26 despite a reported 47% compliance. The bottom line, in my opinion, is that many subjects can demonstrate large LDL-C reductions that, in many cases, are sustained. If approved, individual risk/benefit assessments would need to be made by practicing clinicians; this assessment may be different for those who exhibit erratic LDL-C profiles.

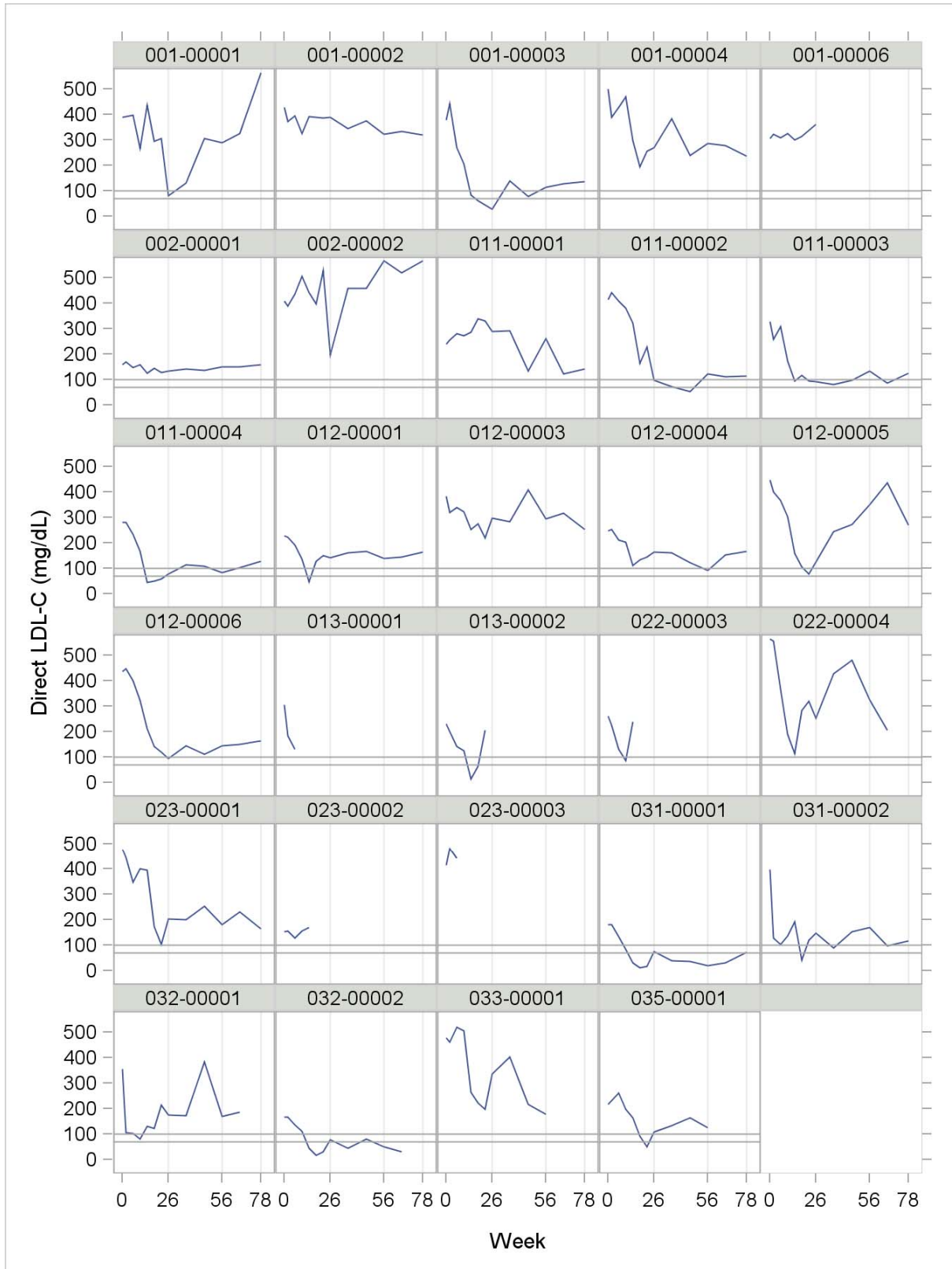


Figure 25. HoFH-pivotal – Subject-level LDL-C Profiles

Source: FDA clinical reviewer's analysis of *ADLP.xpt* dataset (no imputed values).
Horizontal reference lines at 70 mg/dL and 100 mg/dL.

Calculated LDL-C

All primary efficacy results were based on direct LDL-C levels. Results for calculated LDL-C during the efficacy phase were consistent with the direct measurements. Mean % change in calculated LDL-C from baseline to week 26/LOCF was -40.5% (compared with -40.1% for direct LDL-C); for the 23 completers, the mean % change was -49.8% (compared with -50.2%). The mean % change in calculated LDL-C from baseline to week 56 was -44.9% (compared with -44.0%).

Correlations Between Baseline LDL-C and Changes in LDL-C

Although assessing % change in LDL-C is common for lipid-lowering agents, I examined the association of both % change and absolute change with baseline LDL-C in HoFH-pivotal. Although both change parameters correlated with baseline LDL-C (i.e., subjects with higher LDL-C tended to have greater absolute and relative reductions in LDL-C), relative changes correlated less with baseline values (absolute change: Spearman $\rho = -0.58$, $p=0.001$; relative change: $\rho = -0.32$, $p=0.10$). These relationships are depicted in the following scatter plots (Figure 26).

Furthermore, I qualitatively assessed the normality of the distribution of % change measurements for LDL-C with a Q-Q plot, since this is the primary endpoint and analyses used paired t-tests. The normality assumption seems reasonable (Figure 27).

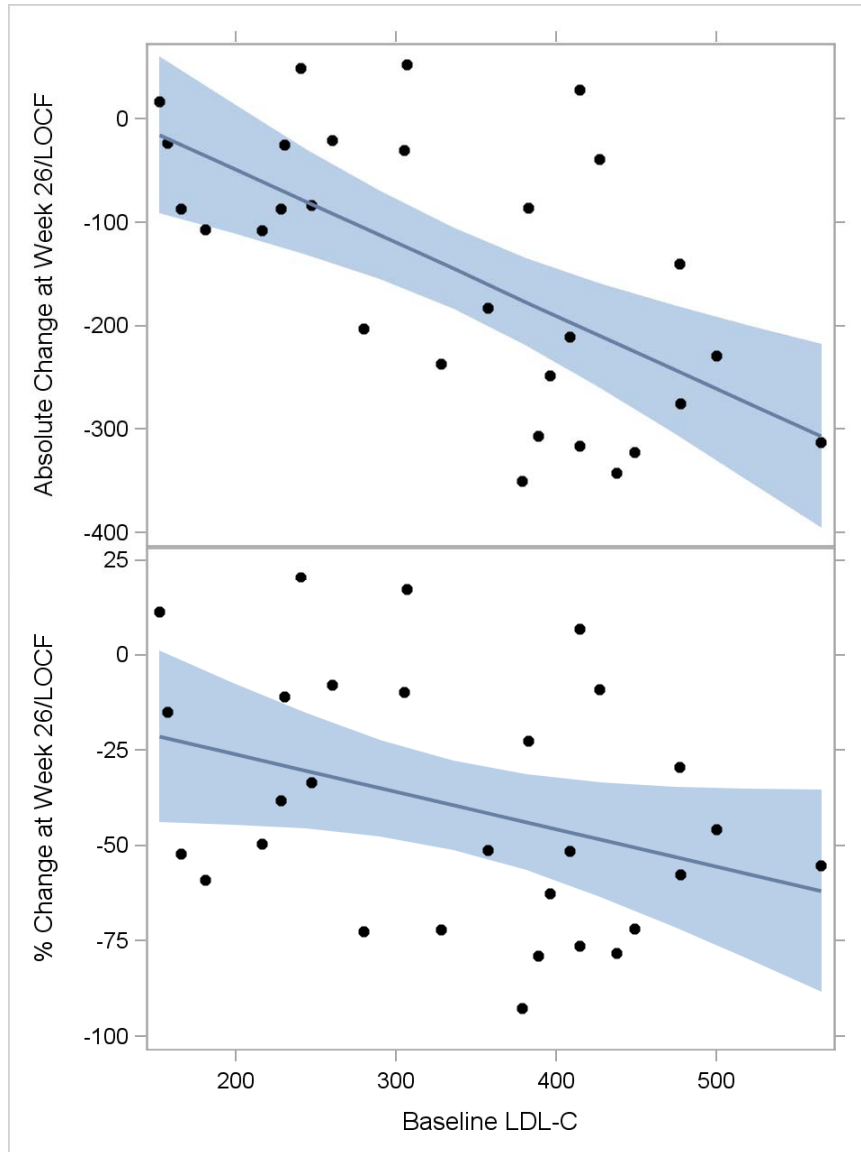


Figure 26. HoFH-pivotal – Correlation of Baseline and Change Measures of LDL-C

Source: FDA clinical reviewer's analysis of submitted HoFH-pivotal data in analysis dataset *ADLP.xpt*.

Regression line derived from simple linear regression; shaded area represents 95% confidence limits of the predicted mean.

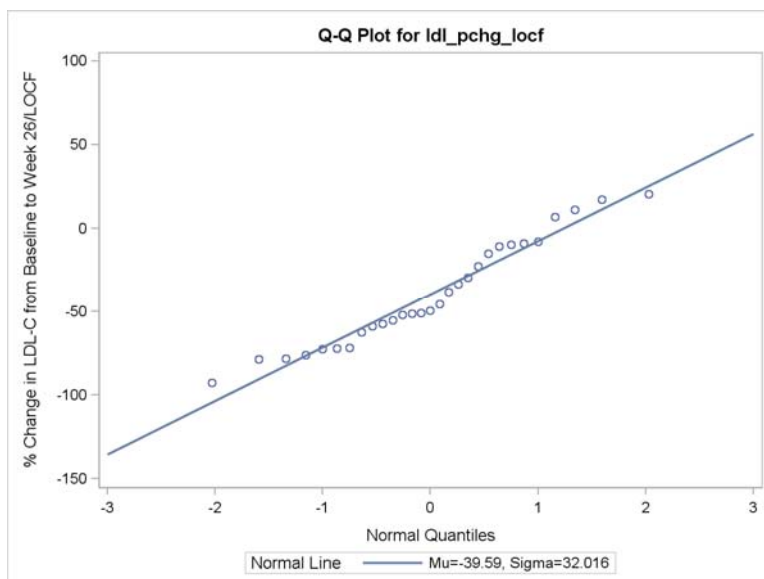


Figure 27. HoFH-pivotal – Q-Q plot of % Change in LDL-C at Week 26/LOCF
Source: FDA clinical reviewer’s analysis of submitted HoFH-pivotal data in analysis dataset *ADLP.xpt*.

Supportive Data for Primary Endpoint from HoFH-pilot

The mean % changes in LDL-C from baseline to the end of the 0.03, 0.1, 0.3, and 1.0 mg/kg/d dosing intervals (approximately 28 days each) were -3.7%, -7.1%, -24.7%, and -50.9%; $p \leq 0.0001$ by paired t-test for the last two time points. Table 70 summarizes the LDL-C values at the end of each dosing interval, the absolute and relative changes in LDL-C from baseline, and the mean daily dose taken during each period. Individual subject profiles are depicted in Figure 28.

Table 70. HoFH-pilot – Changes in LDL-C

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).

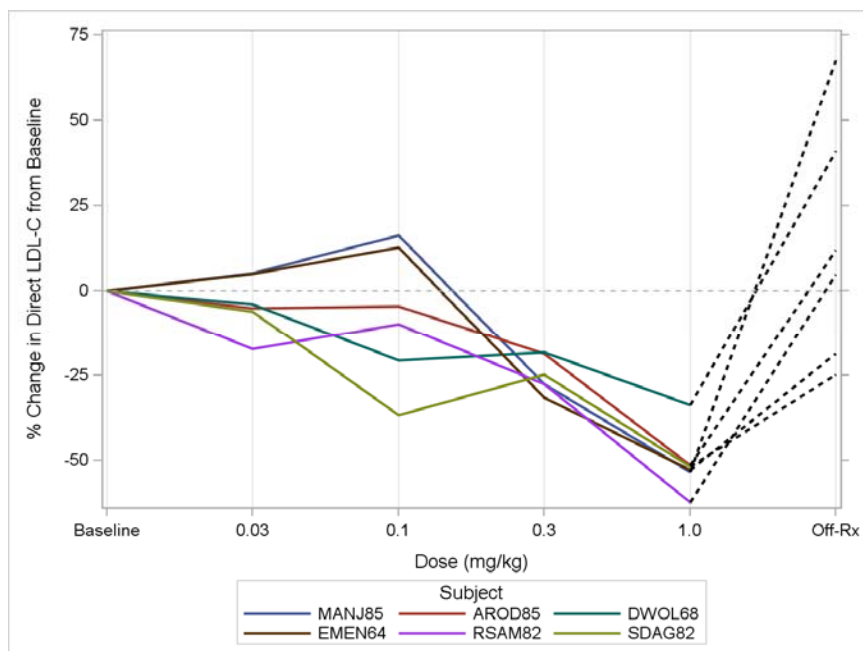


Figure 28. HoFH-pilot – % Change in LDL-C Over Time

Source: FDA clinical reviewer’s depiction of data in HoFH-pilot CSR Appendix 7f
“Off-Rx” represents the assessment conducted approximately 4 weeks after discontinuing lomitapide.

6.1.5 Analysis of Secondary Endpoints(s)

The secondary efficacy parameters for HoFH-pivotal were % change from baseline (mean of values at week -2 and week 0) to week 26 in TC, apoB, TG, non-HDL-C, VLDL-C, and Lp(a). The trial’s statistical analysis plan (v1.6; 17 May 2011) specified that the first three (TC, apoB, TG) were to be evaluated in a sequential fashion in the order listed, each at $\alpha=0.05$, each requiring significance of the preceding parameter. The remaining three parameters were to be evaluated similarly in a separate group of three.

Reviewer Comment: The secondary efficacy parameters were reordered in v1.2 (09 March 2011) of the HoFH-pivotal statistical analysis plan, and ordered testing of secondary endpoints was added in v1.3 (16 March 2011). These versions were not submitted to the NDA. Version 1.0 of the statistical analysis plan (09 August 2010) listed the following secondary efficacy parameters: mean % change and mean absolute change (baseline to week 26/LOCF) in TC, non-HDL-C, TG, VLDL-C, HDL-C, apoB, apoA1, and Lp(a).

Table 71 presents descriptive statistics for the secondary efficacy parameters in the ITT/Safety population. Baseline values were listed in Table 60.

Table 71. HoFH-pivotal – Secondary Efficacy Parameters at Week 26/LOCF

	Observed Value (Week 26/LOCF)	Absolute Change from Baseline	Relative Change from Baseline (%)	P*
Total Chol.				<0.001

	Observed Value (Week 26/LOCF)	Absolute Change from Baseline	Relative Change from Baseline (%)	P*
Mean (SD)	258 (118)	-172 (146)	-36.4 (28.2)	
95% CI	213-303	-227 to -116	-47.1 to -25.7	
Median	229	-131	-40.0	
Min, Max	88, 511	-399, +48	-81.4, +14.8	
ApoB				
Mean (SD)	148 (74)	-111 (97)	-39.4 (30.0)	<0.001
95% CI	120-176	-148 to -75	-50.8 to -28.0	
Median	131	-82	-46.2	
Min, Max	27, 305	-277, +38	-90.4, +19.0	
Triglycerides				
Mean (SD)	64 (45)	-40 (53)	-29.0 (55.7)	0.009
95% CI	46-81	-60 to -19	-50.2 to -7.8	
Median	57	-45	-44.6	
Min, Max	10, 220	-116, +93	-87.4 to +168.8	
Non-HDL-C				
Mean (SD)	217 (113)	-169 (141)	-40.0 (30.0)	<0.001
95% CI	174-260	-223 to -115	-51.3 to -28.8	
Median	195	-126	-47.7	
Min, Max	44, 474	-387, +45.0	-89.7, +15.7	
VLDL-C				
Mean (SD)	13 (9)	-8 (11)	-28.6 (57.5)	0.012
95% CI	9-16	-12 to -4	-50.5 to -6.8	
Median	11	-9	-45.1	
Min, Max	2, 44	-23, +19	-87.5, +183.3	
Lp(a) (nmol/L)				
Mean (SD)	62 (41)	-16 (36)	-11.0 (34.0)	0.094
95% CI	46-78	-30 to -2	-23.9 to +2.0	
Median	61	-9	-13.4	
Min, Max	9, 200	-138, +43	-62.9 to +88.1	

Source: Derived from HoFH-pivotal CSR Tables 16 and 17. Except for Lp(a), units are mg/dL for all observed values and absolute changes from baseline; corresponding units for Lp(a) are nmol/L.

* P-value based on paired t-test for mean % change.

Figure 29 depicts the mean ($\pm$ 95% CI) and median % changes in TC, apoB, TG, non-HDL-C, VLDL-C, and Lp(a) from baseline to each study visit through week 56 using available data (i.e., without LOCF imputation). In addition, the week 26/LOCF values for the mean ($\pm$ 95% CI) and median changes from baseline are shown.

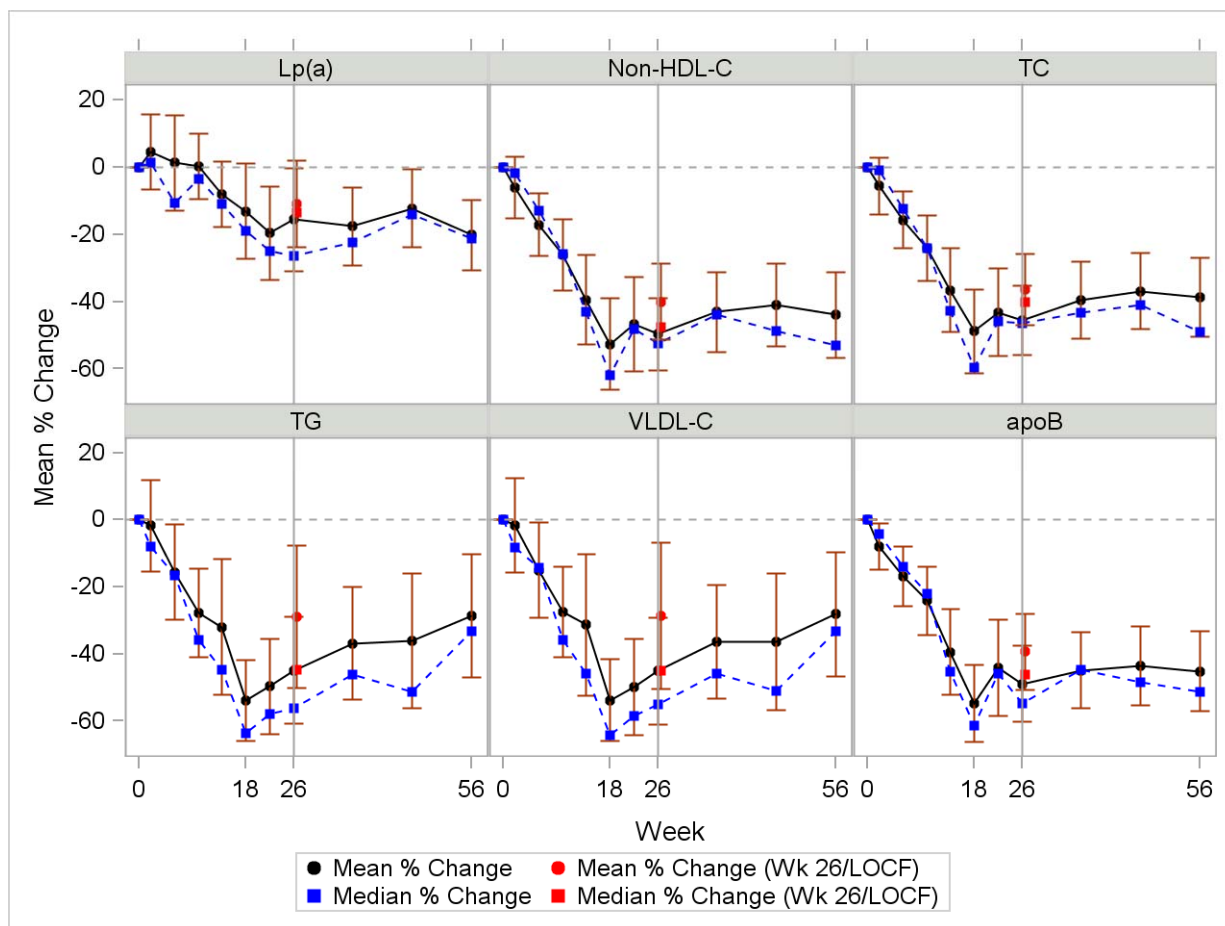


Figure 29. HoFH-pivotal – % Changes in Secondary Lipid Parameters

Source: FDA clinical reviewer's depiction of data in HoFH-pivotal CSR, Tables 14.2.2.4.1-6.1.

Error bars indicate 95% CI of mean values.

Vertical line at week 26 marks the end of the efficacy period.

Reviewer Comment: The applicant proposes that lomitapide should be indicated for the reduction of TG in the HoFH population. The data supporting a TG-lowering effect are somewhat sensitive to imputation: among the 23 completers, the upper bound of the 95% CI is an absolute 35.5 mg/dL reduction (-29% from baseline), but with LOCF imputation the upper bound is an absolute 19.3 mg/dL reduction (-7.8% from baseline). Although the P values for both are <0.001, these effect sizes are of questionable clinical significance, especially given that the HoFH population is not characterized by hypertriglyceridemia (median 92 mg/dL with a maximum of 253 mg/dL at baseline in HoFH-pivotal). Furthermore, the putative effect on TG appears to wane with time. Last, given that this was a single-arm uncontrolled trial, it seems plausible that dietary changes could account for some degree of the TG lowering observed.

HoFH-pilot Supportive Data for Secondary Endpoints

Mean (SD) % changes from baseline following each dosing period for several fasting lipid parameters in HoFH-pilot are summarized in Table 72.

Table 72. HoFH-pilot – Mean (SD) % Changes in Lipids after Each Dosing Period

Lipid Parameter	Lomitapide Dose [†]			
	0.03 mg/kg (Visit 5)	0.1 mg/kg (Visit 8)	0.3 mg/kg (Visit 11)	1.0 mg/kg (Visit 14)
LDL-C (direct)	-3.7 (8.3)	-7.1 (20.0)	-24.7 (5.3)****	-50.9 (9.3)****
Total chol.	-4.8 (9.9)	-9.3 (16.6)	-29.8 (9.2)***	-58.4 (8.6)****
ApoB	+10.2 (14.0)	-3.2 (18.8)	-14.7 (16.0)	-55.6 (13.5)***
Triglycerides	+4.1 (43.5)	-24.9 (39.7)	-34.1 (22.8)*	-65.2 (13.3)****
Non-HDL-C	-4.6 (10.1)	-9.7 (17.5)	-31.0 (9.3)***	-60.1 (8.9)****
VLDL-C	+34.4 (103.4)	+42.3 (142.5)	+3.3 (103.7)	-78.7 (23.1)***
Lp(a)	+1.0 (34.6)	+6.0 (22.9)	-18.7 (16.6)*	-10.5 (20.5)
HDL-C	-10.4 (9.0)*	+9.9 (25.6)	+11.6 (43.5)	-2.2 (18.0)
ApoAI	+34.2 (90.9)	+22.4 (61.5)	+38.7 (86.2)	-6.1 (26.4)

Source: HoFH-pilot CSR, Table 4 (and CSR's errata).

[†] Each subject's dose was escalated every ~28 days to the daily doses indicated; N=6 at each dose level.

* P<0.05; **P<0.01; ***P<0.001; ****P≤0.0001 (change from baseline; paired t test)

To show the consistency across subject for most parameters, subject-level % changes in fasting lipid parameters from baseline to the end of treatment with 1.0 mg/kg/d lomitapide in HoFH-pilot are presented in Table 73.

Table 73. HoFH-pilot – % Changes in Select Lipid Parameters after Lomitapide 1.0 mg/kg

Parameter	Subject						Mean
	MANJ85	AROD85	DWOL68	EMEN64	RSAM82	SDAG82	
TC	-62.4	-51.0	-50.9	-50.3	-66.8	-68.7	-58.4
apoB	-64.4	-45.4	-36.8	-49.6	-70.0	-67.2	-55.6
TG	-82.1	-56.9	-71.8	-43.9	-70.4	-66.0	-65.2
Non-HDL-C	-65.0	-52.1	-52.1	-52.4	-68.7	-70.5	-60.1
VLDL-C	-87.7	-76.2	-93.3	-33.3	-90.8	-92.0	-78.9
Lp(a)	+8.0	-21.1	-11.2	-21.7	+18.8	-36.1	-10.6

Source: HoFH-pilot CSR Table 5.

Reviewer Comments:

1. *These data are qualitatively similar to those observed in HoFH-pivotal.*
2. *Although not shown here, the values obtained approximately 4 weeks after stopping lomitapide were substantially higher than the results above, with most exceeding baseline levels. Post-treatment TG levels, however, remained lower than baseline for 5 of 6 subjects (-52%, -42%, -41%, -21%, -8%, and +185% compared with baseline at post-treatment followup). It cannot be determined from this trial design to what degree this reflects a residual drug effect versus dietary changes associated with the trial.*

6.1.6 Other Endpoints

Exploratory efficacy parameters in HoFH-pivotal were % change from baseline to each visit during the efficacy phase and to week 26 for calculated LDL-C (if TG <400 mg/dL), TC/HDL-C ratio, hsCRP, HDL-C, and apoAI. Calculated LDL-C results were presented in Section 6.1.4. In addition, the reduction or discontinuation of apheresis was examined.

HDL-C and ApoAI

Table 74 presents the descriptive statistics for changes in HDL-C and apoAI at week 26/LOCF. Baseline values were listed in Table 60. As shown in the figure and table that follow, these results were sensitive to imputation: at week 26, the mean % change in HDL-C from baseline was -6.9% with LOCF imputation (p=0.07) but -12.3% among completers (P=0.004); the changes in apoAI were similar.

Table 74. HoFH-pivotal – HDL-C and ApoAI at Week 26/LOCF (ITT/Safety)

	Observed Value (Week 26/LOCF)	Absolute Change from Baseline	Relative Change from Baseline (%)	P*
HDL-C				
Mean (SD)	41 (13)	-2.9 (8.7)	-6.9 (19.8)	0.072
95% CI	36-46	-6.3 to +0.4	-14.4 to +0.6	
Median	39	-2.5	-5.6	
Min, Max	17, 83	-18, +14	-48.5 to +28.4	
ApoAI				
Mean (SD)	105 (22)	-9.4 (20.4)	-6.5 (16.1)	0.038
95% CI	97-114	-17.1 to -1.7	-12.6 to -0.4	
Median	108	-4.5	-3.8	
Min, Max	50, 138	-57.5, +17.5	-40.8, +18.3	

Source: HoFH-pivotal CSR, Table 19.

Figure 30 depicts the mean ($\pm$ 95% CI) and median % changes in HDL-C and apoAI from baseline to each study visit through week 56 using available data (i.e., without LOCF imputation). In addition, the week 26/LOCF values for the mean ($\pm$ 95% CI) and median changes from baseline are shown.

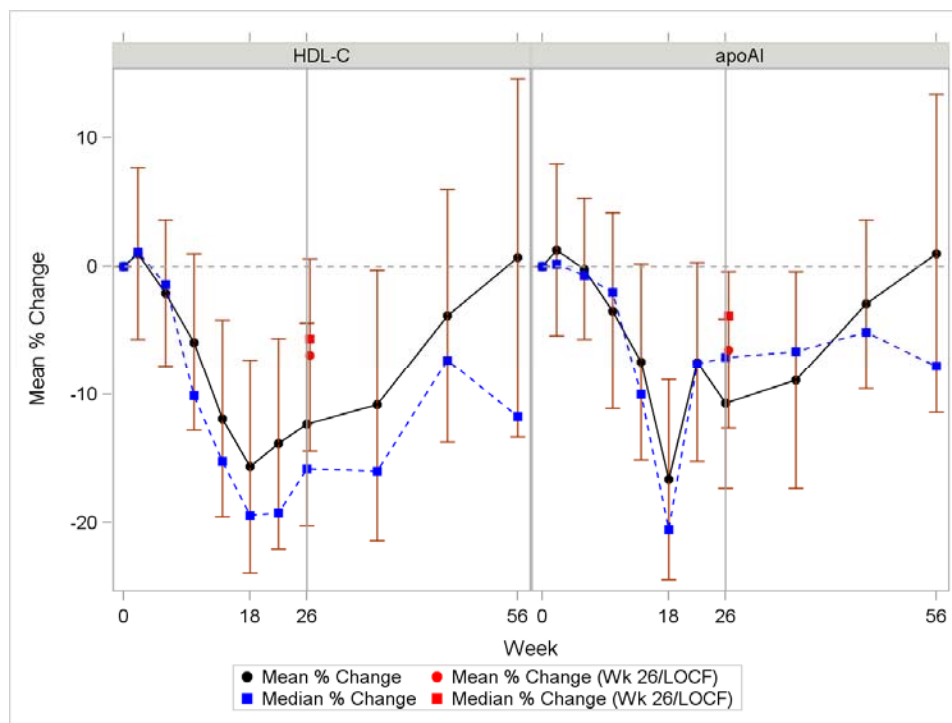


Figure 30. HoFH-pivotal – % Changes in HDL-C and ApoAI

Source: FDA clinical reviewer’s depiction of data in HoFH-pivotal CSR Tables 14.2.2,4.10-11.1. Error bars represent 95% CI of mean. Vertical line at week 26 marks the end of the efficacy period.

Values for changes in HDL-C and apoAI in the completers population (n=23) from baseline to weeks 26 and 56 are presented in Table 75.

Table 75. HoFH-pivotal – HDL-C and ApoAI at Weeks 26 & 56 (Completers)

VARIABLE STATISTIC	OBSERVED VALUE	OBSERVED CHANGE	PERCENT CHANGE	P-VALUE ¹
HDL-C (mg/dL), Mean (SD)				
Week 26	39.7 (14.16)	-5.2 (8.33)	-12.3 (18.23)	0.004
Week 56	44.8 (15.44)	-0.1 (12.53)	0.7 (32.25)	0.920
Apo AI (mg/dL), Mean (SD)				
Week 26	103.2 (23.95)	-14.4 (19.79)	-10.7 (15.20)	0.003
Week 56	114.4 (27.91)	-3.2 (28.22)	1.0 (28.74)	0.870

Source: Table 14.2.2.10.3, Table 14.2.2.11.3, Table 14.2.4.10.1.2 and Table 14.2.4.11.1.2

¹ p-value on the mean percent change from Baseline based on paired t-test.

Source: HoFH-pivotal CSR, Table 20.

Reviewer Comment: The mean changes in HDL-C and apoAI are in clinically undesirable directions at week 26; the lack of statistical significance in the week 26/LOCF analysis is not reassuring since the trial was not powered to detect changes of the observed magnitude. Furthermore, these results were sensitive to imputation. Whether the “return to baseline” in HDL-C observed from week 26 to week 56 reflects a

biological phenomenon (adaptation?) is speculative, but it seems more favorable than if the HDL-C reduction had been sustained. Ultimately, whether changes in HDL-C and apoA1 modify any potential effect of lomitapide on clinical outcomes is unknown, but this would be more of a concern for the general hypercholesterolemic population. HoFH is a disease of markedly abnormal levels of LDL that result from LDLR mutations; therefore, I would expect the benefit of lomitapide-associated observed reductions in LDL-C to outweigh any risk of the modest decreases in HDL-C.

In an exploratory analysis, I examined the association between changes in LDL-C and HDL-C from baseline to week 26/LOCF among the 29 subjects in HoFH-pivotal. As shown in Figure 31, there was a positive correlation between changes in LDL-C and HDL-C; i.e., larger reductions in LDL-C were associated with larger reductions in HDL-C, on average. A simple linear regression analysis suggested that each 100 mg/dL reduction in LDL-C is associated with an average HDL-C reduction of 3.8 mg/dL ($p=0.0013$; $R^2 = 32\%$). Adjusting for baseline HDL-C did not affect this result; additional covariates were not explored.

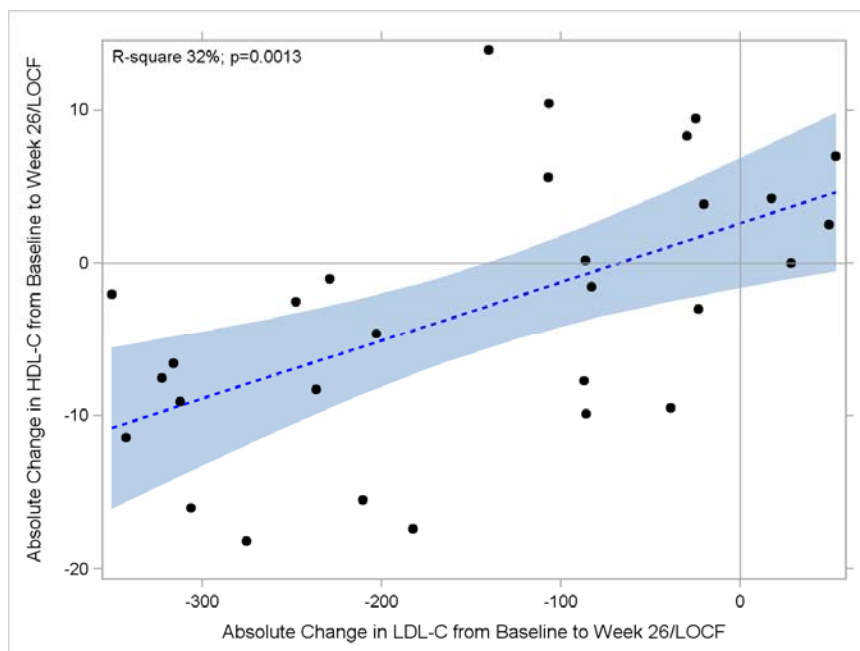


Figure 31. HoFH-pivotal – Association of Changes in LDL-C and HDL-C

Source: FDA clinical reviewer’s analysis of HoFH-pivotal data in submitted analysis dataset (*ADLP xpt*). Regression line (simple linear regression) with shaded 95% confidence limits for predicted mean values.

***Reviewer Comment:** From a risk/benefit perspective, it is reassuring that the larger reductions in HDL-C were typically observed in subjects who also exhibited the larger reductions in LDL-C.*

HoFH-pilot Data for HDL-C and Apo-A1

In HoFH-pilot, the mean % changes in HDL-C and apoA1 from baseline to approximately 4 weeks after the 1.0 mg/kg dose were -2.2% and -6.1%, respectively, and there was *not* a consistent trend over time. The mean % (SD) change in HDL-C from baseline to

approximately 4 weeks after dosing at 0.03, 0.1, 0.3, and 1.0 mg/kg lomitapide daily were -10.4% (9.0), +9.9% (25.6), +11.6% (43.5), and -2.2% (18.0), respectively. The corresponding values for apoA1 were +34.2% (90.9), +22.4% (61.5), +38.7% (86.2), and -6.1 (26.4), respectively.

Reviewer Comment: This observation of an increase in HDL-C and apoA1 from baseline to the end of the 0.3 mg/kg period, with a marked fall by the end of the 1.0 mg/kg period, was not observed in HoFH-pivotal (see Figure 30).

TC/HDL-C Ratio

For the 29 subjects in the HoFH-pivotal ITT/Safety population, the mean % change in TC/HDL-C ratio from baseline to week 26/LOCF was -33% ($p < 0.001$). For the 23 completers, the mean % changes from baseline to week 26 and week 56 were both -38% ($p < 0.001$ for both).

High-sensitivity C-Reactive Protein

hsCRP was measured at each study visit during the efficacy and safety phases of HoFH-pivotal. For the 29 subjects in the HoFH-pivotal ITT/Safety population, the median hsCRP was 2.0 mg/L at baseline and 0.9 mg/L at week 26/LOCF; the median change from baseline was -0.5 mg/L ($p = 0.052$). For the 23 completers, the median hsCRP was 1.7 mg/L at baseline, 1.2 mg/L at week 26, and 1.1 mg/L at week 56; the median changes from baseline to weeks 26 and 56 were -0.2 mg/L and -0.5 mg/L, respectively.

Reduction or Discontinuation of Apheresis

Subjects in HoFH-pivotal were not supposed to alter their apheresis regimens during the efficacy phase of the trial. During the safety phase, regimens could be altered at the discretion of the investigators. Of the 18 subjects on apheresis at the beginning of the trial, 5 discontinued prior to week 26 (subjects 01-006, 13-001; 13-002; 23-002; 23-003). Of the 13 subjects who entered the safety phase on apheresis, 6 were able to either stop (subjects 01-003, 31-001, and 31-002) or increase the typical interval between apheresis treatments (subjects 02-001, 23-001, and 35-001) (Figure 23).

Appendix Figure 65 through Figure 70 depict the LDL-C profiles for these six subjects and include overlays for apheresis treatments, the time of last apheresis (or approximate time of last apheresis on the “typical” schedule), and all changes in concomitant lipid-lowering medications listed in the HoFH-pivotal concomitant medication dataset (*CM.xpt*). Among the three subjects who discontinued apheresis entirely during the pivotal trial, two appeared to have a subsequent rise in LDL-C but remained $\geq 50\%$ below baseline without changes in concomitant medications to account for the maintained reduction. Among the three who reduced the frequency of apheresis, one had relatively well-maintained LDL-C levels (Appendix Figure 70); one had a relatively flat LDL-C profile throughout the study with a slight continued upward trend that predated the reduction in apheresis frequency (Appendix Figure 68); and one reduced apheresis frequency during the lomitapide titration period (initially noncompliant but with permission sometime after week 26), precluding assessment of what the

maximal effect of lomitapide and apheresis would have been in this subject (Appendix Figure 69).

Six (32%) of the 19 subjects who entered HoFH-extension were receiving apheresis at the time of entry into the extension study. According to the applicant, one of these subjects (11-003) was able to permanently discontinue apheresis during the extension study. The submitted concomitant dataset for HoFH-extension, which lists apheresis treatments, is incomplete, precluding my confirmation of this additional subject.

Combining HoFH-pivotal and its extension, therefore, presumably a total of 7 subjects were able to either stop (n=4) or increase the interval between apheresis treatments (n=3).

Reviewer Comment: It should not be assumed that reducing the frequency or discontinuing apheresis will benefit patients with HoFH; in fact, this may be detrimental given the increase in time-averaged LDL-C concentration that likely accompanies the reduction or removal of an LDL-lowering treatment. Although this is a time-consuming, costly procedure associated with its own set of complications and challenges, the net risk/benefit of apheresis compared with lomitapide on clinical outcomes is unknown.

6.1.7 Subpopulations

Because HoFH-pivotal involved 29 subjects total, subgroup analyses related to age, gender, race, and ethnicity were not performed for the HoFH population. LDL-C reduction by apheresis status was described in Section 6.1.4 (p. 132). Subgroup analyses by region (US/Canada, n=12; S. Africa/Italy, n=17) did not suggest clinically meaningful differences in treatment effect by region.

Using a pool of five phase 2 studies (A-001, A-003b, A-004, A-006, and C-009), which ranged from 4 to 12 weeks in duration and used lomitapide dosages of 2.5 to 25 mg daily, the applicant performed subgroup analyses by age (<65, ≥65 years), sex, race (Caucasian vs. non-Caucasian), ethnicity (Hispanic/Latino vs. non-Hispanic/Latino), BMI (<30 vs. ≥30 kg/m²), smoking status (current vs. not current smoker), and baseline LDL-C tertiles. Efficacy was assessed across subgroups at week 4 and week 8 within pools of lomitapide dose groups. These analyses were extremely limited based on their sample sizes, but no consistent differences in treatment effect were observed in these subgroups.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The applicant's dosing recommendations include (1) escalation from 5 mg daily to a maximum of 60 mg daily; (2) adherence to a diet consisting of <20% total energy as fat; (3) administration with a glass of water at bedtime without food; (4) dietary supplements, as described previously.

The applicant notes that early clinical development of lomitapide focused on fixed doses of lomitapide without strict control of dietary fat. In the phase 2 study CV145-009, involving subjects with hypercholesterolemia, lomitapide 25 mg daily for 4 weeks led to diarrhea in 31 (82%) of 38 subjects, with 23 episodes graded as moderate or severe, leading to early discontinuation for 5 (13%) lomitapide-treated subjects. Subsequently, the 6-subject HoFH-pilot trial used a dose-escalation regimen (approximately 2 mg daily to 67 mg daily during the 16-week trial) and instructed the subjects to consume <10% energy from dietary fat. All of these subjects completed the trial; the mean dietary fat intake was 17% overall, and gastrointestinal adverse events were described as “manageable.” This pilot study informed the design of HoFH-pivotal, in which the dose was escalated every 4 weeks and subjects were instructed to adhere to a diet consisting of <20% total energy as fat. Despite this recommendation, gastrointestinal adverse events were near-ubiquitous.

The applicant’s rationale for taking lomitapide without food is, in part, based on food-effect study CV145-005, in which the incidence of adverse events (primarily gastrointestinal) doubled when lomitapide was administered with a high-fat breakfast (Table 122) compared with the fasting state or placebo. In addition, the applicant suggests that taking lomitapide in the evening may be better tolerated than morning (fasting) administration so that the drug is well absorbed prior to eating.

Changes in fat-soluble nutrients associated with lomitapide, which form the basis for the recommendation to take dietary supplements, are discussed in Section 7.3.5 (p. 191).

Reviewer Comments:

1. *I agree with recommending a dose-escalation regimen.*
2. *The infrequent diet records collected during this trial provide inadequate data to support the recommendation to maintain a diet with <20% energy as fat, but the mechanism of action of the drug and the experience early in development do provide some basis.*
3. *Although the recommendation for evening dosing has not been formally tested to show improved tolerability, it seems reasonable.*
4. *It is unknown whether lomitapide affects the absorption of dietary supplements or whether the doses of supplement components are optimal.*

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Durability of LDL-C Reduction in HoFH-pivotal

During the safety phase of HoFH-pivotal, LDL-C increased modestly, predominantly during the first 10 weeks of this period. Recall that changes to background lipid-lowering therapy could be made during this period; therefore, changes in lipid parameters after week 26 may not be related to effects of lomitapide. Table 76 shows the baseline, week 26, and safety phase LDL-C values for the 23 subjects who completed week 56. At week 56, the mean % change in LDL-C from baseline among these 23 subjects was -44%.

Table 76. HoFH-pivotal – LDL-C During Safety Period through Week 56

	Mean (SD)	Mean Absolute Change (mg/dL) From . . .		Median Absolute Change (mg/dL) From . . .	
		Baseline	Week 26	Baseline	Week 26
LDL-C (mg/dL)					
Baseline	352 (116)	-	-	-	-
Week 26	168 (96)	-185 (115)	-	-203	-
Week 36	202 (127)	-150 (109)	+35 (77)	-137	+7
Week 46	210 (134)	-142 (117)	+43 (109)	-125	+15
Week 56	199 (123)	-153 (114)	+31 (110)	-162	+15

Source: HoFH-pivotal CSR, Tables 14.2.1.1.3, 14.2.3.1.1.2, and 14.2.3.1.2.1
N=23 for all cells.

The sponsor has not submitted efficacy analyses between weeks 56 and 78, but my analysis of the datasets provided does not suggest a substantial attenuation of effect during these 22 weeks. The mean (SD) direct LDL-C at week 66 was 195 (124) mg/dL and at week 78 was 211 (133) mg/dL (Figure 32).

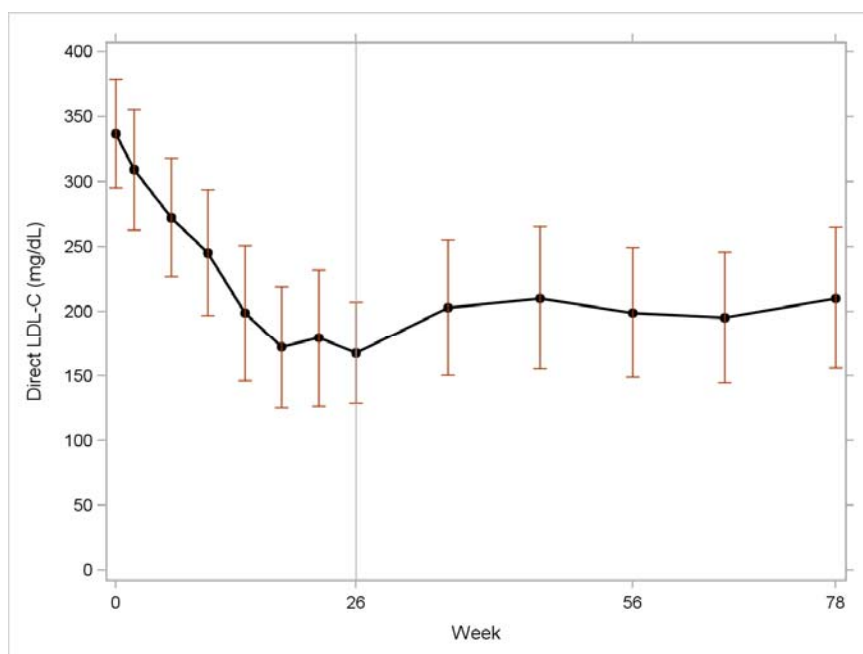


Figure 32. HoFH-pivotal – LDL-C Through End of Trial (Week 78)

Source: FDA clinical reviewer’s analysis of submitted HoFH-pivotal laboratory dataset (LB.xpt). Only available data were used (i.e., no LOCF imputation). Unscheduled visits were excluded. N=23 for all time points from week 22 through 78. Error bars indicate 95% CI of the mean.

Secondary Lipid Parameters

In support of durability of effect of lomitapide on secondary lipid parameters in HoFH-pivotal, the applicant provided values for the completers population (n=23) at weeks 26 and 56 (Table 77). Note that the p-values are based on mean % change from baseline based on the paired t-test, even for triglycerides and Lp(a), which are skewed distributions (median values are listed in the table).

Table 77. HoFH-pivotal – Secondary Efficacy Parameters at Weeks 26 & 56 (Completers)

VARIABLE STATISTIC	OBSERVED VALUE	OBSERVED CHANGE	PERCENT CHANGE	P-VALUE ²
TC (mg/dL), Mean (SD)				
Week 26	235.8 (112.29)	-215.5 (131.84)	-45.7 (23.70)	< 0.001
Week 56	274.0 (144.19)	-177.2 (138.33)	-38.8 (27.02)	< 0.001
apo B (mg/dL), Mean (SD)				
Week 26	132.9 (70.81)	-138.6 (90.10)	-48.9 (26.12)	< 0.001
Week 56	148.8 (83.13)	-122.7 (83.30)	-45.2 (27.63)	< 0.001
Triglycerides (mg/dL), Median				
Week 26	43.0	-54.0	-56.1	< 0.001
Week 56	61.0	-34.0	-33.3	0.004
Non-HDL-C (mg/dL), Mean (SD)				
Week 26	196.1 (107.22)	-210.3 (128.43)	-49.7 (24.95)	< 0.001
Week 56	229.3 (138.71)	-177.1 (131.80)	-43.9 (29.39)	< 0.001
VLDL-C (mg/dL), Mean (SD)				
Week 26	11.3 (7.61)	-10.9 (8.84)	-45.1 (36.53)	< 0.001
Week 56	16.3 (13.93)	-6.0 (11.27)	-28.2 (42.81)	0.005
Lp(a) (nmol/L), Median				
Week 26	48.4	-12.8	-26.4	0.048
Week 56	56.2	-15.9	-21.1	< 0.001

Source: Table 14.2.2.1.3, Table 14.2.4.1.1.2, Table 14.2.2.2.3, Table 14.2.4.2.1.2, Table 14.2.2.3.3, Table 14.2.4.3.1.2, Table 14.2.2.4.3, Table 14.2.4.4.1.2, Table 14.2.2.5.3, Table 14.2.4.5.1.2, Table 14.2.2.6.3, and Table 14.2.4.6.1.2

1 Medians are presented for triglycerides and Lp(a); p-value is based on the mean percent change

2 p-value on the mean percent change from Baseline based on paired t-test.

Source: HoFH-pivotal CSR, Table 18.

6.1.10 Additional Efficacy Issues/Analyses

Not applicable; additional analyses were presented in the preceding sections.

7 Review of Safety

Safety Summary

The primary database used to evaluate the long-term safety of lomitapide in HoFH is the 29-subject pivotal phase 3 trial and its extension study. Of the 23 subjects who completed the pivotal trial, 19 enrolled in the ongoing extension study as of 31 December 2011, and 18 have had at least one follow-up visit. Although the applicant also generated a safety pool from two phase 1 and five phase 2 trials, which comprises 482 subjects exposed to lomitapide, the doses used in these trials were generally far

lower than those proposed for HoFH (i.e., not exceeding 10 mg daily for trials of 8-12-week duration).

Deaths

There has been one death in the lomitapide development program. A 54-year-old man completed a 12-week phase 2 study in which he received lomitapide 5-10 mg daily; seven days after drug discontinuation, he died of a myocardial infarction.

Serious Adverse Events

In the HoFH pivotal trial, 3 (10%) of 29 subjects had at least one serious adverse event (SAE). In the extension study, 4 (22%) of 18 subjects have had at least one SAE as of the cutoff date for the 120-day safety update (31 December 2011), including one subject who had a hepatotoxicity event leading to drug withdrawal (ALT 24x ULN). In the HoFH pilot study, one of the six subjects had an SAE. A total of eight SAEs were reported in the phase 1 and 2 programs combined, including two myocardial infarctions in subjects taking lomitapide 5 mg or 10 mg daily in an 8-week phase 2 trial.

Adverse Events Leading to Discontinuation

Six (21%) of the 29 subjects in the HoFH pivotal trial discontinued study treatment prematurely: two subjects withdrew for gastrointestinal symptoms, three withdrew consent with AEs suspected to have played a role (headaches; unstable INR and gastrointestinal symptoms; and diarrhea), and one stopped lomitapide after four days because of "anxiety related to experiencing possible GI side effects." In the ongoing extension study, two of the four subjects who discontinued prior to the data cutoff date stopped because of AEs (both related to abnormal serum transaminases). None of the six subjects in the HoFH pilot study discontinued prematurely. In the applicant's phase 1/2 safety pool, 118 (24%) of 482 lomitapide-treated subjects prematurely discontinued because of AEs, the majority of which were related to gastrointestinal symptoms or transaminase abnormalities.

Common Adverse Events

In the HoFH pivotal trial, the most common adverse events fell in the Gastrointestinal Disorders Systems Organ Class (SOC), with 27 (93%) of 29 subjects experiencing at least one such event. Diarrhea, nausea, vomiting, dyspepsia, and abdominal pain all occurred in >25% of subjects. Adverse events in the Infections and Infestations SOC occurred in 17 (59%) of subjects, with influenza being the most common (21%). Adverse events in the Investigations SOC occurred in 15 (52%) of subjects in the pivotal trial, including decreased weight (24%), increased ALT (17%), increased AST (7%), and increased transaminases (7%). Additional common adverse events are described later in this document; note that the lack of a control arm and the small size of the pivotal trial limit interpretation of many of the non-serious adverse events that occurred in few patients.

Targeted Safety Issues

Hepatic Safety

In the HoFH phase 3 program (pivotal trial and its extension), 11 (38%) of the 29 subjects ever experienced ALT ≥ 3 x ULN, and 7 (24%) had a peak ≥ 5 x ULN. None of these subjects had concomitant bilirubin, alkaline phosphatase, or INR values that raised concern for abnormal liver function. These abnormalities occurred across a wide range of lomitapide doses (10 mg to 60 mg). Although most subjects had a first abnormality during the efficacy phase of the trial (i.e., before week 26), this was not universal; one subject had a first ALT ≥ 3 x ULN during the extension study. Review of narratives and longitudinal profiles of transaminases over time revealed that transaminase abnormalities ≥ 5 x ULN were reversible, with improvements typically noted within 2-4 weeks of dose modification. Because dose reduction was not mandated for ALT values in the 3-5xULN range, these profiles also demonstrated that transaminases sometimes decrease despite continued dosing.

Regarding hepatic fat, all eligible subjects had hepatic fat measured by NMRS/MRI at weeks 0, 26, 56, and 78 in the pivotal trial. The mean absolute change in % hepatic fat from baseline to week 26 was +8.1% and to week 78 was +7.4%. Eighteen (78%) of 23 subjects with available data demonstrated a maximum absolute increase in hepatic fat $>5\%$, and three (13%) had an absolute increase $>20\%$. Data from an early phase 2 study conducted by BMS, in addition to limited data from the HoFH program, suggest that the accumulation of hepatic fat is reversible following discontinuation of lomitapide. Whether histologic sequelae remain, however, is unknown given the lack of protocol-mandated liver biopsies.

Fat-soluble Vitamins and Fatty Acids

Given its mechanism of action, lomitapide could potentially lead to deficiencies in fat-soluble nutrients by inducing intestinal fat malabsorption. In the phase 2 HoFH proof-of-concept study, mean decreases from baseline to the end of treatment were observed in several fatty acid parameters (alpha-linolenic acid, gamma-linolenic acid, linoleic acid, arachidonic acid, eicosapentaenoic acid, docosahexaenoic acid, and docosapentaenoic acid), with statistically significant reductions at daily doses of 0.3 mg/kg and 1.0 mg/kg. Thus, in the pivotal trial, subjects were provided dietary supplements containing vitamin E, linoleic acid, alpha-linolenic acid, EPA, and DHA. On average, levels of vitamins A and D tended to increase over time, and there was no substantial change in vitamin K deficiency as assessed by proportion of osteocalcin that was uncarboxylated. Total vitamin E decreased a median -43.3% at week 26 and -40.7% at week 78, which was not unexpected given that apoB-containing lipoproteins are required for vitamin E absorption and transport. Notably, however, the ratio of serum vitamin E:lipid (TC+TG) was relatively stable, suggesting that the observed decrease in vitamin E was not the result of malabsorption but rather the result of lomitapide's effect on serum lipoproteins. Regarding fatty acids, the trends over time suggest reductions in all fatty acids during approximately the first 26 weeks of therapy with subsequent stabilization and/or trends toward baseline.

Body Weight

Given the potential for lomitapide to induce fat malabsorption, body weight and dietary intake were monitored during the pivotal trial. The mean change in weight from baseline

to week 26/LOCF was -4.3%, followed by relative stability through the subsequent one-year safety phase.

Pulmonary Function

Early in the lomitapide development program, a nonclinical signal suggesting pulmonary phospholipidosis was identified that led to MTP inhibitors, as a class, being placed on partial clinical hold (with the exception of study in HoFH). This concern was later contextualized with the identification of approved products that demonstrated similar preclinical findings at similar exposure safety margins. Nevertheless, pulmonary function was assessed by spirometry with DLCO during several trials of the development program. To date, no lomitapide-associated changes in pulmonary function have been detected.

Bleeding/Coagulation-related Issues

In the HoFH pilot study, two subjects who were receiving concomitant warfarin required warfarin dose adjustments based on INR levels. A dedicated drug-drug interaction study subsequently confirmed a lomitapide-warfarin pharmacokinetic and pharmacodynamic interaction; therefore, INR was prospectively measured during the pivotal trial. One subject discontinued prematurely, in part, as a result of an unstable INR spanning weeks 6 through 22. Another subject taking warfarin had four SAEs related to bleeding/anticoagulation management (menorrhagia leading to hypovolemic shock; hospitalization for heparinization as a result of subtherapeutic INR; hospitalization for transfusion as a result of menorrhagia; and a hospitalization for stroke symptoms with acute subdural and intraventricular hemorrhages). Without a placebo group and with so few subjects in the pivotal trial, it is difficult to ascertain whether these events may have occurred with greater regularity than expected from warfarin alone.

Myopathy

The definitions and reporting of rhabdomyolysis and myopathy as adverse events were not pre-specified in the lomitapide development program. Using the Standardized MedDRA Query (SMQ) for "Rhabdomyolysis/Myopathy," the applicant identified six subjects that may have had such an event during the pilot, pivotal, or extension studies. In all cases, the investigators felt these events were unlikely to be related to lomitapide, and no events were reported to be rhabdomyolysis. Four of these subjects were taking concomitant statins at the time these events were reported; no dose adjustments to either lomitapide or statins were made in response to these events. Query of the laboratory dataset revealed that three subjects in the pivotal trial or its extension had CK elevations $\geq 5x$ ULN, the highest of which was an isolated value of $35x$ ULN in the extension study. These three subjects were all taking concomitant statins, but no dose adjustments to either the statin or lomitapide were made.

Neoplasms

Genetic toxicology studies suggest that lomitapide is not a direct-acting mutagen. Two 2-year carcinogenicity studies were conducted in mice and rats, revealing a statistically significant increase in hepatocellular neoplasms and small intestinal adenomas/carcinomas in mice. The no-observed effect levels for drug-related

neoplasms in male and female mice confer clinical safety margins of 0.4 to 2x the exposures expected from lomitapide 60 mg daily in humans. No drug-related neoplasms were observed in the rat at any dose tested, giving clinical safety margins of at least 6-8x. The effect of lomitapide on fecal fat and fecal bile acids, which might promote colonic carcinogenesis, has not been studied in humans. To date, however, no neoplasms have been observed in the lomitapide development program.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary trial used to evaluate the long-term safety of lomitapide in HoFH is the 29-subject HoFH-pivotal trial. This trial provides the longest duration of the highest dosages of any studies in the lomitapide development program, even though relatively few subjects were exposed. The ongoing HoFH extension study provides additional data for this population.

The applicant also generated a safety pool designated “adults with elevated LDL-C and other CV risk factors” from two phase 1 and five phase 2 trials. The lomitapide regimens, sizes, and durations of these trials are briefly summarized in Table 78. Additional details are provided in Table 6 and Table 8, and reviews of the individual phase 2 trials were presented in Section 5.3 (p. 51).

Table 78. Applicant's "Elevated LDL-C" Safety Pool

Study Identifier	N (Any Lomit / Total)	Lomitapide Regimen(s)	Comparator(s)	Duration
CV145-002	24 / 36	10, 25, 50, or 100 mg	placebo	2 weeks (1 week for 100mg)
CV145-010	12 / 18	10 or 25 mg	placebo	2 weeks
CV145-009	38 / 76	25 mg	placebo	4 weeks
AEGR-733-001	56 / 85	5 to 7.5 to 10 mg at 4-week intervals (with ezetimibe)	ezetimibe	12 weeks
AEGR-733-003b	104 / 157	5 or 10 mg alone or with atorvastatin	placebo or atorvastatin	8 weeks
AEGR-733-004	227 / 260	2.5, 5, 7.5, or 10 mg monotherapy, or 5 mg with either atorvastatin, fenofibrate, or ezetimibe	placebo	12 weeks
AEGR-733-006	21 / 44	2.5 to 5 mg daily at 4-week interval (with atorvastatin)	atorvastatin	8 weeks

Given the low doses typically used, the short and heterogeneous durations, and the exploratory nature of these trials, I do not present much from this phase 1/2 pool in this document. This pool was primarily used in an exploratory fashion to screen for safety signals that may not have been identified in the 29-subject HoFH phase 3 trial.

As described in Section 5.3, a total of 915 subjects ever received an oral dose of lomitapide, either as monotherapy or combined with other lipid-lowering drugs. Of these,

307 (34%) were enrolled in phase 1 protocols, 446 (49%) in controlled phase 2 protocols (4-12 weeks), 133 (15%) in uncontrolled phase 2 protocols (drug-drug interaction study and HoFH-pilot), and 29 (3%) in the HoFH-pivotal trial (Table 10).

7.1.2 Categorization of Adverse Events

For HoFH-pivotal, MedDRA v11.0 was used to categorize adverse events. My review confirmed that each verbatim term in this trial mapped to a single preferred term. Furthermore, I reviewed the coding of each unique verbatim term with its mapped preferred term and all seemed reasonable.

Several versions of MedDRA were used across the lomitapide phase 2/3 development program. In response to an FDA information request (07 May 2012) regarding the methods used to upversion each trial's adverse events to v14.0 for the ISS, the applicant stated that all unique verbatim terms were pooled across studies and run against the MedDRA dictionary for exact matches. For verbatim terms that did not have an exact match, manual review was performed by a trained medical coder to get the most appropriate match from MedDRA.

Reviewer Comment: This is an acceptable approach since the re-coding was performed from verbatim terms directly instead of from the originally coded preferred terms.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The focus of the safety review was the 29-subject phase 3 HoFH-pivotal trial. These data were not pooled with any other trial, including the 6-subject HoFH-pilot trial.

The applicant pooled data from two 14-day phase 1 and five phase 2 trials, ranging from 4 to 12 weeks, into an "Elevated LDL and Other CV Risk Factors" safety pool as described in Section 7.1.1. Because these trials used a range of lomitapide doses as well as dosing schedules (fixed-dose vs. forced-titration regimens), the applicant pooled lomitapide-treated subjects into the following dose groups:

- *Escalated 5-10 mg*: Lomitapide escalated from 2.5 to 5 mg (8-week study AEGR-733-006) or from 5 to 7.5 to 10 mg (12-week study AEGR-733-001);
- *Low-dose (2.5-7.5 mg)*: Fixed lomitapide dose ± coadministration with other lipid-lowering therapy; AEGR-733-003b and -004 contribute.
- *Mid-dose (10 mg)*: Fixed lomitapide dose ± coadministration with other lipid-lowering therapy; CV145-002, -010, AEGR-733-003b, and -004 contribute.
- *High-dose (25-100 mg)*: Fixed lomitapide dose; CV145-002, -009, and -010 contribute.

Given the marked differences between study designs in the HoFH trials and the rest of the development program, no attempts were made to compare incidence of AEs quantitatively between pools.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Exposure in HoFH Population (Phase 3)

Table 79 summarizes the duration of exposure to lomitapide in the HoFH-pivotal trial, its extension, and overall. The applicant states that this table accounts for recorded interruptions in study drug. The overall phase 3 HoFH safety database includes 23 subjects who were exposed to lomitapide (at any dose) for at least one year, 15 subjects who were exposed for at least two years, and 5 subjects who were exposed for at least three years.

