FDA Briefing Document

NDA 203858

Lomitapide Mesylate Capsules
5 mg, 10 mg, 20 mg

Applicant: Aegerion Pharmaceuticals, Inc.

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

October 17, 2012

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Section:

Draft Discussion Points for Advisory Committee

1. Discuss whether you believe that 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 low-density lipoprotein cholesterol (LDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

2. Provide your assessment of lomitapide's effect on high density lipoprotein cholesterol, triglyceride, apolipoprotein B, apolipoprotein AI, and Lp(a).

3. The reduction of LDL-C is a surrogate endpoint that is expected to correlate with a reduction in cardiovascular morbidity and mortality. The effect of lomitapide on cardiovascular outcomes will not be determined in the HoFH population given the rarity of this disease, and for the purposes of this discussion, assume that no additional outcomes data for lomitapide will be generated in other populations. Discuss whether you consider LDL-C an appropriate surrogate for reduced cardiovascular morbidity and mortality in lomitapide-treated patients with HoFH.

4. Regarding liver-related adverse effects observed in the lomitapide development program:

    a. Discuss your level of concern for the hepatic steatosis associated with lomitapide and the potential for steatohepatitis with chronic drug use.
    b. Discuss your level of concern regarding a possible association between hepatic steatosis and increased risk for cardiovascular morbidity and mortality.
    c. Discuss your level of concern for the transaminase abnormalities associated with lomitapide and the potential for drug-induced liver injury.
    d. If approved for the treatment of HoFH,
        - Discuss how patients treated with lomitapide should be monitored for liver-related adverse effects.
        - Comment on dosing recommendations (dose lowering, interruption or discontinuation) based on quantitative thresholds of liver transaminase elevations or steatotic changes.
        - Discuss population-based approaches to further characterize and assess liver safety post-approval.

5. Regarding the effect of lomitapide on dietary fat absorption:

    a. Discuss whether you believe that the applicant has sufficiently characterized the risk for deficiencies in fat-soluble vitamins and essential fatty acids.
    b. The applicant proposes to recommend through labeling that patients take 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." Discuss whether you believe this is adequate to mitigate the potential adverse effects of lomitapide on these nutrients.

6. Based on the information provided in the briefing materials, the presentations today, and the proposed risk evaluation and mitigation strategy, do you believe that the potential benefits of lomitapide outweigh its potential risks in patients with homozygous familial hypercholesterolemia?
   a. If YES, provide your rationale and any recommendations you have regarding risk management strategies, post-marketing studies, and clinical monitoring.
   b. If NO, provide your rationale and comment on what additional data you believe are required to potentially support approval.

Clinical Briefing Document

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

October 17, 2012

NDA 203858: lomitapide mesylate

Applicant: Aegerion Pharmaceuticals, Inc.

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Food and Drug Administration

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1 Executive Summary

Lomitapide is an orally administered first-in-class small-molecule inhibitor of microsomal triglyceride transfer protein (MTP), an intracellular enzyme critical to the assembly of apolipoprotein B (apoB)-containing lipoproteins in enterocytes and hepatocytes. Inhibition of MTP prevents the synthesis of chylomicrons and very-low-density lipoprotein (VLDL), which are precursors to the atherogenic low-density lipoprotein (LDL) particle. The proposed indication for lomitapide is to reduce LDL-cholesterol (LDL-C), total cholesterol (TC), apoB, and triglycerides (TG) in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis. The proposed recommended starting dose is 5 mg daily; after 2 weeks, the dose may be increased to 10 mg provided acceptable safety and tolerability, and then to 20 mg, 40 mg, and 60 mg at 4-week intervals.

The lomitapide development program spans more than 16 years. Initial clinical development by Bristol-Myers Squibb from 1996 to 2000 was abandoned as a result of concerns regarding gastrointestinal tolerability, hepatic steatosis, and a preclinical observation thought to be pulmonary phospholipidosis. In 2002, development was transferred to Daniel Rader, MD (University of Pennsylvania) for use in patients with homozygous familial hypercholesterolemia (HoFH). In 2007-2008, development of lomitapide was transferred to Aegerion Pharmaceuticals (“the applicant”). Data to support the proposed indication primarily derive from one 18-month pivotal open-label, single-arm trial that enrolled 29 subjects with HoFH and an optional extension study. Supportive data come from a proof-of-concept phase 2 study, conducted at the University of Pennsylvania, in which 6 subjects with HoFH were treated with lomitapide using a forced-titration protocol for 16 weeks. The pivotal trial added lomitapide to a low-fat diet and maximally tolerated lipid-lowering therapy, which could include LDL apheresis; the phase 2 pilot study required washout of all concomitant lipid-lowering therapies. Last, the applicant submitted data from five phase 2 clinical trials of 4-12-weeks duration, all using dosages ≤25 mg daily, to further describe the safety and efficacy of lomitapide.

HoFH is a life-threatening, orphan disease with an estimated prevalence of 1 in 1,000,000 in the United States. Clinical manifestations often present in childhood, with an aggressive atherosclerotic phenotype that can result in cardiovascular mortality within the first few decades of life if untreated. Although statins are the pharmacological agents of choice, individuals with HoFH have absent or dysfunctional LDL-receptors (LDL-R), which substantially attenuates the efficacy of statins. Extracorporeal removal of LDL-C (e.g., LDL apheresis) is the treatment of choice, but this therapy is not widely available, requires repeat procedures on a weekly or biweekly basis for life, and can be complicated by vascular access difficulties. Thus, there is an unmet medical need for additional LDL-lowering therapies for patients suffering from this rare disorder.

1.1 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 1).

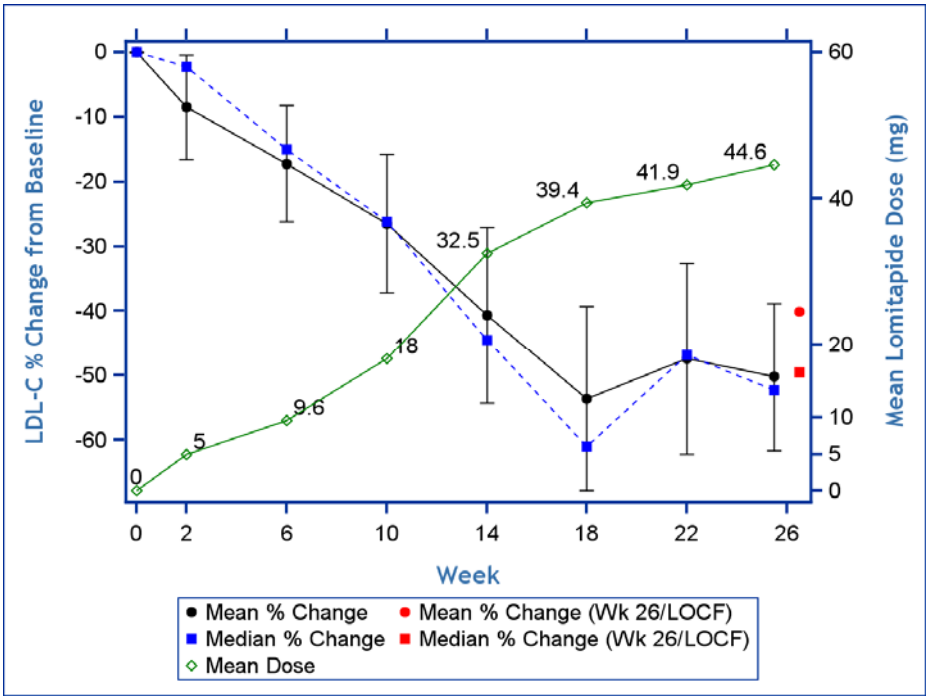


Figure 1. HoFH-pivotal - % Change in LDL-C

Of the 29 subjects who started the trial, 20 (69%) achieved ≥15% reduction in LDL-C from baseline to week 26/LOCF, 19 (66%) achieved ≥25%, and 14 (48%) achieved ≥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.

1.2 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 ≥3x ULN, and 7 (24%) had a peak ≥5x 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 ≥3x ULN during the extension study. Review of narratives and longitudinal profiles of transaminases over time revealed that transaminase abnormalities ≥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, 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.

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 wafarin 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 ≥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.

2 Introduction and Regulatory Background

2.1 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 ≥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.

2.2 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 triglyercide 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]

2.3 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-1α, 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-κB 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.

2.4 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: Vytorin 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,

[*] 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

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 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.

2.5 Regulatory History

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

coronary syndrome, or revascularization. The trial started in October 2005 and the estimated completion date is June 2013.

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 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."
- 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.

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.

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 Pharmacology/Toxicology

4.1 Preclinical Pharmacology/Toxicology

See Dr. Timothy Hummer's review for the preclinical pharmacology/toxicology findings pertinent to the advisory committee's discussion.

4.2 Clinical Pharmacology

4.2.1 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.

4.2.2 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 1, 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 1. CV145-002 – Lomitapide Pharmacodynamics

Geometric Mean (95% C.I.) Percent Change in Lipids from Baseline					
Lipid	Dose of BMS-201038				
Study Day†	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, +26)	-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).

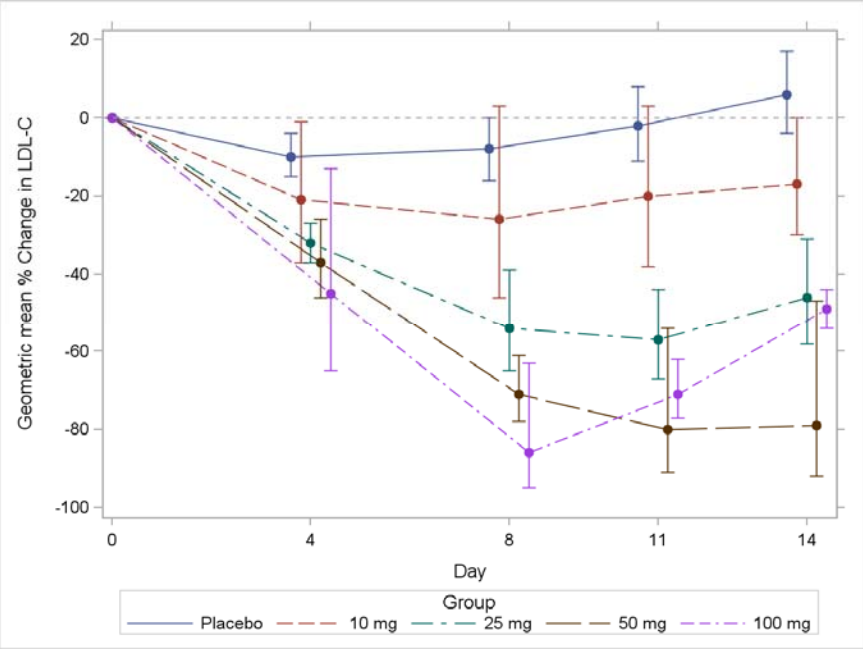


Figure 2. CV145-002 – Lomitapide Dose-Response for LDL-C
Source: FDA clinical reviewer's depiction of data in Table 1, above.
Error bars represent 95% CI of the geometric mean % changes.
Note that dosing was discontinued for all subjects on day 6 or 7 in the 100-mg group.

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.

4.2.3 Pharmacokinetics (ADME)

Throughout development, 15 clinical studies examined the clinical pharamacology 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 2). Except for the special populations, all of these studies were conducted in volunteers who were essentially healthy (some required total cholesterol ≥195-200 mg/dL).

Table 2. 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; *100 mg stopped on day 8 (GI tolerability)*
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)

Study Identifier	Year	Description
CV145-006	1997	ADME; single-dose [^{14}C] 50 mg (100 μCi) solution
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

According to a preliminary review by Dr. S.W. Lau (Office of Clinical Pharmacology), at least 33% of lomitapide is absorbed after oral administration, but the absolute bioavailability is 7%, suggesting the possibility of high first-pass metabolism. The parent compound is highly protein bound (99.5%). It undergoes extensive metabolism by CYP3A4, with the major metabolites (M1 and M3) being pharmacologically inactive with respect to MTP inhibition. The elimination half-life for the parent compound is approximately 34.4 hours, and 33% is excreted in the urine (all as metabolites) and 52.9% in the feces. Exposure is approximately dose-proportional from 10 to 100 mg.

4.2.4 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 (AEGR-733-017). 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 3 describes the Child-Pugh scoring system. Healthy subjects were matched with respect to gender, age (±5 years), and body mass index (±15%). Control subjects had normal values for ALT, AST, GGT, and total bilirubin.

Table 3. 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

[a]Grade 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.

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 3). 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 4). Mean $t_{1/2}$ was not significantly different with moderate impairment (74.6 hours vs. 75.8 hours in controls and moderate impairment, respectively).

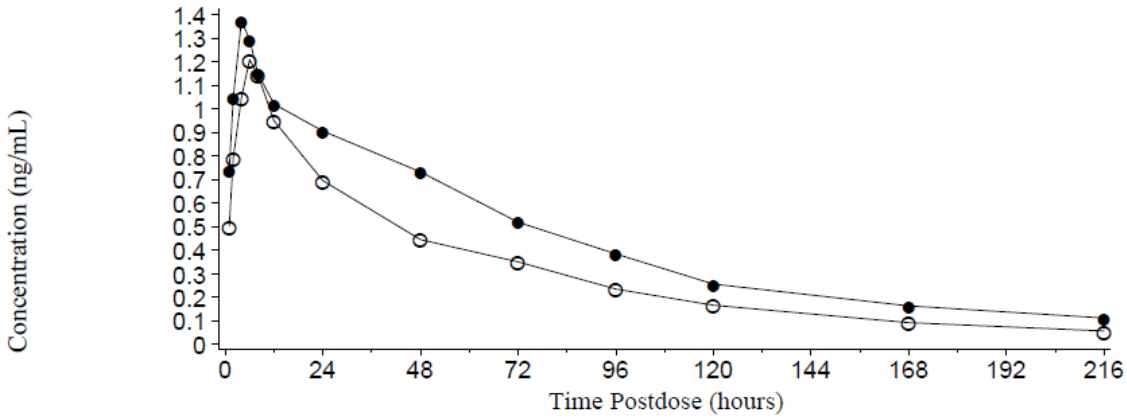


Figure 3. Lomitapide Concentration-Time Profile with Mild Hepatic Impairment
Source: AEGR-733-017 CSR, Figure 11-1.
Filled circles = mild hepatic impairment; open circles = matched controls.

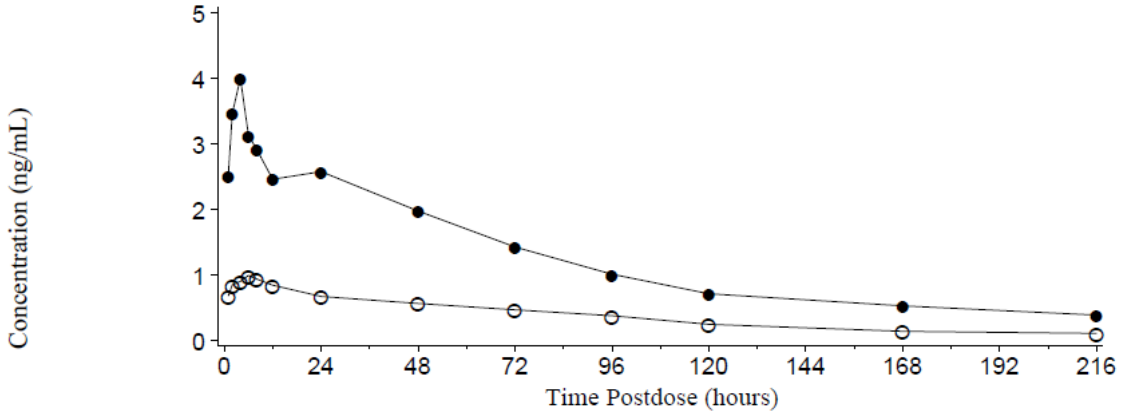


Figure 4. Lomitapide Concentration-Time Profile with Moderate Hepatic Impairment
Source: AEGR-733-017 CSR, Figure 11-2.
Filled circles = mild hepatic impairment; open circles = matched controls.

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 Comments:

1. *Although this study 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.*
2. *Contraindicating lomitapide in patients with "active liver disease" is vague. Presumably "liver function tests" refer to serum transaminases, but these tests do not reflect liver function.*
3. *If approval of lomitapide is favored, further expert discussion is warranted regarding recommendations for use in patients with liver-related abnormalities.*

4.2.5 Renal Impairment

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 (±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.

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)

For labeling, the applicant proposes that no adjustment to the dosage regimen is recommended for patients with mild, moderate, or severe renal impairment.

4.2.6 Drug-Food and 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; final reviews by the agency's Office of Clinical Pharmacology are not yet available.

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 4 summarizes the relevant comparisons, showing statistically significant increases in lomitapide exposure (up to 77% and 58% increases in Cmax and AUC, respectively) with a high-fat breakfast compared with fasting. No food effect on T_{max} was detected (not shown).

Table 4. Effect of Low- and High-Fat Breakfast on Lomitapide PK (CV145-005)

Comparison	C_{max}		$AUC_{0-\tau}$	
	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 5).

Table 5. 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.

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.

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.

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 5.

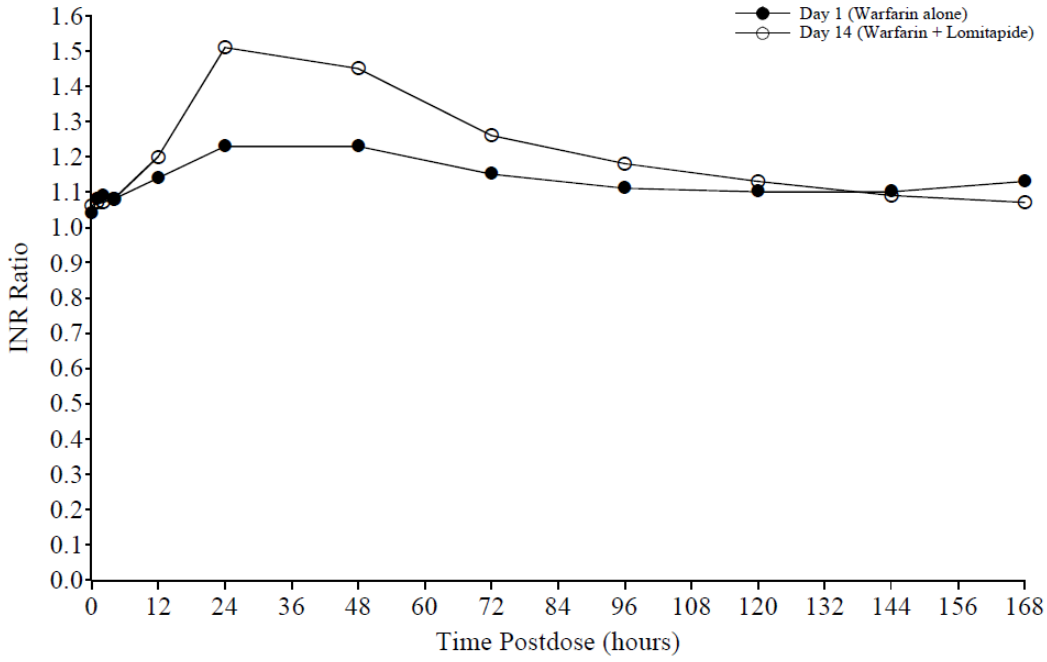


Figure 5. Lomitapide-Warfarin Co-administration - Effect on INR
Source: AEGR-733-013 CSR, Figure 11-4.

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}.

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 6). 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).

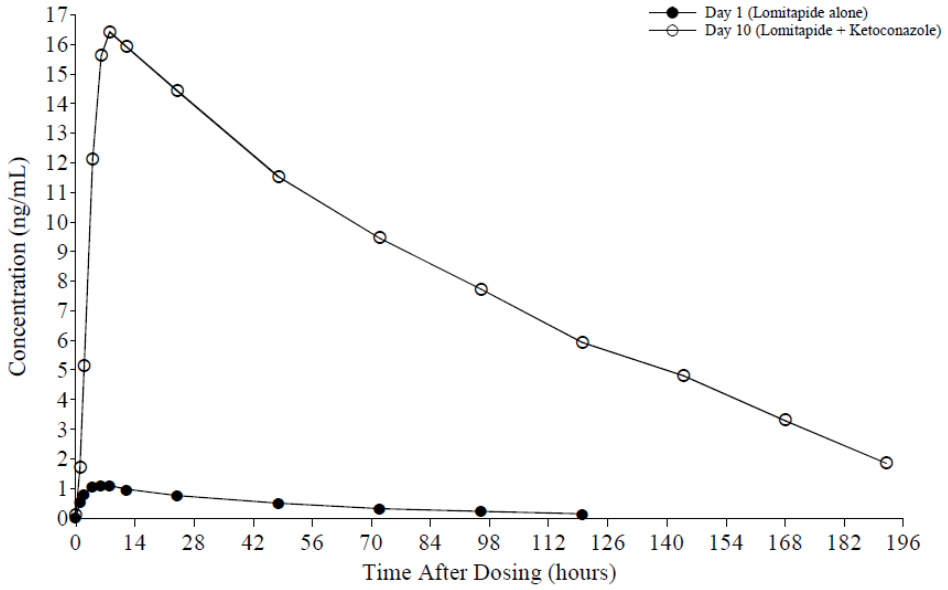


Figure 6. Effect of Ketoconazole on Lomitapide Concentration
Source: AEGR-733-018 CSR, Figure 11-1.

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."

5 Lomitapide Clinical Development

5.1 Overview

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 document. 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.

The efficacy and safety of lomitapide in the HoFH population was evaluated in one, single-arm, 78-week, phase 3 trial involving 28 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 6 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 7 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.

Table 8 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 were presented in Section 4.2.6 (p. 31).

Table 9 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 10 summarizes the investigations of lomitapide PK in special populations (hepatic impairment; end-stage renal disease) and the thorough QTc (TQT) study.

Table 6. 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 7. 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 ≥ 160 TG ≤ 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 ≥130 (≥2 risk factors) or ≥160 (≤1 risk factor) and <250 TG ≤ 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 ≥130 (≥2 risk factors) or ≥160 (≤1 risk factor) and <250 TG ≤ 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 ≥130 (≥2 risk factors) or ≥160 (≤1 risk factor) and <250 TG ≤ 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 8. 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 9. 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 ≥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 ≥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 ≥200	Randomized, double-blind, placebo-control	14 days (8 days in 100 mg group 2^{o} 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 ≥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 10. 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 Exposure to Lomitapide

Table 11 presents a summary of the number of subjects ever exposed to lomitapide during its development, categorized by the phase and type of study. Overall, a total of 925 subjects ever received a dose of lomitapide, either as monotherapy or combined with other lipid-lowering drugs. Of these, 317 (34%) were enrolled in phase 1 protocols, 446 (48%) in controlled phase 2 protocols (4-12 weeks), 133 (14%) in uncontrolled phase 2 protocols (drug-drug interaction study and HoFH-pilot), and 29 (3%) in the HoFH-pivotal trial.

Table 11. 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
Total Phase 1	**80**	**53**	**56**	**80**
Phase 3 [f]	**18**	**0**	**0**	**18**
GRAND TOTAL	**925**	**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.

Exposure in HoFH Population (Phase 3)

Table 12 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 12. 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 13 and Table 14 summarize the durations of exposure by mean daily dose in HoFH-pivotal and its extension study, respectively.

Table 13. Exposure to Lomitapide in HoFH-pivotal

	Mean Lomitapide Daily Dose							
Duration (days)	**≤5**	**(5, 10]**	**(10, 20]**	**(20, 40]**	**(40, 60]**	**>60**	**Any dose**	**%**
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	4	29	100%
%	10%	10%	17%	35%	28%	14%	100%	

Source: 120-day safety update, Table 1.1.4A.
Notation: (10, 20] = 10 < dose ≤ 20

Table 14. Exposure to Lomitapide in HoFH-extension

	Mean Lomitapide Daily Dose							
Duration (days)	**≤5**	**(5, 10]**	**(10, 20]**	**(20, 40]**	**(40, 60]**	**>60**	**Any dose**	**%**
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).

Exposure in Non-HoFH Population (Selected)

The primary source of supportive safety data in the non-HoFH population comes from the phase 2 program. The applicant pools two 14-day phase 1 trials and five phase 2 trials, ranging from 4 to 12 weeks, into an "Elevated LDL-C and Other CV Risk Factors" safety pool. Trials included in this pool are CV145-002 and -010 (phase 1), and CV145-009, AEGR-733-001, -003b, -004, and -006 (phase 2). 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.

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
N (%) of Subjects						
1-28 days	7 (9%)	34 (14%)	46 (47%)	45 (73%)	38 (33%)	4 (5%)

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)
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 text for description of lomitapide dose groups. Note that lomitapide may have been administered with concomitant lipid-lowering therapy.

5.3 Phase 1 Program

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 8, Table 9, and Table 10. 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).

5.4 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 described in Section 4.2.6, p. 31), the six-subject HoFH-pilot, and the five phase 2 studies listed in Table 7, 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 briefly summarize the major design features and results from each of these five trials.

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 ≥160 mg/dL and TG ≤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 (≤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.

Of the 76 subjects enrolled, 63% were men, 91% were white, the mean age was 52 years, and the mean BMI was 28.0 kg/m^2. Mean LDL-C at baseline was 190 mg/dL. Regarding disposition, 12 (32%) of 38 lomitiapide subjects discontinued prematurely, only one of which was clearly not related to an adverse event. One placebo subject discontinued prematurely for a scheduling reason.

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). Effects on additional lipid parameters are presented in Appendix Table 76 and Figure 42.

Subjects treated with lomitapide 25 mg daily for 4 weeks had a mean 20.88% (absolute percentage point) 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 statistically was not significantly different than placebo (mean difference between groups 3.11% [95% CI, -0.98 to 7.20; p=0.13]).

Among the 28 lomitapide subjects with available data at baseline and end-of-treatment, 24 (86%) had an absolute percentage point increase in % hepatic fat ≥10% from baseline; no subjects in the placebo group exhibited a similar increase (Table 15).

Table 15. 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%)
≥ +5% but < +10%	3 (11%)	6 (16%)
≥ +10% but < +20%	10 (36%)	0
≥ +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.

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 ≥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 ≥3x ULN are shown in Appendix Figure 43.

Table 16. C-009 – Peak ALT Abnormalities

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

Additional exploratory analyses that examined the relationships between baseline hepatic fat (or changes in hepatic fat) with ALT abnormalities are provided in the Appendix (p. 176).

There were no SAEs or deaths in this study. Treatment-emergent AEs occurred in 35 (92%) and 17 (45%) of the lomitapide and placebo groups, respectively. The AE profile was qualitatively similar to that observed among subjects with HoFH, i.e., primarily dominated by gastrointestinal events (Appendix Table 77). 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.

Other safety findings included:

- 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; between-group differences in changes in the vitamin E:total lipids ratio, however, were not detected (-0.3% placebo-subtracted; P=0.49). (See Appendix Table 78.) Other fat-soluble nutrients were not assessed;
- Among completers, the mean change in weight from baseline was -1.94% in the lomitapide group and +0.12% in the placebo group (P<0.0001);
- Standard laboratory assessments (except for those discussed above) and vital signs were similar between groups;
- Pulmonary function test results did not suggest lomitapide-associated abnormalities (see Appendix Table 79).

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.*

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).

Of the 85 subjects enrolled, 47% were men, 73% were white, and the mean age was 55 years. Mean LDL-C at baseline was 167 mg/dL. The study population was relatively healthy, with a minority of subjects taking lipid-lowering medications prior to wash-out (29% to 39% across groups) and only one subject having a history of atherosclerotic heart disease. Regarding disposition, the incidence of premature discontinuation was 32% for lomitapide monotherapy, 14% for combination therapy, and 17% for ezetimibe monotherapy; all discontinuations were the result of adverse events for lomitapide-treated subjects, most commonly abnormal transaminases.

In this active-controlled trial, % change in LDL-C from baseline to week 12 was -46.2% for combination therapy, -29.9% for lomitapide monotherapy, and -19.6% for ezetimibe monotherapy; all three between-group comparisons were statistically significant (all P≤0.016). Additional results regarding changes in lipid parameters are provided in the Appendix (p. 178). Note that the effects of lomitapide and ezetimibe appear additive, with regard to LDL-C, TC, Non-HDL-C, and apoB.

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 ≥3x ULN after randomization; no subject assigned to ezetimibe monotherapy had an ALT elevation to this degree (Table 17). All 17 of these subjects had bilirubin levels

<1.2x ULN and normal INR. Longitudinal profiles of ALT for subjects who ever experienced ALT ≥3x ULN are shown in Appendix Figure 47; these elevations typically resolved within 2-4 weeks of drug discontinuation.

Table 17. A-001 – Peak ALT Abnormalities

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

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

Hepatic fat was not measured in study A-001.

The only fatal SAE in the lomitapide development program (myocardial infarction) occurred in this trial. This event is described later in Section 7.3 (p. 107). There were no other SAEs.

Treatment-emergent AEs occurred in 24 (86%), 24 (86%), and 16 (55%) subjects of the lomitapide monotherapy, lomitapide+ezetimibe combination therapy, and ezetimibe monotherapy groups, respectively. 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).

Other safety findings included:

- Among completers, the mean change in weight from baseline was -1.4% in the combination arm, -0.1% in the ezetimibe monotherapy arm, and -1.0% in the lomitapide monotherapy arm (all between-group P≥0.077);
- Standard laboratory assessments (except for those discussed above) were similar between groups;
- According to the applicant, 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 across study visit were submitted;
- Fat-soluble nutrients and pulmonary function were not assessed.

Reviewer Comments:

1. *Although this was one of the phase 2 studies of 12-week duration, the forced-titration regimen led to a median [IQR] exposure to the 10-mg dose of 28 [26, 29] days in 47 subjects, with a range of 4 to 32 days.*
2. *These data demonstrate that escalating the dose of lomitapide even more slowly than performed in the HoFH trials does not prevent the elevation of transaminases, which occurred in 30% of all subjects who received lomitapide in this 12-week trial.*

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).

Of the 157 subjects enrolled, 45% were men, 81% were white, and the mean age was 54 years. Mean LDL-C at baseline was 173 mg/dL. The study population was relatively healthy, with 25% of subjects on statins prior to washout and only 4 (2.5%) subjects reporting a prior history of atherosclerotic cardiovascular disease. Regarding disposition, the drop-out rate was very high for an 8-week study, with 35% and 62% discontinuing prematurely in the lomitapide 5 mg and 10 mg monotherapy groups, respectively; the drop-out rates were similar for the combination therapy groups. Nearly all premature discontinuations were for adverse events (predominantly diarrhea). This led to median durations of exposure of 55 days (lomitapide 5 mg monotherapy), 56 days (lomitapide 5 mg + atorvastatin), 34 days (lomitapide 10 mg monotherapy), and 16 days (lomitapide 10 mg + atorvastatin), compared with 56 days in both the placebo and atorvastatin control groups.

The placebo-subtracted % changes in LDL-C from baseline to week 8 for the lomitapide monotherapy groups were -15.8% and -36.8% for 5 mg and 10 mg daily, respectively (both P<0.01). Additional results regarding changes in lipid parameters are provided in the Appendix (p. 180), which includes comparisons between combination therapy groups and atorvastatin monotherapy even though these comparisons are less relevant for the HoFH population given the attenuated efficacy of statins in HoFH. It should be noted that 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.

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.

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 (ranging 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 18). Longitudinal ALT profiles for these subjects are shown in Appendix Figure 49.

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

Table 18. 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*).
P = placebo; L5 and L10 = lomitapide 5 mg and 10 mg, respectively; A20 = atorvastatin 20 mg.

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

There were two SAEs in study A-003b, both myocardial infarctions. These events are described in Section 7.4.2 (p. 108). There were no deaths. The incidence of treatment-emergent AEs ranged from 81-92% in lomitapide-treated groups compared with 58-63% in the control groups. Tabulations of AEs leading to treatment discontinuation and common AEs are included in Appendix Table 85 and Table 86.

Other safety findings included:
- Among completers, the % changes in body weight were -0.01% for placebo (n=26), -2.48% for lomitapide 5 mg monotherapy (n=19), and -3.48% for lomitapide 10 mg monotherapy (n=10) (P≤0.0005 for both comparisons with placebo).
- Standard laboratory assessments (except for those discussed above) and vital signs were similar between groups (Appendix Table 87 and Table 88);
- Mean Vitamin A levels remained stable during the 8-week trial with no post-baseline values below the lower limit of normal (Appendix Table 89);
- Consistent with other trials in the development program, lomitapide induced a dose-related decrease in total vitamin E (Appendix Table 90);
- Pulmonary function was not assessed in this trial.

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 ≥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/m^2. 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.

Of the 260 subjects enrolled, 48% were men, 70% were white, the mean age was 51 years, and the mean BMI was 27.3 kg/m^2. Mean LDL-C at baseline was 143 mg/dL. Similar to the preceding phase 2 trials described, the study population was relatively health; the majority of subjects in each group had 0 or 1 CHD risk factor (67 to 91%), only 5 subjects reported a history of prior CHD or atherosclerotic disease, and only 11% had a history of statin use. Regarding disposition, 6% of placebo subjects discontinued prematurely compared with 27%, 29%, 15%, and 40% for lomitapide monotherapy 2.5, 5, 7.5, and 10 mg daily, respectively. The incidence of premature discontinuation in the combination therapy groups ranged from 7 to 14%. Similar to other studies, gastrointestinal adverse events contributed the most to premature diarrhea, with diarrhea accounting for 26 of 42 discontinuations.

The placebo-subtracted % changes in LDL-C from baseline to week 12/LOCF were -12.6%, -15.3%, -16.0%, and -32.4% for lomitapide monotherapy 2.5, 5, 7.5, and 10 mg daily, respectively, all of which were statistically significant (P=0.037 for 2.5 mg vs. placebo; P≤0.006 for the remaining groups). The longitudinal LDL-C profiles for these groups are depicted in Figure 7, and quantitative results are provided in the Appendix (p. 185).

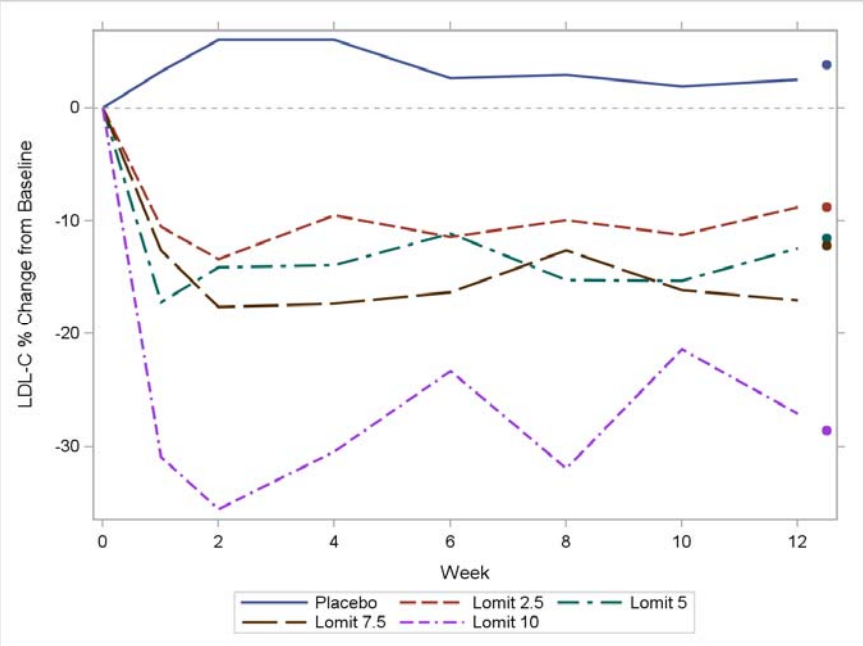


Figure 7. A-004 – % Change in LDL-C from Baseline Over 12 Weeks
Source: FDA clinical reviewer's depiction of data in A-004 CSR, Table 14.2.8.1.
All available data at each time point were used. Dots indicate Week 12/LOCF value.

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 4.68% (95% CI, 2.30% to 7.07%) absolute percentage point increase in % hepatic fat (p<0.001); the placebo group showed no change during the 12 weeks (mean +0.03%). Table 19 summarizes the mean and median changes from baseline to week 12 across lomitapide monotherapy groups compared with placebo.

Table 19. 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 (4.31, 11.33)	<0.001

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 8). 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 9.

