LOMITAPIDE

FOR THE TREATMENT OF PATIENTS WITH HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA (HoFH)

NDA #203858

Sponsor's Background Package

For the

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List of Abbreviations

Abbreviation	Term
AE	Adverse event
ALA	α-linolenic acid
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
apo AI	Apolipoprotein AI
apo B	Apolipoprotein B
ARH	Autosomal recessive hypercholesterolemia
AST	Aspartate aminotransferase
AUC	Area under the curve
BL	Baseline
BMI	Body mass index
BMS	Bristol-Myers Squibb
CABG	Coronary artery bypass graft
CHD	Coronary heart disease
CI	Confidence interval
C_{max}	Maximum concentration
CAD	Coronary artery disease
CV	Cardiovascular
CVD	Cardiovascular disease
DHA	Docosahexaenoic acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eDISH	Evaluation of drug-induced serious hepatotoxicity
EPA	Eicosapentaenoic acid
ER	Emergency room
ESRD	End-stage renal disease
FC	Familial chylomicronemia
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GI	Gastrointestinal
HCP	Healthcare providers
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HOMA-IR	Homeostasis model assessment-insulin resistance
HoFH	Homozygous familial hypercholesterolemia
IC_{50}	Inhibitory concentration, 50%
IND	Investigational New Drug Application
INR	International normalized ratio

Abbreviation	Term
ITT	Intent-to-treat
IV	Intravenous
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDL-R	Low-density lipoprotein receptor
LFT	Liver function test
LLD	Lipid-lowering drug
LLT	Lipid-lowering therapy
LOCF	Last observation carried forward
Lp(a)	Lipoprotein(a)
LSM	Least square means
Max	Maximum
MACE	Major adverse cardiac events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
Min	Minimum
MOA	Mechanism of action
MRI	Magnetic resonance imaging
MTP	Microsomal triglyceride transfer protein
NASH	Non-alcoholic steatohepatitis
NCEP-ATP III	National Cholesterol Education Program Adult Treatment Panel III
NDA	New Drug Application
NMRS	Nuclear magnetic resonance spectroscopy
NYHA	New York Heart Association
PFT	Pulmonary function test
PK	Pharmacokinetic(s)
PT	Prothrombin time
QTc	Corrected QT interval
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious adverse event
SD	Standard deviation
SEM	Standard error of the mean
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
VLDL	Very low-density lipoprotein
VLDL-C	Very low-density lipoprotein cholesterol

1 EXECUTIVE OVERVIEW

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

HoFH is a rare genetic disease caused by mutations in the LDL receptor gene or in genes affecting LDL receptor function, leading to extreme elevations of LDL-C causing premature atherosclerosis and early death. The primary goal of therapy for patients with HoFH involves lowering LDL-C levels, thereby delaying the progression of cardiovascular disease (CVD).

Current treatment options are inadequate and leave patients at high risk of cardiovascular (CV) events due to continuous exposure to high levels of LDL-C. Lomitapide is a first-in-class small molecule inhibitor of microsomal triglyceride transfer protein (MTP). MTP plays a key role in the assembly and release of apo B-containing lipoproteins into the circulation and inhibition of this protein significantly lowers plasma lipid levels. Lomitapide is administered orally once a day with dose level individualized according to safety and tolerability.

The lomitapide clinical development program includes a comprehensive series of Phase 1 studies in healthy subjects, Phase 2 studies in subjects with hypercholesterolemia and other CV risk factors, and Phase 3 studies in subjects with HoFH that provide clinical data demonstrating significant reductions in LDL-C with an acceptable safety profile.

Studies with lomitapide have shown that it is now feasible for some subjects with HoFH to reach target LDL-C goals and maintain these levels during chronic treatment. The safety profile has been consistent across studies; treatment with lomitapide is primarily associated with gastrointestinal (GI) side effects, elevations in liver transaminase levels, and increases in hepatic triglyceride content. Dosing with lomitapide is escalated to each patient's individually-defined maximum tolerated dose from 5 mg up to a maximum dose of 60 mg. With appropriate risk mitigation activities to ensure safe and appropriate use, lomitapide is expected to represent a major advance in the treatment options for patients with HoFH.

1.1 Homozygous Familial Hypercholesterolemia

1.1.1 Overview of the Disease and the Impact of Elevated LDL-C Levels

HoFH is a rare, life-threatening, autosomal co-dominant genetic disease characterized by marked elevations in plasma levels of LDL-C and markedly premature atherosclerotic CVD. The disease is typically caused by homozygosity or compound heterozygosity for loss-of-function mutations in the *LDLR* gene encoding the LDL receptor protein, leading to markedly reduced or absent LDL receptor function. The prevalence of loss-of-function mutations in both alleles of the LDL receptor (HoFH) has been calculated to occur in ~1 in 1 million persons (Moorjani, 1993). This

calculation is based on the estimated prevalence of 1 in 500 for HeFH (Goldstein, 2001), which is caused by a mutation in one allele of the LDL receptor gene and is associated with plasma LDL-C levels and CVD risk intermediate between HoFH and normal individuals.

Patients with HoFH have markedly impaired removal of LDL-C from the circulation resulting from reduced or absent hepatic LDL receptor activity. The hepatic LDL receptor plays a critical role in regulating the concentration of LDL-C in the blood by binding apo B to LDL and mediating its uptake, internalization, and lysosomal degradation. In the absence of functional LDL receptors, the uptake of LDL from the blood is impaired and concentrations are extremely elevated.

As a direct consequence of absent or severely reduced LDL receptor function leading to markedly elevated LDL-C blood levels, patients with HoFH develop dramatically early and severe atherosclerotic CVD and often, early cardiac-related death. Symptomatic CVD often presents during the first 2 decades of life, and includes atherosclerosis in the coronary arteries, the carotid arteries, the aorta and aortic valve, and the peripheral vasculature, often leading to heart attack, stroke, and death (Kwiterovich, 1974; Buja, 1979; Moorjani, 1993; Marais, 2004). Early onset of atherosclerosis is generally accompanied by accelerated disease progression, even in the early teenage years (Kolansky, 2008). If untreated, most HoFH patients do not survive past age 30 due to death from CVD (Buja, 1979; Hobbs, 1992; Beigel and Beigel, 2009).

Evidence that elevated levels of LDL-C are the central causal factor in the onset and severity of CVD in patients with HoFH is substantiated by the observation that patients with receptor-negative HoFH, who have much higher levels of LDL-C (often >750 mg/dL), develop severe CVD at a considerably earlier age than patients with receptor-defective HoFH (LDL-C in the range of 400 to 600 mg/dL) (Goldstein, 2001). One trial found that the receptor-negative patients not only had substantially greater LDL-C levels (mean 1,030 mg/dL vs. 621 mg/dL) but also died of coronary disease at a substantially earlier age (mean 12.7 years vs 23.6 years) (Moorjani, 1993). Results are also available from HoFH patients undergoing LDL apheresis, a mechanical filtration of LDL from the blood that is repeated on a weekly or bi-weekly basis; this treatment is the current approach of choice in patients with HoFH and other forms of severe refractory hypercholesterolemia. While no adequately powered randomized controlled trials of its effect on CVD events have been performed, several groups have independently assessed its effects through rigorous observational approaches. Results of these studies suggest a substantial reduction in CV events associated with the initiation of LDL apheresis (Winters, 2012).

In addition to the data in patients with HoFH, a comprehensive body of data that support the causality of LDL-C in atherosclerotic CVD and that reduction in LDL-C leads to decreased CV risk is derived from interventional randomized controlled clinical trials with statins. Meta-analyses from The Cholesterol Clinical Trialists Collaboration have clearly shown that the magnitude of LDL-C reduction with statin therapy is strongly associated with the magnitude of

coronary artery disease (CAD) risk reduction (NCEP, 2001; Grundy, 2004; Baigent, 2005; Baigent, 2010).

Importantly, statins are not the only intervention that has been shown to reduce CV events in rigorous randomized controlled trials. Consistent evidence that lowering LDL-C levels results in decreased CV events has been shown with immediate-release niacin (Canner, 1986), the bile acid sequestrant cholestyramine (The Lipid Research Clinic1984a; The Lipid Research Clinic1984b), and with partial ileal bypass in patients with severe hypercholesterolemia (Buchwald, 1990). Thus, despite the putative pleiotropic effects of statins, these data indicate that reducing LDL-C through several different types of interventions reduces CVD risk and strengthens the causal link between LDL-C reduction and CVD risk reduction.

In totality, these data strongly support the concept that LDL-C is a causal mediator of CVD in HoFH patients, and that a reduction in LDL-C, even if not to "normal" levels, would be expected to reduce the risk of CVD.

1.1.2 Treatment Goals in Patients with HoFH and Current Treatment Options

The primary goal of therapy for patients with HoFH involves lowering LDL-C levels, thereby delaying the progression of CVD. Unfortunately, dietary intervention, i.e., use of a low-fat diet, is ineffective in patients with this disease due to the markedly elevated levels of LDL-C (Rader, 2003) and patients with HoFH are minimally responsive to conventional LLDs and thus, the effects of available pharmacological treatments are limited and almost always insufficient. Despite the generally poor response, aggressive drug therapy is usually initiated in patients with HoFH upon diagnosis. Pharmacologic options include HMG-CoA reductase inhibitors (statins), cholesterol absorption inhibitors such as ezetimibe, bile-acid sequestrants, and, less commonly, niacin.

Current therapies for reducing LDL-C levels, including statins, work largely through upregulation of the LDL receptor in the liver. Thus, patients with HoFH who lack functional LDL receptor activity generally respond very poorly to current pharmacologic therapies (see Section 2.1.3). However, patients with receptor-defective HoFH who have some residual LDL receptor activity may have some modest reduction in LDL-C with maximal conventional therapy. Thus, patients with HoFH even with maximal pharmacologic LLDs generally have LDL-C levels >300 mg/dL (Gagne, 2002). Consistent with these observations, the mean baseline LDL-C in the Phase 3 lomitapide study was 336 mg/dL despite optimal medical therapy, including the use of statins, ezetimibe, bile acid sequestrants, and, in 62% of subjects, LDL apheresis.

The current recommended and approved therapy for patients with HoFH is LDL apheresis which involves mechanical filtration of the blood to selectively remove LDL (Kolansky, 2008; Thompson, 2010), although the therapy is not widely available. The treatment transiently reduces LDL-C levels by approximately 50% (Uauy, 1992; Jaeger, 2002; Thompson, 2010).

However, treatments must be repeated every 1 to 2 weeks to effect an acceptable time-averaged LDL-C reduction because LDL-C levels rebound after the procedure (Tonstad and Thompson, 2004). While quality of life data are not available for patients with HoFH receiving LDL apheresis, this therapy presents significant challenges for the patient based on its limited availability, considerable time commitment, and requirement for frequent repetitive intravenous (IV) access or creation of an arteriovenous fistula.