Table 79. Duration of Exposure to Lomitapide (HoFH-pivotal and extension)

Duration of Treatment	HoFH-pivotal (N=29)	HoFH-extension (N=18)	Overall (N=29)
Summary Statistics: Days			
Mean (SD)	444 (193)	370 (188)	674 (374)
Median [IQR]	539 [502, 546]	382 [224, 581]	736 [502, 958]
Range	4 to 560	84 to 728	4 to 1274
N (%) of Subjects			
1-30 days	1 (3%)	0	1 (3%)
31-91 days	3 (10%)	2 (11%)	3 (10%)
92-182 days	2 (7%)	1 (6%)	2 (7%)
183-365 days	0	5 (28%)	0
366-545 days	13 (45%)	5 (28%)	4 (14%)
546-730 days	10 (35%)	5 (28%)	4 (14%)
731-1096 days	0	0	10 (35%)
1097-1461 days	0	0	5 (17%)

Source: 120-day safety update, Table 1.1.3.

Regarding dose, Table 80 and Table 81 summarize the durations of exposure by mean daily dose in HoFH-pivotal and its extension study, respectively. Because mean daily dose in these tables incorporates compliance data (pill counts, which were frequently missing), their validity is questionable.

Table 80. Exposure to Lomitapide in HoFH-pivotal

Duration (days)	Mean Lomitapide Daily Dose						Any dose	%
	≤5	(5, 10]	(10, 20]	(20, 40]	(40, 60]	>60		
1-30	1	0	0	0	0	0	1	3%
31-91	2	0	1	0	0	0	3	10%
92-182	0	2	0	0	0	0	2	7%
183-365	0	0	0	0	0	0	0	0
366-545	0	1	3	5	4	0	13	45%
546-730	0	0	1	5	4	0	10	34%
Any time	3	3	5	10	8	0	29	100%
%	10%	10%	17%	35%	28%	0%	100%	

Source: 120-day safety update, Table 1.1.4A.

Notation: (10, 20] = 10 < dose ≤ 20

Table 81. Exposure to Lomitapide in HoFH-extension

Duration (days)	Mean Lomitapide Daily Dose						Any dose	%
	≤5	(5, 10]	(10, 20]	(20, 40]	(40, 60]	>60		
1-30	0	0	0	0	0	0	0	0
31-91	0	0	0	0	1	1*	2	11%
92-182	0	0	1	0	0	0	1	6%
183-365	0	0	1	3	1	0	5	28%
366-545	0	0	1	2	2	0	5	28%
546-730	0	0	1	2	2	0	5	28%
731-1096	0	0	0	0	0	0	0	0
1097-1461	0	0	0	0	0	0	0	0
Any time	0	0	4	7	6	1*	18	100%
%	0	0	22%	39%	33%	6%	100%	

Source: 120-day safety update, Table 1.1.4B.

Notation: (10, 20] = 10 < dose ≤ 20

* In a 17 Aug 2012 response to an FDA information request, the applicant reports that subject 33-001 received 300 20-mg capsules on 08 Sept 2012 and returned 0 capsules on 30 Nov 2012, yielding an assumed daily dose of 71.4 mg (6000 mg / 84 days).

Reviewer Comment: Very few patients have been exposed to the highest proposed doses of lomitapide for a substantial length of time.

In HoFH-pilot, the 6 subjects each received 28 or 29 days of 0.03 mg/kg (mean dose 2.0 mg/day). The median treatment duration was 115 days, with a range of 112 to 148 days. All subjects escalated to 0.1 mg/kg (mean dose 6.7 mg/day) for 25 to 32 days before increasing to 0.3 mg/kg (mean dose 20.1 mg/day) for 27 to 36 days. One subject required a reduction in dose to 0.15 mg/kg for 32 days because of transaminase elevation after 8 days of dosing at 0.3 mg/kg; the subject's dose was escalated back to 0.3 mg/kg for another 28 days without recurrence. All subjects ultimately received 1.0 mg/kg (mean dose 67.0 mg/day) for 25 to 32 days. Two subjects required dose interruptions of 2-3 days because of GI events (subject AROD85) and ALT elevation (subject DWOL68).

Exposure in Non-HoFH Population (Selected)

Section 7.1.1 and 7.1.3 describe the applicant's "Elevated LDL and Other CV Risk Factors" safety pool. Although this is not the target population, Table 82 summarizes exposure data in this pool across dose groups.

Table 82. Exposure to Lomitapide in Applicant's "Elevated LDL" Safety Pool

Duration of Treatment	Lomitapide Dose Group*				Comparator	
	Escalated to 5-10 mg (n=77)	Low-dose (2.5-7.5 mg) (n=244)	Mid-dose (10 mg) (n=99)	High-dose (25-100 mg) (n=62)	Placebo (n=116)	Active Control (n=78)
Summary Statistics: Days						
Mean (SD)	67 (23)	67 (26)	39 (31)	20 (11)	47 (27)	62 (18)
Median [IQR]	82	83	37	16.5	51.5	57
Range	3 to 89	1 to 91	1 to 99	3 to 52	1 to 91	1 to 92

Duration of Treatment	Lomitapide Dose Group*				Comparator	
	Escalated to 5-10 mg (n=77)	Low-dose (2.5-7.5 mg) (n=244)	Mid-dose (10 mg) (n=99)	High-dose (25-100 mg) (n=62)	Placebo (n=116)	Active Control (n=78)
N (%) of Subjects						
1-28 days	7 (9%)	34 (14%)	46 (47%)	45 (73%)	38 (33%)	4 (5%)
29-56 days	14 (18%)	40 (16%)	24 (24%)	17 (27%)	39 (34%)	34 (44%)
57-84 days	46 (60%)	129 (53%)	21 (21%)	0	27 (23%)	32 (41%)
>84 days	10 (13%)	41 (17%)	8 (8%)	0	12 (10%)	8 (10%)

Source: Derived from ISS, Table 39.

* See Section 7.1.3 for description of lomitapide dose groups. Note that lomitapide may have been administered with concomitant lipid-lowering therapy.

Reviewer Comment: This table highlights the heterogeneity of trials that compose this phase 1/2 safety pool with regard to dose and duration of lomitapide.

7.2.2 Explorations for Dose Response

HoFH-pivotal used a forced-titration design. See Section 7.2.1 for summaries of durations of exposure by mean daily dose in the phase 3 HoFH population.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Table 126 in the Appendix lists the safety assessments performed in each clinical trial during the development of lomitapide (including time points).

Prospective evaluation of hepatic fat by NMRS/MRI during two non-HoFH phase 2 trials, the HoFH pilot study, and the HoFH pivotal trial and its extension is a benefit to this safety program.

Fat-soluble nutrients (beyond Vitamins A and E) were only assessed in HoFH trials, which involved co-administration of dietary supplements of varying compositions (see descriptions and results from individual trials).

Pulmonary function was assessed by spirometry and DLCO in the HoFH studies and two phase 2 trials in the non-HoFH population (A-004 and C-009). Because the nonclinical concern regarding pulmonary phospholipidosis was alleviated, in part, by noting that other marketed drugs with a similar signal had not shown evidence for pulmonary toxicity in humans, the available pulmonary safety data for lomitapide seem adequate.

Although the Gastrointestinal Symptoms Rating Scale questionnaire was administered in the HoFH pivotal trial and several phase 2 trials, I did not review these data given that

they neither provide information relevant to labeling if lomitapide is approved nor are expected to provide incremental value to safety analyses.

Reviewer Comment: The long-term effect of lomitapide on fat-soluble nutrients in the absence of supplementation has not been assessed during the development program.

7.2.5 Metabolic, Clearance, and Interaction Workup

See Clinical Pharmacology, Section 4.4 (p. 39).

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Not applicable; lomitapide mesylate is first-in-class.

7.3 Major Safety Results

Table 83 summarizes the number of subjects who experienced at least one adverse event after receiving the first dose of study drug (treatment-emergent AE; TEAE) in HoFH-pivotal, HoFH-extension, and overall. These events will be discussed in their respective sections below.

Table 83. HoFH-pivotal – Treatment-emergent AE Summary

Event	HoFH-pivotal			HoFH-extension (N=18)	HoFH Overall (N=29)
	Efficacy Phase (Wk 0-26) (N=29)	Safety Phase (Wk 26-78) (N=23)	All (Wk 0-78) (N=29)		
Any TEAE	27 (93%)	21 (91%)	27 (93%)	13 (72%)	27 (93%)
SAE	3 (10%)	0	3 (10%)	4 (22%)	5 (17%)
Deaths	0	0	0	0	0
Permanent d/c 2 ^o TEAE	5 (17%)*	0	5 (17%)*	1 (6%)**	5 (17%)
Study drug-related TEAE (investigator opinion)	25 (86%)	17 (74%)	25 (86%)	7 (39%)	26 (90%)

Source: 120-day safety update, revised Table 5 (17 Aug 2012 response to FDA information request).

TEAE = treatment-emergent adverse event.

* Applicant reports 4 discontinuations resulting from AEs. Based on my review, an additional subject who withdrew consent also discontinued as a result of unstable INR, considered an AE. See below.

** Subject 11-004 discontinued from the extension study because of hepatotoxicity (SAE), but reinitiated lomitapide after the data cutoff (31 December 2011).

In HoFH-pilot, all 6 subjects had at least one TEAE. There was one SAE (incision and drainage of a seroma at a former surgical incision site) and no deaths.

7.3.1 Deaths

The applicant reports a single death during the lomitapide development program, occurring in study A-001, a 12-week randomized phase 2 trial that compared lomitapide (dose escalation from 5 to 7.5 to 10 mg daily), lomitapide + ezetimibe, and ezetimibe alone among 85 total subjects with elevated LDL-C (non-HoFH). In this study, a 54-

year-old man (subject 041049) was treated with lomitapide monotherapy for 84 days (10 mg maximum) and died as a result of a myocardial infarction 7 days after completing study treatment:

Subject 041049 was a 54-year-old white man with a medical history of Factor V Leiden, deep vein thrombosis (left leg), hypertension, peptic ulcer, nocturia, and hemorrhoids. Medications included atenolol 50 mg daily for hypertension (since 2004) and aspirin 81 mg daily for cardiac prophylaxis (since 2005). He had neither diabetes mellitus nor a family history of premature coronary disease. At baseline, his blood pressure was 154/94 with a heart rate of 72 bpm on atenolol. His baseline lipid panel included LDL 158 mg/dL, TC 224 mg/dL, HDL 46 mg/dL, and TG 98 mg/dL. His BMI was 42 kg/m². He was randomized to lomitapide monotherapy and received study drug from 09 August 2006 to (b) (6) (Day 84). The subject reported diarrhea through the majority of the trial (Days 8 to 12 and Days 14 to 84) but no other AEs. Seven days after stopping study drug, on (b) (6) (Day 91), while at work “performing defensive tactics,” the subject developed nausea and diaphoresis. Upon EMS arrival, he was in ventricular fibrillation; despite defibrillation, epinephrine, amiodarone, intubation, and CPR, he was pronounced dead in the ER.

Reviewer Comment: *The investigator believed this fatal event was unrelated to lomitapide. This subject had cardiac risk factors including uncontrolled hypertension and hyperlipidemia, and his BMI suggests morbid obesity. Although Factor V Leiden increases the risk for venous thrombosis, its association with arterial thrombosis is less clear. Using this subject’s baseline characteristics, I calculated a 10-yr Framingham CHD Risk of 12%. Certainly, this subject’s cardiovascular event could have been unrelated to lomitapide, but a possible association with the drug should not be entirely excluded given the drug’s relatively small safety database.*

7.3.2 Nonfatal Serious Adverse Events

Serious adverse events (SAEs) were defined as any AE that resulted in death, was life-threatening, required inpatient hospitalization (overnight stay) or prolonged a current hospitalization, caused persistent or significant disability/incapacity, or was a congenital anomaly/birth defect in the offspring of a patient who received study drug. In addition, any event that required intervention to prevent one of these outcomes could be considered an SAE, but this was at the judgment of the investigator.

Phase 1

The only SAE in the phase 1 program was in the TQT study (AEGR-733-011). Subject 55 was a military veteran who had a severe episode of post-traumatic stress disorder, leading to psychiatric hospitalization, which began on day 17 of period 5, approximately 14 days after the last dose of study drug (placebo).

Phase 2 (Excluding HoFH-pilot)

Seven SAEs were reported in the phase 2 program, including the single death described in Section 7.3. One additional SAE was not treatment-emergent: a subject treated with atorvastatin monotherapy in study A-006 had the onset of diverticulitis before randomization and although symptoms did not worsen, an operation was scheduled after randomization. A description of the remaining five phase 2 SAEs follows:

Study A-003b: Two nonfatal myocardial infarctions; one in each of the 26-subject lomitapide monotherapy groups (5 mg daily and 10 mg daily) in this 8-week trial.

- *Subject 19116* was a 47-year-old white man who had a history of hypertension, dyslipidemia, tobacco use, and uric acid renal calculi. His family history included a father with CAD at age 50 and a mother who had a CABG at age 62. At screening, he was taking atenolol, allopurinol, potassium citrate, and a multivitamin. His blood pressure at baseline was 132/90 and his BMI was 34.0 kg/m². Baseline lipid values were LDL 104 mg/dL (for unknown reasons, this is markedly lower than his values at screening visits: 134, 122, and 143 mg/dL at days -35, -10, and -7, respectively), TC 278 mg/dL, HDL 26 mg/dL, and TG 1014 mg/dL; it is not specified why the subject was not taking lipid-lowering therapy at screening. He was assigned to lomitapide 5 mg daily at his baseline visit on 09 April 2008, which he apparently stopped on 21 May 2008 (day 43) for an unreported reason. (b) (6) days later he developed symptoms of upper sternal and throat tightness/discomfort, leading him to present to a local emergency department. The hospital performed an ECG, which is reported as unremarkable. CK-MB was 5.49 ng/mL (ULN 5 ng/mL) and troponin I was 0.366 ng/mL (ULN 0.05 ng/mL). Diagnosed with a non-ST elevation MI, he underwent cardiac catheterization, which revealed nonobstructive disease of the LAD, luminal irregularities of the left circumflex artery, and a 95% focal stenosis of the 3rd or 4th right posterolateral branch artery. Among the medications added to his outpatient regimen was atorvastatin 80 mg daily. He returned for a followup visit on 04 August 2008 (day 118) with LDL 65 mg/dL, HDL 34 mg/dL, and TG 173 mg/dL.
- *Subject 12166* was a 44-year-old black man who had a history of myocardial infarction with stent placement (January 2006), hypertension, hyperlipidemia, and depression. At screening, he was taking aspirin 81 mg daily, metoprolol, enalapril, HCTZ, and clopidogrel. His blood pressure at baseline was 120/73 and his BMI was 25.9 kg/m². Baseline lipid values were LDL 226 mg/dL, TC 297 mg/dL, HDL 41 mg/dL, and TG 148 mg/dL; it is not specified why the subject was not taking lipid-lowering therapy at screening. He was assigned to lomitapide 10 mg daily at his baseline visit on 07 May 2008, which he took through his week 4 visit on 04 June 2008; at that visit, his LDL was 155 mg/dL and HDL 34 mg/dL. Safety laboratories were unremarkable. The next day, he had a myocardial infarction and stent placement. His physician discontinued study drug and initiated ezetimibe/simvastatin 10 mg/40 mg daily; he returned for an early termination visit one week later (12 June 2012) with LDL 99 mg/dL and HDL 39 mg/dL.

Reviewer Comment: Both of these subjects had risk factors for cardiovascular disease, but it is notable that the only two SAEs that occurred in this study were both myocardial infarctions and both were in subjects treated with lomitapide (without concomitant statin). Furthermore, despite their CV risk profiles, these events occurred during an 8-week study. Although one cannot draw conclusions based on 2 events in an isolated trial, the

possibility that lomitapide monotherapy increases the risk for CV events cannot be entirely excluded.

A-004: Three SAEs in this 12-week trial; 1 chest pain among 34 subjects treated with lomitapide 2.5 mg daily, and 1 case each of inflammatory bowel disease and ankle fracture among 35 subjects treated with lomitapide 10 mg daily.

- *Subject 07007* was a 59-year-old black man with a history of cocaine use, hypertension, and hypercholesterolemia who initiated lomitapide 2.5 mg daily on 12 June 2008. On (b) (6) he presented with acute-onset lower quadrant abdominal pain, nausea, diarrhea, bright red blood per rectum, and diaphoresis. He also described left-sided chest pressure associated with the left arm that coincided with the abdominal pain, intermittent in nature, lasting approximately 20 minutes. An ECG showed possible ST elevations in V2, V3, and V4; he was treated with aspirin, clopidogrel 600 mg orally, and heparin 5000 units IV. It was ultimately determined that the ST elevations were a result of early repolarization and no cardiac catheterization was performed. Reportedly, a previous catheterization in June 2008 had shown no significant obstructive CAD. He was admitted for further workup; serial cardiac enzymes were negative and a urine tox screen was positive for cocaine metabolites. Hematocrit remained stable at 40-45%. He was discharged on hospital day 3 with a diagnosis of cocaine-related chest pain and lower GI bleeding from diverticulosis vs. hemorrhoids.
- *Subject 03012* was a 41-year-old black woman who initiated lomitapide 10 mg daily on 01 April 2008. Three weeks later, she developed bloody diarrhea but did not stop study drug for an additional 2 weeks (d/c on 06 May 2008). On May 12, she was diagnosed with ulcerative colitis by endoscopy. She started mesalamine for her colitis and restarted her lomitapide on May 16; four days later, because of recurrence of (non-bloody) diarrhea, she stopped study medication permanently. Colonoscopy on 17 June 2008 revealed “findings of an injury indicative of chronic active colitis and a pattern of injury consistent with inflammatory bowel disease.”
- *Subject 12024* was a 67-year-old white man who initiated lomitapide 10 mg daily on 02 April 2008. On (b) (6) the subject fell from a roof and was admitted to the hospital for an ankle fracture and dislocation requiring open reduction and internal fixation. Study medication was stopped on admission and not restarted.

HoFH Trials

In the HoFH-pivotal trial, 3 (10%) of 29 subjects had at least one SAE. Among the 23 subjects who completed the efficacy phase, none experienced an SAE during the safety phase (week 26-78). The HoFH-extension study is ongoing, but 4 (22%) of 18 subjects have had at least one SAE as of the cut-off date for the 120-day safety update (31 December 2011). In HoFH-pilot, 1 of the 6 subjects had an SAE. These events are listed in Table 84.

Table 84. Serious Adverse Events in HoFH Trials

Trial	Subject	Age ^a	Sex	Dose ^b	Study Day ^c	Verbatim Term ^d	Action Taken
HoFH-pilot	EMEN64	39	F	2.3	30	Hospitalization for chest lump (I&D of seroma at previous incision site)	Drug Interrupted

Trial	Subject	Age ^a	Sex	Dose ^b	Study Day ^c	Verbatim Term ^d	Action Taken
HoFH-pivotal	11-001	22	M	20	65	Acute coronary syndrome	Dose not changed
HoFH-pivotal	11-001	22	M	20	69	Worsening of angina pectoris	Drug interrupted
HoFH-pivotal	11-001	22	M	60	119	Lower respiratory tract infection	Dose not changed
HoFH-ext.	11-001	22	M	60	542	Lower respiratory tract infection	Dose not changed
HoFH-ext.	11-001	22	M	60	673	Enlarged AV fistula	Dose not changed
HoFH-ext.	11-004	54	M	40	960	Hepatotoxicity	Drug withdrawn
HoFH-pivotal	12-004	30	F	40	74	Worsening menorrhagia	Dose not changed
HoFH-ext.	12-004	30	F	60	700	Reflux esophagitis (Hospitalized for chest pain)	Dose not changed
HoFH-pivotal	22-003	40	M	(5) ^b	21 (7d after last dose) ^e	Severe atherosclerotic heart disease	Drug interrupted (prior to event)
HoFH-ext.	01-003	44	F	60	906	Hypovolemic shock	Dose not changed
HoFH-ext.	01-003	44	F	60	1057	Hospitalized for anticoagulation to reach acceptable INR	Drug interrupted
HoFH-ext.	01-003	44	F	NR	1141	Hospitalized for transfusion	Dose not changed
HoFH-ext.	01-003	44	F	60	1374	Hospitalization for stroke symptoms	Dose interrupted

Source: ISS Table 1.2.14, 120-day safety report, and FDA clinical review of patient narratives, case report forms, submitted raw data. Data cutoff for SAEs: 31 December 2011 except for single Medwatch report of the Hospitalization for stroke symptoms event (subject 01-003) with onset 13 February 2012.

SAEs occurring before first dose of study drug were reviewed but are excluded from this table.

^a Age at HoFH-pilot or -pivotal baseline.

^b Dose (mg daily) at time of event. Doses in parentheses indicate the dose that the subject was taking most proximal to the time of the event despite being off study drug on the date of the event.

^c Day of follow-up after first dose of study drug. For events during HoFH-extension, day 1 is first dose of study drug in the HoFH-pivotal trial.

^d Items in parentheses are reviewer comments or descriptions.

^e Subject initiated lomitapide 5 mg on 01 April 2009 but interrupted study drug 15 April 2009 through 22 July 2009 for "surgery for heart disease." An SAE of "severe atherosclerotic heart disease" was recorded as occurring 21 April 2009 through 27 April 2009 (study days 21 to 27). Study drug was restarted (lomitapide 5 mg) on 23 July 2009 and titrated per protocol. The applicant notes that for their analysis datasets, 23 July 2009 was considered study day 1.

Selected narratives from the phase 3 studies follow:

Subject 11-001. This 22 y/o South African man was diagnosed with HoFH at age 6 months on a genetic basis and skin fibroblast assessment. His medical and surgical history included supraaortic stenosis, angina pectoris, NSAID-induced gastritis, bilateral Achilles tendonitis, and several arteriovenous fistulas. Concomitant baseline medications included aspirin, atenolol, and atorvastatin 80 mg daily; he generally received LDL apheresis every 2 weeks. His baseline LDL-C was 240 mg/dL. While taking lomitapide 20 mg daily on study day 65, he developed chest pain that was initially relieved by isosorbide dinitrate, but the pain returned. The next day he presented to the ER and was admitted. An ECG apparently did not reveal any acute ischemic changes or ST segment elevation and no cardiac enzymes were reported by the applicant, but this event was recorded as **acute coronary syndrome**, from which he recovered on day 68. On day 69, he began to experience "serious angina pectoris."

Lomitapide was interrupted, and the subject continued to experience angina pectoris throughout the study (see below).

On day 119, while taking lomitapide 60 mg daily, he developed pleuritic chest pain, non-productive cough, fever, and difficulty breathing. On reporting to the study site two days later, he was found to be febrile with pleuritic chest pain and wheezing. He was admitted for treatment of a **lower respiratory tract infection**; a chest x-ray did not reveal any airspace opacities and blood cultures were negative. He was treated with Augmentin, doxycycline, and diclofenac with symptomatic improvement. He recovered on day 131; lomitapide dose was not changed.

On day 134, he was admitted to the hospital with a diagnosis of **worsening angina pectoris**, which started on day 69 as described above. Coronary angiography was planned but not performed because of iron deficiency anemia that the cardiologist wanted corrected. He was discharged on day 136.

On day 542, while in the extension study, he presented to the ER with chest pain, fever, and new-onset cough. Reportedly, an ECG did not reveal any acute changes and cardiac markers were negative. A chest x-ray did not reveal any airspace opacities. He was initially treated for possible acute coronary syndrome (aspirin, morphine, isosorbide dinitrate, enoxaparin), respiratory infection (ceftriaxone followed by ampicillin and Augmentin), along with acetaminophen and an antacid mix. The final diagnosis was **lower respiratory infection** based on clinical signs and response to antibiotics. He was discharged on hospital day #2 and fully recovered 5 days later; lomitapide was not interrupted.

On day 673, he was admitted to the hospital for surgical intervention on his **enlarging AV fistula**; he was discharged the same day.

Reviewer Comments:

- 1. No supporting evidence for the diagnosis of acute coronary syndrome was submitted and these events were not adjudicated in the lomitapide development program. However, even at age 22, ACS is not completely unexpected in the HoFH population. It should be noted, however, that the uncontrolled design of HoFH-pivotal does not allow for a contemporary assessment of the expected background incidence rate of CV events in the HoFH population. If lomitapide caused a paradoxical increase in CV events despite lowering LDL-C, this would be difficult to detect.*
- 2. As shown later in this review, 59% of HoFH subjects ever had adverse events in the Infections & Infestations SOC, second only to the Gastrointestinal Disorders SOC. Whether extended use of MTP inhibitors somehow predisposes subjects to infection is unknown.*

Subject 11-004. Hepatotoxicity. This 54 y/o South African man was diagnosed with HoFH at age 31 on a genetic basis and also had a history of ischemic heart disease at age 39, CABG at age 40, systolic murmur, xanthelasmata and xanthomas, cholesteatoma, and gout. Before study start, he was on allopurinol 100 mg daily, aspirin 140 mg daily, atorvastatin 80 mg daily, and ezetimibe 10 mg daily. He was not on LDL apheresis. At screening, ALT was 1.4x ULN. At his scheduled baseline visit, when he was placed on lomitapide 5 mg daily, his pre-dose ALT returned 232 IU/L (5.8x ULN) with total bilirubin 0.7 mg/dL and alkaline phosphatase 216 IU/L (1.9x ULN). His lomitapide was discontinued after only 3 days and the DSMB directed a workup for liver disease (per narrative, acute & chronic viral hepatitis, iron overload, autoimmune hepatitis, celiac disease, alpha-1 antitrypsin deficiency, and Wilson's disease). A liver biopsy was performed, revealing "mild steatosis and mild siderosis." After his ALT had returned to <2x ULN (~3 months after the original intended baseline), lomitapide was re-attempted. He was titrated up to 40 mg per protocol but did not escalate to 60 mg because of GI symptoms.

Through the phase 3 trial, his ALT ranged from 1.3x to 4.9x ULN. His hepatic fat was

0.44% at screening, 1.74% at week 0, and 16-17% at week 26, 56, and 78. Going into the extension study, hepatic fat was 15.9% at week 102 and 15.8% at week 126.

At the scheduled week 138 visit (week 60 of the extension), ALT was found to be 954 U/L (23.9x ULN), AST 565 U/L (13.1x ULN), and alk phos 289 (2.5x ULN); total bili was 0.5 mg/dL. **Four days prior to this visit, the subject was placed on clarithromycin, cetirizine, Linctifed cough syrup** for "influenza." He had also received betamethasone IM for "influenza" two days prior to the study visit as well. Other changes to concomitant medications included the **addition of the antidepressant agomelatine 25 mg daily ~ 7 weeks earlier**. Furthermore, he reportedly had a recent history of increased alcohol use while traveling in the UK for a wedding, but not in excess of two drinks per day. Lomitapide, clarithromycin, the cough syrup, and agomelatine were discontinued the day after the study visit and the ALT fell to 5.5x ULN six days later and to 2.4x ULN two weeks after the study visit. Alk phos fell as well.

The subject underwent a liver biopsy approximately 2 months after the marked ALT elevations. The microscopic findings and comment from the biopsy report follow:

MICROSCOPIC:

Sections of a single long core of liver needle biopsy include approximately 6 portal tracts, 5 of which contain appropriate calibre, normal bile ducts. Hepatic architecture is intact, with only minimal pericellular fibrosis focally. Portal tracts contain minimal lymphocytic inflammation. Eosinophils and plasma cells are inconspicuous. No interface hepatitis or bile duct targeting is observed.

Lobular parenchyma displays mild macrovesicular steatosis affecting about 15% of hepatocytes, mainly in zones 2 and 3. No significant necroinflammatory activity, ballooning degeneration, confluent necrosis or collapse are observed. Viral inclusions, cholestasis and granulomas are not features of this biopsy. There is no increase in ceroid-laden Kupffer cells. Zone 3 hepatocytes contain lipofuscin pigment. There is no excess iron deposition on the Perls stain.

COMMENT:

Liver needle biopsy findings are those of mild simple steatosis with no significant haemosiderosis, inflammatory activity or fibrosis. The steatosis is increased compared to the previous liver biopsy, SCA0907792. Case discussed at the Liver Pathology Meeting at (b) (6) on 10/02/2012.

The subject's ALT on the date of the biopsy was 66 IU/L (1.7x ULN), the lowest value he ever had while taking lomitapide.

Reviewer Comments:

1. *This appears to be a case of drug-induced hepatotoxicity, although liver function was not affected.*
2. *Agomelatine is an antidepressant (not approved in the U.S.) with known side effects including transaminase elevations; in fact, baseline and routine monitoring of transaminases is recommended. The product info sheet from the EMA states that caution should be exercised when this drug is administered to patients with pretreatment elevated transaminases, which this subject had; furthermore, caution should be exercised when prescribing agomelatine for patients with hepatic injury risk factors, including NAFLD, substantial alcohol intake, or concomitant drugs associated with risk of hepatic injury. Certainly, agomelatine could have contributed to this ALT elevation.*
3. *Temporally, however, it is concerning that this subject was placed on a strong CYP3A4 inhibitor (clarithromycin) four days prior to the scheduled lab draw, which revealed the*

substantial increase in transaminases. Given the marked elevations in lomitapide exposure (15-fold C_{max} and 27-fold AUC) observed in the ketoconazole drug-drug interaction study, it is certainly plausible that an acute exposure to very high levels of lomitapide precipitated this event.

- 4. The fact that this subject was placed on a known hepatotoxic concomitant medication (agomelatine) and a strong CYP3A4 inhibitor (clarithromycin) despite the protocol contraindicating concomitant 3A4 inhibitors demonstrates that even with the rather close monitoring of a clinical trial, drug-drug interactions may not be recognized. This presents a safety concern for the use of lomitapide in clinical practice, especially if clinically significant drug-drug interactions may occur even with moderate CYP3A4 inhibition (not tested in the lomitapide development program in vivo).*

Subject 12-004. This 30 y/o woman developed **worsening menorrhagia** that ultimately led to a hospitalization for hysterectomy with discharge the same day. She was taking aspirin 300 mg daily but no other anticoagulants. Her hemoglobin four days prior to this event was 13.9 g/dL. This subject was not taking warfarin.

During the extension study, she was admitted to the hospital with chest pain. An endoscopy was performed and revealed **reflux esophagitis**, which resolved within 2 days.

Subject 22-003. This 40 y/o man was diagnosed with HoFH at age 26 and had a history including obesity, a portacaval shunt (age 13), multiple xanthomas and corneal arcus, splenomegaly, and Gilbert syndrome. Lipid-lowering therapy at baseline included daily doses of rosuvastatin 40 mg and ezetimibe 10 mg; his baseline LDL-C was 260 mg/dL. The night before his baseline visit, he experienced at least two hours of moderate retrosternal chest pain with associated dyspnea and diaphoresis. He reported this at his baseline visit the next day. Following a normal ECG, he was initiated on lomitapide and referred for a stress test, which revealed pathological changes including ST depression >4.5mm on study day 2. Coronary angiography performed on day 8 revealed severe 3-vessel CAD with normal LV function. Lomitapide was discontinued on day 14 at the cardiac surgeon's request, and he was **admitted on day 21 for CABG**. His hospital course was complicated by acute renal failure and atrial fibrillation. He was discharged on study day 27. After 99 days of holding lomitapide because of this event, eligibility for the study was re-confirmed, and both the run-in and baseline visits were repeated.

Subject 01-003. Three SAEs related to bleeding and/or anticoagulation. This 44 y/o woman had a history including aortic and mitral valve replacements and atrial fibrillation, with a medication regimen including warfarin. While taking lomitapide 60 mg in the HoFH extension study, she presented to the ER with a two-week history of lightheadedness, shortness of breath, vomiting, and menorrhagia. Hemoglobin was 5 g/dL and systolic BP was 60 mmHg. This event was reported as **hypovolemic shock**. Warfarin was held. The hospital course was complicated by elevation of transaminases (likely shock liver) and acute myocardial infarction complicated by congestive heart failure (no supporting documentation provided). Progesterone therapy improved the menorrhagia; pelvic ultrasound was unremarkable. Cardiac catheterization showed patent grafts from three previous CABG operations. Warfarin was resumed 5 days after admission; hemoglobin and transaminases improved. According to the submitted laboratory dataset, the subject had an INR 2.0 approximately 3 weeks prior to this admission. There was no evidence of previous INR instability during the extension study. While the subject was in the HoFH-pivotal trial, recorded INR values had ranged from 1.7 to 5.2.

Approximately 4 months after discharge from this hospitalization, the subject was hospitalized for anticoagulation because her cardiologist had obtained two INR values below

therapeutic range (INR 1.5 and 1.7 on March 14 and 17, 2011, respectively; target 2.5-3.5). The subject was **admitted for heparinization** and discharged on hospital day #6. The subject did not have her study drug with her during the hospitalization, which was the reason for the recorded drug interruption.

Approximately 3 months later, the subject was **hospitalized for a transfusion** for symptomatic anemia following 2 weeks of menorrhagia (Hgb 7.9 g/dL). INR at presentation was 3.5. She was discharged the following day (b) (6).

An additional SAE was reported for this subject after the data cutoff as a 15-day safety report to the agency. On (b) (6) this subject presented to the ER with left cranial VII palsy, vertical nystagmus, weight loss, and INR 5.7. She had not had her INR monitored since 23 December 2011. She was **hospitalized for stroke symptoms** and found to have acute subdural hematomas with blood in the posterior fossa, multiple small subacute cortical and subcortical infarctions possibly from prior emboli, and a small amount of intraventricular blood. There was associated dural enhancement that included the left internal auditory canal. The intracranial hemorrhages were attributed to supratherapeutic anticoagulation. She was discharged on 12 February 2012 and had another brain MRI performed 4 months later, demonstrating the resolution or partial resolution of subdural and intraventricular hemorrhages. On 26 June 2012, she reported improving facial paralysis but continued decreased hearing in the left ear; an otolaryngologist diagnosed her with left sensorineural hearing loss due to viral infection. She restarted treatment with study drug on 02 March 2012, escalating from 20 mg to 60 mg daily.

Reviewer Comment: These events suggest that the modest lomitapide-warfarin drug-drug interaction observed may be clinically relevant. It is unknown, however, whether this subject would have had a similar clinical course in the absence of lomitapide.

7.3.3 Dropouts and/or Discontinuations

Phase 1 and 2

From the applicant's 97-subject pool of single-dose studies (CV145-001, -003, and -006; AEGR-733-010 and -017), one subject prematurely discontinued because of **decreased consciousness, presyncope, dizziness, pallor, nausea, and headache** after receiving lomitapide 100 mg (CV145-001). Except for the headache, these were all part of a vasovagal reaction according to the investigator.

From the applicant's 241-subject pool of multiple-dose drug-drug interaction or crossover studies (CV145-005, AEGR-733-002, -013, -015, -018, and -019), two subjects prematurely discontinued because of AEs. A subject receiving lomitapide 60 mg in AEGR-733-018 discontinued because of **vomiting** that was considered possibly related to ketoconazole dosing, and a subject receiving lomitapide 60 mg in AEGR-733-019 discontinued because of **pruritus and rash**.

From the applicant's 676-subject pool of adults with elevated LDL-C (CV145-002, -009, and -010; AEGR-733-001, -003b, -004, and -006), 118 (24%) of 482 lomitapide-treated subjects prematurely discontinued because of AEs compared with 2 (2%) of 116 placebo subjects and 5 (6%) of 78 active-control subjects. Overall, the majority of these events were related to GI disorders or transaminase abnormalities.

Table 125 in the Appendix is the applicant’s tabulation of the preferred terms for events leading to discontinuation reported by ≥2 lomitapide-treated subjects in this pool.

Phase 2 and 3 HoFH

There were no premature discontinuations in HoFH-pilot.

In the HoFH-pivotal trial, 6 (21%) of the 29 subjects permanently discontinued study treatment early. All of these discontinuations occurred prior to week 26 (see Table 85). For two subjects, AEs were directly cited as the reason for early withdrawal. Three subjects withdrew consent, two of whom the applicant agrees had AEs listed as leading to drug withdrawal (*not* “drug interruption”); my review suggests that the third withdrawal of consent is also the result of adverse events including INR fluctuation and GI side effects.

Table 85. HoFH-pivotal – Dropouts

Trial	Subject	Dose ^a	Days of AE ^b	Day of Drug D/C ^b	Day of Last Visit	Reported Verbatim Term	Reason for Discontinuation
HoFH-pivotal	01-006	40	119-129	119	199	Headaches and weight loss	Subject withdrew consent (AE suspected)
HoFH-pivotal	13-001	5 5 5	3-40 4-40 31-37	37	55	Anorexia Abdominal discomfort Gastroenteritis	Adverse Event
HoFH-pivotal	13-002	10 (20, 40)	29-139	139	155	Unstable INR & GI AEs (per FDA review of CRF)	Subject withdrew consent (FDA: AE suspected)
HoFH-pivotal	22-003	10	183-185	182	211	Diarrhea	Subject withdrew consent (AE suspected)
HoFH-pivotal	23-002	10	40-86	83	98	Abdominal cramps Diarrhea Nausea	Adverse Event
HoFH-pivotal	23-003	5	N/A	4	35	“Anxiety related to experiencing possible GI side effects” (per narrative)	Non-compliance or lack of cooperation

Source: Review of HoFH-pivotal CSR, ISS, case report forms (CRFs), and SAS datasets.

^a Dose (mg daily) at time of event.

^b Study days of AE or drug discontinuation.

Review of the DSMB minutes (25 May 2010) shows that subject 01-006 withdrew from the study not only as a result of concerns over headaches but also weight loss. This subject had a baseline weight of 68.2 kg and a nadir weight of 62.7 kg at week 14. His weight 80 days after drug discontinuation was 65.8 kg.

Regarding subject 13-002 who withdrew consent, this 38 y/o white woman with HoFH was receiving warfarin for aortic valve replacement. Her INR at weeks 2, 6, 10, 14, and 18 were 3.4, 4.9, 3.0, 6.6, and 1.7, respectively. Ecchymosis was reported as an adverse event two weeks prior to the INR being 6.6. The CRF indicates that the subject stopped study drug as a result of “unstable PI [prothrombin index].” The investigator

also informed the CRO via email that GI side effects contributed to her withdrawing consent (see 18 May 2012 response to FDA information request).

92-1	STOPPED STUDY DRUG DUE TO UNSTABLE PI
	WITH SUBSEQUENT INCREASED MEDICAL AID COSTS

Source: Subject 13-002 CRF.

In the HoFH extension study, which is ongoing, four subjects discontinued prior to the data cut-off date of 31 December 2011:

1. *Subject 11-004* was discontinued for an SAE of hepatotoxicity (see Section 7.3.2, p. 163). The applicant notes that this subject actually resumed lomitapide after the data cut-off.
2. *Subject 11-001* was discontinued at the judgment of the investigator because he moved several hundred miles from the study site.
3. *Subject 01-004* was discontinued because of “sponsor decision.” The narrative reports that this was because of transaminases elevations that persisted despite graded dose reductions from 40 mg to 5 mg daily. The last on-study ALT was 133 IU/L (3.3x ULN), drawn 51 days after discontinuation of lomitapide.
4. *Subject 12-001* was discontinued to plan a pregnancy. Her last dose of lomitapide treatment was 19 October 2010, at which time an end-of-study visit was conducted. She became pregnant in January 2011 and had a normal delivery of a healthy baby (with HeFH). The mother is not breastfeeding. The applicant reports that she re-entered the extension study for a week-48 visit on 10 May 2012 and restarted lomitapide 5 mg daily on 19 May 2012.

Dose Modifications and Interruptions Due to Adverse Events

During the first 56 weeks of HoFH-pivotal, the applicant reports dose *reductions* as a result of AEs for 10 (34%) of the 29 subjects, most commonly due to GI events (7 subjects, 24%) including diarrhea (5 subjects), nausea and abdominal discomfort (3 subjects each), and vomiting (1 subject). One subject each required dose modifications due to AEs with the preferred terms fatigue, ALT increased, transaminase increased, hepatotoxicity, weight loss, and INR fluctuation.

During the first 56 weeks of HoFH-pivotal, the applicant reports dose *interruptions* as a result of AEs for 12 (41%) of the 29 subjects; the events leading to dose interruptions were diarrhea (5 subjects), vomiting (4 subjects), nausea and gastroenteritis (3 subjects each), and influenza, chest pain, and pyrexia (2 subjects each).

In HoFH-pilot, the subject who was hospitalized for an incision & drainage of a seroma (SAE) had a treatment interruption. Two additional subjects had treatment interruptions: one because of GI symptoms (diarrhea and vomiting), the other for elevated transaminase levels; the latter subject also had a dose reduction from 0.3 to 0.15 mg/kg

for the elevated transaminases followed by successful rechallenge at 0.3 mg/kg and escalation to 1.0 mg/kg.

7.3.4 Significant Adverse Events

Gastrointestinal Adverse Events

Gastrointestinal AEs are near universal among subjects taking lomitapide, with 27 (93%) of 29 subjects reporting at least one event. Combining HoFH-pivotal and its extension, the most common were diarrhea (93%), nausea (69%), dyspepsia (41%), vomiting (38%), and abdominal pain (28%). Gastrointestinal AEs are discussed further in Section 7.4.1 (p. 214).

Phase 3 HoFH – Adverse Events of “Severe Intensity”

The applicant reports that 10 (34%) of the 29 subjects experienced at least one AE of “severe” intensity in HoFH-pivotal and/or HoFH-extension. Although this was defined in the protocol as an AE causing the inability to carry out usual activities or very marked discomfort, this remains a subjective description by the subjects and investigators. Nevertheless, the AEs reported as severe intensity (and the number of subjects who experienced ≥ 1 such event) from the time of 1st dose through all available data (HoFH-pivotal + HoFH-extension through 31 December 2011) were: diarrhea (4), increased ALT (3), vomiting (3), dyspepsia (2), and one subject each for increased AST, hepatic steatosis, hepatotoxicity, abdominal distension, abdominal discomfort, abdominal pain, constipation, food poisoning, acute coronary syndrome, anemia, epistaxis, and lower respiratory tract infection, and hypovolemic shock.

Reviewer Comments:

1. *Increased ALT/AST, hepatic steatosis, and hepatotoxicity are reviewed elsewhere.*
2. *The severe AE “epistaxis” was reported by the investigator as “Intermittent Epistaxis” on study day 79 (subject 22-004). This subject was taking aspirin, but not warfarin, at the time; INR values were 0.9-1.0 throughout the study.*

7.3.5 Submission Specific Primary Safety Concerns

Liver-related Safety Concerns

As described in Dr. Hummer’s Pharmacology/Toxicology review, lomitapide induces lipid accumulation in the hepatocytes of mice, rats, hamsters, and dogs. In rats, this reversed within 3 months off treatment after a 3-month treatment period. In addition, slight increases in serum transaminases were observed in rats ($\leq 2x$ increase) and dogs ($\leq 3.5x$ increase) after at least one month of treatment. After two years of dosing, male rats exhibited an increase in the incidence and severity (minimal to moderate) of focal/multifocal fibrosis below the exposure expected with the maximum recommended human dose (MRHD) of 60 mg daily (0.2x MRHD), and females exhibited an increase at doses approximating 2x MRHD.

Transaminase Elevations & Other Liver-related Laboratories

HoFH-pivotal and HoFH-extension

Table 86 and Table 87 summarize the maximum ALT and AST abnormalities, respectively, for each subject in HoFH-pivotal, stratified by study phase, and its extension study. Ten (34%) of the 29 subjects had ALT $\geq 3x$ ULN and 6 (21%) had AST $\geq 3x$ ULN at least once during the pivotal trial. Regarding elevations of larger magnitude, 4 (14%) and 1 (3%) had at least one ALT and AST $\geq 5x$ ULN, respectively. None of the subjects with ALT or AST $\geq 3x$ ULN had bilirubin levels outside of the normal range. One subject with peak ALT 4.8x ULN with concomitant AST 2.3x ULN had an alkaline phosphatase (AP) 3.4x ULN but a normal total bilirubin 0.9 mg/dL and INR (Subject 22-004).

Transaminase elevations occurred in both the efficacy and safety phases of HoFH-pivotal. All patients with a transaminase abnormality $\geq 3x$ ULN in the safety phase had a history of a transaminase abnormality during the efficacy phase. Two subjects had a first transaminase abnormality $\geq 2x$ but $< 3x$ ULN in the safety phase (Subject 31-002: ALT 2.1x ULN at Week 78; Subject 12-006: ALT 2.8x ULN at Week 46).

In the HoFH-extension study, 6 (33%) of 18 subjects had a peak ALT $\geq 3x$ ULN during the extension, with one subject having an SAE for hepatotoxicity with ALT 23.9x ULN (see Section 7.3.2, p. 163). One subject (01-003) had a first ALT $\geq 3x$ ULN during the extension (10.3x ULN on day 128 of the extension study); this subject's peak ALT during the pivotal trial was 2.3x ULN at week 22.

Table 86. HoFH Population – Peak ALT Abnormalities

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)
$\geq 2x, < 3x$ ULN	3 (10%)	4 (17%)	4 (14%)	0	3 (10%)
$\geq 3x, < 5x$ ULN	4 (14%)	3 (13%)	6 (21%)	2 (11%)	4 (14%)
$\geq 5x, < 10x$ ULN	3 (10%)	2 (9%)*	3 (10%)	1 (6%)	4 (14%)
$\geq 10x, < 20x$ ULN	1 (3%)	0	1 (3%)	2 (11%)	2 (7%)
$\geq 20x$ ULN	0	0	0	1 (6%)	1 (3%)

Source: FDA clinical reviewer's analysis of submitted HoFH-pivotal and –extension laboratory data (LB xpt)

* Includes Subject 01-004 whose ALT was rising at week 26 visit (3.7x ULN) but peaked at 7.5xULN approximately 1 month later.

Table 87. HoFH Population – Peak AST Abnormalities

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

Peak AST During Period	Efficacy Phase (N=29)	Safety Phase (N=23)	All HoFH-pivotal (N=29)	HoFH-extension (N=18)	All HoFH (N=29)
≥20x ULN	0	0	0	0	0

Source: FDA clinical reviewer’s analysis of submitted HoFH-pivotal and –extension laboratory data (LB xpt).

Excluding one subject who had elevated total bilirubin (and indirect bilirubin) levels at screening, only one subject ever had a post-baseline total bilirubin >2x ULN (2.2x ULN, or 2.41 mg/dL, for Subject 01-003 at week 10 while taking 40 mg daily; direct bilirubin was 0.40 mg/dL). The concomitant liver-related laboratories at week 10 were all normal (ALT 30 U/L; AST 33 U/L; AP 54 U/L).

The only subject with a post-baseline AP ≥1.5x ULN (peak 3.4x ULN) was Subject 22-004, mentioned above.

Figure 33 illustrates the longitudinal trend of *mean* ALT, AST, and % hepatic fat over time in HoFH-pivotal, truncated at Week 56.

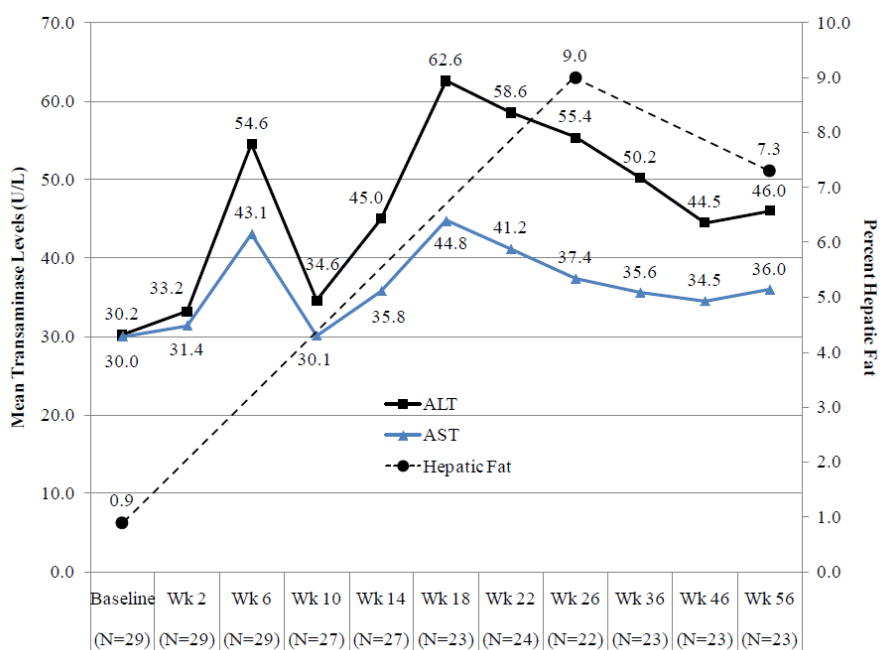


Figure 33. HoFH-pivotal – Mean ALT, AST, % Hepatic Fat Over Time
Source: HoFH-pivotal CSR, Figure 9. Missing data were not imputed.

Reviewer Comment: Although the subjects with significant transaminase elevations skew the mean values, this figure does illustrate that ALT elevations were generally greater than AST elevations, and that elevations occurred throughout the study – as early as week 6, when the dose should not have exceeded 10 mg daily.

Figure 34 illustrates the longitudinal trend of *median* ALT and AST over time in HoFH-pivotal, truncated at Week 56 (initial NDA submission).

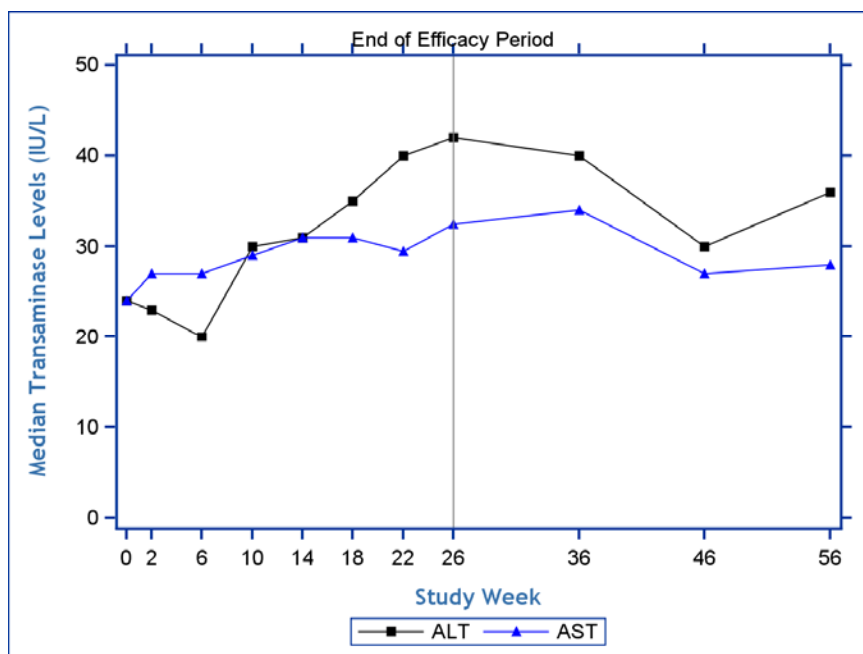


Figure 34. HoFH-pivotal – Median ALT/AST, Baseline to Week 56

Source: FDA clinical reviewer’s depiction of data from HoFH-pivotal CSR Tables 14.3.4.1.4.1, 14.3.4.1.4.2, 14.3.4.2.4.1.1, 14.3.4.2.4.2.1

Consistent with the observation that transaminase elevations were not associated with clinically significant elevations in AP (with one exception noted above) or total bilirubin, the mean (SD) changes from baseline to week 26/LOCF were 0.0 (0.4) mg/dL for bilirubin and -6.6 (31.0) U/L for AP; the mean (SD) changes from baseline to week 56/LOCF were 0.0 (0.2) mg/dL and -14.0 (19.8) U/L.

Among the 10 subjects who ever had a peak ALT ≥ 3 x ULN during HoFH-pivotal, the median time to the first ALT elevation of this magnitude was 126 days [IQR 43, 155], with a range from 43 to 469 days.

The applicant submitted narratives and patient profiles for the 4 patients who had peak ALT ≥ 5 x ULN at least once during the trial (Figure 35). As described in the protocol, confirmed transaminase elevations of this magnitude required dose reduction (or interruption for ≥ 10 x ULN). The ≥ 5 x and < 10 x ULN increases occurred at lomitapide doses of 10 mg (Subject 02-002), 10 mg (Subject 32-001), and 60 mg (Subject 12-004). Subject 01-004 had an ALT ≥ 10 x ULN while taking 20 mg (week 6), although he had exceeded 5x ULN while taking 10 mg, and two subsequent shifts to ≥ 5 x ULN while taking 40 mg (weeks 18 and 26); this subject ultimately discontinued lomitapide during the HoFH-extension study as a result of ALT elevations.

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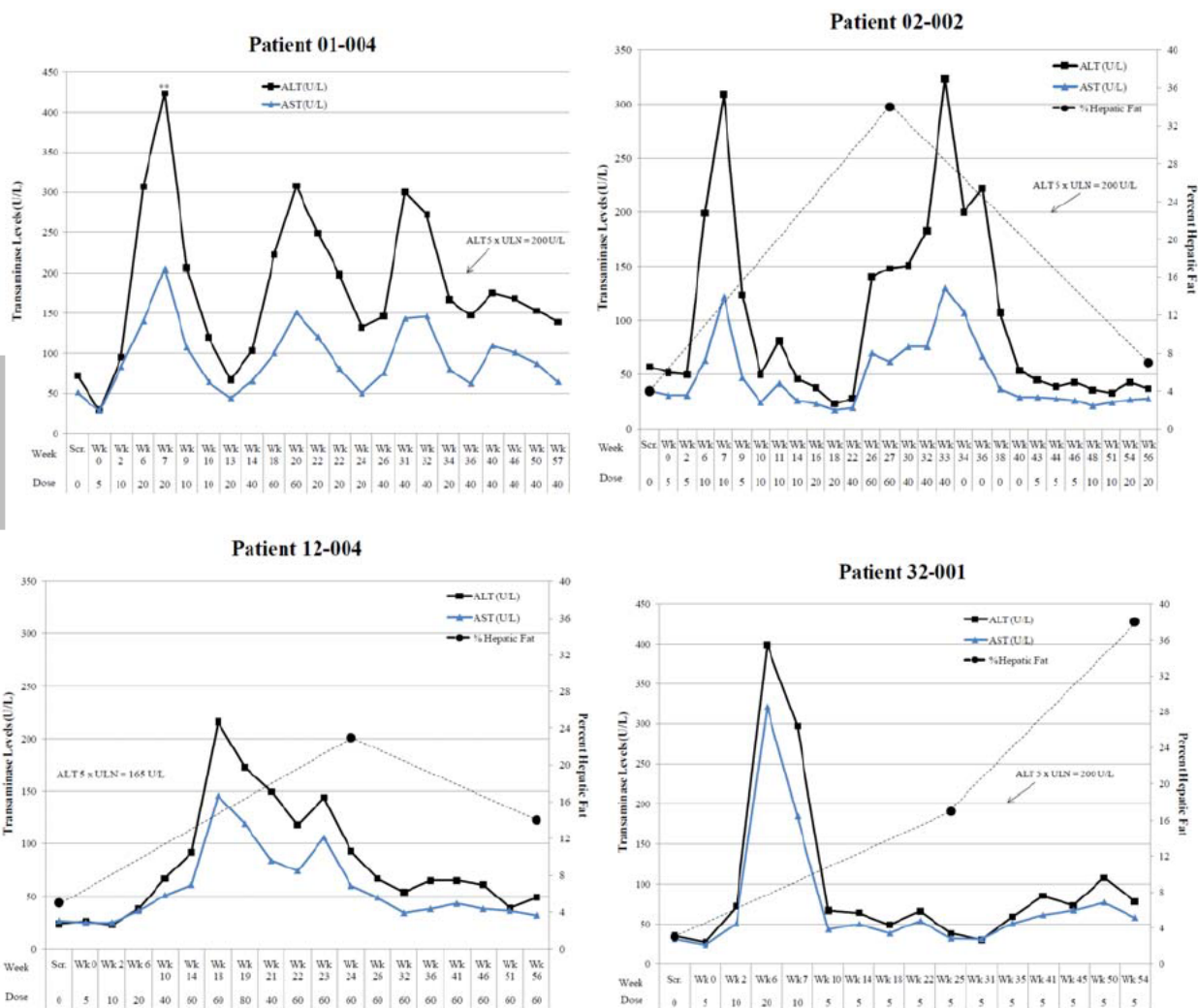


Figure 35. HoFH-pivotal – Selected Transaminase Profiles (ALT ≥5x ULN)
Source: HoFH-pivotal CSR, Figure 10.

Tables containing more granular information regarding the timing of dose modifications and transaminase measurements for these four subjects can be found in Section 9.4 (Appendix, pp. 279-280). Doses at onset of transaminase elevations described here differ in some cases from the applicant's report; on days when blood was drawn *and* the dose was changed, the applicant associated the laboratory abnormality with the post-change dose and I associated it with the pre-change dose.

HoFH-pivotal Brief Subject Summaries for Transaminase Abnormalities

Subject 01-004 (U.S.) was a 39 y/o man with HoFH diagnosed at age 2 with a baseline LDL-C of 500 mg/dL and BMI of 27.6 kg/m². Concomitant lipid-lowering therapy included daily rosuvastatin 10 mg and ezetimibe 10 mg. He had three excursions of ALT ≥5x ULN (including one >10x ULN) during HoFH-pivotal, each leading to a dose reduction. This subject completed the trial taking lomitapide 40 mg daily and enrolled in the extension study. Subsequent ALT elevations in HoFH-extension led to dose reductions to 20 mg, 10 mg, 5 mg, and eventually permanent discontinuation. The subjects peak ALT during the extension study was 13.3x ULN at week 36. The subject reported exceeding recommendations for alcohol intake during the trial.

The applicant speculates that the eventual discontinuation as a result of transaminase elevations $\geq 5x$ ULN may have been complicated by continued excessive alcohol intake.

Subject 02-002 (U.S.) was a 36 y/o obese man with HoFH diagnosed at age 5 with a baseline LDL-C of 409 mg/dL and BMI of 31.6 kg/m². Concomitant lipid-lowering therapy included daily atorvastatin 40 mg and niacin 2000 mg. He had two excursions of ALT $\geq 5x$ ULN during HoFH-pivotal, each leading to a dose reduction/interruption. This subject did not enroll in the extension study.

Subject 12-004 (South Africa) was a 30 y/o morbidly obese white woman with HoFH diagnosed as an infant with a baseline LDL-C of 247 mg/dL and BMI of 41.3 kg/m². Concomitant lipid-lowering therapy included daily rosuvastatin 40 mg, ezetimibe 10 mg, and 16 tablets of nicotinic acid. She had one excursion of ALT $\geq 5x$ ULN during HoFH-pivotal. She completed HoFH-pivotal at a final lomitapide dose of 60 mg and entered the extension study. During the extension, she had ALT 3.2x ULN at her scheduled week 72 and week 96 visits; her dosage was never interrupted or changed from 60 mg daily.

Subject 32-001 (Italy) was a 45 y/o white man with HoFH diagnosed at age 8 with a baseline LDL-C of 357 mg/dL and BMI of 28.7 kg/m². Concomitant lipid-lowering therapy included daily rosuvastatin 30 mg and ezetimibe 10 mg. He had one excursion of ALT $\geq 5x$ ULN. He completed HoFH-pivotal at a final lomitapide dose of 5 mg and did not enter the extension study.

The 120-day safety update identified three additional HoFH subjects who had ALT $\geq 5x$ ULN during HoFH-pivotal and/or HoFH-extension. Two of the subjects (11-004 and 23-001) are described below, since they had peak ALT $\geq 3x$ but $< 5x$ ULN during the pivotal trial. The third subject, 01-003 (U.S.) was a 44 y/o woman at the time of enrollment in HoFH-pivotal with HoFH who completed the pivotal trial and entered the extension study. On day 128 of the extension, while taking lomitapide 60 mg daily, the subject was found to have elevated ALT (412 IU/L, 10.3x ULN) and AST (674 IU/L, 16.9x ULN) through routine lab work performed by her primary care physician. She had been taking cold medicine (Motrin, Mucinex, Robitussin, Nyquil) for the preceding 1-2 months "for a lingering cold." Study medication was stopped, with ALT and AST improving to 147 IU/L and 186 IU/L, respectively, approximately 2 weeks later. Five weeks after interrupting lomitapide, she was restarted on 40 mg daily when ALT and AST were 56 and 57 IU/L, respectively. Transaminases continued to improve over the next several weeks.

Reviewer Comments:

1. Overall, these profiles illustrate that transaminase abnormalities $\geq 5x$ ULN were reversible, with improvements noted within 2-4 weeks of dose modification. In all cases, transaminases fell below 5x ULN although not always below 3x ULN.
2. If the study drug administration records are accurate, it appears that transaminases sometimes decreased despite continued dosing at the dose at onset of the elevated transaminases.
3. There is evidence for positive re-challenge (e.g., subject 01-004), although recurrent episodes could occur at higher doses than the initial abnormality.
4. The applicant does not suggest alternative causes for these transaminase elevations other than study drug with the exception of subject 01-004, where alcohol intake is speculated to have played a contributory role. I searched the

concomitant medication database and did not find evidence of subjects taking moderate or strong CYP3A inhibitors around the time of these events.

- 5. Despite transaminase improvement, effects of lomitapide on liver histology are unknown.*

In addition to the subjects who had at least one transaminase excursion to $\geq 5x$ ULN described above, there were five subjects in HoFH-pivotal who had at least one peak ALT $\geq 3x$ but $< 5x$ ULN:

Subject 11-004 (South Africa) had 3 excursions of ALT to $\geq 3x$ ULN (peaks 4.3x, 3.6x, and 4.9x ULN) with onsets on days 155 (week 22), 286 (week 41), and 393 (week 56). All occurred while the subject was taking lomitapide 40 mg, and all resolved with continued dosing ($< 3x$ ULN).