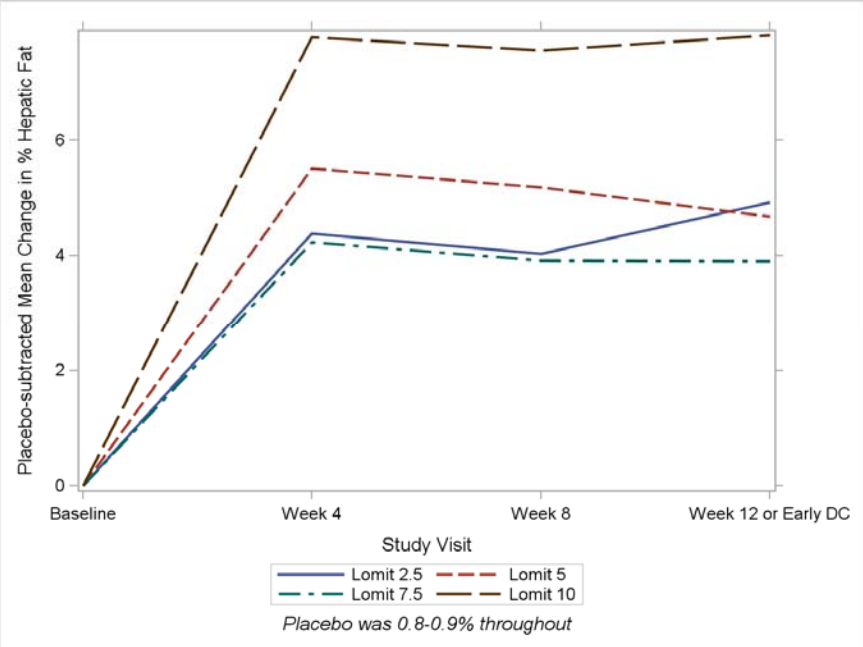


Figure 8. A-004 – Placebo-subtracted Mean Changes in % Hepatic Fat
Source: FDA clinical reviewer's depiction of data in A-004 CSR Tables 14.2.1.1 through 14.2.3.1.3.

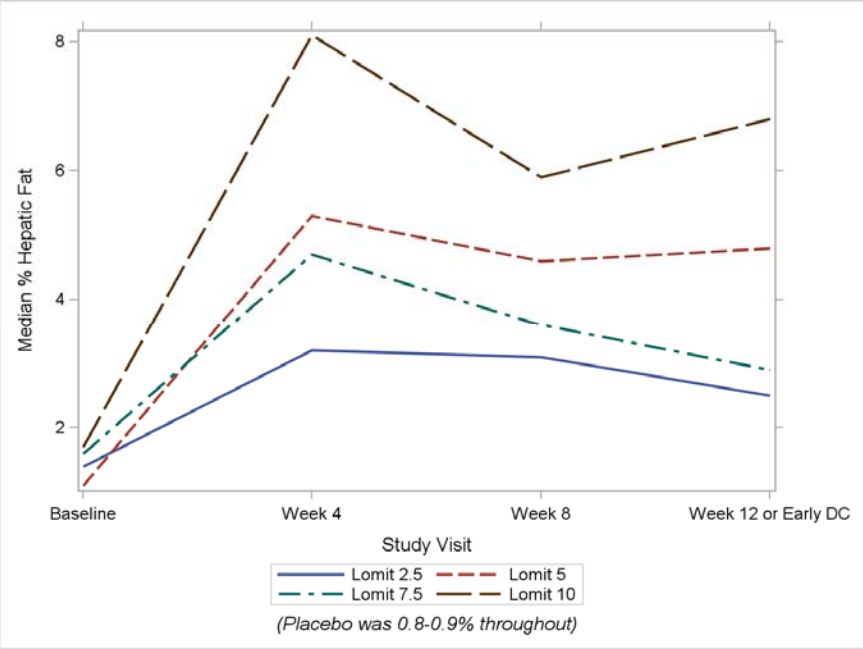


Figure 9. A-004 – Median % Hepatic Fat at Each Visit
Source: FDA clinical reviewer's depiction of data in A-004 CSR Tables 14.2.1.1 through 14.2.3.1.3.

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 (Appendix Table 93).

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, the sponsor 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%) (Appendix Figure 50). Although a repeated-measures model would have been more appropriate given that within-subject observations are not independent over time, these data 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 A-004, use of lomitapide was associated with elevated transaminases; 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).

Table 20. 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)
≥2x, <3x ULN	0	0	3 (9%)	2 (6%)	4 (11%)	0	4 (12%)	3 (10%)
≥3x, <5x ULN	0	1 (3%)	1 (3%)	0	2 (6%)	1 (4%)	2 (6%)	0
≥5x, <10x ULN	0	1 (3%)	0	1 (3%)	0	0	0	0
≥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*).

There were no deaths in A-004. There were three SAEs that occurred after first dose of study drug: (1) chest pain and lower GI bleed; inflammatory bowel disease; and an ankle fracture. These events are described later in Section 7.4.2 (p. 108).

Because this is the longest placebo-controlled trial in the lomitapide development program, I have presented the subject counts of treatment-emergent AEs that were reported by ≥5% of subjects (i.e., ≥2 subjects) in a lomitapide monotherapy group *and* were more frequent than placebo (Table 21). I have not included arms of combination therapy in this table for brevity.

Table 21. 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

SOC / Preferred Term	**Pbo (n=33)**	**Lomitapide (mg daily)**			
		2.5 (n=34)	**5 (n=34)**	**7.5 (n=34)**	**10 (n=35)**
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 (with or without atorvastatin) group than a control (placebo or atorvastatin) group.

Other safety findings included:

- The % changes in body weight from baseline to week 12/LOCF were +0.11% for placebo and -1.59%, -1.00%, -1.81%, and -2.53% for lomitapide 2.5, 5, 7.5, and 10 mg daily, respectively, with the highest two doses having statistically significant changes from baseline compared with placebo (p=0.04 and p=0.001, respectively) (Appendix Table 94);
- Standard laboratory assessments (except for those discussed above) and vital signs were similar between groups (Appendix Table 95 and Table 96);
- Changes in Vitamin A from baseline to week 12 (with or without LOCF) were not statistically or clinically significant;
- Consistent with other trials in the development program, lomitapide induced a dose-related decrease in total vitamin E, but the vitamin E:cholesterol+TG ratio changed minimally;
- PFT data did 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 (Appendix Table 97).

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.

In this 8 week trial, A-006 enrolled 44 subjects with hyperlipidemia (similar to A-001 and -003b above) and treated them with atorvastatin 20 mg daily plus random assignment to add-on lomitapide or placebo. Lomitapide was initiated at 2.5 mg daily for 4 weeks and force-titrated to 5 mg daily for the remaining 4 weeks of the trial. There was no off-

treatment follow-up visit. The mean LDL-C at baseline was 178 mg/dL; at week 8, the % change in LDL-C from baseline was -39.6% in the atorvastatin monotherapy group and -49.9% in the combination therapy group (between-group P<0.0001). Other effects on lipid parameters are provided in Appendix Table 98. With regard to safety, there were no treatment-emergent SAEs or deaths in this study.

5.4 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 total cholesterol (TC), non-HDL-C, HDL-C, triglycerides (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 was 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”).

Trial Population

The protocol anticipated the enrollment of 25 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 22 summarizes the schedule of selected assessments.

Table 22. HoFH-pivotal – Timing of Selected Assessments

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 10.

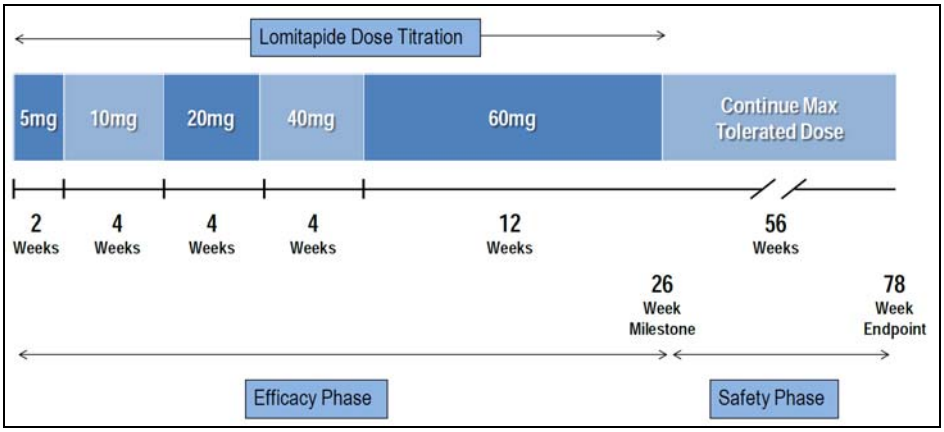


Figure 10. Study Schematic (Post-Baseline)
Source: UP1002/AEGR-733-005 CSR, Figure 1.

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 dietary supplements (provided by the sponsor) 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.*

Reviewer Comment: Review of the DSMB minutes (12 July 2010) confirms that investigators were not blind to LDL-C levels and that some investigators requested protocol waivers to titrate outside of protocol parameters. The availability of the primary outcome measure to subjects and investigators, especially in a single-arm open-label trial, has the potential to influence behavior (subject and/or investigator) and bias the trial's results.

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 ≤24.9 kg/m^2) could not have weight loss ≥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 ≥200 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 23.

Table 23. HoFH-pivotal – Protocol Actions for 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	
*Confirmed** ALT/AST ≥10x 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 ≥ 20.0x ULN on any single measurement		
ALT/AST >5xULN *and* total bilirubin >2x ULN *without symptoms*		
Confirmed alkaline phosphatase >5x 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 ≥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	N/A	Dose could be escalated again per original protocol but not beyond MTD established during

Event	Description	Action
phase (weeks 26-78)		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 ≥10x 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) <10x 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/m^2) 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 22).

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 document.

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 CCBR-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.

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 (FEV_1), forced expiratory flow 25-75% (FEF_{25-75}), 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/m^2) 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

Selected analytical considerations drawn from the statistical analysis plan follow. For a comprehensive review of the statistical considerations relevant to this application and the efficacy analyses, 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, and was 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.

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 are 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 ≥ 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 transaminases 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 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, 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 deficiency. 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, FEV_1, FEF_{25-75}, and DLCO.

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

Endpoints & Assessments
Primary Efficacy Assessment: % 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 Assessments: 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 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]).

5.5 HoFH – Demographics & Baseline Characteristics

Selected demographic and baseline characteristics of the subjects in the HoFH-pilot, -pivotal, and -extension studies are summarized in Table 24 and Table 27. 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/m^2, 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 18^{th} birthday.

Table 24. 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%)
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/m^2)	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 25 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 >25 mg/dL.

Table 25. 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 evident 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 26).

Table 26. HoFH-pivotal – Baseline Lipid-Lowering Therapy

Therapy	HoFH-pivotal (N=29)
Current apheresis	18 (62%)
LDL apheresis	*10*
Plasmapheresis	*6*
Type not reported	*2*

Therapy	HoFH-pivotal (N=29)
Lipid-lowering therapy	
Statin	27 (93%)
Rosuvastatin	*13*
Atorvastatin	*9*
Simvastatin	*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 27). 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 27. 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.

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 28).

Table 28. HoFH-pivotal – Enrollment by Site

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

5.5 HoFH – Subject Disposition

Table 29 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). 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.

Table 29. 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 refusing further MRI evaluations because of pain at the site of sternal wires (32-001).

Table 30 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 30. 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. 115).

The numbers of patients in each analysis dataset for HoFH-pivotal (described in the protocol above, p. 69) are shown in Table 31.

Table 31. 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 32 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).

Table 32. 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 Comment: 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. In addition, the distribution of doses at the end of the trial is quite similar to the distribution at week 26, suggesting that the majority of subjects were able to maintain a stable dose; review of subject-level data confirmed this (not shown).

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 were approximately 55, 58, 60, 66, 75, and 96 mg/day.

6 Review of Efficacy

6.1 Indication

The applicant proposes the following indication:

> *[Lomitapide] 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 (apoB), 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 [lomitapide] treatment, and should continue this diet during treatment;
- [Lomitapide] 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 [lomitapide].

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

6.2 Methods

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

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 5.4. 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.

6.3 Efficacy Results

6.3.1 Primary Endpoint & Supportive LDL-C Analyses

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 33.

Table 33. HoFH-pivotal – Primary Endpoint - LDL-C at Week 26

	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)	
95% CI	150-229	-195, -98	-51.9 to -28.2	<0.001
Median	169	-107	-49.5	
Min, Max	28, 442	-351, +49	-92.6, +20.4	

Source: HoFH-pivotal CSR, Table 12. LDL-C values are directly measured.
* 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 34 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 34. HoFH-pivotal – LDL-C Changes from Baseline to Week 26 (Sensitivity Analyses)

	ITT/Safety		Per-Protocol*	
Changes from Baseline to Week 26	**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
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 35 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 35. 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.

Dose Considerations

Figure 11 shows the relative changes in LDL-C from baseline over time in HoFH-pivotal as well as the average dose being taken at each time point. According to the protocol-specified regimen, the last titration (to 60 mg) would occur at week 18 if the 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.

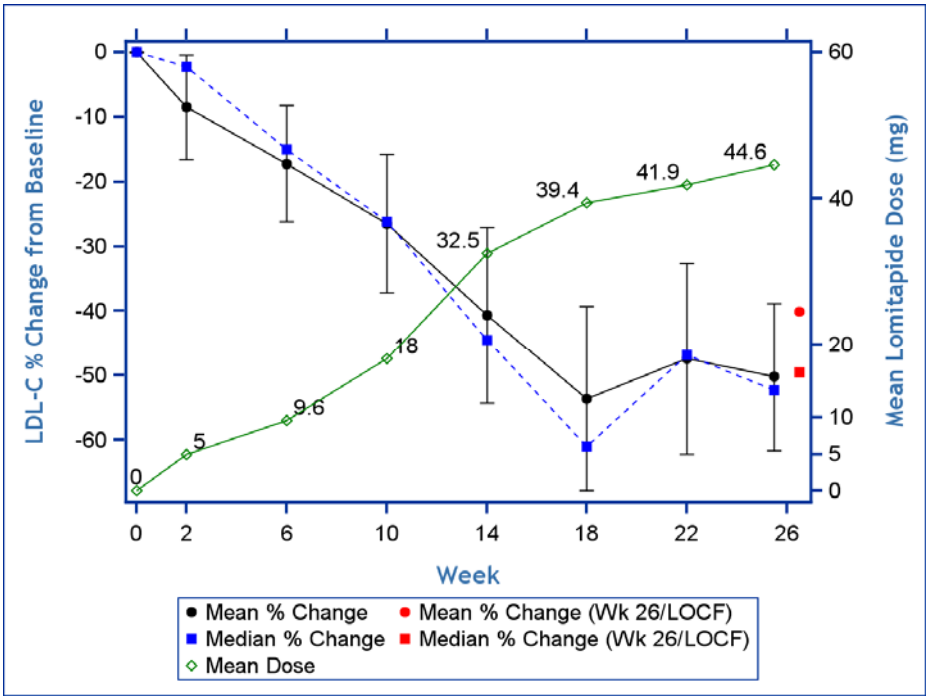


Figure 11. HoFH-pivotal – Relative Changes in LDL-C from Baseline Over Time
Source: FDA clinical reviewer's depiction of data in HoFH-pivotal CSR Tables 14.2.1.1.1 and 14.1.2.8.1.
Error bars represent 95% CI of the mean only.

Figure 12 presents % reduction in direct LDL-C from baseline to week 26/LOCF categorized by maximum tolerated dose. Groups defined based on MTD are not independent in a dose-escalation design; therefore, any comparisons between groups are subject to potential confounding. Given this limitation, it is at least somewhat reassuring that there is a qualitative positive correlation between MTD and mean (or median) % LDL-C reduction from baseline to week 26/LOCF.

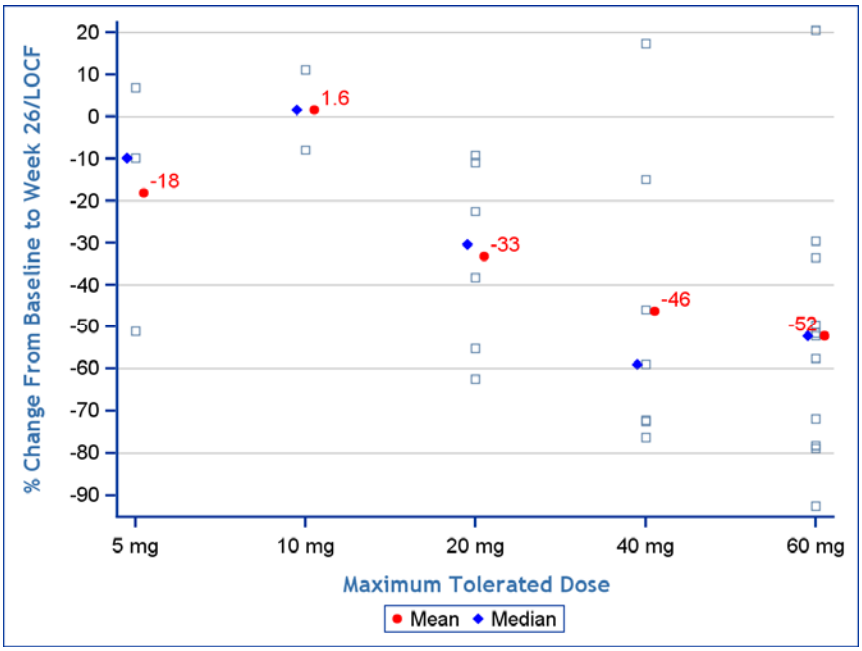


Figure 12. HoFH-pivotal – LDL-C % Change at Week 26/LOCF by Max Tolerated Dose
Source: FDA clinical reviewer's analysis of submitted analysis dataset *ADLB.xpt*. The one subject with an 80-mg maximum tolerated dose is included with the 60-mg group; this subject had a 29% reduction in LDL-C at week 26.

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 subect'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 effects 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 ≥15% reduction in LDL-C from baseline to week 26/LOCF, 19 (66%) achieved ≥25%, and 14 (48%) achieved ≥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 13).

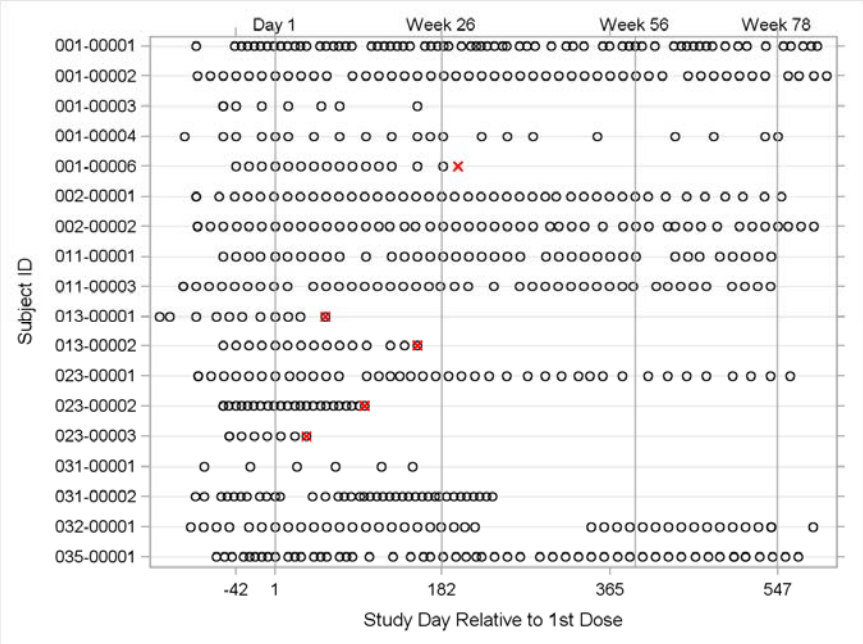


Figure 13. HoFH-pivotal – Apheresis Frequency by Subject
Source: FDA clinical reviewer's analysis of HoFH-pivotal dataset (*CM.xpt*)
Open circles represent apheresis treatments; red Xs denote early termination visits for the 5 apheresis subjects who permanently discontinued study drug prematurely.

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 36). I have highlighted rows with timing discrepancies.

Table 36. 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**
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

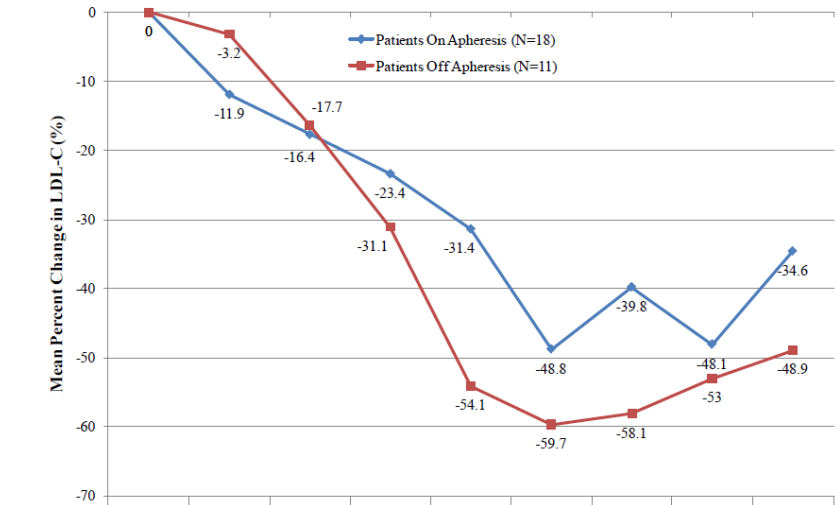
Source: 20 April 2012 response to FDA information request.
Numbers are days from most recent apheresis to the corresponding direct LDL-C measurement.
Shaded, bolded rows indicate timing discrepancies (see text).

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 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.

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 be 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 14 depicts mean % change in LDL-C from baseline over time during the efficacy period.



	Baseline	Week 2	Week 6	Week 10	Week 14	Week 18	Week 22	Week 26	Week 26/LOCF
Drug Dose:									
Off Apheresis:	0 mg	5.0 mg	9.5 mg	18.2 mg	36.0 mg	40.0 mg	46.0 mg	46.0 mg	42.7 mg
On Apheresis:	0 mg	5.0 mg	9.7 mg	17.8 mg	30.3 mg	39.0 mg	38.9 mg	43.5 mg	35.8 mg

Source: Table 14.1.2.8.3 and Table 14.2.2.13

Figure 14. 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.

Taken together, these data suggest that apheresis-related variables – such as improper collection of blood for LDL-C after apheresis – do not substantially contribute to the LDL-C lowering observed in the overall trial.

Durability of LDL-C Reduction

During the safety phase, LDL-C increased modestly, predominantly during the first 10 weeks of this period. Table 37 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 37. 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 15).

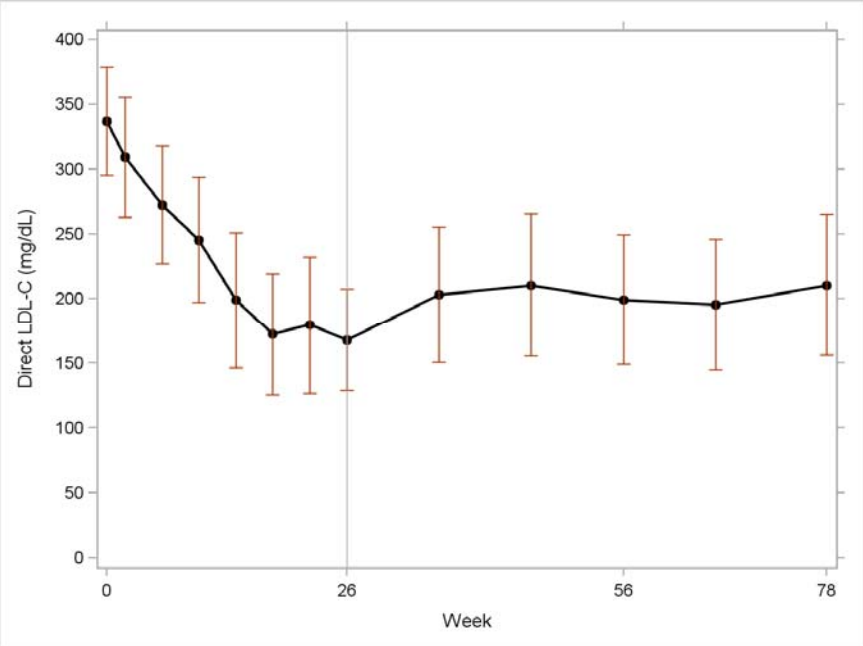


Figure 15. HoFH-pivotal – LDL-C Through End of Trial (Week 78)
Source: FDA clinical reviewer's analysis of submitted HoFH-pivotal laboratory dataset (LB.xpt). Only available data were used (i.e., no LOCF imputation). Unscheduled visits were excluded. N=23 for all time points from week 22 through 78. Error bars indicate 95% CI of the mean.

Individual LDL-C Profiles in HoFH-pivotal

Figure 16 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 more-erratic LDL-C profiles.

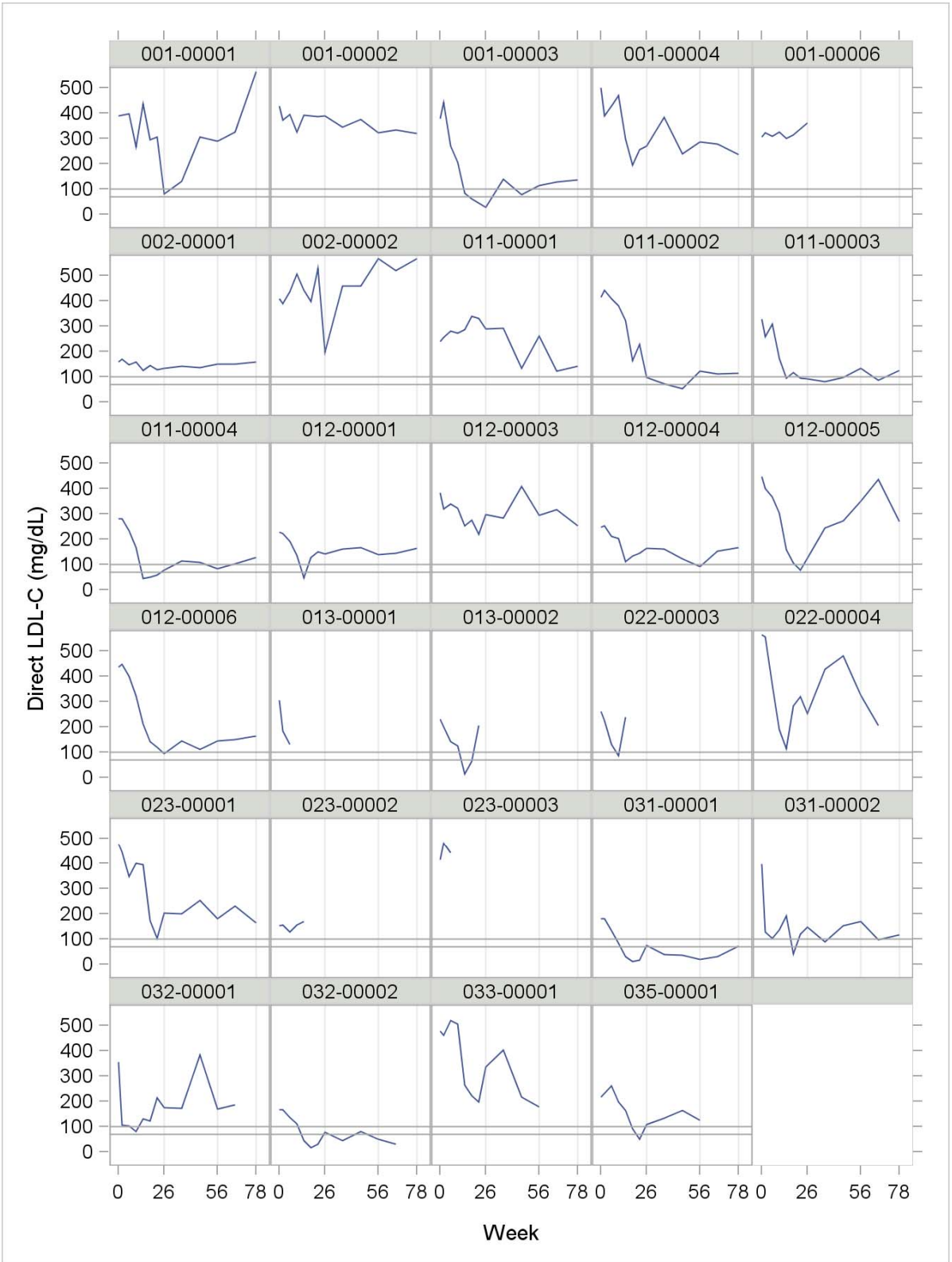


Figure 16. HoFH-pivotal – Subject-level LDL-C Profiles
Source: FDA clinical reviewer's analysis of *ADLP.xpt* dataset (no imputed values).
Horizontal reference lines at 70 mg/dL and 100 mg/dL.

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 ρ = -0.58, p=0.001; relative change: ρ = -0.32, p=0.10). These relationships are depicted in the following scatter plots (Figure 17).

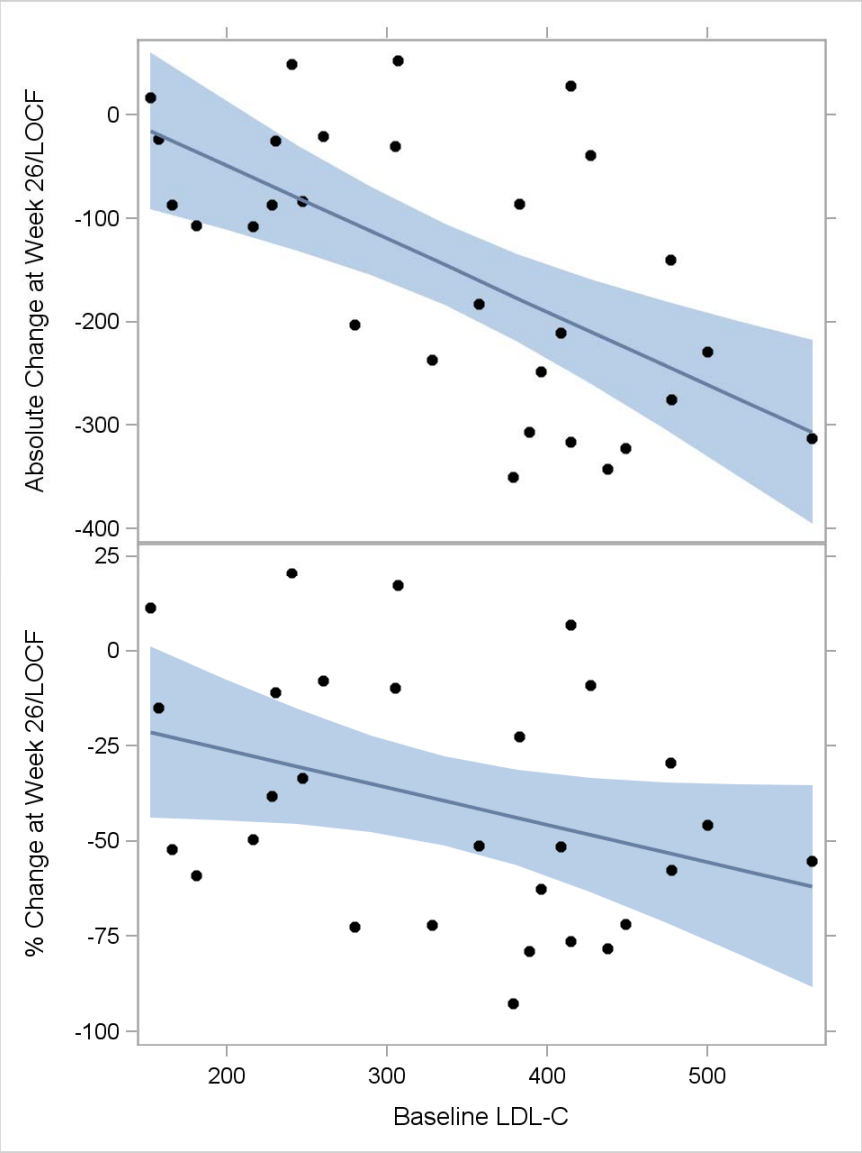


Figure 17. HoFH-pivotal – Correlation of Baseline and Change Measures of LDL-C
Source: FDA clinical reviewer's analysis of submitted HoFH-pivotal data in analysis dataset *ADLP.xpt*.
Regression line derived from simple linear regression; shaded area represents 95% confidence limits of the predicted mean.

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≤0.0001 by paired t-test for the last two time points. Table 38 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 18.

Table 38. 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).

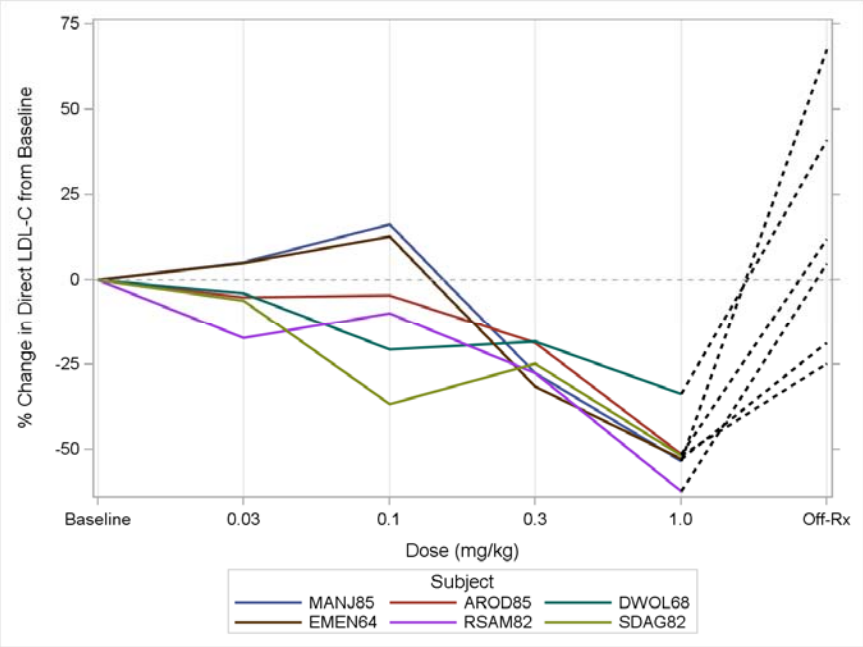


Figure 18. HoFH-pilot – % Change in LDL-C Over Time
Source: FDA clinical reviewer's depiction of data in HoFH-pilot CSR Appendix 7f
"Off-Rx" represents the assessment conducted approximately 4 weeks after discontinuing lomitapide.

6.3.2 Secondary Endpoints

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 α=0.05, each requiring significance of the preceding parameter. The remaining three parameters were to be evaluated similarly in a separate group of three.

Table 39 presents descriptive statistics for the secondary efficacy parameters in HoFH-pivotal. Baseline values were listed in Table 27.

Table 39. 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.				
Mean (SD)	258 (118)	-172 (146)	-36.4 (28.2)	
95% CI	213-303	-227 to -116	-47.1 to -25.7	<0.001
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)	
95% CI	120-176	-148 to -75	-50.8 to -28.0	<0.001
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)	
95% CI	46-81	-60 to -19	-50.2 to -7.8	0.009
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)	
95% CI	174-260	-223 to -115	-51.3 to -28.8	<0.001
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)	
95% CI	9-16	-12 to -4	-50.5 to -6.8	0.012
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)	
95% CI	46-78	-30 to -2	-23.9 to +2.0	0.094
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 19 depicts the mean (±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 (±95% CI) and median changes from baseline are shown.