In summary, a limited number of treatment options exist for patients with HoFH. Yet, even with the aggressive utilization of a combination of these therapies, patients with HoFH generally have LDL-C levels substantially above treatment targets.

Additional effective therapeutic options are urgently needed to optimize the treatment of patients with this rare, life-threatening disease.

1.2 Lomitapide and Microsomal Triglyceride Transfer Protein Inhibition

MTP is an intracellular lipid-transfer protein found in the lumen of the endoplasmic reticulum responsible for binding and shuttling individual lipid molecules between membranes (Hussain, 2003; Liao, 2003). Inhibition of MTP leads directly to decreases in circulating levels of apo B-containing lipoproteins, including LDL-C (see Figure 5). Lomitapide directly inhibits the production of LDL-C, unlike current LLDs, which work by clearing LDL-C via up-regulation of the LDL receptor.

1.3 Lomitapide Clinical Development Program

Lomitapide was granted orphan drug designation for the treatment of HoFH and has been studied in a comprehensive clinical development program over more than 15 years. Evidence of the clinical efficacy and the safety of treatment have been consistently generated from Phase 1 studies in healthy subjects, Phase 2 studies in subjects with hypercholesterolemia and other CV risk factors, and in Phase 2 and Phase 3 studies in subjects with HoFH. An overview of these studies is provided in Table 2. More details on the lomitapide clinical development program are provided in Section 2.3.

1.4 Efficacy and Safety of Lomitapide

The primary efficacy and safety data to evaluate the use of lomitapide in subjects with HoFH come from the Phase 3 study UP1002/AEGR-733-005 and a follow-on, long-term extension study, AEGR-733-012. Supportive efficacy and safety data in the HoFH population are provided from a Phase 2 proof-of-concept study, UP1001.

In addition to the results in the HoFH population, efficacy and safety data are available from Phase 2 placebo- and/or active-control clinical trials in subjects with elevated LDL-C and other CV risk factors.

1.4.1 Key Design Features of the Phase 3 Study UP1002/AEGR-733-005

The pivotal study, UP1002/AEGR-733-005, was a Phase 3, open-label, single-arm, 78-week clinical trial designed to evaluate both the efficacy and long-term safety of lomitapide in subjects with HoFH at an individually-defined maximum tolerated dose. The protocol for the Phase 3 HoFH trial was designed as a single-arm study in order to maximize the number of subjects exposed to long-term active treatment in this rare disease. Details of the Phase 3 study design, including a schematic display (Figure 8) and a summary of the eligibility criteria, are provided in Section 4.

The primary objective of the Phase 3 study was to evaluate the efficacy of lomitapide coadministered with other LLTs as defined by percent change from baseline in LDL-C after 26 weeks of treatment. Subjects were required to be on a stable lipid-lowering regimen, including oral medications and apheresis, and were placed on a diet supplying < 20% energy from fat for at least 6 weeks prior to study entry. The low-fat diet was instituted to improve GI tolerability during lomitapide treatment. Subjects were counseled to follow the low-fat diet throughout the study.

Study drug was initiated at 5 mg/day for 2 weeks, and then escalated to 10, 20, 40, and 60 mg/day at 4-week intervals based on safety and tolerability. Subjects were instructed that all concomitant LLTs should not change for ≥6 weeks prior to the start of lomitapide through the Week 26 on-treatment assessment (primary efficacy endpoint). Following completion of the 26-week Efficacy Phase, subjects entered the 52-week Safety Phase during which they received their maximum tolerated dose of lomitapide defined at Week 26. During the Safety Phase, if LDL-C levels dropped below 100 mg/dL, concomitant LLTs, including LDL apheresis frequency or statin dose, could be decreased.

Following completion of 78 weeks of treatment in Study UP1002/AEGR-733-005, subjects were eligible to enter the long-term efficacy and safety extension Study AEGR-733-012 to receive continued treatment with lomitapide beyond 78 weeks. Subjects who did not enroll into the extension study discontinued lomitapide at Week 78 and returned for a final follow-up visit at Week 84.

1.4.2 Disposition, Baseline Characteristics and Exposure to Treatment in the Phase 3 Study UP1002/AEGR-733-005

A total of 29 subjects with genetically-confirmed HoFH were treated with lomitapide in the Phase 3 study. Twenty-three subjects completed treatment through the primary efficacy endpoint at Week 26 and 6 subjects discontinued prior to that time. Reasons for discontinuation were adverse events (AEs) in 4 subjects (see Section 1.4.4), and withdrawal of consent and noncompliance with protocol procedures in 1 subject each. All 23 subjects who completed the

Efficacy Phase at Week 26 entered the Safety Phase and completed the study through Week 78 of treatment.

The mean age of the 29 subjects was 30.7 years and ranged from 18 to 55 years. Just over half the subjects were male (55%) and the majority were Caucasian (86%).

Overall, 27 (93%) of the 29 subjects were receiving statins at study entry, primarily rosuvastatin and atorvastatin; 22 (76%) were receiving ezetimibe in combination with a statin. The majority of subjects were receiving the maximum approved doses of statins (Section 5.5.1). Eighteen subjects (62%) were undergoing LDL-C apheresis.

Despite treatment for their underlying hypercholesterolemia with maximum tolerated doses of statins, with or without ezetimibe, and the use of apheresis in most subjects, mean levels of LDL-C were markedly elevated at baseline (336 mg/dL). LDL-C levels remained stable during the Run-in Phase of the study; mean percent change from Screening to Week 0 in LDL-C was -1.2%.

Subjects who entered this trial had evidence of significant CV morbidity despite maximal lipid-lowering therapy with 27 of the 29 subjects reporting CVD at study entry (Section 5.5.1). Ten subjects (34%) had undergone coronary artery bypass graft (CABG) surgery, including 3 subjects under the age of 8 at the time of open-heart surgery.

Mean duration of lomitapide treatment was 444 days (14.6 months); 23 of the 29 subjects received >1 year of treatment with lomitapide in this Phase 3 study.

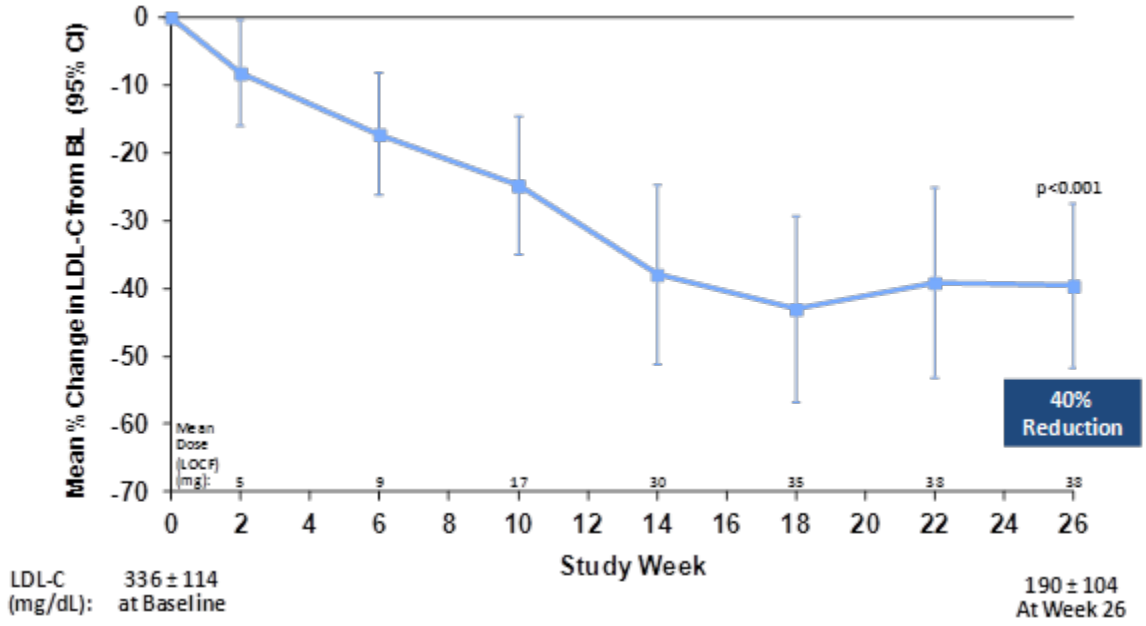
1.4.3 Efficacy Results in the Phase 3 Study UP1002/AEGR-733-005

The primary population for analysis of efficacy was the intent-to-treat (ITT) population, which included all 29 subjects who received lomitapide. Paired t-tests were used to test the hypothesis of no percent change from baseline. Missing data due to subject withdrawal were imputed using a last observation carried forward (LOCF) method to the primary endpoint of Week 26. With the agreement of the Food and Drug Administration (FDA), efficacy data through Week 56 were analyzed and included in the New Drug Application (NDA).

Treatment with lomitapide significantly reduced LDL-C levels in subjects with HoFH with reductions observed after 2 weeks on treatment and a mean reduction of 40% to the primary efficacy time point of Week 26.

Figure 1 presents mean percent changes from baseline in LDL-C at each study week through the primary efficacy time point of Week 26 using LOCF methods. Mean LDL-C decreased from 336 mg/dL at baseline to 190 mg/dL at the end of the Efficacy Phase, representing a clinically meaningful and statistically significant mean percent change of -40% ($p< 0.001$) (see also Table 10).

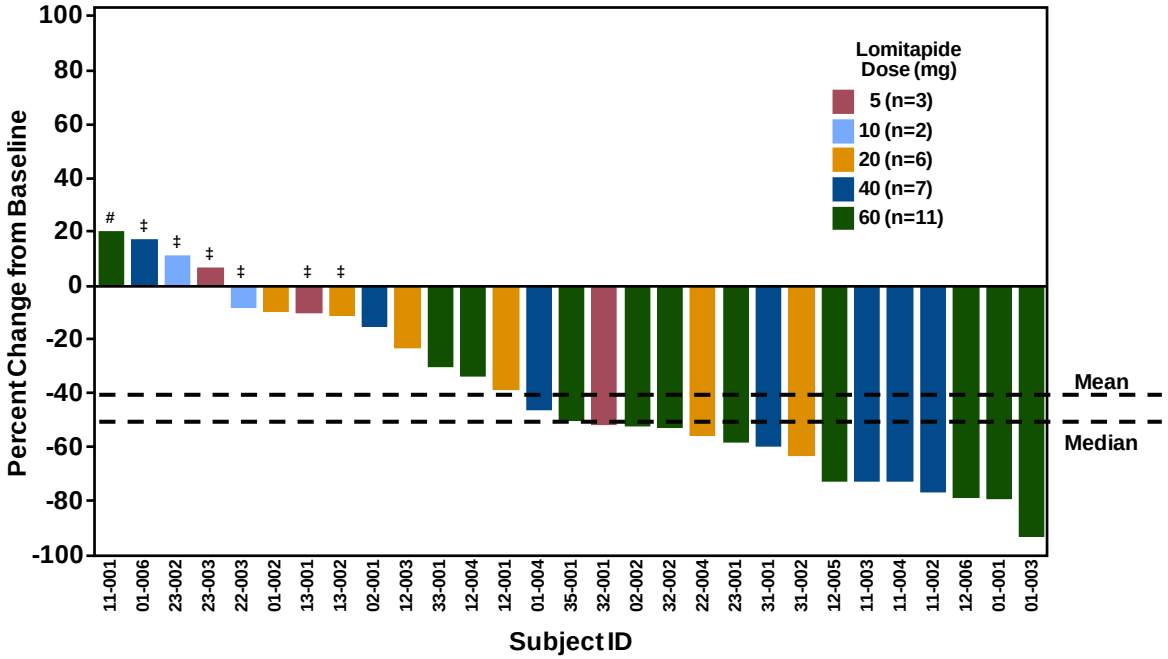
Figure 1: Mean (95% CI) Percent Changes from Baseline in LDL-C in the Phase 3 Study UP1002/AEGR-733-005 through the Primary Endpoint of Week 26 using LOCF (ITT Population, N=29)



The majority of subjects in the study achieved substantial reductions in LDL-C levels by Week 26.