120-day Safety Update: *This subject went on to have an SAE of hepatotoxicity (ALT 23.9x ULN) in the extension study; see Section 7.3.2 (p. 163).*

Subject 12-001 (South Africa) had 1 peak ALT 4.6x ULN after 4 weeks on the 40 mg dose. The investigator reduced the dose to 20 mg because of this abnormality with ALT falling below 3x ULN 28 days later (87 U/L; 2.6x ULN) at the week 18 visit and further to 40 U/L at the week 22 visit.

Subject 22-004 (Canada) had 2 excursions of ALT to $\geq 3x$ ULN (peaks 4.8x and 3.8x) with onsets on days 126 (week 18) and 169 (unscheduled visit between weeks 22 and 26). Both occurred while the subject was taking lomitapide 20 mg. The investigator interrupted lomitapide for 5 days in response to the first elevation during which time the ALT fell to 84 U/L (2.6x ULN) and lomitapide was restarted at 10 mg, titrating to 20 mg. The second elevation resolved with continued dosing (two weeks later, ALT had fallen to 40 U/L).

Subject 23-001 (Canada) had 1 peak ALT 3.6x ULN at week 66 while taking lomitapide 60 mg. This resolved with continued dosing (ALT 53 U/L at week 78).

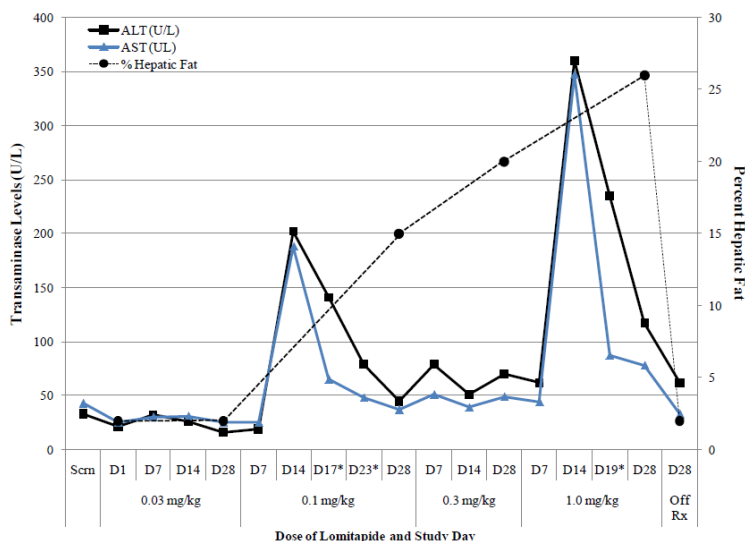
120-day Safety Update: *This subject entered the extension study had was found to have ALT 6.9x ULN at the scheduled week 36 visit. Labs were followed approximately every 2 weeks and the dose of lomitapide was reduced from 60 mg to 40 mg to 20 mg daily. The ALT fell below 3x ULN approximately 10 weeks after the initial abnormal value. Concomitant total bilirubin and alkaline phosphatase levels were normal.*

Subject 31-001 (Italy) had 1 peak ALT 3.2x ULN at week 22 while taking lomitapide 40 mg. This resolved with continued dosing (ALT 64 U/L at week 26 and 21 U/L at week 31).

Reviewer Comment: *These data demonstrate that transaminase elevations to $\geq 3x$ but $< 5x$ ULN, which did not necessarily demand dose modification per protocol, can improve without dose modification or interruption. Because elevations of this magnitude did not trigger more frequent monitoring per protocol, the time to improvement is largely dictated by the study visit schedule and would underestimate the true rate of resolution.*

HoFH Pilot

In HoFH-pilot, 3 (50%) of the 6 subjects had ALT and AST elevations $\geq 5x$ ULN during treatment. Total bilirubin was $\leq 1.5x$ ULN for all subjects. One subject (DWOL68) had a dose reduction because of the elevation but later escalated to receive the maximum planned dose (1.0 mg/kg). The following patient profiles show the time courses for transaminase elevations in relation to dosing for these subjects:



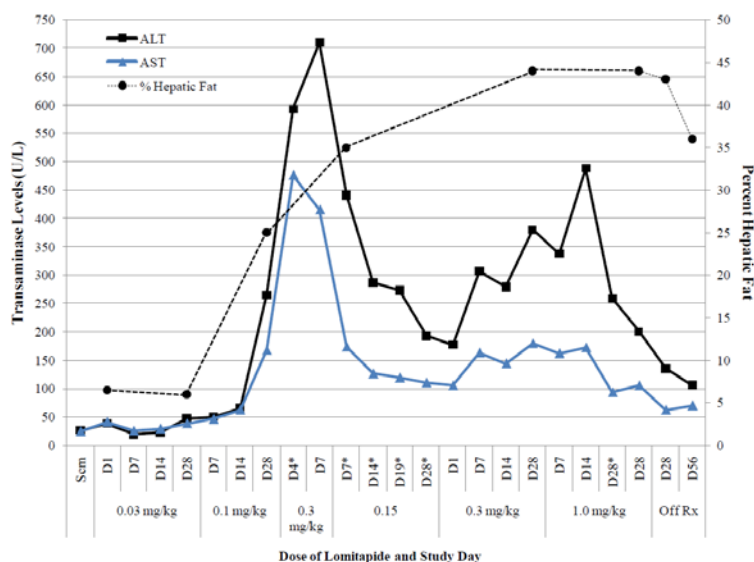
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*Unscheduled assessments

Figure 36. HoFH-pilot – Subject AROD85 Transaminase Profile

Source: HoFH-pilot CSR, narratives.

Based on subject's baseline weight, approximate doses are 1.8, 6, 18, and 60 mg.



*Unscheduled assessments

Figure 37. HoFH-pilot – Subject DWOL68 Transaminase Profile

Source: HoFH-pilot CSR, narratives.

Based on subject's baseline weight, approximate doses are 2.5, 8, 25, and 80 mg.

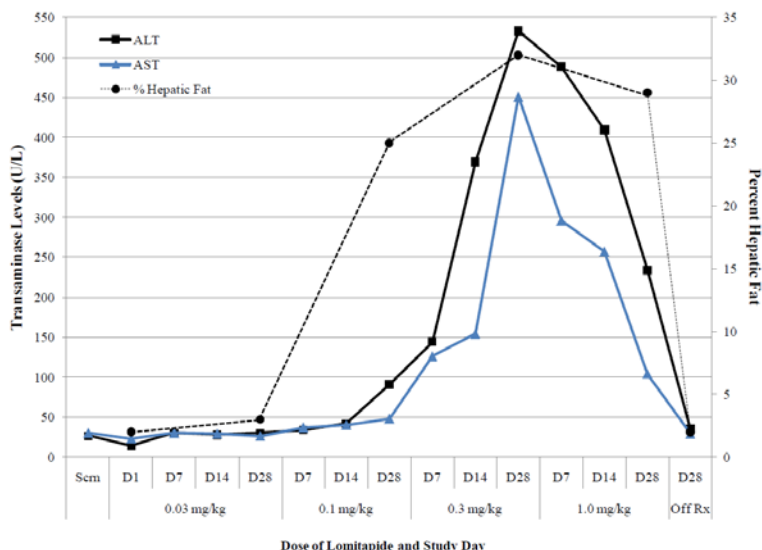


Figure 38. HoFH-pilot – Subject SDAG82 Transaminase Profile

Source: HoFH-pilot CSR, narratives.

Based on subject's baseline weight, approximate doses are 2, 6, 20, and 60 mg.

Reviewer Comment: These profiles from HoFH-pilot support the observation that substantial transaminase abnormalities can improve despite continued dosing. In fact, subject SDAG82 (Figure 38) underwent dose escalation from 0.3 mg/kg to 1.0 mg/kg despite ALT 5.1xULN two weeks prior and ALT 7.4xULN on the day that the dose was increased (protocol violation; labs were not reviewed at the time of the dose increase). Despite this error, the transaminases improved despite continued dosing at 1.0 mg/kg/d.

Phase 2

Table 88 summarizes the incidence of ALT elevations in the five phase 2 trials intended to support the safety and efficacy of lomitapide. Additional detail was provided in Section 5.3 (p. 51).

Table 88. Phase 2 – Incidence of ALT Elevations

Trial	Weeks	ALT ≥3x ULN
C-009	4	32% lomitapide 25 mg; 0% placebo
A-001	12	36% lomitapide (5 → 7.5 → 10 mg); 25% lomitapide + ezetimibe; 0% ezetimibe
A-003b	8	4-12% lomitapide 5 mg (± atorvastatin); 12-23% lomitapide 10 mg (± atorvastatin); 4% placebo and 0% atorvastatin
A-004	12	6% lomitapide 2.5 mg; 3% lomitapide 5 mg; 3% lomitapide 7.5 mg; 9% lomitapide 10 mg; 0-9% in lomitapide 5 mg combination arms (atorva, fenofibrate, ezetimibe) 0% placebo
A-006	8	14% lomitapide (2.5 → 5 mg) + atorvastatin; 0% atorvastatin

Source: FDA clinical reviewer's summary; see Section 5.3 for individual trials.

Reviewer Comment: Elevations in transaminases were common in phase 2 studies as well, despite the lower doses used and shorter durations.

Hepatic Fat

In HoFH-pivotal, all eligible subjects underwent measurement of hepatic fat by NMRS (primary) and MRI at weeks 0, 26, 56, and 78. In addition, for subjects who did not enter the optional extension study, an evaluation was to be performed 6 weeks after stopping study drug. Table 89 summarizes the observed mean values and, for subjects with data available for both data points, changes in hepatic fat from baseline and during the safety phase. MRI results were similar to those obtained with NMRS.

Table 89. HoFH-pivotal – Absolute Change in % Hepatic Fat From Baseline

	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: 120-day safety update, Table 1.3.20.

All values (except *Baseline*) indicate changes in hepatic fat, in absolute percentage points, from baseline. IQR = interquartile range.

* Week in extension study.

In the phase 3 HoFH program overall, 23 subjects had both a baseline and at least one post-baseline assessment. Among the 6 excluded subjects, 4 had contraindications to NMRS/MRI (3 with implanted metal; 1 with excess weight), 1 discontinued treatment only 4 days after baseline, and 1 discontinued prematurely but a reason for the lack of a follow-up assessments was not specified.

Table 90 summarizes the maximum categorical changes in % hepatic fat observed in the HoFH phase 3 studies. In the pivotal trial, 18 (78%) of 23 subjects with available data demonstrated a maximum absolute increase in hepatic fat >5%; 3 (13%) had an absolute increase >20%. If data from the extension study are included as well, 19 (83%) and 4 (17%) of the 23 subjects with available data had increases of >5% and >20%, respectively.

Table 90. HoFH Phase 3 – Maximum Categorical Changes in % Hepatic Fat

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)	
Evaluable Subjects (N)*	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%)

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)	
>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: 17 August 2012 response to FDA information request. Data cutoff 31 December 2011.

* Subjects with baseline observation and at least one follow-up value. This forms the denominator for the column percentages listed.

The applicant also reported the proportion of subjects in HoFH-pivotal with % hepatic fat exceeding 5.56%, which was the upper bound of the 95% CI in an analysis from the Dallas Heart Study comprising 345 patients with no identifiable risk factors for hepatic steatosis (non-obese, non-diabetic, minimal alcohol consumptions, normal transaminases, no known liver disease).⁴² In HoFH-pivotal through week 56 (initial NDA submission), 17 (74%) of the 23 subjects with baseline and at least one post-baseline assessment of hepatic fat (NMRS) had at least one measurement exceeding 5.56%; 13 of these subjects exceeded this threshold at both weeks 26 and 56 (or last assessment).

Reviewer Comment: The relevance of this 5.56% threshold in the study population is unknown. Although it was derived using NMRS, it might be sensitive to differences in measurement methodology between studies. Furthermore, the long-term outcomes of drug-induced hepatic steatosis may be different than steatosis observed in the general population.

Because of the small number of subjects, I have shown the longitudinal trends in % hepatic fat for each subject with at least one post-baseline assessment in Figure 39. In this figure, the solid blue lines connect assessments that occurred during the 78-week HoFH pivotal trial. The dashed red lines connect assessments during the extension study.

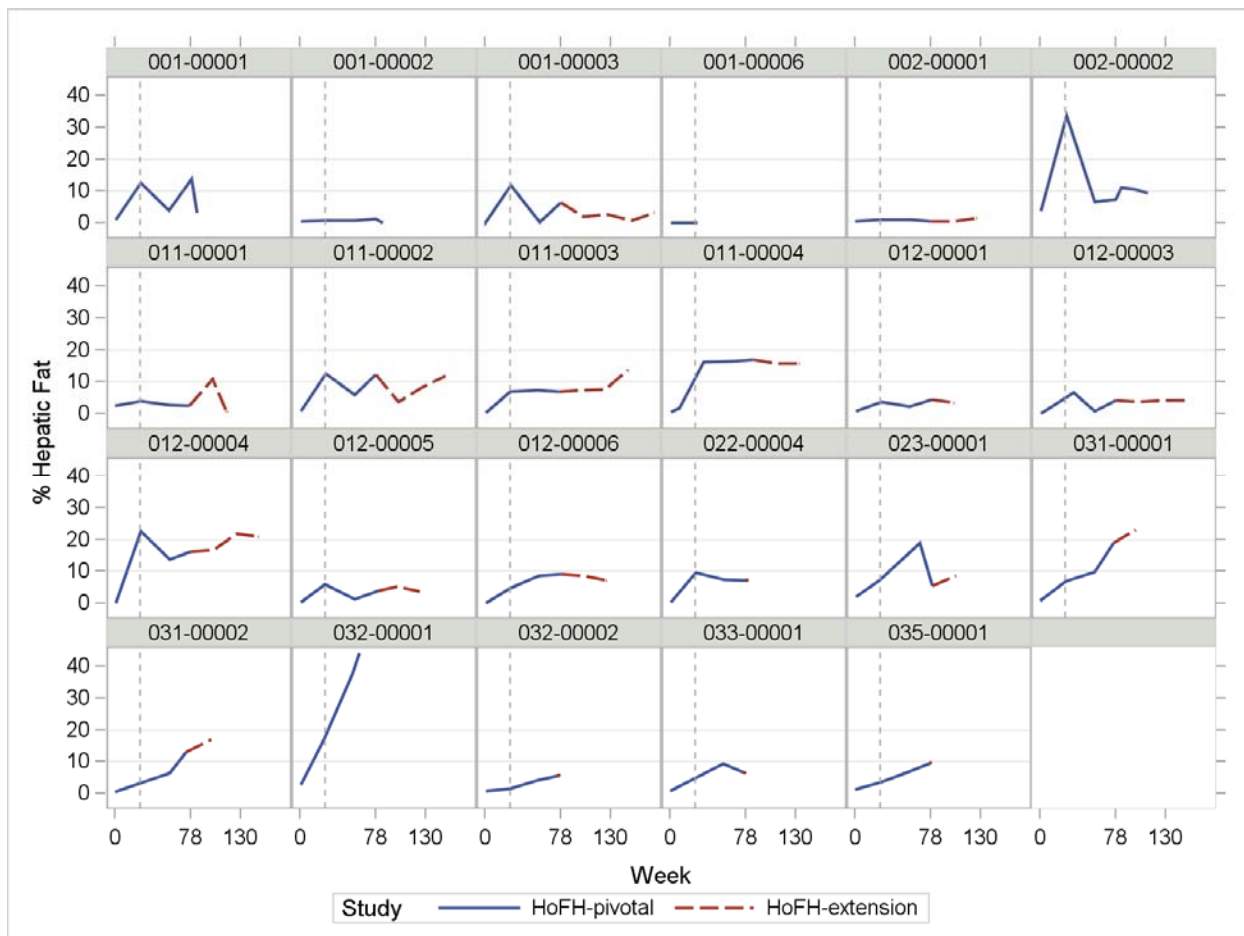


Figure 39. HoFH Phase 3 – % Hepatic Fat Profiles

Source: FDA clinical reviewer’s analysis of submitted hepatic fat datasets from HoFH-pivotal and HoFH-extension (*OM.xpt*).

The dashed vertical lines indicate the end of the efficacy period (week 26) of HoFH-pivotal. Data may include off-treatment follow-up values (e.g., Subject 001-00001, whose last on-drug value was 13.9%). This figure only includes subjects with at least one post-baseline value.

Reviewer Comment: *These profiles demonstrate that, in general, there is typically an early increase in hepatic fat during the first 26 weeks, which often – but does not always – plateau.*

To examine whether some of the observed changes in hepatic fat (increases or decreases) correlated with dose changes at the subject level, I have listed the subjects who had hepatic fat exceed 10% anytime on study in Table 91. For each subject, the available assessments at baseline and weeks 26, 56, 78, and the last measurement for those in the extension study (as of the data cut-off, 31 December 2011) are presented along with the dose being taken immediately prior to the assessment.

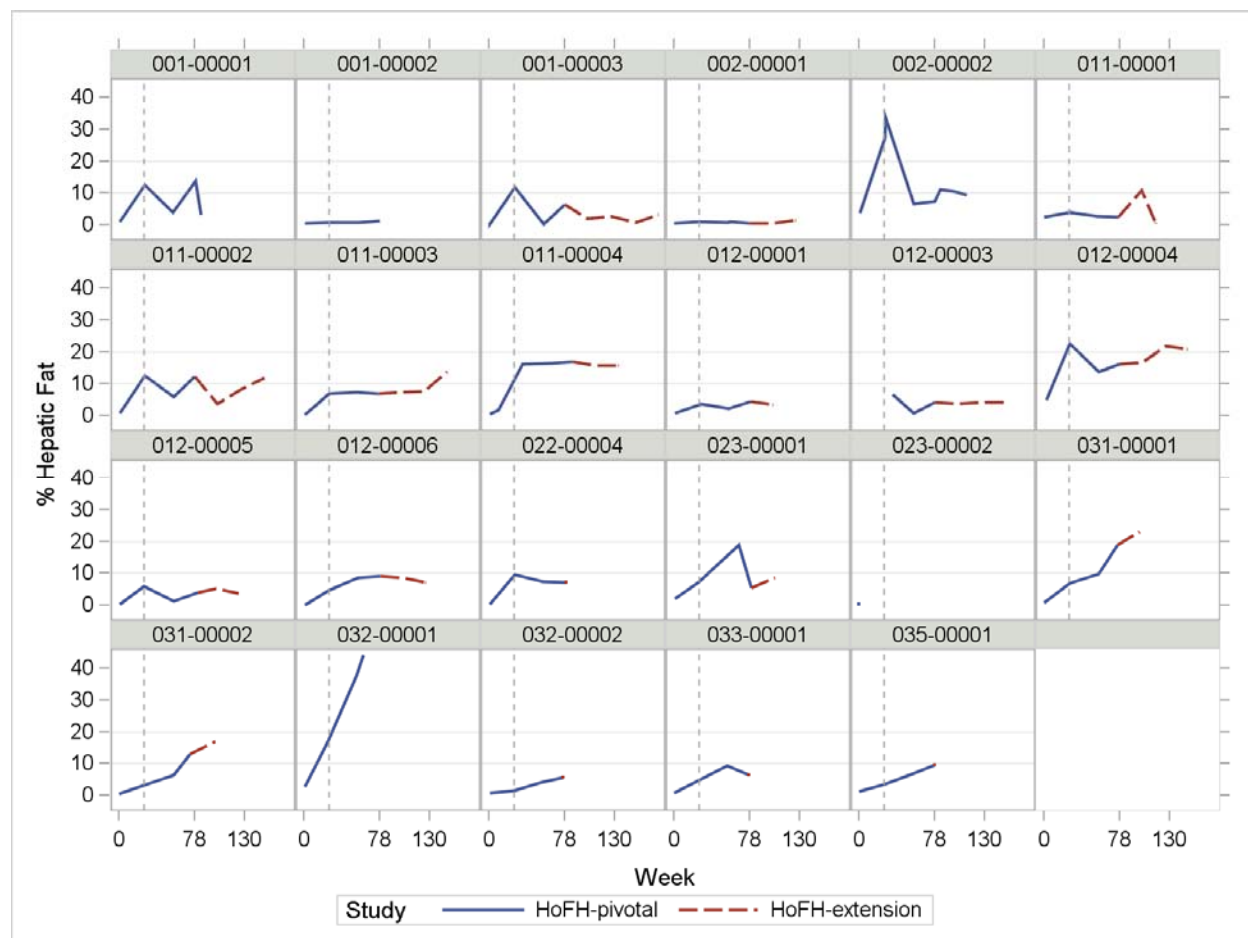


Figure 40. HoFH Population – % Hepatic Fat Profiles

Source: FDA clinical reviewer’s analysis of submitted hepatic fat datasets from HoFH-pivotal and HoFH-extension (*OM.xpt*).

The dashed vertical lines indicate the end of the efficacy period (week 26) of HoFH-pivotal. Data may include off-treatment follow-up values (e.g., Subject 001-00001, whose last on-drug value was 13.9%).

Table 91. HoFH-pivotal – Selected Subject-level % Hepatic Fat & Dose

Category / Subject	Baseline	Week 26	Week 56	Week 78	Last Avail. in Extension
Peak >20%					
32-001	2.7	17.2 (5 mg)	37.7 / 44.3** (5 mg)		
02-002	3.8	33.6 (60 mg)	6.6 (20 mg)	7.4 (20 mg)	(9.3; 34 wks after D/C)
31-001	0.7	6.9 (40 mg)	9.8 (40 mg)	19.0 (40 mg)	23.2 (40 mg)
12-004	0.0*	22.7 (60 mg)	13.9 (60 mg)	16.2 (60 mg)	21.0 (60 mg)
Peak 10-20%					
23-001	2.0	7.3 (60 mg)	19.1 (60 mg)	5.4 (60 mg)	8.6 (60 mg)
31-002	0.5	3.2 (20 mg)	6.3 (20 mg)	13.1 (20 mg)	17.0 (20 mg)
11-004	1.7	16.3 (40 mg)	16.5 (40 mg)	16.9 (40 mg)	15.8 (40 mg)

Category / Subject	Baseline	Week 26	Week 56	Week 78	Last Avail. in Extension
01-001	1.0	12.5 (60 mg)	3.9 (20 mg)	13.9 (20 mg)	(3.2; 6 wks after D/C)
11-003	0.4	6.9 (40 mg)	7.4 (40 mg)	6.8 (40 mg)	13.8 (40 mg)
11-002	0.8	12.7 (40 mg)	6.0 (40 mg)	12.2 (40 mg)	11.8 (40 mg)
01-003	0.9	11.9 (60 mg)	0.4 (60 mg)	6.5 (60 mg)	3.3 (40 mg)
11-001	2.4	3.9 (60 mg)	2.6 (60 mg)	2.4 (60 mg)	10.9 [†] (60 mg)

Source: FDA clinical reviewer’s analysis of submitted HoFH-pivotal and –extension hepatic fat and exposure datasets (OM and EX.xpt).

* By MRI. This subject had a “baseline” value of 5.0% by MRS at week 2, while taking 5 mg.

** Additional assessment 48 days after week 56.

† This subject had an off-treatment measurement of 0.6% approximately 8 weeks after stopping lomitapide.

Reviewer Comment: *These data suggest that the plateaus or observed reductions in hepatic fat cannot often be explained by decreases in dose.*

To explore whether larger increases in hepatic fat during the study are associated with higher amounts of hepatic fat at baseline, I examined the association between % hepatic fat at baseline and at week 26. In a simple linear regression model, each 1% of hepatic fat at baseline was associated with a 4.6% absolute percentage point higher amount of hepatic fat at week 26 ($R^2=32.1\%$, $p=0.006$). This relationship is depicted in Figure 41.

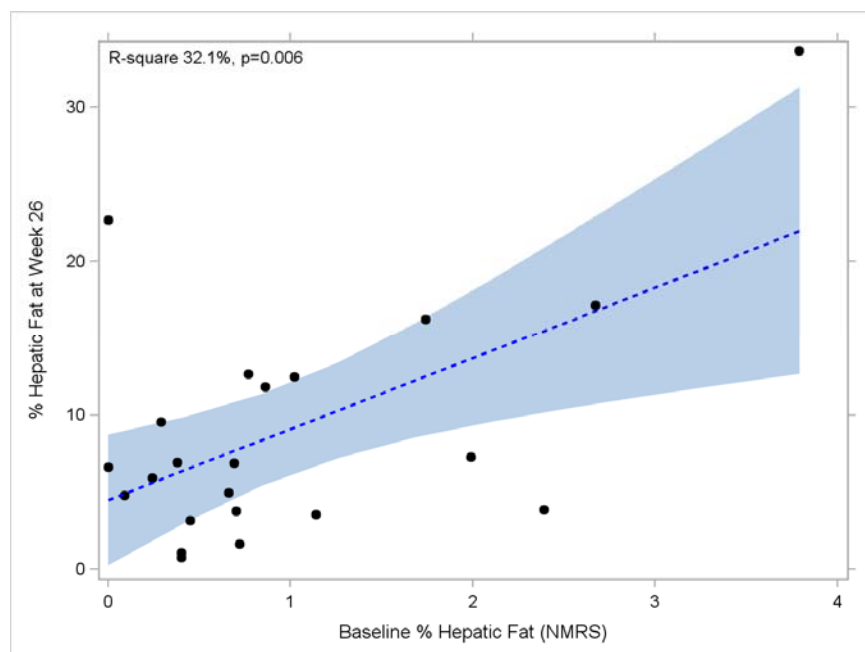


Figure 41. HoFH-pivotal – % Hepatic Fat at Baseline vs. Week 26

Source: FDA clinical reviewer’s analysis of submitted HoFH-pivotal dataset (OM.xpt).

In another exploratory analysis, I examined the relationship between changes in LDL-C from baseline to week 26/LOCF with changes in hepatic fat at the same time points, hypothesizing that the magnitude of LDL-C reduction, as an indicator of pharmacodynamic activity, may correlate with hepatic fat accumulation. My analysis did not reveal a statistically significant association between change in hepatic fat (absolute % points) and either absolute or relative changes in LDL-C, although power to detect such an association is limited given the sample size of 22 subjects. Notably, the point estimate of the slope of the regression line was negative (i.e., larger absolute reductions in LDL-C were associated with greater increases in hepatic fat, on average), but a larger sample size would be required to define this association with more certainty. These data are presented in Figure 42.

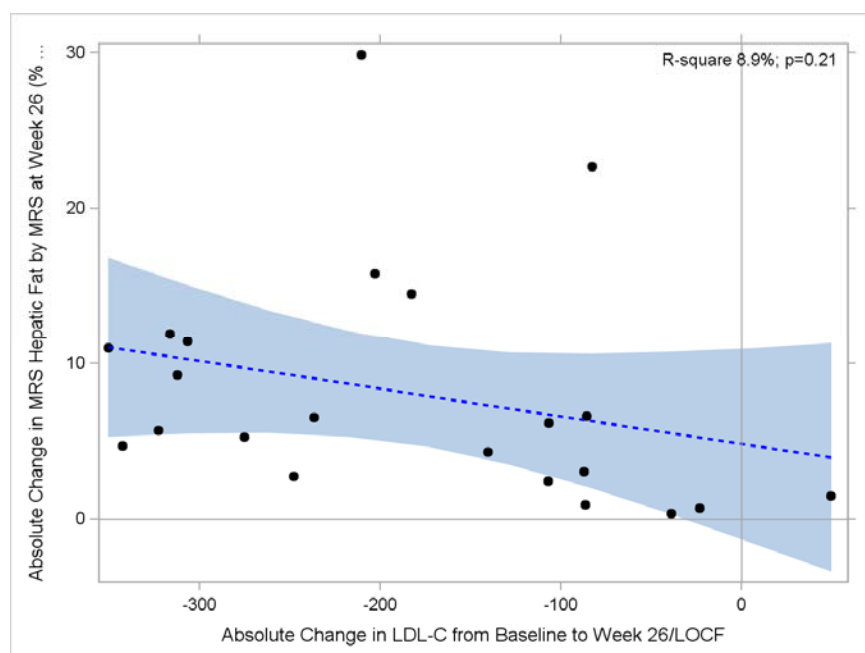


Figure 42. HoFH-pivotal – Association Between Changes in LDL-C and Hepatic Fat at Week 26

Source: FDA clinical reviewer’s analysis of submitted HoFH-pivotal data in analysis datasets (*ADLP xpt* and *ADOM.xpt*).

Regression line (simple linear regression) with shaded 95% confidence limits for predicted mean values.

Regarding the cross-sectional relationship between hepatic fat and absolute transaminase levels, hepatic fat percentages (NMRS) at week 26 and week 56 each correlated significantly with both ALT and AST (Table 92).

Table 92. HoFH-pivotal – Correlation of Transaminases and % Hepatic Fat

Correlation of hepatic fat with	Week 26 (n=24)	Week 56 (n=22)
ALT	0.76 (p<0.0001)	0.59 (p=0.004)
AST	0.76 (p<0.0001)	0.58 (p=0.004)

Source: HoFH-pivotal CSR, Tables 14.3.4.1.15.3 and 14.3.4.2.15.3.

Values are Pearson correlation coefficients (r).

Reviewer Comment: *A statistically significant cross-sectional correlation does not prove causality. For an individual patient, elevated transaminases may or may not accompany an increase in hepatic fat, and vice versa. Therefore, the clinical utility of these observations is limited.*

In HoFH-pivotal alone, 7 (39%) of the 18 subjects who ever had >5% hepatic fat also had a peak ALT $\geq 3x$ ULN on-study compared with 1 (20%) of the 5 subjects who always had $\leq 5\%$ hepatic fat. Three of the four subjects in HoFH-pivotal who had at least one measurement of hepatic fat >20% also had at least one elevation in ALT $\geq 5x$ ULN on-study, with the remaining subject having a peak ALT 3.5x ULN. The temporal relationships cannot be discerned conclusively given the widely spaced measurements of hepatic fat (Figure 35), however.

In an exploratory analysis, I considered whether ALT $\geq 3x$ ULN might serve as a screening test for changes in hepatic fat. Figure 43 shows the association between the peak ALT on or prior to the date of the peak change in % hepatic fat; this maintains the temporal relationship between obtaining ALT as a screening test and the detection of the outcome. (The results were very similar when the peak on-study ALT value was used instead, disregarding the temporal association with peak change in hepatic fat.)

Keeping the “screening test” constant (ALT $\geq 3x$ ULN), I calculated its sensitivity and specificity for detecting various thresholds of changes in hepatic fat, realizing that these are preliminary estimates from a dataset of only 23 subjects.

Table 93. Exploration of ALT $\geq 3x$ ULN as Screen for Hepatic Fat

Outcome	Test: ALT $\geq 3x$ ULN (prior to outcome)	
	Sensitivity	Specificity
+5% hepatic fat	38%	80%
+10% hepatic fat	44%	86%
+15% hepatic fat	80%	88%
+20% hepatic fat	100%	85%

Source: FDA clinical reviewer’s analysis of HoFH-pivotal datasets (*OM and LB.xpt*). Changes in hepatic fat represent the maximum change observed on-study, expressed as an absolute percentage point increase.

Reviewer Comment: *Monitoring transaminases would be an insensitive method to screen for hepatic fat accumulation, especially if increases of 10% absolute could be clinically important. The clinical significance of hepatic steatosis in the absence of elevated transaminases is unclear, however.*

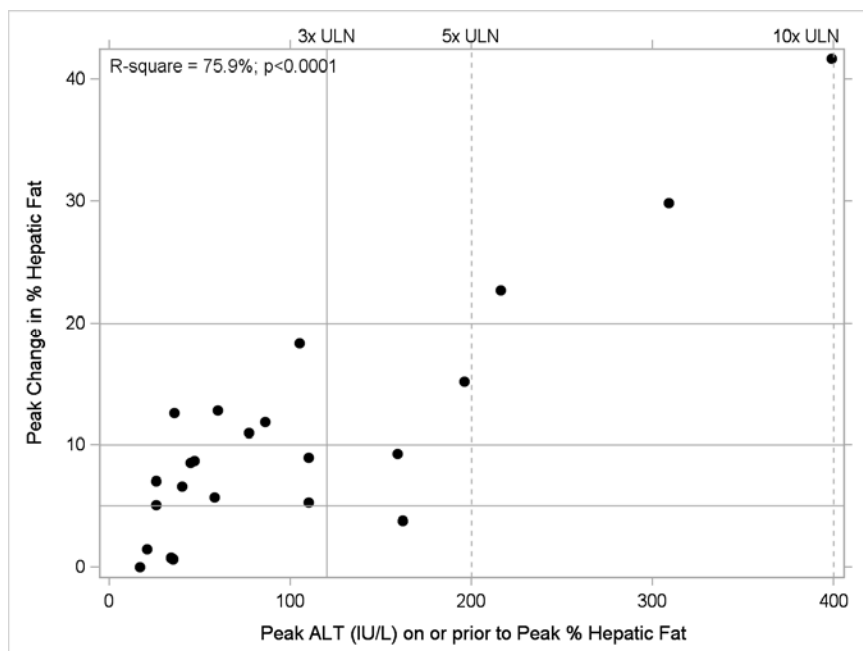


Figure 43. HoFH-pivotal – Peak ALT vs. Peak Change in Hepatic Fat

Source: FDA clinical reviewer’s analysis of submitted HoFH-pivotal datasets (*OM and LB.xpt*).

Regarding reversibility of hepatic fat accumulation, follow-up NMRS or CT scans were available for 7 HoFH subjects after discontinuing lomitapide (Table 94). These data suggest partial or complete reversibility of hepatic fat accumulation following discontinuation of lomitapide. Whether histologic sequelae remain, however, is unknown given the lack of protocol liver biopsies.

Table 94. HoFH-pivotal – Reversibility of Hepatic Fat

Subject	Baseline	Peak % Hepatic Fat on Study	% Hepatic Fat at Week 78	Follow-up
01-001	1%	14% at week 78	14%	3% (~6 wks post)
01-004	Mild-to-mod by CT at week 40	Moderate by CT at week 78	Moderate by CT	Mild-to-moderate (~6 wks post)
01-006	0%	None	(Early DC after ~6 months)	0% (~2 wks post)
01-002	0.4%	1.1% at week 78	1.1%	0% (~7 wks post)
02-002	4%	34% at week 26	7%	11%, 11%, and 9% (~1, 6, 9 months post)
11-001	2%	11% at week 102 (extension)	2%	0.6% (~8 wks post)
32-001	3%	44%	Not Done	Mild (~7-15%) by CT (~6 wks post)

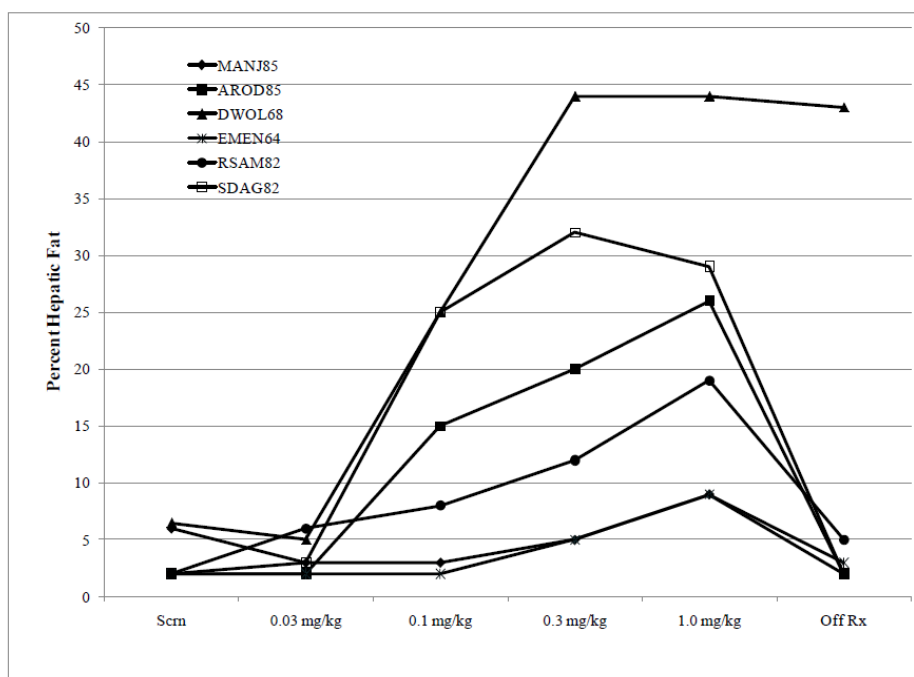
Source: 17 August 2012 response to FDA information request.

As described in Section 2 (p. 22), some have suggested that hepatic fat might promote insulin resistance (in addition to insulin resistance promoting hepatic fat). Serum insulin, C-peptide, or HbA1c were not assessed during HoFH-pivotal. As described in Section

5.3, the 12-week phase 2 study AEGR-733-004 did not reveal an association between hepatic fat accumulation and serum C-peptide (Figure 13), and subjects who had the greatest increases in hepatic fat did not demonstrate the greatest increases in insulin resistance, at least as measured by HOMA-IR (Figure 14).

HoFH-pilot Supportive Hepatic Fat Data

The profiles of % hepatic fat over time in HoFH-pilot are shown in Figure 44. All 3 subjects in this trial who had transaminase elevations $\geq 5x$ ULN also had elevations in hepatic fat to $>25\%$. By the time of the off-treatment follow-up visit approximately 4 weeks after last dose, hepatic fat had decreased to $\leq 5\%$ in five of six subjects; one subject had hepatic fat 41-43% at followup.



Hepatic fat % was reported as a range: the maximum value of the range is displayed graphically.
Source: Appendix 4 and Appendix 7

Figure 44. HoFH-pilot – % Hepatic Fat over Time

Source: HoFH-pilot CSR, Figure 4.

Reviewer Comment: In 5 of the 6 subjects in HoFH-pilot, the accumulation of hepatic fat appears largely reversible over a relatively short period of time (~4 weeks). The applicant speculates that alcohol played a role in the persistent level of hepatic fat in the remaining subject (DWOL68). The NEJM publication of this trial states, “Aminotransferase and hepatic fat levels returned to baseline levels 4 weeks after the therapy was ceased in all patients except Patient 3 [DWOL68], in whom they did not return to the normal range until 14 weeks after cessation of therapy.”⁴³ This subject subsequently enrolled in HoFH-pivotal (Subject 01-004), but the interim insertion of a pacemaker/ICD precluded assessments of hepatic fat by MRI/MRS. This subject did,

however, have several episodes of elevated transaminases, ultimately leading to his discontinuation during HoFH-extension as previously described.

Hepatic Fat Data from Phase 2 (Non-HoFH)

The phase 2 trials CV145-009 and AEGR-733-004 each assessed hepatic fat accumulation with lomitapide. The results from these trials are presented in Section 5.3 (p. 51).

Liver Biopsies

Protocol liver biopsies have not been conducted during the lomitapide development program.

A single subject (11-004) in the phase 3 program underwent two liver biopsies, the latter in follow-up to an SAE for hepatotoxicity in the HoFH extension study. This subject's course is described in Section 7.3.2 (p. 163).

One individual with familial chylomicronemia has been treated with lomitapide for approximately 13 years through compassionate use. Her dosage has typically been 20-25 mg daily. She started lomitapide in June 2000 and had liver biopsies in October 2000, October 2002, August 2004, January 2008, and most recently June 2012. In 2004, her biopsy showed a "liver parenchyma with marked, predominantly macrovesicular steatosis; no significant inflammation or fibrosis." In 2008, mild steatohepatitis without significant fibrosis was mentioned. According to the applicant, her transaminases increased from her typical 2-3x ULN to approximately 4x ULN in September 2011, ultimately prompting a repeat biopsy in June 2012. She now has

- (1) severe mixed large and small droplet steatosis, involving >66% of the core biopsy;
- (2) frequent ballooning degeneration with focal material suspicious for intracytoplasmic hyaline;
- (3) **mild portal/septal and mild to focally moderate lobular mixed inflammation** consisting of lymphocytes, neutrophils, and rare eosinophils and plasma cells with few apoptotic hepatocytes; and
- (4) trichrome stain demonstrates **portal, septal, and sinusoidal fibrosis with delicate bridging and rare foci of early, incomplete nodule formation**; some central veins are identified (at least Stage 3 fibrosis, focally early Stage 3-4)."

The applicant reports that the investigator continues to treat this patient with lomitapide, considering the benefit/risk ratio favorable for her individual situation, given a history of repeated bouts of acute pancreatitis that lomitapide seems to have reduced.

Reviewer Comment: This is the first known biopsy-proven case of NASH in a patient being treated with lomitapide, but we certainly do not know the contribution of lomitapide, if any, versus the underlying disease in the development of NASH in this patient.

Putative Serum Biomarkers of Liver Histology

Although liver biopsy is the current gold standard for diagnosing and assessing NASH and hepatic fibrosis, there is growing interest in the development of relatively non-invasive serum biomarkers for these conditions. Cytokeratin-18 (CK-18) is a hepatic intermediate filament protein released by necrotic cells, and a caspase-3-generated fragment of this protein is released by apoptotic cells. Because NASH is characterized by both hepatocellular apoptosis and necrosis, CK-18 and “CK-18 fragment” are potential biomarkers of this process. Furthermore, an “enhanced liver fibrosis” (ELF) panel has been proposed as an assessment of hepatic fibrosis; this panel includes serum metalloproteinase-1 (TIMP), hyaluronic acid (HA), and N-terminal peptide of procollagen type III (PN3P).⁴⁴

Observational studies suggest that CK-18 and its fragment independently predict the presence of NASH even after adjusting for potential confounders (e.g., age, diabetes, hyperlipidemia, serum transaminases, among others). Studies have varied, however, with regard to the definition of NASH and the resulting threshold values proposed to suggest a diagnosis of NASH. The ELF panel has been studied more extensively, with levels of the individual 3 markers and a composite “discriminant score” correlating with the extent of fibrosis.^{44, 45} The clinical utility of monitoring this panel in individuals without known liver disease or, more specifically, in individuals at risk or known to have drug-induced hepatic steatosis, however, is unknown.

As an exploratory post hoc study, however, hepatic biomarker data were measured in the HoFH phase 3 program and a summary of results through week 56 (initial NDA submission) is included in this section.

Descriptive statistics for CK-18, CK-18 fragments, and the ELF panel with its discriminant score are shown in Table 95. All biomarkers except for P3NP increased from baseline through week 56.

Table 95. HoFH-pivotal – Hepatic Biomarker Descriptive Statistics

	Mean (SD)	Median	Absolute Mean (SD) Change from Baseline [95% CI]
CK-18 (IU/L)			
Baseline	285 (68)	271	
Week 26	445 (234)	358	+158 (237) [50, 266]
Week 56	408 (184)	370	+115 (194) [19, 212]
CK-18 fragment (IU/L)			
Baseline	110 (46)	110	
Week 26	158 (100)	122	+47 (99) [2, 92]
Week 56	135 (58)	121	+22 (64) [-10, +53]

	Mean (SD)	Median	Absolute Mean (SD) Change from Baseline [95% CI]
TIMP (ng/mL)			
Baseline	87 (24)	83	
Week 26	94 (24)	87	+12 (29) [-1, +25]
Week 56	87 (18)	87	+4 (21) [-6, +13]
HA (ng/mL)			
Baseline	23 (20)	20	
Week 26	30 (19)	29	+8 (23) [-2, +19]
Week 56	34 (26)	29	+12 (24) [-10, +53]
P3NP (ng/mL)			
Baseline	8.2 (1.9)	8.1	
Week 26	8.4 (1.7)	8.1	-0.01 (1.9) [-0.9, +0.9]
Week 56	8.7 (1.3)	8.3	+0.3 (1.8) [-0.5, +1.1]
Discriminant Score			
Baseline	-1.7 (0.6)	-1.6	
Week 26	-1.4 (0.5)	-1.5	Not reported
Week 56	-1.3 (0.6)	-1.3	Not reported

Source: UP1002/733-005 Hepatic Biomarker Interim Report, Table 1.

N varies from 22-26 at baseline, 21-22 at week 26, and 18-23 at week 56. Changes from baseline only include subjects with assessments at both time points.

See text for abbreviations. Note that the mean changes in CK-18 from baseline to weeks 26 and 56, and the mean change in CK-18 fragment from baseline to week 26, are statistically significant at the 0.05 level.

The applicant tested correlations between hepatic biomarkers and serum transaminases, % hepatic fat measurements, AST/ALT ratio, age, and LDL-C at baseline, week 26, and week 56. Because these biomarkers would be intended to detect conditions expected to develop with increased exposure, I focused on selected cross-sectional correlations at week 56. Table 96 summarizes the correlation coefficients (Spearman's ρ) for each biomarker with ALT, % hepatic fat, age, and LDL-C. Note that the correlations between CK-18 and its fragment are especially strong with ALT, which would be expected since both can derive from hepatocellular death.

Table 96. HoFH-pivotal – Correlations with Hepatic Biomarkers at Week 56

Variable	CK-18	CK-18 fragment	TIMP	HA	P3NP	Discrim. Score
ALT	0.77*	0.68*	0.43*	0.35	0.10	0.44*
% Hep Fat	0.24	0.86*	-0.07	0.01	-0.06	0.01
Age	0.40	0.07	0.42	0.32	-0.36	0.30
LDL-C	-0.53*	-0.30	-0.04	-0.19	0.01	-0.20

Source: UP1002/733-005 Hepatic Biomarker Interim Report, Table 3.1.3.

Values are Spearman's ρ . See text for abbreviations. * P<0.05.

Interestingly, CK-18 fragment strongly correlated with % hepatic fat. This bivariate relationship is depicted in Figure 45 for the 14 subjects who had detectable CK-18 fragments (an additional 2 subjects had CK-18 fragments recorded as “<75 IU/L”). At week 56, CK-18 fragments explained 67% of the variation in % hepatic fat measured at the same time point ($P=0.0003$). Not unexpected given the observed correlation between ALT and CK-18 fragment, adjusting for week 56 ALT attenuated the magnitude of the association between CK-18 fragment and % hepatic fat from 0.15 to 0.10 absolute percentage points per IU/L of CK-18 fragment, but the association remained nominally statistically significant ($P=0.04$).

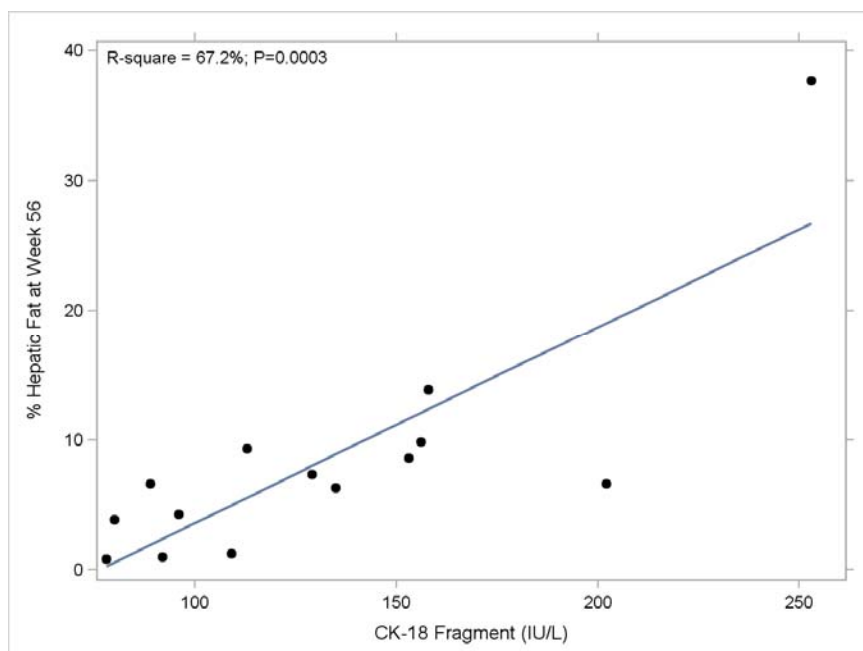


Figure 45. HoFH-pivotal – Cross-sectional Association Between CK-18 Fragment and % Hepatic Fat at Week 56

Source: FDA clinical reviewer’s analysis of submitted HoFH-pivotal datasets (*LB.xpt* and *OM.xpt*). An additional two subjects had CK-18 measured but the values were “<75 IU/L.” These two subjects were excluded from this figure and the simple linear regression analysis that yielded the R^2 and P values shown. Imputing values of “0,” which would be the most extreme case, gave $R^2 = 59.4\%$ and $P=0.0005$.

Reviewer Comment: Whether these biomarkers would have clinical utility in monitoring subjects treated with lomitapide would require further study. The fact that CK-18 fragments are significantly associated with hepatic fat is interesting, but hepatic fat could be measured directly by non-invasive means. The relevant question is whether CK-18 fragments, or any other hepatic biomarker for that matter, would allow early detection of adverse liver histology that could lead to an intervention to improve clinical outcomes. The current data are inadequate to answer this question.

Effects on Fat-Soluble Vitamins & Fatty Acids

As described in Dr. Hummer's Pharmacology/Toxicology review, deficiencies in fat-soluble vitamins were observed in animal studies, leading to systemic hemorrhage in rats at exposures ~22-fold higher than those expected at the maximum recommended human dose (MRHD) of 60 mg daily. This toxicity resulted in death at higher exposures (~70x MRHD). When fat-soluble vitamins were supplemented, systemic bleeding was not observed. As described in Section 5.3, only vitamin A (studies A-003b and -004) and vitamin E (studies C-009, A-003b, and A-004) were assessed in the phase 2 non-HoFH program. A more comprehensive panel was studied in HoFH-pilot (see below), which included systemic fatty acid measurements for the first time. Because of a statistically significant reduction in fat-soluble nutrients with use of lomitapide ≥ 0.3 mg/kg in this six-subject trial, dietary supplements containing vitamin E (400 IU), linoleic acid (200 mg), alpha-linolenic acid (220 mg), EPA (110 mg), and DHA (80 mg) were provided to subjects in the pivotal trial.

In HoFH-pivotal, Vitamin A, 25-OH vitamin D, vitamin E, and uncarboxylated osteocalcin as a measure of functional vitamin K were measured at every visit during the efficacy phase and every 10 weeks during the safety phase (weeks 36, 46, 56, 66) with a final measurement at week 78. Serum levels of essential fatty acids (alpha-linolenic acid [ALA] and linoleic acid [LA]), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), arachidonic acid (AA), and eicosatrienoic (Mead) acid were measured at the same time points. In the extension study, only Vitamins A and E were measured.

Reviewer Comment:

- 1. Although any observed changes may or may not be causally related to lomitapide given that this is an uncontrolled trial and non-drug-related factors could contribute to observed trends, reductions in fat-soluble nutrients were observed in preclinical studies and are consistent with lomitapide's mechanism of action.*
- 2. Because similar profiling of fat-soluble vitamins and fatty acids (to this extent) was not performed during placebo-controlled trials when multivitamins were not issued, the effect of lomitapide without supplementation on these nutrients is unknown.*
- 3. To what extent the dietary changes enforced in this trial would contribute to changes in fatty acids, for example, is unknown.*
- 4. Whether concomitant administration of lomitapide and the recommended dietary supplement, as opposed to separating administration by several hours, would reduce the absorption of the supplement's components is unknown. The HoFH-pivotal protocol did not specify how the supplement was to be taken.*

Boxplots showing the distributions of each of these fat-soluble nutrients at each study visit are presented in the Appendix (Figure 71 through Figure 82). The trends suggest that, on average, levels of vitamins A and D tended to increase over time and that there were no substantial changes in functional vitamin K deficiency (as assessed by proportion of osteocalcin that was uncarboxylated) or beta-carotene. Vitamin E levels

decreased substantially, however, with a profile similar to the changes in LDL-C observed. Because lipoproteins are required for vitamin E absorption and transport, this is not unexpected, and the ratio of serum vitamin E:lipid (TC+TG) is valuable as an index of vitamin E status in situations where plasma lipids are either increased or decreased.⁴⁶ The relative stability of the vitamin E/lipid (TC+TG) ratio with lomitapide would suggest that the observed decrease in vitamin E is not the result of malabsorption.

Regarding fatty acids, the trends over time suggest reductions in all fatty acids during approximately the first 26 weeks of therapy (efficacy period) with subsequent stabilization and/or trends toward baseline. The magnitudes of these reductions vary (Table 97). Because some parameters had highly skewed distributions for % change, which is bounded by -100% and +∞, median values are presented. Examination of the Week 84/Early Termination visits typically show higher levels at these off-treatment visits, strengthening the likelihood that lomitapide induces these changes as opposed to being the result of regression to the mean (data not shown).

Table 97. HoFH-pivotal – Median Changes in Fat-soluble Nutrients

Parameter	Baseline Median [IQR]	% Change at Week 26 Median [IQR]	% Change at Week 78 Median [IQR]
Vitamin A	1.43 [1.20, 1.74] μmol/L	+5.9% [-8.7, 33.3]	+19.4% [-8.2, 27.5]
Vitamin D	34.9 [20.0, 64.9] nmol/L	+59.4% [10.9, 120.4]	+121.7% [22.1, 189.2]
Vitamin E	64.8 [51.2, 81.9] μmol/L	-43.3% [-63.3, -22.9]	-40.7% [-61.6, -17.0]
Vitamin E / Lipid (TC+TG)	5.4 [3.9, 7.7]	+0.3 absolute [-0.4, 1.1]	-0.6 absolute [-1.3, 1.6]
Uncarbox. osteocalcin*	23.5 [18.9, 28.1] %	+2.7% absolute [-7.2, 6.9]	+4.1% absolute [-3.5, 8.1]
Beta-carotene	0.44 [0.27, 0.84] μmol/L	-34.1% [-76.2, -22.2]	-24.7% [-44.2, 9.0]
ALA	56 [34, 107] μmol/L	-53.6% [-65.8, -35.3]	-41.2% [-66.1, -13.6]
LA	3867 [3499, 4799] μmol/L	-25.0% [-40.8, -9.8]	-17.0% [-27.5, 16.3]
EPA	164 [126, 288] μmol/L	-64.1% [-80.3, -42.5]	-66.6% [-77.2, -20.3]
DHA	367 [230, 439] μmol/L	-47.3% [-61.5, -23.6]	-46.3% [-64.6, -5.2]
AA	2220 [1742, 2438] μmol/L	-54.7% [-62.5, -34.5]	-50.9% [-63.9, -9.4]
Mead*	20 [16, 23] μmol/L	-43.8% [-57.1, -28.6]	-51.5% [-60.0, -26.1]

Source: 120-day safety update, Table 1.3.10

ALA = alpha-linolenic acid; LA = linoleic acid; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; AA = arachidonic acid; Mead = eicosatrienoic acid

* *Increased* values of uncarboxylated osteocalcin (as % of total) suggest functional vitamin K deficiency, and *increased* values of Mead acid suggest essential fatty acid deficiency.

Shift tables present the incidence of individual subjects having values that change with respect to the reference range at various time points. Table 98 shows the data for shifts in fat-soluble vitamins at week 26 and 78, stratified by baseline level. Bolded values in red font represent those that shifted categories in an undesirable direction.

Table 98. HoFH-pivotal – Fat-Soluble Vitamin Shift Table

Variable	Baseline	Week 26			Week 78		
		< LLN	Normal	> ULN	< LLN	Normal	> ULN
Vit. A	< LLN	1 (5%)	2 (10%)		1 (4%)	3 (13%)	
	NL	2 (10%)	15 (71%)			18 (78%)	
	> ULN			1 (5%)			
Vit. D	< LLN						
	NL		20 (100%)		1 (5%)	17 (77%)	4 (18%)
	> ULN						
Vit. E	< LLN						
	NL	1 (5%)	3 (14%)	1 (5%)		5 (22%)	
	> ULN		8 (38%)	8 (38%)		9 (39%)	9 (39%)
Beta-carotene	< LLN						
	NL	2 (10%)	14 (70%)	1 (5)		19 (83%)	1 (4%)
	> ULN		2 (10%)	1 (5%)		1 (4%)	2 (9%)
ucOC	< LLN	1 (5%)				1 (4%)	
	NL		14 (70%)	2 (10%)		14 (61%)	5 (22%)
	> ULN		2 (10%)	1 (5%)		2 (9%)	1 (4%)

Source: Derived from 120-day safety update, Table 1.3.12. Values represent counts of subjects.

LLN and ULN refer to lower and upper limits of normal reference range, respectively.

Values in bold, red font represent shifts between categories in an undesired direction (downward for all except uncarboxylated osteocalcin [ucOC]).

A similar shift analysis for fatty acids is shown in Table 99. The essential fatty acids ALA and LA were most commonly measured below the reference range. Of the 11 subjects with ALA levels above LLN at baseline, 7 (64%) were below LLN at week 26; of the 18 subjects with LA levels above LLN at baseline, 4 (22%) were below LLN at week 26. During the subsequent year, the proportion below the reference range did not increase; in fact, fewer subjects were below LLN at week 78 than week 26. Mead acid levels did not increase, which can occur with severe essential fatty acid deficiency. Thus, it is unlikely that these shifts are clinically significant for the adult population, but it does seem prudent to supplement essential fatty acids if lomitapide is approved, until more data are available.

Table 99. HoFH-pivotal – Fatty Acid Shift Table

Variable	Baseline	Week 26			Week 78		
		< LLN	Normal	> ULN	< LLN	Normal	> ULN
ALA	< LLN	8 (42%)	1 (5%)		9 (43%)	3 (14%)	1 (5%)
	NL	6 (32%)	1 (5%)		3 (14%)	3 (14%)	1 (5%)
	> ULN	1 (5%)	2 (11%)	1 (5%)	1 (5%)	3 (14%)	
LA	< LLN	1 (5%)				1 (5%)	
	NL	2 (11%)	5 (26%)		1 (5%)	5 (23%)	2 (9%)
	> ULN	2 (11%)	5 (26%)	4 (21%)	2 (9%)	4 (18%)	7 (32%)
EPA	< LLN						
	NL		3 (16%)			2 (9%)	1 (5%)

Variable	Baseline	Week 26			Week 78		
		< LLN	Normal	> ULN	< LLN	Normal	> ULN
	> ULN		13 (68%)	3 (16%)		11 (50%)	8 (36%)
DHA	< LLN						
	NL		2 (11%)	1 (5%)		4 (18%)	1 (5%)
	> ULN		10 (53%)	6 (32%)		10 (45%)	7 (32%)
AA	< LLN						
	NL		1 (5%)			1 (5%)	
	> ULN		16 (84%)	2 (11%)	1 (5%)	14 (64%)	6 (27%)
Mead	< LLN						
	NL	1 (5%)	16 (84%)		1 (5%)	19 (86%)	
	> ULN		2 (11%)		1 (5%)	1 (5%)	

Source: 120-day safety update, Table 1.3.12. Values represent counts of subjects.

ALA = alpha linolenic acid; LA = linoleic acid; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; AA = arachidonic acid; Mead = eicosatrienoic acid.

Values in bold, red font represent shifts between categories in an undesired direction.

Subject-level longitudinal trends of fat-soluble nutrients are depicted in through . Gray lines depict trends for subjects who never had values below the LLN, and the colored lines depict the trends for subjects who had at least one value below the LLN (excluding baseline); for Mead acid and uncarboxylated osteocalcin, for which higher levels could be potential for concern, upper thresholds were used to highlight individual subjects. In addition, the thick red lines represent a fitted penalized B-spline surrounded by a 95% confidence band. Levels of 25-OH Vitamin D reported as “below LLN” were imputed as 5 ng/mL for the purposes of this graphical exploration.

My integration of these data follows:

- Regarding fat-soluble vitamins, excursions beyond the established reference range toward regions of potential deficiency were, for the most part, transient.
- Trends for vitamin A and D suggested an increase, on average, especially during the first 26 weeks of the trial.
- Beta-carotene largely remained stable and within the normal range with only a few transient excursions below LLN.
- Total vitamin E trended downward as one would expect given the concomitant reduction in total lipids, but this stabilized at the end of the efficacy period. There were no concerning excursions below the reference range.
- The mean proportion of total osteocalcin that was uncarboxylated (% ucOC) increased modestly during the study. The cutoff for functional vitamin K deficiency using this assessment is not well established; one study of children and young adults with cystic fibrosis considered >50% ucOC an indicator of vitamin K deficiency and 20-50% an indicator of insufficiency.⁴⁷ The applicant reports a normal range of 13-33%. Values above 50% in HoFH-pivotal were few and isolated.
- In general, mean levels of fatty acids decreased during the first 26 weeks of the trial followed by relative stability. Patient profiles demonstrate substantial intra-

subject variation for several of these analytes (e.g., see alpha-linolenic acid), hindering the interpretation of shift tables. Instead, it can be said that there were only occasional and transient excursions below the reference range for most fatty acids measured (linoleic acid, EPA, DHA, AA, Mead acid). Alpha-linoleic acid was most commonly found to be below the reference range.