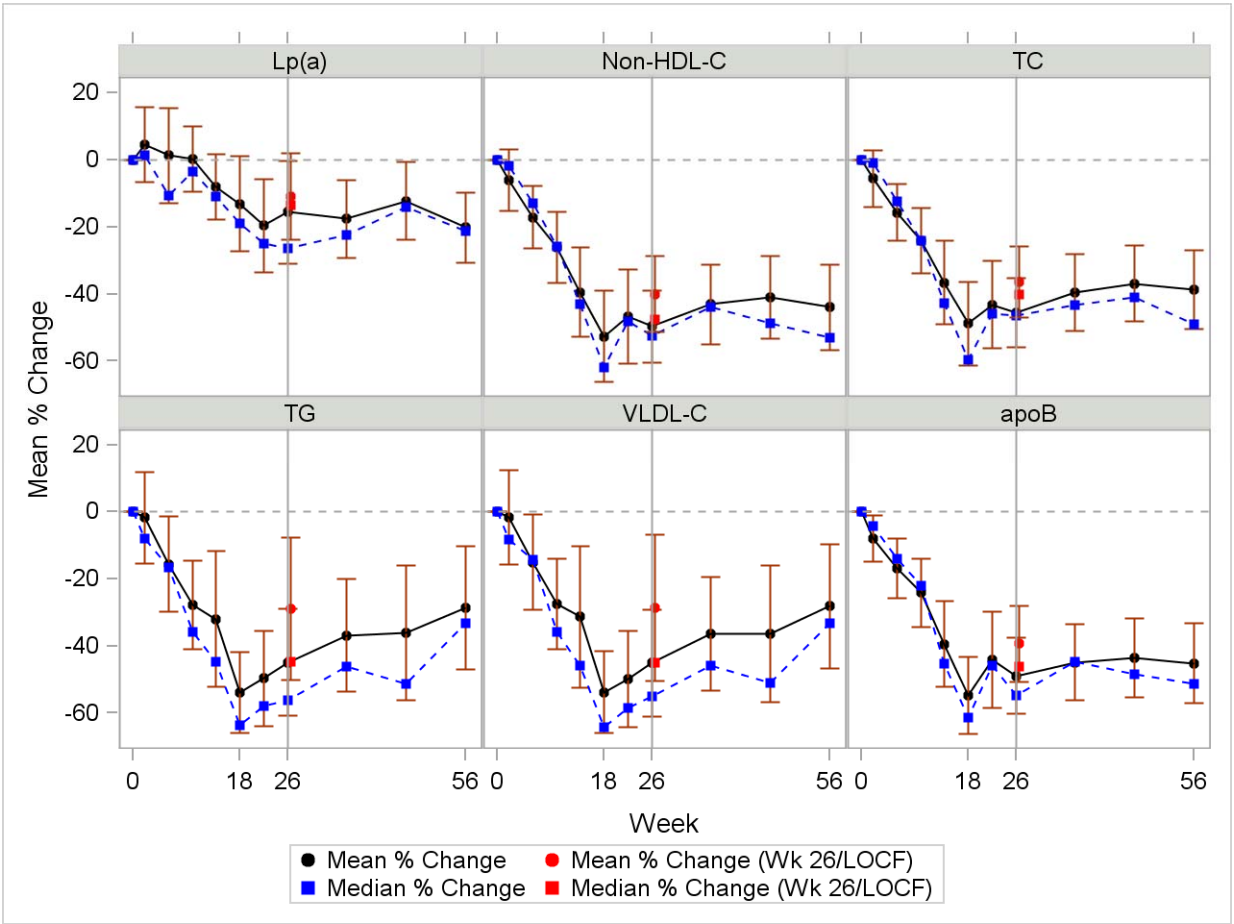


Figure 19. HoFH-pivotal – % Changes in Secondary Lipid Parameters
Source: FDA clinical reviewer's depiction of data in HoFH-pivotal CSR, Tables 14.2.2,4.1-6.1.
Error bars indicate 95% CI of mean values.
Vertical line at week 26 marks the end of the efficacy period.

In my opinion, the clinical benefit expected from the changes observed in some of these parameters (e.g., triglycerides, Lp(a)) in this population is far from certain. Note that 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 40.

Table 40. 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 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 41.

Table 41. 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.

6.3.3 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 6.3.1. In addition, the reduction or discontinuation of apheresis was exaxmined.

HDL-C and ApoAI

Table 42 presents the descriptive statistics for changes in HDL-C and apoAI at week 26/LOCF. Baseline values were listed in Table 27. 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 42. HoFH-pivotal – HDL-C and ApoAI at Week 26/LOCF

	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)	
95% CI	36-46	-6.3 to +0.4	-14.4 to +0.6	0.072
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)	
95% CI	97-114	-17.1 to -1.7	-12.6 to -0.4	0.038
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 20 depicts the mean (±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 (±95% CI) and median changes from baseline are shown.

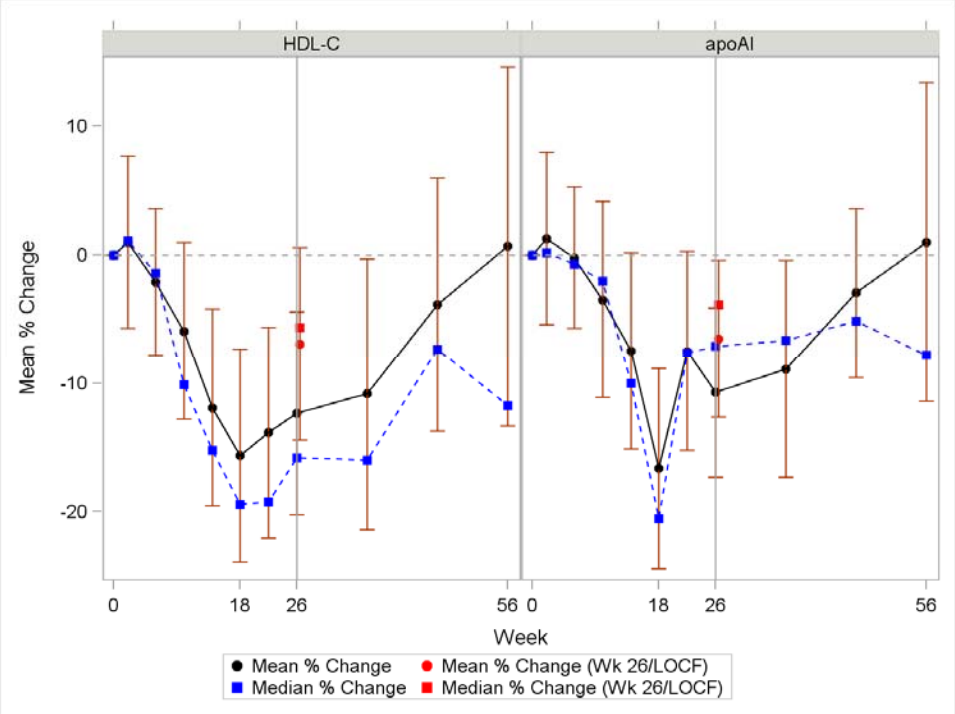


Figure 20. HoFH-pivotal – % Changes in HDL-C and ApoAI
Source: FDA clinical reviewer's depiction of data in HoFH-pivotal CSR Tables 14.2.2,4.10-11.1.
Error bars represent 95% CI of mean.
Vertical line at week 26 marks the end of the efficacy period.

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 43.

Table 43. 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, as noted above, 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 apoAI modify any potential effect of lomitapide on clinical outcomes is unknown.

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 21, 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.

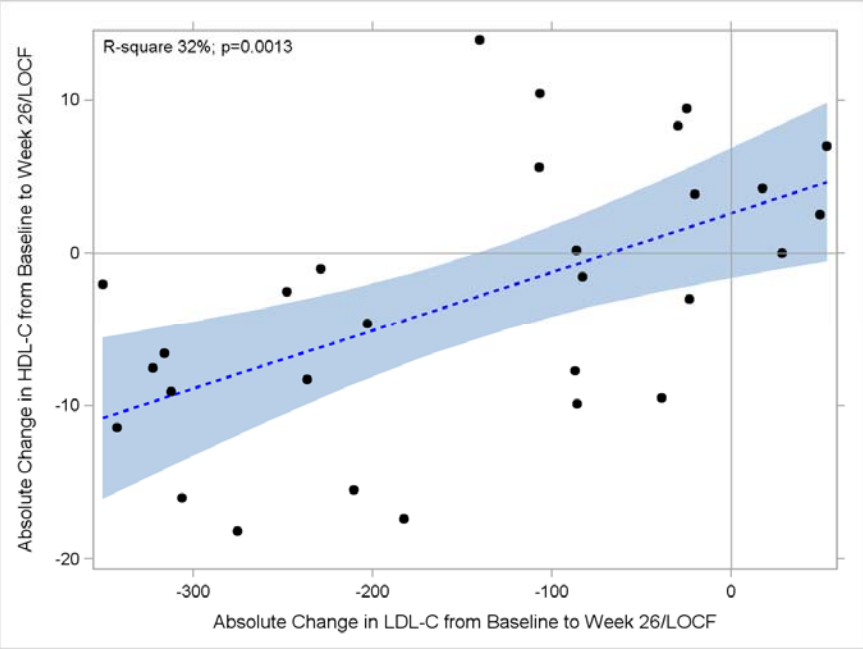


Figure 21. HoFH-pivotal – Association of Changes in LDL-C and HDL-C
Source: FDA clinical reviewer's analysis of HoFH-pivotal data in submitted analysis dataset (*ADLP xpt*). Regression line (simple linear regression) with shaded 95% confidence limits for predicted mean values.

Although the net effect of the LDL-C and HDL-C changes on clinical outcomes is speculative, 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-AI

In HoFH-pilot, the mean % changes in HDL-C and apoAI 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 apoAI were +34.2% (90.9), +22.4% (61.5), +38.7% (86.2), and -6.1 (26.4), respectively. This observation of an increase in HDL-C and apoAI 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 20).

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 ITT 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 13).

Appendix Figure 51 through Figure 56 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 ≥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 56); 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 54); 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 55).

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.

7 Review of Safety

7.1 Methods

The primary trial used to evaluate the long-term safety of lomitapide in HoFH is the 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 44). Additional details are provided in Table 7 and Table 9, and brief reviews of the individual phase 2 trials were presented in Section 5.4.

Table 44. 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.

7.1.1 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. When the applicant combined data across trials, all unique verbatim terms

were pooled and run against the MedDRA v14.0 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. This is an acceptable approach since the re-coding was performed from verbatim terms directly instead of from the originally coded preferred terms.

7.1.2 Safety Assessments

Table 99 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). The long-term effect of lomitapide on fat-soluble nutrients in the absence of supplementation has not been assessed during the development program.

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.

7.2 Adverse Event Summary

Table 45 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 45. 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%)

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)		
Deaths	0	0	0	0	0
Permanent d/c 2° 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 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/m^2. 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 Comments:

> *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.

7.4 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.

7.4.1 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).

7.4.2 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/m^2. 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/m^2. 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.

7.4.3 Phase 2 and 3 HoFH

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 46.

Table 46. 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
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	Hospitalization for anticoagulation (to reach acceptable INR)	Drug interrupted
HoFH-ext.	01-003	44	F	60	1141	Hospitalization 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 supravalvular aortic 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 agomelatin 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'es 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.

7.5 Dropouts and Discontinuations

7.5.1 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 100 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.

7.5.2 Phase 2 and 3 HoFH

There were no premature discontinuations in HoFH-pilot.

HoFH-Pivotal
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 47). 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.

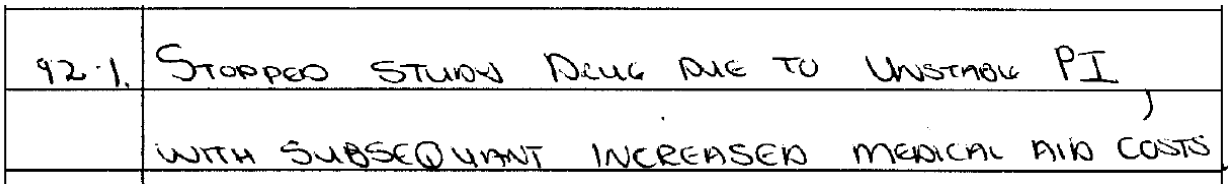
Table 47. HoFH-pivotal – Dropouts

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 (*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 (18 May 2012 response to FDA information request).



Source: Subject 13-002 CRF.

<u>HoFH-Extension</u>

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 7.4.3, p. 110). The applicant notes that this subject 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 "physician decision," although 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.

7.6 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 21.

Table 48 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., ≥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 48. 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
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%)

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)	
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 Disorders	**9 (31%)**	**4 (14%)**	**3 (13%)**	**7 (24%)**	**2 (11%)**
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%)**

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)	
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 ≥3 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."

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.

HoFH-pivotal Dose-AE Associations

Table 101 in the Appendix 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). 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.

HoFH-pilot Supportive Data for Common AEs

Table 49 summarizes AEs report in two or subjects during HoFH-pilot. Conclusions regarding relationships between dose and outcome are limited and potentially biased for the same reasons described in the preceding paragraph.

Table 49. 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.

7.7 Targeted Safety Issues

7.7.1 Liver-related Safety Concerns

As described in the Pharmcology/Toxicology briefing document, 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 (≤2x increase) and dogs (≤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.

Tranaminase Elevations & Other Liver-related Laboratories

HoFH-pivotal and HoFH-extension

Table 50 and Table 51 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 ≥3x ULN and 6 (21%) had AST ≥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 ≥5x ULN, respectively. None of the subjects with ALT or AST ≥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 ≥3x ULN in the safety phase had a history of a transaminase abnormality during the efficacy phase. Two subjects had a first transaminase abnormality ≥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 ≥3x ULN during the extension, with one subject having an SAE for hepatotoxicity with ALT 23.9x ULN (see Section 7.4.3, p. 110). One subject (01-003) had a first ALT ≥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 50. 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)
≥2x, <3x ULN	3 (10%)	4 (17%)	4 (14%)	0	3 (10%)
≥3x, <5x ULN	4 (14%)	3 (13%)	6 (21%)	2 (11%)	4 (14%)
≥5x, <10x ULN	3 (10%)	2 (9%)*	3 (10%)	1 (6%)	4 (14%)
≥10x, <20x ULN	1 (3%)	0	1 (3%)	2 (11%)	2 (7%)
≥20x ULN	0	0	0	1 (6%)	1 (3%)

Source: 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 51. 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)
≥2x, <3x ULN	4 (14%)	3 (13%)	4 (14%)	0	1 (3%)
≥3x, <5x ULN	4 (14%)	2 (9%)	5 (17%)	2 (11%)	5 (17%)
≥5x, <10x ULN	1 (3%)	0	1 (3%)	1 (6%)	2 (7%)
≥10x, <20x ULN	0	0	0	2 (11%)	2 (7%)
≥20x ULN	0	0	0	0	0

Source: FDA clinical reviewer's analysis of 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 22 illustrates the longitudinal trend of *mean* ALT, AST, and % hepatic fat over time in HoFH-pivotal, truncated at Week 56. 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 where the dose should not have exceeded 10 mg daily.

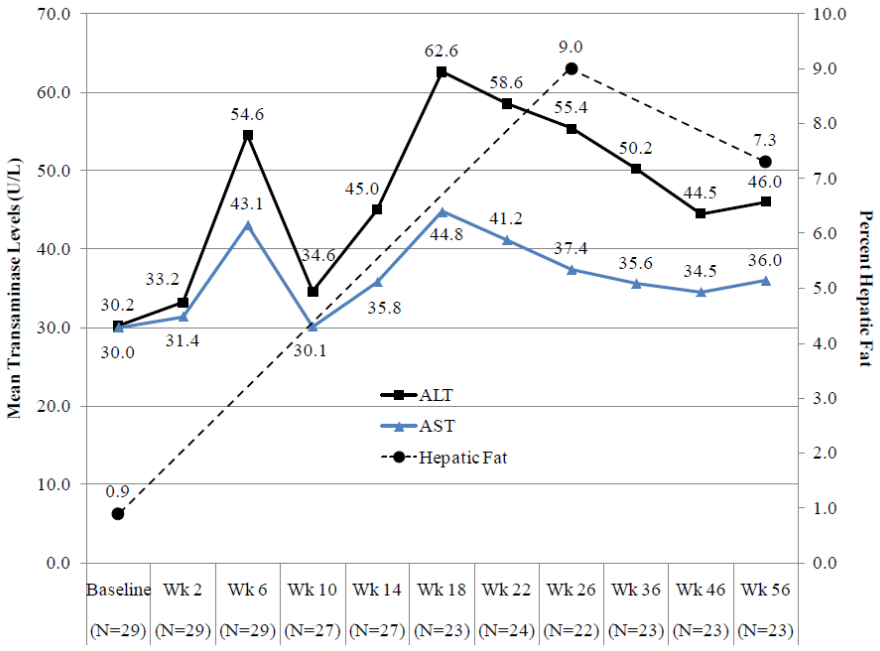


Figure 22. HoFH-pivotal – Mean ALT, AST, % Hepatic Fat Over Time
Source: HoFH-pivotal CSR, Figure 9. Missing data were not imputed.

Figure 23 illustrates the longitudinal trend of *median* ALT and AST over time in HoFH-pivotal, truncated at Week 56 (initial NDA submission).

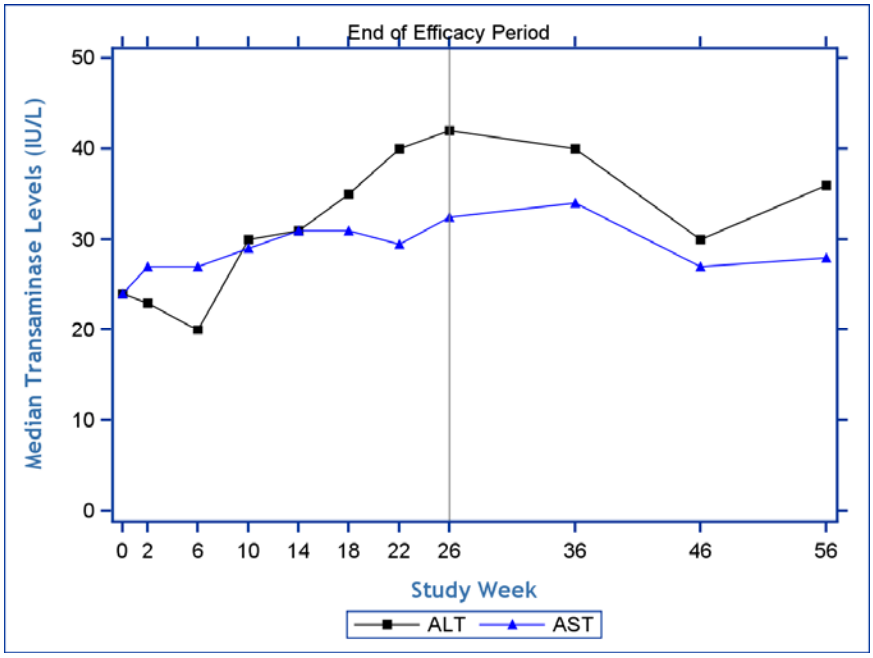


Figure 23. HoFH-pivotal – Median ALT/AST, Baseline to Week 56
Source: Derived from HoFH-pivotal CSR Tables 14.3.4.1.4.1, 14.3.4.1.4.2, 14.3.4.2.4.1.1, 14.3.4.2.4.2.1

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 ≥3x 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 ≥5x ULN at least once during the trial (Figure 24). As described in the protocol, confirmed transaminase elevations of this magnitude required dose reduction (or interruption for ≥10x ULN). The ≥5x and <10x 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 ≥10x ULN while taking 20 mg (week 6), although he had exceeded 5x ULN while taking 10 mg, and two subsequent shifts to ≥5x 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.

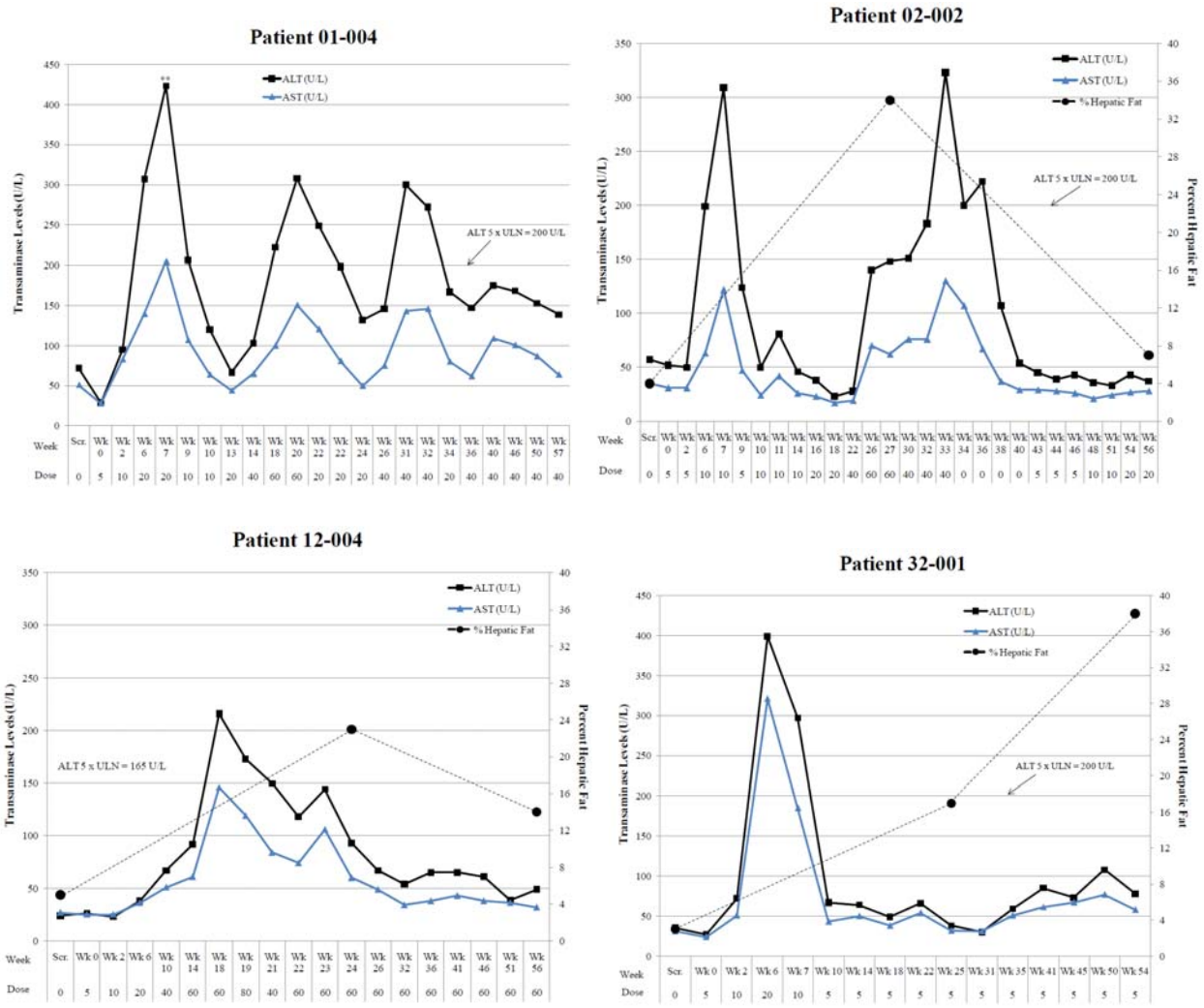


Figure 24. HoFH-pivotal – Selected Transaminase Profiles (ALT ≥5x ULN)
Source: HoFH-pivotal CSR, Figure 10.

Tables containing more granular information regarding the timing of dose modifications and transaminase measurements for these four subjects can be found in the Appendix (pp. 198-199). 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.

<u>HoFH-pivotal Brief Subject Summaries for Transaminase Abnormalities</u>

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/m^2. 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 ≥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/m^2. Concomitant lipid-lowering therapy included daily atorvastatin 40 mg and niacin 2000 mg. He had two excursions of ALT ≥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/m^2. Concomitant lipid-lowering therapy included daily rosuvastatin 40 mg, ezetimibe 10 mg, and 16 tablets of nicotinic acid. She had one excursion of ALT ≥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/m^2. Concomitant lipid-lowering therapy included daily rosuvastatin 30 mg and ezetimibe 10 mg. He had one excursion of ALT ≥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 ≥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 ≥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 ≥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.*
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 ≥5x ULN described above, there were five subjects in HoFH-pivotal who had at least one peak ALT ≥3x but <5x ULN:

Subject 11-004 (South Africa) had 3 excursions of ALT to ≥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 7.4.3 (p. 110).

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 ≥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).

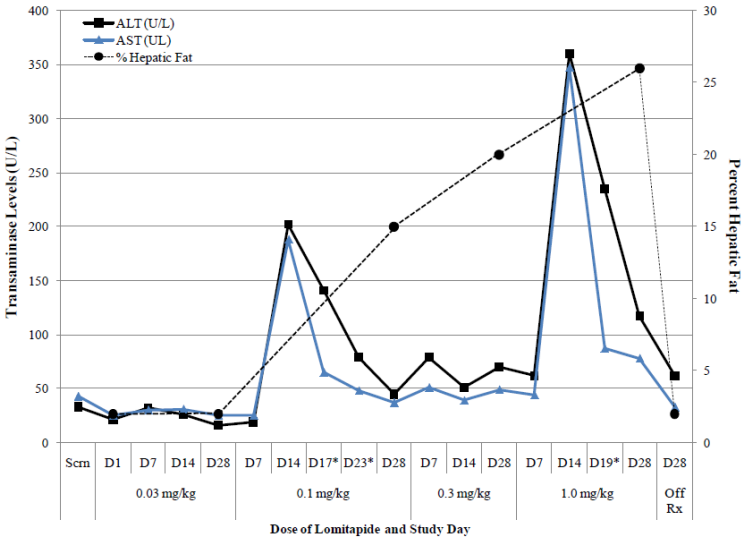
120-day Safety Update: This subject entered the extension study had was found to have ALT 6.9x ULN at the scheduled week 36 visit. Labs were followed approximately every 2 weeks and the dose of lomitapide was reduced from 60 mg to 40 mg to 20 mg daily. The ALT fell below 3x ULN approximately 10 weeks 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).

These data demonstrate that transaminase elevations to ≥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 ≥5x ULN during treatment. Total bilirubin was ≤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:

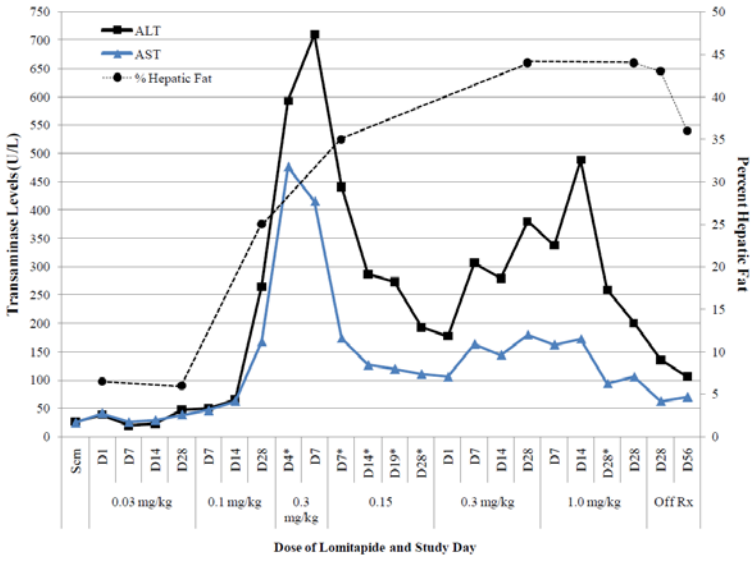


*Unscheduled assessments

Figure 25. 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 26. 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.

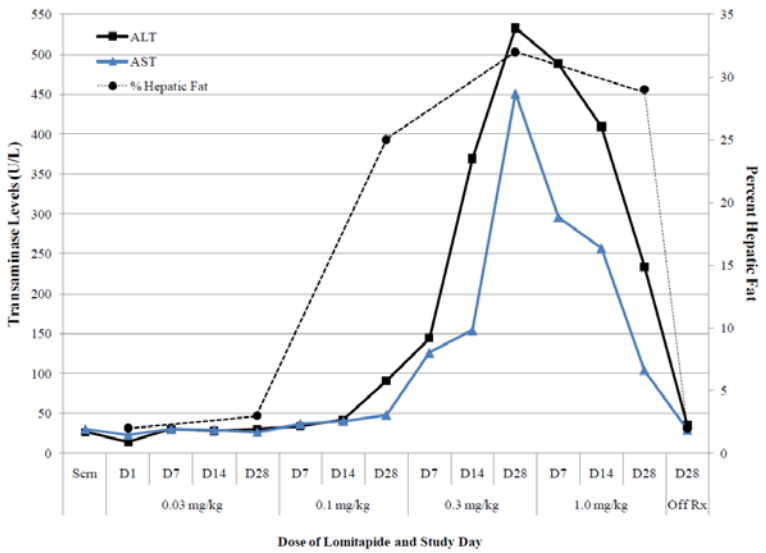


Figure 27. HoFH-pilot – Subject SDAG82 Transaminase Profile
Source: HoFH-pilot CSR, narratives.
Based on subject's baseline weight, approximate doses are 2, 6, 20, and 60 mg.

These profiles from HoFH-pilot support the observation that substantial transaminase abnormalities can improve despite continued dosing. In fact, subject SDAG82 (Figure 27) 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 increased). Despite this error, the transaminases improved despite continued dosing at the increased dose.
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Hepatic Fat

HoFH-pivotal and HoFH-extension
In HoFH-pivotal, all eligible subjects underwent measurement of hepatic fat by NMRS/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 52 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 (data not shown).

Table 52. HoFH-pivotal – Absolute Change in % Hepatic Fat From Baseline

Visit	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.
* 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 53 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 53. 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)	
# of Evaluable Subjects*	**23**	**22**	**22**	**23**	**18**
≤5%	4 (17%)	9 (41%)	6 (27%)	5 (22%)	4 (22%)
>5% to ≤10%	8 (35%)	6 (27%)	8 (36%)	8 (35%)	8 (44%)
>10% to ≤15%	4 (17%)	4 (18%)	3 (14%)	4 (17%)	2 (11%)
>15% to ≤20%	3 (13%)	1 (5%)	4 (18%)	3 (13%)	2 (11%)
>20% to ≤25%	2 (9%)	1 (5%)	0	1 (4%)	2 (11%)
>25%	2 (9%)	1 (5%)	1 (5%)	2 (9%)	0

Source: 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 on-study assessment in Figure 28. 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. 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.

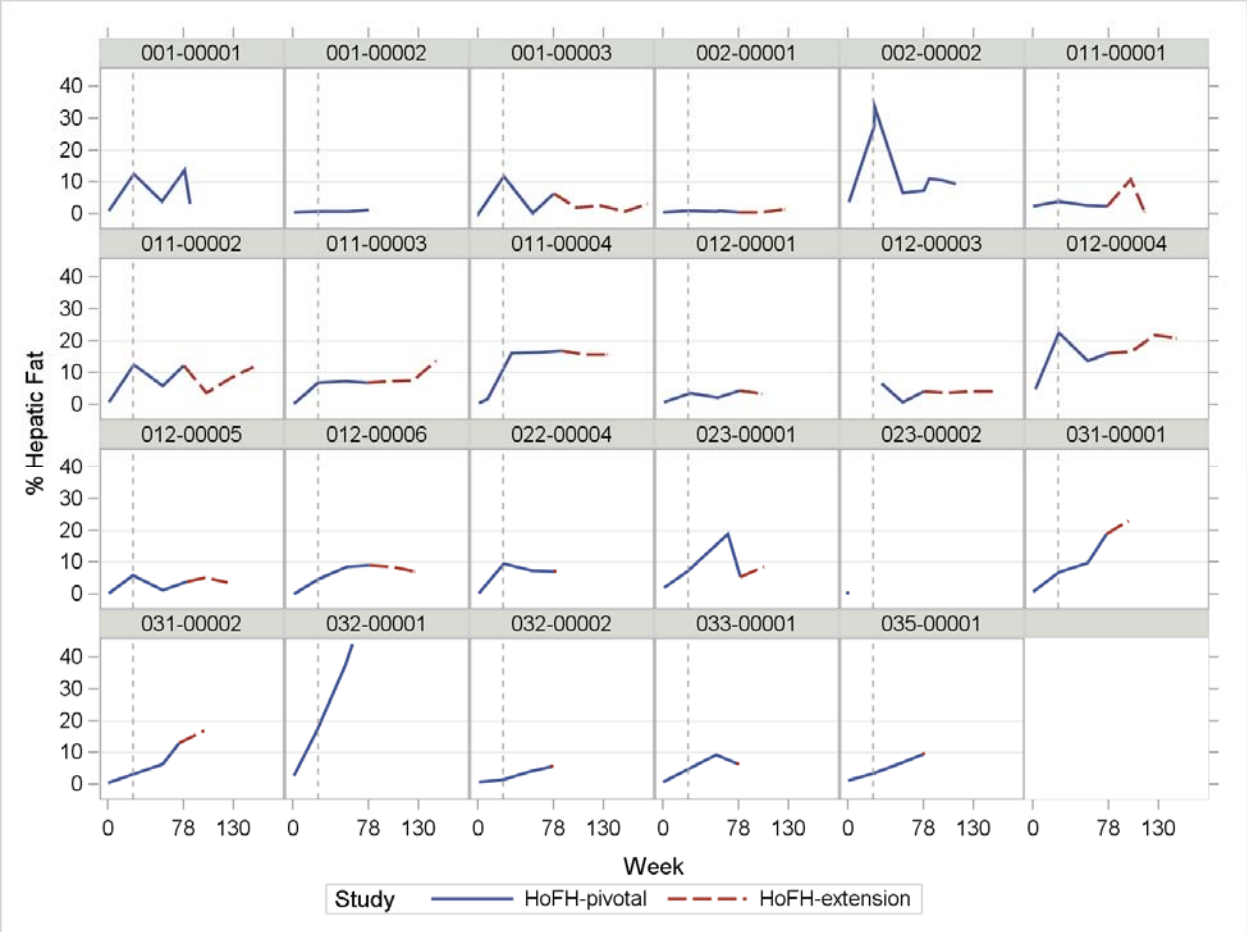


Figure 28. HoFH Phase 3 – % Hepatic Fat Profiles
Source: FDA clinical reviewer's analysis of submitted hepatic fat datasets from HoFH-pivotal and HoFH-extension (*OM.xpt*).
The dashed vertical lines indicate the end of the efficacy period (week 26) of HoFH-pivotal. Data may include off-treatment follow-up values (e.g., Subject 001-00001, whose last on-drug value was 13.9%).

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 exceeding 10% anytime on study in Table 54. 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. These data

suggest that the plateaus or observed reductions in hepatic fat cannot often be explained by decreases in dose.

Table 54. 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	5.0* (5 mg)	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)
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)*.
* Week 2.
** Additional assessment 48 days after week 56.
† This subject had an off-treatment measurement of 0.6% approximately 8 weeks after stopping lomitapide.

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 4.7% absolute percentage point higher amount of hepatic fat at week 26 (R^2=57.4%, p<0.0001). This relationship is depicted in Figure 29.

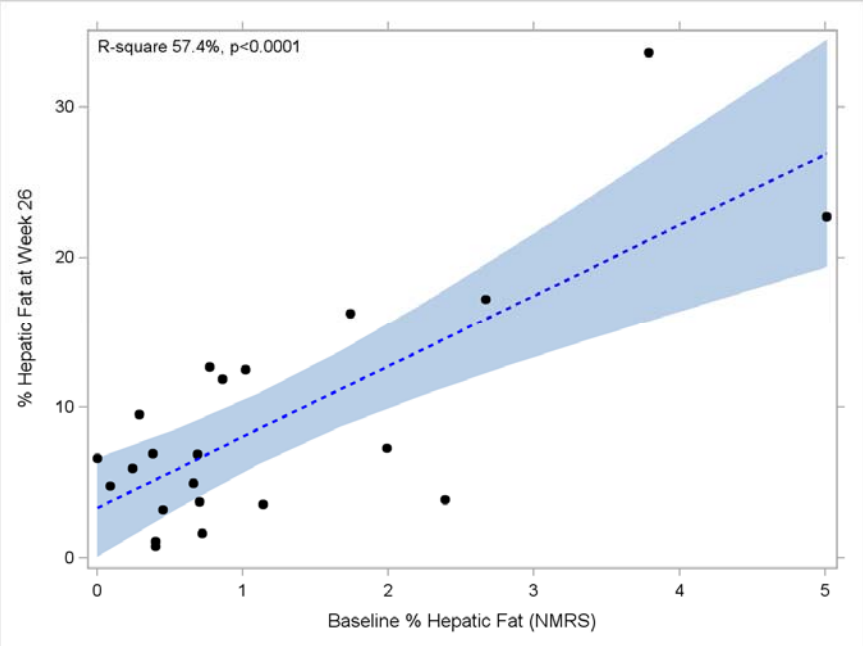


Figure 29. HoFH-pivotal – % Hepatic Fat at Baseline vs. Week 26
Source: FDA clinical reviewer's analysis of submitted HoFH-pivotal dataset (*OM.xpt*).

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 30.

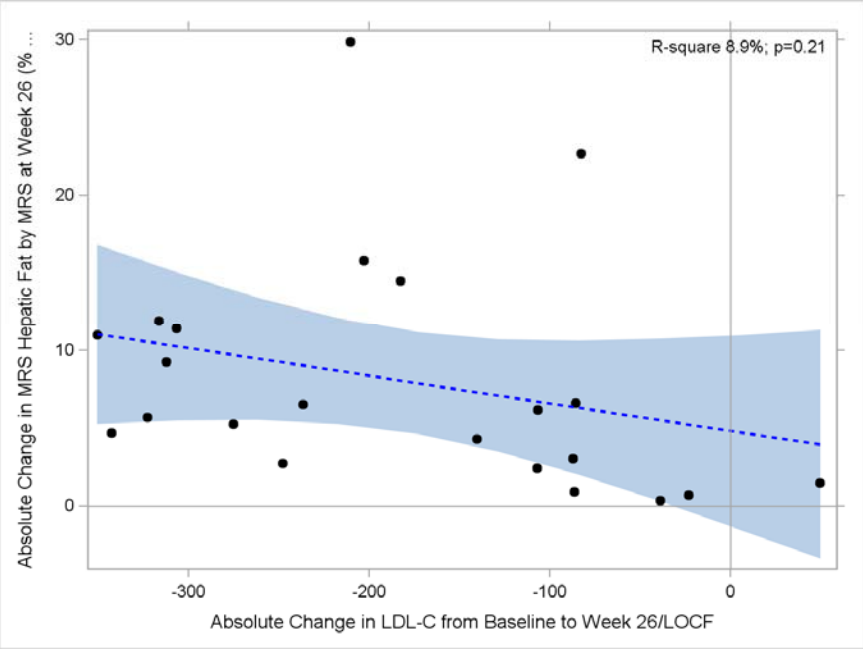


Figure 30. HoFH-pivotal – Association Between Changes in LDL-C and Hepatic Fat at Week 26

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 55). However, 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.