Figure 2 presents a waterfall plot of percent change from baseline in LDL-C to Week 26 or the last assessment for subjects who discontinued prior to that time point. Overall, 16 (55%) of the 29 subjects had a reduction in LDL-C of >40% at Week 26 with 15 (52%) achieving a ≥50% reduction.

Figure 2: Waterfall Plot of Percent Change from Baseline in LDL-C at Week 26/LOCF by Subject (ITT Population)



Subject was a responder after Week 26
‡ Subject discontinued from treatment prior to Week 26
Note: Dose is the final titrated dose administered at Week 26
Note: One subject (Subject 33-001), who is depicted as receiving 60 mg, received a maximum dose of 80 mg at Week 26 outside of protocol required criteria.

The reductions in LDL-C were maintained over 1 year of treatment.

Persistence of the lipid-lowering effect was observed between Weeks 26 and 56 of treatment (see Figure 11), during the time when subjects were permitted to modify their background LLTs. Among the 23 subjects who completed the Efficacy Phase and entered the Safety Phase of the study, the mean percent change from baseline in LDL-C at Week 26 was -50% and at Week 56 was -44%.

Subjects were able to meet target LDL-C treatment goals, which is rarely seen in clinical practice.

The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) has recommended an LDL-C treatment target of <100 mg/dL for subjects at high-risk of CVD (NCEP, 2001) and a target of <70 mg/dL for subjects at very high-risk, often requiring LDL-C reductions of >50% (Grundy, 2004).

More than half (55%, 16 of 29) of the subjects were able to achieve an LDL-C level <100 mg/dL, including 9 (31%) with LDL-C <70 mg/dL at one or more time points during treatment with lomitapide. Achievement of these target goals is rarely seen in subjects with HoFH.

Consistent reductions from baseline were observed in the secondary efficacy variables of total cholesterol, apo B, non-high-density lipoprotein cholesterol (HDL-C) and triglycerides.

Clinically meaningful and statistically significant mean percent changes from baseline to the Week 26/LOCF assessment also were noted for total cholesterol, apo B, non-HDL-C and triglycerides (see Figure 15). These reductions were maintained over 1 year of treatment.

Treatment with lomitapide did not adversely affect HDL-C or apolipoprotein AI (apo AI) levels.

In Study UP1002/AEGR-733-005, mean HDL-C initially decreased to Week 26/LOCF (see Figure 17). By Week 56, mean HDL-C was at baseline level with a mean percent change from baseline of 1%. Similar results were noted for apo AI.

As evidence of the lipid-lowering effect of lomitapide, some subjects on the study stopped or permanently reduced the frequency of apheresis after Week 26.

Overall, 13 subjects who entered the Safety Phase were on apheresis. Among these 13 subjects, 4 (31%) either stopped apheresis (n=3) or permanently increased (n=1) the interval between apheresis treatments. Of note, between Weeks 56 and 78, 2 additional subjects increased the interval between treatments.

Efficacy Conclusions

The significant reduction in LDL-C and other apo B-containing lipoproteins observed in subjects with HoFH in the Phase 3 study reflect the pharmacodynamic effect of lomitapide based on the following factors:

- The design of the Phase 3 study included elements to control potential confounding factors, including: 1) a Run-in Phase for stabilization of background LLTs and the low fat diet; 2) determination of baseline LDL-C based on an average of 2 measures (Week -2 and Day 0); and 3) a requirement that all LLTs remain stable prior to determination of the primary endpoint at Week 26.
- There was minimal change in LDL-C levels during the Run-in Phase of the study indicating that stabilization of LLTs and the institution of the low-fat diet during this phase had no meaningful impact on lowering LDL-C levels in these subjects.
- Following initiation of lomitapide treatment, there was a rapid and significant reduction in LDL-C by Week 2. The reduction continued as the dose was escalated. The magnitude of the reduction at Week 26, following escalation to each subject's maximum tolerated dose, was substantial with a mean percent change in LDL-C using LOCF methods of -40%.

Furthermore, the significant reduction in LDL-C and other apo B-containing lipoproteins observed in subjects with HoFH in the Phase 3 study is supported by data from Phase 2 studies:

- In the Phase 2 HoFH study UP1001 that evaluated lomitapide monotherapy, a mean reduction of 51% was observed after 16 weeks on lomitapide. Notably, there was a rapid return to baseline levels following discontinuation of lomitapide (see Section 5.6.1).
- In Phase 2 studies conducted in subjects with elevated LDL-C and other CV risk factors, statistically significant reductions in LDL-C were observed relative to placebo (see Section 5.6.3). The demonstration of efficacy in subjects with hypercholesterolemia would be expected to predict response in subjects with HoFH as the mechanism of action of lomitapide is independent of LDL receptor function.

Given the fact that elevations in LDL-C mediate CVD in HoFH patients, reduction of LDL-C in these patients is expected to confer clinical benefit.

1.4.4 Safety of Treatment with Lomitapide

Lomitapide has been evaluated in a comprehensive series of nonclinical studies and in clinical studies in which nearly 1000 subjects have been exposed to oral lomitapide at doses ranging from 1 to 200 mg (see Table 2). An overview of the safety of treatment with lomitapide, including a detailed discussion of the results of nonclinical studies and the safety of treatment across multiple-dose clinical trials, is provided in Section 6. A brief summary of the results of safety in the Phase 3 HoFH study are provided in this section.

Table 17 in Section 6.6.1 presents the most commonly reported treatment-emergent adverse events (TEAEs) during the Phase 3 HoFH study. Note that at the time of submission, safety data included in the NDA was through Week 56 of treatment; the data were updated in the 4-month Safety Update Report to include information through Week 78 and data from the extension study.

Consistent with the mechanism of action of lomitapide, the safety profile was characterized principally by GI disturbances and elevations in liver transaminase levels, both of which were managed by dose reduction or interruption.

A total of 27 (93%) of the 29 subjects experienced at least 1 TEAE during the Phase 3 study. The most commonly reported TEAEs were GI events, including diarrhea (79%), nausea (66%), vomiting and dyspepsia (each 35%), abdominal discomfort (31%), abdominal pain (28%), and constipation and flatulence (each 21%). Other events reported in 20% or more of subjects were chest pain and decreased weight (each 24%), and influenza (each 21%).

There were no deaths reported during the study. Serious adverse events (SAEs) were reported in 3 subjects, including acute coronary syndrome, angina pectoris and lower respiratory infection in 1 subject, coronary artery arteriosclerosis in 1, and menorrhagia requiring hysterectomy in 1. None of the SAEs were assessed by the investigator as related to treatment with lomitapide.

Four (14%) of the 29 subjects experienced TEAEs leading to treatment discontinuation, primarily GI disturbances. One subject discontinued because of abdominal pain, nausea, and diarrhea; and 1 subject each discontinued because of diarrhea, gastroenteritis, and headache.

Treatment with lomitapide is associated with transient and reversible increases in transaminase levels, including elevations >5×upper limit of normal, without clinically meaningful concomitant increases in serum bilirubin or alkaline phosphatase and with no associated symptoms.

During the Phase 3 trial, the effects of lomitapide on aminotransferase levels during long-term exposure were investigated. An algorithm for dose modification based on liver function test (LFT) criteria (dose reduce when alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) >5× upper limit of normal (ULN); interrupt/stop if >10×ULN) was utilized. A Data Safety Monitoring Board (DSMB) reviewed safety data, including hepatic events during the trial. The conclusion of the committee during each review of the data was that the balance of benefit and risk favored the continued use of lomitapide for HoFH subjects. The Committee was reassured regarding the hepatic profile given the absence of Hy's law cases, acute liver failure, histological evidence of progressive fatty liver changes, or other signs of hepatotoxicity.

The maximum post-baseline LFT values through Week 78/end of treatment relative to the upper limit of the normal range are summarized in Table 1 for the 29 subjects in the Phase 3 trial.

Table 1: Maximum Abnormal Liver Function Test Results Post First Dose, Study UP1002/AEGR-733-005 (Safety Population)

ALT AND/OR AST:[a]	TOTAL SUBJECTS (N=29)
≤2×ULN	15 (51.7)
>2 to ≤3×ULN	4 (13.8)
>3 to ≤5×ULN	6 (20.7)
>5 to ≤10×ULN	3 (10.3)
>10 to ≤20×ULN	1 (3.4)
>20×ULN	0

Note: Includes data through Week 78/end of treatment
[a] Only values greater than the Baseline value were considered.

Overall, 4 subjects developed ALT and/or AST elevations > 5×ULN during the study (see Figure 19). In all 4 subjects, the initial elevations in transaminase levels occurred during the Efficacy Phase of the study, i.e., during the first 26 weeks of treatment. Dose interruption or reduction was used per protocol algorithm to achieve aminotransferase levels <5×ULN in all 4 subjects. The transaminase levels decreased rapidly (7 to 28 days) following dose modification. Three of the 4 subjects with elevations >5×ULN were re-challenged successfully at the dose associated with initial ALT/AST elevation. The fourth subject had lomitapide reduced to a lower dose. Of note, alcohol intake was reported outside of protocol limits in 3 of these 4 subjects.