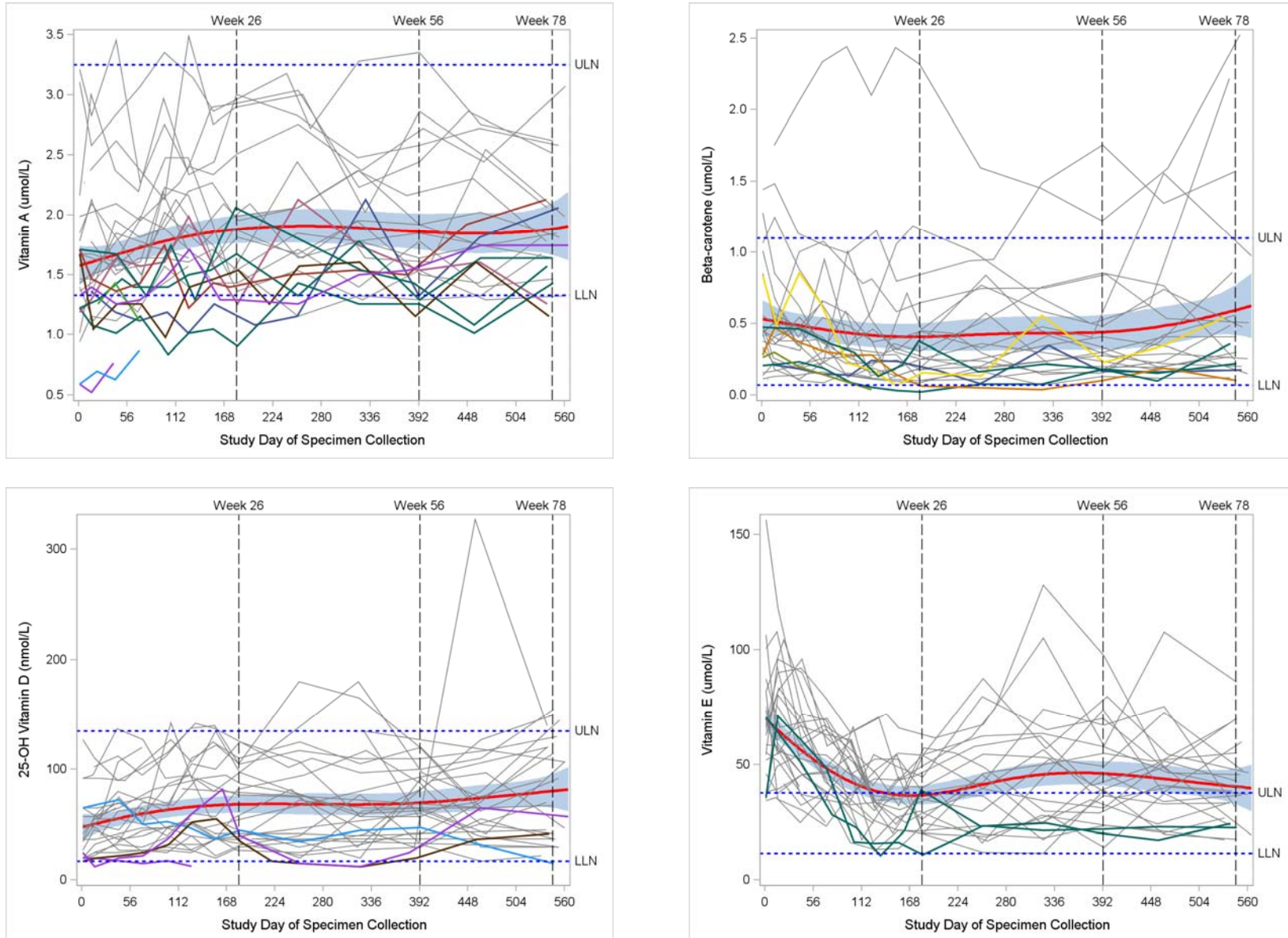


Figure 46. HoFH-pivotal – Fat-Soluble Nutrient Trends

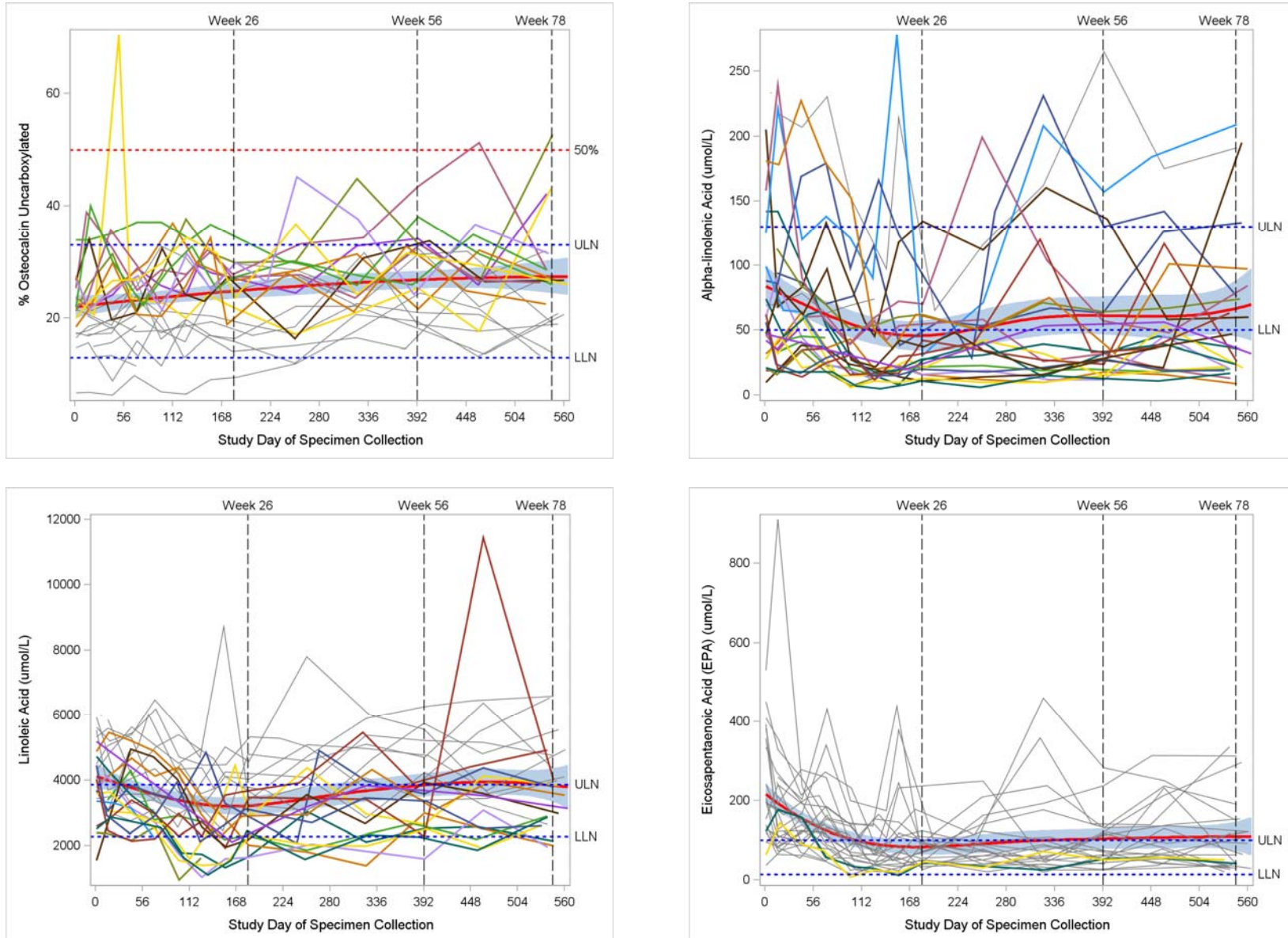


Figure 46. HoFH-pivotal – Fat-Soluble Nutrient Trends

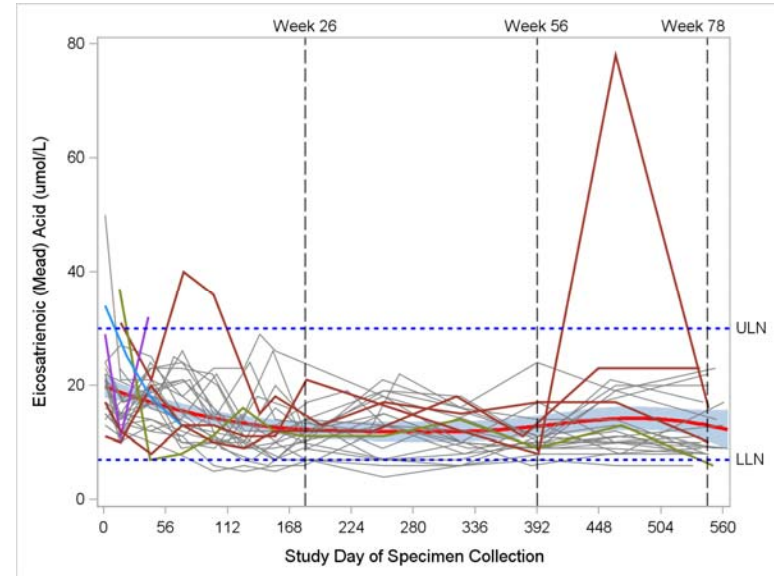
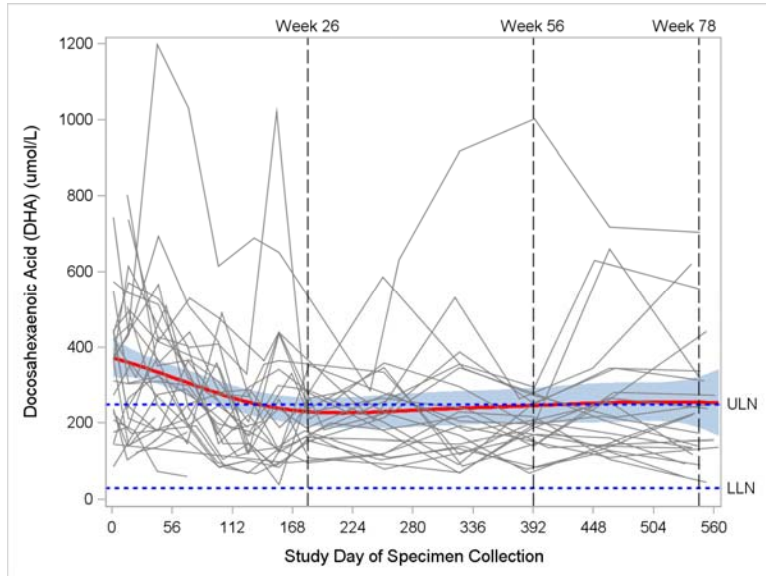


Figure 46. HoFH-pivotal – Fat-Soluble Nutrient Trends

Source: FDA clinical reviewer's analysis of submitted HoFH-pivotal dataset (LB.xpt).

Thin colored lines represent subjects who ever exceeded a threshold of potential concern (i.e., LLN for all but uncarboxylated osteocalcin and Mead acid). Thick red line is a fitted spline for the mean, surrounded by a 95% confidence band.

Subjects taking warfarin were excluded from the figure for uncarboxylated osteocalcin.

In an exploratory analysis, I examined changes in the Holman index, which is an index of essential fatty acid deficiency. This index is the “triene to tetraene ratio,” or the ratio of Mead acid (20:3[n-9]) to arachidonic acid (20:4[n-6]). Most arachidonic acid derives from linoleic acid; therefore, in the case of linoleic acid deficiency, arachidonic acid becomes an essential fatty acid and the denominator of this index decreases. In addition, in severe fatty acid deficiency, humans endogenously convert oleic acid into Mead acid, increasing the numerator. Thus, higher levels of the Holman index suggest essential fatty acid deficiency; many consider values <0.02 to be normal.^{48, 49} The values from HoFH-pivotal are depicted in Figure 47.

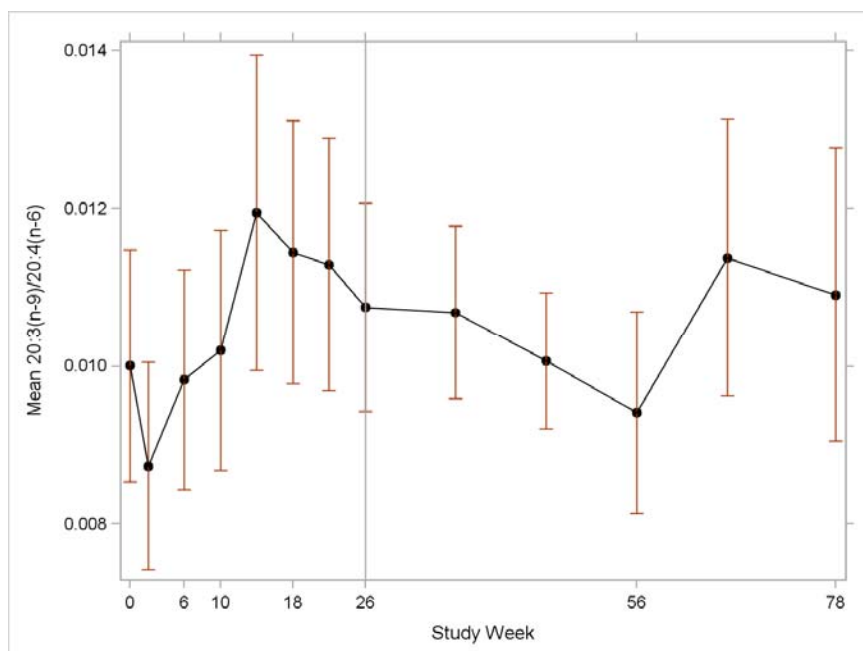


Figure 47. HoFH-pivotal – Holman Index Over Time

Source: FDA clinical reviewer’s analysis of submitted HoFH-pivotal laboratory data (LB.xpt).

Error bars represent 95% CI of the mean. Values >0.02 are often cited to indicate essential fatty acid deficiency.

At baseline, 1 of 23 subjects with available data had a Holman index ≥ 0.02 . At weeks 26 and 56, no subjects exceeded this threshold (n=19 and 22, respectively). At week 78, 1 of 23 subjects had a Holman index ≥ 0.02 ; this subject had a sufficient level of linoleic acid (2975 $\mu\text{mol/L}$), which was nearly double his baseline value.

HoFH-pilot Supporting Data for Fat-soluble Vitamins and Fatty Acid Levels

In HoFH-pilot, subjects were provided a *standard multivitamin*, which supplied 100% of the daily required intake for all essential vitamins and minerals (including fat-soluble vitamins). In contrast to HoFH-pivotal, these supplements did not contain EPA or DHA, and they did contain vitamin D.

Vitamin A levels were in the normal range at baseline and throughout treatment for 5 of 6 subjects; one subject had low levels at baseline with improvement to normal by the end of treatment.

Vitamin E levels were in the normal range or elevated at baseline for all patients. The mean vitamin E level was significantly lower (-56%) at the last on-treatment assessment, but the levels remained within the normal range for 5 of 6 subjects and remained elevated in one subject.

Levels of 25-hydroxy vitamin D were below normal at baseline for all 6 subjects and remained below normal throughout treatment. The mean absolute and relative decreases from baseline at the end of treatment were -2.6 ng/mL and -4%, respectively.

Mean decreases from baseline to the end of the treatment period were observed across all fatty acid parameters with statistically significant reductions at doses of 0.3 mg/kg and 1.0 mg/kg. The individual subject profiles are presented in the figures on the following pages.

Reviewer Comment: The increases observed in fatty acid levels after cessation of treatment supports a causal relationship between lomitapide treatment and the observed decreases. The clinical sequelae of these decreases are not known and might vary depending on the population (e.g., when lomitapide is studied in children). Although the sponsor notes that "Importantly, none of the patients exhibited signs of essential fatty acid deficiency based on clinical assessments," this 16-week, six-subject pilot study is inadequate to be confident in such assessments, especially since exposure to the highest 2 doses – where the most substantial decreases were observed – was ≤8 weeks.

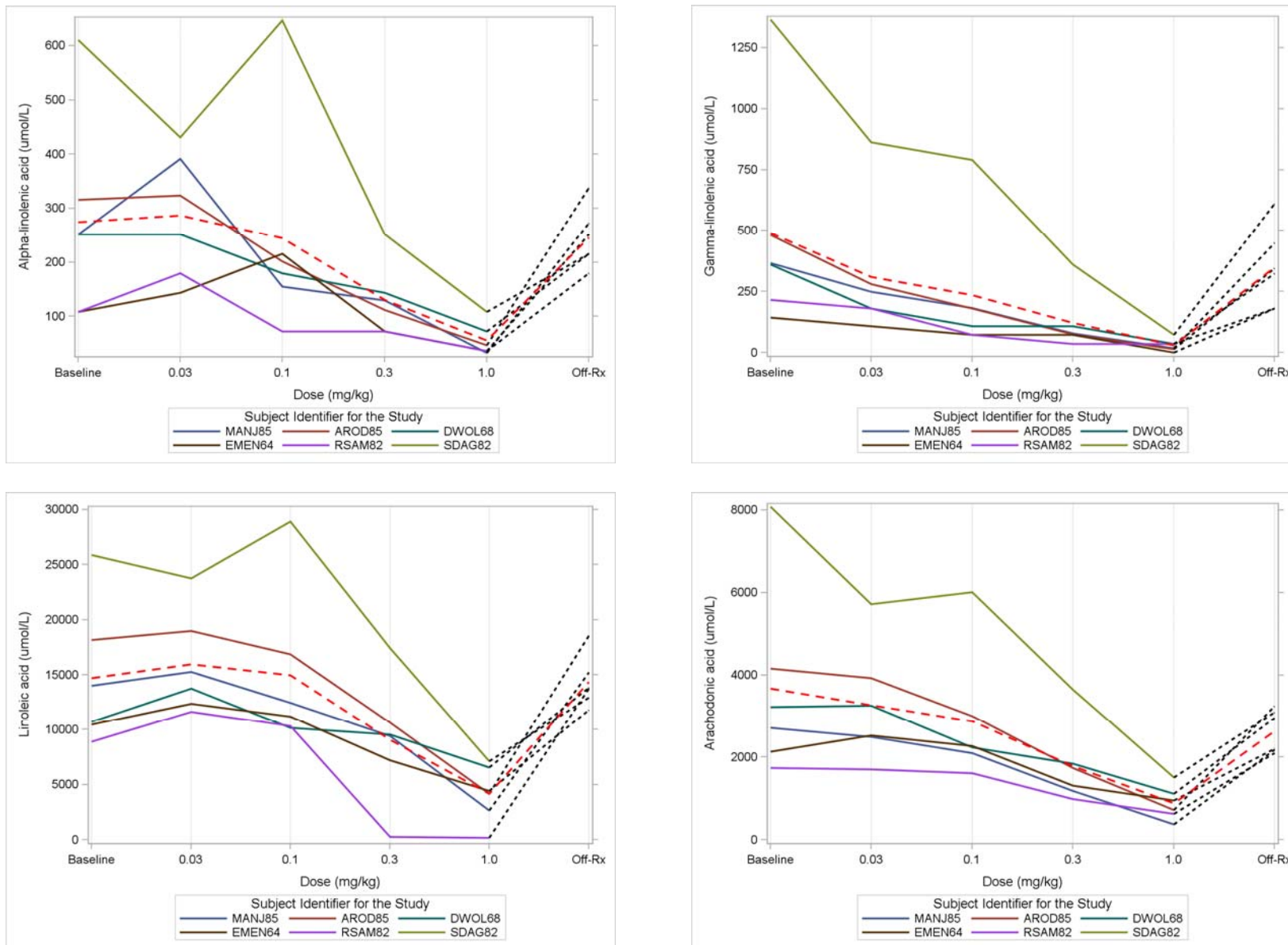


Figure 48. HoFH-pilot – Fatty Acid Trends

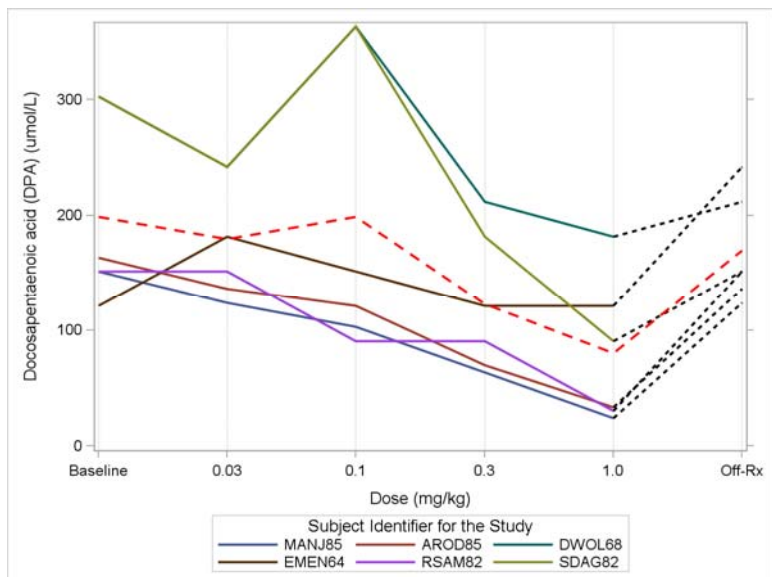
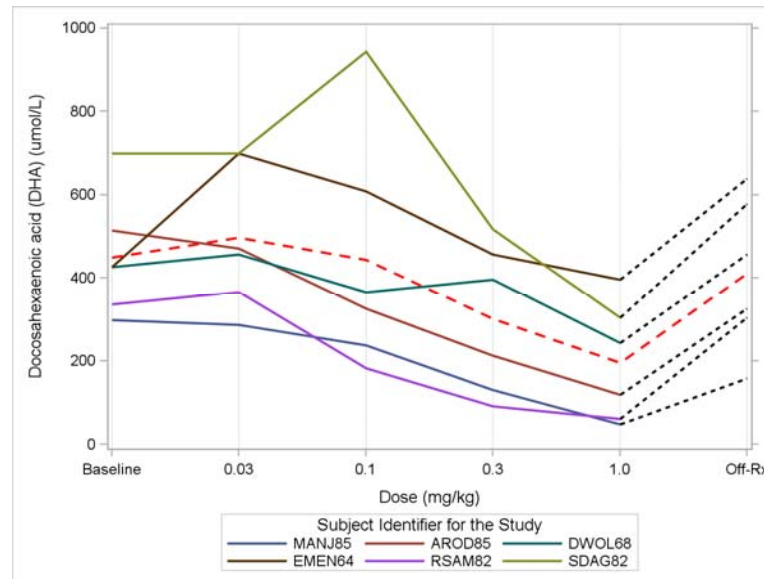
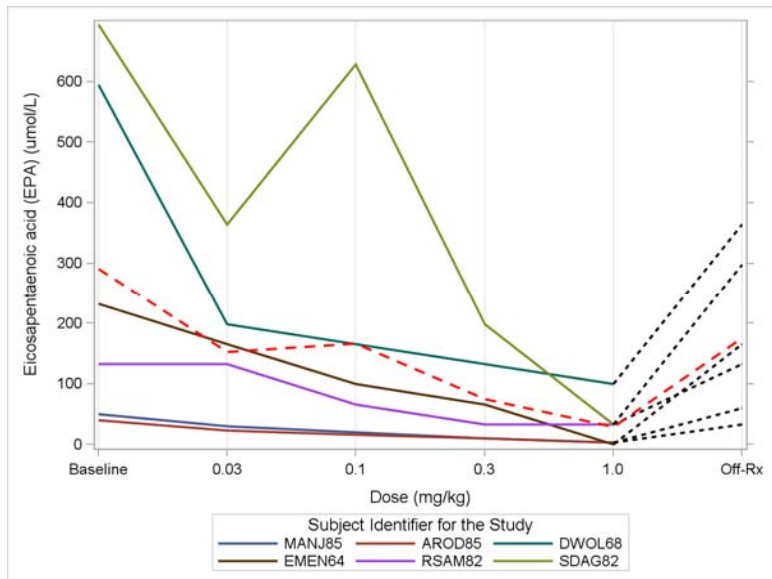


Figure 48. HoFH-pilot – Fatty Acid Trends (cont.)

Source: FDA clinical reviewer's analysis of submitted HoFH-pilot laboratory dataset (LB.xpt)

Changes in Body Weight

Figure 49 shows the longitudinal trend of mean and median body weight over time in HoFH-pivotal. Overall, the mean (SD) weight at baseline was 73.5 (18.1) kg. At week 26, with LOCF imputation, the mean weight had decreased 3.1 (2.5) kg from baseline, a mean -4.3% (3.3) change (P<0.0001). For the 23 subjects who completed the efficacy period, the mean weight decreased 3.4 (2.6) kg from their baseline, a mean -4.7% (3.6) change (P<0.0001). Between weeks 26 and 78, these 23 subjects gained 1.1 kg, on average, ending the trial 2.3 (3.5) kg below baseline, a mean -3.1% (4.5) change (P=0.004 by paired t test).

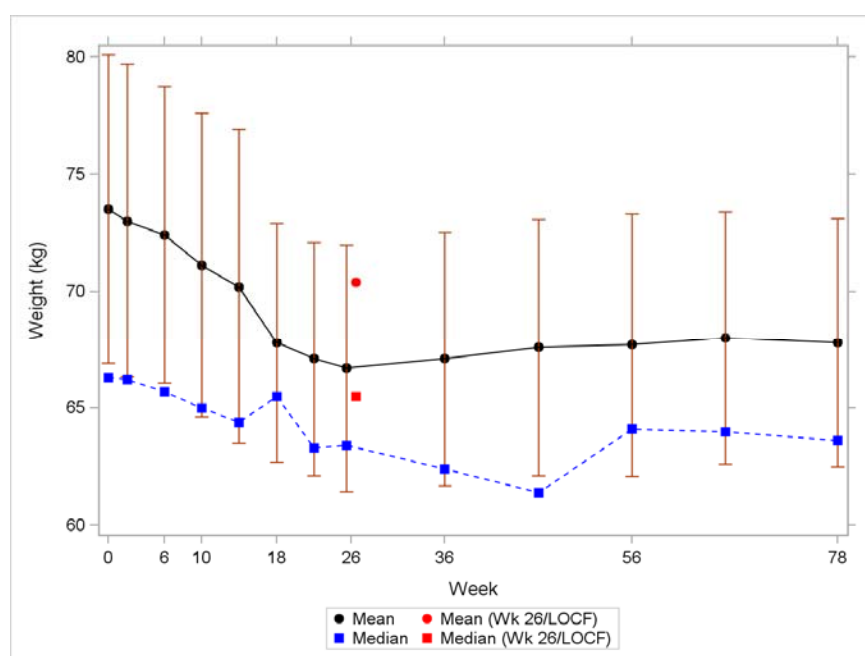


Figure 49. HoFH-pivotal – Body Weight Trend

Source: Derived from HoFH-pivotal CSR, Tables 14.3.4.1.17.5 and 14.3.4.2.17.5.1.

Week 66 and 78 values calculated from dataset submitted with 120-day safety update.

Error bars represent 95% CI of the mean.

No subject had a BMI value <18.5 kg/m² at any time during HoFH-pivotal.

The applicant reports that the changes in body weight are consistent with the collected dietary intake data, which suggest that energy intake declined during the efficacy phase (mean intake 1668 kcal at baseline, 1576 kcal at week 10, and 1434 kcal at week 26) and then improved at week 36 (1535 kcal).

Table 100 summarizes categorical weight changes from baseline to weeks 26 and week 78 in HoFH-pivotal. Although there were a few subjects who lost ≥10% during the study, these data suggest that weight loss does not appear to be progressive over time, or at least it is manageable with dietary intervention.

Table 100. HoFH-pivotal Subject-Level Weight Changes

Weight Change from Baseline	Week 26 (n=23)	Week 78 (n=23)
Absolute Change		
No change or any gain	2 (9%)	6 (26%)
<2 kg loss	5 (22%)	8 (35%)
≥2 kg but <5 kg loss	12 (52%)	4 (17%)
≥5 kg loss	4 (17%)	5 (22%)
Relative Change		
No change or any gain	2 (9%)	6 (26%)
<2% loss	4 (17%)	3 (13%)
≥2% but <5% loss	7 (30%)	9 (39%)
≥5% but <10% loss	8 (35%)	2 (9%)
≥10% loss*	2 (9%)	3 (13%)

Source: FDA clinical reviewer’s analysis of HoFH-pivotal vital signs dataset (VS xpt).
Baseline = week 0, *not* screening visit.

Subject 02-001 had weight changes of -12.9% and -15.2% at weeks 26 and 78, respectively; the other subject who lost ≥10% at week 26 (31-001) ended the trial at week 78 with a weight 1.7% above baseline. In contrast, the remaining two subjects with weight loss ≥10% at week 78 (01-003 and 22-004) had weight losses of 5.5% and 3.9% at week 26.

Figure 50 shows the relationship between baseline weight and absolute change in weight at week 26/LOCF. Although this exploratory analysis suggests a statistically significant association between baseline weight and change in weight, this association is influenced by the two subjects with baseline weight >105 kg.

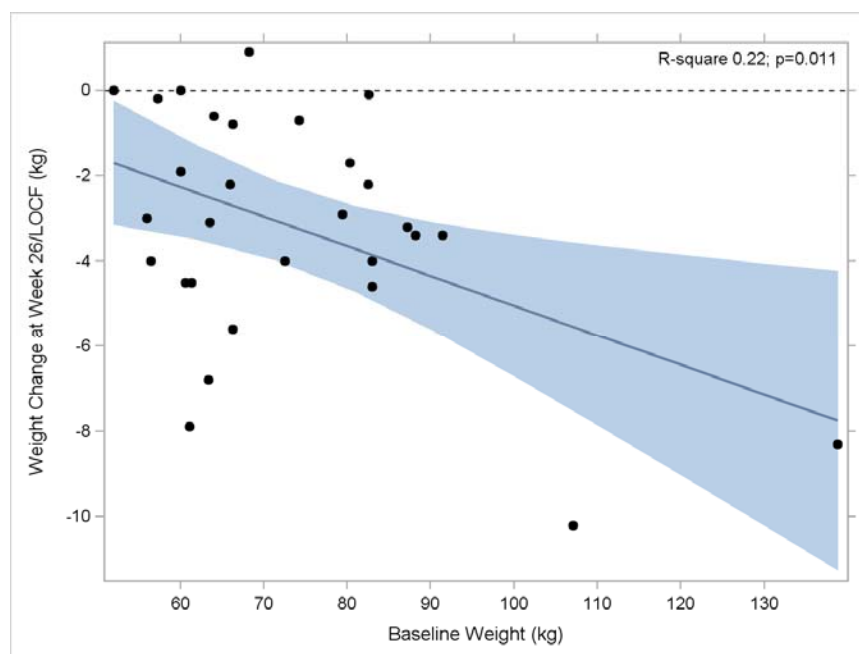


Figure 50. HoFH-pivotal – Baseline Weight vs. Weight Change at Week 26/LOCF

Source: FDA clinical reviewer’s analysis of HoFH-pivotal VS.xpt dataset.

Regression line with shaded 95% confidence limits for the predicted mean values.

In another exploratory analysis, the change in weight from baseline to week 26 was compared with the subsequent change in weight from week 26 to week 78 for the 23 subjects who completed the trial (Figure 51). Data points above the dashed horizontal reference line represent subjects that *gained* weight during the safety phase, and those below the reference line represent subjects that *continued losing* weight during the safety phase. Overall, 8 (35%) of the 23 subjects with data at all three time points progressively lost some degree of weight through week 78, although one can see that the magnitude of weight loss was modest for most subjects.

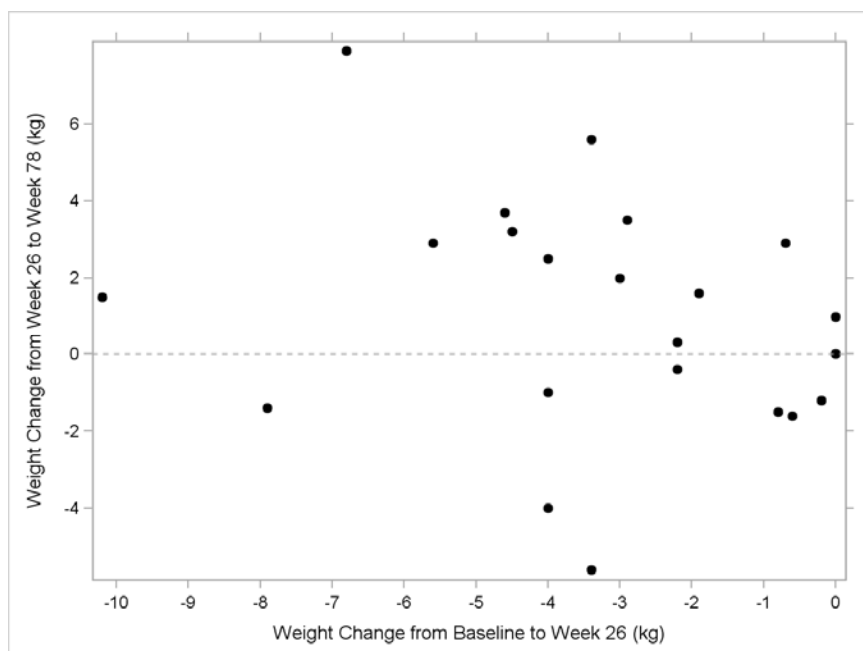


Figure 51. HoFH-pivotal – Weight Changes During Efficacy & Safety Phases

Source: FDA clinical reviewer’s analysis of HoFH-pivotal VS.xpt dataset.

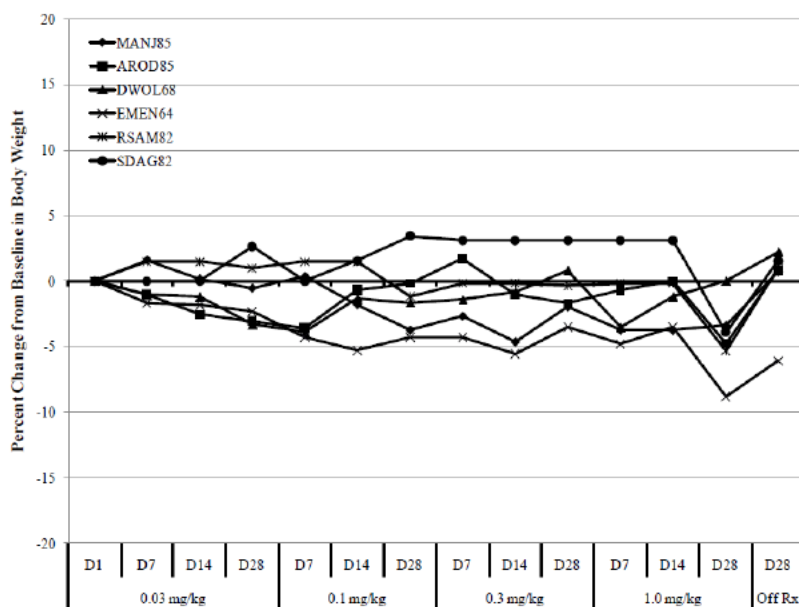
Data points above the dashed horizontal reference line represent subjects that *gained* weight during the safety phase, and those below the reference line represent subjects that *continued losing* weight during the safety phase.

Seven (24%) of the 29 subjects in HoFH-pivotal had an AE recorded as “weight decreased” (6 prior to week 56). Although the AE dataset does not reflect it, the DSMB minutes (25 May 2010) suggest that concerns regarding weight loss, in addition to headaches, led subject 01-006 to withdraw consent from the study; he lost a maximum of 5.5 kg (8.1%) from baseline before stopping study drug. No subject in HoFH-extension has had a similar AE recorded.

Reviewer Comment: Taken together, despite the limitation of HoFH-pivotal being a small, uncontrolled trial, which precludes accounting for regression to the mean, the observed weight loss would be with the drug’s mechanism of action and adverse effect profile. The changes in weight are relatively modest, do not appear to be progressive, and would be a monitorable and reversible adverse effect.

HoFH-pilot Supportive Weight Data

In HoFH-pilot, weight decreased a mean -2.9 kg (-4.4%) from baseline to the end of treatment. At the off-treatment follow-up visit approximately four weeks later, weight increased a mean 2.8 kg, yielding a mean absolute and relative change from baseline of -0.1 kg and 0.0%, respectively, at the end of the study. Figure 52 shows the weight change over time for each subject, relative to baseline. The most rapid declines in weight were observed during the last 2 weeks of dosing with 1.0 mg/kg (4 of 6 subjects lost weight during this period). At the end of treatment, one subject had no change from baseline (DWOL68), four subjects lost 3-5%, and one subject lost 9% (EMEN64); the latter subject had a baseline BMI of 30.2 kg/m² (weight 77.3 kg), which fell to 27.5 kg/m² (70.5 kg) at the end of treatment.



Note: Each patient's dose was escalated approximately every 28 days from 0.03 to 0.1 to 0.3 and to 1.0 mg/kg.

Source: [Appendix 3d](#)

Figure 52. HoFH-pilot – Weight Changes Over Time

Source: HoFH-pilot CSR, Figure 6.

Pulmonary Function

Given a nonclinical signal of possible pulmonary toxicity during the lomitapide development program (see Dr. Hummer's Pharmacology/Toxicology review), spirometry with carbon monoxide diffusing capacity (DLCO) was performed in HoFH-pivotal at baseline and weeks 26, 56, 78. Spirometry and DLCO measurement methodology was not standardized across sites, which limits the interpretability of these data when analyzed in aggregate. DLCO, for example, depends on several factors that can vary with time (hemoglobin, carboxyhemoglobin, altitude, exercise, body position, lung volume) and others that are fixed (age, sex, height, possibly race). Nevertheless, examining subject-level changes from baseline as well as the measures of central

tendency, there does not appear to be a clear pulmonary signal. The sensitivity of these measurements to detect pulmonary phospholipidosis, however, is likely quite low.

Table 101 provides summary statistics, only including subjects who had a parameter assessed at baseline and at least one follow-up.

Table 101. HoFH-pivotal – Pulmonary Function Descriptive Statistics

	N	Mean (SD)	Median [IQR]	Mean (SD) Absolute Change from Baseline
FEV₁ (L)				
Week 26	18	3.22 (0.64)	3.17 [2.80, 3.90]	-0.16 (0.50)
Week 56	18	3.20 (0.71)	3.22 [2.70, 3.72]	-0.18 (0.36)
Week 78	17	3.17 (0.76)	3.11 [2.47, 3.95]	-0.23 (0.41)
FVC (L)				
Week 26	18	3.93 (0.83)	4.01 [3.38, 4.58]	+0.01 (0.19)
Week 56	18	3.83 (0.84)	3.98 [3.26, 4.36]	-0.09 (0.27)
Week 78	17	3.81 (0.88)	3.82 [3.01, 4.69]	-0.11 (0.25)
FEV₁/FVC				
Week 26	18	0.83 (0.08)	0.81 [0.77, 0.88]	-0.04 (0.13)
Week 56	18	0.84 (0.07)	0.84 [0.77, 0.88]	-0.03 (0.11)
Week 78	17	0.83 (0.07)	0.84 [0.77, 0.89]	-0.03 (0.11)
FEF_{25-75%} (L/sec)				
Week 26	18	3.41 (1.01)	3.26 [2.74, 3.85]	-0.95 (2.22)
Week 56	18	3.59 (1.24)	3.27 [2.54, 4.84]	-0.77 (2.03)
Week 78	17	3.84 (1.47)	3.47 [2.63, 4.79]	-0.65 (2.46)
DLCO (mL CO/min/mmHg)				
Week 26	18	23.6 (6.5)	23.5 [18.2, 28.9]	-2.4 (4.8)
Week 56	19	24.3 (6.5)	22.8 [19.1, 30.1]	-1.1 (5.5)
Week 78	18	26.8 (8.6)	24.9 [18.6, 32.3]	+0.9 (6.2)

Source: 120-day safety update, Table 1.3.24.

Because one might speculate that pulmonary phospholipidosis would affect diffusing capacity more than promote airway obstruction, I plotted the within-subject trends of available DLCO values obtained from pulmonary function tests at baseline and weeks 26, 56, and 78 (Figure 53).

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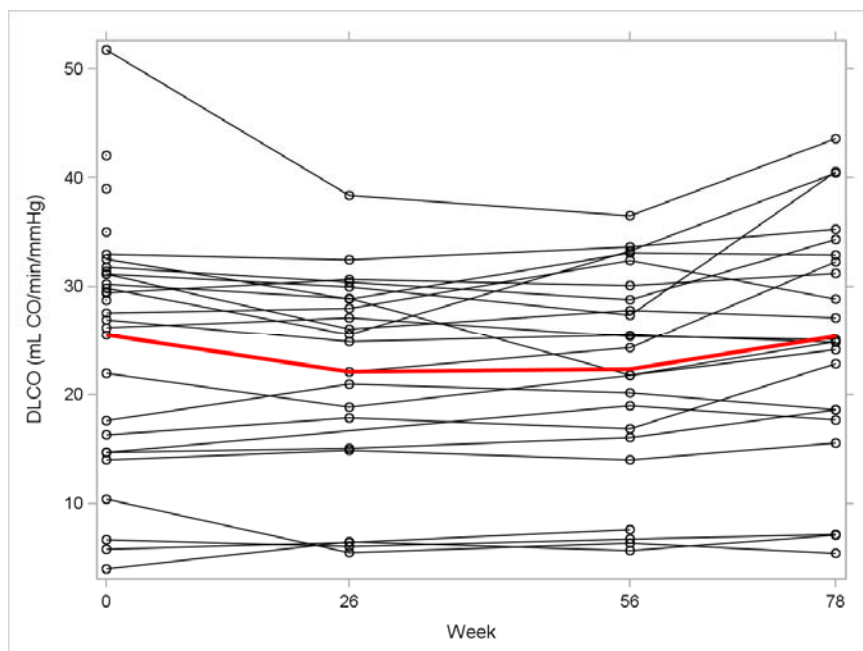


Figure 53. HoFH-pivotal – DLCO Trend

Source: FDA clinical reviewer's analysis of HoFH-pivotal *RE xpt* dataset.
Thick red line connects the mean values at each time point (no imputation).

The applicant did not use regression equations to describe PFT results as either % predicted or above/below the 5th percentile of an appropriate reference range; therefore, shift tables of individual changes are not presented.

In HoFH-pivotal, one subject had an AE of expiratory wheezing (days 33-36) associated with concomitant AEs of cough and nasal congestion. Another subject reported cough (days 11-18), although the same subject reported cough during the screening period as well. In HoFH-extension, one subject had “episodes of apnea” recorded as an AE for extension days 80-83; one subject had “dyspnea at effort 1/4” recorded as an ongoing AE starting on extension day 145; and one subject had shortness of breath and “pain with deep breath” each recorded as AEs of one-day duration on extension days 235 and 241, respectively.

HoFH-pilot Supportive PFT Data

The applicant states that there were no clinically meaningful changes over time on treatment for FEV₁, FVC, FEF₂₅₋₇₅, or DLCO. Summary statistics were not provided by the applicant. I reviewed the submitted data for each subject (baseline, visits following the 4 treatment intervals, and off-treatment follow-up) for these parameters and concur. My calculations of the mean (SD) absolute differences from baseline to end-of-treatment for these parameters follow: FVC, -0.01 (0.21) L; FEV₁, 0.01 (0.23) L; FEF₂₅₋₇₅, 0.14 (0.38) L/sec; and DLCO -3.1 (5.4) mL/min/mmHg. DLCO was only available for 4 subjects at baseline and end-of-treatment; the individual values for absolute change from baseline were -10.42, -3.8, +0.93, and +0.97. The subject with the largest decrease had a baseline value that seemed to be an outlier (27.31, with a value of 20.9 four weeks later).

Bleeding / Coagulation-related Issues

Concomitant Administration with Warfarin

In HoFH-pilot, two patients who were receiving concomitant warfarin required warfarin dose adjustments based on INR levels (see below); therefore, INR was measured at each visit in HoFH-pivotal. Five of the 29 subjects were taking warfarin during HoFH-pivotal. Table 102 displays the longitudinal INR results and reported warfarin dosages for these 5 subjects according to the applicant, although in a 15 June 2012 response to an FDA information request, the applicant clarified that any INR values obtained outside of the study (e.g., a subject’s anticoagulation clinic) were *not* obtained.

Table 102. HoFH-pivotal – INR and Warfarin Dosages for Relevant Subjects

PT ID	PARAMETER	PRE	WK 0	WK 2	WK 6	WK 10	WK 14	WK 18	WK 22	WK 26	WK 36	WK 46	WK 56	
01-003	INR	NR	5.1	2.2	2.1	5.2	5.0	1.7	3.0	4.4	1.8	2.6	1.7	
	Warfarin (mg)	4	Details on warfarin dosing by visit not provided in CRF – reported as 2 or 4 mg through the end of treatment											
01-004 ⁵	INR	NR	2.5	2.7	2.6	2.9	1.0	2.7	1.8	4.5	1.8 ¹	5.2	2.3	
	Warfarin (mg)	7.5	5 mg							10 mg				
02-001	INR	NR	NR	1.9	6.1	3.4	3.3	3.7	2.7	2.3	2.7	2.9	2.3	
	Warfarin (mg)	9.5	9.5	Tapers 9.5 to 9.25 to 8.5 to 8				Alternates 8, 10 and 12 mg		Alternates 4, 8 and 12 mg				
13-001	INR	NR	2.6	1.2	2.0	1.8 ²	Discontinued due to gastroenteritis							
	Warfarin (mg)	0/2.5/5 /7.5	2.5	Alternates 0 and 2.5										
13-002	INR		NR	3.4	4.9 ³	3.0	6.6 ⁴	1.7	1.6	Withdrew consent				
	Warfarin (mg)	2.5/5	Alternates 2.5 and 5			Alternates 0 and 2.5								

Source: Listing 16.2.4.5.1, Listing 16.2.4.5.2, Listing 16.2.4.5.3, Listing 16.2.7.1.1, Listing 16.2.7.1.2 and Listing 16.2.8.6

- 1 Patient developed a mild hematoma on the arm at ~Week 34 assessed as unrelated to study treatment
- 2 Unscheduled assessment conducted 2 weeks after Week 6 visit
- 3 Adverse event of ‘INR fluctuation’ reported between Weeks 6 and 22
- 4 Patient developed mild ecchymosis assessed as possibly related to study treatment.
- 5 Patient had elevations >10 x ULN in ALT at Week 6 (see Section 12.4.4.3).

Source: HoFH-pivotal CSR, Table 32.

Subject 01-003 had four SAEs related to bleeding/anticoagulation management: menorrhagia leading to hypovolemic shock and ensuing complications; hospitalization for heparinization as a result of subtherapeutic INR; hospitalization for transfusion as a result of menorrhagia; and a hospitalization for stroke symptoms with acute subdural and intraventricular hemorrhages (see Section 7.3.2, p. 161). INR at the time of the first hospitalization is not available; INR values at the time of the admissions for transfusion and stroke symptoms were 3.5 and 5.7, respectively. “Small nosebleeds” were also reported from days 404-464 during the extension study.

Subject 01-004 reported a mild subconjunctival hematoma of the left eye on day 540. The flanking INR values were 2.8 (day 467) and 2.3 (day 561).

Subject 02-001 reported a mild “left upper arm hematoma” on day 237 and moderate “bleeding, right ear, probable scratch” on day 551. INR values were 2.7-2.8.

Subject 13-002 had an AE reported as “Unstable INR” spanning weeks 6 through 22. Furthermore, this subject developed mild ecchymosis at the time of elevated INR. The subject withdrew consent; the fluctuation in INR contributed to the withdrawal of consent

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(see Section 7.3.3, p. 167) as recorded on the case report form, which differs from CSR text (“The discontinuations were unrelated to warfarin or INR levels”).

Reviewer Comment: Given that only INR values measured at study-related visits were recorded, these trends may not fully describe the INR profiles for trial subjects. There could have been much more INR variability and more warfarin dosage adjustments performed than described by the trial’s data. For the three subjects who completed week 56, however, there is not an obvious pattern of reduced warfarin requirements with concomitant lomitapide.

Other Bleeding / Coagulation Analyses

Because of the potential for lomitapide to reduce vitamin K absorption, a search for bleeding-related adverse events among subjects not receiving warfarin was conducted. Four (17%) of 24 warfarin-naïve subjects had at least one bleeding event: Subject 11-003 reported moderated “bleeding hemorrhoids” on day 170 and again during the extension study. Subject 12-004 had an SAE related to worsening menorrhagia (Section 7.3.2, p. 161). Subject 12-005 reported a mild nosebleed on day 62. Subject 22-004 reported intermittent nosebleeds on days 78 and 79. PT/INR and platelets around the time of these events were normal for all of these subjects based on my review of the laboratory datasets.

Overall, the mean (SD) changes in PT from baseline to week 26/LOCF and week 56/LOCF were 0.0 (3.7) sec and -1.2 (3.0) sec, respectively. Mean (SD) changes in INR from baseline to the same time points were 0.1 (0.6) and -0.2 (0.7). I calculated the same descriptive statistics, limiting to subjects not taking warfarin and including data from week 78, and obtained similar results.

Cardiovascular Events

In a post hoc exploratory analysis using Standardized MedDRA Queries (SMQs), the applicant sought events in the HoFH-pivotal AE database using a broad CV search (combined SMQs for myocardial infarction, other ischemic heart disease, and ischemic cerebrovascular conditions) and a narrow CV search (combined SMQs for myocardial infarction and ischemic cardiovascular conditions), which identified 7 events in 6 subjects (Table 103).

Table 103. HoFH-pivotal – Broad & Narrow Cardiovascular SMQs

Subject	Preferred Term	Broad SMQ	Narrow SMQ	SAE
02-002	Blood creatine phosphokinase increased	X	X	No
11-001	Acute coronary syndrome	X	X	Yes
	Angina pectoris	X		Yes
11-003	Angina pectoris	X		No
13-002	Angina pectoris	X		No
22-003	Arteriosclerosis coronary artery	X		Yes

Subject	Preferred Term	Broad SMQ	Narrow SMQ	SAE
22-004	Transient ischemic attack	X	X	No

Source: 17 August 2012 Response to FDA information request. See text for details.

In the applicant's "elevated LDL-C" phase 1/2 pool, the same queries identified 4 events in 3 subjects (Table 104).

Table 104. Elevated LDL-C Phase 1/2 Pool – Broad & Narrow Cardiovascular SMQs

Study	Subject	Treatment Arm	Preferred Term	Broad SMQ	Narrow SMQ	SAE
A-001	1049	Lomitapide + Placebo	Myocardial infarction	X	X	Yes
A-003B	12166	Lomitapide 10 mg	Myocardial infarction	X	X	Yes
A-003B	19116	Lomitapide 5 mg	Myocardial infarction	X	X	Yes
			Coronary artery disease	X		No

Source: 17 August 2012 Response to FDA information request. See text for details.

Therefore, 3 (1.2%) of 255 subjects treated with lomitapide monotherapy had at least one cardiovascular event recorded compared with none of the 191 subjects treated with lomitapide combination therapy (e.g., lomitapide + lipid-lowering therapy), none of the 98 treated with placebo, and none of the 78 subjects treated with an active control.

Given the paucity of events in the lomitapide development program, none of which were adjudicated, it is premature to make conclusions regarding the effect of lomitapide on cardiovascular events.

Myopathy

The definitions and reporting of rhabdomyolysis and myopathy as adverse events were not pre-specified in the lomitapide development program. The applicant analyzed the HoFH AE databases using the SMQ for "Rhabdomyolysis/Myopathy" and suggested that 6 HoFH subjects (5 unique individuals given one subject who was in both the pilot and pivotal trials) may have had such an event during the pilot, pivotal, or extension studies. The associated preferred terms included myalgia (n=2 subjects); musculoskeletal pain (n=2); myalgia and blood creatine phosphokinase increased (n=1); and musculoskeletal pain and acute renal failure (n=1). In all cases, the investigators felt these events were unlikely related to lomitapide, and lomitapide dose was not adjusted in response to any of these events.

Given the design of the pilot study, the single event of myalgia in the pilot study occurred in the absence of concomitant statin; the same subject (01-003) reported musculoskeletal pain while taking rosuvastatin 40 mg daily after 678 days in the extension study (i.e., 3.3 years after first dose in the pivotal trial). One additional subject (01-001) in the pivotal trial reported myalgia in the absence of concomitant statin; this subject stopped atorvastatin 55 days prior to first dose of lomitapide and reported mild myalgias of one-day duration on day 420 of the pivotal trial. The remaining 3 subjects

were taking concomitant statins at the time of the reported AEs (daily doses of atorvastatin 40mg, atorvastatin 80mg, and rosuvastatin 40 mg); the statin doses were not changed.

My review of the AE and laboratory databases shows that the subject with myalgia and “CK increased” recorded as AEs in HoFH-pivotal (subject 02-002) reported “muscle soreness” spanning study days 237 to 239. The concomitant CK was 450 IU/L, which was modestly elevated from the subject’s typical values ~200 IU/L from baseline through this time point. The “CK increased” event, however, was reported on day 309 with a CK 413 IU/L, falling to 305 IU/L on day 323.

The subject with musculoskeletal pain and acute renal failure (22-003) reported AEs of right and left shoulder pain (coded “musculoskeletal pain”) and right wrist pain (coded “arthralgia”) all beginning on the day of first lomitapide dose. This subject received lomitapide for 2 weeks before it was interrupted for a hospitalization for CABG complicated by acute renal failure. It is unlikely that these events are drug-related.

My review of the laboratory dataset shows three subjects in HoFH-pivotal or its extension that had CK elevations $\geq 5x$ ULN, the highest of which was an isolated value of 35x ULN in the extension study that does not appear to have been associated with other signs or symptoms.

Subject 23-001 was a 22-y/o Hispanic man (Canada) taking rosuvastatin 40 mg daily and ezetimibe who had normal CK until his week 10 visit when his CK was 1035 U/L (5.0x ULN). His CK fell with continued lomitapide therapy, which escalated according to protocol to 60 mg daily. At week 46 his CK was 172 U/L, but at week 56 his CK was 1816 U/L (8.8x ULN). This fell to 369 U/L at week 66 and increased again to 1007 U/L at week 78 before entering the extension study. During the extension study, his CK has been $< 5x$ ULN for 60 weeks. His rosuvastatin dose was not changed during the trial. Furthermore, the dose of lomitapide was never reduced in response to these CK values, and the observed increases in CK did not correlate with increases in lomitapide dose.

Subject 32-001 was a 45-y/o white man (Italy) taking rosuvastatin 30 mg daily who had normal CK through week 66. At an unscheduled visit at approximately week 71, his CK was 1366 IU/L (6.6x ULN); the reason for this visit is not clear. There were no AEs reported and it does not appear that his statin dose was changed. His dose of lomitapide had been 5 mg daily for the preceding 1.2 years; it was not changed as a result of this CK abnormality. At week 78, his CK was 120 IU/L. He did not enter the extension study.

Subject 12-004 was a 32 y/o white woman (S. Africa) taking rosuvastatin 40 mg daily who had normal CK through HoFH-pivotal and through week 96 of the extension study, at which time her CK was found to be 5930 IU/L (35x ULN). There were no concomitant AEs associated with this elevation. According to a 21 September 2012 response to an FDA information request, the applicant reports that

this subject had labs drawn again 5 days later and was found to have a CK 267 IU/L. The subject informed the site that she had started doing intense aerobic exercise 2 weeks prior to having the elevated CK level. Her rosuvastatin and lomitapide dosages were not changed.

“Elevated LDL-C” Phase 1/2 Pool

The applicant performed a similar query using the elevated LDL-C phase 1/2 pool previously described. A total of 17 subjects with at least one event categorized in the rhabdomyolysis/myopathy SMQ were identified: 2 (2.6%) of 77 subjects in the escalated 5-10 mg group, 12 (4.9%) of 244 subjects who received fixed-dose low-dose lomitapide (2.5 to 7.5 mg), no subjects in either the mid-dose (10 mg; n=99) or high-dose (25-100 mg; n=62) groups, 1 (0.9%) of 116 placebo subjects, and 2 (2.6%) of 78 active-control subjects. One subject in the low-dose group and two subjects in the active-control group discontinued for an AE in this category. There were no AEs of rhabdomyolysis. The incidence of these events was the same among subjects who received lomitapide monotherapy (6 of 167; 4%) compared with those who received lomitapide + statin (5 of 142; 4%); the incidence among subjects who received placebo was lower (1 of 78; 1%).

Neoplasms

Genetic toxicology studies suggest that lomitapide is not a direct-acting mutagen. Two 2-year carcinogenicity studies were conducted in mice and rats; the results are described in Dr. Hummer’s Pharmacology/Toxicology review. Briefly, there was a statistically significant increase in the incidence of hepatocellular neoplasms in male mice given ≥ 1.5 mg/kg/day ($\geq 2x$ MRHD) and females given ≥ 7.5 mg/kg/day ($\geq 9x$ MRHD). In addition, statistically significant increases in small intestinal adenomas/carcinomas (combined) were noted in both sexes at ≥ 15 mg/kg/day (24x MRHD), with the jejunum being the most common site. The no-observed effect levels (NOEL) for drug-related neoplasms in male and female mice confer clinical safety margins of 0.4x and 2x, respectively. In the rat, there was no suggestion of drug-related neoplasms at any dose tested; therefore, the NOEL was considered the highest dose tested (7.5 mg/kg/day for males and 2 mg/kg/day for females), representing clinical safety margins of 6x MRHD for males and 8x MRHD for females.

Based on its mechanism of action at the enterocyte, lomitapide would be expected to increase fecal fat and alter the composition of fecal bile acids. Given the widely cited hypotheses that dietary fats may stimulate damage and proliferation of colonic mucosal epithelial cells by increasing exposure to cytotoxic fecal bile acids or fecal diacylglycerols,^{50, 51} it is plausible that lomitapide could alter intestinal biology in a manner that promotes neoplastic growth. The lomitapide development program has not assessed these potential effects in humans.

There have been no reports of cancer in the lomitapide development program. The only AE in the Neoplasms SOC was a single case of “xanthoma.”

Reviewer Comment: The absence of neoplasms in the lomitapide development program is not surprising given the extremely limited size and duration of the clinical trials. Exposure of many more subjects for a much longer duration would be required to provide any reassurance that the preclinical observations may not translate to humans.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

This section includes AE tabulations from the HoFH phase 3 program. Although the applicant pools phase 1/2 data into an “elevated LDL-C” non-HoFH safety pool, these trials differ substantially from the phase 3 program in ways that would be expected to modify the incidence of AEs (e.g., fixed-dose vs. dose-escalation regimens and substantially lower doses of lomitapide for the majority). Therefore, although the events in this pool were reviewed, they are not summarized further other than to note that they are generally consistent with those observed in phase 3. Common AEs observed in the longest-duration placebo-controlled phase 2 trial (AEGR-733-004) were presented in Table 48.

Table 105 summarizes the incidence of AEs recorded in HoFH-pivotal and its extension phase, derived from my analysis of the submitted adverse event datasets (*AE.xpt* for each trial). Each subject contributes a maximum of one event *per column*. The recorded start date of each adverse event was used to categorize when the event occurred during the pivotal trial (i.e., efficacy phase or safety phase; pivotal trial or extension), even if the end date indicated that the event had a duration that spanned more than one phase; therefore, each subject could contribute counts to multiple columns for a given AE if distinct events were recorded with start dates occurring in more than one phase. Any events with a start date prior to the first dose of drug were excluded. Any HoFH-pivotal events that had a missing start date were considered treatment-emergent and were counted as occurring during the efficacy phase. Last, I took an ITT approach to the analysis, including all post-baseline events; in contrast, the applicant excluded events reported >30 days after the last dose of lomitapide. According to the applicant, only 7 events were reported >30 days after last dose (lower back pain, neck pain, and muscle spasms for subject 01-006; fever, flu, and acid reflux for subject 02-001; and urine ketones for subject 02-002).

Recall that these are descriptive data only since these are single-arm uncontrolled trials.

Organized by MedDRA SOC, the table shows all preferred terms recorded for at least two (i.e., $\geq 5\%$) subjects any time during HoFH-pivotal and/or the extension study. SOCs are listed in descending order of frequency, and preferred terms are listed in descending order of frequency within each SOC.

GI adverse events were near universal, with only two subjects not reporting any gastrointestinal symptoms. Of these two subjects, one received study drug for only four days before withdrawing consent, apparently because he was concerned about the

potential for GI adverse effects according to the narrative. The other subject (32-002), an 18-y/o female who had received study drug for ~15 months at the time of data cutoff, had not reported a single AE during the trial as of April 2011. This subject also answered “No discomfort at all” to every item of the 15-item GSRS questionnaire (i.e., the lowest level of the 7-level Likert-type scale) for all 11 questionnaires that she had completed before data cutoff. This seems to be highly suspicious for an underreporting subject given the AE profile of lomitapide.

Among the 27 subjects who reported gastrointestinal events in HoFH-pivotal, the applicant reports that the median time to first GI event *after initiating a given dose* was 9.1 days, ranging from 1 to 39 days. According to my analysis, the median time to first GI event from 1st dose of lomitapide (study day 1) was 23 days, ranging from 1 to 141 days. Eight (30%) of the 27 subjects who reported at least one GI event experienced their first event within the first week of dosing.

The incidence of reported AEs was lower, in general, during the safety phase of the study. This could represent the development of tolerance to the drug, but it could also result from subjects no longer reporting common symptoms that they had reported previously. Because AEs were not pre-specified on the case report form and queried each visit (with the exception of the GSRS), a decrease in reporting may not necessarily represent a true improvement in symptoms. The fact that 6 of 29 subjects dropped out before week 26 but none of the remaining subjects dropped out through week 56, however, suggests that the AEs may have truly occurred less frequently (or were more tolerable) with continued dosing.