Table 55. 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).

In HoFH-pivotal alone, 7 (39%) of the 18 subjects who ever had >5% hepatic fat also had a peak ALT ≥3x ULN on-study compared with 1 (20%) of the 5 subjects who always had ≤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 ≥5x ULN on-study, with the remaining subject having a peak ALT 3.5x ULN. The temporal relationships between transaminase elevations and hepatic fat cannot be discerned conclusively given the widely spaced measurements of hepatic fat (Figure 24), however.

Reviewer Comment: Monitoring transaminases would be an insensitive method to screen for hepatic fat accumulation, but the clinical significance of lomitapide-induced hepatic steatosis in the absence of elevated transaminases is unclear.

Regarding reversibility of hepatic fat accumulation, follow-up NMRS or CT scans were available for 7 HoFH subjects after discontinuing lomitapide (Table 56). 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 56. HoFH-pivotal – Reversibility of Hepatic Fat

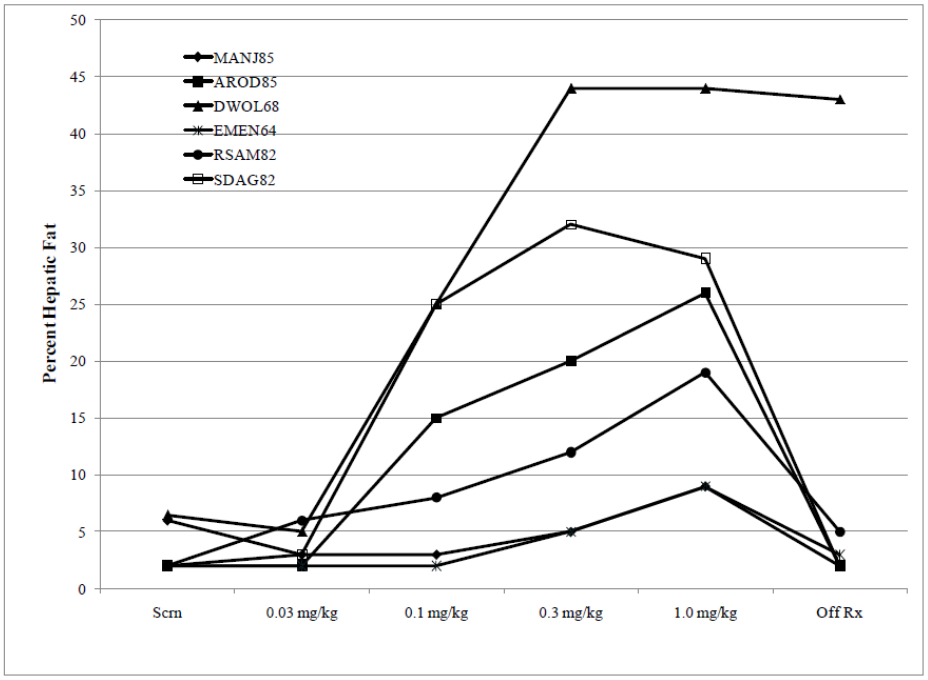
Subject	Baseline	Peak % Hepatic Fat on Study	% Hepatic Fat at Week 78	Follow-up
01-001	1%	14% at week 78	14%	3% (~6 wks post)
01-004	Mild-to-mod by CT at week 4	Moderate by CT at week 78	Moderate by CT	Mild-to-moderate (~6 wks post)
01-006	0%	None	(Early DC after ~6 months)	0% (~2 wks post)
01-002	0.4%	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 2.3 (p. 18), some have suggested that hepatic fat might promote insulin resistance (in addition to insulin resistance promoting hepatic fat). Serum insulin, C-peptide, and HbA1c were not assessed during HoFH-pivotal. The 12-week phase 2 study AEGR-733-004 did not reveal an association between hepatic fat accumulation and serum C-peptide (Appendix Figure 50).

HoFH-pilot Supportive Hepatic Fat Data

The profiles of % hepatic fat over time in HoFH-pilot are shown in Figure 31. All 3 subjects in this trial who had transaminase elevations ≥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 ≤5% in five of six subjects. One subject (DWOL68) had hepatic fat 41-43% at follow-up, which the applicant speculates might have been a result of alcohol use. 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 % was reported as a range; the maximum value of the range is displayed graphically.
Source: Appendix 4 and Appendix 7

Figure 31. HoFH-pilot – % Hepatic Fat over Time
Source: HoFH-pilot CSR, Figure 4.

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 5.4 (p. 46).

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 7.4.3 (p. 110).

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: FDA requested additional details about case, including data prior to initiating lomitapide if available, on 22 August 2012. Regardless, it will not be possible to establish with any certainty whether lomitapide was responsible for, or contributed to, the progression of the liver histology in this subject given her underlying disease, which itself is associated with hepatomegaly and hepatic steatosis.

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, hyperlpidemia, 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 57. All biomarkers except for P3NP increased from baseline through week 56.

Table 57. 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]
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 58 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 58. 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 32 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).

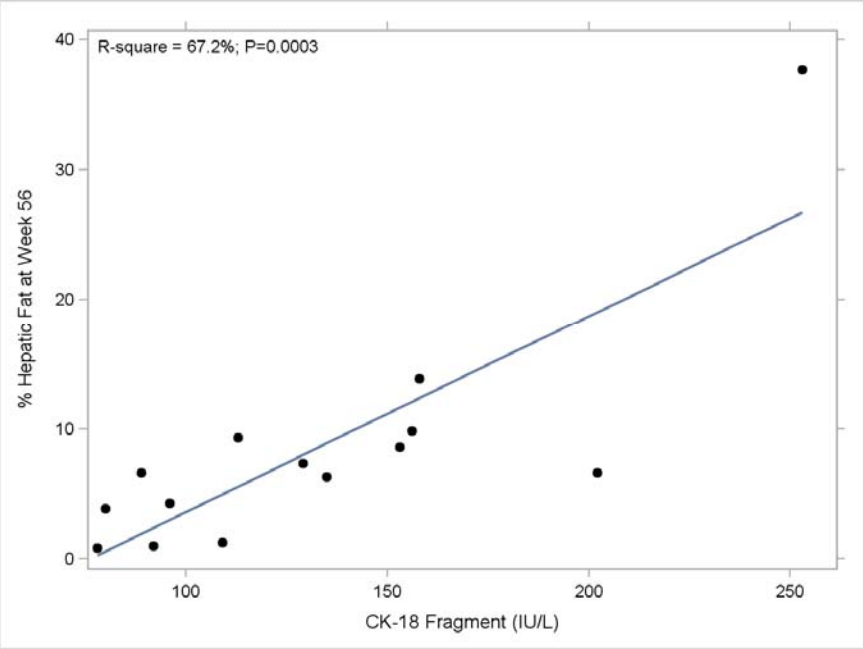


Figure 32. HoFH-pivotal – Cross-sectional Association Between CK-18 Fragment and % Hepatic Fat at Week 56
Source: FDA clinical reviewer's analysis of submitted HoFH-pivotal datasets (*LB.xpt* and *OM xpt*).
An additional two subjects had CK-18 measured but the values were "<75 IU/L." These two subjects 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.

7.7.2 Fat-Soluble Vitamins and Fatty Acids

As described in the Pharmacology/Toxicology briefing document, 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 5.4.2 (p. 46), 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.

Boxplots showing the distributions of each of these fat-soluble nutrients at each study visit are presented in the Appendix (Figure 57 through Figure 68). 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 59). 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 59. 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]

Parameter	Baseline Median [IQR]	% Change at Week 26 Median [IQR]	% Change at Week 78 Median [IQR]
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) suggests functional vitamin K deficiency, and *increased* values of Mead acid suggests 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 60 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 60. HoFH-pivotal – Fat-Soluble Vitamin Shift Table

		Week 26			Week 78		
Variable	**Baseline**	**< 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 61. The essential fatty acids ALA and LA were most commonly measured below the reference range, with 37% and 22% of subjects, respectively, having values that fell below the LLN from baseline to week 26. The proportion below the reference range did not increase over the next year, however; in fact, at week 78, 19% and 14% had fallen below LLN from a baseline above LLN. 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 61. HoFH-pivotal – Fatty Acid Shift Table

		Week 26			Week 78		
Variable	**Baseline**	**< LLN**	**Normal**	**> ULN**	**< LLN**	**Normal**	**> ULN**
ALA	< LLN	8 (42%)			9 (43%)		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%)
	> 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.

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.[47, 48] The values from HoFH-pivotal are depicted in Figure 33.

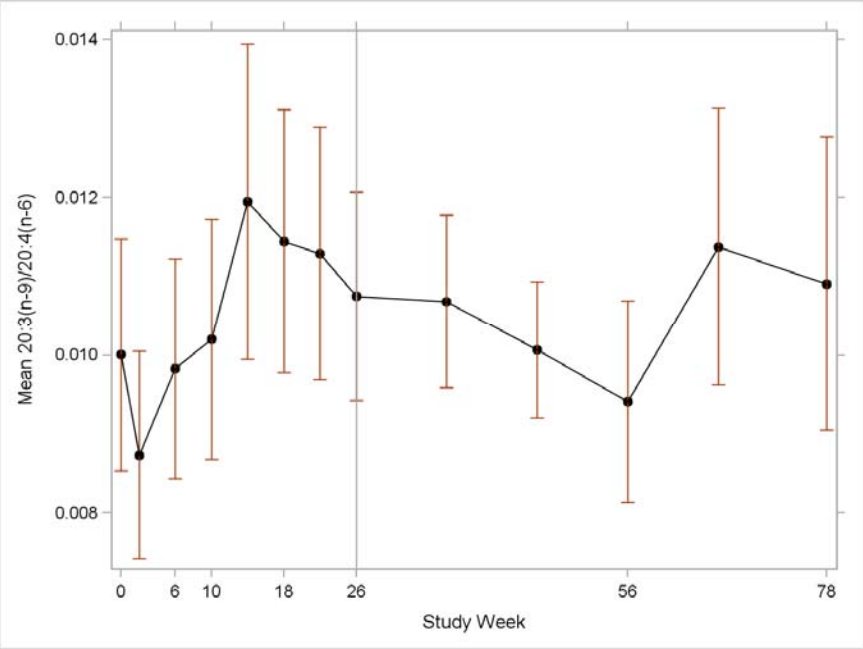


Figure 33. HoFH-pivotal – Holman Index Over Time
Source: FDA clinical reviewer's analysis of submitted HoFH-pivotal laboratory data (LB.xpt).
Error bars represent 95% CI of the mean. Values >0.02 are often cited to indicate essential fatty acid deficiency.

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 μmol/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. 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.

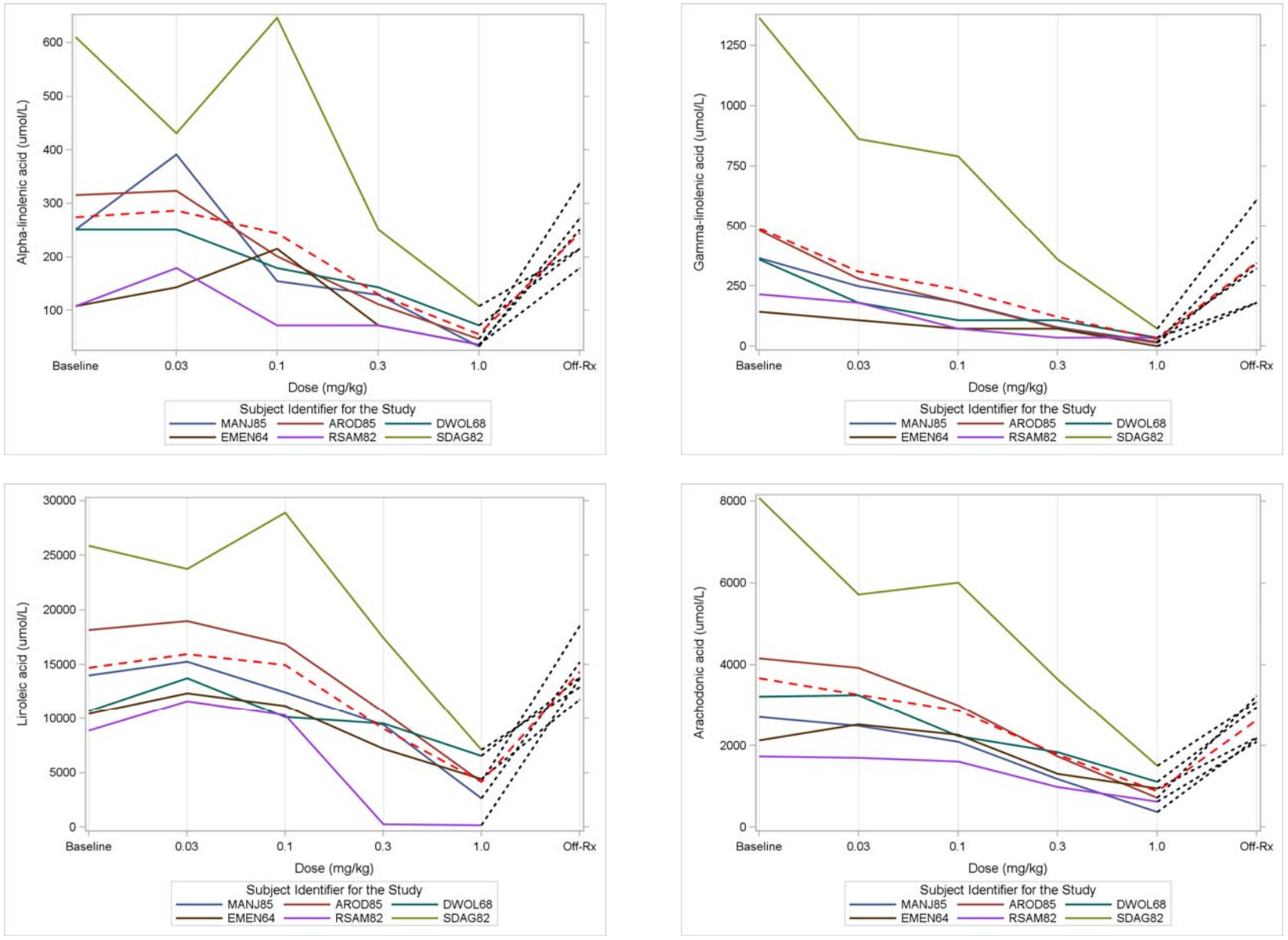
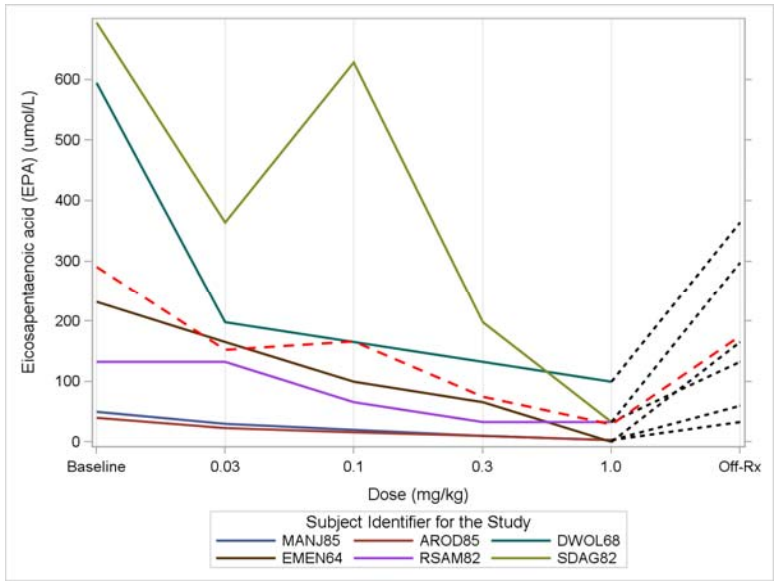
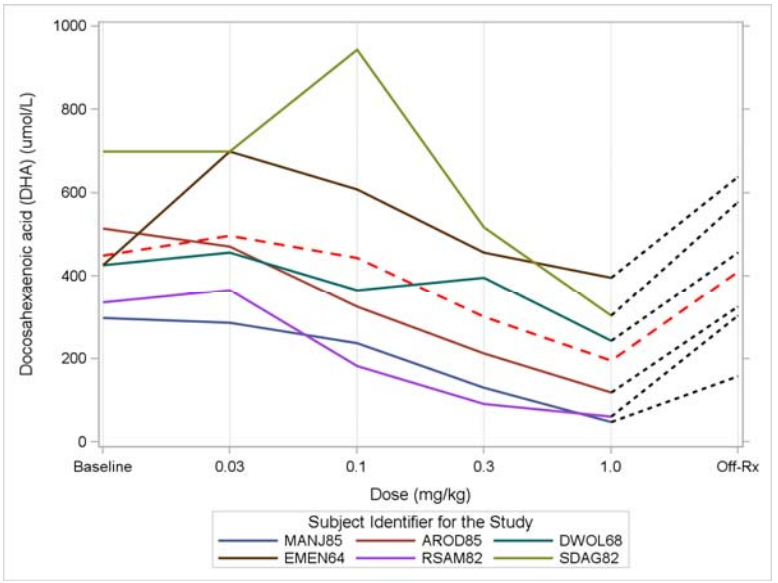


Figure 34. HoFH-pilot – Fatty Acid Trends





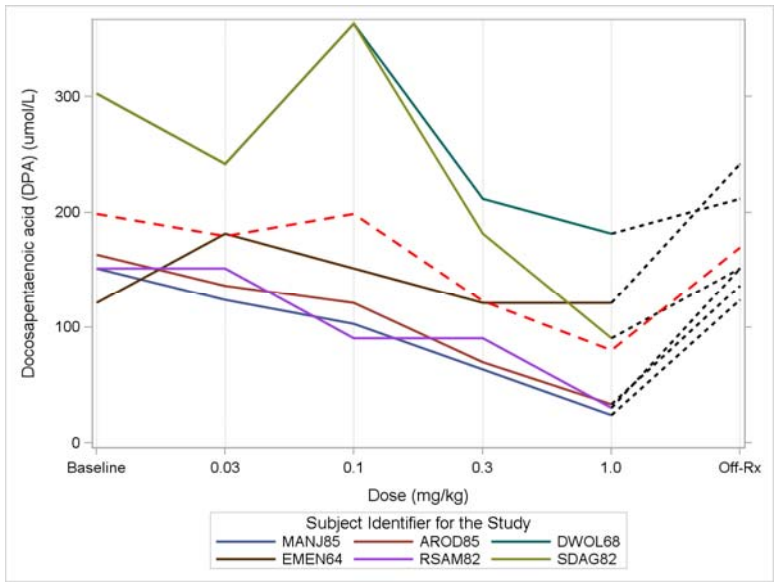


Figure 34. HoFH-pilot – Fatty Acid Trends (cont.)
Source: FDA clinical reviewer's analysis of submitted HoFH-pilot laboratory dataset (*LB.xpt*)

7.7.3 Body Weight

Figure 35 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).

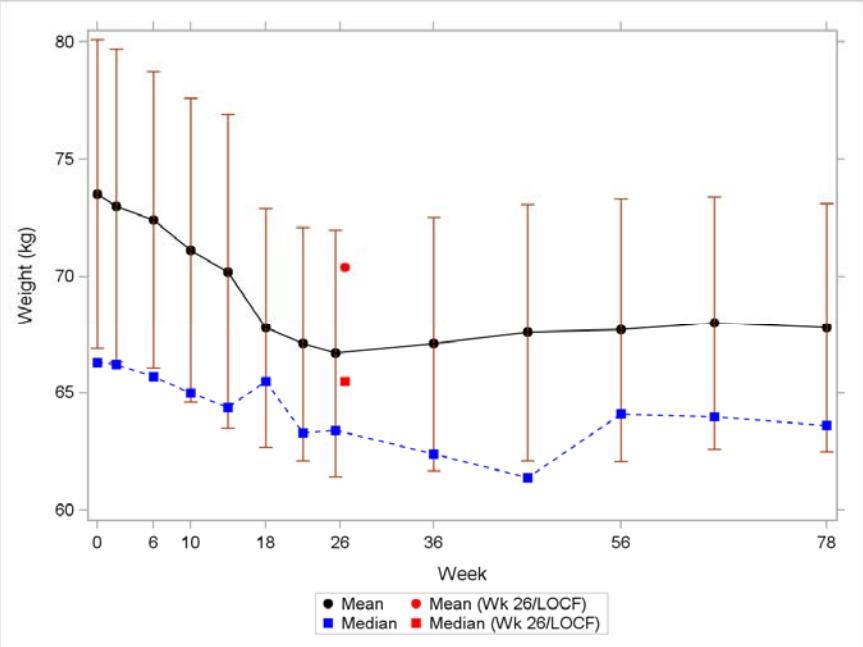


Figure 35. HoFH-pivotal – Body Weight Trend
Source: Derived from HoFH-pivotal CSR, Tables 14.3.4.1.17.5 and 14.3.4.2.17.5.1.
Week 66 and 78 values calculated from dataset submitted with 120-day safety update.
Error bars represent 95% CI of the mean.

No subject had a BMI value <18.5 kg/m^2 at any time during HoFH-pivotal.

Table 62 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 62. 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 36 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.

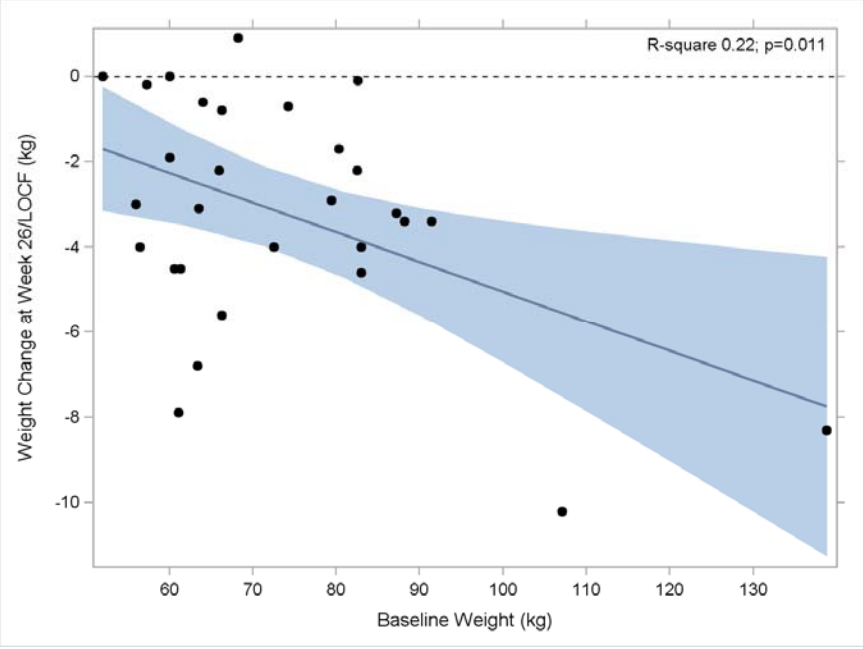


Figure 36. HoFH-pivotal – Baseline Weight vs. Weight Change at Week 26/LOCF
Source: FDA clinical reviewer's analysis of HoFH-pivotal *VS.xpt* dataset.
Regression line with shaded 95% confidence limits for the predicted mean values.

In a further 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 37). 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.

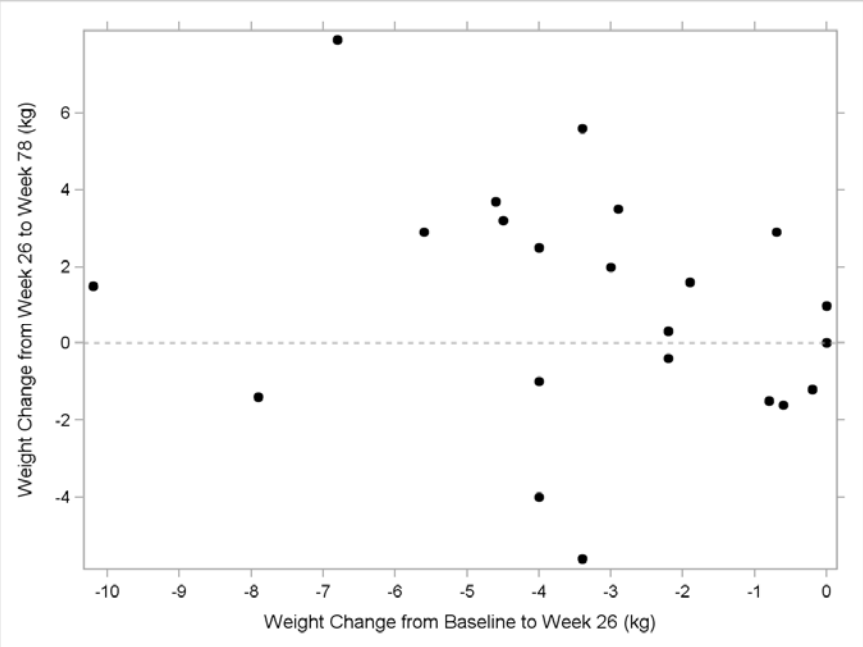


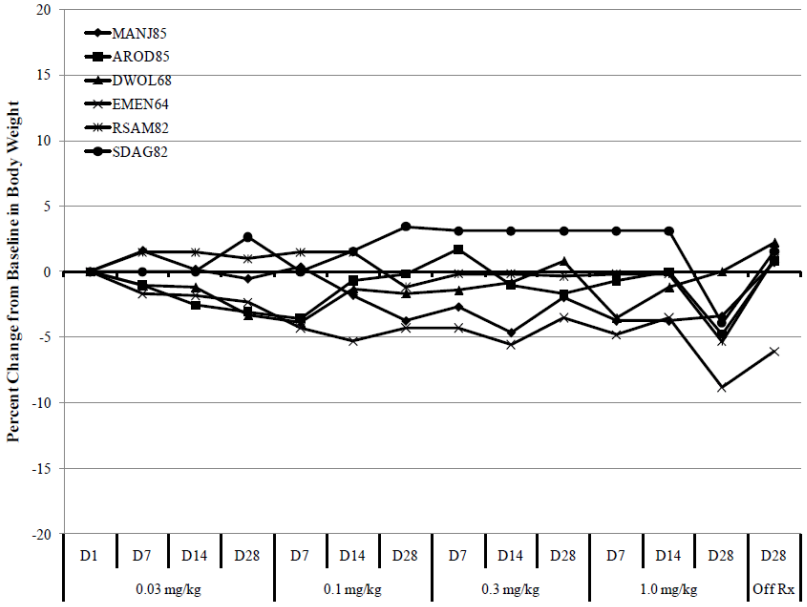
Figure 37. HoFH-pivotal – Weight Changes During Efficacy & Safety Phases
Source: FDA clinical reviewer's analysis of HoFH-pivotal *VS.xpt* dataset.
Data points above the dashed horizontal reference line represent subjects that *gained* weight during the safety phase, and those below the reference line 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.

Taken together, despite the limitation of HoFH-pivotal being a small, uncontrolled trial, which precludes accounting for regression to the mean and other non-drug-related changes, the observed weight loss would be consistent 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.

<u>HoFH-pilot Supportive Weight Data</u>
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 38 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/m^2 (weight 77.3 kg), which fell to 27.5 kg/m^2 (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 38. HoFH-pilot – Weight Changes Over Time
Source: HoFH-pilot CSR, Figure 6.

7.7.4 Pulmonary Function

Given a nonclinical signal of possible pulmonary toxicity during the lomitapide development program (see Pharm/Tox briefing document), 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 63 provides summary statistics, only including subjects who had a parameter assessed at baseline and at least one follow-up.

Table 63. HoFH-pivotal – Pulmonary Function Descriptive Statistics

	N	Mean (SD)	Median [IQR]	Mean (SD) Absolute Change from Baseline
FEV_1 (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)
FEV_1/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 39).

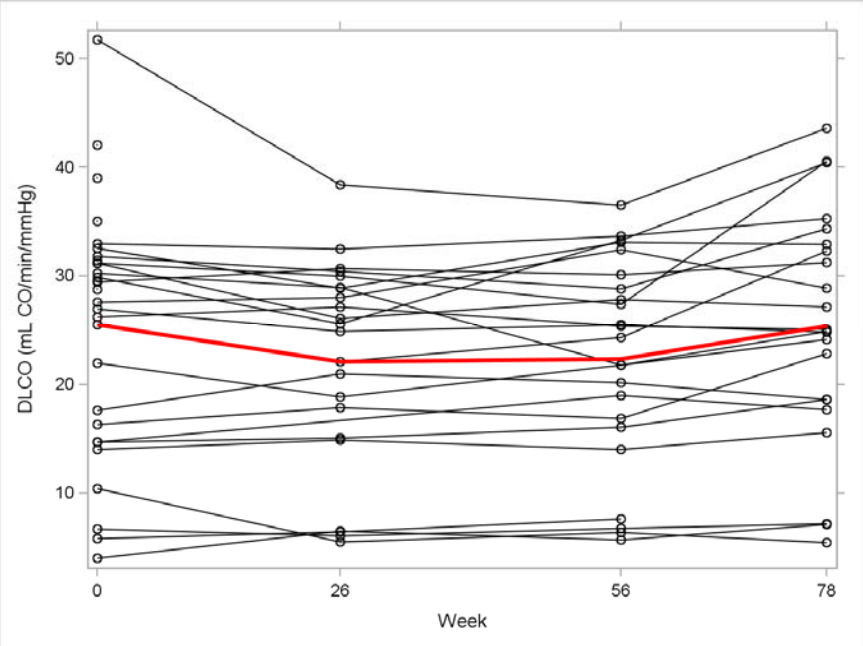


Figure 39. HoFH-pivotal – DLCO Trend
Source: FDA clinical reviewer's analysis of HoFH-pivotal *RE xpt* dataset.
Thick red line connects the mean values at each time point (no imputation).

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.

<u>HoFH-pilot Supportive PFT Data</u>
The applicant states that there were no clinically meaningful changes over time on treatment for FEV_1, FVC, FEF_{25-75}, 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; FEV_1, 0.01 (0.23) L; FEF_{25-75}, 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).

7.7.5 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 64 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 64. 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 7.4.3, p. 110). 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

(see Section 7.5.2, p. 115) as recorded on the case report form, which differs from CSR text ("The discontinuations were unrelated to warfarin or INR levels").

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 7.4.3, p. 110). 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.

7.7.6 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 65).

Table 65. 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
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 66).

Table 66. 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.

7.7.7 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 ≥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). No concomitant AEs are listed in the database and it does not appear that her statin dose was changed, although the date of this laboratory abnormality is 19 January 2012 (i.e., after the data cutoff of 31 December 2011), so these datasets may be incomplete. At the same visit, her urinalysis was dipstick negative for blood, her creatinine was 0.7 mg/dL, her potassium was 3.5 mEq/L, and her AST was 133 IU/L. At the extension week 108 visit, she had a CK of 173 IU/L.

"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%).

7.7.8 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 summarized in the Pharmacology/Toxicology briefing document. Briefly, there was a statistically significant increase in the incidence of hepatocellular neoplasms in male mice given ≥1.5 mg/kg/day (≥2x MRHD) and females given ≥7.5 mg/kd/day (≥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,[49, 50] 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.

7.8 Additional Safety Analyses

7.8.1 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 67 presents descriptive statistics for hematology laboratories in HoFH-pivotal at baseline and weeks 26 and 56. Table 68 describes the frequency of subjects who shifted categories relative to the normal reference range from baseline to weeks 26 and 56.

Table 67. HoFH-pivotal – Hematology Trends

	Mean (SD)	Median	Absolute Mean Change from…	
			Baseline*	Week 26*
WBC (x10^9/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)	
Week 56/LOCF [1]	13.2 (2.5)	12.9	+0.1 (1.1)	0.0 (1.1)
Platelet count (x10^9/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 68. HoFH-pivotal – Hematology Shift Tables

		Week 26			Week 56		
Variable	**Baseline**	**< 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 67 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 69 presents descriptive statistics for clinical chemistry laboratories in HoFH-pivotal at baseline and weeks 26 and 56.

Table 69. 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)	
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		

	Mean (SD)	Median	Absolute Mean Change from…	
			Baseline*	Week 26*
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 7.7.7 (p. 158).
- 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.

7.8.2 Vital Signs

Similar to the laboratory data described in Section 7.8.1, 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 70 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 70. 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					
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.

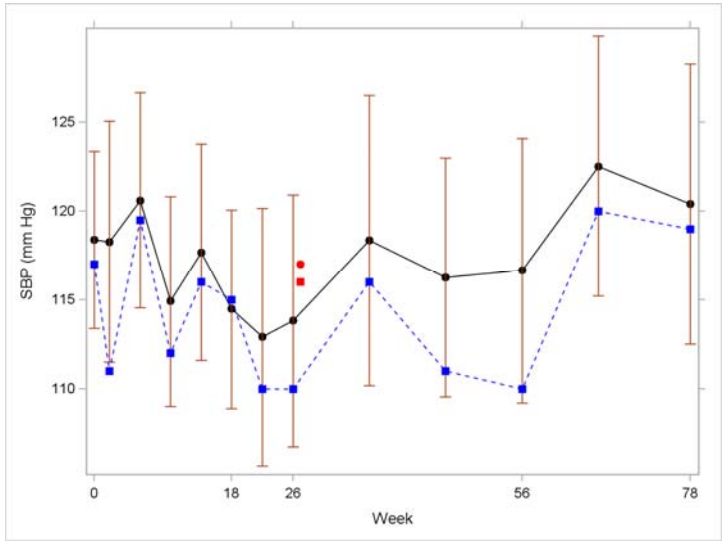
Note that toward the end of the safety phase, the point estimates for the mean changes from baseline in systolic and diastolic blood pressure achieve values as high as +5.7 mmHg and +3.1 mmHg, respectively. Examining these measures of central tendency at all time points of the trial, however, do not suggest consistent trends in these

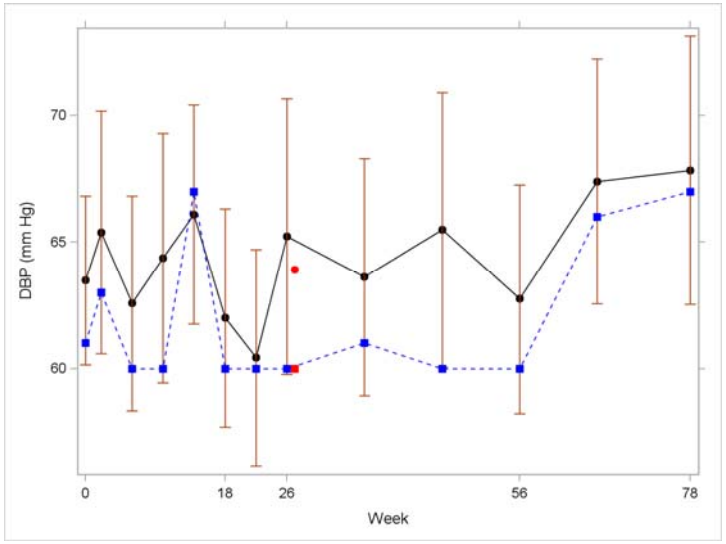
parameters (Figure 40). There was no suggestion of adverse changes to respiration rate or body temperation (not shown).

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.

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.





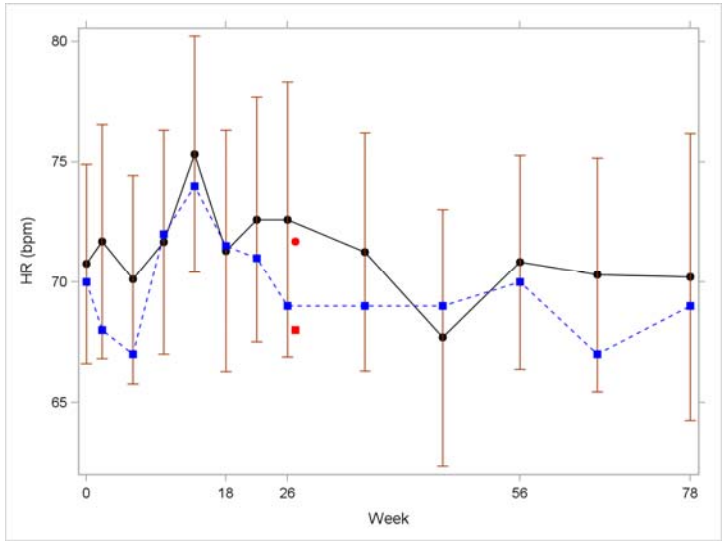


Figure 40. HoFH-pivotal – Vital Sign Trends
Source: FDA clinical reviewer's analysis of data submitted in HoFH-pivotal laboratory dataset (*LB.xpt*).
Black solid line connects mean observed values (black, filled circles); error bars represent 95% CI of the mean.
Blue dashed line connects median observed 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 71 summarizes the mean (SD) changes in vital sign parameters and weight following each dosing period in HoFH-pilot.