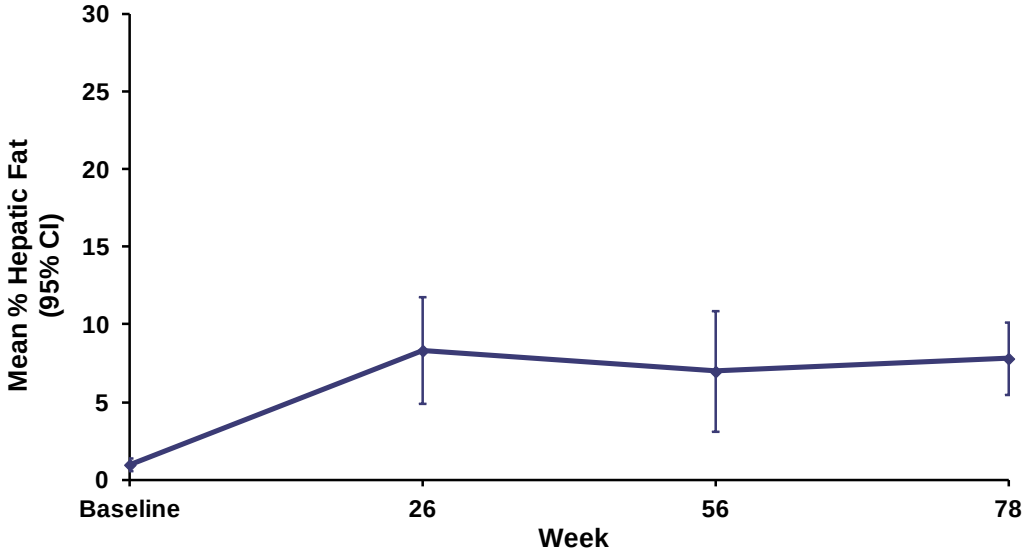
Note that 1 subject had an elevation in ALT to 24×ULN during the extension Study AEGR-733-012. This subject had corresponding elevations in AST to 13×ULN; bilirubin levels were within the normal range. The elevations were reported as a SAE and occurred in the setting of concomitant medications known to cause liver injury (agomelatine and clarithromycin) which may have played a role in the event.

Increases in hepatic triglyceride content were observed based on evaluation by nuclear magnetic resonance spectroscopy (NMRS) or magnetic resonance imaging (MRI). Rapid reversal of hepatic fat accumulation was observed when subjects discontinued lomitapide.

Steatosis has been observed in some subjects due to the pharmacodynamic effect of lomitapide on MTP. Mean hepatic fat levels over time for subjects in the Phase 3 Study UP1002/AEGR-733-005 are provided in Figure 3. Results are based on evaluation by nuclear magnetic resonance spectroscopy (NMRS). A mean absolute increase in percent hepatic fat of 8% was observed at the Week 26 assessment. Little change was observed from Week 26 to Weeks 56 and 78 with mean absolute changes from baseline in percent hepatic fat of 6% and 7%, respectively.

Hepatic steatosis is quite prevalent in Western populations. Hepatic fat is seen on ultrasound examination among 46% of middle-aged adults, is even more common among subjects with Type 2 diabetes (69% of cases), and occurs in more than 50% of dyslipidemic subjects. When NMRS is used to detect hepatic fat, the incidence of steatosis has been estimated to occur in 31% of the general population in the United States (US) (Szczepaniak, 2005). The estimated world-wide prevalence of non-alcoholic fatty liver disease (NAFLD) is approximately 20% (range 6-33%), with the prevalence of non-alcoholic steatohepatitis (NASH) estimated to be 3-5% (Chalasani, 2012). Histologic progression from simple steatosis to NASH in patients with obesity and diabetes is uncommon, and when it does occur, takes many years (Chalasani, 2012). It is of note that liver transplant donors with up to 30% steatosis have demonstrated acceptable graft survival.

Figure 3: Mean (95% CI) Absolute Percent Hepatic Fat Based on NMRS in Study UP1002/AEGR-733-005 (Subjects with Baseline and Post-baseline Data Available)



	Baseline	26	56	78
N:	22	21	20	20
Mean (%):	0.97	8.32	6.97	7.80
Range (%):	0 to 3.8	0.8 to 33.6	0.4 to 37.7	0.6 to 19.0

In 20 (87%) of the 23 subjects in the Phase 3 study with baseline and post-baseline hepatic fat assessments, all measurements were <20%. Three subjects (13%) had hepatic fat measurements >20%, including 2 with measurements >25%; all 3 of these subjects had ALT and/or AST elevations >5×ULN during the study. The remaining subject with transaminase elevations >5×ULN did not have hepatic fat assessed by NMRS as the subject was contraindicated for this procedure due to a metal heart valve.

1.5 Risk Mitigation

Aegerion is committed to ensuring safe and appropriate use of lomitapide, and has proposed a risk evaluation and mitigation strategy (REMS) as part of the planned risk mitigation activities (see Section 7).

The goals of the REMS are: 1) 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; and 2) to limit access to therapy with lomitapide to patients in whom therapy with lomitapide is medically appropriate. As proposed, all health care providers (HCPs) who prescribe lomitapide will be required to be certified by the Sponsor. Further, the Sponsor will distribute lomitapide to a limited number of specialty pharmacies that are certified and agree to follow the REMS requirements.

1.6 Future Clinical Development Plans

In order to continue to collect information on identified and potential risks of lomitapide treatment, the Sponsor will conduct a prospective observational cohort study (Registry) focused on hepatic safety, pregnancy outcomes (if use in pregnancy occurs despite safe use advice), malignancies of the liver and small intestine, and other safety variables.

The Sponsor plans to conduct a clinical trial in pediatric subjects with HoFH (age 8 to 17 inclusive) following approval of lomitapide in the adult HoFH patient population. The details of this proposed clinical trial protocol will be discussed and agreed with the FDA prior to initiation of the study.

1.7 Benefits and Risks Conclusions

Hypercholesterolemia caused by HoFH is difficult to treat, and currently available options are inadequate as evidenced by the unsatisfactory baseline LDL-C levels and history of significant CV morbidity on maximum tolerated therapy observed in the lomitapide clinical trials and reports in the clinical literature. Despite pharmacological intervention (including maximally tolerated doses of statins), and, in most subjects, the addition of frequent LDL apheresis, HoFH subjects entered the lomitapide Phase 3 study with average LDL-C levels well above consensus targets. This elevated level of LDL-C exposes patients to a continuous high risk of serious or fatal CV events such as MI and/or stroke. Furthermore, many of these young patients have already experienced these events, and have undergone CV interventions, including coronary angioplasty, stenting, and coronary bypass surgery. The highly unsatisfactory and perilous situation in which these patients find themselves demands the addition of further intervention to reduce LDL-C levels, ideally to targets recommended for patients at high risk for CV events.

Lomitapide treatment reduced mean LDL-C levels in the Phase 3 study by 40% in the ITT population and 50% in the completer population. With appropriate information on safe and appropriate use, the physicians who manage these patients will be well positioned to optimize the benefit that can be derived from the dramatic reductions in LDL-C achievable with lomitapide treatment while closely monitoring safety and tolerability. In this context, lomitapide treatment represents a potential major advancement in the treatment of a devastating disease through modification of a risk factor that is currently uncontrolled by available treatment interventions, supporting a favorable benefit-risk assessment for its use in this high-risk patient population.

2 INTRODUCTION

2.1 Homozygous Familial Hypercholesterolemia

2.1.1 Overview of the Disease

Homozygous familial hypercholesterolemia (HoFH) is a rare, life-threatening, autosomal co-dominant genetic disease characterized by marked elevations in plasma levels of LDL-C and markedly premature atherosclerotic CVD. The disease is typically caused by homozygosity or compound heterozygosity for loss-of-function mutations in the *LDLR* gene encoding the LDL receptor protein, leading to markedly reduced or absent LDL receptor function. Heterozygous FH (HeFH) is caused by a mutation in one allele of the LDL receptor gene and is associated with plasma LDL-C levels and CVD risk intermediate between HoFH and normal individuals. Phenocopies of HoFH and HeFH can result from mutations in other genes that influence LDL receptor function, including apo B (the major ligand for the LDL receptor), proprotein convertase subtilisin/kexin type 9 (PCSK9; a protein that controls cell surface LDL receptor expression), and the *LDLRAP1* gene encoding the autosomal recessive hypercholesterolemia (ARH) LDL receptor adapter protein (Hegele, 2001; Marais, 2004). These proteins can alter the function or expression of the LDL receptor or adversely affect LDL binding to the LDL receptor.

The prevalence of loss-of-function mutations in both alleles of the LDL receptor ("homozygous familial hypercholesterolemia" or HoFH) has been calculated to occur in ~1 in 1 million persons (Moorjani, 1993). This calculation is based on the estimated prevalence of 1 in 500 for HeFH (Goldstein, 2001). The prevalence of HoFH has been reported to be 10 times higher in certain populations with a presumed founder effect (Khachadurian, 1988; Goldstein, 2001). The frequency of HoFH exceeds 0.2% in Ashkenazi Jews of Lithuanian descent, Afrikaners, French Canadians, Christian Lebanese, Druze, Sephardic Jews, and Finns (Hobbs, 1992).

Patients with HoFH have markedly impaired removal of LDL-C from the circulation resulting from reduced or absent hepatic LDL receptor activity. The hepatic LDL receptor plays a critical role in regulating the concentration of LDL-C in the blood by binding apo B to LDL and mediating its uptake, internalization, and lysosomal degradation. In the absence of functional LDL receptors, the uptake of LDL from the blood is impaired and concentrations are extremely elevated. In HoFH, circulating LDL-C levels are highly variable depending on the nature of the LDL receptor mutations and other factors. Patients with HoFH have been classified as *receptor negative* (mutations result in elimination of LDL receptor activity which is measured as < 2% of normal activity on skin fibroblasts) or receptor defective (mutations result in some residual LDL receptor activity in the range of 2 to 20% on skin fibroblasts). Patients with receptor-negative HoFH have substantially higher plasma levels of LDL-C (often >750 mg/dL) than patients with receptor-defective HoFH (often 400-600 mg/dL), and as discussed below, develop atherosclerotic CVD at an earlier age. The specific importance of the hepatic LDL receptors in

maintaining LDL homeostasis was demonstrated by the fact that liver transplantation in a patient with HoFH resulted in near normalization of LDL-C levels in the blood (Starzl, 1984).

Current therapies for reducing LDL-C levels, including statins, work largely through upregulation of the LDL receptor in the liver. Thus, patients with HoFH who lack functional LDL receptor activity generally respond very poorly to these therapies. However, patients with receptor-defective HoFH who have some residual LDL receptor activity may have some modest reduction in LDL-C with maximal conventional therapy. Thus, patients with HoFH even with maximal pharmacologic LLDs generally have LDL-C levels >300 mg/dL (Gagne, 2002). Consistent with these observations, the mean baseline LDL-C in the Phase 3 lomitapide study was 336 mg/dL despite optimal medical therapy, including the use of statins, ezetimibe, bile acid sequestrants, and, in 62% of subjects, LDL apheresis.