Table 105. HoFH-pivotal & -extension – Common Treatment-emergent AEs (≥5% incidence)

MedDRA SOC Preferred Term	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)	
Gastrointestinal Disorders	27 (93%)	27 (93%)	17 (74%)	27 (93%)	11 (61%)
Diarrhea	23 (79%)	23 (79%)	8 (35%)	23 (79%)	6 (33%)
Nausea	20 (69%)	18 (62%)	7 (30%)	19 (66%)	4 (22%)
Dyspepsia	12 (41%)	7 (24%)	4 (17%)	11 (38%)	2 (11%)
Vomiting	11 (38%)	8 (28%)	5 (22%)	10 (34%)	3 (17%)
Abdominal pain	8 (28%)	8 (28%)	1 (4%)	8 (28%)	0
Flatulence	7 (24%)	6 (21%)	2 (9%)	6 (21%)	1 (6%)
Abdominal discomfort	6 (21%)	6 (21%)	0	6 (21%)	0
Abdominal distension	6 (21%)	6 (21%)	2 (9%)	6 (21%)	1 (6%)
Constipation	6 (21%)	6 (21%)	3 (13%)	6 (21%)	0
Abdominal pain upper	5 (17%)	5 (17%)	2 (9%)	5 (17%)	0
Gastroesophageal reflux disease	4 (14%)	3 (10%)	0	3 (10%)	1 (6%)
Defecation urgency	3 (10%)	3 (10%)	0	3 (10%)	0
Rectal tenesmus	3 (10%)	3 (10%)	1 (4%)	3 (10%)	0
Epigastric discomfort	2 (7%)	0	0	0	2 (11%)
Eructation	2 (7%)	2 (7%)	0	2 (7%)	0
Gastritis	2 (7%)	2 (7%)	0	2 (7%)	0

MedDRA SOC Preferred Term	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)	
Gastrointestinal sounds abnormal	2 (7%)	2 (7%)	0	2 (7%)	0
Gingivitis	2 (7%)	0	2 (9%)	2 (7%)	0
Stomach discomfort	2 (7%)	1 (3%)	1 (4%)	2 (7%)	0
Infections & Infestations	17 (59%)	15 (52%)	10	17 (59%)	10 (56%)
Influenza	7 (24%)	2 (7%)	4 (17%)	6 (21%)	2 (11%)
Nasopharyngitis	5 (17%)	5 (17%)	3 (13%)	5 (17%)	2 (11%)
Gastroenteritis	5 (17%)	4 (14%)	0	4 (14%)	2 (11%)
Bronchitis	3 (10%)	1 (3%)	1 (4%)	2 (7%)	2 (11%)
Tooth abscess	3 (10%)	1 (3%)	1 (4%)	1 (3%)	2 (11%)
Upper respiratory tract infection	3 (10%)	0	2 (9%)	2 (7%)	1 (6%)
Sinusitis	2 (7%)	0	0	0	2 (11%)
Investigations	16 (55%)	13 (45%)	5 (22%)	15 (52%)	5 (28%)
Weight decreased	7 (24%)	6 (21%)	1 (4%)	7 (24%)	0
Alanine aminotransferase increased	6 (21%)	5 (17%)	1 (4%)	5 (17%)	2 (11%)
Aspartate aminotransferase increased	3 (10%)	2 (7%)	0	2 (7%)	1 (6%)
Transaminases increased	2 (7%)	2 (7%)	0	2 (7%)	1 (6%)
General Disorders & Administration Site Conditions	13 (45%)	8 (28%)	7 (30%)	12 (41%)	4 (22%)
Chest pain	8 (28%)	3 (10%)	4 (17%)	7 (24%)	1 (6%)
Fatigue	5 (17%)	3 (10%)	2 (9%)	5 (17%)	0
Pyrexia	4 (14%)	1 (3%)	2 (9%)	3 (10%)	1 (6%)
Peripheral edema	2 (7%)	1 (3%)	0	1 (3%)	1 (6%)
Pain	2 (7%)	1 (3%)	0	1 (3%)	1 (6%)
Musculoskeletal & Connective Tissue Disorders	13 (45%)	9 (31%)	5 (22%)	11 (38%)	3 (17%)
Back pain	6 (21%)	3 (10%)	2 (9%)	5 (17%)	1 (6%)
Arthralgia	3 (10%)	2 (7%)	0	2 (7%)	1 (6%)
Musculoskeletal pain	3 (10%)	2 (7%)	0	2 (7%)	1 (6%)
Tendonitis	3 (10%)	1 (3%)	1 (4%)	1 (3%)	2 (11%)
Muscle spasms	2 (7%)	1 (3%)	1 (4%)	2 (7%)	0
Myalgia	2 (7%)	0	2 (9%)	2 (7%)	0
Neck pain	2 (7%)	2 (7%)	0	2 (7%)	0
Pain in extremity	2 (7%)	2 (7%)	1 (4%)	2 (7%)	0
Injury, Poisoning, & Procedural Complications	11 (38%)	7 (24%)	5 (22%)	10 (34%)	1 (6%)
Limb injury	2 (7%)	1 (3%)	1 (4%)	2 (7%)	0
Skin laceration	2 (7%)	2 (7%)	0	2 (7%)	0
Thermal burn	2 (7%)	0	2 (9%)	2 (7%)	0
Nervous System Disorders	11 (38%)	6 (21%)	3 (13%)	7 (24%)	7 (39%)
Headache	6 (21%)	1 (3%)	2 (9%)	3 (10%)	4 (22%)
Dizziness	3 (10%)	3 (10%)	2 (9%)	3 (10%)	1 (6%)
Paresthesia	3 (10%)	1 (3%)	1 (4%)	2 (7%)	2 (11%)
Metabolism & Nutrition	9 (31%)	4 (14%)	3 (13%)	7 (24%)	2 (11%)

MedDRA SOC Preferred Term	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)	
Disorders					
Anorexia	2 (7%)	2 (7%)	0	2 (7%)	1 (6%)
Iron deficiency	2 (7%)	1 (3%)	0	1 (3%)	1 (6%)
Respiratory, Thoracic, & Mediastinal Disorders	9 (31%)	6 (21%)	1 (4%)	7 (24%)	4 (22%)
Pharyngolaryngeal pain	4 (14%)	3 (10%)	1 (4%)	4 (14%)	0
Epistaxis	3 (10%)	2 (7%)	0	2 (7%)	1 (6%)
Nasal congestion	3 (10%)	3 (10%)	0	3 (10%)	0
Cough	2 (7%)	2 (7%)	0	2 (7%)	0
Vascular Disorders	8 (28%)	2 (7%)	3 (13%)	5 (17%)	3 (17%)
Hot flush	2 (7%)	1 (3%)	1 (4%)	2 (7%)	0
Hypertension	2 (7%)	1 (3%)	1 (4%)	2 (7%)	0
Cardiac Disorders	7 (24%)	5 (17%)	2 (9%)	7 (24%)	2 (11%)
Angina pectoris	3 (10%)	3 (10%)	0	3 (10%)	2 (11%)
Palpitations	3 (10%)	1 (3%)	2 (9%)	3 (10%)	0
Skin & Subcutaneous Disorders *	7 (24%)	4 (14%)	2 (9%)	6 (21%)	1 (6%)
Psychiatric Disorders	7 (24%)	3 (10%)	4 (17%)	5 (17%)	4 (22%)
Anxiety	3 (10%)	2 (7%)	1 (4%)	2 (7%)	2 (11%)
Depression	3 (10%)	0	2 (9%)	2 (7%)	2 (11%)
Blood & Lymphatic System Disorders	4 (14%)	4 (14%)	1 (4%)	4 (14%)	0
Anemia	2 (7%)	1 (3%)	1 (4%)	2 (7%)	0
Lymphadenopathy	2 (7%)	2 (7%)	0	2 (7%)	0
Eye Disorders *	4 (14%)	2 (7%)	2 (9%)	4 (14%)	1 (6%)
Hepatobiliary Disorders	3 (10%)	1 (3%)	2 (9%)	2 (7%)	1 (6%)
Hepatic steatosis	2 (7%)	2 (7%)	1 (4%)	2 (7%)	0
Hepatotoxicity	2 (7%)	1 (3%)	1 (4%)	1 (3%)	1 (6%)
Immune System Disorders *	2 (7%)	0	2 (9%)	2 (7%)	1 (6%)
Renal & Urinary Disorders *	2 (7%)	2 (7%)	0	2 (7%)	0
Reproductive System & Breast Disorders *	2 (7%)	2 (7%)	0	2 (7%)	0
Surgical & Medical Procedures *	2 (7%)	0	1 (4%)	1 (3%)	1 (6%)

Source: FDA clinical reviewer's analysis of submitted HoFH-pivotal and -extension AE datasets (AE.xpt).

* No single preferred term was recorded for ≥2 subjects.

Percentages indicate simple incidence (# with event / total number of subjects, with N varying by column as indicated). See text for additional analytical details.

Reviewer Comment: With the exception of the AEs with particularly high incidence (i.e., GI), it is difficult to comment on potential drug-associated events without a control arm. Although attempts using historical controls could be considered, given the fact that these are non-serious AEs, I have not done so; instead, I would favor simply describing the occurrence of these events in labeling if approved.

I reviewed each AE term for the less common events (i.e., those occurring in only one subject) in HoFH-pivotal and -extension. Most other AEs will be incorporated into analyses in other sections of this review (CK increase, hypokalemia, INR fluctuation,

report of fatty acid deficiency, hepatic steatosis). There was one report of “drug hypersensitivity,” but the implicated drug was clopidogrel. There was one event in the Neoplasms SOC, but this was “xanthoma.”

AEs reported as “severe” intensity are summarized in Section 7.3.4 (p. 169).

Among the 27 subjects who reported gastrointestinal events in HoFH-pivotal, the applicant reports that the median time to first GI event *after initiating a given dose* was 9.1 days, ranging from 1 to 39 days. According to my analysis, the median time to first GI event from 1st dose of lomitapide (study day 1) was 23 days, ranging from 1 to 141 days. Eight (30%) of the 27 subjects who reported at least one GI event experienced their first event within the first week of dosing.

Table 106 shows the most commonly reported AEs among subjects taking concomitant statins by type of statin (atorvastatin/simvastatin, which are metabolized by CYP3A4, or rosuvastatin, which is principally metabolized by CYP2C9).

Table 106. Most Commonly Reported AEs by Type of Concomitant Statin

MEDDRA PREFERRED TERM	TYPE OF STATIN		All Statins (N=27) n (%)
	Atorvastatin/ Simvastatin (N=14) n (%)	Rosuvastatin (N=13) n (%)	
Number of Patients with at Least 1 TEAE	13 (92.9)	12 (92.3)	25 (92.6)
Diarrhoea	13 (92.9)	9 (69.2)	22 (81.5)
Nausea	9 (64.3)	9 (69.2)	18 (66.7)
Dyspepsia	6 (42.9)	5 (38.5)	11 (40.7)
Vomiting	7 (50.0)	2 (15.4)	9 (33.3)
Abdominal Pain	5 (35.7)	2 (15.4)	7 (25.9)
Abdominal Distension	3 (21.4)	3 (23.1)	6 (22.2)
Flatulence	4 (28.6)	2 (15.4)	6 (22.2)
Weight Decreased	5 (35.7)	1 (7.7)	6 (22.2)
Abdominal Discomfort	3 (21.4)	2 (15.4)	5 (18.5)
Constipation	3 (21.4)	2 (15.4)	5 (18.5)
Alanine Aminotransferase Increased	3 (21.4)	2 (15.4)	5 (18.5)
Chest Pain	3 (21.4)	2 (15.4)	5 (18.5)
Abdominal Pain Upper	3 (21.4)	1 (7.7)	4 (14.8)
Influenza	1 (7.1)	3 (23.1)	4 (14.8)
Nasopharyngitis	1 (7.1)	3 (23.1)	4 (14.8)
Defaecation Urgency	3 (21.4)	0 (0.0)	3 (11.1)
Gastroesophageal Reflux Disease	3 (21.4)	0 (0.0)	3 (11.1)
Rectal Tenesmus	3 (21.4)	0 (0.0)	3 (11.1)

Source: HoFH-pivotal CSR, Table 28.

Reviewer Comment: *There is a suggestion that several AEs may be modestly more common among those taking atorvastatin or simvastatin, compared with rosuvastatin, but the numbers are small, precluding definitive conclusions.*

HoFH-pilot Supportive Data for Common AEs

Table 107 summarizes AEs reported by two or more subjects during HoFH-pilot. Conclusions regarding dose dependency are limited, since dose and time dependency cannot easily be separated given the forced-titration design.

Table 107. HoFH-pilot - AEs Reported by Two or More Subjects

MEDDRA SOC PREFERRED TERM	LOMITAPIDE DOSE ¹ (N=6)				ALL DOSES ² (N=6)
	0.03 MG/KG N (%)	0.1 MG/KG N (%)	0.3 MG/KG N (%)	1.0 MG/KG N (%)	
Respiratory, Thoracic and Mediastinal Disorders	2 (33.3)	3 (50.0)	3 (50.0)	4 (66.7)	6 (100.0)
Lung Disorder	1 (16.7)	1 (16.7)	0	4 (66.7)	4 (66.7)
Oropharyngeal Pain	1 (16.7)	1 (16.7)	2 (33.3)	1 (16.7)	4 (66.7)
Cough	2 (33.3)	1 (16.7)	1 (16.7)	0	2 (33.3)
Nasal Congestion	0	0	2 (33.3)	0	2 (33.3)
Gastrointestinal Disorders	3 (50.0)	2 (33.3)	2 (33.3)	5 (83.3)	5 (83.3)
Diarrhoea	1 (16.7)	2 (33.3)	1 (16.7)	4 (66.7)	5 (83.3)
Abdominal Pain Upper	1 (16.7)	0	0	2 (33.3)	2 (33.3)
Nausea	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)	2 (33.3)
Vomiting	0	1 (16.7)	0	2 (33.3)	2 (33.3)
Investigations	0	2 (33.3)	3 (50.0)	3 (50.0)	4 (66.7)
Alanine Aminotransferase Increased	0	1 (16.7)	2 (33.3)	3 (50.0)	3 (50.0)
Aspartate Aminotransferase Increased	0	1 (16.7)	2 (33.3)	2 (33.3)	3 (50.0)
International Normalised Ratio Increased	0	1 (16.7)	1 (16.7)	0	2 (33.3)
Nervous System Disorders	2 (33.3)	2 (33.3)	1 (16.7)	2 (33.3)	3 (50.0)
Headache	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)	3 (50.0)
General Disorders and Administration Site Conditions	1 (16.7)	1 (16.7)	0	2 (33.3)	2 (33.3)
Fatigue	0	1 (16.7)	0	2 (33.3)	2 (33.3)

Note that patients can report the same event at different dose levels, thus the sum of the number of patients across the dose levels can be greater than the total column across all doses.

- 1 Each patient's dose was escalated approximately every 28 days from 0.03 to 0.1 to 0.3 and to 1.0 mg/kg.
- 2 Includes events reported in 1 patient during dosing with 0.15 mg/kg and patients reported off-drug through the follow-up visit.

Source: [Appendix 6b](#)

Source: HoFH-pilot CSR, Table 6.

I reviewed the coding of all verbatim terms with preferred terms. All appeared reasonable, although the four verbatim terms "Pulmonary Other," which were coded to "Lung Disorder," contain little information. Two of these subjects had case report forms available to review (EMEN64 and SDAG82), which showed descriptions of "Cold" (EMEN64) and "Cold/flu symptoms" (SDAG82). The applicant reports that the other two subjects with these events also experienced cold and/or flu-like symptoms.

I also reviewed AEs that occurred in only one subject, which are not included in the preceding table. Subject SDAG82 had an AE of “Hemoglobinuria” of mild severity from study day 112-144 (i.e., last visit on treatment after 1.0 mg/kg through end-of-study follow-up visit), which the investigator thought unlikely related to lomitapide. Reviewing the subject’s laboratory data from that time, this 21 y/o male subject (SDAG82) did not have hemoglobinuria but rather had hematuria. At visit 14 (end of 1.0 mg/kg) he had large blood on urinalysis with microscopy showing 699 RBCs/hpf; at his end-of-study followup visit on day 144, his urinalysis was negative for blood with 0 RBCs/hpf. He had sporadic trace or small amounts of blood on dipstick U/As throughout the study, including a small amount on study day 1 with 5-10 RBCs/hpf on microscopy. There was no proteinuria by dipstick except trace at day 112. The subject’s medical history did not cite urologic or renal disorders. The etiology of the hematuria is unknown.

7.4.2 Laboratory Findings

Descriptive statistics for safety laboratory parameters through week 56 were submitted with the initial NDA. The 120-day safety update did not describe similar descriptive statistics through week 78; instead, it presented “mean maximum changes from baseline” similar to presentations in the Integrated Summary of Safety. These point estimates are difficult to interpret, especially without a control group, since isolated values that deviate substantially from baseline for a given patient will drive these “mean worst values.” These values did not differ substantially between the 56-week and 78-week datasets, however, suggesting that the 56-week data presented below are likely representative of the entire trial. In support of this, I used the submitted laboratory datasets to calculate mean and median values for each of the following laboratory parameters between weeks 56 and 78; no concerning trends were observed (data not shown).

Hematology

Table 108 presents descriptive statistics for hematology laboratories in HoFH-pivotal at baseline and weeks 26 and 56. Table 109 describes the frequency of subjects who shifted categories relative to the normal reference range from baseline to weeks 26 and 56.

Table 108. HoFH-pivotal – Hematology Trends

	Mean (SD)	Median	Absolute Mean Change from...	
			Baseline*	Week 26*
WBC (x10⁹/L) [3.7 – 11 x 10 ⁹ /L]				
Baseline	5.5 (1.4)	5.0		
Week 26/LOCF [7] [†]	5.3 (1.6)	4.8	-0.2 (1.1)	
Week 56/LOCF [1]	5.5 (1.5)	5.4	-0.1 (1.1)	+0.1 (1.1)
Hemoglobin (g/dL) [M: 12.5-17 g/dL; F: 11-15.5 g/dL]				
Baseline	13.2 (2.1)	13.0		
Week 26/LOCF [7]	13.3 (2.3)	13.5	+0.1 (1.2)	

	Mean (SD)	Median	Absolute Mean Change from...	
			Baseline*	Week 26*
Week 56/LOCF [1]	13.2 (2.5)	12.9	+0.1 (1.1)	0.0 (1.1)
Platelet count (x10⁹/L) [125-375 x10 ⁹ /L]				
Baseline	232 (69)	217		
Week 26/LOCF [7]	226 (70)	223	-7 (43)	
Week 56/LOCF [1]	227 (65)	218	-22 (56)	-14 (38)

Source: HoFH-pivotal CSR, Tables 14.3.4.1.1.1-4 and 14.3.4.2.1.1-4.1-2

* Changes from baseline or week 26 only include subjects with values at both time points.

† Number in brackets indicates the number imputed using LOCF.

N=29 for baseline and week 26/LOCF; N=23 for week 56/LOCF. Week 56/LOCF only carries forward observations within safety phase (week 26 onward).

Table 109. HoFH-pivotal – Hematology Shift Tables

Variable	Baseline	Week 26			Week 56		
		< LLN	Normal	> ULN	< LLN	Normal	> ULN
WBC	< LLN						
	NL	3 (11%)	25 (89%)		2 (9%)	21 (91%)	
	> ULN						
Hgb	< LLN	5 (18%)	1 (4%)		3 (13%)	2 (9%)	
	NL		21 (75%)		2 (9%)	14 (61%)	1 (4%)
	> ULN			1 (4%)		1 (4%)	
Platelets	< LLN						
	NL	1 (4%)	24 (89%)		1 (5%)	18 (82%)	
	> ULN		2 (7%)			2 (9%)	

Source: HoFH-pivotal CSR, Table 14.3.4.1.3.1 and 14.3.4.2.3.1.1.

Values represent counts of subjects; empty cells = 0.

See Table 108 for reference ranges. Values in bold, red font represent shifts between categories in an undesired direction (including ULN to Normal), although these shifts may or may not be clinically significant.

Mean (SD) values for MCV at baseline (n=29), week 26 (n=23), and week 56 (n=23) were 87 (9), 87 (10), and 89 (8) fL, respectively. Mean (SD) values for RDW at the same time points were 16% (3), 18% (3), and 16% (3). Iron studies or assessments of vitamin B12 status were not made, but these limited data do not suggest a signal with regard to deficiencies.

Red blood cell smears were not performed, so comment cannot be made with regard to any potential effects on RBC morphology, such as changes associated with vitamin E deficiency.

Three (10%) of 29 subjects in HoFH-pivotal had at least one hematology-related AE recorded; verbatim terms were “worsening of anemia” (2 episodes, subject 01-001); “iron-deficiency anemia” (subject 13-002), and “anemia” (subject 22-003). Subject 01-001 was on apheresis, anemic at baseline, and treated with iron supplements. Subject

13-002 was on apheresis, anemic at baseline, and treated with iron supplements. Subject 22-003 developed anemia following CABG while off lomitapide. In the extension study, one additional subject has reported “worsening of pre-existing iron deficiency” (subject 11-003).

The applicant did not submit summary statistics for hematology parameters in HoFH-pilot. They simply summarized, “Four of the six patients had consistently low red cell parameters, including hemoglobin and hematocrit, at Screening and through the treatment period. White cell parameters and platelet count were in the normal range for the majority of time points for all patients; sporadic values outside the normal range were noted.” My review of the submitted raw data largely concurs, although one subject (EMEN64) demonstrated a downward hemoglobin (and Hct) trend during the trial: Hemoglobin values at screening and baseline were 12.3 and 11.6 g/dL, respectively; at the end of the four dosing periods, the values were 11.5, 11.7, 9.6, and 8.5 g/dL. At the off-treatment end-of-study visit 30 days later, Hgb was 10.3 g/dL. There were no AEs related to bleeding or anemia.

Clinical Chemistry

Table 110 presents descriptive statistics for clinical chemistry laboratories in HoFH-pivotal at baseline and weeks 26 and 56.

Table 110. HoFH-pivotal – Clinical Chemistry Descriptive Statistics

	Mean (SD)	Median	Absolute Mean Change from...	
			Baseline*	Week 26*
Sodium (mEq/L) [133-145 mEq/L]				
Baseline	139.7 (1.9)	140		
Week 26/LOCF [7] [†]	139.7 (1.9)	140	+0.1 (2.6)	
Week 56	140.0 (2.3)	140	+0.3 (2.4)	+0.2 (2.7)
Potassium (mEq/L) [3.5-5 mEq/L]				
Baseline	4.2 (0.4)	4.2		
Week 26/LOCF [7]	4.2 (0.3)	4.3	0.0 (0.4)	
Week 56	4.1 (0.4)	4.1	-0.1 (0.4)	-0.1 (0.4)
Chloride (mEq/L) [95-110 mEq/L]				
Baseline	103.3 (4.4)	103		
Week 26/LOCF [7]	103.3 (2.6)	103	0.0 (4.9)	
Week 56	103.5 (2.2)	104	+0.7 (5.1)	+0.8 (2.8)
Bicarbonate (mEq/L) [21-33 mEq/L]				
Baseline	24.2 (2.4)	25		
Week 26/LOCF [7]	25.1 (2.4)	26	+0.9 (2.3)	
Week 56	25.7 (2.9)	25	+1.4 (2.2)	+0.3 (2.7)
BUN (mg/dL) [5-20 mg/dL]				
Baseline	13.6 (4.5)	13		
Week 26/LOCF [7]	12.8 (4.7)	12	-0.8 (2.3)	

	Mean (SD)	Median	Absolute Mean Change from...	
			Baseline*	Week 26*
Week 56	12.0 (3.2)	12	-1.1 (3.8)	-0.2 (3.2)
Creatinine (mg/dL) [0.7-1.4 mg/dL]				
Baseline	0.9 (0.1)	0.9		
Week 26/LOCF [7]	0.9 (0.2)	0.9	0.0 (0.1)	
Week 56	0.9 (0.2)	0.9	0.0 (0.1)	0.0 (0.1)
Glucose (mg/dL) [65-105 mg/dL]				
Baseline	83.2 (8.0)	83		
Week 26/LOCF [7]	83.1 (8.7)	82	-0.1 (10.5)	
Week 56	85.0 (9.4)	83	+0.4 (9.1)	+2.8 (6.4)
Creatine kinase (U/L) [M: 50-297; F: 33-198 U/L]				
Baseline	141 (100)	110		
Week 26/LOCF [7]	140 (117)	107	0 (119)	
Week 56	211 (357)	125	+23 (88)	+67 (241)
Calcium (mg/dL) [8.5-10.5 mg/dL]				
Baseline	9.6 (0.4)	9.5		
Week 26/LOCF [7]	9.5 (0.4)	9.5	-0.1 (0.5)	
Week 56	9.3 (0.4)	9.4	-0.3 (0.5)	-0.2 (0.5)
Total Protein (g/dL) [6-8 g/dL]				
Baseline				
Week 26/LOCF [7]	7.2 (0.6)	7.2	-0.1 (0.4)	
Week 56	7.0 (0.5)	6.9	-0.3 (0.5)	-0.3 (0.4)
Albumin (g/dL) [3.5-5.5 g/dL]				
Baseline	4.5 (0.4)	4.5		
Week 26/LOCF [7]	4.6 (0.3)	4.6	+0.1 (0.4)	
Week 56	4.4 (0.3)	4.4	-0.1 (0.3)	-0.2 (0.3)

Source: HoFH-pivotal CSR, Tables 14.3.4.1-2.2.1-11.

* Changes from baseline or week 26 only include subjects with values at both time points.

† Number in brackets indicates the number imputed using LOCF.

N=29 for baseline and week 26/LOCF; N=23 for week 56 (no missing data requiring imputation).

The applicant's clinical chemistry shift tables were reviewed (HoFH-pivotal CSR Tables 14.3.4.1.3.2.*). There were very few shifts that resulted in values outside of the normal range in potentially undesirable directions:

- Two (7%) of 29 subjects had normal bicarbonate at baseline but low values at week 26.
- Two (7%) of 29 subjects had normal CK at baseline but high values at week 26. Three (13%) of 23 subjects had normal CK at baseline but high values at week 56.
- One (3%) of 29 subjects had normal total protein at baseline but a low value at week 26.
- One (4%) of 23 subjects had normal potassium at baseline but a low value at week 56.

Recorded AEs (verbatim terms) related to the chemistry laboratories above included:

- Subject 02-002: “CPK elevated” on day 309 (two weeks prior to week 46 visit). Corresponding CK value was 413 U/L (2x ULN). See Section 7.3.5 (p. 211).
- Subject 12-001: “Hypokalemia” on day 415. No supporting potassium value provided; flanking values were 3.8 and 3.9 mEq/L on days 393 (week 56) and 463 (week 66). The subject was initiated on K+ supplementation.
- Subject 23-001: “Low potassium” on day 114. No supporting potassium value provided; flanking values were 4.1 and 4.0 mEq/L on days 100 (week 14) and 126 (week 18). The subject was initiated on K+ supplementation.

For HoFH-pilot, the mean (SD) absolute changes in clinical chemistry parameters from baseline to the end of the 1.0 mg/kg period follow: creatinine -0.10 (0.11) mg/dL, sodium -0.17 (2.8) mEq/L, potassium +0.12 (0.31) mEq/L, chloride +1.5 (3.5) mEq/L, and glucose -2.5 (15.3) mg/dL. CK was not measured in HoFH-pilot.

Reviewer Comment: Although limited by the small sample size, these data do not raise additional safety concerns.

7.4.3 Vital Signs

Similar to the laboratory data described in Section 7.4.2, descriptive statistics for vital signs through week 56 were submitted with the initial NDA. The 120-day safety update did not describe similar descriptive statistics through week 78; instead, it presented “mean maximum changes from baseline” similar to presentations in the Integrated Summary of Safety. I used the submitted vital sign datasets to calculate mean and median values for vital sign parameters between weeks 56 and 78.

Table 111 provides the values for cross-sections at Weeks 26 (completers), 56, 66, and 78 for systolic and diastolic blood pressure, heart rate, and respiratory rate. Imputing the six missing values at week 26 with LOCF imputation did not substantially change these results.

Table 111. HoFH-pivotal – Vital Sign Descriptive Statistics

	N	Mean (SD)	Median	Absolute Change from Baseline*	
				Mean (SD) Change	Median [IQR] Change
SBP					
Baseline	29	118.4 (13.7)	117		
Week 26	23	113.8 (17.3)	110	-3.0 (15.6)	-3 [-14, 7]
Week 56	23	116.7 (18.2)	110	-0.1 (11.8)	0 [-9, 9]
Week 66	23	122.5 (17.9)	120	+5.7 (11.3)	+10 [-2, 11]
Week 78	23	120.4 (19.3)	119	+3.6 (12.4)	+2 [-6, 10]
DBP					
Baseline	29	63.5 (9.2)	61		
Week 26	23	65.2 (13.3)	60	+0.5 (11.7)	0 [-5, 5]
Week 56	23	62.7 (11.1)	60	-2.0 (9.5)	0 [-6, 6]
Week 66	23	67.4 (11.9)	66	+2.7 (8.1)	+1 [-1, 7]
Week 78	23	67.8 (13.0)	67	+3.1 (10.0)	+4 [-2, 10]
Heart Rate					

	N	Mean (SD)	Median	Absolute Change from Baseline*	
				Mean (SD) Change	Median [IQR] Change
Baseline	29	70.8 (11.4)	70		
Week 26	23	72.6 (14.0)	69	+0.4 (11.9)	-1 [-6, 6]
Week 56	23	70.8 (10.9)	70	-1.4 (9.1)	-2 [-8, 5]
Week 66	23	70.3 (11.9)	67	-1.9 (9.7)	-4 [-8, 7]
Week 78	23	70.2 (14.6)	69	-2.0 (11.1)	-1 [-10, 5]
Respiratory Rate					
Baseline	29	19.2 (10.5)	17		
Week 26	23	19.0 (4.7)	18	-1.4 (9.9)	0 [-2, 4]
Week 56	23	17.6 (4.0)	17	-2.8 (10.2)	0 [-4, 2]
Week 66	23	18.1 (4.5)	17	-2.4 (9.9)	0 [-3, 2]
Week 78	23	18.7 (4.7)	18	-1.8 (10.4)	0 [-2, 3]

Source: FDA clinical reviewer's analysis of submitted HoFH-pivotal laboratory dataset (LB.xpt).

* Changes from baseline only include subjects with values at both time points.

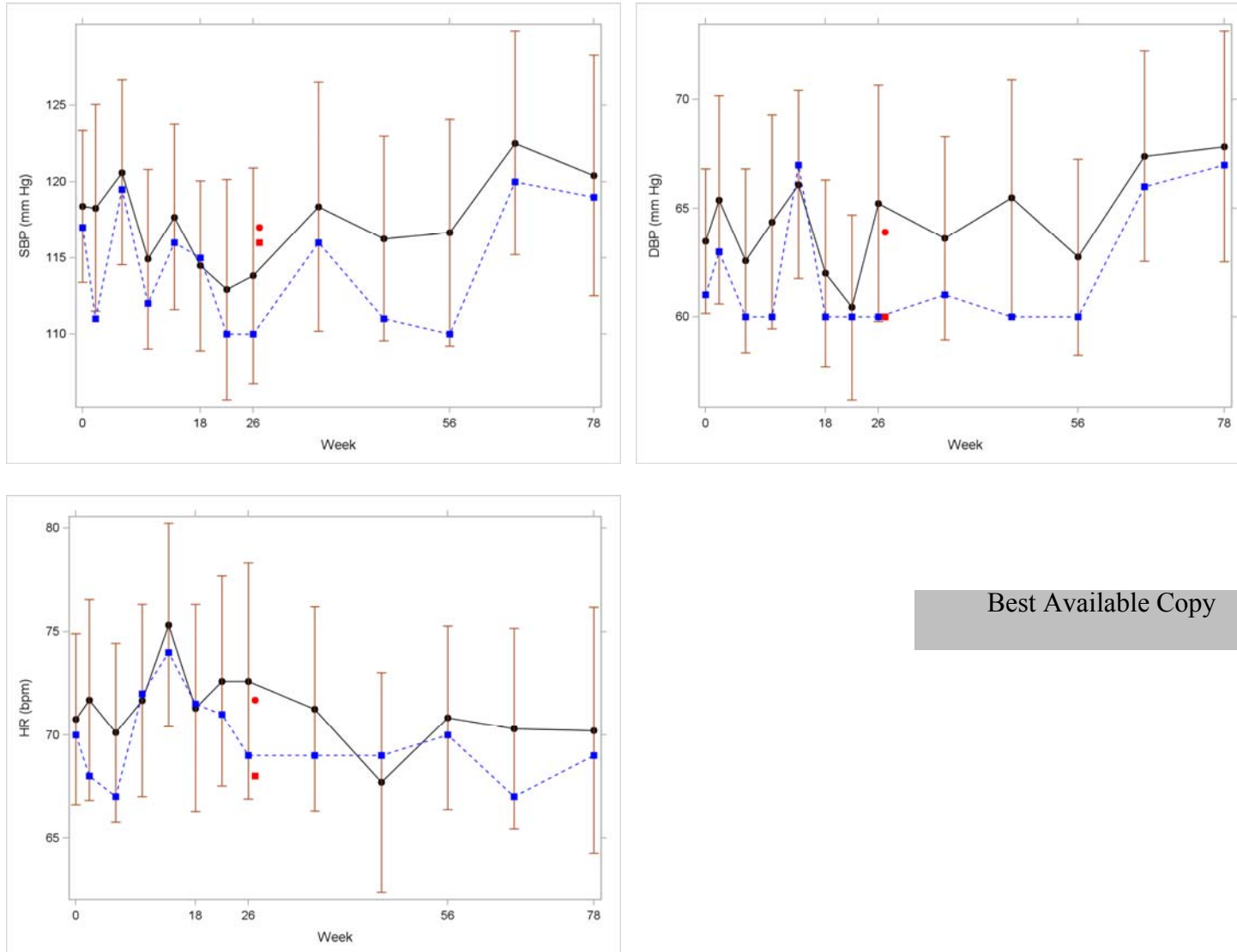
No subjects were lost between weeks 26 and 78.

Note that toward the end of the safety phase, the point estimates for the mean changes from baseline in systolic and diastolic blood pressure achieve values as high as +5.7 mmHg and +3.1 mmHg, respectively. Examining these measures of central tendency at all time points of the trial, however, do not suggest consistent trends in these parameters (Figure 54). There was no suggestion of adverse changes to respiration rate or body temperature (not shown).

In HoFH-pivotal, AEs related to vital sign abnormalities were uncommon. Pyrexia was reported in three subjects, and hypertension and elevated blood pressure were reported in one subject each. Elevated blood pressure has been reported in one additional subject in the extension study.

Subject 35-001 (Italy) had respiratory rates of 65, 70, 32, 39, and 32 breaths/min recorded at screening, baseline, weeks 6, 10, and 14, respectively; these values seem implausible. From week 18 through 78, respiratory rates ranging from 24 to 28 breaths/min were recorded. The narrative makes no mention of this apparently extreme tachypnea, and this 26-year-old subject's medical history (mild hypochromic anemia related to apheresis) does not explain these values. There were no respiratory AEs recorded for this subject.

Reviewer Comment: Taken together, there does not appear to be a definite safety signal with regard to vital sign changes from the HoFH phase 3 program, although making such a conclusion is limited by the small sample size and lack of a control group.



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Figure 54. HoFH-pivotal – Vital Sign Trends

Source: FDA clinical reviewer’s analysis of data submitted in HoFH-pivotal laboratory dataset (*LB.xpt*).

Black solid line connects mean observed values (black, filled circles); error bars represent 95% CI of the mean.

Blue dashed line connects median observed values (blue, filled squares). Red open circle and square represent Week 26/LOCF mean and median values, respectively.

HoFH-pilot Supportive Vital Sign Data

Table 112 summarizes the mean (SD) changes in vital sign parameters and weight following each dosing period in HoFH-pilot.

Table 112. HoFH-pilot – Mean (SD) Vital Signs Over Time

PARAMETER	LOMITAPIDE DOSE				OFF-TREATMENT VISIT (VISIT 15)
	0.03 MG/KG (VISIT 5)	0.1 MG/KG (VISIT 8)	0.3 MG/KG (VISIT 11)	1.0 MG/KG (VISIT 14)	
Heart Rate	-2.8 (16.20)	-1.7 (11.36)	0.3 (8.21)	1.8 (11.39)	-3.2 (8.04)
Systolic BP	-10.2 (16.41)	-8.8 (13.91)	-5.8 (12.61)	-3.3 (17.21)	-7.8 (17.16)
Diastolic BP	-10.7 (12.13)	-6.5 (12.08)	-10.5 (9.23)	-5.0 (12.52)	-6.2 (16.28)
Weight	-0.7 (1.70)	-0.9 (1.88)	-0.4 (1.62)	-2.9 (2.23)	-0.05 (2.34)

Note: Each patient's dose was escalated approximately every 28 days from 0.03 to 0.1 to 0.3 and to 1.0 mg/kg; assessments conducted at the end of each dosing period.

Source: [Appendix 3a](#), [Appendix 3b](#), [Appendix 3c](#), and [Appendix 3d](#)

Source: HoFH-pilot CSR, Table 10.

Note that mean systolic blood pressure increases during dose escalation (-10.2 mmHg to -3.3 mmHg, relative to baseline, from visit 5 to visit 14) and then falls when lomitapide is discontinued (-3.3 mmHg to -7.8 mmHg from visit 14 to visit 15). Mean heart rate increases on treatment, and then decreases off treatment, in a similar pattern. Similar to the pivotal trial, these data are difficult to interpret given the small sample size and the absence of a control group.

Examination of the individual profiles for these parameters shows substantial within-subject variation (Figure 55). Taken alone, these data do not raise a safety concern, but they do not provide much reassurance given the paucity of subjects.

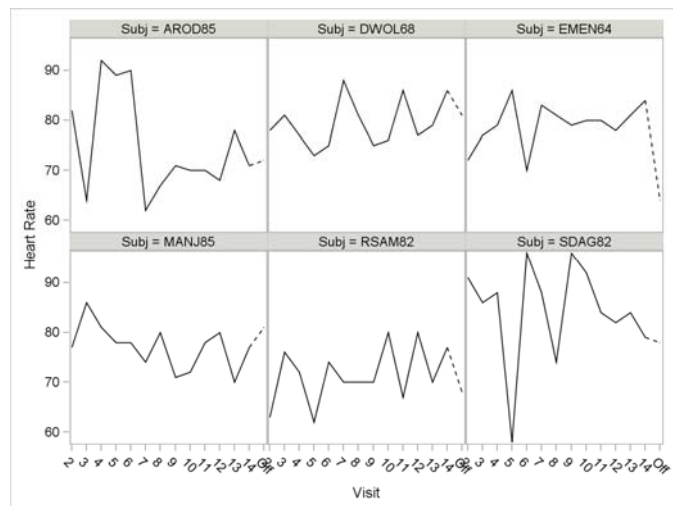
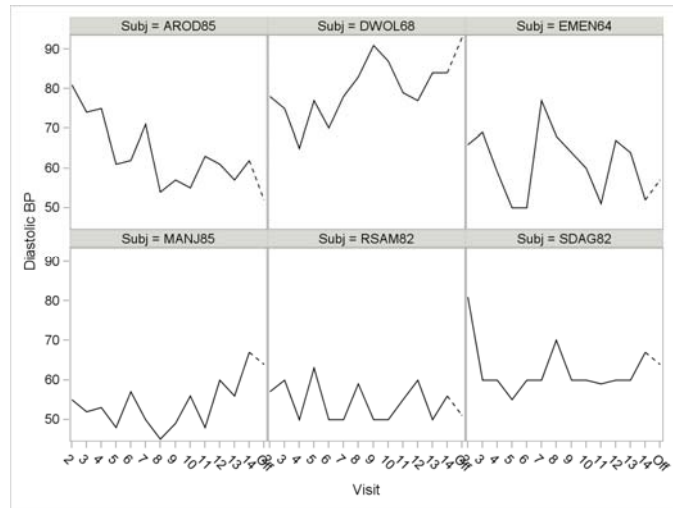
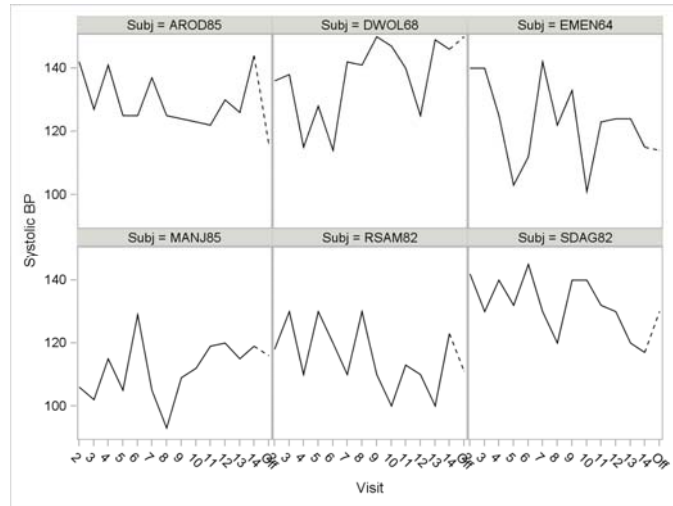


Figure 55. HoFH-pilot – SBP, DBP, and Heart Rate Over Time
Source: FDA clinical reviewer’s analysis of submitted HoFH-pilot dataset (LB xpt)
Dashed lines connect values at the last on-treatment visit and the off-treatment follow-up.

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Physical Examinations

The protocol for HoFH-pivotal does not provide detailed standards regarding physical examination at each study visit. The case report forms simply provide blanks for written comments next to each organ system; there was no pre-specification of specific abnormalities to seek and record. Furthermore, my review of case report forms and data clarification requests revealed that physical examination results were often provided by investigators, in retrospect, months or even years after study visits. Thus, these data are suspect.

One cannot determine, for example, whether lomitapide potentially improves xanthomata. From a safety perspective, one might question whether long-term administration of lomitapide leads to any neurologic signs or symptoms; detailed neurologic exams were almost certainly not conducted. If one were concerned about the possibility of insidious retinopathy, which occurs with complete MTP deficiency (abetalipoproteinemia), systematic retinal examinations have not been performed. The preclinical development program did not reveal signs of neurotoxicity or ophthalmologic toxicity in animals, however.

I reviewed all physical examination findings marked “abnormal” in the submitted datasets for HoFH-pivotal and its extension study. Most abnormal findings related to xanthomas and cardiac murmurs. One subject (02-002) had “bleeding around gums” recorded on study day 449; the investigator reported an adverse event of “exacerbation of gingivitis” on the same day. Platelets and INR were normal (236k and 0.9, respectively).

7.4.4 Electrocardiograms (ECGs)

In HoFH-pivotal, single ECGs were recorded on paper at screening, baseline, and study visits corresponding to 2, 6, 10, 14, 18, 22, and 26 weeks of treatment. The statistical analysis plan pre-specified criteria for change in QTcF (Δ QTcF) from baseline that would trigger the requirement for a centralized blinded review of ECG tracings: If the upper one-sided 95% CI for Δ QTcF at any time point, subtracted from baseline, was >10 msec, coincident with a point estimate >3 msec, then the paper ECGs were to be analyzed in a blinded fashion by a core ECG laboratory. The core laboratory analysis was to constitute the primary ECG analysis. This criterion was satisfied, therefore, a central analysis of all ECGs was performed. Interval measurements were made by a single trained reader using manual calipers on three consecutive beats. A cardiologist verified the interval durations, performed morphology analysis, and noted any T- and U-wave complex alterations compatible with an effect on cardiac repolarization. The ECG analysis was conducted in Lead II, or in lead V5, followed by V2 or most appropriate lead if Lead II could not be analyzed. ECG readers were blinded to subject identifiers, treatment, and visit.

Table 113 presents mean changes (with 90% CI) in heart rate (60/RR), QTcF, PR, and QRS from baseline to each study visit during the efficacy period. At week 18, with mean change in QTcF of +3 msec, the upper bound of the 90% CI was 11.7 msec, i.e., exceeding the 10 msec threshold. At subsequent visits during the efficacy period, the mean Δ QTcF values were lower and the upper bounds of the 90% CIs were <10 msec.

Table 113. HoFH-pivotal – Mean Changes in ECG Intervals (Central Read)

Visit (n)	Δ DHR	Δ QTcF	Δ PR	Δ QRS
Week 2 (26)*	-2.7 (-5.8, 0.5)	-5.7 (-13.2, 1.8)	3.4 (-0.9, 7.7)	-2.1 (-5.0, 0.8)
Week 6 (25)	-1.8 (-5.1, 1.4)	-0.1 (-6.2, 6.0)	-0.6 (-5.9, 4.7)	-1.8 (-4.3, 0.6)
Week 10 (24)	-2.8 (-6.8, 1.2)	-8.9 (-16.5, -1.3)	0.8 (-4.4, 6.0)	-0.7 (-3.0, 1.6)
Week 14 (20)	-3.3 (-7.2, 0.7)	-7.5 (-17.8, 2.8)	-1.4 (-7.7, 4.8)	-2.2 (-5.3, 1.0)
Week 18 (21)	-5.4 (-9.5, -1.4)	3.0 (-5.6, 11.7)	-2.1 (-9.0, 4.7)	-3.7 (-6.8, -0.7)
Week 22 (19)	-3.1 (-6.6, 0.5)	-3.4 (-11.4, 4.5)	-4.6 (-11.0, 1.9)	-4.7 (-8.3, -1.1)
Week 26 (21)	-2.4 (-5.7, 0.9)	0.2 (-9.1, 9.5)	0.2 (-5.2, 5.6)	-4.8 (-7.9, -1.6)

Source: HoFH-pivotal Appendix 16.2.8, Tables 3, 4, A7, and A8.

Values are mean (90% CI) changes from baseline to the listed study visits.

* For Δ PR, n = 26, 24, 25, 23, 21, 20 and 21 across weeks 2-26, respectively; for Δ QRS, N = 27, 26, 26, 24, 22, 21, and 22.

No subject had a QTcF exceeding 500 msec or a Δ QTcF from baseline exceeding 60 msec (Table 114). Because the mean dose of lomitapide increased over time, there does not appear to be an association between dose and Δ QTcF. Treatment-emergent changes of T-wave morphology or presence of U waves were infrequent and did not increase in frequency with study duration (data not shown).

Table 114. HoFH-pivotal – QTcF Outliers (Central Read)

Visit (n)	QTcF			Δ QTcF	
	>450 msec	>480 msec	>500 msec	>30 msec	>60 msec
Week 2 (26)	0	0	0	0	0
Week 6 (25)	1 (4%)	1 (4%)	0	1 (4%)	0
Week 10 (24)	1 (4%)	0	0	2 (8%)	0
Week 14 (20)	0	0	0	1 (5%)	0
Week 18 (21)	2 (10%)	0	0	2 (10%)	0
Week 22 (19)	2 (11%)	0	0	1 (5%)	0
Week 26 (21)	1 (5%)	0	0	2 (10%)	0

Source: HoFH-pivotal CSR Appendix 16.2.8 Tables 5 and 6.

Reviewer Comment: The TQT study is described in Section 7.4.5. ECG data from HoFH-pivotal does not raise additional safety concerns.

7.4.5 Special Safety Studies/Clinical Trials

Thorough QT Study: AEGR-733-011

In 2011, Aegerion sponsored a thorough QT study. This was a single-center, randomized, 6-treatment, 5-period cross-over study involving 56 healthy subjects (50 completed). The 6 study treatments were lomitapide (75 and 200 mg doses sequentially and 75 mg co-administered with ketoconazole), placebo, ketoconazole alone, and moxifloxacin (positive control). The study was double-blind with regard to lomitapide and placebo but open-label for ketoconazole and moxifloxacin. The cardiologist responsible for over-reading the ECGs was blind to all study treatments and sequences. Continuous ECG recordings were performed up to 24 hours postdose on Days 1 and 3 of each period. The protocol for this study was reviewed by the agency's Interdisciplinary Review Team for QT Studies (IRT/QT) prior to its conduct.

The IRT/QT reviewed the results from this study. Overall, no significant QTc prolongation effects of lomitapide were detected. The largest upper bounds of the 2-sided 90% CI for the mean differences between lomitapide (75 and 200 mg) and placebo, and between 75 mg lomitapide co-administered with ketoconazole and ketoconazole, were below 10 ms (regulatory threshold for concern; see ICH E14). The largest lower bound of the 2-sided 90% CI for the moxifloxacin $\Delta\Delta$ QTcI was >5ms. The team noted that the rising phase for moxifloxacin was missing based on its time profile and requested one more time point, either at 15 or 30 minutes after moxifloxacin administration, but the sponsor responded that additional time points were not available (13 July 2012).

A summary of the results from this study is shown in Table 115, excerpted from the IRT/QT review.

Table 115. Thorough QT Study – Summary of QTcI Results

Table 1: The Point Estimates and the 90% CIs for 75 mg Lomitapide, 200 mg Lomitapide, 75 mg Lomitapide + Ketoconazole, Moxifloxacin and Ketoconazole (FDA Analysis)

Treatment	Time (h)	$\Delta\Delta$ QTcI (ms)	90% CI (ms)
75 mg Lomitapide	24	1.1	(-0.8, 3.1)
200 mg Lomitapide	12	2.8	(0.3, 5.4)
75 mg Lomitapide + Ketoconazole*	24	2.7	(0.2, 5.3)
Moxifloxacin 400 mg**	1	12.5	(9.8, 15.2)
Ketoconazole	3	6.4	(3.7, 9.2)

* Ketoconazole-corrected change from baseline in QTcI.

** Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 8.8 ms.

Source: FDA IRT/QT review (09 July 2012).

The IRT/QT review also analyzed changes in heart rate, PR interval, and QRS duration. Table 116 summarizes the highest point estimates and highest upper bounds of the 2-sided 90% CI of the between-group differences in changes from baseline for each parameter.

Table 116. Thorough QT Study – Max Changes in HR, PR, QRS

	$\Delta\Delta$ HR (bpm)		$\Delta\Delta$ PR (ms)		$\Delta\Delta$ QRS (ms)	
	Max. Est.	Max. UB	Max. Est.	Max. UB	Max. Est.	Max. UB
75 mg lomit vs. placebo	0.6	2.0	1.1	3.1	0.4	0.8
200 mg lomit vs. placebo	1.5	3.1	4.2	7.2	0.7	1.5
75 mg lomit + keto vs. keto	0.0	1.6	2.4	5.2	-0.05	0.2

Source: FDA IRT/QT review (09 July 2012), Tables 11-16 and 18-20.

Max. Est. = maximum point estimate of the between-group differences in changes from baseline; Max.

UB = maximum upper bound of the 2-sided 90% CI of the same between-group differences.

Time points = 1, 2, 3, 4, 5, 7, 12, and 24 hours.

- **Heart Rate:** There were no subjects with heart rate greater than 100 bpm in lomitapide-treated groups.
- **PR Interval:** Two subjects who had PR interval >200 ms were in lomitapide-treated groups; one in the lomitapide 200 mg group and one in the lomitapide 75 mg + ketoconazole group. One subject had PR >200 ms in the placebo group.
- **QRS Duration:** Across groups, 23-26 subjects had QRS $\geq$ 110 ms; an association with lomitapide was not detected.

One subject in this trial had an SAE of post-traumatic stress disorder requiring hospitalization. This subject was in the placebo group.

Two subjects were withdrawn from the study as a result of elevated

transaminases following lomitapide 75 mg + ketoconazole. In this study, safety laboratories were drawn on Day -1 and Day 5 of each period, with 5 planned periods per subject. Study drugs were administered on days 1, 2, and 3 of each period. There was a ~14-day washout between Day 3 of one period and Day 1 of the subsequent period. Four subjects had a peak ALT >3x ULN detected during this study, with time courses described briefly below:

- Subject 40 was a 28 y/o white man who had ALT values of 21 and 23 IU/L at screening and day -1, respectively. He received ketoconazole + lomitapide on study day 3 with ALT 19 IU/L two days later. On study day 18 when he returned for period 2, his ALT was 291 IU/L (4.6x ULN), which increased to a peak of 396 IU/L (6.3x ULN) two days later. No further treatments were administered and the ALT was followed; it fell to 310 IU/L on day 23 and to 65 IU/L on day 33.
- Subject 53 was a 23 y/o white female who had values of 18 and 19 IU/L at screening and day -1, respectively. Her first exposure to lomitapide was during period 2. Her pre-dose ALT was 24 IU/L and she received single doses of lomitapide 75 mg and 200 mg on study days 20 and 22, respectively, with a follow-up ALT 21 IU/L two days later. When she returned for period 3 on study day 35, her ALT had increased to 61 IU/L. She received ketoconazole + lomitapide

on study day 38, with an ALT 57 IU/L on day 40. When she returned for period 4 on study day 51, however, her ALT had risen to 107 IU/L; it was followed to a peak of 206 IU/L (3.8x ULN) two days later. She was withdrawn from the study and ALT was followed down to 82 IU/L on study day 65.

- Subject 44 was a 23 y/o Mexican man who had ALT values of 46 and 79 IU/L at screening and day -1, respectively. His first exposure to lomitapide was during period 3. His pre-dose ALT was 56 IU/L and he received single doses of lomitapide 75 mg and 200 mg on study days 38 and 40, with a follow-up ALT 42 IU/L two days later. When he returned for period 4 on study day 53, however, his ALT had increased to 127 IU/L. During period 4, he received ketoconazole + lomitapide on study day 56 with follow-up ALT values of 109 and 119 IU/L on days 58 and 61, respectively. When he returned for period 5 on study day 69, his ALT had increased to 212 IU/L, which was followed to a peak of 276 IU/L (4.4x ULN) two days later when it gradually declined to 105 IU/L at an unscheduled follow-up visit on study day 96.
- Subject 01 was a 41 y/o white man who had ALT values of 17 and 20 IU/L at screening and day -1, respectively. He received single doses of lomitapide 75 mg and 200 mg on study days 17 and 19 (period 2), and ketoconazole + lomitapide on study day 36 (period 3). On presenting for period 4 on day 53, his ALT was 48 IU/L. He only received placebo during period 4 according to the sponsor, and his ALT was found to be 280 IU/L (4.4x ULN) at the end of this period (day 58). His ALT fell to 120 IU/L on day 64 and to 60 IU/L when he presented for period 5 on day 69. At the end of the study, his ALT was 26 IU/L (day 78).

Reviewer Comments:

1. *The IRT recommends the following text for labeling:*

The effect of single doses of lomitapide on QTc interval was evaluated in a randomized, placebo- and active-controlled crossover study. The upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc for lomitapide was below 10 ms, the threshold for regulatory concern. However, assay sensitivity was not established in this study. Therefore, a small increase in mean QTc interval (i.e., <10 ms) cannot be ruled out.

2. *There is a temporal association between ALT abnormalities following ketoconazole + lomitapide co-administration in 3 subjects. I note that peak ALT occurred 15, 15, and 17 days after co-administration in these cases.*

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Table 117 is the applicant's summary of treatment-emergent AEs reported in ≥10% of all patients during HoFH-pivotal through week 56, excerpted from the submitted clinical study report. Given the dose-escalation study design, dose is an outcome in itself, which is determined by tolerability (reflected, in part, by AE incidence). Furthermore, dose-dependency cannot generally be distinguished from time-dependency with such a

design. Thus, analyzing dose as a predictor of events would be expected to generate biased estimates. In addition, presenting AE counts and simple incidence calculations is potentially misleading given the trial design; since most patients only spent 2 weeks at the 5 mg dose, the incidence of events attributed to this dose would be lower than the incidence of events attributed to the higher maintenance doses achieved, even if the incidence rates (i.e., per patient-time) were similar at each dose. Thus, although I have included this table for the interested reader, I believe it is more appropriate to describe the overall incidence of events for the titration regimen studied, as presented in Section 7.4.1 (p. 214).

Table 117. HoFH-pivotal – AEs in ≥10% of Subjects by Dose at Onset (through Week 56)

MEDDRA SOC PREFERRED TERM	DOSE OF LOMITAPIDE AT THE TIME OF ONSET OF THE TEAE ¹						All Patients (N=29)
	5 mg (N=29)	10 mg (N=27)	20 mg (N=26)	40 mg (N=21)	60 mg (N=13)	80 mg (N=2)	
<i>Number of Patients with at Least 1 TEAE</i>	<i>18 (62.1)</i>	<i>20 (74.1)</i>	<i>19 (73.1)</i>	<i>18 (85.7)</i>	<i>12 (92.3)</i>	<i>1 (50.0)</i>	<i>27 (93.1)</i>
Gastrointestinal Disorders	9 (31.0)	18 (66.7)	12 (46.2)	14 (66.7)	10 (76.9)	1 (50.0)	27 (93.1)
Diarrhoea	5 (17.2)	14 (51.9)	5 (19.2)	11 (52.4)	5 (38.5)	0	23 (79.3)
Nausea	4 (13.8)	6 (22.2)	5 (19.2)	8 (38.1)	5 (38.5)	0	19 (65.5)
Dyspepsia	2 (6.9)	1 (3.7)	2 (7.7)	5 (23.8)	2 (15.4)	0	11 (37.9)
Vomiting	0	3 (11.1)	3 (11.5)	4 (19.0)	2 (15.4)	1 (50.0)	10 (34.5)
Abdominal Pain	1 (3.4)	4 (14.8)	2 (7.7)	2 (9.5)	1 (7.7)	1 (50.0)	8 (27.6)
Abdominal Discomfort	1 (3.4)	0	1 (3.8)	3 (14.3)	1 (7.7)	0	6 (20.7)
Abdominal Distension	1 (3.4)	2 (7.4)	1 (3.8)	2 (9.5)	2 (15.4)	1 (50.0)	6 (20.7)
Constipation	0	3 (11.1)	1 (3.8)	0	4 (30.8)	1 (50.0)	6 (20.7)
Flatulence	1 (3.4)	4 (14.8)	0	0	2 (15.4)	1 (50.0)	6 (20.7)
Abdominal Pain Upper	0	2 (7.4)	1 (3.8)	1 (4.8)	1 (7.7)	0	5 (17.2)
Defaecation Urgency	0	0	0	2 (9.5)	0	1 (50.0)	3 (10.3)
Gastroesophageal Reflux Disease	0	0	0	1 (4.8)	2 (15.4)	1 (50.0)	3 (10.3)
Rectal Tenesmus	0	0	1 (3.8)	1 (4.8)	1 (7.7)	1 (50.0)	3 (10.3)
Infections and Infestations	3 (10.3)	1 (3.7)	7 (26.9)	4 (19.0)	7 (53.8)	0	17 (58.6)
Nasopharyngitis	0	0	3 (11.5)	0	3 (23.1)	0	5 (17.2)
Gastroenteritis	1 (3.4)	0	0	2 (9.5)	1 (7.7)	0	4 (13.8)
Influenza	1 (3.4)	0	2 (7.7)	1 (4.8)	0	0	4 (13.8)
Investigations	4 (13.8)	4 (14.8)	4 (15.4)	4 (19.0)	3 (23.1)	0	14 (48.3)
Weight Decreased	1 (3.4)	2 (7.4)	0	3 (14.3)	0	0	6 (20.7)
Alanine Aminotransferase Increased	0	1 (3.7)	3 (11.5)	2 (9.5)	1 (7.7)	0	5 (17.2)

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MEDDRA SOC PREFERRED TERM	DOSE OF LOMITAPIDE AT THE TIME OF ONSET OF THE TEAE ¹						All Patients (N=29)
	5 mg (N=29)	10 mg (N=27)	20 mg (N=26)	40 mg (N=21)	60 mg (N=13)	80 mg (N=2)	
General Disorders and Administration Site Conditions	0	3 (11.1)	3 (11.5)	2 (9.5)	3 (23.1)	0	10 (34.5)
Chest Pain	0	2 (7.4)	1 (3.8)	1 (4.8)	1 (7.7)	0	5 (17.2)
Fatigue	0	1 (3.7)	0	0	2 (15.4)	0	3 (10.3)
Pyrexia	0	1 (3.7)	1 (3.8)	0	1 (7.7)	0	3 (10.3)
Nervous System Disorders	2 (6.9)	1 (3.7)	2 (7.7)	2 (9.5)	1 (7.7)	0	7 (24.1)
Dizziness	1 (3.4)	0	1 (3.8)	1 (4.8)	1 (7.7)	0	3 (10.3)
Headache	0	0	2 (7.7)	1 (4.8)	0	0	3 (10.3)
Cardiac Disorders	1 (3.4)	0	2 (7.7)	1 (4.8)	1 (7.7)	0	6 (20.7)
Angina Pectoris	1 (3.4)	0	1 (3.8)	1 (4.8)	0	0	3 (10.3)
Respiratory, Thoracic and Mediastinal Disorders	3 (10.3)	1 (3.7)	3 (11.5)	1 (4.8)	1 (7.7)	0	6 (20.7)
Nasal Congestion	1 (3.4)	1 (3.7)	0	1 (4.8)	0	0	3 (10.3)
Pharyngolaryngeal Pain	1 (3.4)	0	1 (3.8)	0	1 (7.7)	0	3 (10.3)

Source: Table 14.3.1.4.1

¹ Patients may be counted more than once across lomitapide dose levels as the TEAEs are tabulated by dose at onset and patients were escalated through the dose levels to achieve maximum tolerated dose. The All Patients column includes overall incidence with patients counted only once if they experienced the event.

Source: HoFH-pivotal CSR, Table 25.

Reviewer Comments:

1. *Combining these data with observations from the narratives, gastrointestinal adverse events (especially diarrhea, nausea/vomiting, dyspepsia) appear to be dose-related.*
2. *The “infections and infestations” SOC appears to show an association with dose, but I suspect this may be a result of the bias described previously; i.e., subjects who achieved the 60 mg dose were also in the trial for the longest period of time. Given that this was a 78-week study, it is not surprising that the cumulative incidence of nasopharyngitis, etc. increased during this time period. Attempting to determine whether these types of events are related to lomitapide requires pure speculation in the absence of a control group.*

The applicant tabulated common adverse events across lomitapide dose groups from their phase 1/2 “elevated LDL-C and other risk factors” safety pool. Recall that these 7 trials (two phase 1 and five phase 2) were heterogeneous with regard to doses used and durations; for example, the 62-subject high-dose lomitapide group provides 8.5 person-exposure years (PEYs), but the modestly larger 77-subject escalated-dose group provides more than double this exposure (20.4 PEYs) as a result of differences in the durations of trials comprising these groups. The trials included in each dose group are summarized in Section 7.1.3 (p. 154).

Counts and simple incidences of treatment-emergent AEs reported by $\geq 5\%$ of subjects in any treatment group are summarized in Table 118. Because of the differences in exposure in each dose group, I have also included counts and incidence rates (per PEY) in Table 119.