Table 71. HoFH-pilot – Mean (SD) Vital Signs Over Time

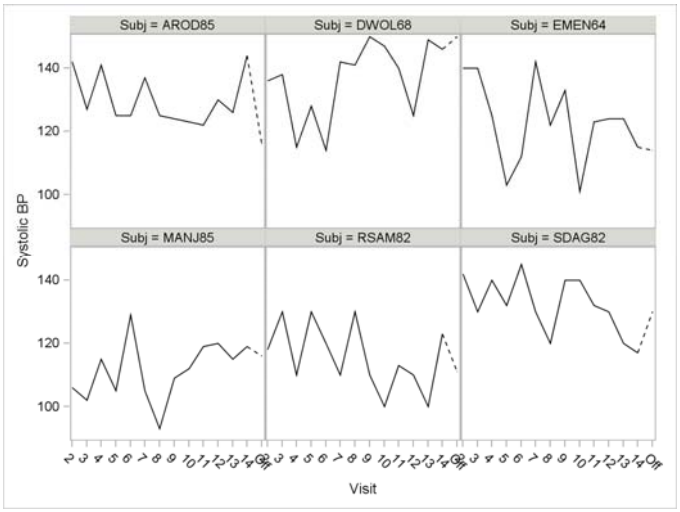
Parameter	Lomitapide Dose				Off-Treatment Visit (Visit 15)
	0.03 mg/kg (Visit 5)	0.1 mg/kg (Visit 8)	0.3 mg/kg (Visit 11)	1.0 mg/kg (Visit 14)	
Heart Rate	-2.8 (16.20)	-1.7 (11.36)	0.3 (8.21)	1.8 (11.39)	-3.2 (8.04)
Systolic BP	-10.2 (16.41)	-8.8 (13.91)	-5.8 (12.61)	-3.3 (17.21)	-7.8 (17.16)
Diastolic 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)

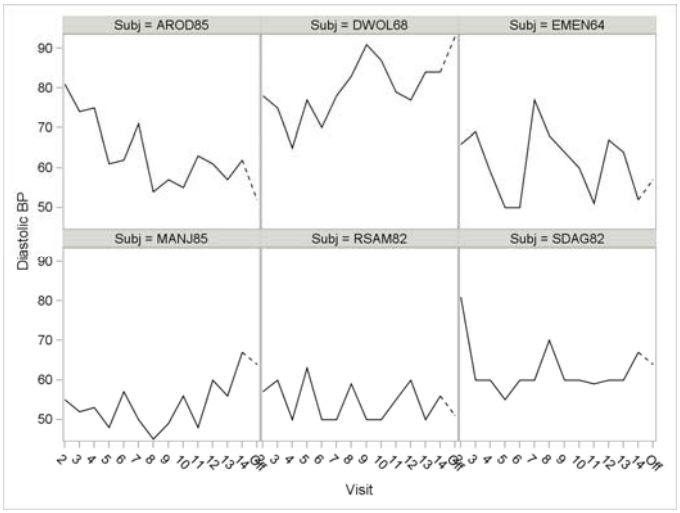
Note: Each patient's dose was escalated approximately every 28 days from 0.03 to 0.1 to 0.3 and to 1.0 mg/kg; assessments conducted at the end of each dosing period.
Source: Appendix 3a, Appendix 3b, Appendix 3c, and Appendix 3d

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 41). Taken alone, these data do not raise a safety concern, but they do not provide much reassurance given the paucity of subjects.





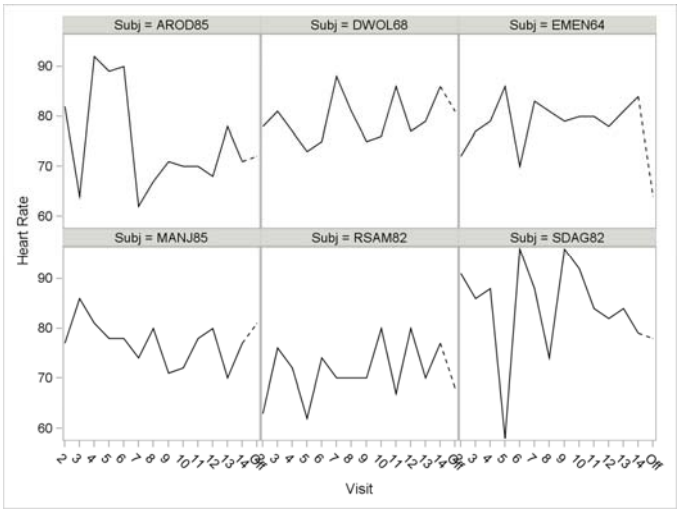


Figure 41. HoFH-pilot – SBP, DBP, and Heart Rate Over Time
Source: FDA clinical reviewer's analysis of submitted HoFH-pilot dataset (*LB xpt*)
Dashed lines connect values at the last on-treatment visit and the off-treatment follow-up.

7.8.3 Electrocardiograms

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 FDA 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 ΔΔQTcI 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 moxifloxicin 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 72, excerpted from the IRT/QT review.

Table 72. 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)	ΔΔQTcI (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 73 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 73. Thorough QT Study – Max Changes in HR, PR, QRS

	ΔΔHR (bpm)		ΔΔPR (ms)		ΔΔQRS (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 ≥110 ms; an association with lomitapide was not detected.

HoFH-Pivotal

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 (ΔQTcF) from baseline that would trigger the requirement for a centralized blinded review of ECG tracings: If the upper one-sided 95% CI for ΔQTcF 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 74 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 ΔQTcF values were lower and the upper bounds of the 90% CIs were <10 msec.

Table 74. HoFH-pivotal – Mean Changes in ECG Intervals (Central Read)

Visit (n)	ΔDHR	ΔQTcF	ΔPR	ΔQRS
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 ΔPR, n = 26, 24, 25, 23, 21, 20 and 21 across weeks 2-26, respectively; for ΔQRS, N = 27, 26, 26, 24, 22, 21, and 22.

No subject had a QTcF exceeding 500 msec or a ΔQTcF from baseline exceeding 60 msec (Table 75). Because the mean dose of lomitapide increased over time, there does not appear to be an association between dose and ΔQTcF. 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 75. HoFH-pivotal – QTcF Outliers (Central Read)

Visit (n)	QTcF			ΔQTcF	
	>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.

7.8.4 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).

7.9 Potential for Teratogenicity

The battery of toxicology studies to investigate the effects of lomitapide on reproduction and embryo-fetal development is summarized in the Pharmacology/Toxicology briefing document. In rats and ferrets, treatment with lomitapide during the period of organogenesis resulted in embryonic death and fetal malformations of the abdomen, limbs, tail, and head at clinically relevant exposures.

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.

8 Appendices

8.1 Non-HoFH Phase 2 Supplemental Data

Table 76. 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.

Reviewer Comment: Note that these values, and those in the subsequent figure, result from a completers analysis.

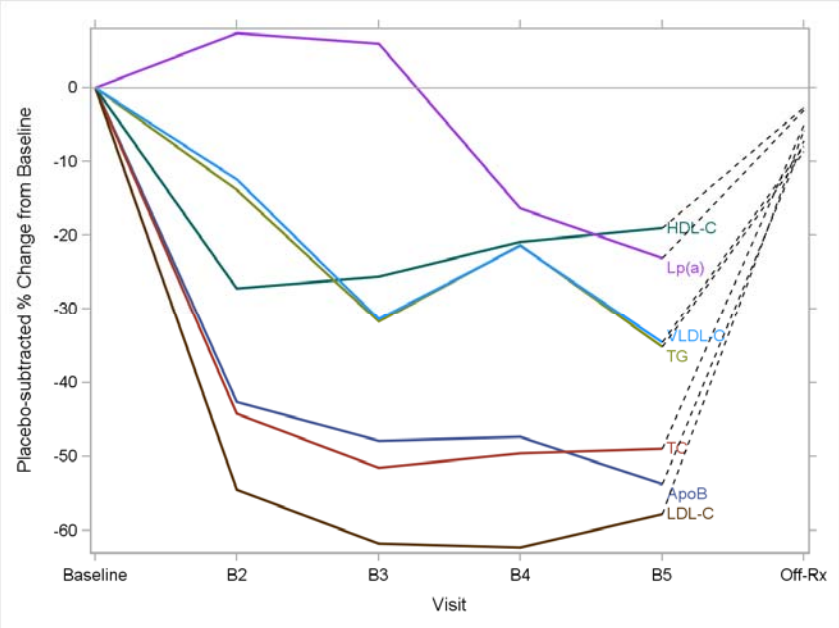


Figure 42. C-009 – Lipid Parameters Over Time
Source: FDA clinical reviewer's depiction of data derived from C-009 CSR, Table 14.4.
Approximately 1 week separates each on-treatment visit (Baseline through B5), with ~6 weeks elapsing between B5 and the off-treatment follow-up visit.

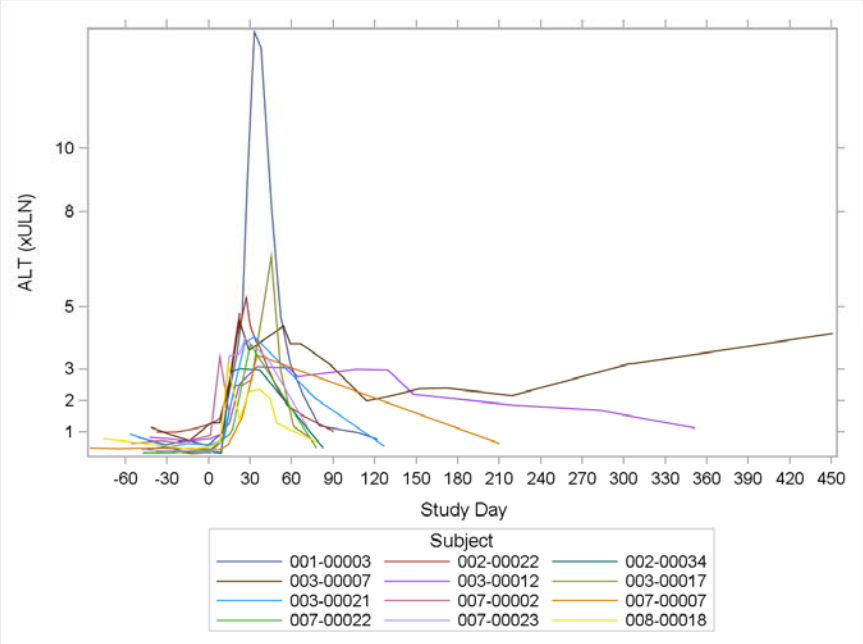


Figure 43. C-009 – ALT Profiles for Subjects with Peak ALT ≥3x ULN
Source: FDA clinical reviewer's analysis of submitted C-009 laboratory dataset (*LB.xpt*). First dose of lomitapide = study day 1 (i.e., Period B). Recall that the expected dosing duration was approximately 28 days followed by a 42-day off-drug follow-up period (i.e., to approximately day 70).

Table 77. 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.
Limited to AEs that were both more common in the lomitapide than placebo group and reported by ≥5% of lomitapide-treated subjects (i.e., ≥2 subjects).

I explored the association between baseline % hepatic fat and peak ALT observed on study among lomitapide-treated subjects in study C-009. Among the 8 lomitapide-treated subjects with baseline hepatic fat >15%, 6 had a peak ALT ≥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 44).

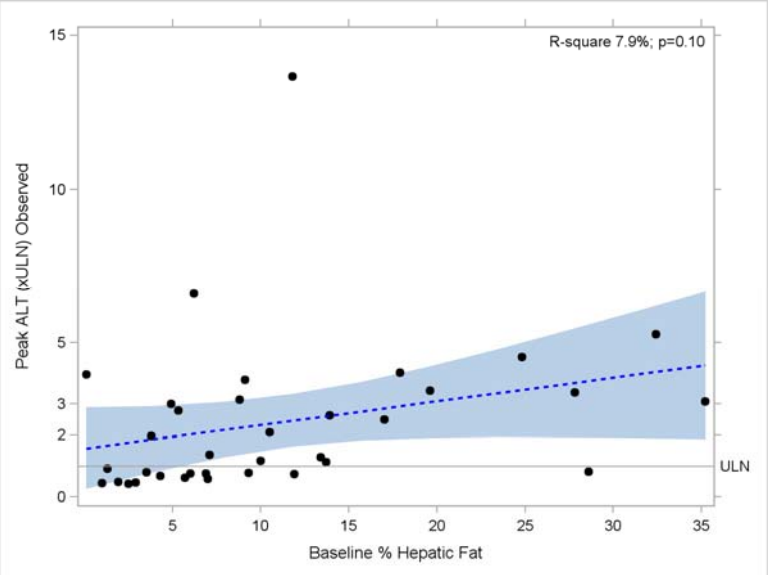


Figure 44. C-009 – Baseline Hepatic Fat vs. Peak ALT Observed
Source: FDA clinical reviewer's analysis of C-009 submitted datasets (*OM, LB xpt*).
This figure only includes data from the lomitapide arm.
Regression line (simple linear regression) with shaded 95% confidence limits for predicted mean values.

In addition, 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 45). 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 (Figure 46).

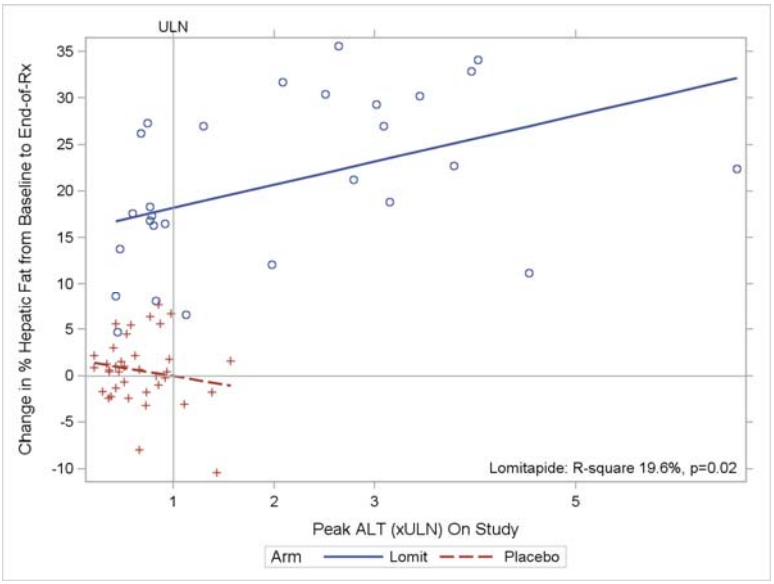


Figure 45. C-009 – Peak ALT (x ULN) vs. Change in Hepatic Fat
Source: FDA clinical reviewer's analysis of submitted C-009 datasets (*LB, OM xpt*).

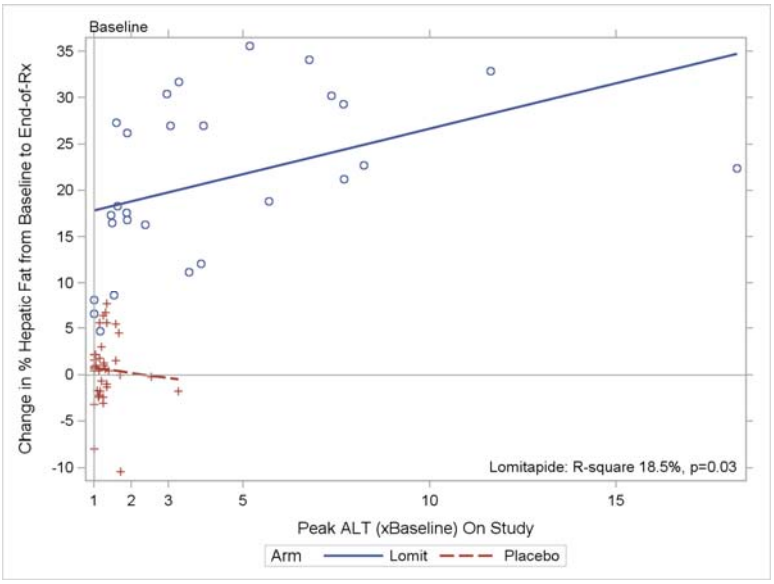


Figure 46. C-009 – Peak ALT (x Baseline) vs. Change in Hepatic Fat
Source: FDA clinical reviewer's analysis of submitted C-009 datasets (*LB, OM xpt*).
Note the difference in the scale of the x-axis compared with the previous figure.

Table 78. 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

	Lomitapide 25 mg		Placebo		P
	Mean (SD)	% Change from Baseline	Mean (SD)	% Change from Baseline	
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.

Table 79. 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 (end-of-treatment)	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
FEF_{25-75} (% 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
FEV_1 (% 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.

Table 80. 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

	Lomitapide Monotherapy (n=28)	Ezetimibe Monotherapy (n=29)	Combination (n=28)
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 81. 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).
Only subjects with available data are included.
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.

Table 82. 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

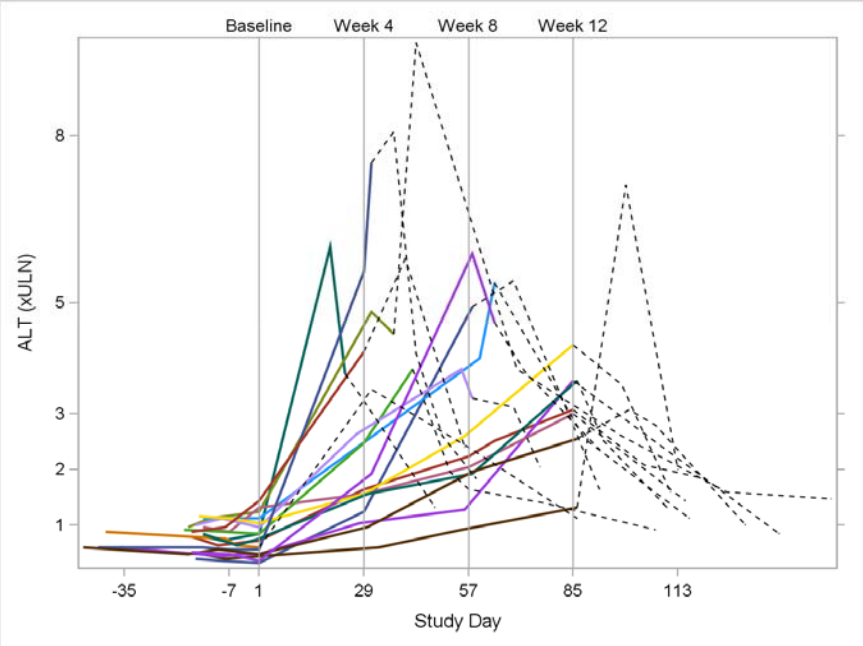


Figure 47. A-001 – ALT Profiles for Subjects with Peak ALT ≥3x ULN
Source: FDA clinical reviewer's analysis of submitted A-001 datasets (*LB and EX.xpt*).
Black, dashed lines indicate values following treatment discontinuation.
Lomitapide monotherapy and combination therapy groups are combined. All of 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.

Table 83. A-003b – Mean (SD) Baseline Lipid Parameters

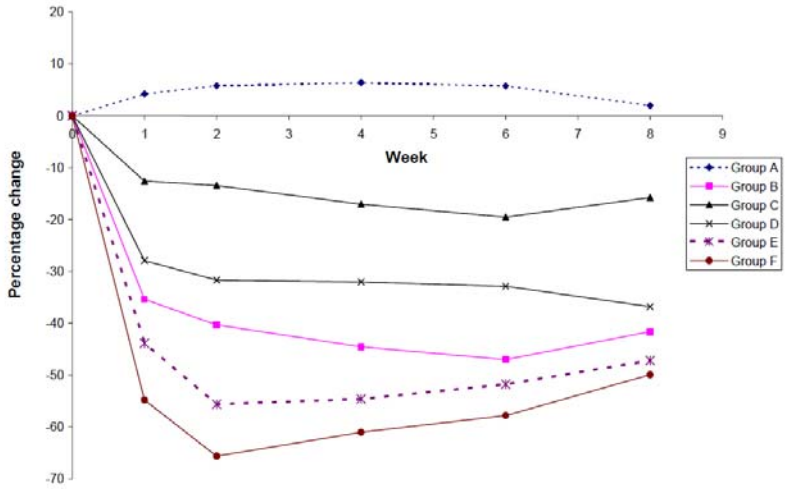
	P (n=27)	L5 (n=26)	L10 (n=26)	A20 (n=26)	L5+A20 (n=26)	L10+A20 (n=26)	All (n=157)
LDL-C	166 (25)	177 (38)	172 (29)	174 (24)	169 (17)	179 (33)	173 (28)
TC	251 (29)	265 (37)	261 (37)	262 (28)	248 (24)	259 (38)	257 (33)
TG*	176 (111)	178 (186)	171 (92)	173 (83)	161 (57)	131 (67)	165 (107)
ApoB	149 (22)	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.

Table 84. 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[§]	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.
Only includes subjects with available data (no imputation).



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 48. A-003b – Mean % Change in LDL-C Over Time
Source: A-003b CSR, Figure 11-1.
AEGR-733 = lomitapide.

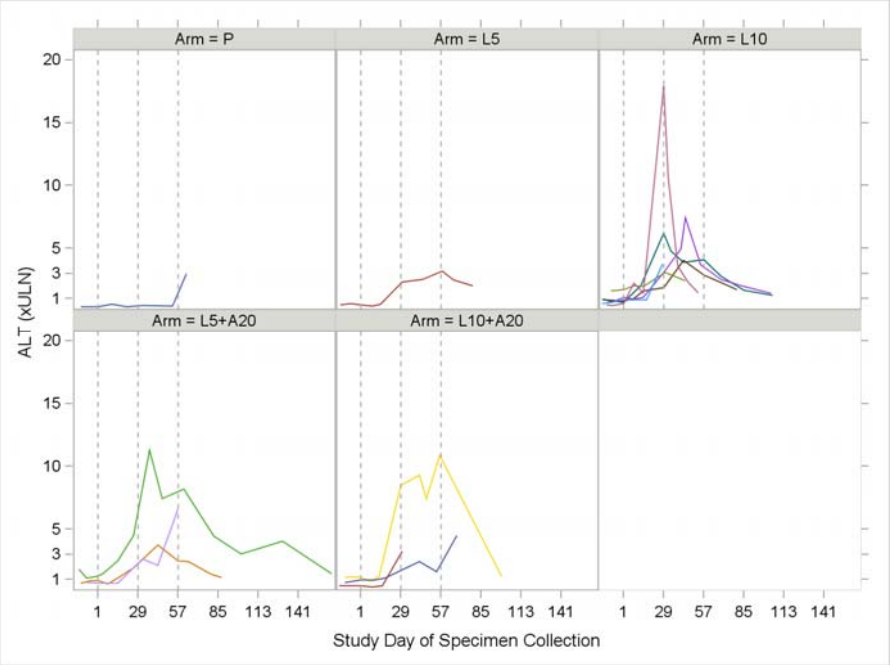


Figure 49. A-003b – ALT Profiles for Subjects with Peak ALT ≥3x ULN
Source: FDA clinical reviewer's analysis of A-003b laboratory dataset (*LB.xpt*)
Dashed lines are the approximate times of the week 4 and week 8 visits for reference. Only subjects with peak ALT ≥3x ULN after baseline are included in this figure.

Table 85. 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%)**

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)
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 86. 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%)
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 (i.e., ≥2 subjects) and by more subjects in a lomitapide (with or without atorvastatin) group than a control (placebo or atorvastatin) group.

Table 87. 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)
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).

Table 88. 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*).

Table 89. A-003b – Mean (SD) Vitamin A Levels Over 8 Weeks

Vitamin A (μmol/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

Vitamin A (μmol/L)	P (n=27)	L5 (n=26)	L10 (n=26)	A20 (n=26)	L5+A20 (n=26)	L10+A20 (n=26)
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 90. 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 89 above.

Table 91. 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 92. A-004 – Mean Placebo-subtracted % Changes in Lipids at Week 12/LOCF

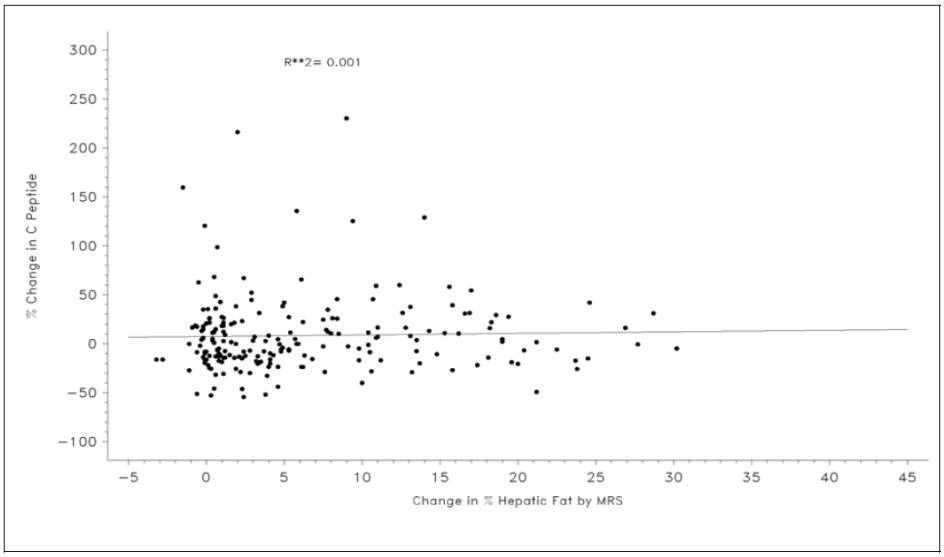
Parameter	Lomit 2.5 mg (n=34)	Lomit 5 mg (n=33)	Lomit 7.5 mg (n=34)	Lomit 10 mg (n=34)
LDL-C	-12.6 (-24.6, -0.5)*	-15.3 (-27.3, -3.2)**	-16.0 (-28.1, -3.9)**	-32.4 (-44.4, -20.4)†
TC	-9.3 (-18.6, 0.0)	-11.4 (-20.7, -2.1)**	-14.3 (-23.6, -5.0)†	-27.1 (-36.3, -17.8)†
TG	-5.5 (-30.0, 19.0)	-4.9 (-29.4, 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.
Results with and without LOCF are modest and do not affect interpretation of the results.

Table 93. 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



Data source: Section 14.2, Figure 15.3.6

Figure 50. A-004 – Change in % Hepatic Fat vs. % Change in C-peptide
Source: A-004 CSR, Figure 10.

Table 94. 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

Group	% Change in Body Weight from Baseline to Week 12/LOCF			Placebo-subtracted difference (95% CI)	P (vs. pbo)
	Mean (SD)	Median	Min, Max		
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.

Table 95. 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)
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.
Only lomitapide monotherapy groups are shown. Differences between the mean values with and without LOCF were modest and did not change the interpretation of these results.

Table 96. 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
Only lomitapide monotherapy groups are shown.

Table 97. 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
FEV_1 (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)
FEF_{25-75} (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
Only lomitapide monotherapy groups are shown.

Table 98. 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).

8.2 Safety Assessment Schedules by Trial

Table 99. 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[6], 36, 41[6], 46, 51[6], 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 12 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	ECGs	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 (D 1 – 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	ECGs	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

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 imagining/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.

8.3 AEs Leading to Discontinuation in Phase 1/2 Pool

Table 100. AEs Leading to Discontinuation (Elevated LDL-C Phase 1/2 Study Pool)

	Lomitapide Dose Group[1]				Comparator	
Preferred Term	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
Gastrooesophageal 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.

8.4 HoFH Phase 3 Supplemental Data

The following conventions apply for Figure 51 through Figure 56, 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 qualtitative 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).

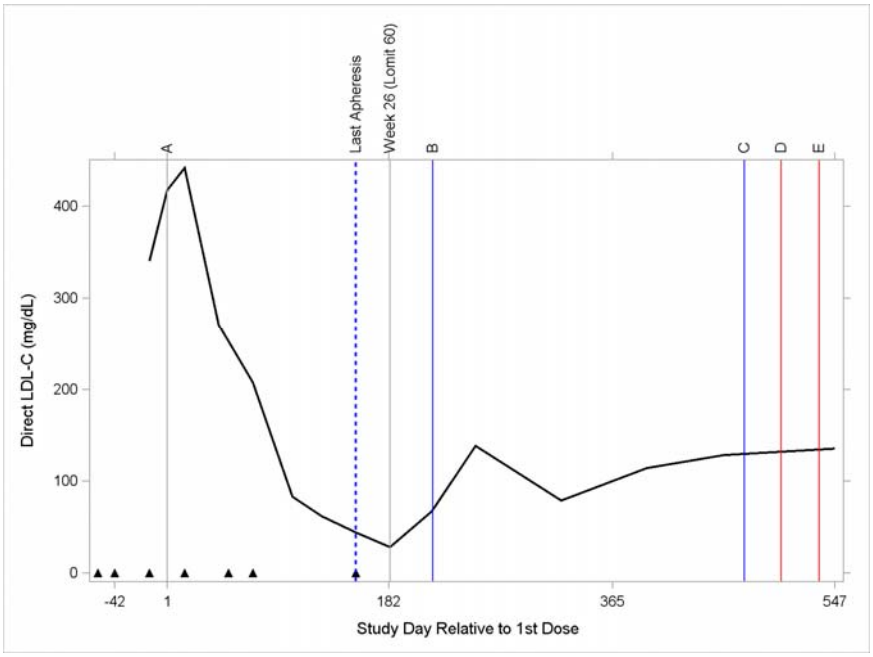


Figure 51. HoFH-pivotal – Subject 01-003 (Apheresis Discontinued)
Source: FDA clinical reviewer's analysis of HoFH-pivotal datasets (*LB*, *CM, EX.xpt*)
See text for explanation of figure notation.
(A) At baseline, rosuvastatin 40 mg, ezetimibe 10 mg, and colsevelam 3750 mg daily.
(B) Colsevalam d/c'd.
(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.

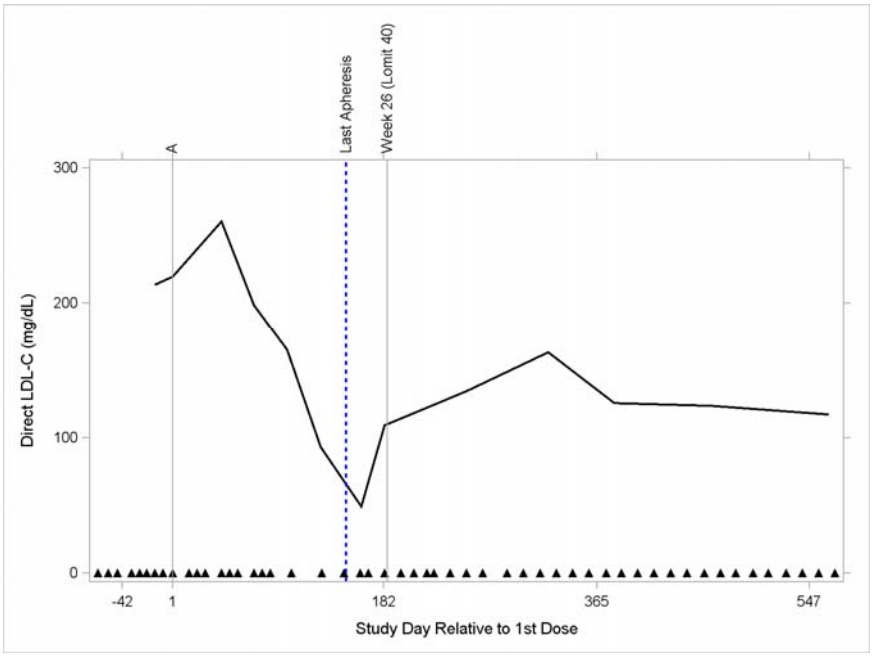


Figure 52. HoFH-pivotal – Subject 31-001 (Apheresis Discontinued)
Source: FDA clinical reviewer's analysis of HoFH-pivotal datasets (*LB*, *CM, EX.xpt*)
See text for explanation of figure notation.
(A) On simvastatin 20 mg and ezetimibe 10 mg daily throughout.

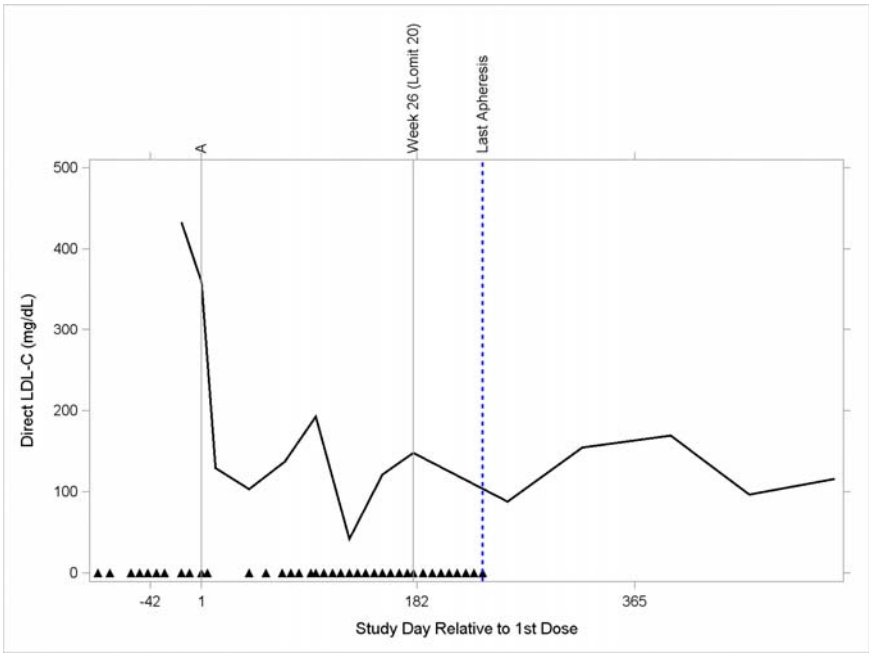


Figure 53. HoFH-pivotal – Subject 31-002 (Apheresis Discontinued)
Source: FDA clinical reviewer's analysis of HoFH-pivotal datasets (*LB*, *CM, EX.xpt*)
See text for explanation of figure notation.
(A) On simvastatin 40 mg and ezetimibe 10 mg daily throughout.

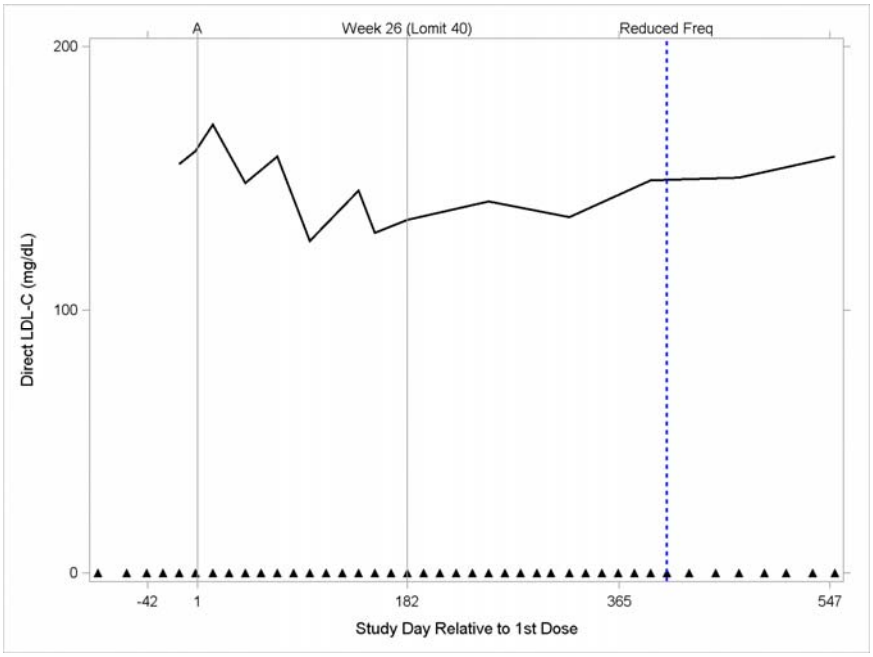


Figure 54. HoFH-pivotal – Subject 02-001 (Apheresis Frequency Reduced)
Source: FDA clinical reviewer's analysis of HoFH-pivotal datasets (*LB*, *CM, EX.xpt*)
See text for explanation of figure notation.
(A) On atorvastatin 80 mg and ezetimibe 10 mg daily throughout.