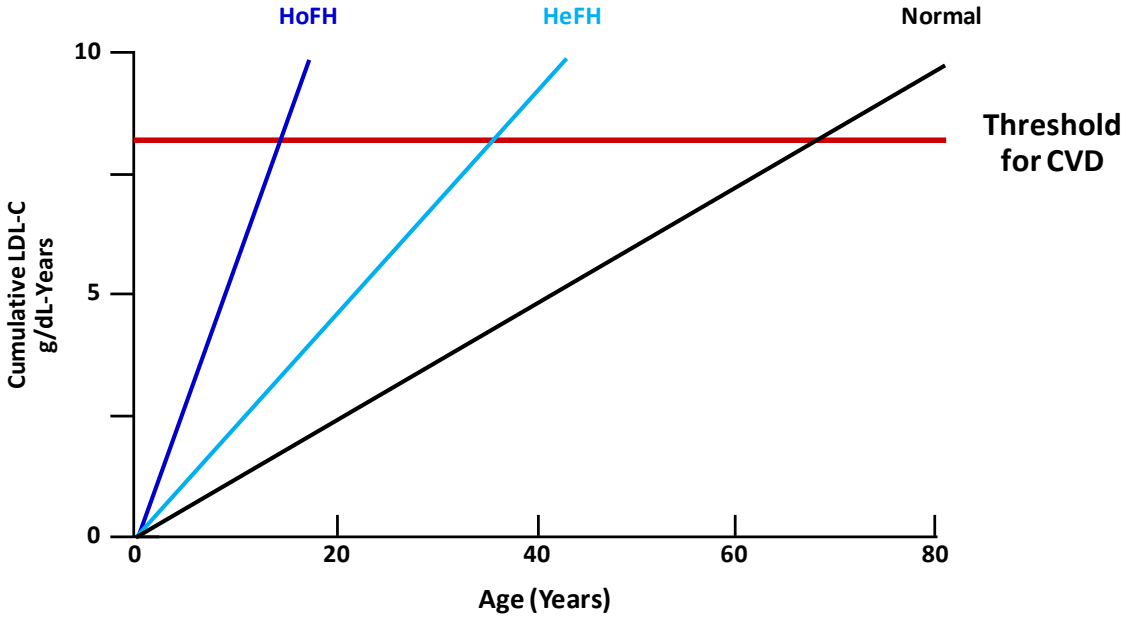
2.1.2 Impact of Elevated LDL-C Levels on Atherosclerotic Cardiovascular Disease

Markedly elevated LDL-C levels are the direct consequence of the primary defect HoFH, and lead to the premature onset of cardiovascular disease.

As a direct consequence of absent or severely reduced LDL receptor function leading to markedly elevated LDL-C blood levels, patients with HoFH develop dramatically early and severe atherosclerotic CVD and often, early cardiac-related death. Symptomatic CVD often presents during the first 2 decades of life, and includes atherosclerosis in the coronary arteries, the carotid arteries, the aorta and aortic valve, and the peripheral vasculature, often leading to heart attack, stroke, and death (Kwiterovich, 1974; Buja, 1979; Moorjani, 1993; Marais, 2004). Early onset of atherosclerosis is generally accompanied by accelerated disease progression, even in the early teenage years (Kolansky, 2008). If untreated, most HoFH patients do not survive past age 30 due to death from CVD (Buja, 1979; Hobbs, 1992; Beigel and Beigel, 2009).

The early development of CVD in patients with HoFH gave rise to the concept of cumulative lifetime exposure to LDL-C as a determinant of age of onset of CVD. This concept is illustrated in Figure 4, which is adapted from a review by Horton, Cohen and Hobbs (Horton, 2009) and shows the relationship between life-time exposure to LDL-C expressed as grams of cholesterol per year and the onset of CVD for patients with HoFH relative to persons with HeFH and those with normal functioning LDL receptors. As shown, by their early teenage years, patients with HoFH have an LDL-C burden surpassing the threshold for CVD that is similar to subjects who are ~70 years of age with normal functioning LDL receptors and average lifetime plasma LDL-C. Persons with HeFH who have intermediate levels of LDL-C cross the threshold for CVD at an age intermediate between HoFH and normal subjects.

Figure 4: Conceptual Relationship Between Cumulative LDL-C Exposure, Cardiovascular Disease Risk and Age



Source: Adapted from Horton, et al. (Horton, 2009).
Data to support the diagram: HoFH and HeFH (Goldstein, 2001) and normal subjects (Hickman, 1998; NCEP, 2002); threshold for CVD. The horizontal red line represent a theoretical threshold of the cumulative LDL exposure required for development of CHD; the height of the red line is lower in the presence of additional risk factors (e.g., smoking, diabetes, hypertension).

Further evidence that elevated levels of LDL-C are the central causal factor in the onset and severity of CVD in patients with HoFH is substantiated by the observation that patients with receptor-negative HoFH, who have much higher levels of LDL-C, develop severe CVD at a considerably earlier age than patients with receptor-defective HoFH (Goldstein, 2001). For example, one study carefully compared 11 patients with receptor-negative HoFH due to a 10 kb gene deletion to 10 patients with receptor-defective HoFH due to a missense mutation in exon 3, and found that the receptor-negative patients not only had substantially greater LDL-C levels (mean 1,030 mg/dL vs. 621 mg/dL) but also died of coronary disease at a substantially earlier age (mean 12.7 years vs 23.6 years) (Moorjani, 1993). These data strongly support the concept that LDL-C is a causal mediator of CVD in HoFH patients, and that a reduction in LDL-C, even if not to "normal" levels, would be expected to reduce the risk of CVD.

Familial hypercholesterolemia due to LDL receptor mutations is not the only genetic condition in which genetically-elevated LDL-C is associated with premature CVD. For example, familial defective apo B-100 due to mutations in the LDL receptor binding region of apo B causes impaired LDL uptake and increased plasma levels of LDL-C, and has been firmly linked to increased risk of premature CAD (Shen, 2010). Indeed, the majority of genetic variants associated with plasma LDL-C levels are also associated with CAD. A recent comprehensive study utilizing Mendelian randomization indicated unequivocally that single nucleotide

polymorphisms associated with reduced levels of LDL-C are also associated with reduced CAD and those associated with increased LDL-C are associated with increased CAD (Voight, 2012). This analysis strongly supports the concept the LDL-C is causally related to risk of CVD.

A comprehensive body of data that support the causality of LDL-C in atherosclerotic CVD is derived from interventional studies in which LDL-C reduction leads to decreased CV risk. The most extensive body of interventional data involve the dozens of randomized clinical trials with statins (NCEP, 2001; Grundy, 2004; Baigent, 2005; Baigent, 2010). The Cholesterol Clinical Trialists Collaboration has shown clearly that the magnitude of LDL-C reduction with statin therapy is strongly associated with the magnitude of CAD risk reduction. Data from a large meta-analysis in 2005 showed that lowering LDL-C by 38 mg/dL with standard statin therapy reduces the 5-year incidence of major coronary events, coronary revascularization, and stroke by about one fifth and that this relationship between LDL-C reduction and CVD risk reduction is linear (Baigent, 2005). Since that time, several trials have investigated the effects of more intensive statin therapy on CV outcomes. An updated meta-analysis by the same group in 2010 reported that additional reduction in LDL-C by 77 to 116 mg/dL would further reduce risk by about 40 to 50% (Baigent, 2010). The overall body of data from statin intervention trials overwhelmingly supports the causal link between LDL-C reduction and CVD risk reduction.

Importantly, statins are not the only intervention that has been shown to reduce CV events in rigorous randomized controlled trials. In the pre-statin era, the Coronary Drug Project showed that immediate-release niacin reduced cholesterol levels as well as CV events and long-term mortality (Canner, 1986). The Lipid Research Clinics Coronary Primary Prevention trial showed that the bile acid sequestrant cholestyramine, which works solely within the gut lumen to lower plasma LDL-C, significantly reduced CV events (The Lipid Research Clinic1984a; The Lipid Research Clinic1984b). The POSCH trial, a randomized controlled trial of partial ileal bypass in patients with severe hypercholesterolemia (primarily familial hypercholesterolemia) achieved mean reductions in LDL-C of 38% and reduced major coronary events by 35% compared with the control group (Buchwald, 1990). Thus, despite the putative pleiotropic effects of statins, these data indicate that reducing LDL-C through several different types of interventions reduces CVD risk and strengthens the causal link between LDL-C reduction and CVD risk reduction.

The current approach of choice in patients with HoFH and other forms of severe refractory hypercholesterolemia is LDL apheresis, which involves mechanical filtration of LDL from the blood that is repeated on a weekly or bi-weekly basis (Section 2.1.3). While no adequately powered randomized controlled trials of its effect on CVD events have been performed, several groups have independently assessed its effects on CVD events through rigorous observational approaches. The frequency of CV events in each patient is assessed for a period of time prior to starting LDL apheresis and then for a similar period of time after starting the procedure. These studies have produced findings that suggest a substantial reduction in CV events associated with

initiation of LDL apheresis (Winters, 2012). For example, an analysis by Dr Rader's group in 34 LDL apheresis patients found that initiation of LDL apheresis was associated with a 3.2-fold reduction in CV events and a 20-fold reduction in CV interventions (Sachais, 2005). Another study published in 2010 found that major CVD events decreased from 7% per patient per year prior to LDL apheresis to 1.2% per patient per year after starting LDL apheresis (Koziolek, 2010). While not randomized, these studies support the clinical benefit of this mechanical approach to reducing LDL-C in reducing CV events.

In summary, there is an abundance of observational, genetic, and randomized controlled trial data that converge to unequivocally support the concept that LDL is a causal factor in the development of atherosclerotic CVD and that intervention to reduce LDL-C reduces CV events. Importantly, the relationship between LDL-C reduction and CV event reduction appears to be continuous, such that the expectation is that reduction of LDL-C by 40 to 50% in HoFH, even if it does not 'normalize' the LDL-C level, would be expected to provide clinical benefit. Indeed, receptor-negative HoFH patients have the highest LDL-C and the highest CVD risk, receptor-defective HoFH patients have somewhat lower LDL-C and lower CVD risk, and HeFH patients have yet lower LDL-C levels and yet lower CVD risk.

2.1.3 Treatment Goals in Patients with HoFH and Current Treatment Options

The primary goal of therapy for patients with HoFH involves lowering LDL-C levels, thereby delaying the progression of CVD. Unfortunately, dietary intervention, i.e., use of a low-fat diet, is ineffective in patients with this disease due to the markedly elevated levels of LDL-C (Rader, 2003) and patients with HoFH are minimally responsive to conventional LLDs and thus, the effects of available pharmacological treatments are limited and almost always insufficient. Despite the generally poor response, aggressive drug therapy is usually initiated in patients with HoFH upon diagnosis. Pharmacologic options include HMG-CoA reductase inhibitors (statins), cholesterol absorption inhibitors such as ezetimibe, bile-acid sequestrants, and, less commonly, niacin.