Table 118. "Elevated LDL-C" Safety Pool – Incidence of Common AEs

PREFERRED TERM	LOMITAPIDE DOSE GROUP ¹				COMPARATOR	
	ESCALATED (5-10 MG) (N=77) N (%)	LOW DOSE (2.5-7.5 MG) (N=244) N (%)	MID DOSE (10 MG) (N=99) N (%)	HIGH DOSE (25-100 MG) (N=62) N (%)	PLACEBO (N=116) N (%)	ACTIVE CONTROL (N=78) N (%)
Diarrhoea	30 (39.0)	122 (50.0)	63 (63.6)	46 (74.2)	13 (11.2)	7 (9.0)
Nausea	9 (11.7)	46 (18.9)	36 (36.4)	19 (30.6)	4 (3.4)	5 (6.4)
Flatulence	9 (11.7)	27 (11.1)	9 (9.1)	12 (19.4)	7 (6.0)	2 (2.6)
Headache	4 (5.2)	28 (11.5)	4 (4.0)	7 (11.3)	13 (11.2)	4 (5.1)
Abdominal distension	4 (5.2)	19 (7.8)	8 (8.1)	8 (12.9)	4 (3.4)	6 (7.7)
Vomiting	6 (7.8)	15 (6.1)	8 (8.1)	7 (11.3)	3 (2.6)	0
Alanine aminotransferase increased	17 (22.1)	13 (5.3)	3 (3.0)	3 (4.8)	1 (0.9)	1 (1.3)
Dyspepsia	8 (10.4)	16 (6.6)	6 (6.1)	1 (1.6)	3 (2.6)	4 (5.1)
Abdominal pain upper	2 (2.6)	17 (7.0)	9 (9.1)	4 (6.5)	4 (3.4)	0
Abdominal pain	4 (5.2)	10 (4.1)	7 (7.1)	9 (14.5)	2 (1.7)	3 (3.8)
Fatigue	2 (2.6)	17 (7.0)	4 (4.0)	5 (8.1)	3 (2.6)	0
Aspartate aminotransferase increased	11 (14.3)	12 (4.9)	3 (3.0)	2 (3.2)	1 (0.9)	1 (1.3)
Constipation	5 (6.5)	12 (4.9)	0	1 (1.6)	4 (3.4)	3 (3.8)
Back pain	1 (1.3)	9 (3.7)	2 (2.0)	4 (6.5)	6 (5.2)	3 (3.8)
Nasopharyngitis	0	11 (4.5)	2 (2.0)	1 (1.6)	6 (5.2)	4 (5.1)
Abdominal discomfort	5 (6.5)	4 (1.6)	5 (5.1)	4 (6.5)	1 (0.9)	2 (2.6)
Decreased appetite	1 (1.3)	4 (1.6)	7 (7.1)	4 (6.5)	0	0
Dizziness	0	4 (1.6)	2 (2.0)	4 (6.5)	3 (2.6)	2 (2.6)
Eructation	4 (5.2)	0	4 (4.0)	2 (3.2)	1 (0.9)	0
Asthenia	0	4 (1.6)	1 (1.0)	4 (6.5)	0	0

Source: ISS, Table 42.

Common AEs = Treatment-emergent AEs reported in ≥5% of subjects in any treatment group.

¹ Includes subjects who received lomitapide with or without concomitant lipid-lowering drugs.**Table 119. "Elevated LDL-C" Safety Pool – Incidence Rates of Common AEs**

Preferred Term	Lomitapide						Active Control (N=78) n (per PEY)
	Titrated (5-10 mg) (N=77) n (per PEY)	Low Dose (2.5-7.5 mg) (N=244) n (per PEY)	Mid Dose (10 mg) (N=99) n (per PEY)	High Dose (25-100 mg) (N=62) n (per PEY)	Placebo (N=116) n (per PEY)		
Person Exposure Years (PEY)	20.42	64.46	18.75	8.52	24.53	19.75	
DIARRHOEA	30 (2.08)	122 (3.11)	63 (6.86)	46 (15.37)	13 (0.58)	7 (0.38)	
NAUSEA	9 (0.49)	46 (0.84)	36 (2.63)	19 (2.99)	4 (0.17)	5 (0.26)	
FLATULENCE	9 (0.49)	27 (0.46)	9 (0.51)	12 (1.67)	7 (0.30)	2 (0.10)	
HEADACHE	4 (0.20)	28 (0.48)	4 (0.22)	7 (0.90)	13 (0.58)	4 (0.21)	
ABDOMINAL DISTENSION	4 (0.21)	19 (0.31)	8 (0.44)	8 (1.05)	4 (0.17)	6 (0.32)	
VOMITING	6 (0.31)	15 (0.25)	8 (0.45)	7 (0.91)	3 (0.12)	0	
ALANINE AMINOTRANSFERASE INCREASED	17 (0.91)	13 (0.21)	3 (0.16)	3 (0.36)	1 (0.04)	1 (0.05)	
DYSPEPSIA	8 (0.42)	16 (0.27)	6 (0.34)	1 (0.12)	3 (0.13)	4 (0.21)	
ABDOMINAL PAIN UPPER	2 (0.10)	17 (0.28)	9 (0.52)	4 (0.49)	4 (0.17)	0	
ABDOMINAL PAIN	4 (0.20)	10 (0.16)	7 (0.39)	9 (1.19)	2 (0.08)	3 (0.16)	
FATIGUE	2 (0.10)	17 (0.28)	4 (0.22)	5 (0.63)	3 (0.12)	0	
ASPARTATE AMINOTRANSFERASE INCREASED	11 (0.57)	12 (0.19)	3 (0.16)	2 (0.24)	1 (0.04)	1 (0.05)	
CONSTIPATION	5 (0.26)	12 (0.19)	0	1 (0.12)	4 (0.17)	3 (0.16)	
BACK PAIN	1 (0.05)	9 (0.14)	2 (0.11)	4 (0.49)	6 (0.25)	3 (0.16)	
NASOPHARYNGITIS	0	11 (0.18)	2 (0.11)	1 (0.12)	6 (0.25)	4 (0.21)	
ABDOMINAL DISCOMFORT	5 (0.26)	4 (0.06)	5 (0.28)	4 (0.49)	1 (0.04)	2 (0.10)	
DECREASED APPETITE	1 (0.05)	4 (0.06)	7 (0.40)	4 (0.50)	0	0	
DIZZINESS	0	4 (0.06)	2 (0.11)	4 (0.50)	3 (0.12)	2 (0.10)	
ERUCTATION	4 (0.20)	0	4 (0.22)	2 (0.24)	1 (0.04)	0	
ASTHENIA	0	4 (0.06)	1 (0.05)	4 (0.49)	0	0	

Source: ISS, Table 1.2.3D

Common AEs = Treatment-emergent AEs reported in ≥5% of subjects in any treatment group.

¹ Includes subjects who received lomitapide with or without concomitant lipid-lowering drugs.

Reviewer Comment: The AE profile observed in this phase 1/2 pool is consistent with that described from the studies involving the HoFH population.

7.5.2 Time Dependency for Adverse Events

No attempts were made to analyze time dependency for adverse events because of the limitations described in Section 7.5.1.

7.5.3 Drug-Demographic Interactions

All subjects in the HoFH pool (HoFH-pilot and HoFH-pivotal) were younger than 65, 80% were white, 86% were not Hispanic or Latino, and 86% had a BMI <30 kg/m²; therefore, the applicant did not examine the incidence of adverse events across categories of these subgroups. Using laboratory data, maximum elevations of transaminases were similar between men and women in the HoFH pool.

The applicant performed subgroup analyses of adverse events in the “elevated LDL-C and other risk factors” study pool, which comprised two phase 1 and five phase 2 studies (see Section 7.1.1, p. 153). Recall that this pool consisted of trials using lower doses and much shorter durations than the phase 3 HoFH trial. Regarding common AEs (incidence ≥5%), there were no consistent differences in AE incidence across lomitapide dose categories by age (<65 vs. ≥65 years). The incidence of nausea was higher among women than men in all lomitapide dose groups but also in the active control group. Headache, flatulence, vomiting, and abdominal distension also had a higher incidence among females in all lomitapide dose groups; dyspepsia was more common among men (see Appendix Table 131). Meaningful differences in AEs were not consistently noted across dose groups by race subgroups (Caucasian vs. non-Caucasian). Ethnicity was not available for the majority of subjects, precluding analysis across this subgroup.

7.5.4 Drug-Disease Interactions

PK studies were conducted for hepatic impairment (based on Child-Pugh classification) and renal impairment (ESRD on hemodialysis). These comorbidities do not typically accompany HoFH, and no patients with hepatic or renal disease were enrolled in the pivotal trial. Furthermore, patients with abnormal transaminases, known hepatic steatosis or steatohepatitis, etc. were excluded. In addition, there were few subjects with obesity or type 2 diabetes, both of which are associated with hepatic steatosis. To what extent these patients are at higher risk for lomitapide-induced hepatotoxicity is unknown.

Hepatic Impairment

Aegerion sponsored an open-label study to compare the PK of single-dose lomitapide 60 mg between subjects with mild and moderate hepatic impairment and matched

subjects with normal hepatic function. Thirty-two subjects were assigned to one of the following 4 groups: mild hepatic impairment (Child-Pugh 5 or 6 [Class A]), moderate hepatic impairment (Child-Pugh 7 to 9 [Class B]), healthy subjects matched to mild impairment group, and healthy subjects matched to moderate impairment group. Table 120 describes the Child-Pugh scoring system. Healthy subjects were matched with respect to gender, age (± 5 years), and body mass index ($\pm 15\%$). Control subjects had normal values for ALT, AST, GGT, and total bilirubin.

Table 120. Child-Pugh Scoring System

	Points Scored for Observed Findings:		
	1	2	3
Encephalopathy grade ^a	0	1 or 2	3 or 4
Ascites ^b	absent	slight	moderate
Serum total bilirubin (mg/dL)	<2	2 to 3	>3
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
INR ^c	<1.7	1.7 to 2.3	>2.3
Prothrombin time (seconds prolonged) ^c	<4	4 to 6	>6

^aGrade 0: normal consciousness, personality, neurological examination. Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves. Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves. Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves. Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cycles per second delta activity.

^b slight = diuretic responsive ascites; moderate = diuretic refractory ascites.

^c International Normalized Ratio (INR) as primary classification. Prothrombin time as secondary classification.

Source for INR: <http://depts.washington.edu/uwhep/calculations/childspugh.htm>. Accessed on 27 April 2011.

Source: AEGR-733-017 CSR, Table 9-2.

Following an overnight fast from food of approximately 8 hours, subjects received a single dose of lomitapide 60 mg (3 x 20 mg capsules). PK blood sampling (lomitapide and metabolites M1 and M3) was performed pre-dose and 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 168, and 216 hours post-dose.

Overall, the mean (SD) age was 52 (6) years, 24 (75%) were men, and 27 (84%) were white, 4 (13%) black, and 1 (3%) Mid-Eastern Indian; 14 (44%) were Hispanic or Latino.

Figure 56 and Figure 57 show the geometric mean plasma concentrations of lomitapide following single-oral dose administration of lomitapide 60 mg to subjects with mild and moderate hepatic impairment (with matched healthy controls), respectively.

Mild Hepatic Impairment: Mean (90% CI) C_{max} and AUC_{inf} values among those with mild hepatic impairment were 104% (58% to 185%) and 147% (100% to 216%) of matched control values, respectively (Figure 56). In addition, mean $t_{1/2}$ was 12 hours longer among those with mild impairment (68.0 hours vs. 80.1 hours).

Moderate Hepatic Impairment: Mean (90% CI) C_{max} and AUC_{inf} values among those with moderate hepatic impairment were 461% (258% to 823%) and 264% (178% to 392%) of matched control values, respectively (Figure 57). Mean $t_{1/2}$ was not

significantly different with moderate impairment (74.6 hours vs. 75.8 hours in controls and moderate impairment, respectively).

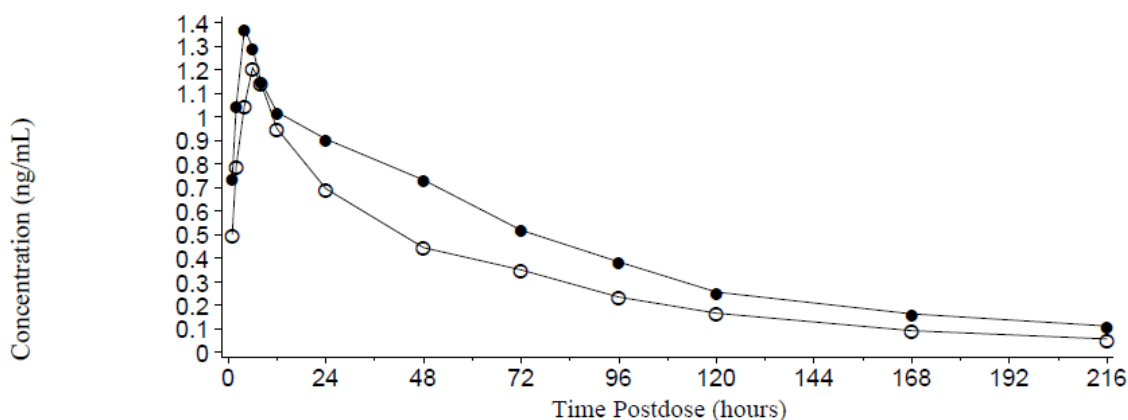


Figure 56. Lomitapide Concentration-Time Profile with Mild Hepatic Impairment

Source: AEGR-733-017 CSR, Figure 11-1.

Filled circles = mild hepatic impairment; open circles = matched controls.

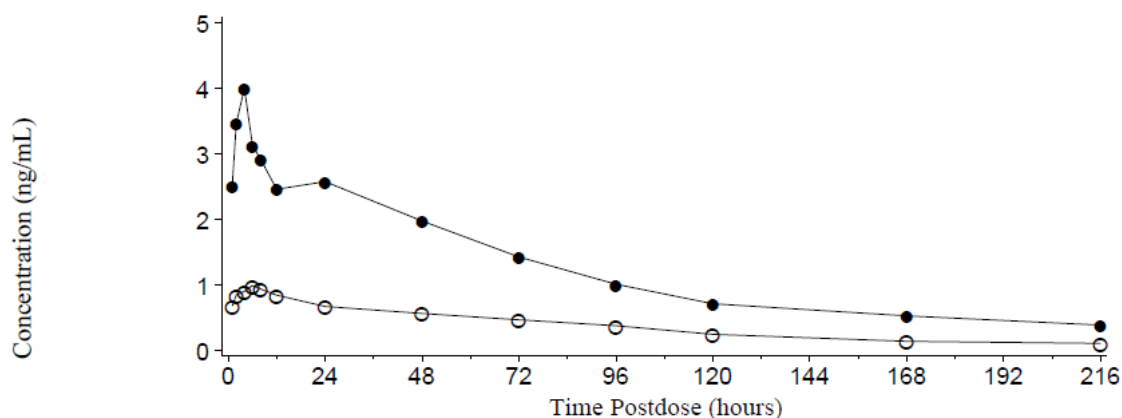


Figure 57. Lomitapide Concentration-Time Profile with Moderate Hepatic Impairment

Source: AEGR-733-017 CSR, Figure 11-2.

Filled circles = mild hepatic impairment; open circles = matched controls.

Similarly, impaired hepatic function had a statistically significant effect on the exposure to the M1 and M3 lomitapide metabolites. See the Clinical Pharmacology review by Dr. Johnny Lau for further details.

There were no SAEs. Seven subjects (2 hepatic impairment; 5 controls) reported a total of 12 AEs (4 in hepatic impairment, 8 in controls). Adverse events reported by 2 subjects included abdominal pain, myalgia, and headache. All other AEs were reported by only 1 subject each.

For labeling, the applicant proposes “No adjustment to the dosage regimen is recommended for patients with mild hepatic impairment. TRADENAME is contraindicated in patients with moderate or severe hepatic impairment and patients

with active liver disease including those with unexplained persistent abnormal liver function tests.”

Reviewer Comment: Although these studies demonstrate an effect of functional hepatic impairment, as measured by the Child-Pugh scoring system, on lomitapide PK, these data do not inform dosing recommendations for subjects with baseline liver-related abnormalities (e.g., elevated transaminases, known NAFLD, etc.) with preserved liver function.

End-stage Renal Disease

Aegerion sponsored an open-label study to compare the PK of single-dose lomitapide 60 mg between subjects with end-stage renal disease (ESRD) on hemodialysis and matched healthy subjects (AEGR-733-021). Seven subjects in each of 2 groups were enrolled: (1) subjects with ESRD on hemodialysis, and (2) healthy subjects with estimated creatinine clearance (Cockcroft-Gault) ≥ 80 mL/min. Healthy subjects were matched with respect to gender, age (± 10 years), and body mass index ($\pm 15\%$). On Day 1, subjects received a single dose of lomitapide 60 mg (3 x 20-mg capsules). ESRD subjects received the dose within 2 hours of completing hemodialysis, with the next hemodialysis session planned approximately 72 hours of study drug administration.

Fourteen subjects enrolled (7 per group) and one ESRD subject withdrew for an unstated reason on Day 3. Overall, the mean (SD) age was 36 (12) years, 10 (71%) were men, and 6 (43%) were white, 6 (43%) black, and 2 (14%) multi-racial; one was Hispanic or Latino. Mean (SD) BMI was 27.0 (6.1) kg/m².

Figure 58 shows the geometric mean plasma concentrations of lomitapide following single-oral dose administration of lomitapide 60 mg to subjects with ESRD and matched healthy controls.

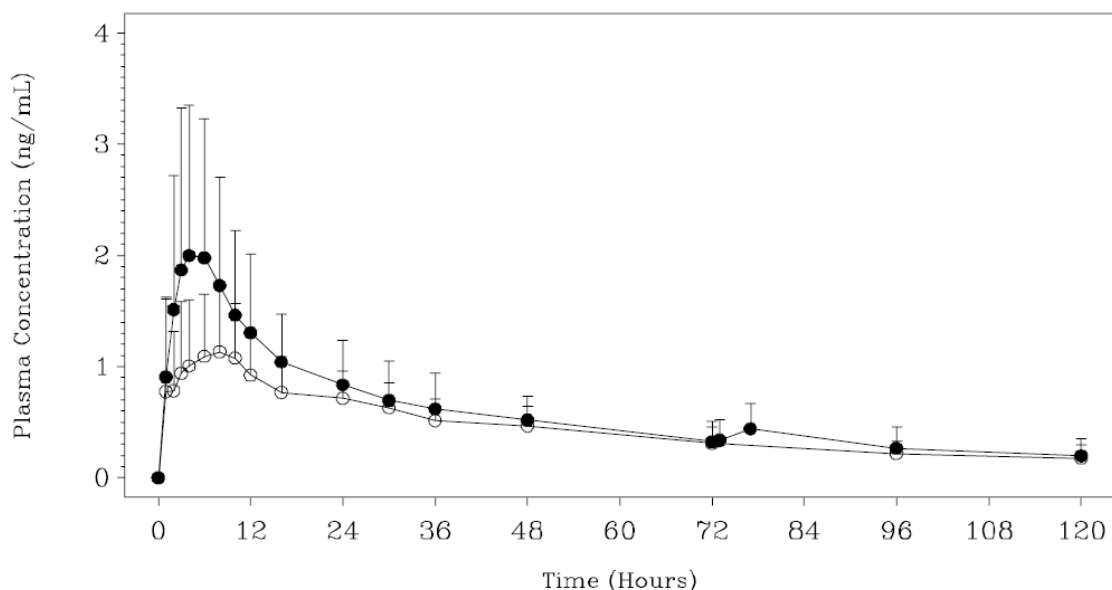


Figure 58. Lomitapide Concentration-Time Profile with ESRD

Source: AEGR-733-019 CSR, Figure 11-1.

ESRD: Mean (90% CI) C_{max} and AUC_{0-72} values among those with ESRD were 151% (84% to 270%) and 140% (100% to 194%) of matched control values, respectively. (AUC_{0-t} and AUC_{inf} showed similar increases.) Furthermore, ESRD was associated with higher levels of the M1, but not the M3, metabolite (C_{max} 4.69 vs. 2.26 ng/mL; AUC_{0-72} 170.56 vs. 61.85 ng•hr/mL).

There were no SAEs. Three healthy subjects reported 3 AEs (headache, nausea, and rash); one subject on ESRD reported orthostatic hypotension.

In part, the applicant's conclusion regarding these study results states:

Although the differences observed crossed the pre-defined statistical criteria in the study protocol, these observations are not considered to be clinically important. The pharmacological activity of lomitapide is limited to the gastrointestinal tract and liver, consistent with the indirect PK/pharmacodynamic model developed by Bristol-Myers Squibb in the rat model. As a result, the observed increase in AUC and C_{max} of 40% to 50% is not considered clinically important since the impact is confined to a systemic compartment in which the drug does not have pharmacological effect and is present at very low concentration. Also, the rise in lomitapide plasma concentration observed immediately after dialysis is suggestive of hemoconcentration, which may partially explain the increase in lomitapide plasma concentrations. Finally, any impact of renal function on systemic pharmacokinetics would be mitigated by the adjustment in dosing over time, designed to accommodate individual patient responsiveness in terms of efficacy and safety. Therefore, no change in the dosing regimen for lomitapide is suggested for patients with renal impairment. Based on the fact that the differences observed in lomitapide pharmacokinetics in subjects with ESRD are considered not to

be clinically meaningful, no further clinical evaluations are planned in this patient population.

Reviewer Comments:

- 1. The applicant's conclusion that the pharmacological activity of lomitapide is limited to the gastrointestinal tract and liver, and therefore the increases in the systemic compartment are not relevant, is unconvincing.*
- 2. Fluid shifts between body compartments and plasma occur during, and immediately following, hemodialysis. Apparently, the applicant is speculating that the reduced plasma volume (more appropriately, volume of distribution) immediately following hemodialysis – when lomitapide was administered in this study – may be responsible for the increase in C_{max} and AUC. The applicant does not consider, however, that the redistribution of fluid to the plasma space after hemodialysis could potentially lower plasma concentrations of lomitapide. Therefore, one should not conclude that hemodialysis-related factors caused the observed increase in lomitapide exposure.*
- 3. The applicant's last argument that any impact of renal function on systemic PK could be mitigated by dose adjustments over time is the most tenable, in my opinion. At the proposed starting dose of 5 mg daily, the observed increases in systemic exposure would not be expected to be problematic. If one titrates to effect on LDL-C and tolerability, with appropriate liver-related safety monitoring, the increases in exposure related to reduced renal function seem manageable. Consideration could be given to limiting the maximum dose in renal impairment, however.*

7.5.5 Drug-Drug Interactions

The lomitapide development program included one study of the effect of food on lomitapide bioavailability, sponsored by BMS in 1997, and five drug-drug interaction (DDI) studies, sponsored by Aegerion. The primary results from these studies are summarized below. These data derive primarily from the applicant's presentation of results. See the Clinical Pharmacology review by Dr. Johnny Lau for further information.

Food: CV145-005 was a single-site, phase 1, randomized, open-label, 3-way crossover study involving 25 healthy volunteers (24 completed) sponsored by BMS in 1997. Subjects were randomly assigned to 6 treatment sequences of 4 subjects each to receive a single dose of lomitapide 50 mg orally on day 1 following either an overnight fast or 5 minutes after the completion of a low-fat or high-fat breakfast. Table 121 summarizes the relevant comparisons, showing statistically significant increases in lomitapide exposure (up to 77% and 58% increases in C_{max} and AUC, respectively) with a high-fat breakfast compared with fasting. No food effect on T_{max} was detected (not shown).

Table 121. Effect of Low- and High-Fat Breakfast on Lomitapide PK (CV145-005)

Comparison	C_{max}	AUC _{0-τ}

	Ratio of Geo. Means (90% CI)	P	Ratio of Geo. Means (90% CI)	P
Low-fat vs. Fasted	1.70 (1.39 to 2.07)	<0.001	1.28 (1.08 to 1.51)	0.02
High-fat vs. Fasted	1.77 (1.46 to 2.16)	<0.001	1.58 (1.33 to 1.87)	<0.001
High-fat vs. low-fat	1.05 (0.86 to 1.27)	0.71	1.24 (1.04 to 1.46)	0.04

Source: CV145-005 CSR, Table 11.6.1.

Gastrointestinal adverse events were most common following dosing with a high-fat breakfast. Eight (33%) of 24 subjects reported 12 gastrointestinal events in the fasted condition; 9 (36%) of 25 subjects reported 14 gastrointestinal events with a low-fat breakfast; and 16 (67%) of 24 subjects reported 34 gastrointestinal events with a high-fat breakfast (Table 122).

Table 122. CV145-005 – Gastrointestinal Adverse Events

Primary Term	Fasted (n=24)	Low-fat (n=25)	High-fat (n=24)
Abdominal pain	2 (8%)	1 (4%)	2 (8%)
Decreased appetite	0	0	1 (4%)
Dental abnormal	0	0	1 (4%)
Diarrhea	2 (8%)	5 (20%)	12 (50%)
Distention abdomen	0	2 (8%)	1 (4%)
Dry mouth	1 (4%)	0	0
Dyspepsia/heartburn	2 (8%)	1 (4%)	2 (8%)
Epigastric pain	0	0	1 (4%)
Flatulence	2 (8%)	4 (16%)	4 (17%)
Nausea/vomiting	3 (13%)	1 (4%)	10 (42%)
Total Events	12	14	34
Total Subjects	8 (33%)	9 (36%)	16 (67%)

Source: CV145-005 CSR, Appendix 12.1.3.

Reviewer Comment: These data suggest a statistically significant, and potentially clinically important, increase in lomitapide exposure with food. This study was conducted, however, using a 50-mg formulation of lomitapide that is qualitatively, but not quantitatively, similar to contemporary formulations. Therefore, the effect of food on the final formulations to be marketed has not been established.

In the HoFH phase 3 pivotal trial, the protocol did not specify when lomitapide was to be taken with regard to time of day or meals. In their 07 September 2012 response to an FDA information request, the applicant stated that subjects in the pivotal trial were advised to take the drug in the evening at least 2 hours after dinner; this instruction was provided with guidelines provided to each subject at the start of the study. Using the PK dataset from the pivotal trial, which includes time-of-last-dose prior to each clinic visit, approximately 80% of records indicated that the study drug was taken between 6pm and 11pm.

In their proposed label, the applicant suggests that lomitapide be administered once daily at bedtime, with a glass of water and without food. Their rationale is based

on the increased incidence of GI adverse events when lomitapide was administered with a high-fat meal in this food-effect study.

AEGR-733-002 was a single-center, phase 2, open-label, fixed-sequence (*not randomized*) study to evaluate the potential effects of lomitapide on CYP3A4 and 2D6 and on the PK of commonly prescribed lipid-lowering drugs in healthy volunteers. Subjects took a single dose of the probe drug and then initiated seven daily doses of lomitapide 10 mg; the effect of lomitapide 60 mg daily was also investigated with atorvastatin and rosuvastatin. The seventh dose of lomitapide was taken in the clinic on Day 8 along with the second dose of the probe drug. The results are summarized below and in Appendix Table 132.

Atorvastatin 20 mg: Lomitapide 10 mg and 60 mg daily increased atorvastatin C_{max} by 12% and 38% for the sum of active atorvastatin moieties, respectively. The effects on AUC were less, with increases of 5% and 29% for the low and high lomitapide dosages, respectively.

Simvastatin 20 mg: Lomitapide 10 mg daily increased simvastatin acid C_{max} and AUC by 35% and 39%, respectively, and increased simvastatin lactone C_{max} and AUC both by approximately 65%.

Rosuvastatin 20 mg: No significant effects of lomitapide 10 mg daily on rosuvastatin exposure were detected, but lomitapide 60 mg daily increased rosuvastatin AUC by 32% with a decrease in the rate of absorption (delayed T_{max}) and no significant change to C_{max} .

Ezetimibe 10 mg: No significant effects of lomitapide 10 mg daily on total, conjugated, and unconjugated ezetimibe exposure were detected.

Niacin extended-release 1000 mg: Lomitapide 10 mg daily increased the AUC of the N-methylnicotinamide metabolite by 36%, but no other changes to C_{max} or AUC of niacin metabolites were detected.

Micronized Fenofibrate 145 mg: Lomitapide 10 mg daily reduced the C_{max} and AUC of fenofibric acid by 30% and 10%, respectively.

Dextromethorphan 30 mg (CYP2D6 probe): No significant effects of lomitapide 10 mg daily on the urine log(Dm/Dx) ratio were detected.

There were no SAEs in AEGR-733-002. Overall, 87 (67%) of the 129 subjects experienced a total of 246 adverse events. The most common AE was diarrhea (26% of subjects), which was associated with lomitapide dosage (0-30% of subjects in the groups receiving lomitapide 10 mg daily, and 27-56% of subjects in the groups receiving lomitapide 60 mg daily).

Because the maximum dose of lomitapide to be administered to patients is 60 mg and because both lomitapide and simvastatin are CYP3A4 substrates, Aegerion sponsored an open-label study (AEGR-733-019) to evaluate the effects of lomitapide 60 mg daily, at steady state, on the PK of single-dose simvastatin 40 mg in 16 healthy subjects (15 completed).

Simvastatin 40 mg: Lomitapide 60 mg daily increased both the C_{max} and AUC_{inf} of simvastatin by approximately 2-fold, and increased the C_{max} and AUC_{inf} of simvastatin acid by 1.6-fold and 1.7-fold, respectively.

There were no SAEs in study AEGR-733-019. One subject was withdrawn because of a pruritic rash on his forearm, abdomen, and thighs, which the investigator thought possibly related to lomitapide. This occurred 1-2 hours after the first dose of lomitapide. One subject had an ALT level $>3x$ ULN. This subject had a baseline ALT and AST of 35 and 31 IU/L, respectively. At study completion (Day 16), ALT and AST were 84 and 85 IU/L, respectively. At an unscheduled follow-up visit on Day 30, ALT and AST were 227 IU/L ($3x$ ULN) and 108 IU/L; these returned to within the reference range at a second unscheduled visit on Day 41.

Reviewer Comment: The increase in simvastatin exposure as a result of co-administration of lomitapide 60 mg is important for labeling, if lomitapide is approved. Based on data in this drug-drug interaction study, I would favor that simvastatin dosage be kept <40 mg daily to avoid exposure equivalent to simvastatin 80 mg daily.

Warfarin: In 2010, Aegerion sponsored an open-label, two-period sequential study in 16 healthy male subjects to evaluate the effects of lomitapide on the PK of warfarin stereoisomers and PD (assessed by AUC_{INR} and INR_{max}) (AEGR-733-013). Lomitapide 60 mg daily led to statistically significant increases exposure to both warfarin R(+) and S(-). For warfarin R(+), C_{max} increased by 14% (90% CI, 7% to 21%) and AUC_{inf} increased by 28% (90% CI, 22% to 34%). Similarly, for warfarin S(-), C_{max} increased by 15% (90% CI, 6% to 25%) and AUC_{inf} increased by 30% (90% CI, 25% to 36%).

Compared with warfarin administered alone, co-administration of lomitapide 60 mg daily led to statistically significant increases in measures of pharmacodynamics: INR_{max} increased by 22% (90% CI, 14% to 32%) and AUC_{INR} increased by 7% (90% CI, 4% to 10%). The effect of co-administration on INR is depicted graphically in Figure 59.

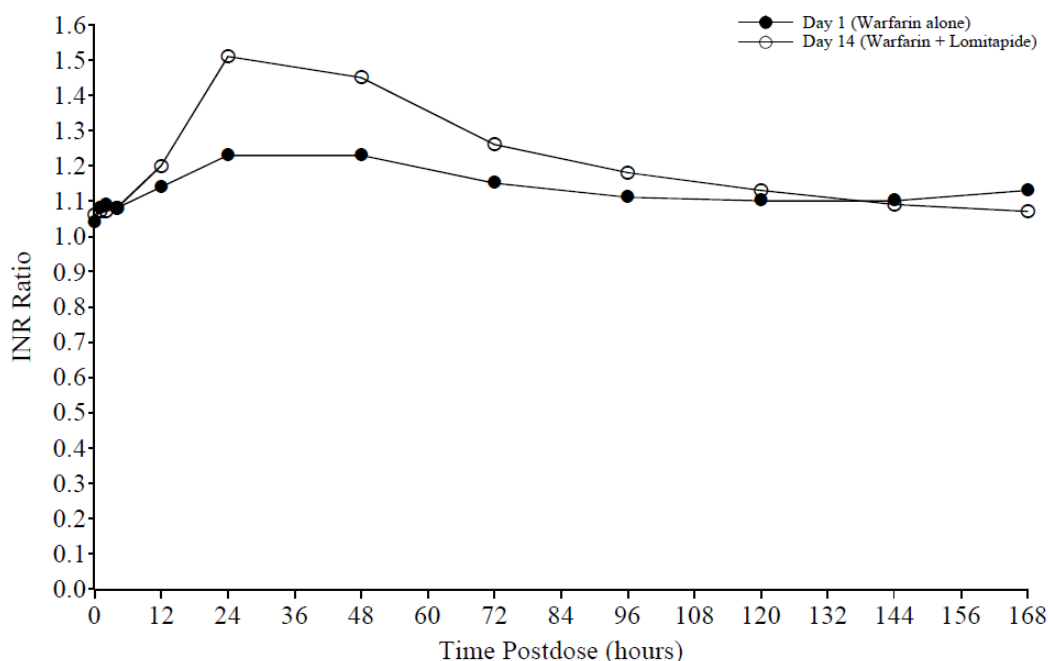


Figure 59. Lomitapide-Warfarin Co-administration – Effect on INR

Source: AEGR-733-013 CSR, Figure 11-4.

There were no SAEs in study AEGR-733-013. Six (38%) of 16 subjects reported 17 “mild” adverse events during lomitapide treatment in this study. These events included rhinitis, headache, chapped lips, and cough.

Reviewer Comment: The interaction between warfarin and lomitapide will need to be addressed in labeling if lomitapide is approved. One subject in HoFH-pivotal discontinued because of unstable INR and one subject had several SAEs in the HoFH extension study related to bleeding and/or anticoagulation, suggesting that this drug-drug interaction might not be inconsequential.

Oral Contraceptives: Aegerion sponsored a randomized, double-blind, three-period, two-way crossover study in 28 healthy female subjects to evaluate the effects of lomitapide 50 mg, at steady state, on the PK of the oral contraceptive Ortho Cyclen[®] (OC; ethinyl estradiol [EE]/norgestimate) (AEGR-733-015).

Ethinyl estradiol: For EE, the point estimates (90% CI) of the geometric mean ratios of OC+lomitapide vs. OC+placebo were 92% (86% to 98%) for C_{max} and 92% (87% to 97%) for AUC_{0-t} .

Norgestimate: For 17-deacetyl norgestimate, the point estimates (90% CI) of the geometric mean ratios of OC+lomitapide vs. OC+placebo were 102% (97% to 107%) for C_{max} and 106% (102% to 109%) for AUC_{0-t} .

There were no SAEs in study AEGR-733-015. During treatment with OC alone, 12 (44%) of 27 subjects reported 38 mild AEs; with OC + Placebo, 13 (50%) of 26 subjects

reported 38 mild AEs; with OC + lomitapide, 12 (44%) of 27 subjects reported 21 mild AEs. The only adverse event reported by at least 2 subjects that was more common the OC+lomitapide period than the other periods was nausea.

Reviewer Comment: These data do not suggest clinically significant changes in the PK of OC with co-administration of lomitapide 50 mg daily, but it seems that PK could be altered among patients who develop diarrhea as a result of reduced absorption. Diarrhea was only reported by one subject during the OC+lomitapide period in this study. Given that lomitapide is a potential human teratogen based on nonclinical data, women who develop gastrointestinal side effects should not rely on oral contraception alone.

Ketoconazole: Aegerion sponsored an open-label, non-randomized study to evaluate the effects of the strong CYP3A4 inhibitor ketoconazole on the single-dose PK of lomitapide 60 mg in 30 healthy volunteers (28 completed) (AEGR-733-018). Ketoconazole markedly increased lomitapide exposure (Figure 60). The geometric mean C_{max} and AUC_{inf} of lomitapide increased approximately 15-fold and 27-fold, respectively, with ketoconazole coadministration. In addition, the half-life of lomitapide was prolonged from 39.0 hours to 63.7 hours (~60% increase).

There were no SAEs. One subject withdrew because of vomiting thought possibly related to ketoconazole (lomitapide had not yet been administered). Following the first single dose of lomitapide (without ketoconazole), 8 (27%) of 30 subjects reported 24 AEs. Following the second single dose of lomitapide (with ketoconazole), 16 (57%) of 28 subjects reported 138 AEs. Gastrointestinal AEs were more common with co-administration of ketoconazole, including diarrhea (32%), nausea (25%), abdominal pain (11%), eructation (18%), dry lips (14%), and vomiting (7%). In addition, pruritus (25%), headache (18%), dizziness (14%), decreased appetite (11%), rash (11%), xeroderma (7%), asthenia (7%), and vaginal discharge (7%) occurred more often following the second dose of lomitapide.

Regarding safety laboratories, following the second dose of lomitapide (i.e., with ketoconazole), only one set of safety laboratories was drawn 7 days later. Given the concern regarding transaminase elevations with lomitapide, I note that there were no elevated ALT levels at this time point (range 10 to 47 IU/L).

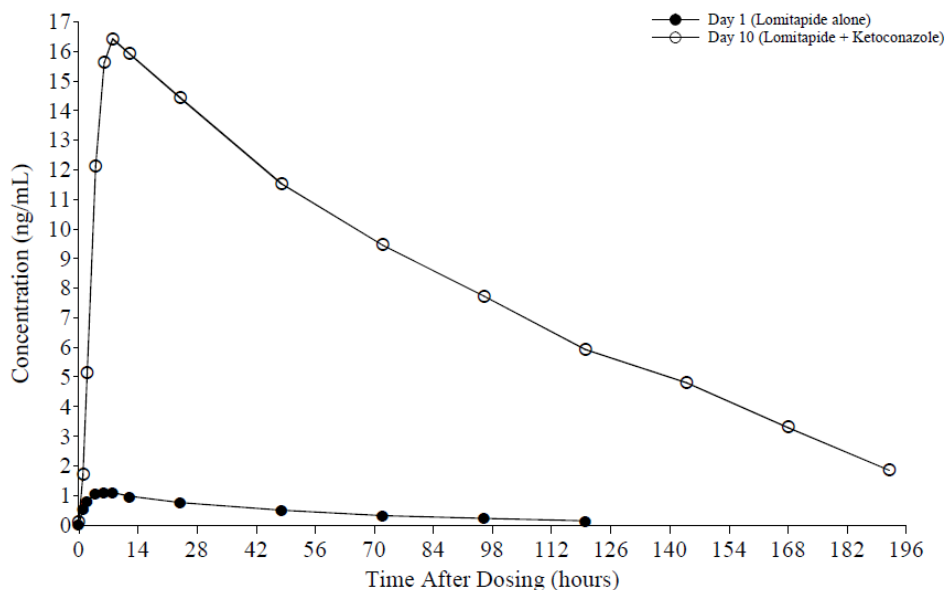


Figure 60. Effect of Ketoconazole on Lomitapide Concentration
Source: AEGR-733-018 CSR, Figure 11-1.

Reviewer Comment: Strong CYP3A4 inhibitors should be avoided with lomitapide given this marked drug-drug interaction. The applicant has not investigated the effects of weaker CYP4A4 inhibitors, however, which may be more commonly prescribed and less-often recognized by clinicians for their drug-drug interaction potential.

The applicant’s proposed labeling includes the following text under CONTRAINDICATIONS: “Concomitant use of [lomitapide] with moderate CYP3A4 inhibitors (e.g., diltiazem, fluconazole, erythromycin) or strong CYP3A4 inhibitors (e.g., antifungal azoles such as itraconazole or ketoconazole; macrolide antibiotics such as erythromycin or clarithromycin; ketolide antibiotics such as telithromycin; HIV protease inhibitors; or the antidepressant nefazodone.”

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There have been no reports of cancer in the lomitapide development program, but this is not reassuring given the limited size and duration of the clinical trials. See Section 7.3.5 (p. 213) for additional discussion.

7.6.2 Human Reproduction and Pregnancy Data

One HoFH subject in the lomitapide development program suspended therapy with lomitapide to plan a pregnancy. Her last dose of lomitapide treatment was 19 October 2010 and she became pregnant in January 2011. She had a normal delivery of a baby who appears healthy at present. The mother is not breastfeeding. The applicant reports that she restarted lomitapide 5 mg daily on 19 May 2012.

7.6.3 Pediatrics and Assessment of Effects on Growth

Lomitapide has not been studied in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose of lomitapide has not been reported. Lomitapide is not believed to have potential for drug abuse, and withdrawal/rebound effects have not been described.

7.7 Additional Submissions / Safety Issues

Data from the 120-day safety update and from FDA information requests that occurred during the review have been integrated where appropriate.

8 Postmarket Experience

None.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

My major labeling recommendations include the following:

- I recommend a boxed warning for the risk of hepatotoxicity to be consistent with the “Warnings and Precautions, Contraindications, and Boxed Warning Guidance,” which states that a boxed warning is included in labeling when FDA approves a drug with restricted distribution to ensure safe use.
- Although lomitapide might reduce TG, hypertriglyceridemia is not a typical clinical feature of HoFH; the effect of reducing TG on clinical outcomes in HoFH is far from certain. I recommend removing this from the proposed indications. Given that there is a growing interest in following non-HDL-C, I would be in favor of adding non-HDL-C to the list of lipid parameter levels that lomitapide reduces.
- Given that lomitapide was studied only in 29 subjects with HoFH at sufficient doses and duration, I recommend adding the following limitation of use: “The safety and effectiveness of lomitapide have not been established in patients with hypercholesterolemia who do not have HoFH.”
- In general, I agree with the applicant’s proposed Dosage & Administration schedule, but this section will need to be reorganized for clarity. In addition, I agree that daily supplements of vitamin E and fatty acids should be taken as the applicant proposes. As I mentioned in the review, it is unknown what effect lomitapide would have on these nutrient levels in the absence of supplements, and the optimal doses of supplement components are not known, but supplementation as performed in the pivotal/extension trials is the best available option given the available data.
- Liver monitoring requires further discussion with our hepatology consultants. In general, I do not believe that prescriptive monitoring of liver fat should be specified in labeling since we cannot provide recommendations regarding when to modify or discontinue lomitapide for a given value (or change) in hepatic fat. One could consider measuring hepatic fat at baseline, but I do not believe that there is a hepatic fat level that would contraindicate one from attempting lomitapide for a patient with HoFH. One would have to suggest that liver monitoring (e.g., frequency) would be distinct for subjects with “high” levels of hepatic fat, but I would recommend monthly monitoring of liver-related tests for the first year even for patients with “low” levels of hepatic fat, and it would be unreasonable for routine monitoring to occur with greater frequency than this. Thus, I favor describing lomitapide-associated hepatic steatosis in labeling, along with the concern that it may lead to chronic liver disease, and allow practicing physicians to incorporate liver imaging into their individual management plans.
- I suggest revising the contraindications to include: Pregnancy, Concomitant administration with moderate or strong CYP3A inhibitors, and Moderate or

severe hepatic impairment (i.e., Child-Pugh B and C) and patients with active liver disease). The applicant proposed additional contraindications, which I suggest incorporating elsewhere in the label for the following reasons:

- *Patients with a known significant or chronic bowel disease such as inflammatory bowel disease or malabsorption.* This is a theoretical risk. Chronic bowel diseases, including inflammatory bowel disease (e.g., ulcerative colitis), may not predispose to fat-soluble nutrient deficiency; therefore, for patients with HoFH and these conditions, benefit could certainly overcome the putative risk. Although I agree that patients with “malabsorption” may be at higher risk for these deficiencies, it is possible that increased supplementation may overcome the underlying problem depending on its severity. Thus, I recommend removing this as a contraindication and placing relevant text into the Warnings & Precautions section where the effect of lomitapide on fat-soluble nutrients should be discussed.
- *Concomitant administration of ≥ 80 mg simvastatin.* First, since lomitapide roughly doubles simvastatin exposure, patients should limit to 20 mg simvastatin or, in cases where they have already tolerated 80 mg simvastatin monotherapy for at least a year, they should limit to 40 mg simvastatin. These dose caps for simvastatin, however, do not belong in the Contraindications section; one could argue that they truly belong in simvastatin labeling since they describe simvastatin dosing instructions. Regardless, if they are to be included in the lomitapide labeling, I would place in Warnings & Precautions and Drug Interactions.
- *Patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency, or glucose-galactose malabsorption.* This contraindication stems from the EMA guidelines (volume 3B) that address excipients in the label. The EMA guidelines state that for products containing lactose (<5 g), the proposal for the Summary of Product Characteristics (SPC) is “Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.” This warning does *not* apply to individuals who have typical “lactose intolerance,” as they can typically tolerate 12-15 grams of lactose with minimal (or no) symptoms. Lomitapide contains 73.81 mg lactose per 5 mg capsule, 147.62 mg per 10 mg capsule, and 136.73 mg lactose per 20 mg capsule; therefore, the dose of lactose will remain well under 1 gram daily. The target population for this risk is those with congenital glucose-galactose malabsorption, which appears to have been described in approximately 300 individuals worldwide. These individuals typically have symptom onset within the first days of life because infants cannot tolerate milk, leading to extreme osmotic diarrhea, acidosis, volume depletion, and their consequences. I did find one drug (Zortress [everolimus]) that contains this statement in the Warnings & Precautions section of U.S. labeling, and I would agree with this approach. I have not found other drugs with this statement listed as a Contraindication. Individuals with this severe, rare disorder from birth

would be well aware of checking all labels for lactose, and it appears that the initial symptoms would be osmotic diarrhea if lomitapide were taken by an affected individual, leading to osmotic diarrhea that would prompt discontinuation.

- I suggest the following Warnings & Precautions: (1) Risk of hepatotoxicity (both elevated transaminases and hepatic steatosis); (2) Potential for embryo-fetal toxicity based on nonclinical data; (3) Reduced absorption of fat-soluble vitamins and serum fatty acids; (4) Gastrointestinal adverse reactions (given their nearly universal occurrence); (5) Drug-drug interaction with CYP3A inhibitors; (6) Potential for increased risk of myopathy with concomitant simvastatin (based on lomitapide increasing simvastatin exposure); (7) Drug-drug interaction with warfarin; and (8) use in individuals with rare hereditary disorders of glucose-galactose metabolism as discussed above.
- Adverse reaction incidences require updating based on 78-week data, and some minor discrepancies in subject counts between my review of the final AE dataset and the 120-day safety update will require clarification.

-  (b) (4)

- Clinical Pharmacology input is required for the many drug-drug interactions (especially CYP3A) identified.
- In the Clinical Studies section, additional detail is required regarding the trial and demographics; the figure depicting LDL-C over time could be improved (error bars, adding mean dose at each visit given the dose-titration regimen, using completers population);  (b) (4)



9.3 Advisory Committee Meeting

The efficacy and safety of lomitapide mesylate for HoFH was discussed with the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) on 17 October 2012. Meeting materials, slides, and transcripts can be found at www.fda.gov. A brief summary of the discussion and voting questions follows.

Discussion question #1 asked the committee to discuss whether the applicant has provided adequate evidence to support the efficacy of lomitapide (up to 60 mg per day) as an adjunct to a low-fat diet and other lipid-lowering drugs for the reduction of LDL-C

in patients with HoFH. The committee agreed that even though the phase 3 trial was uncontrolled and very small, the applicant provided adequate evidence to support a claim in this population.

Discussion question #2 asked the committee to provide an assessment of lomitapide's effect on HDL-C, TG, apo B, apo AI, and Lp(a). The committee noted that lomitapide's effects on all but HDL-C were in clinically desirable directions, and that the decrease in HDL-C was not worrisome, especially for this population that is characterized by extremely high LDL-C. The return of HDL-C to baseline provided some reassurance as well.

Discussion question #3 asked the committee to discuss whether LDL-C is an appropriate surrogate for reduced CV morbidity and mortality in lomitapide-treated patients with HoFH. The committee agreed that LDL-C was an appropriate surrogate for this orphan population, emphasizing that this recommendation was specific to the HoFH population.

Discussion question #4 asked the committee to discuss the liver-related effects observed in the lomitapide development program, including transaminase abnormalities and hepatic steatosis, and to discuss any concern regarding a possible association between hepatic steatosis and increased risk for CV morbidity and mortality. The committee expressed a moderate to high level of concern for the liver-related effects of lomitapide. The committee warned that the magnitude of transaminase elevations observed seems higher than one would expect from hepatic steatosis alone, suggesting the possibility of an alternative cause of the elevations. Although it was somewhat reassuring to the committee that transaminase levels and hepatic steatosis reversed when lomitapide was discontinued, they stressed that there is insufficient information regarding its long-term effects. Last, the committee was not concerned about a hypothetical link between hepatic steatosis and increased risk for CV morbidity/mortality.

Discussion question #4 also asked the committee to discuss monitoring for liver-related adverse effects, dosing recommendations based on quantitative thresholds of transaminase elevations or changes in hepatic steatosis, and population-based approaches to further characterize and assess liver safety post-approval. Although recommendations were heterogeneous, there was general consensus that full liver panels should be followed rather than only transaminases (i.e., include bilirubin, alkaline phosphatase, consider GGT). The committee expressed concerns about the variability in upper limits of normal across laboratories and suggested that absolute values are used instead (e.g., assuming 30 IU/L is the upper limit of normal for ALT, one might make a recommendation for dose reduction at 90 IU/L and for drug interruption at 150 IU/L. Regarding imaging of hepatic fat, a hepatologist stated that non-contrast MRI would need to be used, as ultrasound and CT are not quantitative. There was no agreement with regard to what level of hepatic fat might prompt changes to the dosing regimen or stopping the drug entirely. Some cautioned that the progression of liver disease is distinct in adults and children, and one might consider restricting lomitapide

to adults via the REMS. The committee acknowledged that there are a lot of uncertainties with regard to the liver risk, and that a liver-related death should be expected in the post-market setting.

Discussion question #5 asked the committee to discuss whether the applicant has sufficiently characterized the risk for deficiencies in fat-soluble vitamins and essential fatty acids and whether the applicant's proposal to mitigate this risk through recommending dietary supplements is adequate. The committee was generally agreeable with this approach, highlighting that vitamin E may benefit steatohepatitis as well. Some did express concern regarding the effects of lomitapide on these nutrients in developing children.

The voting question was, "Based on the information included in the briefing materials and presented today, has the applicant provided sufficient efficacy and safety data to support marketing of lomitapide for the treatment of HoFH?" Thirteen members voted in favor, two against. Most members who voted for approval emphasized that their vote was specifically for the HoFH population, and that the proposed REMS should be tightened beyond prescribers attesting that lomitapide is "medically appropriate" for a patient. The two who voted against were both pediatric hepatologists; they cited concerns regarding the adverse effects of lomitapide on the liver, use of lomitapide in children, and off-label use in non-HoFH adult populations. The committee also emphasized the importance of obtaining more data through a post-marketing observational study.

9.4 Supplemental Tables and Figures

Phase 2 Non-HoFH Study Designs

Study CV145-009

Title: "The Effects of Chronic Dosing of BMS-201038 (lomitapide or AEGR-733) on Hepatic Fat Accumulation and Reversibility as Assessed by Nuclear Magnetic Resonance Spectroscopy (NMRS)"

Dates: 20 Jan 1999 to 22 Dec 1999

Sponsors: Bristol-Myers Squibb Pharmaceutical Research Institute (prior to 22 Aug 2002); Daniel J. Rader, MD, University of Pennsylvania School of Medicine (22 Aug 2002 to 12 Apr 2007); Aegerion Pharmaceuticals, Inc. (13 Apr 2007 to present)

Objective: Compare the effects of lomitapide 25 mg daily x 4 weeks with matched placebo on the reversibility of hepatic fat content as measured by MRI/NMRS in subjects with hypercholesterolemia.

Size: 76 subjects in 5 sites in U.S.

Population: Healthy male or female subjects not of childbearing potential, age 18-65 years, with fasting LDL-C $\geq$ 160 mg/dL and TG $\leq$ 500 mg/dL (obtained off lipid-lowering agents after a lipid stabilization period; see below).

Withdrawal of lipid-lowering agents was required prior to the first qualifying lipid assessment (8 weeks for statins, niacin, or bile-acid sequestrants; 12 weeks for fibrates; 4 weeks for OTC treatments such as “herbal or natural” therapies; 1 year for probucol). Treatment with steroids (inhaled or oral), immunosuppressive agents, estrogens/progesterones (except stable HRT in post-menopausal women), androgens, and fish oil preparations within 8 weeks were exclusions.

Multiple exclusions, including (but not limited to) a history of diabetes mellitus (or fasting blood glucose >140 mg/dL), an average ethanol consumption in excess of 14 drinks per week, CK >1.5x ULN of laboratory, or any obstructive hepatobiliary disease or other significant hepatic disease (defined as AST, ALT, GGT, total bilirubin, or alkaline phosphatase >1.5x ULN of laboratory).

Treatment Duration: 4 weeks (with follow-up 6 weeks after discontinuation)

Design:

- *Stabilization*: 4 weeks on a low-fat, low-cholesterol diet and non-lipid-lowering drugs prior to first lipid profile. Diet was a NCEP Step I diet, comprising 8-10% total calories from saturated fat, ≤30% of total calories from total fat, ≤300 mg/day cholesterol.
- *Period A*: 4 weeks of a placebo lead-in (Week A1 to A4)
 - The mean fasting LDL-C at weeks A2 and A3 needed to be ≥160 mg/dL to qualify, with the lower LDL-C within 15% of the higher value; if the two values differed by ≥15%, a third value could be obtained at week A4.
- *Period B*: Randomized, double-blind, parallel-treatment involving 4 weeks of lomitapide 25 mg daily or matched placebo (1:1) (Week B1 to B4), followed by 6 weeks of drug discontinuation (Week B5 to B11)

Interventions:

- Lomitapide 25 mg daily or matched placebo (Lot numbers N97018 [lomitapide] and N97014 [placebo]).
- Subjects were instructed to take their study drug in the morning, but relationship to food was not specified in the protocol.
- Supplemental vitamins were not provided.

Primary Pharmacodynamic Assessment: Evaluation of the reversibility of fat accumulation in the liver based on MRI/NMRS radiologic imaging at baseline, end of treatment (after 4 weeks), and end of study (6 weeks post treatment).

Secondary Pharmacodynamic Assessments: Change in lipid profile from baseline (Week B1) to Weeks B2, B3, B4, and B5 (four weeks on treatment), and B11 (6 weeks post treatment). Lipid profile included TC, LDL-C, VLDL-C, HDL-C, apoB, Lp(a), and TG.

Safety Assessments: AEs (BMS categorization; not MedDRA), clinical laboratories (hematology, chemistry, urinalysis, coagulation parameters), vital signs, physical examinations, ECGs, and PFTs (spirometry and DLCO).

- Protocol amendment #3 (06 July 1999) added a discontinuation criterion for ALT >3x ULN as a result of 4 (10%) of 41 subjects randomized at the time having been discontinued because of abnormal transaminases as high as 643 U/L.

Interim Analysis: An interim analysis was performed by a panel of BMS staff after at least 20 subjects (~1/3) had completed the full study to determine whether to continue the study. “For the NMRS results, clinical laboratory data, and SAEs, line listings and/or summary statistics by letter-coded treatment group were provided to the safety advisory panel as deemed necessary. The treatment decode was provided to the Vice-President-BDM by the randomization coordinator.”

Study AEGR-733-001

Title: "A randomized, double-blind, active-controlled, parallel-group study to evaluate the safety and efficacy of the combination AEGR-733 and ezetimibe vs. monotherapy in subjects with moderate hypercholesterolemia."

Dates: 30 June 2006 to 27 December 2006

Sponsors: Aegerion Pharmaceuticals, Inc.

Objective: Evaluate the efficacy of combination therapy (lomitapide force-titrated from 5 mg to 10 mg daily + ezetimibe 10 mg) vs. monotherapy of each agent on serum lipoproteins over 12 weeks of therapy. Characterize the safety and tolerability of these regimens.

Size: 85 subjects in 6 sites in U.S. (Sample size increased from 75 to 85 with protocol amendment 1 on 27 March 2006.)

Population: Men and women (with appropriate contraception if applicable), age 18-70 years, with fasting LDL-C ≥ 160 and < 250 mg/dL if 0-1 NCEP risk factors or ≥ 130 and < 250 mg/dL if ≥ 2 NCEP risk factors or prior CHD, and TG ≤ 400 mg/dL (obtained after a 4-wk washout period of lipid-lowering agents).

NCEP risk factors include cigarette smoking, hypertension (BP $> 140/90$ or on antihypertensive medication), low HDL (< 40 mg/dL), family history of premature CHD (CHD in first-degree male relative < 55 years or female < 65 years), age (men > 45 years, women > 55 years).

Multiple exclusions, including (but not limited to) a history of diabetes mellitus, cardiac insufficiency (functional NYHA class II-IV), history of regular alcohol use (> 1 drink per day), acute cardiovascular event within previous 6 months, serum creatinine > 2.5 mg/dL, or a history of liver disease or transaminases > 1.5 x ULN at screening.

Treatment Duration: 12 weeks

Design:

- 3-arm, double-blind, active-controlled, parallel-group, randomized trial with equal allocation
- *Screening/Washout*: 1-2-week screening period with 2 visits, where baseline lipids and other eligibility criteria were evaluated; this period also included a 4-week washout for subjects on prior lipid-lowering therapies. Subjects were counseled to implement a low-fat diet ($< 20\%$ calories from fat).
- *Treatment Period*: 12 weeks (with interim visits at weeks 4 and 8 at the end of each lomitapide dose-escalation [see below])
 - Arm 1 (lomitapide monotherapy): lomitapide + placebo-ezetimibe
 - Arm 2 (ezetimibe monotherapy): placebo-lomitapide + ezetimibe 10 mg
 - Arm 3 (combination therapy): lomitapide + ezetimibe 10 mg
- Initial lomitapide daily dose was 5 mg in Arms 1 and 3, force-titrated to 7.5 mg at week 4, and to 10 mg at week 8. Final visit was at week 12. There was no scheduled off-treatment follow-up.

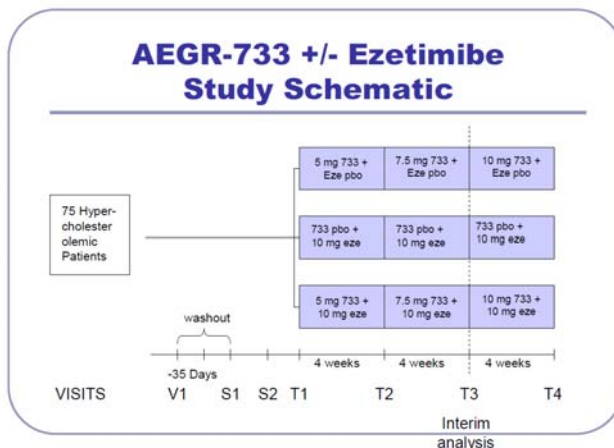


Figure 61. A-001 – Study Design

Source: A-001 CSR, p. 22.

Interventions:

- Lomitapide (force-titration 5 mg/day x 4 wk, 7.5 mg/day x 4 wk, 10 mg/day x 4 wk), ezetimibe 10 mg daily, or the combination. Matched placebos were used to blind in a double-dummy fashion. The clinical study report has lot numbers and expiration dates for lomitapide 5, 7.5, and 10-mg doses; ezetimibe; and matching placebos (A-001 CSR, Table 2).
- Subjects were instructed to take their study drugs each morning with a low-fat breakfast.
- Supplemental vitamins were not provided.

Primary Efficacy Endpoint: % change in calculated LDL-C after 12 weeks of therapy (visit 6). (LDL-C was estimated from the Friedewald equation unless TG >400 mg/dL, in which case it was measured directly.)

Secondary Efficacy Endpoints:

- Absolute and % change from baseline to 12 weeks in each of the following: TC, non-HDL-C, TG, HDL-C, Lp(a), apoA1, apoB, hsCRP, body weight;
- % change from baseline for all efficacy endpoints at 4 and 8 weeks of therapy (i.e., after the 4-week dosing periods of 5 mg and 7.5 mg, respectively) (visits 4 and 5).

Safety Assessments: AEs (MedDRA v8.1), clinical laboratories (hematology, chemistry, urinalysis, coagulation parameters), vital signs, physical examinations, ECGs, and Gastrointestinal Symptoms Rating Scale (GSRs) self-administered questionnaire. Hepatic fat, fat-soluble nutrients, and pulmonary function were not assessed.

Interim Analysis: A pre-specified interim analysis was conducted on Week 8 data to evaluate the 5-mg and 7.5-mg doses to guide future development. At the time the interim analysis was conducted, however, the applicant states that the study had been completed.

Reviewer Comment: *Although a 12-week phase 2 study, the maximum duration of exposure to the maximum tested dose of lomitapide was 4 weeks at 10 mg. Thus, the safety data obtained from this study is limited in its generalizability to the regimen proposed for the HoFH population.*

Study AEGR-733-003b (“A-003b”)

Title: “A randomized, double-blind, placebo-controlled, parallel-group study to evaluate the safety and efficacy of the combination of AEGR-733 (formerly BMS 201038) and atorvastatin 20 mg vs. monotherapy in subjects with moderate hypercholesterolemia.”

Dates: 05 November 2007 to 04 August 2008

Sponsors: Aegerion Pharmaceuticals, Inc.

Objectives: Evaluate the efficacy of combination therapy (fixed-dose lomitapide 5 mg or 10 mg + atorvastatin 20 mg) vs. placebo and monotherapy of each agent on serum lipoproteins over 8 weeks of therapy. Characterize the safety and tolerability of these regimens.

Size: 157 subjects in 17 sites in U.S.

Population: Men and women (with appropriate contraception if applicable), age 18-70 years, with fasting LDL-C ≥ 160 and < 250 mg/dL if 0-1 NCEP risk factors or ≥ 130 and < 250 mg/dL if ≥ 2 NCEP risk factors or prior CHD, and TG ≤ 400 mg/dL (obtained after a ~4-wk washout period of lipid-lowering agents).

NCEP risk factors include cigarette smoking, hypertension (BP $> 140/90$ or on antihypertensive medication), low HDL (< 40 mg/dL), family history of premature CHD (CHD in first-degree male relative < 55 years or female < 65 years), age (men > 45 years, women > 55 years).

Multiple exclusions, including (but not limited to) a history of diabetes mellitus, fasting glucose > 110 mg/dL, cardiac insufficiency (functional NYHA class II-IV), history of regular alcohol use (> 1 drink per day), acute cardiovascular event within previous 6 months, serum creatinine > 2.5 mg/dL, history of liver disease or transaminases $> 1.5x$ ULN at screening, positivity for hepatitis B or C, or BMI ≥ 40 kg/m².

Treatment Duration: 8 weeks

Design:

- 6-arm, double-blind, placebo- and active-controlled, parallel-group, randomized trial with equal allocation
- *Screening/Washout:* 5-week screening period with an initial screening at day -35, when washout from other lipid-lowering medications began and when subjects were counseled to implement a low-fat/low-cholesterol diet ("old NCEP Step II diet, supplying $< 30\%$ kcal as fat, $< 7\%$ kcal as saturated fatty acid, and < 200 mg dietary cholesterol). Follow-up screening visits were scheduled at day -10 and day -7.
- *Treatment Period:* 8 weeks (with interim visits at weeks 1, 2, 4, and 6).
 - Group A: Placebo daily
 - Group B: atorvastatin 20 mg daily
 - Group C: lomitapide 5 mg daily
 - Group D: lomitapide 10 mg daily
 - Group E: lomitapide 5 mg + atorvastatin 20 mg daily
 - Group F: lomitapide 10 mg + atorvastatin 20 mg daily
- Final visit was at week 8 (visit 8). There was no scheduled off-treatment follow-up.