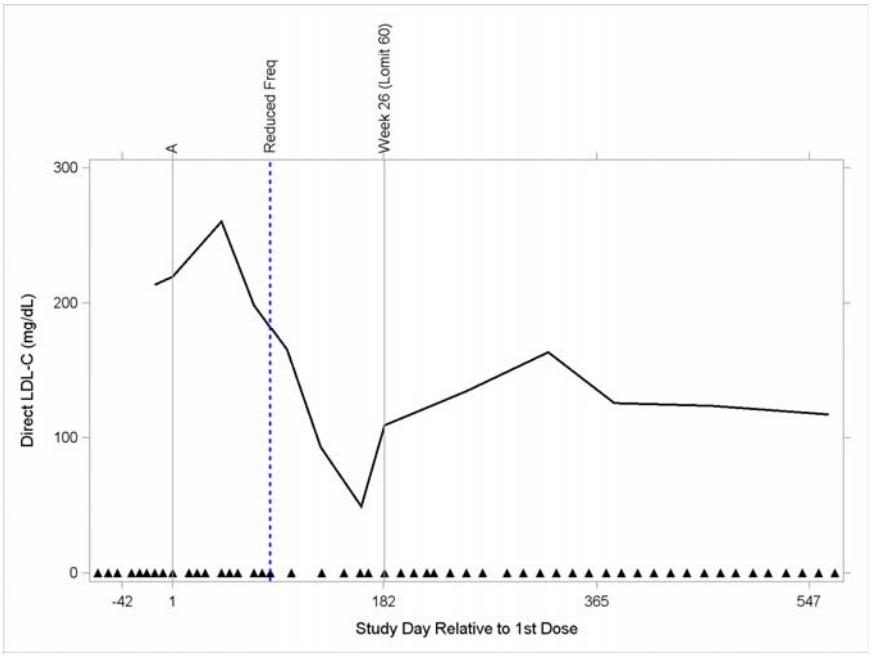


Figure 55. HoFH-pivotal – Subject 35-001 (Apheresis Frequency Reduced)
Source: FDA clinical reviewer's analysis of HoFH-pivotal datasets (*LB*, *CM, EX.xpt*)
See text for explanation of figure notation.
(A) On simvastatin 20 mg and ezetimibe 10 mg daily throughout.

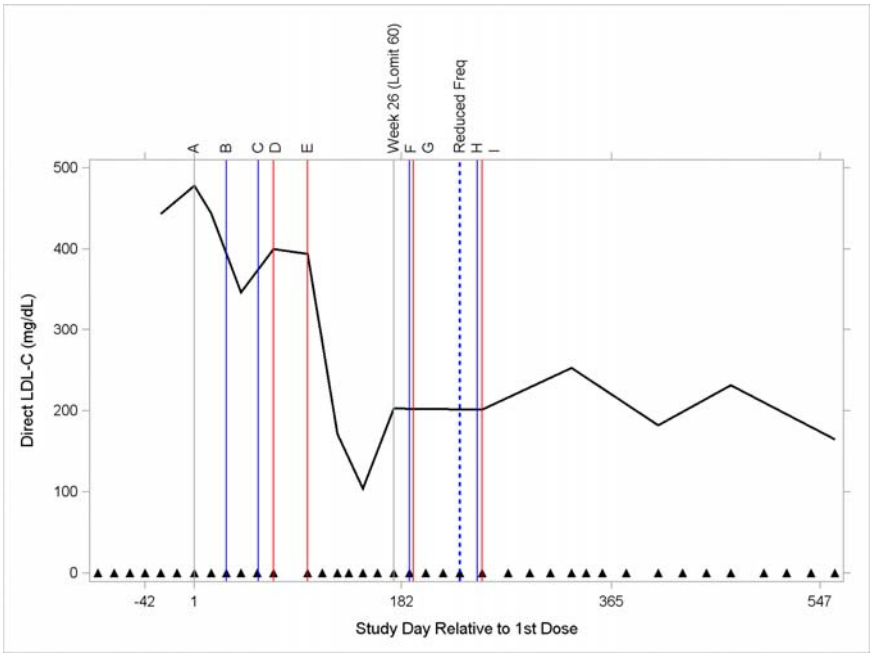


Figure 56. HoFH-pivotal – Subject 23-001 (Apheresis Frequency Reduced)
Source: FDA clinical reviewer's analysis of HoFH-pivotal datasets (*LB*, *CM, EX.xpt*)
See text for explanation of figure notation.
(A) Rosuvastatin 40 mg and ezetimibe 10 mg daily at baseline.
(B) Ezetimibe d/c'd (reason not specified).
(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 101. 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)	
Number of Patients with at Least 1 TEAE	*18 (62.1)*	*20 (74.1)*	*19 (73.1)*	*18 (85.7)*	*12 (92.3)*	*1 (50.0)*	*27 (93.1)*
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)
Gastrooesophageal 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)

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.

Table 102. 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 103. 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 104. 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 105. 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)**	
	44	↓ 10			Dose reduction for ALT
	50		**297 (7.4x)**	185 (4.3x)	
	53	↓ 5			Further dose reduction for

Visit	Day	Dose	ALT	AST	Notes
					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 ≥5x <10x ULN.

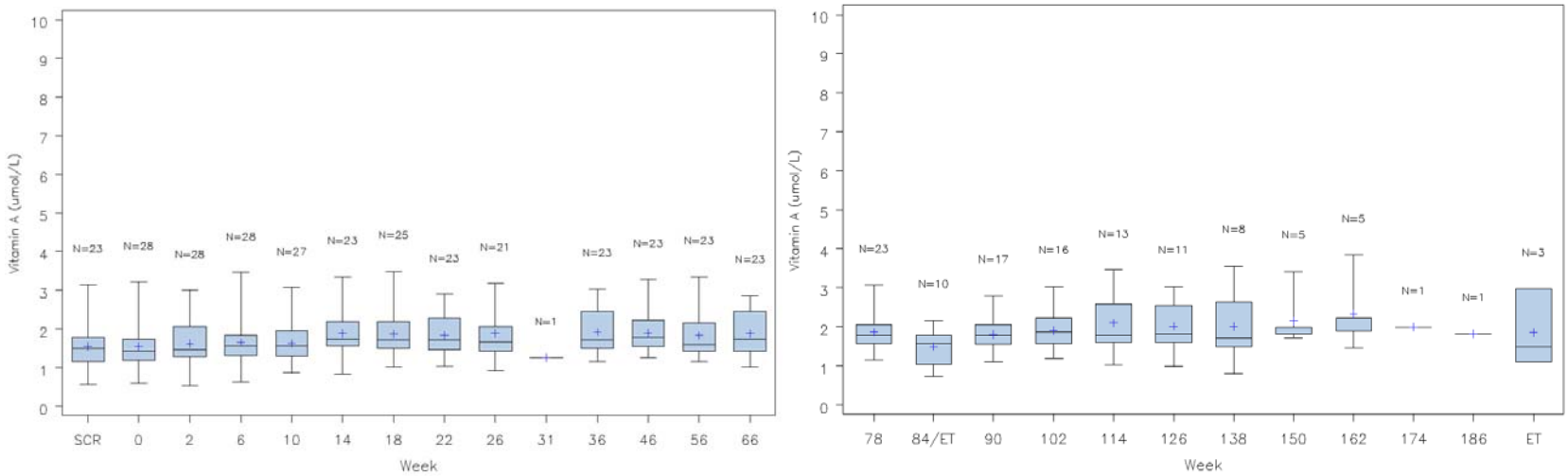


Figure 57. HoFH-pivotal & extension – Vitamin A
Source: 120-day safety update, Figure 1.3.11. "84/ET" = Off-treatment HoFH-pivotal visit or early termination (ET).

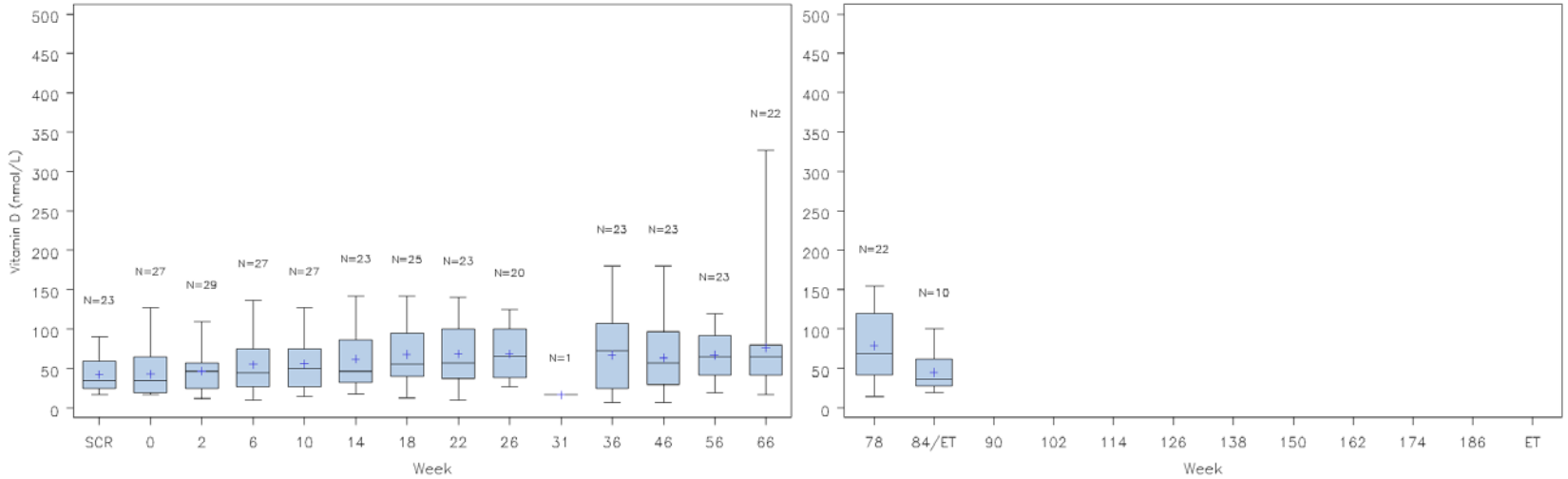


Figure 58. HoFH-pivotal – Vitamin D
Source: 120-day safety update, Figure 1.3.11. "84/ET" = Off-treatment HoFH-pivotal visit or early termination (ET).

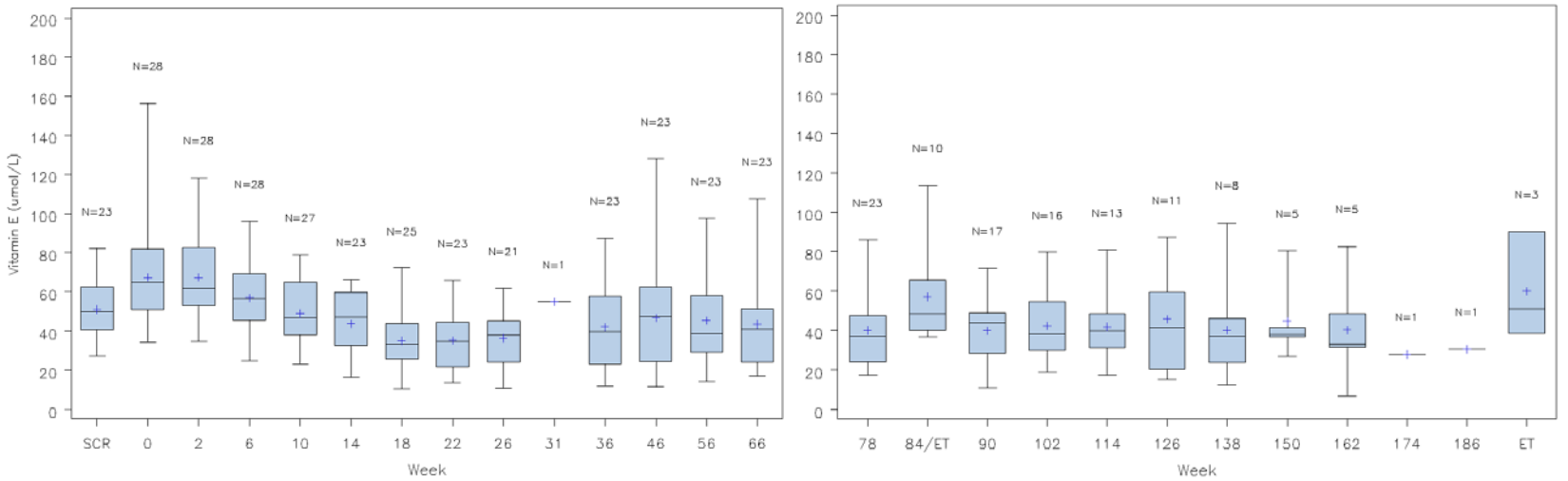


Figure 59. HoFH-pivotal & extension – Vitamin E
Source: 120-day safety update, Figure 1.3.11. "84/ET" = Off-treatment HoFH-pivotal visit or early termination (ET).

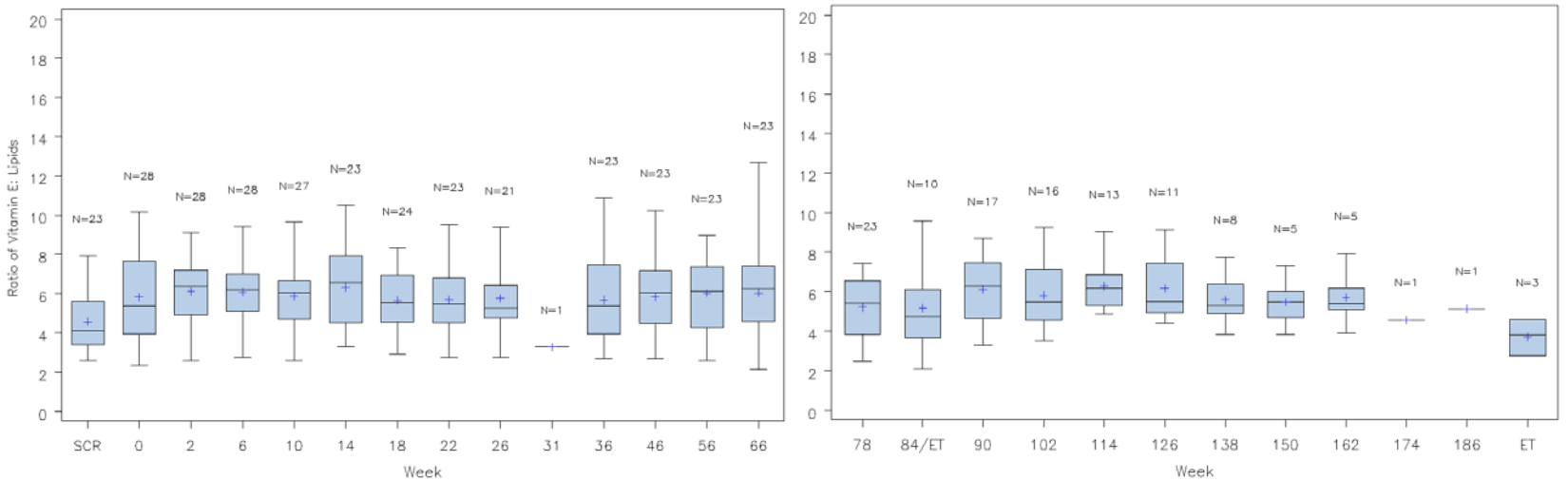


Figure 60. HoFH-pivotal & extension – Vitamin E/Lipid (TC+TG) Ratio
Source: 120-day safety update, Figure 1.3.11. "84/ET" = Off-treatment HoFH-pivotal visit or early termination (ET).

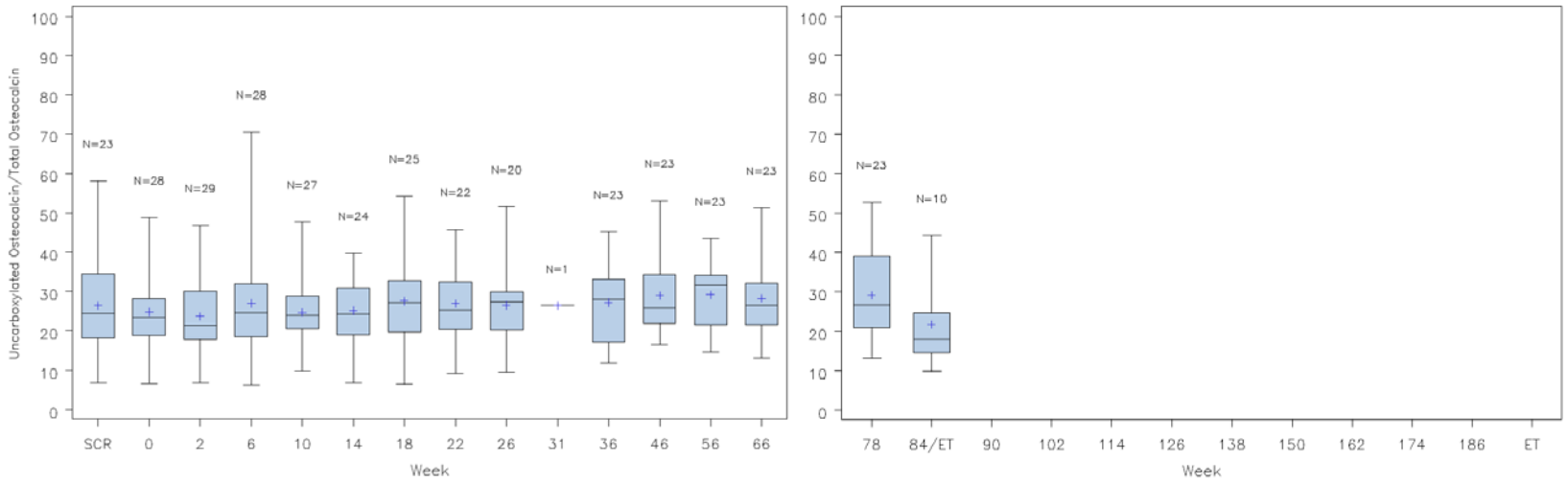


Figure 61. HoFH-pivotal – % Osteocalcin Uncarboxylated
Source: 120-day safety update, Figure 1.3.11. "84/ET" = Off-treatment HoFH-pivotal visit or early termination (ET).
Higher proportions of uncarboxylated osteocalcin suggest functional vitamin K deficiency.

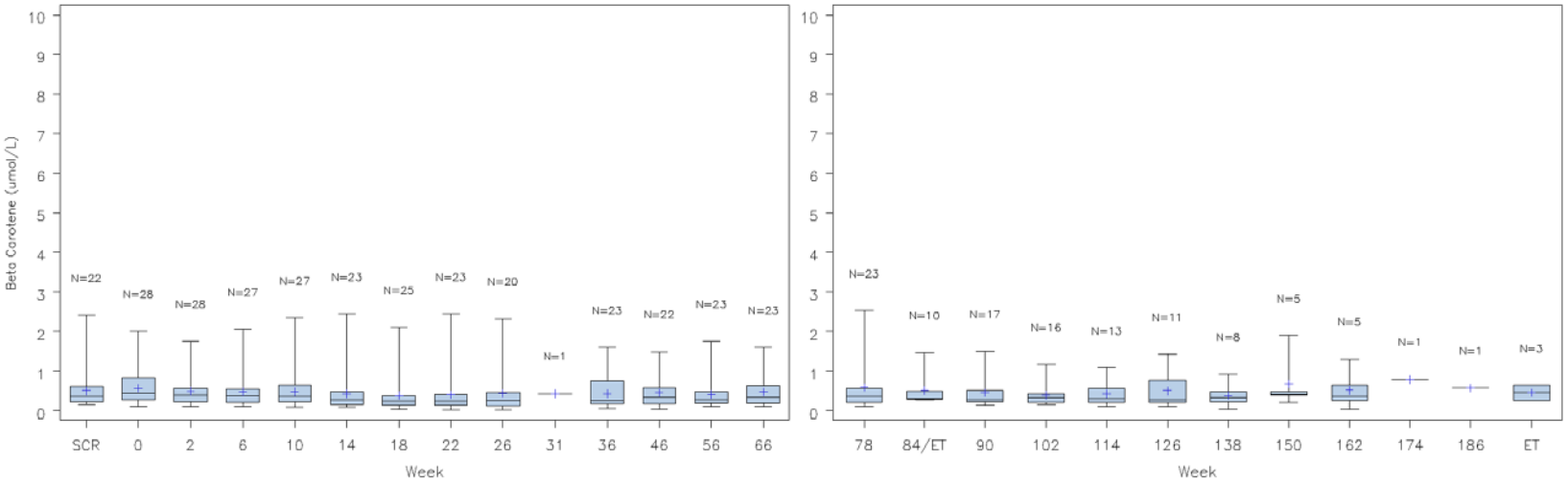


Figure 62. HoFH-pivotal – Beta-carotene
Source: 120-day safety update, Figure 1.3.11. "84/ET" = Off-treatment HoFH-pivotal visit or early termination (ET).

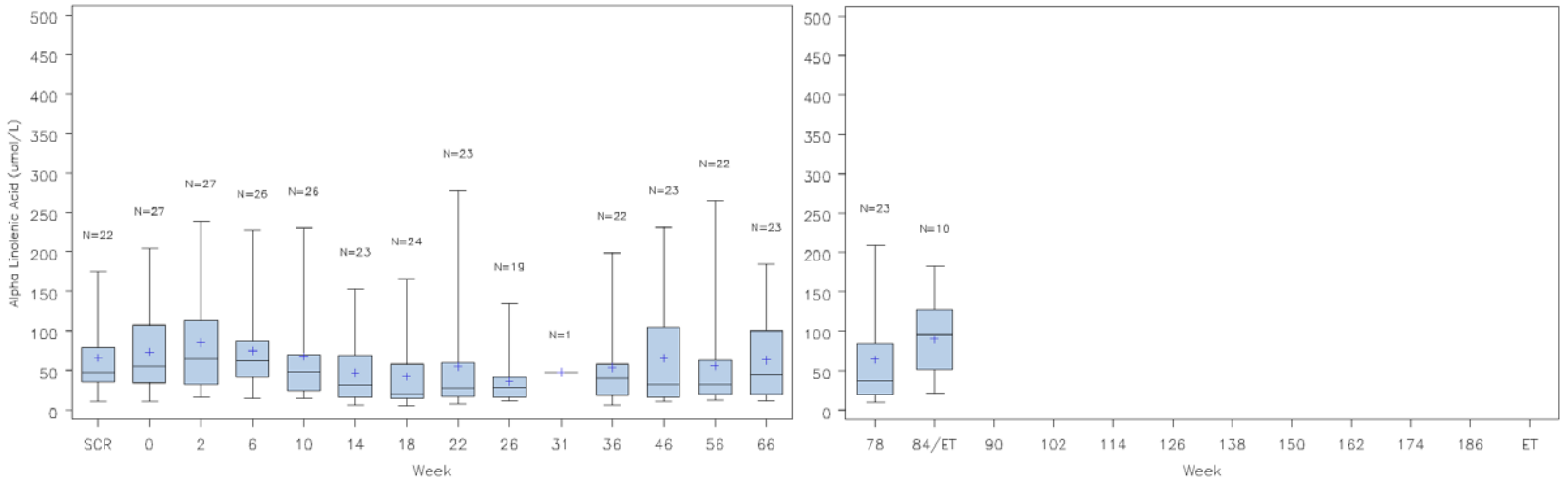


Figure 63. HoFH-pivotal – Alpha-Linolenic Acid
Source: 120-day safety update, Figure 1.3.11. "84/ET" = Off-treatment HoFH-pivotal visit or early termination (ET).

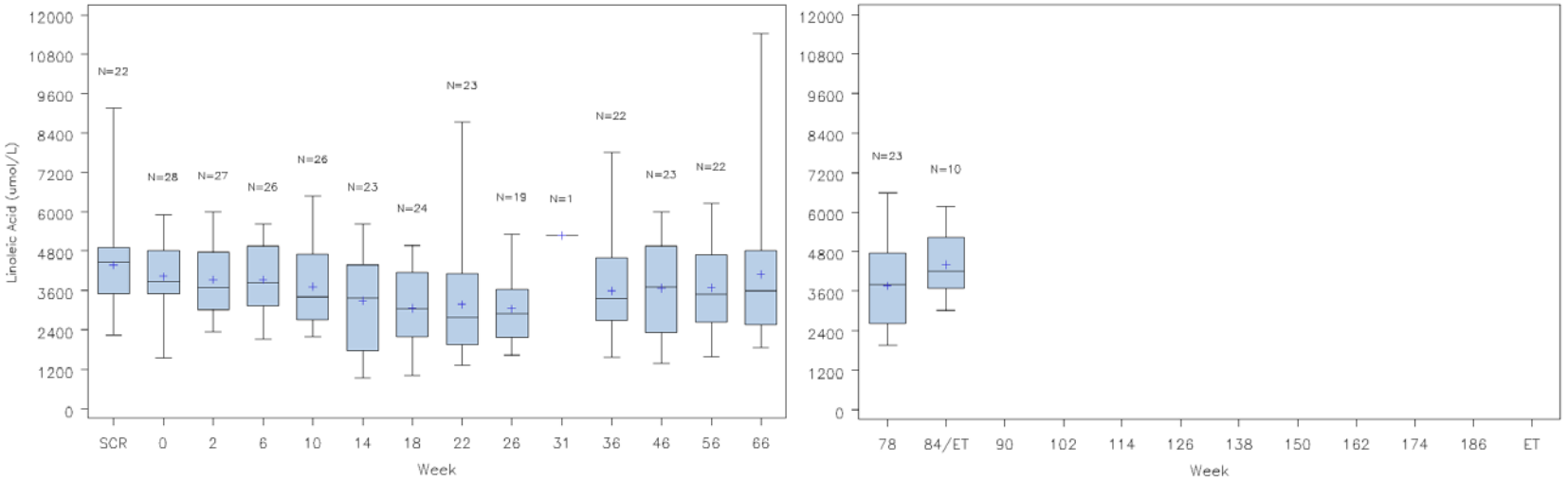


Figure 64. HoFH-pivotal – Linoleic Acid
Source: 120-day safety update, Figure 1.3.11. "84/ET" = Off-treatment HoFH-pivotal visit or early termination (ET).

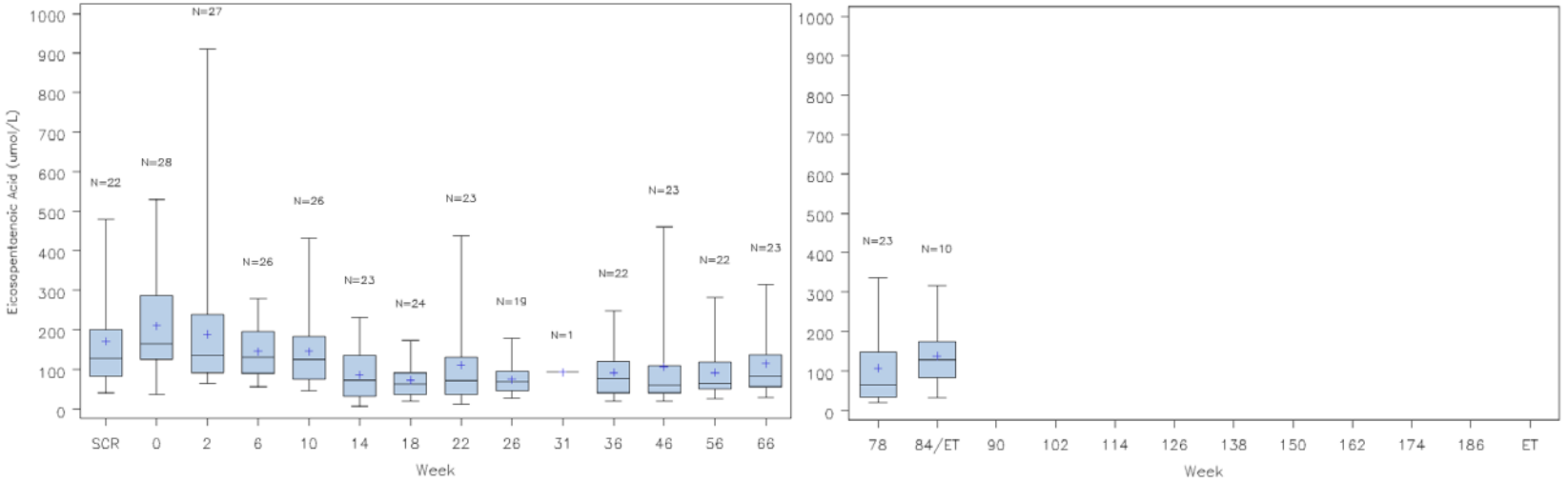


Figure 65. HoFH-pivotal – Eicosapentaenoic Acid (EPA)
Source: 120-day safety update, Figure 1.3.11. "84/ET" = Off-treatment HoFH-pivotal visit or early termination (ET).

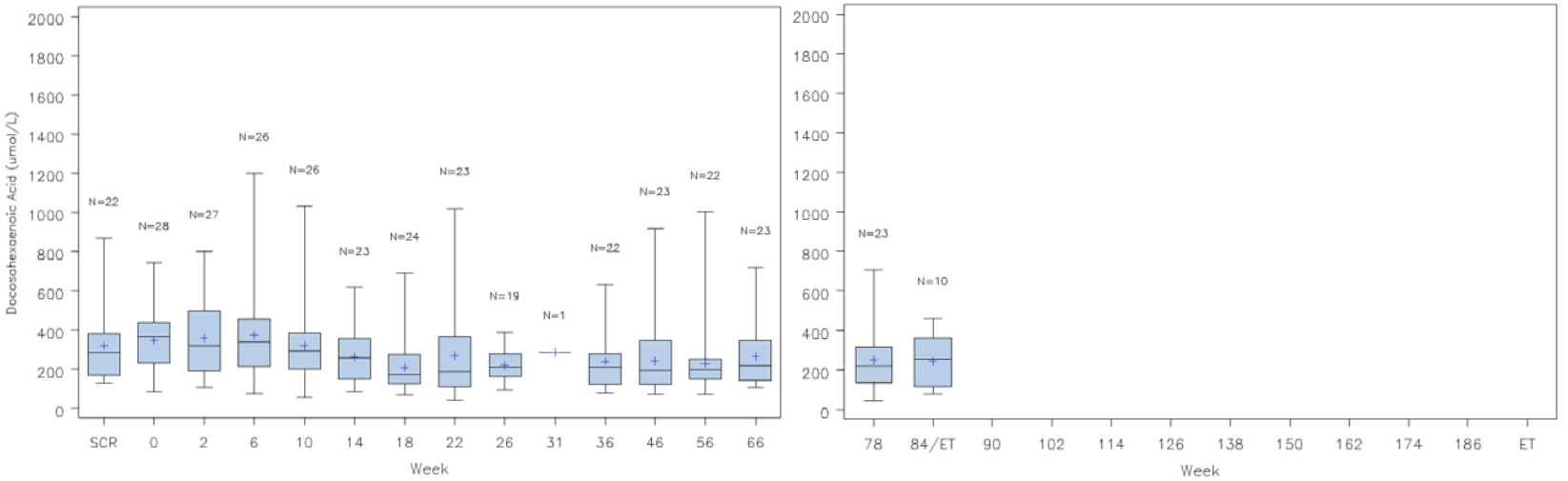


Figure 66. HoFH-pivotal – Docosahexaenoic Acid (DHA)
Source: 120-day safety update, Figure 1.3.11. "84/ET" = Off-treatment HoFH-pivotal visit or early termination (ET).

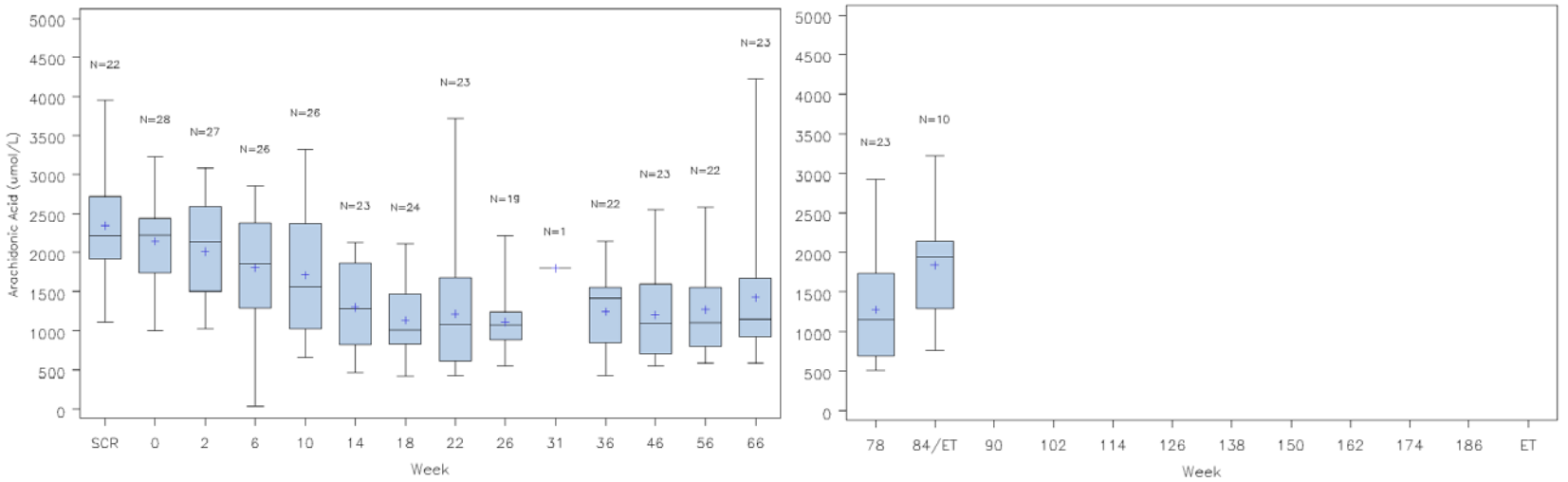


Figure 67. HoFH-pivotal – Arachidonic Acid
Source: 120-day safety update, Figure 1.3.11. "84/ET" = Off-treatment HoFH-pivotal visit or early termination (ET).

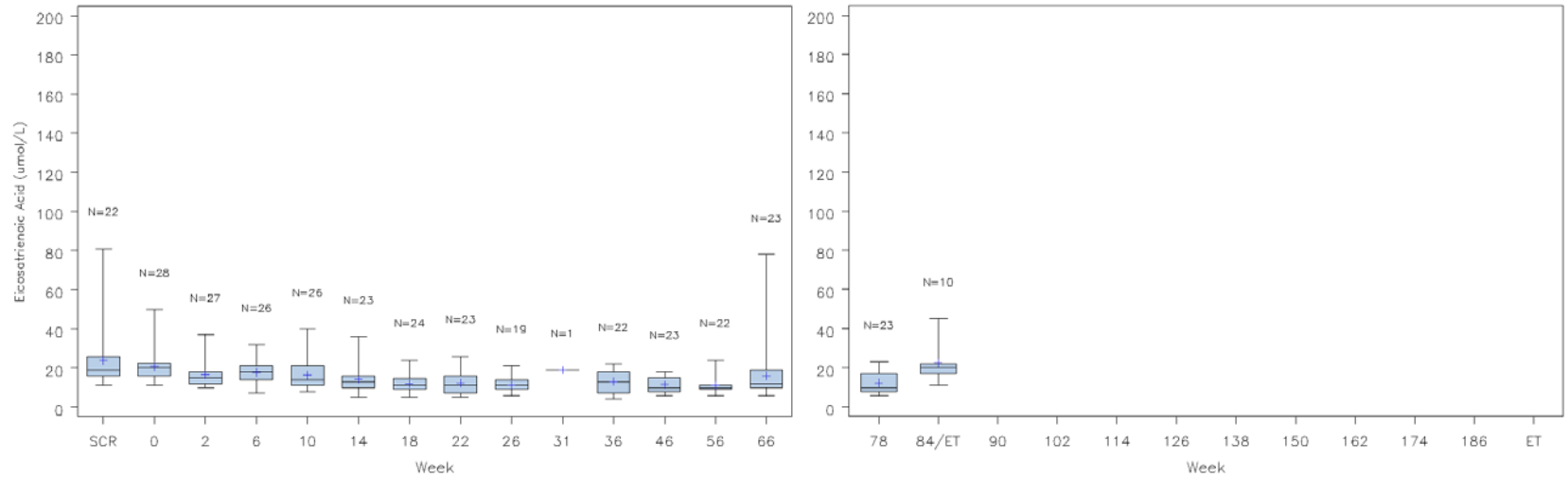


Figure 68. HoFH-pivotal – Eicosatrienoic (Mead) Acid
Source: 120-day safety update, Figure 1.3.11. "84/ET" = Off-treatment HoFH-pivotal visit or early termination (ET).
Increased values of Mead acid can accompany essential fatty acid deficiency.