In subjects with hypercholesterolemia who do not have HoFH, LDL-C reductions of up to approximately 60% have been reported for the top doses of the most potent statins (atorvastatin, 80 mg; rosuvastatin, 40 mg) (Vaughan and Gotto, 2004). However, because statins require a functioning LDL receptor, patients with HoFH are relatively refractory to the effects of statins, with LDL-C reductions ranging from 0 to approximately 30% depending upon the nature of the LDL receptor defect (Lipitor [Package Insert], 2009; Crestor [Package Insert], 2010; Zocor [Package Insert], 2010; Zocor [Summary of Product Characteristics], 2011; Lipitor [Summary of Product Characteristics], 2011; Crestor [Summary of Product Characteristics], 2011). Nonetheless, statins remain the standard pharmacologic therapy for these subjects due to the lack of other effective agents. The outcome benefits of statins in large clinical trials are largely attributed to the LDL-C-lowering effects (Baigent, 2005; Robinson, 2005); thus, these benefits

are almost certainly reduced in patients with HoFH who continue to exhibit high LDL-C levels despite aggressive lipid-lowering therapy. The addition of ezetimibe or bile-acid sequestrants (e.g., colestipol, cholestyramine) can result in incremental LDL-C lowering in patients with HoFH in the range of approximately 10% to 20% above those achieved with statins (Gagne, 2002; Marais, 2004) but this level of reduction falls short of established LDL-C goals in patients with HoFH.

Patients with HoFH may be treated surgically. Surgical intervention such as portacaval shunt (Forman, 1982; Bilheimer, 1989) and ileal bypass (Deckelbaum, 1977) have resulted only in partial and transient LDL-C lowering and are now rarely used due to disappointing durability of efficacy and problematic side effects.

The most extreme treatment option is liver transplantation, which offers potential long-term benefit for children (Schmidt, 2008). Owing to the shortage of suitable donor organs and the risks associated with the surgical procedure, as well as the requirement for lifelong immunosuppressive therapy, liver transplantation is not widely used for patients with HoFH.

As previously mentioned, LDL apheresis is a mechanical filtration of the blood to selectively remove LDL, and is an approved and recommended therapy for patients with HoFH (Kolansky, 2008; Thompson, 2010). The procedure transiently reduces LDL-C levels by approximately 50% (Uauy, 1992; Jaeger, 2002; Thompson, 2010). There is a large body of evidence in the published scientific literature to support the safety and efficacy of LDL apheresis for the treatment of familial hypercholesterolemia (Kroon, 1996; Donner, 1997; Gordon, 1998; Moga and Harstall, 2004; Sachais, 2005; Ontario Health Technology Advisory Committee, 2007; Winters, 2012). Several clinical trials have demonstrated that lipid apheresis is associated with a greater reduction in LDL levels when compared to medication alone and many authors have reported that LDL apheresis, both with and without LLDs, has been shown to reduce total cholesterol levels, LDL-C, and lipoprotein (a) (Lp(a)), in addition to inducing atherosclerosis regression, improving myocardial blood flow and endothelial function, and in decreasing the rate of CV events (Nishimura, 1999; Matsuzaki, 2002; Bambauer, 2003; Moga and Harstall, 2004; Koga, 2005; Ziajka, 2005; Thompsen and Thompson, 2006). Additionally, when evaluating long-term safety and efficacy of LDL apheresis in children, studies have also demonstrated efficient lowering of baseline LDL-C levels (Hudgins, 2008; Palcoux, 2008; Coker, 2009). Thus, the preponderance of evidence in the medical literature supports that there is overall clinical benefit of LDL apheresis.

Although LDL apheresis lowers LDL-C levels, the effects are transient. Treatments must be repeated every 1 to 2 weeks to effect an acceptable time-averaged LDL-C reduction because LDL-C levels rebound after the procedure (Tonstad and Thompson, 2004). The interval mean values of LDL-C (time-averaged mean LDL-C levels between sequential LDL apheresis treatment procedures) for 27 patients (Palcoux, 2008) and 29 patients (Hudgins, 2008) were

calculated to be 255 mg/dL and 251 mg/dL, respectively, which remain well above target LDL-C levels supporting the need for additional therapeutic options.

While quality of life data are not available for patients with HoFH receiving LDL apheresis, it is worth noting that this therapy presents additional challenges for the patient based on its limited availability, lifelong time commitment, and requirement for frequent repetitive IV access.

In summary, a number of treatment options exist for reducing LDL-C in patients with HoFH including LLDs, LDL-C apheresis, and several surgical procedures. Yet, even with the aggressive utilization of these therapies, absent successful liver transplantation, patients with HoFH generally have LDL-C levels substantially above treatment targets due to the severity of the initial LDL-C elevations. As a result, patients frequently suffer major adverse CV events such as heart attack and stroke in adolescence and early adulthood. This aggressive and premature CVD often requires interventions such as coronary bypass surgery, coronary stenting, carotid endarterectomy, and aortic valve replacement as demonstrated in the patients enrolled in the Phase 3 HoFH study (see Section 5.5.1). Additional effective therapeutic options are urgently needed to optimize the treatment of patients with this rare, life-threatening disease.

2.2 Rationale for Use of Lomitapide in HoFH

2.2.1 Overview of Microsomal Triglyceride Transfer Protein Inhibition

MTP plays a key role in the assembly and release of apo B-containing lipoproteins, including LDL-C, and inhibition of this protein significantly lowers associated plasma lipid levels.

MTP is an intracellular lipid-transfer protein found in the lumen of the endoplasmic reticulum and is responsible for binding and shuttling individual lipid molecules between membranes (Hussain, 2003; Liao, 2003). Normal concentrations and function of MTP in the liver and intestine are necessary for the proper assembly and secretion of apo B-containing lipoproteins including very-low-density lipoprotein (VLDL) (which is converted into LDL) from the liver and chylomicrons (containing dietary cholesterol and triglycerides) from the intestine (Liao, 2003).

The development of MTP inhibitors was facilitated by the identification of patients with abetalipoproteinemia, a condition resulting from inhibition of the assembly of apo B-containing lipoproteins due to the absence of functional MTP (Stein, 2009). Abetalipoproteinemia is characterized by very low levels of VLDL and LDL and a virtually complete absence of plasma apo B (Benayoun, 2007). Individuals with abetalipoproteinemia were found to have mutations in the gene encoding MTP resulting in the loss of functional MTP protein (Wetterau, 1997).

Inhibition of MTP activity has been shown to prevent both hepatic VLDL-C and intestinal chylomicron secretion, and consequently lowers plasma lipids. Thus, it was initially considered likely that compounds that inhibit MTP would have the ability to profoundly reduce serum levels of both cholesterol and triglycerides (Wetterau, 1998). Both *in vitro* (Jamil, 1996; Bakillah,

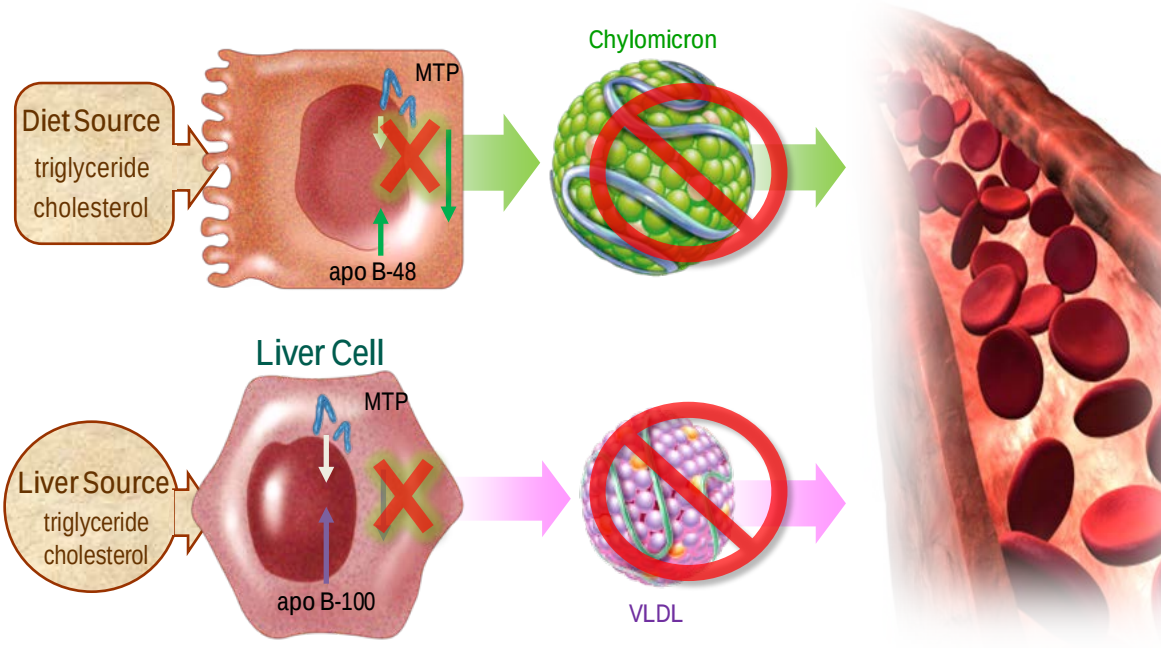
2000) and *in vivo* animal studies (Wetterau, 1998) with MTP inhibitors support the concept that inhibition of MTP results in decreased secretion of apo B-containing lipoproteins and consequent reduction of plasma cholesterol levels.

2.2.2 Overview of Lomitapide

Lomitapide inhibits lipid transfer by directly binding to MTP in the liver and intestines (Figure 5). In *in vitro* experiments using unilamellar vesicles, lomitapide inhibited rat, hamster and human MTP with an inhibitory concentration 50% (IC_{50}) of 5 to 7 nM. Kinetic studies performed as part of the Phase 2 lomitapide study in subjects with HoFH confirmed that the mechanism of the reductions seen in LDL-C was associated with a reduction in apo B output (Cuchel, 2007), thus providing supportive evidence for the mechanism of action in humans.

Since lomitapide directly inhibits production of LDL-C in the liver and chylomicron formation in the intestine (Figure 5), it is expected to result in greater enhanced efficacy in reducing LDL-C in patients with HoFH than existing therapies that require a functional LDL receptor as they target the LDL receptor pathway (e.g., statins), or only act to address cholesterol absorption in the intestine (ezetimibe).

Figure 5: Mechanism of Action of Lomitapide



2.3 Lomitapide Clinical Development Program and Regulatory History

2.3.1 Clinical Development Program

A total of 24 clinical studies have been conducted to date with lomitapide, including Phase 1, 2, and 3 studies conducted in healthy adults, adults with HoFH, adults with elevated LDL-C levels (without HoFH), adults with hepatic impairment, and adults with end-stage renal disease (ESRD) on hemodialysis. An overview of each of these 24 clinical studies, including the type of study and the population enrolled is provided in Table 2. Across these studies, a total of 1269 subject-courses of treatment were administered, including 997 courses of treatment with oral lomitapide administered as monotherapy or coadministered with another LLT (e.g., atorvastatin or ezetimibe).