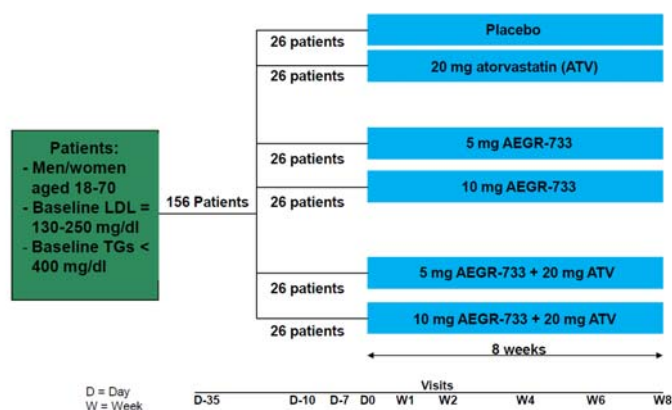


Figure 62. A-003b – Study Design

Source: A-003b CSR, Figure 9-1.

Note: Actual N=157 (placebo n=27).

Interventions:

- Lomitapide (fixed-dose 5 mg or 10 mg daily), atorvastatin 20 mg daily, the combination, or placebo. Matched placebos were used to blind in a double-dummy fashion, and active atorvastatin was over-encapsulated.
- Subjects were instructed to take their study drugs in the evening at least 2 hours after dinner, with a low-fat snack.
 - The original protocol stated that subjects “will be instructed to take . . . study medication either: In the morning along with a low-fat breakfast OR in the evening at least 2 hours after dinner, with a low-fat snack.” As explained in response to an FDA information request, Aegerion amended the protocol, in a letter sent to sites in January 2008, to change the lomitapide dosing time for all subjects to the evening.
- Subjects were instructed to take a multivitamin tablet first thing in the morning. It does not appear that this was provided by the sponsor.

Primary Efficacy Endpoint: % change in calculated LDL-C after 8 weeks of therapy (visit 8). (LDL-C was estimated from the Freidewald equation unless TG >400 mg/dL or the sample was non-fasting, in which case it was measured directly.)

Reviewer Comment: *Although the CSR describes using the “ITT dataset” for the primary efficacy analysis, subjects who did not complete the treatment period and who did not have an 8-week LDL-C value were not included in the analysis (i.e., their data were not used in a repeated-measures model, for example). Furthermore, I note that “Blood draws for lipid and other efficacy measures (not safety) were only drawn if the study subject had received study medication in the past 3 days.” This design element precludes ITT analyses; instead, the only efficacy analyses possible will be akin to per-protocol analyses of completers. This certainly has potential to introduce bias.*

Secondary Efficacy Endpoints:

- % changes from baseline to 4 and 8 weeks in each of the following: TC, non-HDL-C, TG, HDL-C, apoA1, apoB, hsCRP, body weight, and waist circumference;
- subgroup analyses by baseline TG (>150 and ≤150 mg/dL) and BMI (>30 and ≤30 kg/m²);
- % changes from baseline to weeks 1, 2, and 6 for all primary and secondary endpoints

Safety Assessments: AEs (MedDRA v10.1), clinical laboratories (hematology, chemistry, urinalysis, coagulation parameters), vitamins A and E, plasma insulin and C-peptide, hs-CRP, vital signs, physical examinations, ECGs, and Gastrointestinal Symptoms Rating Scale (GSRS) self-administered questionnaire. Hepatic fat and pulmonary function were not assessed.

Liver-related Safety:

Any subject who developed ALT and/or AST >10x ULN and/or bilirubin >2x ULN would have been removed from the study and followed until resolution or stabilization of these laboratory values.

Any subject with ALT and/or AST >5x ULN, alkaline phosphatase >3x ULN, or bilirubin >1.5x ULN (unless evidence of underlying Gilbert's syndrome) would have the result(s) confirmed within 7-14 days. If repeat values remained greater than the above thresholds, study medication was to be discontinued until values decreased to ALT or AST <2x ULN, alkaline phosphatase <1.5x ULN, or bilirubin <1.0x ULN. At that point, drug could be restarted.

Any subject with ALT and/or AST >2x but <5x ULN and otherwise asymptomatic (liver-related), and/or bilirubin >1.0x but <1.5x ULN (with normal pre-treatment levels) were to be carefully followed for further evaluation but would have continued on study drug.

Statistical Considerations:

- No sample size calculations were performed. "The sample size chosen for this study was based upon precedent set by other studies of similar nature...."
- The primary efficacy null hypothesis was "There is no difference among the 6 treatment groups in the % change in LDL-C," and excluding the null with $P \leq 0.05$ prompted pairwise t-tests for each pair of treatments (i.e., 15 comparisons) without adjustment for multiplicity. Excluding the null with a one-way ANOVA was essentially certain when two of the six groups were placebo and atorvastatin 20 mg.

Study AEGR-733-004

Title: "A randomized, double-blind, placebo-controlled, parallel-group study to evaluate low doses of the MTP inhibitor AEGR-733 on hepatic fat accumulation as measured by magnetic resonance spectroscopy."

Dates: 06 September 2007 to 05 September 2008

Sponsor: Aegerion Pharmaceuticals, Inc.

Objectives: Evaluate the impact of low-dose therapeutic regimens of lomitapide ± atorvastatin, ezetimibe, or fenofibrate, compared with placebo, on hepatic fat accumulation (% hepatic fat) as measured by MRS. Briefly, secondary objectives were to evaluate these regimens on safety parameters and lipid profiles.

Size: 260 subjects (240 planned) in 16 sites in U.S.

Population: Men and women (with appropriate contraception if applicable, although women *only* relying on oral contraceptives were ineligible), age 18-70 years, with LDL-C ≥ 100 and <190 mg/dL (after ~4-wk washout period of lipid-lowering agents), with *screening hepatic fat* <6.2% (by MRS).

Multiple exclusions, including (but not limited to) a history of diabetes mellitus, cardiac insufficiency (functional NYHA class II-IV), history of regular alcohol use (>1 drink per day), acute cardiovascular event within previous 6 months, serum creatinine >2.5 mg/dL, history of liver disease or transaminases >ULN at screening (allowed for retest if first screening value was within 10% of ULN), positivity for hepatitis B or C, or BMI >35 kg/m².

Treatment Duration: 12 weeks

Design:

- 8-arm, double-blind, placebo-controlled, fixed-dose, parallel-group, randomized trial with equal allocation

- **Screening/Washout:** 5- to 9-week screening period with an initial screening visit to begin washout from other lipid-lowering medications and to counsel subjects to implement a low-fat/low-cholesterol diet (“old NCEP Step II diet, supplying <30% kcal as fat, <7% kcal as saturated fatty acid, and <200 mg dietary cholesterol). Follow-up screening visits were scheduled at day -10 and day -7.
- **Treatment Period:** 12 weeks (with interim visits at weeks 1, 2, 4, 6, 8, and 10).
 - Group A: Placebo
 - Group B: lomitapide 2.5 mg daily
 - Group C: lomitapide 5 mg daily
 - Group D: lomitapide 7.5 mg daily
 - Group E: lomitapide 10 mg daily
 - Group F: lomitapide 5 mg + atorvastatin 20 mg daily
 - Group G: lomitapide 5 mg + micronized fenofibrate 145 mg daily
 - Group H: lomitapide 5 mg + ezetimibe 10 mg
- Final visit was at week 12 (visit 11). There was no scheduled off-treatment follow-up.
- After randomization, all lipid measurements and MRS/MRI results were blinded to the investigator starting at Day 0/visit 4.

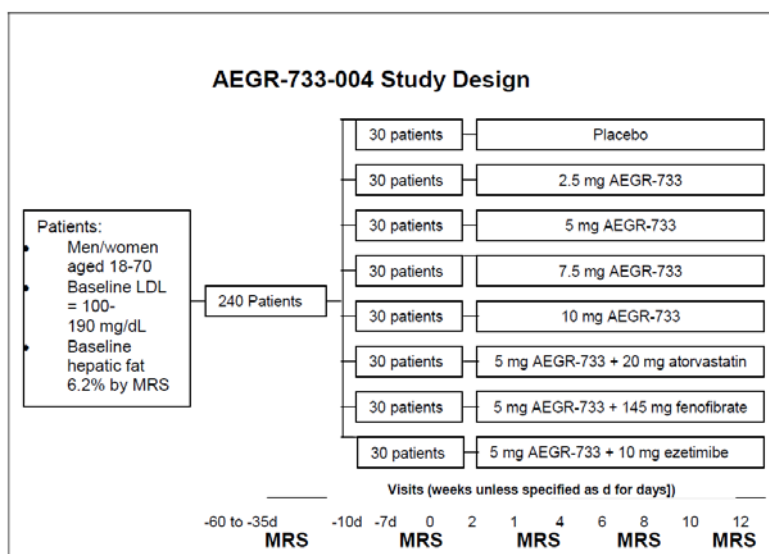


Figure 63. A-004 – Study Design

Source: A-004 CSR, Figure 1.

Note: Actual N=160 (n=28 to 35 per group).

Interventions:

- Each subject received 3 capsules as follows:

Study Arm	AEGR Capsules	Comparator Capsule
A. Placebo	Placebo × 2	Placebo
B. AEGR-733 2.5 mg	Placebo + AEGR 2.5 mg	Placebo
C. AEGR-733 5 mg	AEGR 2.5 mg × 2	Placebo
D. AEGR-733 7.5 mg	AEGR 2.5 mg + 5 mg	Placebo
E. AEGR-733 10mg	AEGR-733 5 mg × 2	Placebo
F. AEGR-733 5 mg + atorvastatin 20 mg	AEGR 2.5 mg × 2 +	atorvastatin 20mg
G. AEGR-733 5 mg + micronized fenofibrate 145 mg	AEGR 2.5 mg × 2 +	fenofibrate 145 mg
H. AEGR-733 5 mg + ezetimibe 10 mg	AEGR 2.5 mg × 2 +	ezetimibe 10

- Atorvastatin, fenofibrate, and ezetimibe were over-encapsulated to maintain blinding, with matching placebos provided.
- Subjects were instructed to take their study drugs in the late evening along with a low-fat snack at least 2 hours after dinner.
- Subjects were instructed to take a multivitamin tablet each morning starting at Day 0 (baseline).

Primary Efficacy Endpoint: Hepatic fat content as measured by MRS at baseline and week 12.

Secondary Efficacy Endpoints:

- Hepatic fat content at week 4, 8, 12/End-of-study (LOCF) as measured by MRS
- Hepatic safety biomarkers (ALT, AST, alkaline phosphatase, total bilirubin) at baseline, weeks 4, 8, 12/end-of-study (LOCF)
- Occurrence of biopsy-proven hepatic steatosis
- Lipids (LDL-C, TC, TG, HDL-C), apoB, and apoAI at baseline, weeks 1, 2, 4, 6, 8, 10, 12/end-of-study (LOCF)
- hs-CRP at baseline and week 12/end-of-study (LOCF)
- Weight and waist circumference at baseline, weeks 4, 8, 12/end-of-study (LOCF)

Safety Assessments: AEs (MedDRA v10.1; collected between date of first dose and 30 days after last dose), clinical laboratories (hematology, chemistry, urinalysis, coagulation parameters), vitamins A and E, plasma insulin and C-peptide (both added with protocol amendment on 04 April 2008), hs-CRP, vital signs, physical examinations, ECGs, Gastrointestinal Symptoms Rating Scale (GSRS) self-administered questionnaire, hepatic fat by MRS/MRI (screening, baseline, and weeks 4, 8, and 12), and pulmonary function tests (spirometry + DL_{CO} at baseline and week 12).

Liver-related Safety:

Any subject who developed ALT and/or AST >10x ULN and/or bilirubin >2x ULN would have been removed from the study and followed until resolution or stabilization of these laboratory values.

Any subject with ALT and/or AST >5x ULN, alkaline phosphatase >3x ULN, or bilirubin >1.5x ULN (unless evidence of underlying Gilbert's syndrome) would have the result(s) confirmed within 2-14 days. If repeat values remained greater than the above thresholds, study medication was to be discontinued until values decreased to ALT or AST <2x ULN, alkaline phosphatase <1.5x ULN, or bilirubin <1.0x ULN. At that point, drug could be restarted.

Any subject with ALT and/or AST >2x but <5x ULN and otherwise asymptomatic (liver-related), and/or bilirubin >1.0x but <1.5x ULN (with normal pre-treatment levels) were to be carefully followed for further evaluation but would have continued on study drug.

Statistical Considerations:

- The primary endpoint analysis was a one-way ANOVA at week 12 to compare the absolute change from baseline in % hepatic fat (by MRS) between lomitapide 5 mg daily and placebo.
- For secondary endpoints of change in hepatic fat from baseline to weeks 4, 8, and 12, each lomitapide monotherapy group was to be compared with placebo and each lomitapide 5 mg + atorvastatin/fenofibrate/ezetimibe group was to be compared with both placebo and lomitapide 5 mg monotherapy.
- No sample size calculations were performed. "It was expected, however, that a sample size of 30 subjects per treatment group would yield sufficient data to provide reasonable point estimates and confidence intervals for the between-group differences in percent change in hepatic fat content."

Study AEGR-733-006

Title: "A randomized, double-blind, comparator-controlled, parallel-group study to evaluate the safety and efficacy of the combination of AEGR-733 and atorvastatin 20 mg vs. atorvastatin monotherapy in subjects with moderate hypercholesterolemia."

Dates: 12 May 2008 to 29 August 2008

Sponsor: Aegerion Pharmaceuticals, Inc.

Objectives: Evaluate the efficacy of combination therapy lomitapide + atorvastatin 20 mg versus atorvastatin monotherapy on LDL-C over 4 and 8 weeks of therapy. Briefly, secondary objectives were to evaluate the effects on other serum lipoproteins, hsCRP, body weight, markers of safety, and overall safety and tolerability.

Size: 44 subjects (50 planned) in 5 sites in U.S.

Population: Men and women (with appropriate contraception if applicable), age 18-70 years, with fasting LDL-C ≥ 160 and < 250 mg/dL if 0-1 NCEP risk factors or ≥ 130 and < 250 mg/dL if ≥ 2 NCEP risk factors or prior CHD, and TG ≤ 400 mg/dL (obtained after a ~5-wk washout period of lipid-lowering agents).

NCEP risk factors include cigarette smoking, hypertension (BP $> 140/90$ or on antihypertensive medication), low HDL (< 40 mg/dL), family history of premature CHD (CHD in first-degree male relative < 55 years or female < 65 years), age (men > 45 years, women > 55 years).

Multiple exclusions, including (but not limited to) a history of diabetes mellitus, fasting glucose > 110 mg/dL, cardiac insufficiency (functional NYHA class II-IV), history of regular alcohol use (> 1 drink per day), acute cardiovascular event within previous 6 months, serum creatinine > 2.5 mg/dL, history of liver disease or transaminases > 1.5 x ULN at screening (one retest allowed), positivity for hepatitis B or C, or BMI ≥ 40 kg/m².

Treatment Duration: 8 weeks

Design:

- 2-arm, double-blind, randomized (blocks of 4), active-controlled, parallel-group trial with equal allocation
- *Screening/Washout*: 5-week screening period with an initial screening at day -35, when washout from other lipid-lowering medications began and when subjects were counseled to implement a low-fat diet. Follow-up screening visits were scheduled at day -10 and day -7.
- *Treatment Period*: 8 weeks (with interim visits at weeks 1, 2, 4, and 6)
 - atorvastatin 20 mg daily
 - atorvastatin 20 mg daily + lomitapide 2.5 mg daily, force-titrated to 5 mg daily at week 4
- Final visit was at week 8 (visit 9). There was no scheduled off-treatment follow-up.

		N=109		N=44		atorvastatin 20 mg N=23		atorvastatin 20 mg	
						atorvastatin 20 mg + AEGR-733 2.5 mg N=21		atorvastatin 20 mg + AEGR-733 5 mg	
Visit	↑	↑	↑	↑	↑	↑	↑	↑	↑
Day	-35	-10	-7	0					
Week					1	2	3	4	5
Period	Screening/Diet Run-In			Treatment					

Figure 64. A-006 – Study Design

Source: A-006 CSR, Figure 9.1.1

Interventions:

- Lomitapide 2.5 mg or 5 mg capsules (2.5 mg daily x 4 weeks followed by 5 mg daily x 4 weeks) or matching placebo capsules; atorvastatin 20 mg daily.
- Subjects were instructed to take their study drugs in the evening at least 2 hours after dinner, with a low-fat snack.
- The protocol states “Subjects should take a multivitamin first thing in the morning.” The clinical study report does not mention the use of multivitamins.

Primary Efficacy Endpoints: % change in LDL-C after 4 weeks of therapy (i.e., after lomitapide 2.5-mg dosing period) and % change in LDL-C after 8 weeks of therapy (i.e., after the lomitapide 5-mg dosing period).

Secondary Efficacy Endpoints: % change from baseline to 4 and 8 weeks in each of the following: TC, TG, HDL-C, non-HDL-C, apoB, apoAI, hsCRP, weight, waist circumference.

Safety Assessments: AEs (MedDRA v11.0), clinical laboratories (hematology, chemistry, urinalysis, coagulation parameters), vitamins A and E, plasma insulin and C-peptide, hs-CRP, vital signs, physical examinations, ECGs, and GSRs scores. Hepatic fat and pulmonary function were not assessed.

Liver-related Safety: Any subject who developed ALT and/or AST >10x ULN and/or bilirubin >2x ULN would have been removed from the study and followed until resolution or stabilization of these laboratory values.

Any subject with ALT and/or AST >5x ULN, alkaline phosphatase >3x ULN, or bilirubin >1.5x ULN (unless evidence of underlying Gilbert’s syndrome) would have the result(s) confirmed within **2-4** days. If repeat values remained greater than the above thresholds, study medication was to be discontinued until values decreased to ALT or AST <2x ULN, alkaline phosphatase <1.5x ULN, or bilirubin <1.0x ULN. At that point, drug could be restarted.

Any subject with ALT and/or AST >2x but <5x ULN and otherwise asymptomatic (liver-related), and/or bilirubin >1.0x but <1.5x ULN (with normal pre-treatment levels) were to be carefully followed for further evaluation but would have continued on study drug.

Statistical Considerations:

- No sample size calculations were performed. “The sample size chosen for this study was based upon precedent set by other studies of similar nature....”
- The hypothesis to be tested for the primary efficacy endpoint was the between-group comparison in % change in LDL-C from baseline to week 8.

Table 123. A-003b – Adverse Events Leading to Discontinuation

System Organ Class Preferred Term	P (n=27)	L5 (n=26)	L10 (n=26)	A20 (n=26)	L5+A20 (n=26)	L10+A20 (n=26)
GI Disorders	0	8 (31%)	8 (31%)	0	4 (15%)	17 (65%)
Diarrhea	0	8 (31%)	7 (27%)	0	4 (15%)	14 (54%)
Nausea	0	2 (8%)	2 (8%)	0	0	8 (31%)
Abd. Pain	0	1 (4%)	1 (4%)	0	1 (4%)	3 (12%)
Abd. Distension	0	1 (4%)	1 (4%)	0	0	2 (8%)
Abd. Pain Upper	0	1 (4%)	1 (4%)	0	0	1 (4%)
Vomiting	0	0	0	0	1 (4%)	2 (8%)
Dyspepsia	0	0	0	0	0	2 (8%)
Flatulence	0	0	0	0	0	2 (8%)
Eructation	0	0	0	0	0	1 (4%)
GERD	0	0	0	0	1 (4%)	0
Investigations	0	0	4 (15%)	0	1 (4%)	0
ALT Increased	0	0	2 (8%)	0	1 (4%)	0
AST Increased	0	0	2 (8%)	0	0	0
Hep. Enz. Increased	0	0	2 (8%)	0	0	0
PT Prolonged	0	0	1 (4%)	0	0	0
Cardiac Disorders	0	1 (4%)	1 (4%)	0	0	0
Myocardial Infarction	0	1 (4%)	1 (4%)	0	0	0
General Disorders	0	1 (4%)	1 (4%)	0	0	0
Asthenia	0	1 (4%)	0	0	0	0
Gait Disturbance	0	0	1 (4%)	0	0	0
Musculoskeletal	0	0	2 (8%)	0	0	0
Muscle Spasms	0	0	2 (8%)	0	0	0
Metab. & Nutrition	0	0	0	0	0	1 (4%)
Decreased Appetite	0	0	0	0	0	1 (4%)
Nervous System	0	0	0	0	0	1 (4%)
Dysgeusia	0	0	0	0	0	1 (4%)
Headache	0	0	0	0	0	1 (4%)
Skin & Subcutaneous	0	0	1 (4%)	0	0	0
Rash	0	0	1 (4%)	0	0	0

Source: A-003b CSR, Table 12-2.

Table 124. A-003b – Selected Common Treatment-Emergent Adverse Events

System Organ Class Preferred Term	P (n=27)	L5 (n=26)	L10 (n=26)	A20 (n=26)	L5+A20 (n=26)	L10+A20 (n=26)
GI Disorders	10 (37%)	17 (65%)	18 (69%)	4 (15%)	18 (69%)	24 (92%)
Diarrhea	2 (7%)	16 (62%)	15 (58%)	2 (8%)	11 (42%)	20 (77%)
Nausea	1 (4%)	5 (19%)	7 (27%)	2 (8%)	5 (19%)	14 (54%)
Flatulence	2 (7%)	1 (4%)	2 (8%)	0	4 (15%)	4 (15%)
Abdominal distension	1 (4%)	2 (8%)	2 (8%)	3 (12%)	2 (8%)	4 (15%)
Abdominal pain	0	1 (4%)	1 (4%)	0	2 (8%)	3 (12%)
Abdominal pain upper	1 (4%)	3 (12%)	3 (12%)	0	0	1 (4%)
Dyspepsia	2 (7%)	0	1 (4%)	2 (8%)	2 (8%)	2 (8%)

System Organ Class Preferred Term	P (n=27)	L5 (n=26)	L10 (n=26)	A20 (n=26)	L5+A20 (n=26)	L10+A20 (n=26)
Vomiting	1 (4%)	1 (4%)	0	0	1 (4%)	3 (12%)
Constipation	1 (4%)	1 (4%)	0	0	2 (8%)	0
GERD	0	0	0	0	3 (12%)	0
Eructation	1 (4%)	0	0	0	0	2 (8%)
Infections/Infestations	6 (22%)	3 (12%)	3 (12%)	7 (27%)	8 (31%)	4 (15%)
Nasopharyngitis	3 (11%)	1 (4%)	0	2 (8%)	4 (15%)	1 (4%)
Gastroenteritis viral	1 (4%)	0	0	0	3 (12%)	0
Urinary tract infection	1 (4%)	0	1 (4%)	2 (8%)	1 (4%)	1 (4%)
Upper resp. infection	0	0	2 (8%)	0	0	0
Investigations	2 (7%)	3 (12%)	6 (23%)	4 (15%)	6 (23%)	2 (8%)
ALT increased	1 (4%)	2 (8%)	2 (8%)	1 (3%)	1 (4%)	0
AST increased	1 (4%)	3 (12%)	2 (8%)	1 (3%)	1 (4%)	0
Hepatic enz. increased	0	0	2 (8%)	0	1 (4%)	0
Blood urine present	0	0	0	0	2 (8%)	0
General Disorders	0	6 (23%)	1 (4%)	1 (4%)	2 (8%)	3 (12%)
Chest pain	0	3 (12%)	0	0	0	0
Asthenia	0	2 (8%)	0	0	0	0
Musculoskeletal Disorders	0	2 (8%)	3 (12%)	3 (12%)	0	3 (12%)
Muscle spasms	0	1 (4%)	2 (8%)	2 (8%)	0	2 (8%)
Nervous System	5 (19%)	0	0	1 (4%)	1 (4%)	3 (12%)
Respiratory Disorders	2 (7%)	3 (12%)	2 (8%)	2 (8%)	0	0
Pharyngolaryngeal pain	1 (4%)	2 (8%)	0	0	0	0
Metabolism & Nutrition	0	1 (4%)	2 (8%)	0	1 (4%)	2 (8%)
Anorexia	0	1 (4%)	2 (8%)	0	1 (4%)	1 (4%)
Skin & Subcutaneous	1 (4%)	0	4 (15%)	1 (4%)	0	0
Dry Skin	0	0	2 (8%)	0	0	0
Renal & Urinary Disorders	1 (4%)	0	0	1 (4%)	1 (4%)	2 (8%)
Ear & Labyrinth Disorders	0	2 (8%)	0	0	0	0

Source: FDA clinical reviewer's analysis of submitted A-003b AE dataset (AE.xpt).

Events with a start date prior to first dose are excluded.

A preferred term is listed only if it was reported by ≥5% of subjects (≥2 subjects) and by more subjects in a lomitapide (with or without atorvastatin) group than a control (placebo or atorvastatin) group.

Table 125. “Elevated LDL-C” Safety Pool – AEs Leading to Discontinuation

PREFERRED TERM	LOMITAPIDE DOSE GROUP ¹				COMPARATOR	
	ESCALATED (5-10 MG) (N=77) N (%)	LOW DOSE (2.5-7.5 MG) (N=244) N (%)	MID DOSE (10 MG) (N=99) N (%)	HIGH DOSE (25-100 MG) (N=62) N (%)	PLACEBO (N=116) N (%)	ACTIVE CONTROL (N=78) N (%)
At least one TEAE resulting in DC	15 (19.5)	44 (18.0)	42 (42.4)	17 (27.4)	2 (1.7)	5 (6.4)
Myocardial infarction	0	1 (0.4)	1 (1.0)	0	0	0
Abdominal discomfort	1 (1.3)	2 (0.8)	1 (1.0)	0	0	0
Abdominal distension	0	2 (0.8)	3 (3.0)	1 (1.6)	0	0
Abdominal pain	0	6 (2.5)	5 (5.1)	3 (4.8)	0	0
Abdominal pain lower	0	1 (0.4)	0	1 (1.6)	0	0
Abdominal pain upper	1 (1.3)	5 (2.0)	3 (3.0)	2 (3.2)	1 (0.9)	0
Diarrhoea	3 (3.9)	33 (13.5)	26 (26.3)	13 (21.0)	1 (0.9)	0
Dyspepsia	1 (1.3)	0	3 (3.0)	0	0	0
Eructation	0	0	1 (1.0)	1 (1.6)	0	0
Flatulence	1 (1.3)	1 (0.4)	2 (2.0)	2 (3.2)	0	0
Gastroesophageal reflux disease	0	2 (0.8)	0	0	0	0
Nausea	0	4 (1.6)	15 (15.2)	6 (9.7)	0	1 (1.3)
Vomiting	0	2 (0.8)	2 (2.0)	3 (4.8)	0	0
Asthenia	0	1 (0.4)	0	3 (4.8)	0	0
Fatigue	0	3 (1.2)	0	1 (1.6)	0	0
Alanine aminotransferase increased	6 (7.8)	2 (0.8)	3 (3.0)	1 (1.6)	0	0
Aspartate aminotransferase increased	2 (2.6)	0	3 (3.0)	1 (1.6)	0	0
Hepatic enzyme increased	2 (2.6)	0	2 (2.0)	0	0	0
Liver function test abnormal	2 (2.6)	0	0	2 (3.2)	0	0
Decreased appetite	0	0	1 (1.0)	1 (1.6)	0	0
Arthralgia	0	3 (1.2)	0	0	0	0
Muscle spasms	1 (1.3)	0	2 (2.0)	0	0	0
Headache	0	1 (0.4)	1 (1.0)	1 (1.6)	0	0
Rash	0	1 (0.4)	1 (1.0)	0	0	0

Source: Table 1.2.1C and Table 1.2.10C

¹ Includes subjects who received lomitapide alone and coadministered with other lipid-lowering drugs.

Source: ISS, Table 54.

Preferred terms are shown for treatment-emergent AEs leading to treatment discontinuation for ≥2 lomitapide-treated subjects.

“Escalated 5-10mg” includes AEGR-733-001 and -006; “Low-dose” includes AEGR-733-003b and -004; “Mid-dose” includes CV145-002, -010, AEGR-733-003b, and -004; “High-dose” includes CV145-002, -009, and -010.

HoFH Phase 3 Supplemental Data

The following conventions apply for Figure 65 through Figure 70, which depict LDL-C profiles in HoFH-pivotal for subjects who either discontinued apheresis entirely or reduced the frequency of apheresis during the trial. The black solid line represents direct LDL-C values over time. The black triangles represent times of apheresis treatments. Gray vertical reference lines mark the subject's baseline visit and the primary efficacy endpoint at week 26. The lomitapide dose taken during the period immediately prior to the week 26 visit is noted in parentheses. Colored reference lines represent changes in concomitant lipid-lowering therapies: red lines indicate additions to therapy (including increases in dose) and blue lines indicate withdrawal of therapy; further details are provided in the footnotes for each change. The thick blue dashed lines mark the date of last apheresis or the approximate date of the last apheresis on the "typical" schedule for subjects who had the frequency reduced. I chose these dates *post hoc* based on qualitative assessment of apheresis intervals; they may or may not have corresponded to dates that the apheresis prescription was actually changed (not available on case report forms or datasets).

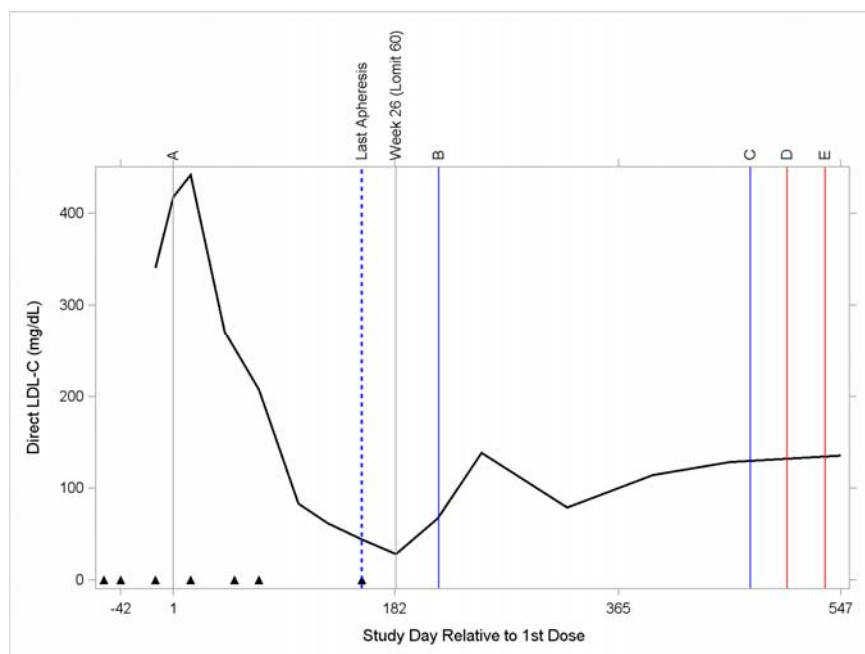


Figure 65. HoFH-pivotal – Subject 01-003 (Apheresis Discontinued)

Source: FDA clinical reviewer's analysis of HoFH-pivotal datasets (*LB, CM, EX.xpt*)
See text for explanation of figure notation.

- (A) At baseline, rosuvastatin 40 mg, ezetimibe 10 mg, and colsevelam 3750 mg daily.
- (B) Colsevelam d/c'd.
- (C) Rosuvastatin and ezetimibe d/c'd (reason not specified in narrative).
- (D) Added rosuvastatin 20 mg and ezetimibe 10 mg daily.
- (E) Increased rosuvastatin to 40 mg daily.

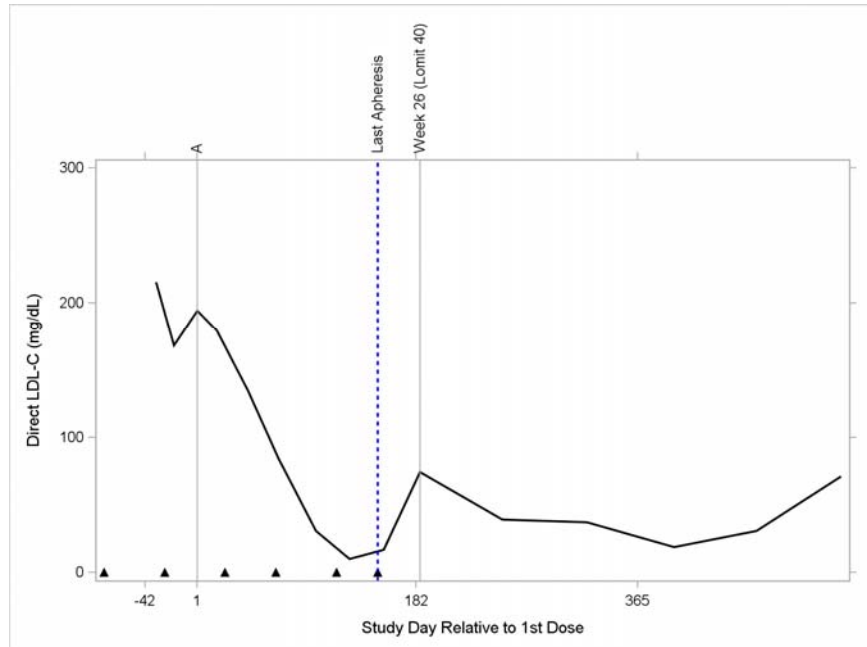


Figure 66. HoFH-pivotal – Subject 31-001 (Apheresis Discontinued)

Source: FDA clinical reviewer's analysis of HoFH-pivotal datasets (*LB, CM, EX.xpt*)

See text for explanation of figure notation.

(A) On simvastatin 20 mg and ezetimibe 10 mg daily throughout.

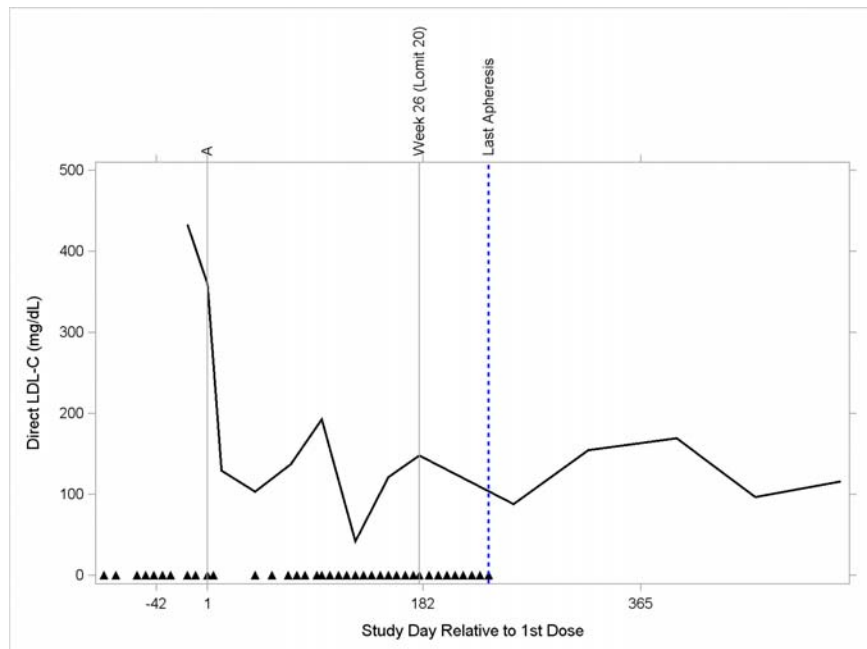


Figure 67. HoFH-pivotal – Subject 31-002 (Apheresis Discontinued)

Source: FDA clinical reviewer's analysis of HoFH-pivotal datasets (*LB, CM, EX.xpt*)

See text for explanation of figure notation.

(A) On simvastatin 40 mg and ezetimibe 10 mg daily throughout.

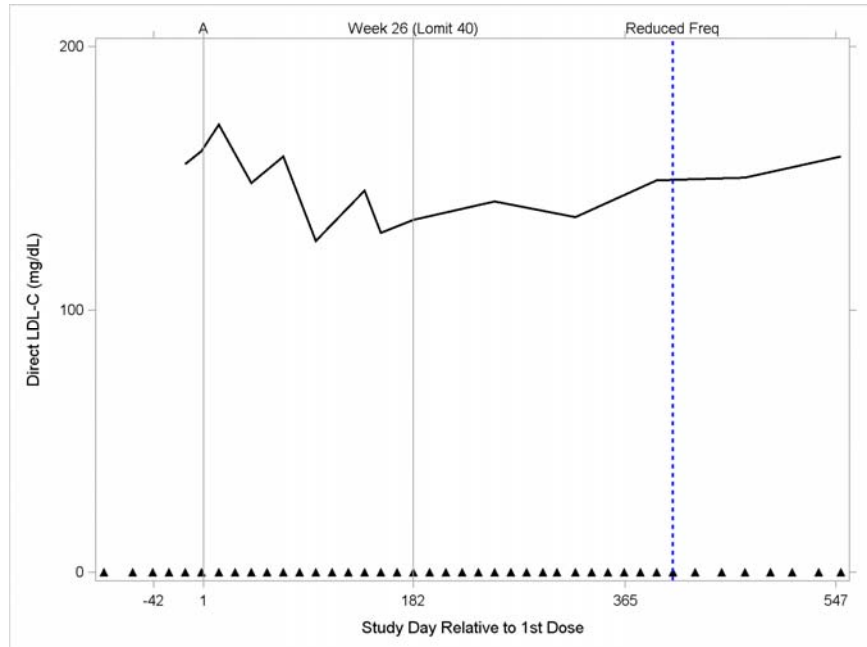


Figure 68. HoFH-pivotal – Subject 02-001 (Apheresis Frequency Reduced)

Source: FDA clinical reviewer's analysis of HoFH-pivotal datasets (*LB, CM, EX.xpt*)

See text for explanation of figure notation.

(A) On atorvastatin 80 mg and ezetimibe 10 mg daily throughout.

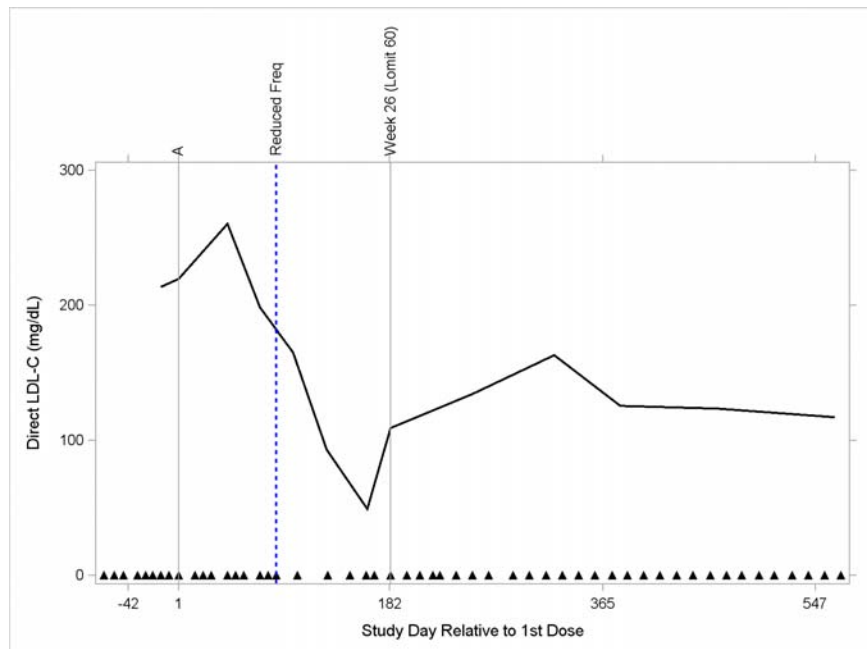


Figure 69. HoFH-pivotal – Subject 35-001 (Apheresis Frequency Reduced)

Source: FDA clinical reviewer's analysis of HoFH-pivotal datasets (*LB, CM, EX.xpt*)

See text for explanation of figure notation.

(A) On simvastatin 20 mg and ezetimibe 10 mg daily throughout.

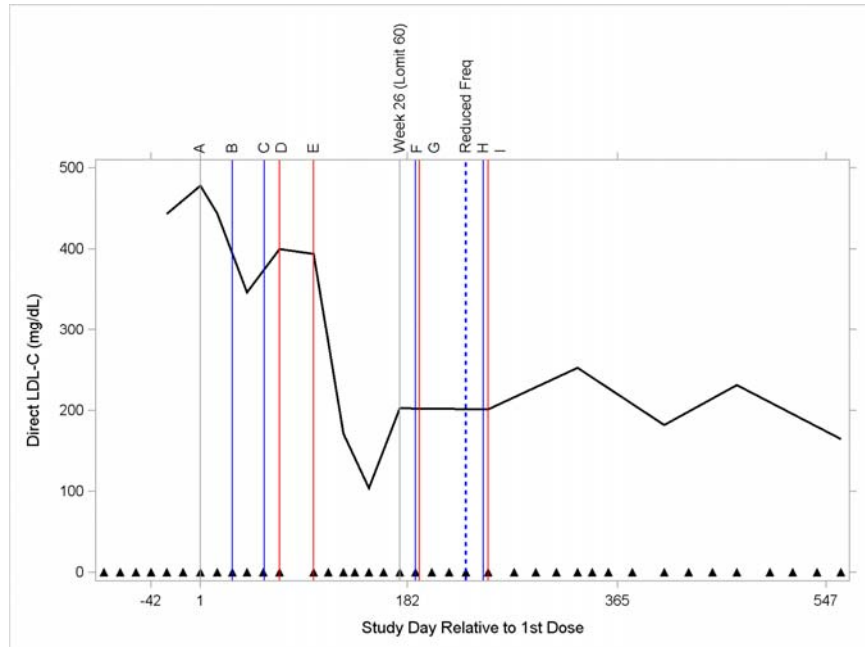


Figure 70. HoFH-pivotal – Subject 23-001 (Apheresis Frequency Reduced)

Source: FDA clinical reviewer's analysis of HoFH-pivotal datasets (*LB, CM, EX.xpt*)

See text for explanation of figure notation.

- (A) Rosuvastatin 40 mg and ezetimibe 10 mg daily at baseline.
- (B) Ezetimibe d/c'd (reason not specified).
- (C) Rosuvastatin d/c'd (reason not specified).
- (D) Added ezetimibe 10 mg daily.
- (E) Added rosuvastatin 40 mg daily.
- (F) Rosuvastatin d/c'd (reason not specified).
- (G) Added rosuvastatin 40 mg daily.
- (H) Rosuvastatin d/c'd (reason not specified).
- (I) Added rosuvastatin 40 mg daily (ezetimibe remains).

Table 126. Safety Assessments in Lomitapide Clinical Trials

STUDY	SAFETY EVALUATIONS										
	AEs	GSRs	PE	SAFETY LABS	FAT SOLUBLE NUTRIENTS	VITAL SIGNS	WEIGHT/ BMI	ECGs	CON-COMITANT MEDI-CATIONS	PFTs	NMRS/ MRI
HoFH Studies											
UP1001	BL, Days 7, 14, 28, 35, 42, 56, 63, 70, 84, 91, 98, 112, (EOT), 140 (EOS)	ND	SCR, BL, Days 7, 14, 28, 35, 42, 56, 63, 70, 84, 91, 98, 112, (EOT), 140 (EOS)	SCR, BL, Days 7, 14, 28, 35, 42, 56, 63, 70, 84, 91, 98, 112, (EOT), 140 (EOS)	BL, Days 28, 56, 84, 112, (EOT), 140 (EOS)	SCR, BL, Days 7, 14, 28, 35, 42, 56, 63, 70, 84, 91, 98, 112, (EOT), 140 (EOS)	SCR, BL, Days 7, 14, 28, 35, 42, 56, 63, 70, 84, 91, 98, 112, (EOT), 140 (EOS)	SCR, BL, Days 28, 56, 84, 112, (EOT), 140 (EOS)	SCR, BL, Days 7, 14, 28, 35, 42, 56, 63, 70, 84, 91, 98, 112, (EOT), 140 (EOS)	BL, Days 28, 56, 84, 112, (EOT), 140 (EOS)	BL, Days 28, 56, 84, 112, (EOT), 140 (EOS)
UP1002/AEGR-733-005 ¹	SCR (RI) through /ET	BL, Wks 2, 6, 10, 14, 18, 22, 26, 36, 46, 56, 66, 78; Wk 84 ⁵ , ET	SCR, BL, Wks 2, 6, 10, 14, 18, 22, 26, 36, 46, 56, 66, 78 (EOT), 84 ⁵ (EOS); ET	SCR, BL, Wks 2, 6, 10, 14, 18, 22, 26, 31 ⁵ , 46, 51 ⁵ , 56, 66, 78 (EOT), 84 ⁵ (EOS); ET	SCR (RI), BL, Wks 2, 6, 10, 14, 18, 22, 26, 36, 46, 56, 66, 78 (EOT), 84 ⁵ (EOS); ET	SCR, BL, Wks 2, 6, 10, 14, 18, 22, 26, 36, 46, 56, 66, 78 (EOT), 84 ⁵ (EOS); ET	SCR, BL, Wks 2, 6, 10, 14, 18, 22, 26, 36, 46, 56, 66, 78 (EOT), 84 ⁵ (EOS); ET	SCR, BL, Wks 2, 6, 10, 14, 18, 22, 26, 36, 46, 56, 66, 78 (EOT), 84 ⁵ (EOS); ET	SCR (RI), BL, Wks 2, 6, 10, 14, 18, 22, 26, 36, 46, 56, 66, 78 (EOT), 84 ⁵ (EOS); ET	BL, Wks 26, 56, 78 (EOT), 84 ⁵ (EOS), ET	BL, Wks 26, 56, 78 (EOT), 84 ⁵ (EOS), ET
AEGR-733-012 ²	BL ⁷ , Wks 12, 24, 36, & q 12 wks, EOS/ ET	ND	BL ⁷ , Wks 24, 48, 72, & q 24 wks, EOS/ ET	BL ⁷ , Wks 12, 24, 36, & q 12 wks, EOS/ ET	BL ⁷ , Wks 12, 24, 36, & q 12 wks, EOS/ ET	BL ⁷ , Wks 12, 24, 36, & q 12 wks, EOS/ ET	BL ⁷ , Wks 12, 24, 36, & q 12 wks, EOS/ ET	BL ⁷ , Wks 24, 48, 72, & q 24 wks, EOS/ ET	BL ⁷ , Wks 12, 24, 36, & q 24 wks, EOS/ ET	BL ⁷ , Wks 24, 48, 72, & q 24 wks, EOS/ ET	BL ⁷ , Wks 24, 48, 72, & q 24 wks, EOS/ ET

STUDY	SAFETY EVALUATIONS										
	AEs	GSRs	PE	SAFETY LABS	FAT SOLUBLE NUTRIENTS	VITAL SIGNS	WEIGHT/ BMI	ECGs	CON-COMITANT MEDI-CATIONS	PFTs	NMRS/ MRI
Studies in Subjects with Elevated LDL-C											
AEGR-733-001	BL, Wks 4, 8, 12 (EOT/ EOS), ET	BL, Wks 4, 8, 12 (EOT/ EOS), ET	SCR, BL, Wks 4, 8, 12 (EOT/ EOS), ET	SCR, BL, Wks 4, 8, 12 (EOT/ EOS), ET	ND	SCR, BL, Wks 4, 8, 12 (EOT/ EOS), ET	SCR, BL, Wks 4, 8, 12 (EOT/ EOS), ET	SCR, Wk 12 (EOT/ EOS), ET	SCR, BL, Wks 4, 8, 12 (EOT/ EOS), ET	ND	ND
AEGR-733-003a	SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	BL, Wk 8 (EOT/ EOS); ET	SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	ND	SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	Weight: SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	SCR, Wk 8 (EOT/ EOS); ET	SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	ND	ND
AEGR-733-003b	SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	BL, Wk 8 (EOT/ EOS); ET	SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	Vitamins A & E: SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	Weight: SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	SCR, Wk 8 (EOT/ EOS); ET	SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	ND	ND
AEGR-733-004	SCR, BL, Wks 1, 2, 4, 6, 8, 12 (EOT/ EOS); ET	BL, Wk 12 (EOT/ EOS); ET	SCR, Wk 12 (EOT/ EOS); ET	SCR, BL, Wks 1, 2, 4, 6, 8, 12 (EOT/ EOS); ET	Vitamins A & E: BL, Wks 1, 2, 4, 6, 8, 12 (EOT/ EOS); ET	SCR, BL, Wks 1, 2, 4, 6, 8, 12 (EOT/ EOS); ET	Weight: SCR, BL, Wks 1, 2, 4, 6, 8, 12 (EOT/ EOS); ET	SCR, Wk 12 (EOT/ EOS); ET	SCR, BL, Wks 1, 2, 4, 6, 8, 12 (EOT/ EOS); ET	BL, Wk 12 (EOT/ EOS); ET	SCR, BL, Wks 4, 8, 12 (EOT/ EOS); ET
AEGR-733-006	SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	BL, Wks 4, 8 (EOT/ EOS); ET	SCR, Wk 8 (EOT/ EOS); ET	SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	Not evaluated	SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	Weight: SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	SCR, BL, Wk 8 (EOT/ EOS); ET	SCR, BL, Wks 1, 2, 4, 6, 8 (EOT/ EOS); ET	ND	ND

STUDY	SAFETY EVALUATIONS										
	AEs	GSRS	PE	SAFETY LABS	FAT SOLUBLE NUTRIENTS	VITAL SIGNS	WEIGHT/ BMI	EKGs	CON-COMITANT MEDI-CATIONS	PFTs	NMRS/ MRI
CV145-002	SCR through EOS (D1 – 15)	ND	SCR; BL; D15 (EOS)	H, C, U: SCR; BL; D15 (EOS) PT: SCR; BL; D7, 15 Lipids, LFTs: also D4, 8, 11	ND	SCR; pre-Rx & 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hrs post-Rx on D1 & 14; pre-Rx D2, 13; D15 (EOS)	SCR	SCR; BL; D8, 15 (EOS)	SCR through EOS (D1 – 15)	ND	SCR; within 48 hrs prior to D14 (last) dose
CV145-009	SCR through EOS (Wk +6)	ND	SCR (RI), D1, Wks 2, 3, 4 & +6	SCR (RI), Wks 5, +6 Lipids, LFTs: also D1, Wks 1, 2, 3	Vitamin E: SCR (RI), Wks 4, +6	SCR (RI), D1, Wks 2, 3, 4 & +6	SCR (RI), D1 Wks 2, 3, 4 & +6	SCR, D1, Wks 4 +6	SCR through EOS (Wk +6)	SCR (RI), Wks 4, +6	SCR (RI), Wks 4, +6
CV145-010	SCR through EOS (D1 – 15)	ND	SCR; BL; D15 (EOS)	H, C, U: SCR; BL; D15 (EOS) Coag: SCR; BL; D7, 15 Lipids, LFTs: also on D4, 8, 11	ND	SCR; pre-Rx & 0.5, 1, 2, 3, 4, 6, 8, 12, 24 hrs post-Rx on Days 1 & 14; pre-Rx Days 2, -13; Day 15 (EOS)	SCR	SCR; BL; D8, 15 (EOS)	SCR through EOS (D1 – 15)	BL; D15 (EOS)	ND
Single Dose Studies											
AEGR-733-010	BL through discharge (D7)	ND	SCR; BL; D7 (EOS)	SCR; BL; D7 (EOS)	ND	SCR; BL; D1-7 (EOS)	SCR	SCR; BL; D7 (EOS)	BL through discharge (D7)	ND	ND
AEGR-733-017	BL through D10 (EOS)	ND	SCR; BL & D10 (EOS)	SCR; BL & D10 (EOS)	ND	SCR; BL; D1-9; D10 (EOS)	BL, D10 (EOS)	SCR; BL & 10 (EOS)	BL through D10 (EOS)	ND	ND

STUDY	SAFETY EVALUATIONS										
	AEs	GSRS	PE	SAFETY LABS	FAT SOLUBLE NUTRIENTS	VITAL SIGNS	WEIGHT/ BMI	EKGs	CON-COMITANT MEDI-CATIONS	PFTs	NMRS/ MRI
AEGR-733-021	BL through discharge (D6)	ND	SCR; BL; D6 (EOS)/ET	SCR; BL; D6 (EOS)/ET	ND	SCR; BL; D1-5; D6 (EOS)/ET	SCR; BL; D6 (EOS)/ET	SCR; BL; D6 (EOS)/ET	SCR through discharge (D6)	ND	ND
CV145-001	BL through EOS (T0 – T72)	ND	SCR; BL; D4 (T72) (EOS)	SCR; BL; T24, 48, 72	ND	SCR; BL; T0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72h	SCR	SCR; BL; T4, 24, 72 (EOS)	SCR through EOS	ND	ND
CV145-003	SCR through EOS (T0 – 72)	ND	SCR; BL; D4 (T72) (EOS)	SCR; BL; T72	ND	SCR; BL; T20, 30m, T1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72h	SCR	SCR; BL; T4, 24, 72 (EOS)	SCR through EOS	ND	ND
CV145-006	BL through EOS (D1 – D11)	ND	SCR; EOS	SCR; BL; EOS	ND	SCR; BL; EOS	SCR; EOS	SCR; EOS	SCR through EOS	ND	ND
Drug-Drug Interaction Studies											
AEGR-733-002	BL through EOS (D1 – 15)	ND	BL	SCR; BL; D8, D15	ND	SCR; BL; D8	SCR; BL; D8	SCR	SCR through EOS	ND	ND
AEGR-733-013	BL through EOS (D21)	ND	SCR; BL; D21 (EOS)	SCR; BL; D1, 9, 14, 17, 21 (EOS)	ND	SCR; BL; D1; 9-21 (EOS)	SCR	SCR; BL; D21 (EOS)	SCR through EOS	ND	ND
AEGR-733-015	BL through EOS	ND	SCR; BL; D28 (EOS)	SCR; BL; D14, 28 (EOS)	ND	SCR; BL; D14-22; D28 (EOS)	SCR	SCR; BL; D14, 28 (EOS)	SCR through EOS	ND	ND
AEGR-733-018	BL through EOS	ND	SCR; BL; D18 (EOS)	SCR; BL; D1, 7, 10, 17, 18 (EOS)	ND	SCR; BL; D1, 7-10, 17, 18 (EOS)	SCR	SCR; BL; D18 (EOS)	SCR through EOS	ND	ND

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STUDY	SAFETY EVALUATIONS										
	AEs	GSRs	PE	SAFETY LABS	FAT SOLUBLE NUTRIENTS	VITAL SIGNS	WEIGHT/ BMI	ECGs	CON-COMITANT MEDI-CATIONS	PFTs	NMRS/ MRI
AEGR-733-019	BL through D+7-10 (EOS)	ND	SCR; BL; D9	SCR; BL; D1, 2, 8, 9 +7-10 (EOS)	ND	SCR; BL; D1 to 9, D+7-10 (EOS)	SCR	SCR; BL; D9	SCR through EOS	ND	ND
CV145-005 ³	SCR through discharge	ND	SCR, pre-Rx (each period); discharge	SCR, pre-Rx (each period); discharge	ND	SCR, pre-Rx & end of Rx (each period); discharge	SCR	SCR; discharge	SCR through discharge	ND	ND
Special Safety Study											
AEGR-733-011 ⁴	BL through D5	ND	BL; D5, +6-10	SCR; BL; D5, +6-10	ND	SCR; BL; D1&3; T0, 3, 10, 24, 48; D+6-10	SCR; BL; D+6-10	See Note ⁸	SCR through D+6-10	ND	ND

AE=adverse events, BL = baseline, BMI=body mass index, C = chemistry, Coag = coagulation, D=day, ECG=electrocardiogram, EOS = end of study, EOT = end of treatment, ET = early termination; GSRs=Gastrointestinal Symptom Rating Scale, h = hour, H = haematology, m=minute, LFT = liver function tests, ND=not done, NMRS/MRI=nuclear magnetic resonance imaging/magnetic resonance imaging, PE=physical examination, PFT=pulmonary function tests, PT = prothrombin time, RI = Run-In, Rx = treatment, SCR = screening; U = urinalysis, T1, T2, Txx = 1, 2, xx hours (or minutes) post-dose, Wk = week.

- 1 Safety data through the Week 56 assessment are summarized.
- 2 Extension study for patients treated in UP1002/AEGR-733-005; only AEs of special interest, serious adverse events and AEs leading to discontinuation are summarized for this ongoing study.
- 3 Food effect PK study
- 4 Thorough QTc study
- 5 Wk 84 only for patients who did not enter the optional extension study.
- 6 LFTs only
- 7 Week 78 from UP1002/AEGR-733-005
- 8 Continuous ECG monitoring Predose at -45, -30, and -15 minutes (baseline) on Day 1 and at 1, 2, 3, 4, 5, 7, 12, and 24 hours postdose on Days 1 and 3.

Source: Summary of Clinical Safety (M2.7.4), Table 2.

Table 127. HoFH-pivotal – Subject 01-004 Transaminase Trend

Visit	Day	Dose	ALT	AST	Notes
Wk 0	1	↑ 5	29	28	Baseline
Wk 2	15	↑ 10	95 (2.4x)	83 (1.9x)	
Wk 6	43	↑ 20	307 (7.7x)	140 (3.3x)	
	53	20	423 (10.6x)	205 (4.8x)	
	56	↓ 10			Dose reduction for ALT
	62	10	206 (5.2x)	107 (2.5x)	
Wk 10	71	10	120 (3.0x)	64 (1.5x)	
	82	↑ 20			
	91	20	67 (1.7x)	44	
Wk 14	99	↑ 40	103 (2.6x)	65 (1.5x)	
Wk 18	127	↑ 60	222 (5.6x)	100 (2.3x)	
	140	60	308 (7.7x)	151 (3.5x)	
	144	↓ 20			Dose reduction for ALT
	153	20	249 (6.2x)	121 (2.8x)	
Wk 22	155	20	198 (5.0x)	81 (1.9x)	
	167	20	132 (3.3x)	50 (1.2x)	
	169	↑ 40			
Wk 26	183	40	146 (3.7x)	75 (1.7x)	
	218	40	300 (7.5x)	143 (3.3x)	
	225	40	272 (6.8x)	146 (3.4x)	
	229	↓ 20			Dose reduction for ALT
	238	20	167 (4.2x)	80 (1.9x)	
Wk 36	253	↑ 40	147 (3.7x)	62 (1.4x)	
	...	40	...	...	ALT remained ≥3x but <5x ULN (with one exception of 2.5x ULN)
Wk 78	561	40	192 (4.8x)	127 (3.0x)	

Source: FDA clinical reviewer's analysis of submitted laboratory and exposure datasets (*LB xpt* and *EX.xpt*).

Arrows denote a change in dose on the respective study day. For example, "↑ 40" on day 99 indicates that the dose was changed from 20 mg to 40 mg on study day 99.

Table 128. HoFH-pivotal – Subject 02-002 Transaminase Trend

Visit	Day	Dose	ALT	AST	Notes
Wk 0	1	↑ 5	52 (1.3x)	31	
Wk 2	15	↑ 10	50 (1.3x)	31	
Wk 6	43	10	199 (5.0x)	63 (1.5x)	
	50	10	309 (7.7x)	122 (2.8x)	
	51	↓ 5			Dose reduction for ALT
	58	5			
	62	5	124 (3.1x)	47 (1.1x)	
	64	↑ 10			
Wk 10	71	10	50 (1.3x)	24	
	103	↑ 20			
	126	↑ 40			
Wk 22	153	40	28	19	
	154	↑ 60			
Wk 26	183	60	140 (3.5x)	70 (1.6x)	
	198	↓ 40			Didn't complete 60mg phase prior to week 26 (dose

Visit	Day	Dose	ALT	AST	Notes
					interruptions for GI AEs); MTD = 40 mg
	225	40	183 (4.6x)	76 (1.8x)	
	232	40	323 (8.1x)	130 (3.0x)	
	233	0			Dose interruption for ALT
	239	0	200 (5.0x)	107 (2.5x)	
Wk 36	253	0	222 (5.6x)	67 (1.6x)	
	265	0	107 (2.7x)	37	
Wk 41	281	0	54 (1.4x)	29	
	285	↑ 5			
	327	↑ 10			
	359	↑ 20			
	...	20	...	...	ALT remained <1.3x ULN
Wk 78	547	20	35	22	

Source: FDA clinical reviewer's analysis of submitted laboratory and exposure datasets (LB xpt and EX.xpt).

Table 129. HoFH-pivotal – Subject 12-004 Transaminase Trend

Visit	Day	Dose	ALT	AST	Notes
Wk 0	1	↑ 5	26	25	
Wk 2	15	↑ 10	23	25	
Wk 6	43	↑ 20	38	36	
Wk 10	70	↑ 40	67 (2.0x)	51 (1.4x)	
Wk 14	99	↑ 60	92 (2.8x)	61 (1.7x)	
Wk 18	127	60	216 (6.6x)	146 (4.1x)	
	128	↑ 80			Protocol violation; escalated dose despite ALT & LDL-C <200 mg/dL
	134	80	173 (5.2x)	119 (3.3x)	
	139	↓ 60			Dose reduction for ALT
	142	↓ 40			Dose reduction for ALT (incorrectly reduced to 60 mg instead of 40 mg on day 139)
	149	40	150 (4.6x)	84 (2.3x)	
Wk 22	155	↑ 60	118 (3.6x)	74 (2.1x)	
	162	60	144 (4.4x)	106 (2.9x)	
	169	60	93 (2.8x)	60 (1.7x)	
Wk 26	183	60	67 (2.0x)	49 (1.4x)	
Wk 31	228	60	54 (1.6x)	34	
	...	60	...	...	ALT remained <2x ULN
Wk 78	547	60	51 (1.5x)	35	

Source: FDA clinical reviewer's analysis of submitted laboratory and exposure datasets (LB xpt and EX.xpt).