8.5 References

1. Marais AD, Firth JC, Blom DJ. Homozygous familial hypercholesterolemia and its management. Semin Vasc Med 2004;4(1):43-50.

2. Beigel R, Beigel Y. Homozygous familial hypercholesterolemia: long term clinical course and plasma exchange therapy for two individual patients and review of the literature. J Clin Apher 2009;24(6):219-224.

3. Goldstein JL, Brown MS. Molecular medicine. The cholesterol quartet. Science 2001;292(5520):1310-1312.

4. Raal FJ, Pilcher GJ, Panz VR et al. Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy. Circulation 2011;124(20):2202-2207.

5. Lopez-Santamaria M, Migliazza L, Gamez M et al. Liver transplantation in patients with homozygotic familial hypercholesterolemia previously treated by end-to-side portocaval shunt and ileal bypass. J Pediatr Surg 2000;35(4):630-633.

6. Thompsen J, Thompson PD. A systematic review of LDL apheresis in the treatment of cardiovascular disease. Atherosclerosis 2006;189(1):31-38.

7. Thompson GR, Barbir M, Davies D et al. Efficacy criteria and cholesterol targets for LDL apheresis. Atherosclerosis 2010;208(2):317-321.

8. Thompson GR. Recommendations for the use of LDL apheresis. Atherosclerosis 2008;198(2):247-255.

9. Zamel R, Khan R, Pollex RL, Hegele RA. Abetalipoproteinemia: two case reports and literature review. Orphanet J Rare Dis 2008;3:19.

10. Shoulders CC, Brett DJ, Bayliss JD et al. Abetalipoproteinemia is caused by defects of the gene encoding the 97 kDa subunit of a microsomal triglyceride transfer protein. Hum Mol Genet 1993;2(12):2109-2116.

11. Wetterau JR, Gregg RE, Harrity TW et al. An MTP inhibitor that normalizes atherogenic lipoprotein levels in WHHL rabbits. Science 1998;282(5389):751-754.

12. Levy E, Stan S, Garofalo C, Delvin EE, Seidman EG, Menard D. Immunolocalization, ontogeny, and regulation of microsomal triglyceride transfer protein in human fetal intestine. Am J Physiol Gastrointest Liver Physiol 2001;280(4):G563-G571.

13. Swift LL, Zhu MY, Kakkad B et al. Subcellular localization of microsomal triglyceride transfer protein. J Lipid Res 2003;44(10):1841-1849.

14. Krzystanek M, Pedersen TX, Bartels ED, Kjaehr J, Straarup EM, Nielsen LB. Expression of apolipoprotein B in the kidney attenuates renal lipid accumulation. J Biol Chem 2010;285(14):10583-10590.

15. Nielsen LB, Veniant M, Boren J et al. Genes for apolipoprotein B and microsomal triglyceride transfer protein are expressed in the heart: evidence that the heart has the capacity to synthesize and secrete lipoproteins. Circulation 1998;98(1):13-16.

16. Nielsen LB, Perko M, Arendrup H, Andersen CB. Microsomal triglyceride transfer protein gene expression and triglyceride accumulation in hypoxic human hearts. Arterioscler Thromb Vasc Biol 2002;22(9):1489-1494.

17. Li CM, Presley JB, Zhang X et al. Retina expresses microsomal triglyceride transfer protein: implications for age-related maculopathy. J Lipid Res 2005;46(4):628-640.

18. Braegger CP, Belli DC, Mentha G, Steinmann B. Persistence of the intestinal defect in abetalipoproteinaemia after liver transplantation. Eur J Pediatr 1998;157(7):576-578.

19. SALT HB, WOLFF OH, LLOYD JK, FOSBROOKE AS, CAMERON AH, HUBBLE DV. On having no beta-lipoprotein. A syndrome comprising a-beta-lipoproteinaemia, acanthocytosis, and steatorrhoea. Lancet 1960;2(7146):325-329.

20. Talmud PJ, LLOYD JK, Muller DP, Collins DR, Scott J, Humphries S. Genetic evidence from two families that the apolipoprotein B gene is not involved in abetalipoproteinemia. J Clin Invest 1988;82(5):1803-1806.

21. Schonfeld G. Familial hypobetalipoproteinemia: a review. J Lipid Res 2003;44(5):878-883.

22. Chalasani N, Younossi Z, Lavine JE et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 2012;142(7):1592-1609.

23. Szczepaniak LS, Nurenberg P, Leonard D et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. Am J Physiol Endocrinol Metab 2005;288(2):E462-E468.

24. Larter CZ, Farrell GC. Insulin resistance, adiponectin, cytokines in NASH: Which is the best target to treat? J Hepatol 2006;44(2):253-261.

25. Pagano G, Pacini G, Musso G et al. Nonalcoholic steatohepatitis, insulin resistance, and metabolic syndrome: further evidence for an etiologic association. Hepatology 2002;35(2):367-372.

26. Westerbacka J, Kolak M, Kiviluoto T et al. Genes involved in fatty acid partitioning and binding, lipolysis, monocyte/macrophage recruitment, and inflammation are overexpressed in the human fatty liver of insulin-resistant subjects. Diabetes 2007;56(11):2759-2765.

27. Stefan N, Kantartzis K, Haring HU. Causes and metabolic consequences of Fatty liver. Endocr Rev 2008;29(7):939-960.

28. Targher G, Bertolini L, Rodella S et al. Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. Diabetes Care 2007;30(8):2119-2121.

29. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease. N Engl J Med 2010;363(14):1341-1350.

30. Wong VW, Wong GL, Yip GW et al. Coronary artery disease and cardiovascular outcomes in patients with non-alcoholic fatty liver disease. Gut 2011;60(12):1721-1727.

31. Sabio G, Das M, Mora A et al. A stress signaling pathway in adipose tissue regulates hepatic insulin resistance. Science 2008;322(5907):1539-1543.

32. Matikainen N, Manttari S, Westerbacka J et al. Postprandial lipemia associates with liver fat content. J Clin Endocrinol Metab 2007;92(8):3052-3059.

33. Baigent C, Blackwell L, Emberson J et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376(9753):1670-1681.

34. Cannon CP, Braunwald E, McCabe CH et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350(15):1495-1504.

35. LaRosa JC, Grundy SM, Waters DD et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352(14):1425-1435.

36. Pedersen TR, Faergeman O, Kastelein JJ et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005;294(19):2437-2445.

37. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol 2006;48(3):438-445.

38. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285(19):2486-2497.

39. Grundy SM, Cleeman JI, Merz CN et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110(2):227-239.

40. Barter PJ, Caulfield M, Eriksson M et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007;357(21):2109-2122.

41. Cannon CP, Giugliano RP, Blazing MA et al. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. Am Heart J 2008;156(5):826-832.

42. Szczepaniak LS, Nurenberg P, Leonard D et al. Magnetic resonance spectroscopy to measure hepatic triglyceride content: prevalence of hepatic steatosis in the general population. Am J Physiol Endocrinol Metab 2005;288(2):E462-E468.

43. Cuchel M, Bloedon LT, Szapary PO et al. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. N Engl J Med 2007;356(2):148-156.

44. Guha IN, Parkes J, Roderick P et al. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers. Hepatology 2008;47(2):455-460.

45. Parkes J, Roderick P, Harris S et al. Enhanced liver fibrosis test can predict clinical outcomes in patients with chronic liver disease. Gut 2010;59(9):1245-1251.

46. Thurnham DI, Davies JA, Crump BJ, Situnayake RD, Davis M. The use of different lipids to express serum tocopherol: lipid ratios for the measurement of vitamin E status. Ann Clin Biochem 1986;23 (Pt 5):514-520.

47. Jeppesen PB, Hoy CE, Mortensen PB. Deficiencies of essential fatty acids, vitamin A and E and changes in plasma lipoproteins in patients with reduced fat absorption or intestinal failure. Eur J Clin Nutr 2000;54(8):632-642.

48. Holman RT, Smythe L, Johnson S. Effect of sex and age on fatty acid composition of human serum lipids. Am J Clin Nutr 1979;32(12):2390-2399.

49. Newmark HL, Wargovich MJ, Bruce WR. Colon cancer and dietary fat, phosphate, and calcium: a hypothesis. J Natl Cancer Inst 1984;72(6):1323-1325.

50. Pickering JS, Lupton JR, Chapkin RS. Dietary fat, fiber, and carcinogen alter fecal diacylglycerol composition and mass. Cancer Res 1995;55(11):2293-2298.

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

STATISTICAL BRIEFING

CLINICAL STUDIES

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

TABLE OF CONTENTS

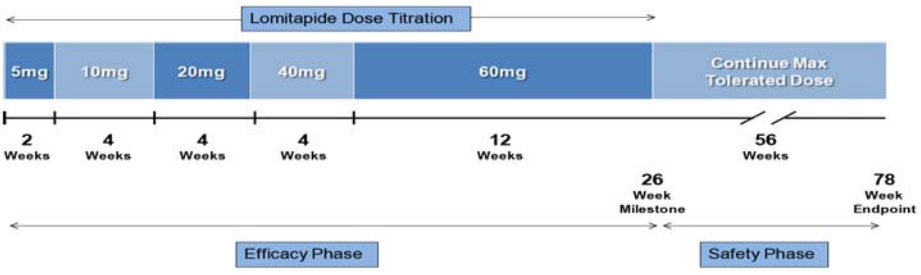
1. INTRODUCTION

Aegerion Pharmaceuticals, Inc. has submitted an original NDA seeking approval of lomitapide mesylate capsules for the treatment of homozygous familial hypercholesterolemia (HoFH) when used as an adjunct to a low-fat diet and other lipid-lowering therapies with or without LDL apheresis. Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor. It has received an orphan drug designation for this indication on 10/23/2007. In this NDA, results from 24 clinical trials ranging from Phase 1 to Phase 3 were submitted by the sponsor. The efficacy of lomitapide in patients with HoFH will be determined primarily based on the results from a pivotal Phase 3 trial UP1002/AEGR-733-005 (29 patients) and a supportive Proof-of-Concept Phase 2 trial UP1001 (6 patients), since the other studies were conducted in different populations. Therefore, this briefing document focuses on the efficacy evaluation of these two studies. See Dr. James Smith's report for safety evaluation.

2. STUDY DESIGN AND ENDPOINTS

2.1 Phase 3 Study UP1002/AEGR-733-005

The pivotal Phase 3 study was a 78-week, open-label, single-arm, dose-escalation (5, 10, 20, 40, 60 mg/day), multicenter, multinational trial, conducted at 11 sites located in US (2 sites), Canada (2 sites), South Africa (3 sites), and Italy (4 sites). After completing 26 weeks of treatment (Efficacy Phase, see the study design schema below), patients entered the Safety Phase at their established dose defined at Week 26 for an additional 52 weeks. The primary objective of this study was to evaluate the efficacy of lomitapide as defined by percent change from baseline in LDL-C at an individually-identified maximum tolerated dose after 26 weeks of treatment in patients with HoFH. Based on the assumptions of 25% change in LDL-C after 26 weeks of treatment with a 30% SD and 15% dropout rate, 29 subjects were enrolled to obtain at least 90% power for the study. The clinical study report covers only the data and results through Week 56 based on the data cut-off date of 04/12/2011.



2.2 Phase 2 Study UP1001

The supportive Phase 2 study was a 16-week, open-label, single-arm, dose-escalation (0.03, 0.1, 0.3, 1.0 mg/kg/day), single-center (in US) trial. The primary objective of this study was to evaluate the safety and tolerability of 4 doses of lomitapide. Evaluation of the efficacy

(lipid panel) was secondary. In contrast to Study UP1002/AEGR-733-005, subjects in this trial were required to stop all lipid-lowering therapies including apheresis within 4 weeks prior to the Baseline visit and throughout the trial.

3. STATISTICAL EVALUATION

3.1 Statistical Methods

For Study UP1002/AEGR-733-005, the primary efficacy endpoint was percent change from baseline in LDL-C at Week 26 and was analyzed using paired t-test by the sponsor. This reviewer also analyzed the data using Wilcoxon signed-rank test which can accommodate small sample sizes and non-normality. The proportions of LDL-C responders defined as greater than 15%, 25%, and 50% decreases from baseline to Week 26/LOCF were summarized. There were 3 key secondary efficacy variables: total cholesterol (TC), Apo B, and triglycerides (TRIG). They were prioritized sequentially by the sponsor and analyzed using the same test to preserve the Type 1 error rate at $\alpha = 0.05$. Other lipid variables such as non-HDL-C, VLDL-C, Lp(a), and HDL-C were also analyzed in a similar fashion, but without multiplicity adjustment. The baseline value was calculated as the average of Week -2 and Week 0 values. The ITT population consisting of subjects who had received at least one dose of lomitapide, and had a baseline and a post-baseline LDL-value was the primary population for efficacy analyses. Missing data at Week 26 were imputed using the LOCF method.

For Study UP1001, there was no formal statistical analysis plan developed. Although safety and tolerability were the primary interest of this study, percent change from baseline in LDL-C at Week 16 was the primary efficacy endpoint. For the ease of discussion, efficacy evaluation for this supportive study was performed similarly to the pivotal study.

3.2 Subject Disposition

For Study UP1002/AEGR-733-005, a total of 29 subjects were enrolled and treated with lomitapide. As of 04/12/2011 the data cut-off date, 6 patients discontinued from the trial prior to Week 26; 23 of the 29 enrolled patients completed Week 56; and 18 of the 23 patients completed the entire 78-week trial. Among the 6 dropouts (21%), 3 (10%) discontinued due to withdrawn consent, 2 (7%) due to adverse event, and 1 (3%) due to non-compliance or lack of cooperation. Their final titrated doses were 5 mg (n = 2), 10 mg (n = 2), 20 mg (n = 1), and 40 mg (n = 1). For Study UP1001, all the 6 enrolled subjects completed the trial.

3.3 Demographic and Baseline Characteristics

There were no geriatric ($\geq$ 65 years) patients enrolled in these 2 studies. Most patients were White. Males and females were approximately equally distributed. Half of the population in

each study had BMI < 25 kg/m^2. As shown in Table 1, the mean baseline LDL-C in Study UP1001 (614.2 mg/dL) was much higher than that in Study UP1002/AEGR-733-005 (337.0 mg/dL), as were the mean baseline values of TC, ApoB, and triglycerides. As explained by the sponsor, the high elevation in baseline lipids in Study UP1001 was due to the requirement of no lipid-lowering therapies within 4 weeks of the study entry; while in Study UP1002/AEGR-733-005, subjects were required to be on a stable regimen of their standard of care therapies during the run-in period. The majority of subjects in Study UP1002/AEGR-755-005 received their maximum tolerated doses of statins with or without ezetimibe at baseline.

Table 1 – Demographic and Baseline Characteristics – ITT Population

Characteristic		UP1002/AEGR-733-005 (N = 29)	UP1001 (N = 6)
Age (years):	Mean ± SD	30.7 ± 10.6	25.0 ± 9.2
	Median	30	21.0
	Range	18.0 – 55.0	17.0 – 39.0
Sex:	Male (%)	16 (55.2)	3 (50.0)
	Female (%)	13 (44.8)	3 (50.0)
Race:	White (%)	25 (86.2)	3 (50.0)
	Asian (%)	2 (6.9)	1 (16.7)
	Black or African American (%)	1 (3.4)	0
	Other (%)	1 (3.4)	2 (33.3)
Country:	USA (%)	7 (24.1)	6 (100.0)
	Canada (%)	5 (17.2)	0
	Italy (%)	6 (20.7)	0
	South Africa (%)	11 (37.9)	0
BMI (kg/m^2):	Mean ± SD	25.9 ± 5.5	24.9 ± 4.0
	Median	23.9	24.8
	Range	19.3 – 41.3	18.5 – 30.2
LDL-C (mg/dL):	Mean ± SD	337.0 ± 113.8	614.2 ± 105.8
	Median	357.1	622.5
	Range	152.4 – 565.0	480 – 789
TC (mg/dL):	Mean ± SD	430.4 ± 135.3	850.5 ± 194.8
	Median	459.5	796.5
	Range	191.4 – 721.6	684.0 – 1212.0
ApoB (mg/dL):	Mean ± SD	260.1 ± 80.1	310.0 ± 51.6
	Median	262.0	309.0
	Range	124.0 – 431.5	240.0 – 387.0
TRIG (mg/dL):	Mean ± SD	102.7 ± 47.8	282.8 ± 187.7
	Median	92.1	259.0

	Range	31.9 – 253.0	82.0 – 605.0
Use of Apheresis:	Yes (%)	18 (62.1)	NA
	No (%)	11 (37.9)	NA
Use of Statins:	Yes (%)	27 (93.1)	NA
	No (%)	2 (6.9)	NA
Use of Ezetimibe:	Yes (%)	22 (75.9)	NA
	No (%)	7 (24.1)	NA

3.4 Efficacy Results and Discussion

The sponsor provided datasets with SDTM format for individual studies and ADaM format for ISS and ISE. Since datasets with SDTM format contained multiple measurements from the same visit window for some patients, included data in the US unit for the US sites only, and did not have LOCF flag, this reviewer had to use the ISE dataset to extract study-specific data for the purpose of statistical analyses. However, there were some slight discrepancies between the results presented in the clinical study report (CSR) of the UP1002/AEGR-733-005 trial and the clinical overview (ISE). The sponsor stated that the differences were due to the baseline date used between the CSR and ISE analyses. In CSR, the lab assessment Visit 3 date was used as the baseline date to calculate subsequent visit windows; while in ISE, the first dose date was used as the baseline date. The differences in results for the primary efficacy endpoint between the CSR and ISE analyses appeared to be small.

3.4.1 Primary Efficacy Endpoint

In Study UP1002\AEGR-733-005, after treatment with lomitapide, mean LDL-C in patients with HoFH was significantly reduced from 337.0 mg/dL at baseline to 191.3 mg/dL at Week 26 (Table 2). The mean % change from baseline in LDL-C at Week 26 in this pivotal trial was -40% based on the ITT/LOCF population ($p < 0.0001$) and the median % change was -50%. In Study UP1001, mean LDL-C was also significantly reduced from 614.2 mg/dL at baseline to 303.0 mg/dL at Week 16. The mean and median % changes from baseline in LDL-C at Week 16 in this supportive trial were -51% and -52%, respectively ($p < 0.0001$).

Table 2 – Statistical Results for LDL-C (mg/dL)

ITT/LOCF population		UP1002/AEGR-733-005 (26-week)	UP1001 (16-week)
Baseline	Mean ± SD (N)	337.0 ± 113.8 (29)	614.2 ± 105.8 (6)
	Median	357.1	622.5
	Min, Max	152.4, 565.0	480.0, 789.0
Endpoint	Mean ± SD (N)	191.3 ± 106.6 (29)	303.0 ± 81.3 (6)
	Median	169.4	303.5
	Min, Max	28.0, 442.8	201.0, 403.0

% Change	Mean ± SD (N)	-39.6 ± 32.0 (29)	-50.9 ± 9.3 (6)
	95% CI	(-51.8, -27.4)	(-60.7, -41.2)
	Median	-49.6	-52.3
	Min, Max	-92.6, 20.5	-62.4, -33.8
	Paired t-test p-value	< 0.0001	< 0.0001
	Signed-rank test p-value	< 0.0001	0.0313
Results were generated using the study-specific data extracted from the ISE ADaM dataset.			

For the completer cohort in Study UP1002/AEGR-733-005 (N = 23), similar significant findings were also observed (mean % change at Week 26 = -50%, p < 0.0001). The following Figure 1 depicts that the mean % reductions from baseline in LDL-C were 9%, 15%, 27%, 44%, and 53% by Week 2, 6, 10, 14, and 18, respectively, where the corresponding mean doses were 5, 10, 18, 33, and 40 mg, implying that the reductions in LDL-C were increasing as the doses were increased during the titration period. Then the mean % reduction was reduced to 50% by Week 26 with a mean dose of 45 mg, and further reduced to around 40%-45% between Weeks 36 and 56 with mean doses around 40 mg. At Week 26, the mean % reductions in LDL-C associated with the 5, 10, 20, 40, and 60 mg doses were 51% (n = 1), NA (n = 0), 38% (n = 5), 57% (n = 6), and 55% (n = 10), respectively. One patient received 80 mg at Week 26 and experienced a 29% reduction in LDL-C. In Study UP1001, the mean % reductions from baseline in LDL-C were small and insignificant during the 1st half of the study, which was probably due to the small doses used (2 mg at Week 4 and 7 mg at Week 8). By Week 12, the mean dose was increased to 20 mg and the mean % reduction was 25%. At the end of the 16-week study, 51% mean reduction in LDL-C was observed and it was associated with a higher mean dose of 67 mg.

Figure 1

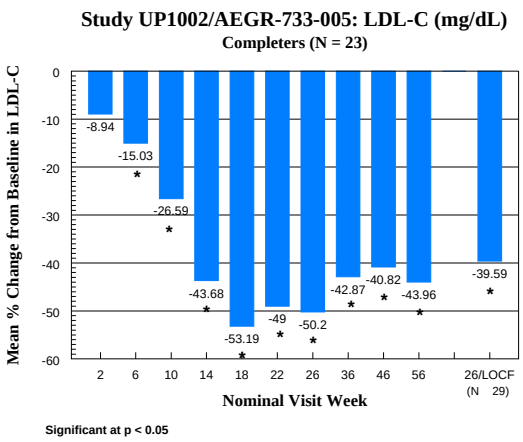
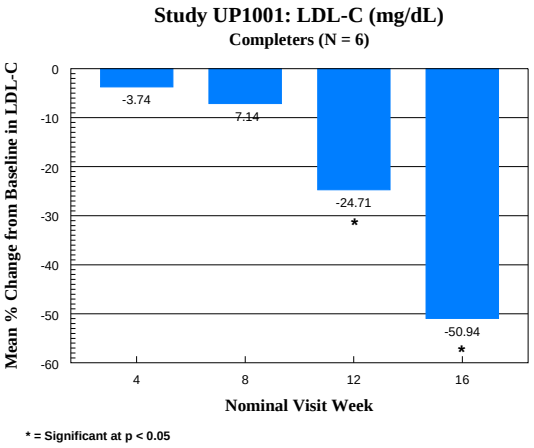


Figure 2



Slightly more than 2/3 of the 29 patients in the pivotal trial and all of the 6 enrolled patients in the supportive trial had greater than 15% of decrease in LDL-C from baseline at the end of the efficacy phase (Table 3). From Figures 3 and 4 below, one can easily obtain the % of subjects achieving a given level of response for any definition of responders. There were 4 patients (14%) in Study UP1002/AEGR-733-005 with an increased LDL-C from baseline after 26 weeks of treatment with lomitapide.

Table 3 – Responders for LDL-C (mg/dL)

	UP1002/AEGR-733-005		UP1001	
	Yes	No	Yes	No
> 15% reduction from baseline to Week 26/LOCF	20/29 (69%)	9/29 (31%)	6/6 (100%)	0
> 25% reduction from baseline to Week 26/LOCF	19/29 (66%)	10/29 (34%)	6/6 (100%)	0
> 50% reduction from baseline to Week 26/LOCF	14/29 (48%)	15/29 (52%)	5/6 (83%)	1/6 (17%)

Figure 3

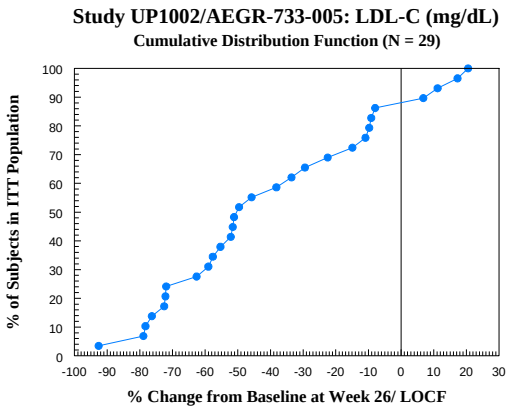
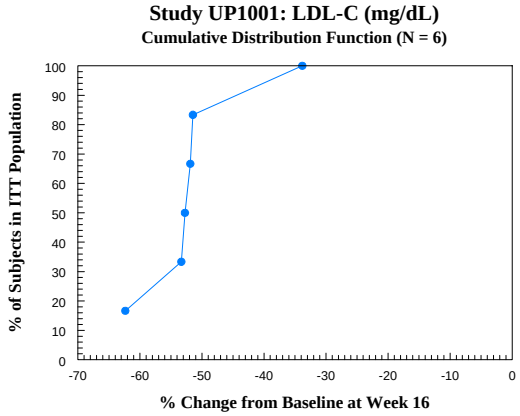


Figure 4



3.4.2 Key Secondary Efficacy Endpoints

As Table 4 shows, lomitapide significantly reduced total cholesterol (TC), ApoB, and triglycerides (TRIG) in patients with HoFH after 26 weeks of treatment in Study UP1002/AEGR-733-005 and after 16 weeks of treatment in Study UP1001 (all $p < 0.05$).

Table 4 – Statistical Results for % Change from Baseline for Key Secondary Efficacy Endpoints

Study	ITT/LOCF Population	TC (mg/dL)	ApoB (mg/dL)	TRIG (mg/dL)	Ln TRIG (mg/dL)
UP1002	Mean ± SD (N)	-35.7 ± 29.4 (29)	-39.3 ± 30.3 (29)	-28.2 ± 57.6 (29)	-0.60 ± 0.75 (29)
/AEGR-	95% CI	(-46.9, -24.5)	(-50.8, -27.8)	(-50.1, -6.3)	(-0.88, -0.31)
733-005	Median	-40.0	-46.2	-44.5	-0.59
	Min, Max	-81.4, 24.2	-90.4, 19.0	-87.4, 169.4	-2.07, 0.99

	Paired t-test p	< 0.0001	< 0.0001	0.0136	0.0002
	Signed-rank test p	< 0.0001	< 0.0001	0.0023	< 0.0001
UP1001	Mean ± SD (N)	-58.4 ± 8.6 (6)	-55.6 ± 13.5 (6)	-65.2 ± 13.3 (6)	-1.12 ± 0.39 (6)
	95% CI	(-67.4, -49.3)	(-69.7, -41.4)	(-79.1, -51.3)	(-1.53, -0.71)
	Median	-56.7	-57.0	-68.2	-1.15
	Min, Max	-68.7, -50.3	-70.0, -36.8	-82.1, -43.9	-1.72, -0.58
	Paired t-test p	< 0.0001	0.0002	< 0.0001	0.0009
	Signed-rank test p	0.0313	0.0313	0.0313	0.0313
Results were generated using the study-specific data extracted from the ISE ADaM dataset. Note: The raw TRIG data in Study UP1002/AEGR-733-005 were not normally distributed. Ln TRIG = Log-transformed triglycerides					

The response patterns of TC, ApoB, and TRIG over time in both studies (Figures 5 and 6) were similar to that of the primary efficacy variable, LDL-C (Figures 1 and 2). That is, in the pivotal study, the reductions were seen as early as Week 2 and were continuously decreased until Week 18, then slightly went back up, but were sustained through Week 56 (except for TRIG of which reduction at Week 56 was smaller). In the supportive study, the reductions were continuous until the end of the trial.

Figure 5

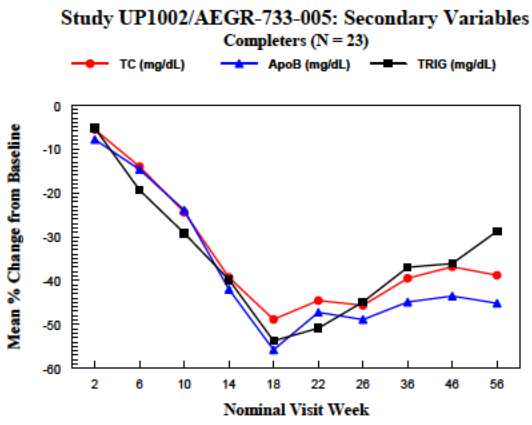
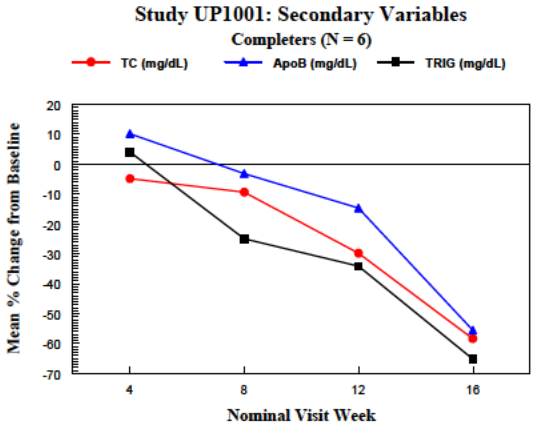


Figure 6



3.4.3 Other Efficacy Endpoints

As Table 5 shows, lomitapide also significantly reduced non-HDL-C and VLDL-C in patients with HoFH after 26 weeks of treatment in Study UP1002/AEGR-733-005 and after 16 weeks of treatment in Study UP1001 (nominal $p < 0.05$). The reductions in Lp(a) and HDL-C at the end of the efficacy phase in both studies were observed, but not statistically significant.

Table 5 – Statistical Results for % Change from Baseline for Other Efficacy Endpoints

Study	ITT/LOCF Population	Non-HDL-C (mg/dL)	VLDL-C (mg/dL)	Lp(a) (nmol/L)	HDL-C (mg/dL)
UP1002 /AEGR-733-005	Mean ± SD (N)	-39.2 ± 31.1 (29)	-27.9 ± 58.4 (29)	-10.6 ± 33.9 (29)	-7.0 ± 19.7 (29)
	95% CI	(-51.1, -27.4)	(-50.1, -5.7)	(-23.5, +2.3)	(-14.5, +0.6)
	Median	-47.7	-45.1	-13.4	-5.6
	Min, Max	-89.7, 25.9	-87.5, 175.0	-62.9, 88.1	-48.5, 28.3
	Paired t-test p	< 0.0001	0.0155	0.1034	0.0683
	Signed-rank test p	< 0.0001	0.0021	0.0324	0.0751
UP1001	Mean ± SD (N)	-60.1 ± 8.9 (6)	-78.7 ± 23.1 (6)	-10.5 ± 20.5 (6)	-2.2 ± 18.0 (6)
	95% CI	(-69.4, -50.8)	(-103.0, -54.5)	(-32.0, +11.0)	(-21.1, +16.7)
	Median	-58.7	-88.8	-16.1	-9.9
	Min, Max	-70.5, -52.1	-93.3, -33.3	-36.1, 18.8	-18.5, 30.0
	Paired t-test p	< 0.0001	0.0004	0.2632	0.7742
	Signed-rank test p	0.0313	0.0313	0.2188	0.5625

Results were generated using the study-specific data extracted from the ISE ADaM dataset.

Note: The raw VLDL-C data in both studies were not normally distributed.

Note: The raw Lp(a) data in Study UP1002/AEGR-733-005 were not normally distributed.

In the pivotal study, the response patterns of non-HDL-C and VLDL-C over time were similar to that of LDL-C and TRIG, respectively. As exhibited in Figure 7, the reductions in HDL-C from baseline were continued through Week 18, and then were gradually reversed to the baseline level at Week 56. In contrast to the pivotal study, mean HDL-C in the supportive study was increased from Week 4 to Week 12, and then decreased back to the baseline level at Week 16 (Figure 8).

Figure 7

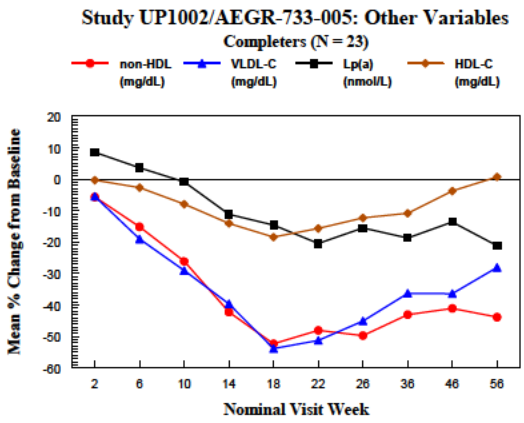
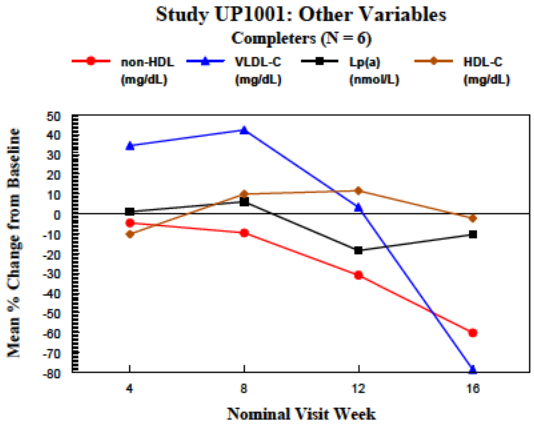


Figure 8



3.4.4 Findings in Special/Subgroup Populations

In the pivotal study, mean % decreases from baseline in LDL-C at Week 26/LOCF were similar between males and females (-40% vs. -39%), between US/Canada and other countries (-32% vs. -45%), between baseline BMI < 30 and ≥ 30 kg/m^2 (-40% vs. -37%), and between the use (yes or no) of apheresis at entry (-34% vs. -49%).

There were 2 sites (Nos. 31 and 32, two patients each, all completers) showing larger mean % changes from baseline in LDL-C at Week 26 with very small standard deviations (-61% ± 2.5% and -52% ± 0.7%) when compared to the other sites in the study. When the 2 sites were excluded from the primary efficacy analysis, similar results were observed (-37% ± 34%, n = 25, p < 0.0001).

As seen in Figure 9, there was a negative, but weak, correlation between the baseline LDL-C (x-axis) and % change from baseline in LDL-C at Week 26/LOCF (y-axis) in Study UP1002/AEGR-733-005.

Figure 9

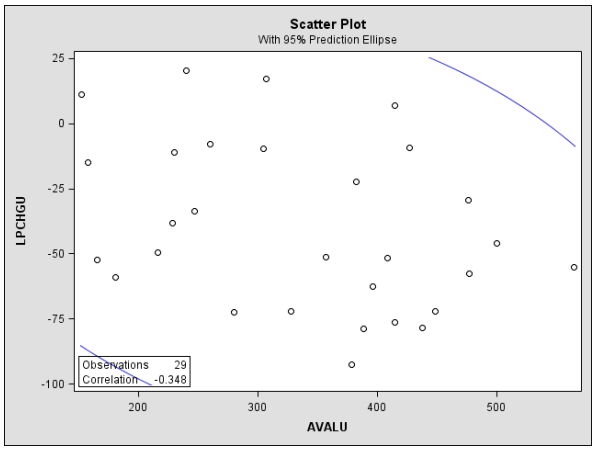
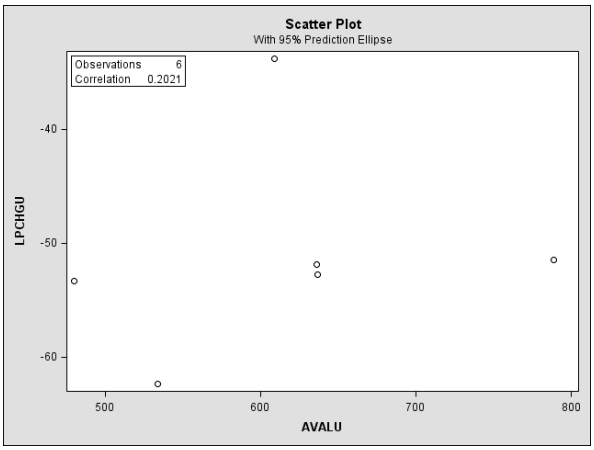


Figure 10



4. CONCLUSIONS

Data from Study UP1002/AEGR-733-005 (the pivotal Phase 3 trial) have demonstrated that lomitapide was effective in reducing LDL-C, total cholesterol, Apo B, triglycerides, non-HDL-C, and VLDL-C in patients with HoFH after 26 weeks of treatment when used as an adjunct to a low-fat diet and other lipid-lowering therapies with or without LDL apheresis. The reductions were maintained through Week 56, as shown in Table 6.

Specifically, the mean % decrease in LDL-C from baseline to Week 26 was about 40% for the ITT/LOCF population (N = 29) and 50% for the completers (N = 23). In addition, a total of 20 patients had a > 15% decrease in LDL-C at Week 26. It was noted that the mean reductions in LDL-C were increasing as doses were increased during the titration period

(Table 7). However, the reduction reached a plateau at Week 18, and was sustained around 40-45% between Weeks 36 and 56 with the mean maximum tolerated dose (MTD) about 40 mg. At Week 26, in the completer cohort, 5 patients received 20 mg with 38% reduction in LDL-C, 6 patients received 40 mg with 57% reduction, and 10 patients received 60 mg with 55% reduction. It appears that the mean % reductions in LDL-C were similar between the patients receiving 40 mg and 60 mg at Week 26.

There was no marked change in Lp(a) after 26 weeks of treatment with lomitapide when compared with baseline. There was, however, a beneficial reduction in Lp(a) after 56 weeks of treatment.