Table 2: Overview of Clinical Studies in the Lomitapide Clinical Development Program

Study Type Protocol	Single-dose Studies (N_T/N_L)	Adults with Elevated LDL-C (N_T/N_L)	HoFH (N_T/N_L)	Multiple-dose DDI/ Crossover Studies (N_T/N_L)
Phase 1, PK ADME (N_T/N_L=199/137)				
CV145-001	55/37			
CV145-002		36/24 (14 days)[b]		
CV145-003	32/6[a]			
CV145-006 (ADME)	6/6			
AEGR-733-010 (ADME)	6/6			
CV145-010		18/12 (14 days)[b]		
AEGR-733-017 (Hepatic Impairment)	32/32			
AEGR-733-021 (Renal Impairment)	14/14			
Drug-drug Interaction Studies (N_T/N_L =244/241)				
CV145-005 (Food Effect)				25/25
AEGR-733-002 (Lipid-lowering drugs)				129/127
AEGR-733-013 (Warfarin)				16/16
AEGR-733-015 (Ortho-Cyclen)				28/27
AEGR-733-018 (Ketoconazole)				30/30
AEGR-733-019 (Simvastatin)				16/16
Thorough QT Study (N_T/N_L=56/56)				
AEGR-733-011				56/56

STUDY TYPE PROTOCOL	SINGLE-DOSE STUDIES (N_T/N_L)	ADULTS WITH ELEVATED LDL-C (N_T/N_L)	HOFH (N_T/N_L)	MULTIPLE-DOSE DDI/ CROSSOVER STUDIES (N_T/N_L)
Phase 2 Studies (N_T/N_L=741/534)				
CV145-009		76/38 (4 wks)[b]		
AEGR-733-001		85/56 (12 wks)[b]		
AEGR-733-003a		113/82 (8 wks)[b,c]		
AEGR-733-003b		157/104 (8 wks)[b]		
AEGR-733-004		260/227 (8 wks)[b]		
AEGR-733-006		44/21 (12 wks)[b]		
UP1001			6/6 (16 wks)[b]	
Phase 3 Studies (N_T/N_L=29/29)				
UP1002/ AEGR-733-005			29/29 (78 wks)[b]	
AEGR-733-012 (Extension)			19/19[d]	
Total Subjects in Study Group	**145/101[a]**	**789/564**	**35/35**	**300/297**

Note: ADME= Absorption, distribution, metabolism, and excretion; DDI=drug-drug interaction; N_T=total number treated; N_L=treated with lomitapide

[a] Does not include 18 subjects who received only the IV formulation of lomitapide

[b] Duration of treatment

[c] This study was prematurely terminated and re-initiated as Study AEGR-733-003b; only safety data from this study were used to support treatment with lomitapide.

[d] Ongoing extension study for the Phase 3 HoFH study; not included in the total.

Clinical trials of lomitapide were initiated by Bristol-Myers Squibb (BMS) in 1996. The BMS Phase 1 program included a series of studies designed to assess the safety, pharmacokinetics (PK), and pharmacodynamics (i.e., lipid lowering effect) of lomitapide in healthy volunteers with elevated total cholesterol levels (≥200 mg/dL). Early clinical development by BMS focused on developing lomitapide as a monotherapy for broad use to treat subjects with hyperlipidemia. In the BMS studies, lomitapide monotherapy was administered at fixed doses in subjects with hypercholesterolemia. Substantial dose-related decreases in serum lipid parameters were observed; however, the fixed-dose regimens, at doses ranging from 25 mg/day to 100 mg/day were associated with dose-limiting AEs, primarily GI events (e.g., diarrhea) and aminotransferase elevations that led to a high rate of treatment discontinuations. BMS elected to discontinue the development of lomitapide in 2000 because the dose-limiting GI AEs would have greatly limited the addressable broad market on which BMS was focusing its development.

The lomitapide Investigational New Drug (IND) application was subsequently transferred to Daniel Rader, MD at the University of Pennsylvania School of Medicine, Philadelphia, PA, based on his interest in continuing to develop the compound in subjects with HoFH where there was a clear unmet medical need. In 2003, Dr. Rader and his colleague, Dr. Marina Cuchel, initiated Study UP1001, a Phase 2, single-arm, proof-of-concept study designed to evaluate the efficacy and safety of lomitapide in the treatment of subjects with HoFH. This was the first

study to evaluate the administration of lomitapide using dose escalation, i.e., initiating lomitapide at a low dose (0.03 mg/kg) with escalation to higher doses every 4 weeks (0.1 mg/kg, 0.3 mg/kg and 1.0 mg/kg, respectively) and the first to include a requirement that subjects follow a rigorous low-fat diet (containing <10% energy from fat). Both the dose escalation regimen and the low-fat diet were implemented in an attempt to improve GI tolerability. All LLTs, including drugs and apheresis, were suspended within 4 weeks prior to the start of study drug treatment and subjects remained off these therapies until after the 4-week post-treatment follow-up assessment. Study UP1001 showed a substantially improved tolerability profile when lomitapide was administered at a low starting dose with subsequent step-wise dose escalation where subjects consumed, on average, 17% energy from fat. Furthermore, a significant lipid-lowering effect was observed. Since this study, the lomitapide development program has successfully utilized the dose escalation regimen within the setting of a low-fat (<20% energy from fat) diet.

Based on the results observed in Study UP1001, Dr. Cuchel initiated the Phase 3 study of lomitapide in December 2007 to confirm the efficacy and safety of lomitapide in subjects with HoFH. This study was designed in collaboration with the FDA's Office of Orphan Product Development, which provided funding through a grant to support the study. The study was subsequently transferred to the current sponsor, Aegerion, which provided additional funding required to complete the study. Study UP1002/AEGR-733-005 was a single-arm, 78-week efficacy and safety study that evaluated lomitapide administered concurrent with other LLTs, including drugs and apheresis, in the setting of a low-fat diet. Study UP1002/AEGR-733-005 provides the primary data to support the request for approval to commercialize lomitapide for the treatment of subjects with HoFH. The study was conducted at 11 study centers in US, Canada, Italy and South Africa. These locations were selected because of the known prevalence of HoFH in these countries and their expertise to conduct clinical studies in patients with dyslipidemia.

Following completion of treatment in Study UP1002/AEGR-733-005, subjects were eligible to enter a long-term follow-on Study AEGR-733-012 to receive continued treatment with lomitapide beyond 78 weeks.

The lomitapide clinical development program also includes a series of 6 randomized, double-blind, placebo- and/or active-controlled studies with lomitapide at doses ranging from 2.5 to 25 mg daily administered as monotherapy and/or coadministered with other LLDs in subjects with elevated LDL-C and other CV risk factors (non-HoFH subjects). Results from these studies show that lomitapide, when administered as a monotherapy and when coadministered with atorvastatin or ezetimibe, significantly reduced LDL-C compared with placebo and that the reduction in LDL-C was dose-dependent. The data from these studies provide relevant and supportive evidence of the efficacy of lomitapide in lowering LDL-C and are consistent with findings from the pivotal Phase 3 trial in HoFH.

To further evaluate the safety of lomitapide, Aegerion has also conducted a series of studies to evaluate potential drug-drug interactions with LLDs, with warfarin, with an oral contraceptive, and with ketoconazole; a thorough corrected QT interval (QTc) study; and studies to assess the PK of the compound in subjects with hepatic impairment and with renal impairment.

2.3.2 Key Regulatory History

Lomitapide has been granted orphan drug designation for 2 indications: HoFH and familial chylomicronemia (FC). The NDA for lomitapide (NDA #203858) for the treatment of subjects with HoFH was submitted to the Division of Metabolism and Endocrinology Drug Products of the FDA on February 29, 2012. The 4-Month Safety Update Report was submitted on June 27, 2012.

2.4 Proposed Indication, Dose and Administration

Aegerion is requesting that lomitapide be approved for 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, total cholesterol, apolipoprotein B and triglycerides in subjects with homozygous familial hypercholesterolemia.

Based on the dosing regimen and dietary supplements used in the Phase 3 HoFH study (see Section 4.1) and data from the food effect study (see Section 3), the following dosing recommendations were included in the proposed prescribing information:

> 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. Appropriate control of the fat content in the diet is essential to reduce the occurrence and severity of GI side effects associated with the use of lomitapide. Dietary counseling should be provided.
>
> 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 eicosapentaenoic acid (EPA), 220 mg α-linolenic acid (ALA) and 80 mg docosahexaenoic acid (DHA) per day, throughout treatment with lomitapide.

3 OVERVIEW OF CLINICAL PHARMACOLOGY AND DOSE SELECTION

The key points from the lomitapide clinical pharmacology/Phase 1 program are as follows:

- The proposed dose range for lomitapide is based on a well-characterized dose-response relationship. LDL-C lowering is indirectly related to plasma concentration (BMS-910061832, CV145-001 and CV145-002) with a plateau in LDL-C-lowering effect observed after 14 days of daily dosing (Study CV145-002, CV145-009).
- Lomitapide has an absolute bioavailability of 7% (CV145-003) that is likely due to a high first-pass effect.
- Lomitapide has a terminal half-life of approximately 29 hours upon single-dose intravenous administration, consistent with the time it takes to reach PK steady-state (6 days) and its PK appears approximately dose-proportional between 10 and 50 mg following multiple dose oral administration.
- Lomitapide is extensively metabolized by CYP3A4 and interacts with drugs metabolized by CYP3A4. Lomitapide and its primary metabolites neither induce nor inhibit any CYP450 enzymes at therapeutic concentrations achieved at the highest tested dose of 60 mg once daily.
- Lomitapide does not require dose adjustment in subjects with impaired renal function or mild hepatic impairment; it is proposed that it be contraindicated in patients with moderate and severe hepatic impairment.

Highlights of the clinical pharmacology/Phase1 program are summarized in Table 3.

Table 3: Overview of Clinical Pharmacology Results

PK PARAMETER	RESULT				
Exposures Achieved at Maximum Tested Dose		Mean C_{max} (ng/mL)	%CV	Mean AUC (h•ng/mL)	%CV
	Single Dose (200 mg, capsule)	17.3	44.5	719.9	54.0
	Single IV Dose (60 mg)	350.7	28.8	1776.5	11.3
	Multiple Dose (50 mg qd x14 d)	8.5	91.7	132.6[a]	92.3
Range of Linear PK	Linear following multiple dosing (10 mg to 50 mg)				
Accumulation at steady-state	Mean of 3.3 (25 and 50 mg qd x 14 d)				
Time to achieve PK steady-state	6 days				
Absorption	Absolute Bioavailability (IV)	Mean = 7%; %CV = 33.8%			
Distribution	Vd (IV)	1200 L			
Protein Binding	% bound	>99.5%			
Metabolism	Metabolized by CYP3A4; Known primary metabolites (inactive): M1; M3				

PK PARAMETER	RESULT	
Potential for Induction or Inhibition[b]	Lomitapide and its primary metabolites, M1 and M3, do not induce CYP P450 1A2, 3A4, and 2B6 enzymes. The metabolites of lomitapide did not inhibit CYP P450 1A2, 2B6, 2C8, 2C9, 2E1 and 3A4 enzymes. Lomitapide is an inhibitor of some CYP P450s but the IC_{50} values were all at least an order of magnitude greater than C_{max} following a 60 mg dose at steady-state.	
Elimination	Route	Renal (at least 33%). No unchanged drug excreted in urine; Fecal (at least 53%) with ~7% in unchanged drug excreted in feces
	Terminal $t_{1/2}$, (3 x 20 mg capsules, single dose)	Parent Mean = 39 hr; %CV = 59% M1 Mean = 29.6 hr; %CV = 14% M3 Mean = 31.7hr; %CV = 26%
	Terminal $t_{1/2}$, IV	Parent Mean = 28.8 hr; %CV = 41%
Intrinsic Factors	Age	Unknown
	Gender	A direct comparison of lomitapide PK at steady-state between male and female subjects in the same study has not been conducted. No apparent differences between males and females after a single dose based on historical data.
	Race	Unknown
	Hepatic Impairment	Hepatic impairment did not change the T_{max} values. A slight increase in exposure (4% for C_{max}, 47% for AUC) was observed in the mild hepatically impaired subjects compared to matched subjects with normal hepatic function. Mean C_{max} and $AUC_{0\text{-}inf}$ values for the moderate hepatic impairment group were approximately 361% and 164% higher, respectively, than those observed in healthy matched controls. No change in half-life for lomitapide was observed in hepatically impaired subjects compared to healthy control subjects. It is proposed that lomitapide be contraindicated in patients with moderate or severe hepatic impairment.
	Renal Impairment	Lomitapide C_{max} and AUC were 51% and 39% higher, respectively, in ESRD patients who received hemodialysis relative to matched healthy controls. These were not considered to be clinically relevant. Therefore, no change in the dosing regimen for lomitapide is suggested for patients with renal impairment.