Table 130. HoFH-pivotal – Subject 32-001 Transaminase Trend

Visit	Day	Dose	ALT	AST	Notes
Wk 0	1	↑ 5	27	24	
Wk 2	15	↑ 10	72 (1.8x)	51 (1.2x)	
Wk 6	43	↑ 20	399 (10.0x)	321 (7.5x)	

Visit	Day	Dose	ALT	AST	Notes
	44	↓ 10			Dose reduction for ALT
	50		297 (7.4x)	185 (4.3x)	
	53	↓ 5			Further dose reduction for ALT
Wk 10	71	5	67 (1.7x)	43	
Wk 14	99	5	64 (1.6x)	50 (1.2x)	
	...	5			ALT varied between 1.2x and 2.7x ULN
Wk 66	447	5	113 (2.8x)	97 (2.3x)	

Source: FDA clinical reviewer's analysis of submitted laboratory and exposure datasets (*LB xpt* and *EX.xpt*).

Peak ALT elevation = 9.98x ULN; therefore, categorized in other tables as $\geq 5x < 10x$ ULN.

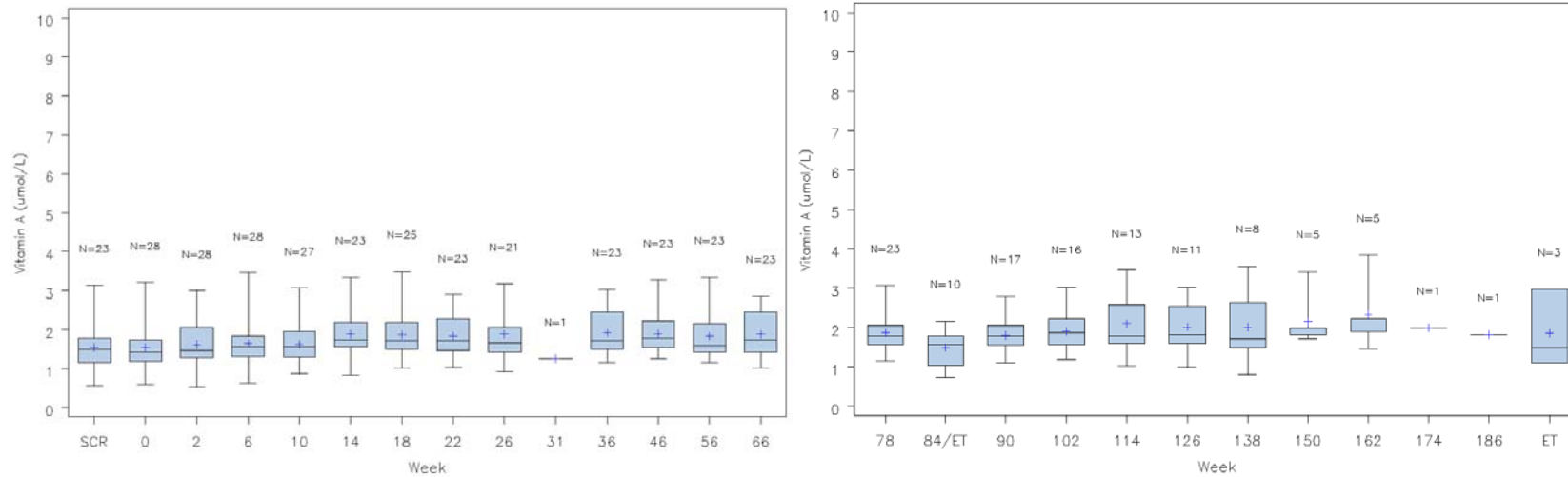


Figure 71. HoFH-pivotal & extension – Vitamin A

Source: 120-day safety update, Figure 1.3.11. “84/ET” = Off-treatment HoFH-pivotal visit or early termination (ET).

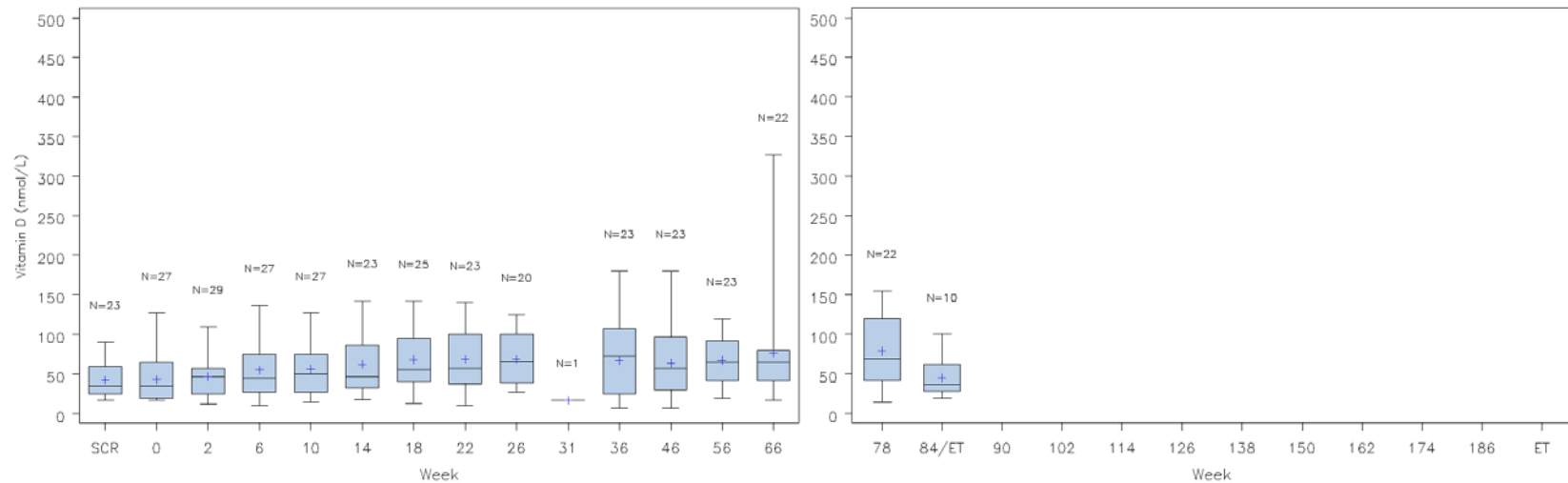


Figure 72. HoFH-pivotal – Vitamin D

Source: 120-day safety update, Figure 1.3.11. “84/ET” = Off-treatment HoFH-pivotal visit or early termination (ET).

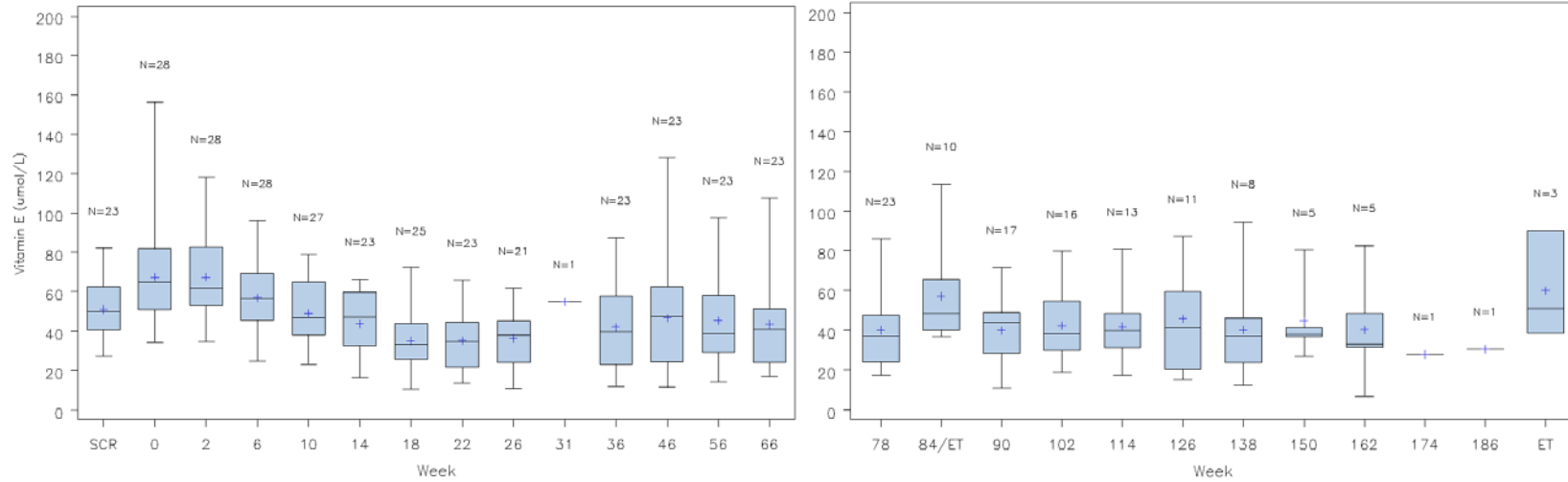


Figure 73. HoFH-pivotal & extension – Vitamin E

Source: 120-day safety update, Figure 1.3.11. “84/ET” = Off-treatment HoFH-pivotal visit or early termination (ET).

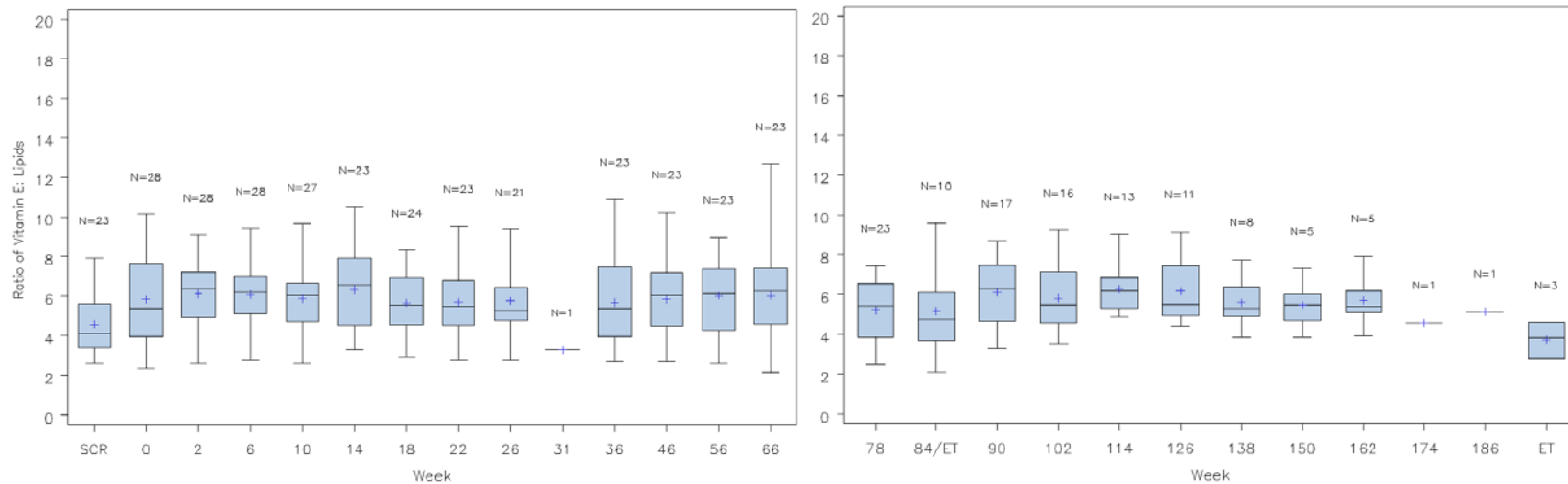


Figure 74. HoFH-pivotal & extension – Vitamin E:Lipids (TC+TG)

Source: 120-day safety update, Figure 1.3.11. “84/ET” = Off-treatment HoFH-pivotal visit or early termination (ET).

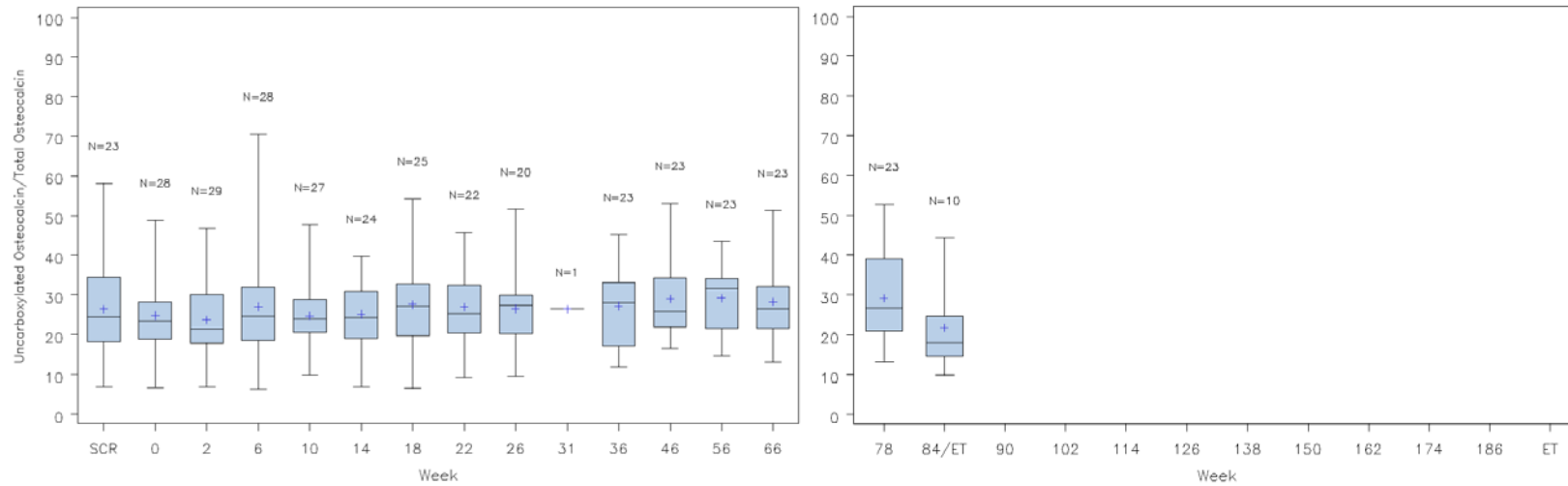


Figure 75. HoFH-pivotal – % Osteocalcin Uncarboxylated

Source: 120-day safety update, Figure 1.3.11. “84/ET” = Off-treatment HoFH-pivotal visit or early termination (ET). Higher proportions of uncarboxylated osteocalcin suggest functional vitamin K deficiency.

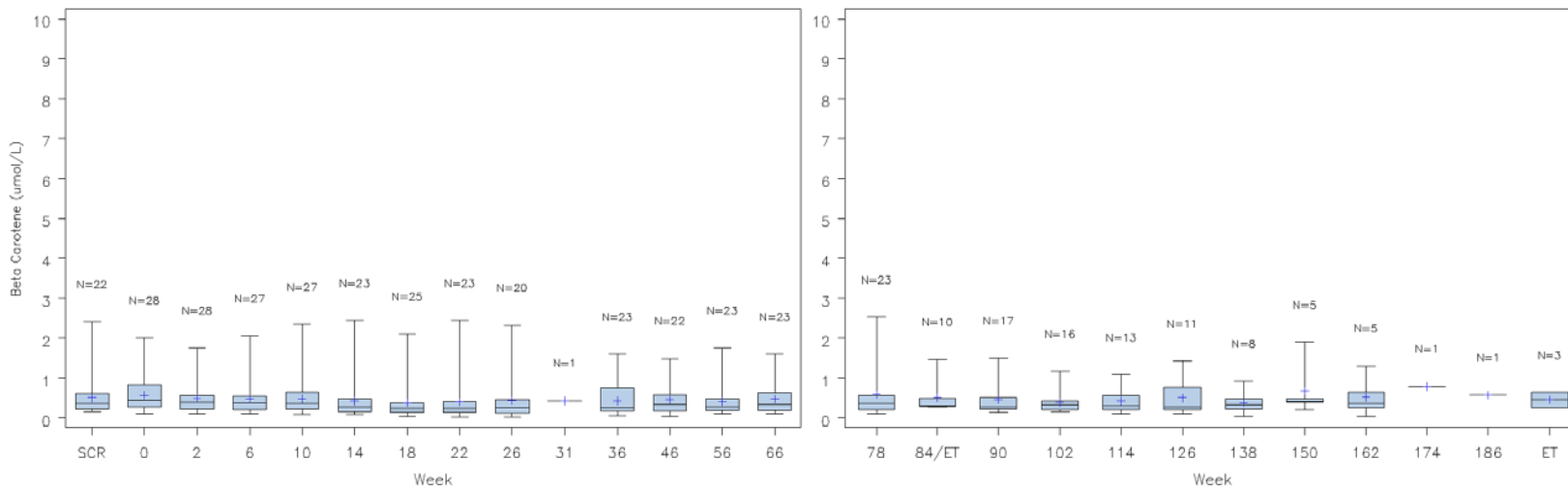


Figure 76. HoFH-pivotal – Beta-carotene

Source: 120-day safety update, Figure 1.3.11. “84/ET” = Off-treatment HoFH-pivotal visit or early termination (ET).

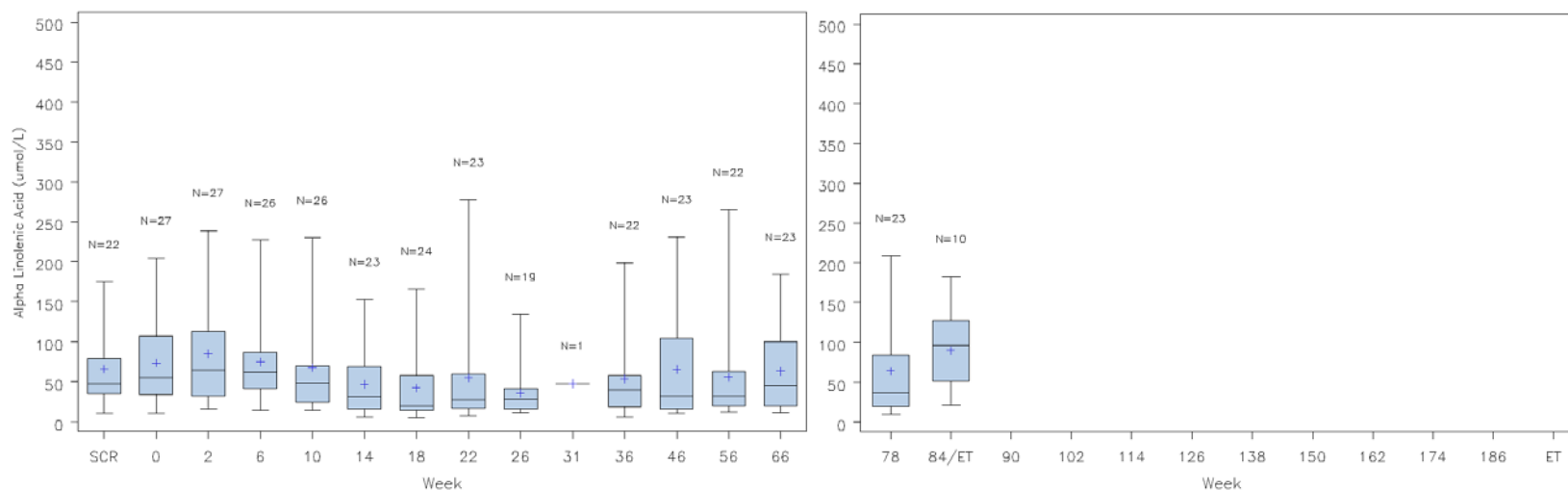


Figure 77. HoFH-pivotal – Alpha-Linolenic Acid

Source: 120-day safety update, Figure 1.3.11. “84/ET” = Off-treatment HoFH-pivotal visit or early termination (ET).

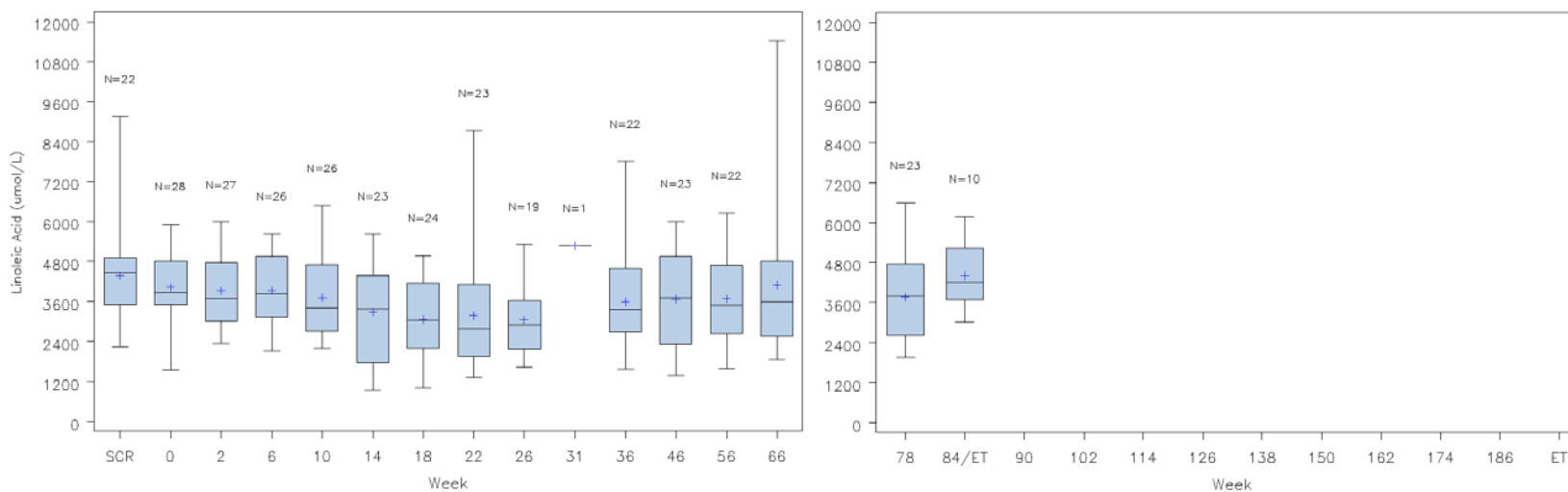


Figure 78. HoFH-pivotal – Linoleic Acid

Source: 120-day safety update, Figure 1.3.11. “84/ET” = Off-treatment HoFH-pivotal visit or early termination (ET).

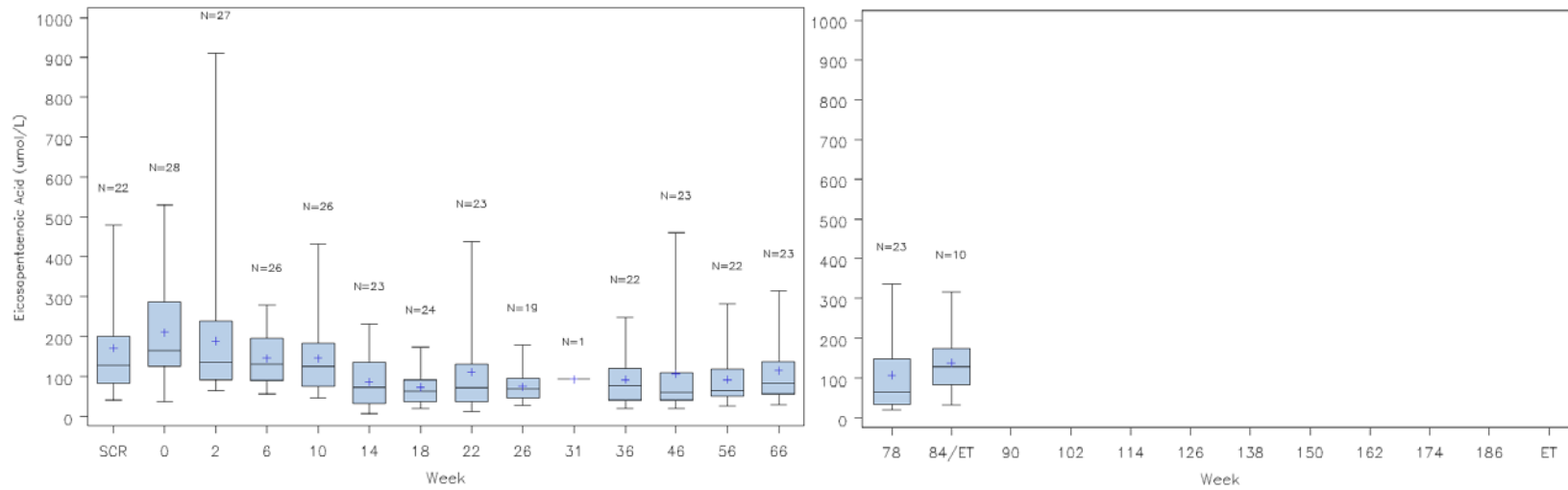


Figure 79. HoFH-pivotal – Eicosapentaenoic Acid (EPA)

Source: 120-day safety update, Figure 1.3.11. “84/ET” = Off-treatment HoFH-pivotal visit or early termination (ET).

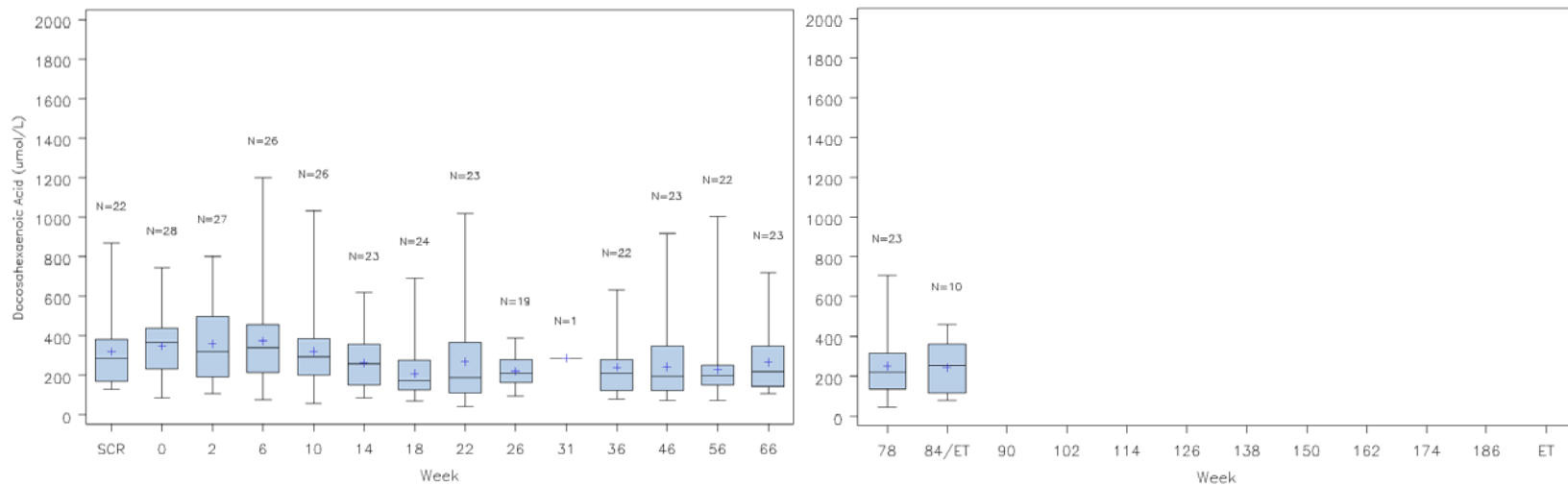


Figure 80. HoFH-pivotal – Docosahexaenoic Acid (DHA)

Source: 120-day safety update, Figure 1.3.11. “84/ET” = Off-treatment HoFH-pivotal visit or early termination (ET).

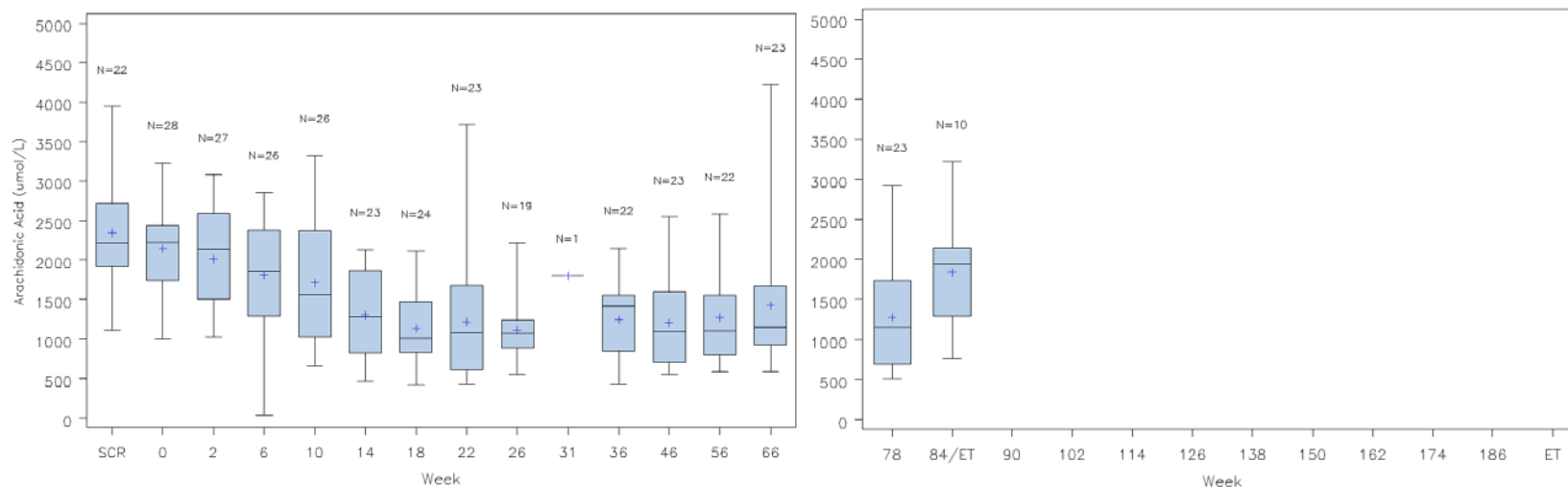


Figure 81. HoFH-pivotal – Arachidonic Acid

Source: 120-day safety update, Figure 1.3.11. “84/ET” = Off-treatment HoFH-pivotal visit or early termination (ET).

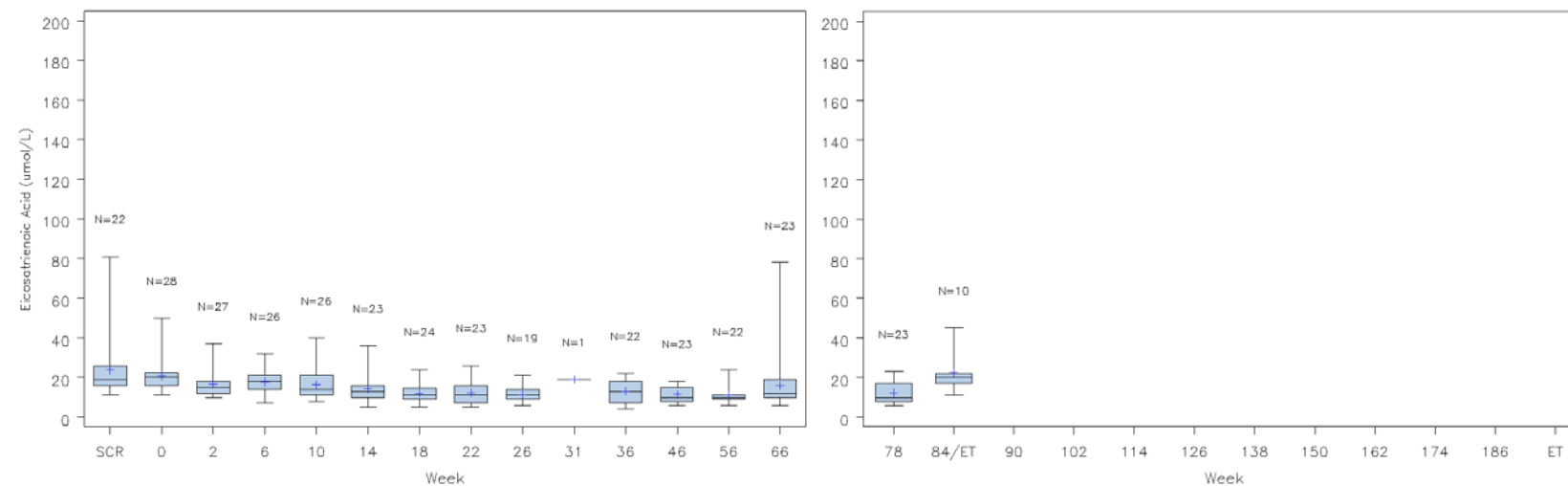


Figure 82. HoFH-pivotal – Eicosatrienoic (Mead) Acid

Source: 120-day safety update, Figure 1.3.11. “84/ET” = Off-treatment HoFH-pivotal visit or early termination (ET).

Increased values of Mead acid can accompany essential fatty acid deficiency.

Table 131. "Elevated LDL-C" Safety Pool – Common AEs by Sex

PREFERRED TERM	LOMITAPIDE DOSE GROUP ¹								COMPARATOR			
	ESCALATED (5-10 MG) N (%)		LOW DOSE (2.5-7.5 MG) N (%)		MID DOSE (10 MG) N (%)		HIGH DOSE (25-100 MG) N (%)		PLACEBO N (%)		ACTIVE CONTROL N (%)	
	MALE (N=39)	FEMALE (N=38)	MALE (N=121)	FEMALE (N=123)	MALE (N=41)	FEMALE (N=58)	MALE (N=42)	FEMALE (N=20)	MALE (N=64)	FEMALE (N=52)	MALE (N=31)	FEMALE (N=47)
Diarrhoea	11 (28.2)	19 (50.0)	64 (52.9)	58 (47.2)	24 (58.5)	39 (67.2)	30 (71.4)	16 (80.0)	8 (12.5)	5 (9.6)	5 (16.1)	2 (4.3)
Nausea	3 (7.7)	6 (15.8)	18 (14.9)	28 (22.8)	11 (26.8)	25 (43.1)	9 (21.4)	10 (50.0)	1 (1.6)	3 (5.8)	0	5 (10.6)
Flatulence	4 (10.3)	5 (13.2)	8 (6.6)	19 (15.4)	4 (9.8)	5 (8.6)	7 (16.7)	5 (25.0)	1 (1.6)	6 (11.5)	1 (3.2)	1 (2.1)
Headache	1 (2.6)	3 (7.9)	8 (6.6)	20 (16.3)	0	4 (6.9)	3 (7.1)	4 (20.0)	5 (7.8)	8 (15.4)	2 (6.5)	2 (4.3)
Abdominal distension	1 (2.6)	3 (7.9)	9 (7.4)	10 (8.1)	3 (7.3)	5 (8.6)	4 (9.5)	4 (20.0)	1 (1.6)	3 (5.8)	0	6 (12.8)
Vomiting	1 (2.6)	5 (13.2)	6 (5.0)	9 (7.3)	3 (7.3)	5 (8.6)	4 (9.5)	3 (15.0)	1 (1.6)	2 (3.8)	0	0
Alanine aminotransferase increased	12 (30.8)	5 (13.2)	7 (5.8)	6 (4.9)	1 (2.4)	2 (3.4)	3 (7.1)	0	1 (1.6)	0	0	1 (2.1)
Dyspepsia	5 (12.8)	3 (7.9)	10 (8.3)	6 (4.9)	3 (7.3)	3 (5.2)	1 (2.4)	0	0	3 (5.8)	1 (3.2)	3 (6.4)
Abdominal pain upper	2 (5.1)	0	7 (5.8)	10 (8.1)	6 (14.6)	3 (5.2)	2 (4.8)	2 (10.0)	0	4 (7.7)	0	0
Abdominal pain	2 (5.1)	2 (5.3)	5 (4.1)	5 (4.1)	1 (2.4)	6 (10.3)	7 (16.7)	2 (10.0)	1 (1.6)	1 (1.9)	1 (3.2)	2 (4.3)
Fatigue	0	2 (5.3)	8 (6.6)	9 (7.3)	2 (4.9)	2 (3.4)	3 (7.1)	2 (10.0)	0	3 (5.8)	0	0
Aspartate aminotransferase increased	7 (17.9)	4 (10.5)	6 (5.0)	6 (4.9)	1 (2.4)	2 (3.4)	2 (4.8)	0	1 (1.6)	0	0	1 (2.1)
Constipation	2 (5.1)	3 (7.9)	8 (6.6)	4 (3.3)	0	0	0	1 (5.0)	2 (3.1)	2 (3.8)	0	3 (6.4)
Back pain	0	1 (2.6)	2 (1.7)	7 (5.7)	1 (2.4)	1 (1.7)	3 (7.1)	1 (5.0)	2 (3.1)	4 (7.7)	0	3 (6.4)
Nasopharyngitis	0	0	7 (5.8)	4 (3.3)	1 (2.4)	1 (1.7)	1 (2.4)	0	3 (4.7)	3 (5.8)	2 (6.5)	2 (4.3)
Abdominal discomfort	4 (10.3)	1 (2.6)	2 (1.7)	2 (1.6)	2 (4.9)	3 (5.2)	3 (7.1)	1 (5.0)	0	1 (1.9)	1 (3.2)	1 (2.1)
Decreased appetite	0	1 (2.6)	2 (1.7)	2 (1.6)	1 (2.4)	6 (10.3)	4 (9.5)	0	0	0	0	0
Dizziness	0	0	0	4 (3.3)	1 (2.4)	1 (1.7)	1 (2.4)	3 (15.0)	1 (1.6)	2 (3.8)	0	2 (4.3)
Eructation	2 (5.1)	2 (5.3)	0	0	2 (4.9)	2 (3.4)	0	2 (10.0)	1 (1.6)	0	0	0
Asthenia	0	0	1 (0.8)	3 (2.4)	1 (2.4)	0	2 (4.8)	2 (10.0)	0	0	0	0

Source: Table 1.3.3

¹ Includes subjects who received lomitapide alone and coadministered with other lipid-lowering drugs.

Source: ISS Table 56.

Common AEs = Treatment-emergent adverse events reported by ≥5% of subjects in a treatment group.

Table 132. AEGR-733-002 DDI Study – Geometric Mean Ratios for C_{max} and AUC

AEGR-733 Dose	Analyte	C _{max}	AUC ₀₋₄
		% MR (90% CI)	% MR (90% CI)*
10 mg	Atorvastatin Acid (Group A)	119.18 (99.89, 142.19)	110.97 (98.42, 125.12)
	2-OH-Atorvastatin (Group A)	101.57 (76.13, 135.50)	100.80 (87.27, 116.43)
	4-OH-Atorvastatin (Group A)**	97.43 (75.94, 125.02)	140.76 (106.28, 186.43)
	Sum of Active Atorvastatin Moieties (Atorvastatin acid + 2-OH + 4-OH metabolites) Group A**	112.17 (88.93, 141.49)	104.63 (92.76, 118.02)
10 mg	Simvastatin Acid (Group B)	134.95 (111.30, 163.63)	138.76 (109.65, 175.61)
	Simvastatin (lactone) (Group B)	165.15 (136.68, 199.56)	162.25 (143.19, 183.86)
10 mg	Total Ezetimibe (Group C)	102.70 (74.10, 142.34)	105.71 (92.62, 120.66)
	Unconjugated Ezetimibe (Group C)	107.78 (75.85, 153.14)	118.33 (95.90, 146.01)
	Conjugated Ezetimibe (Group C)	102.74 (73.45, 143.72)	104.08 (92.26, 117.43)
10 mg	Rosuvastatin (Group D)	106.13 (76.02, 148.17)	102.05 (86.00, 121.10)
10 mg	Fenofibric Acid (Group E)	70.64 (59.64, 83.65)	89.62 (82.76, 97.04)
10 mg	NA (Group I)	111.24 (61.17, 202.29)	110.22 (78.28, 155.18)
	NUA (Group I)	85.04 (65.06, 111.16)	79.15 (59.82, 104.72)
	2PY (Group I)	98.28 (88.28, 109.42)	96.10 (86.51, 106.76)
	MNA (Group I)	105.01 (92.90, 118.69)	135.84 (110.52, 166.97)
60 mg	Atorvastatin Acid (Group F)	163.24 (134.45, 198.20)	152.32 (133.76, 173.45)
	2-OH-Atorvastatin Acid (Group F)	101.41 (86.12, 119.42)	107.27 (97.17, 118.42)
	4-OH-Atorvastatin Acid (Group F)	138.46 (116.66, 164.32)	149.05 (106.73, 208.16)
	Sum of Active Atorvastatin Moieties (Group F)	138.34 (119.74, 159.83)	128.77 (115.29, 143.81)
60 mg	Rosuvastatin (Group G)	103.81 (81.57, 132.10)	132.21 (111.56, 156.70)

*Derived from the ANOVA of ln-transformed parameters

Dose Group A = 20 mg Atorvastatin with 10 mg AEGR-733
 Dose Group B = 20 mg Simvastatin with 10 mg AEGR-733
 Dose Group C = 10 mg Ezetimibe with 10 mg AEGR-733
 Dose Group D = 20 mg Rosuvastatin with 10 mg AEGR-733
 Dose Group E = 145 mg Micronized Fenofibrate with 10 mg AEGR-733
 Dose Group F = 20 mg Atorvastatin with 60 mg AEGR-733
 Dose Group G = 20 mg Rosuvastatin with 60 mg AEGR-733
 Dose Group I = 1000 mg ER Niacin with 10 mg AEGR-733

**Subject AE022 was excluded due to anomalous concentration-time profile

Source: AEGR-733-002 CSR, Synopsis.

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

/s/

JAMES P SMITH
11/27/2012

ERIC C COLMAN
11/27/2012

NDA Number: 203858

Applicant: Aegerion

Stamp Date: 29 Feb 2012

Drug Name: Iomitapide

Filing Meeting: 16 April 2012
 Filing Date: 27 April 2012
 Mid-cycle Review Meeting: 16 July 2012
 Reviews signed-off in DARRTS: 22 October 2012
 Action Goal Date: 10 December 2012
 PDUFA Date: 29 December 2012

Background

Homozygous familial hypercholesterolemia (HoFH) is a rare, autosomal-dominant disease characterized by marked elevations in LDL-C. Individuals with this disease typically are homozygous or compound heterozygous for mutations in the LDL-receptor (LDL-R) gene, which leads to impaired LDL-R function. Because the LDL-R removes LDL particles from plasma via endocytosis, absent or defective LDL-R substantially reduces cellular uptake of LDL-C, leading to abnormally high levels of LDL-C in the systemic circulation. Extremely high levels of LDL-C put these individuals at high risk for early and severe cardiovascular disease: clinical manifestations, which typically present before the age of 20 years, include corneal arcus, xanthomata, and diffuse and accelerated atherosclerotic disease. Untreated, patients typically do not survive beyond 30 years as a result of a high incidence of cardiac death.

The mainstay of treatment for hypercholesterolemia in the general population, HMG-CoA reductase inhibition with statins, is only modestly effective in patients with HoFH. Statins reduce intracellular cholesterol, leading to increased expression of LDL-R, which enhances clearance of LDL-C from the plasma. Because patients with HoFH have severely attenuated LDL-R function, the efficacy of these drugs is impaired. Patients with HoFH, therefore, typically resort to LDL apheresis to reduce levels of LDL-C if this treatment is available; this extracorporeal treatment is often performed weekly to monthly since it only transiently reduces LDL-C. Other more-extreme treatment approaches have included portacaval shunting, ileal bypass surgery, and liver transplantation. All of these therapies carry significant morbidity and long-term consequences.

Lomitapide is a small-molecule inhibitor of microsomal triglyceride transfer protein (MTP), which is responsible for transferring triglycerides (TG) onto apolipoprotein B (apo B) during the assembly of VLDL, the precursor to LDL. Naturally occurring loss-of-function mutations in the MTP protein are responsible for the clinical condition abetalipoproteinemia, which is characterized by very low levels of plasma cholesterol, TG, and apo B. Lomitapide was developed to treat hypercholesterolemia, and because its mechanism of action does not rely on functional LDL-R, it was hypothesized to be an effective therapy for patients with HoFH. Notably, individuals with inherited abetalipoproteinemia can also exhibit marked fat malabsorption, acanthocytosis, hepatomegaly secondary to hepatic steatosis, and a deficiency in fat-soluble vitamins that results in atypical retinitis pigmentosa, coagulopathy, central and peripheral demyelination (e.g., posterior column neuropathy), and myopathy.

Regulatory History

Date	Event / Notes
18 Jun 1996	IND 50820 submitted by Bristol-Myers Squibb (BMS) BMS-201038 for treatment of mixed dyslipidemia.
08 Jan 1997	EOP1 Meeting
18 Feb 1998	Meeting to discuss safety issues and clinical development plan
21 Aug 2002	IND 50820 transferred to Daniel J. Rader, MD, University of Pennsylvania Anticipated for treatment of HoFH
20 July 2004	EOP2 Teleconference

Date	Event / Notes
	• <i>Potential for DDI noted by the Division given that BMS-201038 appeared to be a potent CYP3A4 inhibitor. Given the potential for combination with other lipid-altering drugs in clinical practice, DDI studies with simvastatin, atorvastatin, rosuvastatin, and ezetimibe were considered necessary.</i> • <i>Concern about pulmonary phospholipidosis (PL) in chronic rodent toxicity studies without an established NOAEL. Dr. Rader noted that pulmonary function tests were performed in clinical studies and function was reported as normal.</i> • <i>DMEP asked for information about the metabolic enzyme responsible for the test drug.</i> • <i>DMEP noted that any expanded use of the product beyond HoFH would shift the risk-benefit profile of the development program.</i>
27 Jan 2006	OOPD Grant 1R01 FD003098-01 awarded for MTP Inhibitor for Familial Hypercholesterolemia (PI: Marina Cuchel, MD, PhD)
28 Aug 2006	Division provided comments regarding pivotal Phase 3 trial, "A phase III study of the MTP inhibitor BMS-201038 in patients with severe refractory hypercholesterolemia on current lipid lowering therapy." • <i>PK/PD DDI studies with warfarin and a CYP2D6 substrate were highly recommended.</i>
07 Feb 2007	EOP2 teleconference to discuss pivotal trial for HoFH indication • <i>DMEP agreed that a proposed sample size of 25 subjects diagnosed with HoFH, all of whom would receive BMS-201038 at the maximum tolerated dose for a minimum of 52 weeks, should be adequate for the assessment of efficacy in the proposed population.</i> • <i>DMEP encouraged the sponsor to include "sufficient numbers of women and Asians in the study population given that the behavior and potential toxicity of the drug is likely [to] be enhanced in these populations."</i> • <i>DMEP agreed with a dose-titration scheme to enhance tolerability, but the proposed dosages did not provide adequate safety margins for pulmonary phospholipidosis, which remained a concern.</i> • <i>Discussion of DDI PK study designs</i> • <i>DMEP agreed that no placebo arm would be required given a proposed design that included a minimum 6-week run-in period for all subjects where concomitant lipid-lowering treatment must remain stable. The sponsor stated that the concomitant treatment was to remain stable for the first 26 weeks of the study. In addition, a 6-week follow-up period was added following the last dose of BMS-201038 when concomitant lipid-lowering therapy should remain stable. "In addition, the absence of the placebo group allows that all subjects will be exposed to a minimum of 52 weeks at the maximum tolerated dose of study drug."</i> • <i>DMEP: "The dose titration scheme allows for patients to be treated at their maximum tolerated dose for 8.5-17 months, depending on the duration of their individualized titration. The sponsor is urged to follow patients for one year after their maximum tolerated dose has been achieved." The sponsor concurred.</i> • <i>DMEP and the sponsor agreed to CK monitoring, measurement of beta-carotene, vitamin K levels (via carboxylation of serum osteocalcin), major metabolites, alpha-tocopherol (reported as Vitamin E/LDL or Vitamin E/HDL ratios, and further testing such as adipose-tissue sampling with abnormal ratios), and hepatic fat (¹H MRS instead of MRI). Vitamin E supplementation would be increased to 400 IU daily.</i> • <i>The sponsor agreed to remove diabetes as an exclusion criterion.</i> • <i>Requirements for carcinogenicity, genotoxicity, and reproductive toxicology studies were discussed.</i>

Date	Event / Notes
	<i>DMEP suggested several pulmonary and hepatobiliary exclusions and prohibited concomitant medications (corticosteroids, betaine).</i>
13 Apr 2007	IND 50820 transferred to Aegerion for development of (now) AEGR-733 for "moderate hypercholesterolemia," which included severe refractory hypercholesterolemia
16 May 2007	IND 77775 submitted by Daniel J. Rader, MD, University of Pennsylvania, for HoFH
07 June 2007	Partial clinical hold (PCH) for IND 50820 (studies >6 months duration) <i>In October 2006, after consultation with the Division of Gastroenterology Products, the Division of Pulmonary and Allergy Products, and consideration of the pharm/tox review of the pre-clinical data, all MTP inhibitors – with the exception of IND 77775 – were placed on PCH for clinical protocols >6 months duration because "insufficient information is available to assess the risk for pulmonary phospholipidosis with long-term use of the drug." Sponsors were asked to submit a final report from a completed 3-month, repeat-dose rat toxicology study that included a recovery group and a sufficient number of active doses to establish a NOAEL for pulmonary PL. The protocols were to include electron microscopy. IND 77775 was not placed on PCH because the risk-benefit ratio was considered distinct for the HoFH population.</i>
23 Oct 2007	Orphan drug designation for the treatment of HoFH (Designation 07-2459)
28 Feb 2008	IND 77775 transferred to Aegerion from Dr. Rader to facilitate conducting multi-site trials
10 Aug 2009	Teleconference with Aegerion in lieu of premature EOP2 meeting <i>At an 05 Aug 2009 internal meeting preceding a scheduled 12 Aug 2009 EOP2 teleconference, DMEP determined that lingering concerns regarding PL and the failure to study lomitapide in combination with an optimal statin dose in severe refractory hypercholesterolemia precluded an EOP2 meeting.</i> <i>Dr. Eric Colman informed representatives from Aegerion that the mouse carcinogenicity study results, which would include data on pulmonary PL, would need to be submitted before a discussion of phase 3 studies in the severe refractory hypercholesterolemic population.</i>
09 Nov 2009	Type B Face-to-face EOP2 Meeting with Aegerion <i>Mouse carcinogenicity data: malignant tumors in the small intestine and liver at high doses. Data had not been reviewed in detail by the Agency (submitted 26 Oct 2009). The rat carcinogenicity study was ongoing, but reportedly no tumors had been observed. DMEP stated that the rat results would be important in determining the overall safety implications for humans; "At minimum, the carcinogenicity findings with the respective systemic exposure multiples would be included in the label, if the drug is eventually approved."</i> <i>Pulmonary PL: DMEP had less concern given that a number of approved compounds (e.g., fluoxetine) were identified that were associated with pulmonary PL in animal studies without known pulmonary dysfunction in humans. However, Aegerion was encouraged to resolve this issue from a pre-clinical perspective.</i> <i>Hepatic steatosis: DMEP recommended a 6-month safety study to observe lomitapide's effect on hepatic fat, hepatic structure/function, and insulin sensitivity. Exploratory endpoints such as IL-6, CRP, CK18 fragments, and enhanced liver fibrosis (ELF) panel were suggested. The sponsor cited results from study 733-004 to answer safety questions regarding hepatic fat accumulation with lomitapide use; in this 12-week study in ~250 patients, hepatic fat was measured four times and the</i>

Date	Event / Notes
	<i>company stored samples that could be used to measure biomarkers.</i> <i>The sponsor stated their intent to submit an NDA if the rat carci study was negative and the Agency allowed them to focus on the refractor HeFH population, with appropriate liver monitoring. DMEP replied that additional information would be needed in the broader dyslipidemic population given that the drug would invariably be used by this population, even if approved for a very limited indication. The sponsor was encouraged to submit an updated development plan; this was submitted 18 Nov 2009.</i> <i>In response to pre-clinical questions about fecal fat, the sponsor submitted human study CV145002 report on 18 Dec 2009; on 29 Dec 2009, the agency told the firm that these data were insufficient to address the question of fecal fat excretion with lomitapide because the study was not adequately conducted.</i>
18 Feb 2010	Partial clinical hold lifted
17 May 2010	Type B Face-to-face EOP2 Meeting <i>Several clinical pharmacology comments were relayed to the sponsor prior to this meeting, including clarification of the dosing of lomitapide with respect to meals, requiring a DDI study with warfarin, requiring an investigation of the inhibition/induction potential of the major metabolites (such as M1 and M3) on major CYP enzymes in in vitro and possibly in vivo systems, and a renal impairment study. The sponsor was asked to justify why only the metabolites M1, M2, and M3 were to be monitored given that M8 was the most abundant metabolite.</i> <i>At this meeting, Aegerion informed DMEP that they were only pursuing the HoFH indication as a result of financial constraints. Aegerion was amenable to "whatever post-approval supply constraints were necessary to ensure that the drug was available only to the HoFH poupplation."</i> (b) (4) 
28 Jul 2010	Follow-up teleconference to discuss NDA limited to HoFH <i>"At the time of submission, all patients will have been treated for a minimum of 56 weeks. This was found acceptable by the Agency."</i> <i>Clinical pharmacology concerns were still outstanding. In addition to those mentioned previously, it was also a concern that lomitapide exposure was higher in women than in men. Furthermore, since the DDI study with simvastatin did not use the maximum dose of lomitapide, a separate DDI study with simvastatin and 60-mg lomitapide was recommended.</i>
03 Mar 2011	Orphan drug designation for the treatment of familial chylomicronemia
05 Apr 2011	Type B pre-NDA CMC meeting
14 Apr 2011	Fast-track designation request submitted
14 Jun 2011	Fast-track designation denied, as the development program was not designed to determine whether the product will reduce cardiovascular morbidity or mortality in the HoFH population or lower-risk populations
15 Jun 2011	Type B Face-to-face pre-NDA Meeting (Clinical questions only) <i>The sponsor was encouraged to characterize all metabolites.</i> <i>Regarding CYP3A4 DDIs, the sponsor "proposed to address the CYP3A4 interaction in labeling; the package insert will indicate to avoid taking lomitapide with moderate or mild CYP3A4 inhibitors in addition to strong CYP3A4 inhibitors. The agency agreed with this approach. The</i>

Date	Event / Notes
	<i>firm was encouraged to use simulations to evaluate the effect of mild and moderate CYP3A4 inhibitors on lomitapide. The labeling language will be a review issue. It was also strongly recommended that the sponsor address the in-vitro induction potential of lomitapide and its major metabolites on major CYP enzymes.”</i> • <i>The Agency agreed to the sponsor’s proposal to conduct a population PK analysis later in development by combining data from pediatric studies.</i> • <i>The Agency confirmed that a single, pivotal phase 3 study lacking a placebo control arm would not preclude filing or approval of the lomitapide NDA for the HoFH population.</i> • <i>The Agency agreed that the available exposure data from the single pivotal phase 3 study (UP1002/733-005) are sufficient to support an NDA for HoFH. Briefly, the sponsor stated that data would be available for 18 patients who had been exposed for at least 1.5 years and 10 who had been exposed for at least 2 years; maximum tolerated dose for patients receiving treatment for at least 2 years would range from 20 mg to 60 mg.</i> • <i>The Agency noted that including a “functional HoFH” definition of average fasting LDL > 300 mg/dL on maximally tolerated lipid-lowering therapy closely resembles the severe refractory HeFH population, which would shift the risk-benefit ratio. “Dr. Rader recognized that the treatment indication for lomitapide will need to align with the inclusion criteria of the Phase 3 trial. Additionally, Dr. Rader understood that inclusion of patients on maximal tolerated therapy with LDL >300 mg/dL for treatment with lomitapide (which was not an inclusion criterion in the Phase 3 trial) is a REMS issue that will be addressed as part of the NDA review process.”</i> • <i>Regarding a potential REMS, the sponsor was encouraged to submit all planned materials that would be necessary to implement their proposal and to provide detailed plans of how distribution would be restricted to the HoFH population studied in the Phase 3 trial, including how documentation of HoFH status would be collected and confirmed, how distribution would be accomplished, and how the system would be monitored for compliance.</i> • <i>CDISC SDTM and ADaM datasets would be submitted</i> • <i>The sponsor stated that the primary data to support the effectiveness and safety would come from the phase 3 study UP1002/733-005 with supportive data from UP1001 (HoFH, phase 2) and 5 other phase 2 studies that involved subjects with elevated LDL-C. The Agency agreed with the general approach.</i> • <i>The Agency accepted the proposed dates of database locks as long as adverse events of special interest that occurred afterward would be included in the safety update prior to filing the NDA.</i> • <i>Analyses and tables to facilitate the clinical review were requested (e.g., Hy’s Law cases, categorical laboratory-related analyses, review of reasons for dropout/discontinuation, analyses of changes in concomitant medications, correlations between compliance with dietary fat and adverse events, analyses regarding the number and frequency of adverse events depending on dose of concomitant statin, analyses comparing efficacy with and without LDL apheresis, data presentation to facilitate site selection for inspection).</i>

Labeling

In Module 1.14, the applicant has included draft labeling text in SPL format. Proposed labeling was submitted in both Microsoft Word and pdf format. In addition, annotated prescribing information was submitted.

REMS

The applicant submitted a proposed risk management plan in Module 1.16. Their proposal includes (1) a medication guide; (2) a communication plan, comprising a Dear Healthcare Provider letter, a Dear Professional Society letter, a prescriber's guide to important safety information, and a website; (3) elements to assure safe use, including certification of providers, dispensing drug through a limited number of specialty pharmacy providers, and dispensing drug only to patients with evidence or other documentation of safe-use conditions; (4) description of an implementation system; and (5) a timetable for submission of assessments.

Priority or Standard Review: Standard. This was conveyed to the sponsor in the letter acknowledging receipt of the application (03 March 2012).

Pediatric Waiver: Not required since orphan designation has been granted.

Debarment Certification

Aegerion Pharmaceuticals, Inc. certified that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (Module 1.3.3).

Financial Disclosures

No investigator reported disclosable financial interests or arrangements with the applicant. For study CV145-009, which was conducted in 1999, the applicant could not reach 23 investigators (4 sites); evidence of due diligence was submitted (Module 1.3.4).

Patent Exclusivity Request

The applicant included an exclusivity request in Module 1.3.5.3 for the 5-year exclusivity period applicable to approval of an NME. The applicant expects that approval would ultimately trigger the 7-year orphan exclusivity provision. The applicant included four patents owned by The Trustees of the University of Pennsylvania in Module 1.3.5.1.

Site Inspections

The safety and efficacy database for the HoFH population comprises one phase 2 study (UP1001) conducted by Dr. Daniel Rader (University of Pennsylvania) and one single-arm, open-label phase 3 pivotal study (UP1002/733-005). The phase 3 study included a total of 29 subjects at 11 sites (2 U.S.; 3 South Africa; 2 Canada; 4 Italy).

Each phase 3 study site contributed between 1 and 5 subjects. A preliminary review of AEs, SAEs, deaths, and discontinuations do not reveal any obvious site-level outliers. The FDA Site Selection Tool (v2.2) suggests the following three sites have the highest "total risk:" site 01 (U.S.), 11 (S. Africa), and 12 (S. Africa). These three sites enrolled 14 of the study's 29 subjects. With the exception of one Canadian site that enrolled 3 subjects, all other sites enrolled 1 or 2 subjects. The only other site in the U.S. (site 02) enrolled 2 subjects.

Because there is only one pivotal phase 3 trial, I suggest inspection of the two sites in S. Africa that collectively contributed nine (31%) of the study's 29 subjects.

Furthermore, because of the relatively limited clinical experience of lomitapide in the HoFH population, for whom higher dosages were used than those used for other hypercholesterolemic subjects studied in the development program, I suggest inspection of the only site that conducted a phase 2 study in the HoFH population (Dr. Daniel Rader, University of Pennsylvania).

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	# Subjects Enrolled	Indication
Site 01 (only site) Daniel J. Rader, M.D. University of Pennsylvania School of Medicine Philadelphia, PA	UP1001	6	HoFH
Site 01 Marina Cuchel, M.D., Ph.D. University of Pennsylvania Philadelphia, PA	UP1002/ 733-005	5	HoFH
Site 11 Dr. Dirk J. Blom University of Capetown Health Science Faculty Capetown, South Africa	UP1002/ 733-005	4	HoFH
Site 12 Prof. Hendrik du Toit Theron Netcare Private Hospital Bloemfontein, South Africa	UP1002/ 733-005	5	HoFH

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			Module 5.3.5.3.28
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Module 5.3.5.3.27
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Module 2.5
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	X			505(b)(1)
DOSE					

	Content Parameter	Yes	No	NA	Comment
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (<i>i.e.</i> , appropriately designed dose-ranging studies)?	X			Limited dose-ranging data for dosages exceeding 10 mg daily except for HoFH studies, which used dose-escalation design (5 to 60 mg).
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: UP1002/733-005 (HoFH) Single-arm, open-label trial with 26-wk efficacy phase + 52-wk safety phase (n=29). Submission includes all patients through week 56. Supportive Study: UP1001 (HoFH) Single-arm, open-label pilot study x 16 weeks (n=6).	X			Orphan indication. Pre-NDA agreement (e.g., see 15 June 2011 meeting minutes)
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			Orphan indication. Pre-NDA agreement (e.g., see 15 June 2011 meeting minutes)
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			Typical lipid-lowering endpoints.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		Requested
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			Orphan indication; target US population = 300 patients. Pivotal trial: 6 of 29 d/c'd prematurely; 22 of the remaining 23 had exposure ≥1

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
					yr (not necessarily all at max dose)
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			Pivotal: MedDRA v11.0; ISS recoded using MedDRA v14.0; verbatim & coded terms submitted
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Orphan designation
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

² The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			CV145-009, sponsored by BMS: Aegerion unable to obtain full disclosure information; record of due diligence submitted
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Module 2.7.3 (subheading: Section 1.3)

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No additional requests at this time.

James P. Smith, MD, MS

 Reviewing Medical Officer

April 16, 2012

 Date

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

/s/

JAMES P SMITH
04/27/2012

ERIC C COLMAN
04/27/2012