Note that as depicted in Figures 5 and 7 above, mean % reductions in triglycerides and VLDL-C were reversed after Week 18 and were continued through Week 56. Similarly, the decrease in HDL-C after treatment with lomitapide was also observed, but was reversed after Week 18. The mean % reduction in HDL-C at Week 26 was statistically significant in the completer cohort (-12.3%, nominal p = 0.004), but not in the ITT/LOCF population (-7.0%, nominal p = 0.07). Nevertheless, the decrease was gradually reduced to the baseline level at Week 56. Evaluation of the data after Week 56 may be important for triglycerides, VLDL-C, and especially HDL-C since the long-term effect of lomitapide on these parameters remains to be seen.

Results from the supportive Phase 2 trial (Study UP1001) were similar to the results observed in the pivotal Phase 3 trial.

Table 6 – Summary Statistics (Mean ± SD) and statistical results for Study UP1002/AEGR-733-005

Variable	Baseline (N=29)	Week 26 ITT/LOCF (N=29)	% Change from Baseline	p-value	Week 26 Completers (N=23)	% Change from Baseline	p-value	Week 56 Completers (N=23)	% Change from Baseline	p-value
LDL-C	337.0 ± 113.8	191.3 ± 106.6	-39.6 ± 32.0	< 0.01	167.7 ± 96.2	-50.2 ± 26.5	< 0.01	198.8 ± 122.7	-44.0 ± 29.8	< 0.01
TC	430.4 ± 135.3	261.1± 121.8	-35.7 ± 29.4	< 0.01	236.0 ± 112.4	-45.7 ± 23.7	< 0.01	274.3 ± 144.2	-38.8 ± 27.0	< 0.01
ApoB	260.1 ± 80.1	148.9 ± 74.9	-39.3 ± 30.3	< 0.01	132.9 ± 70.8	-48.9 ± 26.1	< 0.01	148.8 ± 83.1	-45.2 ± 27.6	< 0.01
TRIG	102.7 ± 47.8	63.7 ± 45.5	-28.2 ± 57.6	0.01	57.0 ± 37.6	-44.9 ± 36.8	< 0.01	81.2 ± 69.3	-28.8 ± 42.3	< 0.01
Non-HDL-C	386.4 ± 131.8	220.1 ± 116.6	-39.2 ± 31.1	< 0.01	196.3 ± 107.3	-49.7 ± 24.9	< 0.01	229.5 ± 138.7	-43.9 ± 29.4	< 0.01
VLDL-C	20.5 ± 9.6	12.7 ± 9.2	-27.9 ± 58.4	0.02	11.4 ± 7.6	-45.1 ± 36.6	< 0.01	16.3 ± 13.9	-28.1 ± 42.7	< 0.01
Lp(a)	78.2 ± 64.3	62.3 ± 41.1	-10.6 ± 33.9	0.10	60.7 ± 42.9	-15.5 ± 35.5	0.048	62.1 ± 51.4	-21.2 ± 23.4	< 0.01
HDL-C	44.0 ± 10.7	41.1 ± 13.5	-7.0 ± 19.7	0.07	39.8 ± 14.2	-12.3 ± 18.2	< 0.01	44.8 ± 15.5	+0.7 ± 32.3	0.92

All the variable units were mg/dL, except for Lp(a) where the unit was mmol/L.

p-value was based on paired t-test.

Table 7 – Association of % Reduction in LDL-C and Dose for Study UP1002/AEGR-733-005 – Completers (N = 23)

Week	2	6	10	14	18	22	26	36	46	56
% Reduction in LDL-C	9%	15%	27%	44%	53%	49%	50%	43%	41%	44%
Mean Dose (mg)	5	10	18	33	40	43	45	39	41	40
Median Dose (mg)	5	10	20	40	40	40	40	40	40	40
Minimum Dose (mg)	5	10	5	5	5	5	5	5	5	5
Maximum Dose (mg)	5	10	20	40	60	80	80	60	60	60

Dose information was obtained from the sponsor's clinical study report.

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	**September 18, 2012**
To:	**Members of the Endocrinologic and Metabolic Drugs Advisory Committee**
From:	**Division of Risk Management** **Office of Medication Error Prevention and Risk Management** **Office of Surveillance and Epidemiology (OSE)**
Subject:	**Risk Management Options**
Product:	**Lomitapide (NDA 203858)**

1 INTRODUCTION

This memorandum presents FDA's proposed risk mitigation strategy to minimize the potential risk of serious hepatotoxicity associated with lomitapide.

2 BACKGROUND

Lomitapide is an oral microsomal triglyceride transfer protein (MTP) inhibitor. MTP is an intracellular lipid-transfer protein responsible for transferring triglycerides onto apolipoprotein B (apo-B) during the formation of very-low density lipoprotein (VLDL) in the liver and chylomicrons in the intestine. VLDL is the precursor of low-density lipoprotein (LDL). Through its potent inhibition of MTP, lomitapide therapy results in a reduction in synthesis and transport of apo-B containing lipoprotein and circulating LDL cholesterol (LDL-C).

Aegerion Pharmaceuticals is seeking approval of lomitapide as an adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis to reduce LDL-C, total cholesterol, apo-B, and triglycerides in patients with homozygous familial hypercholesterolemia (HoFH). HoFH is an autosomal dominant genetic disorder found in about 300 patients in the United States and characterized by marked elevations in LDL-C that result in disease complications, including premature coronary artery disease. The proposed dosing regimen is to escalate from 5 mg daily to 60 mg daily, as tolerated, during a 14-week period.

The evaluation of the efficacy and safety of lomitapide included a pivotal phase 3, single-arm trial including 29 patients with HoFH, a pivotal trial extension, and a pilot phase 2, single-arm, 16-week duration trial including 6 HoFH patients. Lomitapide's clinical development program demonstrated LDL-C reduction in the HoFH population greater than that observed with potent statins.

Lomitapide therapy was associated with increased serum transaminases and increased hepatic fat. Thirty-four percent (10/29) of patients with HoFH treated with lomitapide had ALT ≥3x ULN at least once during the pivotal trial; however, none of these subjects had bilirubin levels outside of the normal range. Seventy-eight percent (18/23) subjects in the pivotal trial showed a maximum absolute increase in hepatic fat >5%; 13% or 3 patients had an absolute increase of greater than 20%.

Lomitapide-induced increase in hepatic fat appears to be reversible after short-term (16 weeks) administration in the pilot study. Five of the six subjects in the pilot study showed near-complete resolution of hepatosteatosis after discontinuation of lomitapide and a subsequent publication describing the results of this study indicate that, in the remaining subject, hepatic fat returned to baseline 14 weeks after stopping lomitapide.[1]

It is unknown if long-term exposure to lomitapide will cause irreversible liver injury. The potential for progression of non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH) is unknown, but should this occur, the potential consequences could be severe. Patients would be at risk for cirrhosis and liver-related death. Because

[1] Cuchel M, *et al.* Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. *N Engl J Med*. 2007 Jan 11; 356(2):148-156.

of the severity of vascular disease in patients with HoFH, they may benefit from treatment with lomitapide, even though the liver safety issue has not been fully characterized.

Risk Evaluation and Mitigation Strategy

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food Drug Administration Amendments Act of 2007 (FDAAA) authorizes the FDA to require pharmaceutical sponsors to develop and comply with a Risk Evaluation and Mitigation Strategy (REMS) for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: a Medication Guide or patient package insert (PPI), a communication plan to healthcare providers, elements to assure safe use, and an implementation system. FDAAA also requires that all REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

A Medication Guide provides FDA approved patient-focused labeling and can be required as part of the approved labeling if FDA determines one or more of the following apply:

- Patient labeling could help prevent serious adverse events.
- The product has serious risks that could affect a patient's decision to use or continue to use the drug.
- Patient adherence to directions is crucial to product effectiveness.

A communication plan consists of FDA approved materials used to aid a sponsor's implementation of the REMS and/or inform healthcare providers about serious risk(s) of an approved product. This can include, for example, "Dear Healthcare Professional" letters, collaboration with professional societies, and education pieces (such as letters, drug fact sheets) to inform prescribers of the risks and the safe use practices for the drug.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

3 RISK MANAGEMENT CONSIDERATIONS

A variety of strategies are used to minimize risks associated with drugs and therapeutic biologics. These strategies minimize risks in a number of ways. They can communicate specific risk information, as well as information regarding optimal product use. In addition, they can provide guidance and/or encourage adherence to certain prescribing, dispensing, or monitoring requirements, and/or limit use of a product to only the most appropriate situations or patient populations.

Because of the potential risk of hepatotoxicity, lomitapide could not be approved without the necessary safeguards to restrict prescribing to certified prescribers who understand that lomitapide must be used only for treating patients in whom the benefit is thought to exceed this risk. Requiring a diagnosis of HoFH that relies on genetic testing or a family history in order to receive lomitapide is problematic for the following reasons:

- Genetic testing may not be available to all patients
- Not all of the genetic mutations that define HoFH are known
- Adopted individuals are likely unaware of their family history

The following strategy would provide a mechanism to support prescribers in the safe use of lomitapide in the targeted HoFH population, while deterring its use in the larger population of patients with hypercholesterolemia.

Proposed REMS Strategy

We are proposing that the REMS 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 in whom therapy with lomitapide is medically appropriate

We propose the following components for the REMS.

1) Elements to assure safe use that to include:
    a. Health care professionals (HCP) who prescribe lomitapide are specially certified
    b. Pharmacies that dispense lomitapide are specially certified
    c. Lomitapide will be dispensed to patients with evidence or other documentation of safe-use conditions.
2) An implementation system
3) A timetable for submission of assessments

For HCPs to be certified, they would be required to read educational materials and enroll in the lomitapide REMS program by acknowledging understanding of the risks of lomitapide therapy; the need to monitor serum transaminases during treatment; and the approved indication for use. They would also agree to counsel patients about the risk of hepatotoxicity and the need to have regular blood tests performed to monitor for evidence of liver injury or dysfunction.

We propose the following safe use condition: the prescriber will need to attest on an authorized prescription form, for each prescription, that he/she is aware that lomitapide is indicated for patients with HoFH and the drug is medically appropriate for the patient. The authorized prescription form, completed and signed by the prescriber only, would be sent directly to the certified pharmacy; the form would not require a patient signature.

Certified pharmacies would need to have systems in place to verify that only certified prescribers prescribe lomitapide to patients in whom therapy with lomitapide is medically appropriate. The certified pharmacies would not need to obtain additional documentation in support of the patient's medical need for the drug other than the prescriber attestation in the authorization form, nor would they ensure that the appropriate laboratory testing has been performed prior to dispensing lomitapide.

Discussion of Proposed Strategy

The proposed REMS would restrict prescribing to only certified prescribers and dispensing of lomitapide to only certified pharmacies. Prescribing and dispensing of lomitapide would be contingent on the prescriber being certified in the REMS and attesting to the medical appropriateness of each prescription. Certified pharmacies would dispense lomitapide only if prescribed by a certified prescriber, and if the prescriber attests that lomitapide is medically appropriate for that patient.

A Medication Guide will be required to be dispensed to patients as part of labeling, but it will not be a component of the REMS. The complex issues of NAFLD and the possible progression to NASH will be the focus of prescriber education.

We do not propose including patient enrollment as a component of the REMS nor will the REMS restrict lomitapide to a specific diagnosis or require specific patient monitoring that are linked to dispensing. Additional safety data are needed to address the remaining questions about the best way to monitor for hepatic steatosis and whether there

is an extent of hepatic steatosis that is sufficiently worrisome to warrant discontinuing the drug. Additional safety data will be collected through post marketing requirements.

4 CONCLUSION

FDA has the authority to require a REMS if additional measures beyond the labeling are necessary to ensure the benefits of a drug outweigh the risks. In considering a risk management program for lomitapide, FDA must keep in mind that the HoFH patient population currently has limited therapeutic options. On the other hand, the risk-benefit profile of lomitapide in the larger patient population with hypercholesterolemia has not been established, and there is reason for concern should this larger patient population be exposed to lomitapide. The REMS proposed above would support appropriate use of lomitapide, allowing it to be approved for use in the targeted patient population, a patient population with life threatening illness and limited therapeutic options, while protecting the larger hypercholesterolemic patient population. We believe that this proposed REMS is needed to ensure that the benefits of lomitapide outweigh the potential risk of serious liver injury.

Advisory Committee Briefing Document
Nonclinical Pharmacology and Toxicology Summary

Drug: Lomitapide (AEGR-733; BMS-201038)
Drug class: Microsomal triglyceride transfer protein (MTP) inhibitor
Clinical Indication: Hypercholesterolemia

Introduction

Lomitapide is a microsomal triglyceride transfer protein (MTP) inhibitor that has been developed to reduce cholesterol and triglycerides in patients with homozygous familial hypercholesterolemia (HoFH), an orphan indication. Lomitapide is the first MTP inhibitor being reviewed by the FDA for marketing approval in the United States. Lomitapide is intended to be used as an adjunct therapy to diet and other lipid-lowering medications. The recommended starting dose will be 5 mg taken orally once daily. After 2 weeks, the dose can be escalated to 10 mg followed by incremental increases to 20, 40, and 60 mg at a minimum of 4-week intervals.

Pharmacology

MTP is a soluble protein found primarily in the endoplasmic reticulum of hepatocytes and intestinal epithelium. MTP forms a heterodimer with protein disulfide isomerase and together regulate the assembly of triglycerides with apolipoprotein B (apoB) resulting in the formation of very low-density lipoprotein cholesterol (VLDL), the precursor of low-density lipoprotein cholesterol (LDL). Inhibition of MTP activity prevents the transfer of lipid to apoB resulting in the proteolytic destruction of nascent apoB. MTP is also essential for the formation and secretion of chylomicrons in the intestine. Inhibition of MTP in enterocytes prevents the formation of chylomicrons and thereby inhibits the transfer of dietary-derived lipids to the liver.

Patients with HoFH have high levels of plasma LDL due to mutations in genes involved in the regulation of lipids. LDL receptor mutations are the predominant genetic defect identified in the HoFH population, although the involvement of mutations in other genes, such as apoB, have been reported at a lower incidence. In the absence of a functional LDL receptor or apoB molecule, LDL cannot be efficiently taken up by the liver resulting in a longer circulating half-life and higher plasma LDL levels. By inhibiting MTP, hepatic VLDL and intestinal chylomicron formation and secretion is inhibited, thereby lowering circulating plasma levels of VLDL and LDL.

Pharmacokinetics

The mean plasma half-life of lomitapide was approximately 11 hours in rats and 12 hours in dogs. In humans, the mean plasma half-life ranged from

approximately 34 and 75 hours. Lomitapide is highly bound to plasma proteins (≥99.5%).

Hepatic metabolism of lomitapide occurs through mono-oxidation and N-dealkylation steps at several different positions followed by further oxidation and/or glucuronidation. Metabolites M1 and M3 are the major human metabolites. M1 and M3 represent two halves of the parent molecule. M1 and M3 showed no evidence of MTP inhibition at therapeutic concentrations.

Lomitapide-Mediated Toxicities

In animal toxicology studies, the primary treatment-related finding was lipid accumulation in the liver, small intestine, and lung. Because lomitapide interferes with fat absorption from the small intestine, 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 times higher than at the maximum recommended human dose (MRHD) of 60 mg, and resulted in death at higher exposures (~70X MRHD). In subsequent toxicology studies, animals received supplemental fat-soluble vitamins in the diet and/or through subcutaneous injections. When supplemental vitamin K was provided, systemic bleeding was not observed. The toxicity profile of lomitapide is discussed below by target organ and summarized in Table 1 below.

Liver:

Treatment with lomitapide induces lipid accumulation in hepatocytes of mice, rats, hamsters, and dogs after a single dose (rats) after repeated daily dosing. Lipid vacuolation is primarily periportal and is positive for Oil-Red-O stain, indicating an accumulation of neutral lipids. For exposures between 3 and 6 months, vacuolation was generally scored as minimal to mild in mice, minimal to moderate in male rats, moderate to marked in female rats, and minimal in dogs. Lipid vacuolation was associated with increased mean absolute liver weight for mice, rats, and dogs by up to 28%, 83%, and 31%, respectively. The effect on liver weights was considerably more noteworthy for female rats compared with male rats. In an electron microscopy (EM) evaluation of liver sections from dogs treated for 1 month, hepatocellular lipid deposition was characterized as one or more variably-sized homogenous pale-gray lipid droplets in the cytoplasm. When reversibility was assessed in a 6-month rat study, lipid vacuolation was greatly diminished after a 3-month treatment-free period and not detected after 6 months; liver weights were similar to control values after a 6-month treatment-free period.

In addition to lipid accumulation, slight increases in mean serum alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) were noted in rats (≤2X increase) and dogs (≤3.5X increase) after 1 month of treatment or longer. In rats, mean serum alkaline phosphatase (ALP) was increased up to 4 times compared with concurrent controls after 3 or 6 months of treatment.

Minimal single cell necrosis was seen in rats at 10 mg/kg/d (7X [males] and 34X [females] MRHD) after 3 months and at ≥0.2 (females) or ≥2 mg/kg/d (males) after 6 months (≥2X [males] and ≥1X [females] MRHD). Minimal to moderate subacute inflammation was seen in rats at ≥1 mg/kg/d (≥1X [males] and ≥3X [females] MRHD) after 3 months and at ≥0.2 (females) or 20 mg/kg/d (males) after 6 months (17X [males] and ≥1X [females] MRHD), when vitamin supplementation was provided. After 2 years of dosing in rats, an increase in the incidence and severity (minimal to moderate) of focal/multifocal fibrosis was observed at ≥0.25 mg/kg/d for males (0.2X MRHD) and at ≥0.35 mg/kg/d for females (2X MRHD). An increased incidence of minimal to mild cystic degeneration was observed for males treated at ≥1.7 mg/kg/d (2X MRHD).

Small Intestine:
Treatment with lomitapide induced lipid accumulation in small intestinal absorptive epithelium of mice, rats, hamsters, and dogs at clinically relevant exposures. Moderate microscopic lipid vacuolation was seen as early as after a single oral dose of ≥10 mg/kg in rats (≥1.5X MRHD based on body surface area extrapolation). Within the small intestinal tissue, lipid vacuoles were most prominent in the jejunum followed by the duodenum. Lipid vacuoles were positive for Oil-Red-O staining, indicating an accumulation of neutral lipids. Vacuolation was not accompanied by necrosis or signs of chronic inflammation. EM evaluation of small intestine from dogs treated for 1 month showed lipid deposition as multiple, variably-sized, homogenous pale-gray lipid droplets that were partially enveloped by endoplasmic reticulum. Longer duration dog studies showed the presence of lipid vacuoles but the finding did not exhibit progression after exposures up to 12 months. Reversibility of lipid vacuolation in the small intestine was demonstrated in mice after treatment up to 2 years.

Lung:
In the lungs of treated animals, an increased incidence in the presence of foamy alveolar macrophages (histiocytes) has been observed in mice and rats. In mice, foamy alveolar macrophages were observed in alveolar spaces at ≥5 mg/kg/d (≥5X MRHD) after treatment for 3 months. In a 2 year carcinogenicity study in mice, increases in the incidence of alveolar spicules and lymphocyte infiltration were observed at ≥15 mg/kg/d (≥22X MRHD); histiocytosis was not noted by standard microscopy, but was observed at a low incidence when lung tissue was examined by EM.

In rats, multifocal small collections of foamy macrophages (histiocytes) were noted in alveoli, frequently in subpleural locations; an increased incidence of minimal histiocytosis was observed at doses as low as 0.01 mg/kg/d (<0.1X MRHD) after 3 months of treatment. After 6 months of treatment in rats at ≥0.2 mg/kg/d (≥0.3X MRHD), histiocytosis was characterized by multifocal aggregates of large foamy macrophages within alveoli, either alone or associated with dose-related increasing incidence/severity of subacute inflammation, necrotic cellular debris, cholesterol-like clefts, and/or Type II alveolar cell proliferation. Special

staining with Luxol fast blue and Baker's acid hematin stain for phospholipids and Oil-Red-O for neutral lipids demonstrated that both types of lipids were contained in the macrophages and adjacent Type II alveolar cells. Histiocytosis did appear to be reversible after a 6-month recovery period. In a 2-year carcinogenicity study in rats, increases in the incidence of alveolar spicules, lymphocyte infiltration with macrophage accumulation, and thickened alveolar septa with macrophage infiltrates were observed at ≥0.25 mg/kg/d (≥0.2X MRHD). An increase in septal cell mineralization was noted for males receiving ≥1.7 mg/kg/d (2X MRHD). An increased incidence of pleural/subpleural fibrosis was observed for females receiving ≥0.35 mg/kg/d (≥2X MRHD), although the incidence was similar to the male control group.

The results a 1-year study in dogs showed a low incidence of minimal to mild pleural fibrosis in males and females at ≥0.5 mg/kg/d (≥3X MRHD). Additionally, a slight increase in the incidence of minimal focal mineralization and mild chronic-active inflammation was observed at 5 mg/kg/d (64X MRHD) in males and minimal to mild alveolar edema was noted in females at 5 mg/kg/d (56X MRHD); these findings occurred in the absence of histiocytosis. Histiocytosis was also not observed in a 1-month toxicity study at doses up to 20 mg/kg/d. In dogs treated with lomitapide at doses up to 10 mg/kg/d for 6 months, minimal lung histiocytosis was observed for some animals across most groups including the male control group. The incidence or severity of histiocytosis did not increase with increasing dose level, and thus may have been an incidental background finding. Chronic inflammation and edema were also observed across most dose levels at an incidence and severity similar to control groups.

To further characterize the observation of foamy alveolar macrophages, lung tissue from some rat and mouse studies was evaluated by EM. EM evaluation of lung tissue from a 6-month rat study characterized the histiocytosis as focal aggregates of large foamy alveolar macrophages containing residual/lamellar inclusion bodies, lipid droplets, and phagolysosomes varying in size, shape, and electron density. Occasionally adjacent type II cells were slightly enlarged and contained lipid droplets, as well as a qualitative increase in the size or amount of lamellar inclusion bodies. EM examination of lung tissue from another 6-month rat study showed that alveolar macrophages were enlarged with abundant cytoplasm packed with neutral lipid droplets, electron-dense multi-laminated osmiophilic structures, and cleft-like electron-lucent structures (cholesterol clefts). The pathologist concluded that the EM results of the lungs were consistent with pulmonary phospholipidosis. The EM evaluations for the 6-month studies were conducted during the early phase of drug development and EM evaluations from later studies, evaluated by a different pathologist, resulted in a slightly different interpretation, as described below.

After EM examination of rat lung tissue from a 3-month study, the pathologist described the excessive vacuolation as morphologically consistent with neutral lipid vacuoles because the vacuoles were smoothly contoured with

homogeneous translucent content. The pathologist concluded that the evaluation did not reveal the presence of phospholipidosis, which is characterized by the excessive accumulation of concentric lamellar inclusions in the lysosomes of macrophages or other lung cells. Although concentric lamellar inclusions were seen, they were rarely observed in lysosomes and were present in cells from both control and treated animals. The evaluation also showed no evidence of chronic interstitial reaction in the alveolar wall adjacent to vacuolated macrophages. After a 6-month recovery period, the number of macrophages with lipid vacuoles was low and similar to the control group, indicating that this effect is reversible once the drug is discontinued.

The pathologist also concluded that the lipid accumulation noted for alveolar macrophages in lung tissue from a 2-year mouse carcinogenicity study was not consistent with classical phospholipidosis. Observed alveolar spicules were characterized as long slender crystals that occurred singly or as aggregated multi-layered inclusions in the cytoplasm of alveolar macrophages. Excessive lipid accumulation occurred in the absence of concurrent epithelial degeneration or inflammatory changes in the alveolar wall.

Table 1. Summary of Noteworthy Treatment-Related Effects and Safety Margins by Target Organ/Finding

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
	Mouse	2 years	45†††	~75X
	Rat	3 months	<1	<2X
	Rat	3 months	<0.01	<0.1X
	Rat	6 months	0.02	0.4X
	Rat	2 years	M: 7.5† F: 2†	M: 6X F: 8X
	Dog	6 months	10†	200X
	Dog	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 calculated using a mean $AUC_{0\text{-}24h}$ 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.

Carcinogenicity

Two 2-year carcinogenicity studies were conducted in mice and rats to evaluate the carcinogenic potential of lomitapide (summarized below). Data from genetic toxicology studies indicate that lomitapide is not a direct acting mutagen.

Mice

A 2-year bioassay was conducted in CD-1 mice. Mice (60/sex/group) were administered AEGR-733 by oral administration (mixed in diet) at dose levels of 0 (diet control), 0.3, 1.5, 7.5, 15 or 45 mg/kg/day. Study groups were assessed for neoplasms between Weeks 99 and 104, depending on animal survival for each group. Because AEGR-733 inhibits absorption of fat soluble vitamins from the intestine that can lead to toxicity due to vitamin deficiency, all animals were fed a rodent diet that contained more vitamin A and K than standard rodent diet.

A statistically significant increase in the incidence of hepatocellular neoplasms (adenomas or carcinomas, combined) was observed in males given ≥1.5 mg/kg/day (≥2X MRHD) and females given ≥7.5 mg/kg/d (≥9X MRHD). Both hepatocellular adenomas and carcinomas occurred singly or in multiples and several animals had both adenomas and carcinomas. Statistically significant increases in adenomas or carcinomas, combined, of the small intestine (duodenum, ileum, and jejunum) were observed in males and females at ≥15 mg/kg/day (24X MRHD). The jejunum was the most common site for carcinomas. The incidences of hepatocellular and small intestinal neoplasms was not completely dose dependent, as there were often fewer neoplasms at the high dose compared with lower dose levels; this effect was likely due to the higher mortality rate in the high-dose groups.

On the basis of a statistically significant increase in hepatocellular neoplasms, the NOEL for drug-related neoplasms in mice was 0.3 mg/kg/day for males and 1.5 mg/kg/day for females, which represent clinical exposure margins for the parent drug of 0.4X and 2X, respectively. A summary of neoplasm incidence, statistical significance, and clinical exposure margins for parent compound and its major metabolites are shown in Table 2 below.

Table 2. Neoplastic Findings in Mice

	Males					
Dose (mg/kg/d)	0	0.3	1.5	7.5	15	45
No. Examined	60	60	60	60	60	60
Exposure Margin†						
AEGR-733	NA	0.4X	2X	11X	26X	77X
Metabolite M1	NA	NC	14X	115X	300X	1600X
Metabolite M3	NA	0.2X	0.8X	4.6X	11X	34X
Liver						
Hepatocellular adenoma	**4**** (0.0011)	5	13	11	**16*** (0.0034)	**15*** (0.0013)
Hepatocellular carcinoma	23	22	**40*** (0.0088)	**38*** (0.0076)	36	30
Total with hepato-cellular tumors	25 (0.0131)	25	**44*** (0.0061)	**42*** (0.0024)	**43*** (0.0071)	37 (0.0103)
Small Intestine Combined (duodenum, jejunum, or ileum)						
Adenoma	0	2	0	1	0	0
Carcinoma	**0**** (<0.001)	0	1	1	**9*** (0.0019)	**5*** (0.0144)
Total with small intestinal tumor	**0**** (0.0039)	2	1	2	**9*** (0.0019)	**5*** (0.0144)

	Females					
Dose (mg/kg/d)	0	0.3	1.5	7.5	15	45
No. Examined	60	60	60	60	60	60
Exposure Margin†						
AEGR-733	NA	0.4X	2X	9X	22X	77X
Metabolite M1	NA	NC	14X	86X	290X	1025X
Metabolite M3	NA	0.1X	0.4X	2.5X	8X	20X
Liver						
Hepatocellular adenoma	**1**** (<0.001)	0	1	**12*** (0.0035)	**12*** (0.0051)	**10*** (0.0065)
Hepatocellular carcinoma	**4**** (0.0016)	0	1	**17*** (0.0049)	16 (0.0119)	11
Total with hepato-cellular tumors	**5**** (<0.001)	0	2	**23*** (<0.001)	**25*** (<0.001)	**19*** (0.0025)
Small Intestine Combined (duodenum, jejunum, or ileum)						
Adenoma	0	0	0	0	3	0
Carcinoma	**0**** (0.0086)	0	0	0	5 (0.0542)	3 (0.1304)
Total with small intestinal tumor	**0**** (0.0111)	0	0	0	**8*** (0.0083)	3 (0.1304)

NA = not applicable; NC = not calculated (plasma concentration below the limit of quantitation).

†Based on $AUC_{0\text{-}24}$ (ng·h/mL); mean human exposures at 60 mg/day for parent, M1, and M3 are 69.5, 6.5, and 535 ng·h/mL, respectively.

*Pair-wise analysis: p≤0.01 for common tumors and p≤0.05 for rare tumors.

**Trend analysis: p≤0.005 for common tumors and p≤0.025 for rare tumors.

Rat

A 2-year bioassay was conducted in Sprague-Dawley rats. Rats (60/sex/group) were administered AEGR-733 once daily by oral gavage at dose levels of 0 (vehicle [75% PEG-400]), 0.25, 1.7, or 7.5 mg/kg/day in males or 0 (vehicle), 0.03, 0.35, or 2.0 mg/kg/day in females. Females received lower dose levels due to a greater drug exposure than males at equivalent doses. Treatment groups were assessed for neoplasms between Weeks 94 and 98, depending on animal survival for each group. Because AEGR-733 inhibits absorption of fat soluble vitamins from the intestine that can result in toxicity due to vitamin deficiency, throughout the study, all animals were fed a rodent diet that contains more vitamin A and K than standard rodent diet. Additionally, beginning on Day 407, mid-dose group animals received a vitamin-fortified diet containing 5 times the concentrations of vitamins A, D, and E contained in the standard diet and high-dose group animals received a vitamin-fortified diet containing 10 times the concentrations of vitamins A, D, and E.

There were no increases in neoplasms that were considered to be related to treatment at any dose tested. Therefore, the NOEL for drug-related neoplasms in rats was considered to be the highest dose tested: 7.5 mg/kg/day for males and 2 mg/kg/day for females, which represent 6X MRHD and 8X MRHD, respectively.

Developmental and Reproductive Effects:

The sponsor conducted a standard battery of toxicology studies to evaluate the potential effects of lomitapide on reproduction and embryo-fetal development. When dosed prior to and during mating, there were no treatment-related effects on reproductive endpoints for male or female Sprague-Dawley rats at dose levels up to approximately 3-fold higher than the MRHD.

In an embryo-fetal developmental toxicity study in Sprague-Dawley rats, fetal death and malformations were observed when lomitapide was administered during organogenesis from gestational days (GD) 6 through 15. Decreased fetal body weight and developmental defects were observed at ≥0.4 mg/kg/d (2X MRHD). Fetal malformations included defects to the abdomen (umbilical hernia, gastroschisis); tail (short, stubbed, bent, or absent); heart (alterations in size or shape); limbs (malrotation); and anus (imperforate). At 4 mg/kg/d (10X MRHD), shortened limbs, brain defects (exencephaly, hydrocephaly, cerebral hernia, misshaped cerebral hemispheres), and embryonic mortality were also noted. The no observed adverse effect level (NOAEL) for embryo-fetal development was 0.04 mg/kg/d (less than 1X MRHD).

In an embryo-fetal developmental toxicity study in ferrets, treatment with lomitapide during organogenesis from GD12 through GD28 resulted in maternal body weight loss (associated with decreased food consumption), decreased fetal body weight, and fetal malformations at all doses tested. Malformations at ≥1.6

mg/kg/d included those involving the limbs/paws (rotated medially, digits absent or fused); head (cleft palate, open eye lids, low set ears); tail (kinked); and abdomen (umbilical hernia). The incidence of these findings tended to increase in a dose-related manner. At ≥4 mg/kg/d, increased embryonic resorptions and short limbs were also observed. Because effects on embryo-fetal development were observed at all dose levels, a NOAEL was not identified (<1.6 mg/kg/d; <0.3X MRHD based on body surface area extrapolation).

In an embryo-fetal developmental toxicity study in New Zealand white rabbits, doses of ≥1 mg/kg/d lomitapide resulted in biologically meaningful decreases in maternal body weight gain (65% to 76% less then controls) when administered during organogenesis from GD6 through GD20. Treatment did not result in adverse effects on embryonic survival or development at doses up to 10 mg/kg/d. Accordingly, the NOAEL for effects on embryonic development was 10 mg/kg/d (3X MRHD based on body surface area extrapolation).

In a peri- and post-natal developmental toxicity study in Sprague-Dawley rats, treatment with 0.3 mg/kg/d lomitapide (1X MRHD) from GD7 through lactation day (LD) 20 resulted in decreased fetal body weights and a low incidence of fetal eye anomalies (missing eye, microphthalmia) and dilatation of the lateral ventricles of the brain. At 1 mg/kg/d (3X MRHD), litter sizes were smaller and there was an increase in still-born pups and pups dying between LD1 and LD7. In addition to the malformations noted for the 0.3 mg/kg/d group, an increase in tail anomalies (bent, short, missing or absent, discolored) were observed and a malformed limb was noted for one pup. Body weights for pups whose mothers were treated with 1 mg/kg/d remained lower than controls after weaning. There were no biologically meaningful effects on learning, short-term memory, long-term memory, response inhibition, or mating and fertility parameters for the F1 generation at any dose. There were no treatment-related effects on fetal development for the F2 generation. The NOAEL for the F1 generation was 0.1 mg/kg/d (<1X MRHD) based on the observed fetal malformations and effects on fetal body weight. The NOAEL for maternal reproduction was 0.3 mg/kg/d (1X MRHD) based on a slight increase in the length of gestation observed at 1 mg/kg/d.

Overall Toxicology Conclusions:

Treatment with lomitapide resulted in the accumulation of neutral lipids in small intestinal epithelial cells and hepatocytes in mice, rats, and dogs. Lipid accumulation in alveolar macrophages was also observed in mice and rats. These findings in liver and intestine are considered to be related to the pharmacodynamic activity of lomitapide by inhibiting the incorporation of lipids with apoB, thereby resulting in excess intracellular lipids. Neutral lipid accumulation in alveolar macrophages is also likely related to the pharmacodynamic activity of lomitapide.

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. Lipid accumulation in the small intestine was not associated with signs of toxicity or inflammation. It is anticipated that a similar effect will occur in humans with uncertain safety implications.

Lipid accumulation in hepatocytes occurred at or near clinically relevant exposures in mice, rats, and dogs, although lipid vacuolation was not observed for mice or dogs in longer duration studies for reasons that are unclear. In rats treated for 6 months, lipid vacuolation had reversed after a 6-month treatment-free period. Lipid accumulation was also generally associated with statistically significantly increased liver weights in all species tested. Slight increases in mean serum ALT and/or AST were noted in rats and dogs. Slightly larger increases in mean serum ALP 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 was observed at clinically relevant exposures.

As fatty liver has been observed clinically, this effect has already been identified to occur in humans with uncertain safety implications. Although hepatocyte lipid accumulation observed in animals did not result in overt signs of liver injury, humans with steatosis are at risk for developing nonalcoholic steato-hepatitis, especially when other risk factors are present, such as insulin resistance. As other risk factors are generally not present in laboratory animals, it is difficult to predict how the presence of hepatocellular lipid accumulation observed in nonclinical studies will translate to clinical safety in the general population.

An increased incidence in the presence of foamy alveolar macrophages (histiocytes) was observed 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. Histiocytosis appeared to be reversible after a 6-month recovery period in rats. In dogs, histiocytosis was not observed at a higher incidence or severity compared with the control group. Based on the most recent EM evaluations, the excessive vacuolation was described as morphologically consistent with neutral lipid vacuoles. Earlier EM examinations characterized the histiocytosis as a mixture of both neutral lipid and phospholipid vacuoles. It is uncertain why the conclusions regarding potential phospholipidosis have changed. It is also uncertain whether there is a meaningful difference between the presence of neutral lipids versus phospholipids with regard to pulmonary function and overall safety.

EM evaluation of lung tissue from mice treated for 2 years indicated that excessive lipid accumulation occurred in the absence of concurrent epithelial degeneration or inflammatory changes in the alveolar wall. The sponsor did evaluate the function of rat macrophages isolated by bronchioalveolar lavage

after 3 months of treatment. The results showed that the isolated macrophages had similar phagocytic and respiratory burst activity as control macrophages, although it is felt that the design of the study could have been improved to obtain more definitive results.

After long-term treatment in dogs (1 year) and rats (2 years), there were some apparent treatment-related findings in lung. In the dog study, 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. Although these pulmonary findings were generally low with regard to both incidence and severity, the fact that they only occurred at the highest dose levels suggests that they could be drug-related rather than incidental findings. 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. Although these findings were also observed in the control animals at a low incidence, the incidence and severity generally increased in a dose-related manner suggesting that the findings were treatment related.

Treatment for two 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 also observed in mice but only at approximately 25-fold expected 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.

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. Because of the observed teratogenic activity, lomitapide should not be administered to pregnant women.