PK PARAMETER	RESULT	
Extrinsic Factors	Drug Interactions	Lomitapide is metabolized by CYP3A4 and *in vitro* is a direct inhibitor of CYP3A4. The IC_{50} *in vitro* was 1000 times greater than concentrations achieved clinically. Co-administration of 60 mg lomitapide (at steady-state) with 40 mg simvastatin increased exposure to simvastatin acid approximately 1.7-fold compared to simvastatin alone. C_{max} for simvastatin acid increased about 1.6-fold. Co-administration of 60 mg lomitapide (at steady-state) with 20 mg atorvastatin led to a 52% and 49% increase in the AUC of atorvastatin acid and 4 OH atorvastatin, respectively. Ketoconazole, a strong inhibitor of CYP3A4, increased lomitapide C_{max} and AUC 15-fold and 27-fold, respectively. When dosed to steady-state, lomitapide had no clinically meaningful impact on the PK of estrogen-containing oral contraceptive, niacin, ezetimibe, or fenofibrate. Lomitapide increased exposure to both the R and S forms of warfarin by 28% and 30% and increased $INR_{max.}$ 1.26-fold
Food Effects	Low fat meal + 50 mg Lomitapide vs. Fasted	Mean change in C_{max} +70% Mean change in AUC +27.5%
	High fat meal+ 50 mg Lomitapide vs. Fasted	Mean change in C_{max} +77% Mean change in AUC +57.6%

Abbreviations: AUC=area under the concentration x time curve; C_{max}=maximum concentration; CV=coefficient of variation; ESRD=end-stage renal disease; IC_{50}=inhibitory concentration at 50%; INR=international normalized ratio; IV=intravenous; OH=hydroxide; PK=pharmacokinetic; qd=once daily; T_{max}=time to maximum concentration; Vd=volume of distribution.
[a] AUC_{τ}

Lomitapide has an absolute bioavailability of 7% that is likely to be due to a high first-pass effect

The results of an ascending single-dose Phase 1 study indicated a mean absolute bioavailability of lomitapide of approximately 7%. Concentrations of the metabolites of lomitapide were lower following IV administration than following oral administration and lomitapide concentrations were higher following IV administration than following oral administration. The totality of these data suggests that the low bioavailability of lomitapide was due to a high first-pass effect and not to poor intrinsic absorption. These findings are consistent with observations in a non-clinical study in which bile duct cannulated rats were used to assess the absorption and disposition of lomitapide in bile, urine and feces after a single oral dose of ^{3}H-lomitapide. Urinary excretion represented a minor elimination pathway (approximately 3% of the dose). Approximately 13% of the administered radioactivity was recovered in the feces and 65% was recovered in bile. Radioactivity in the GI tract and carcass accounted for about 18% of the dose. Total recovery of the radiolabeled dose was 98.9%. The total of the dose recovered in bile, urine, and all tissues save the GI tract, suggests that at least 81% of the dose was absorbed.

Additional evidence concerning the absorption of lomitapide is available from a validated *in vitro* model based upon a monolayer of cultured epithelial cells. The Caco-2 cell line is an

intestinal epithelial line derived from a human colorectal carcinoma. In culture, Caco-2 cells grow in monolayers, differentiate spontaneously into polarized enterocytes, and display characteristics typically associated with the physical and metabolic barrier of the intestinal epithelium. The A-B apparent permeability (Papp) across Caco-2 cell monolayers was greater than 1×10^{-6} cm/s.

Lomitapide has a terminal half-life of approximately 29 hours and the pharmacokinetics approach linearity at steady-state

A summary of the PK parameters for lomitapide across studies that evaluated similar doses are presented in Table 4.

Table 4: Mean Pharmacokinetic Parameters for Lomitapide across Studies at Similar Doses

		PHARMACOKINETIC PARAMETER				
STUDY NO.	N	Dose (mg)	C_{max} (ng/mL)	T_{max}[a] (h)	AUC[b] (h·ng/mL)	$t_{1/2}$ (h)
CV145-001(SD)[c]	6	50	2.3	7.5	102.5	34.4
CV145-002 (SD) CV145-002 (MD)[d]	24	50	3.3 8.5	5 3.25	33.6 132.6	51.1 42.0
CV-145-003 (SD, Oral)[c] CV-145-003 (SD, IV)	6 24	50 60	2.2 350.7	ND ND	96.7 1776.5	43.6 24.8
CV145-005 (SD)[c,e]	24	50	2.51	6	94.0	38.2
AEGR733-017 (SD)[c,f]	8 8	60 60	1.45 1.05	4 7	74.3 92.9	68 74.6
AEGR733-018 (SD)[c,g]	30	60	1.21	6	62.39	39.7
AEGR733-021 (SD)[h]	7	60	1.26	8	52.68	46.6

AUC=area under the concentration x time curve; C_{max}=maximum concentration IV=intravenous, MD=multiple dose, ND=not done; SD=single dose; $t_{1/2}$=half life; T_{max}=time to maximum concentration.

[a] Median
[b] $AUC_{0\text{-inf}}$ for single dose; $AUC_{0\text{-tau}}$ for multiple dose
[c] Used in C_{max} and AUC comparison across studies
[d] Value presented is for Day 14.
[e] Fasted
[f] Healthy controls, fasted
[g] Lomitapide only
[h] $AUC_{0\text{-inf}}$, N=4

Lomitapide exposure was modestly increased in the presence of food, but with increased gastrointestinal adverse effects.

A food-effect study in healthy volunteers (CV145-005) demonstrated that administration of lomitapide with food resulted in a modest increase in maximum concentration (C_{max}) and area under the concentration by time curve (AUC) compared to the fasting state. The highest exposures were observed when a high-fat meal was used, as compared to a low-fat meal or fasting. However, there was a much higher rate of GI AEs when lomitapide was dosed with a

high-fat meal (whereas similar rates of GI AEs were observed with the fasted and low-fat-meal dosing conditions).

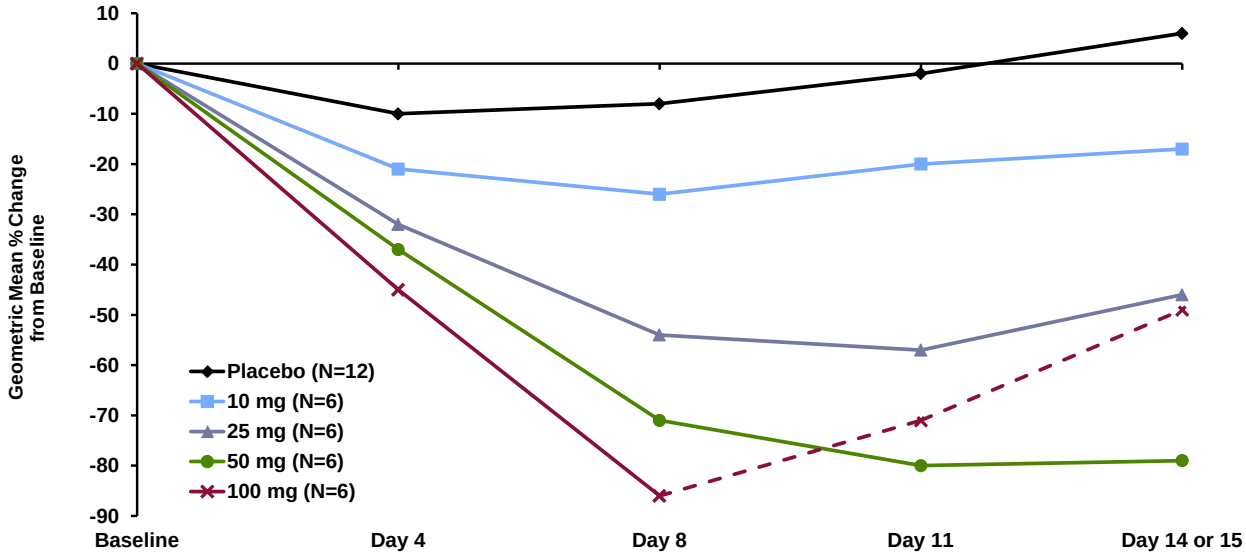
The presence of food would be expected to decrease GI tolerability at maximum local drug concentrations, with lower fat content likely to improve symptoms. It would be expected, therefore, that the optimum conditions for administration of lomitapide would be in the fasting state.

The proposed dose range for lomitapide is based on a well characterized dose-response relationship.

The first-in-man study conducted with lomitapide (CV145-001) was a double-blind, randomized (within dose), placebo-controlled, ascending single-dose, parallel group study to evaluate lomitapide at doses ranging from 1 to 200 mg. Results of this study indicated that a dose response was evident for percent change in LDL-C at single doses of 50 mg and higher; the LDL-C decreased by 24 hours and the effect was maintained through 72 hours.

The results of Study CV145-001 led to the design and conduct of Study CV145-002, a double-blind, randomized, placebo-controlled, ascending multiple-dose, study designed to evaluate the safety, tolerability, PK and pharmacodynamics of ascending doses of 10, 25, 50, 100 and 200 mg lomitapide or placebo administered once daily for 14 days in hypercholesterolemic (total cholesterol ≥200 mg/dL) subjects. A total of 36 subjects were randomized. All subjects in the 10, 25, and 50 mg dose cohorts received 14 days of dosing as planned; dosing in the 100 mg dose group was stopped after Day 8 due to GI AEs and the 200 mg dose level was not evaluated. Results of the study showed that the decreases from baseline in LDL-C were dose dependent with maximal decreases noted between Days 8 and 11 (Figure 6). The patterns were similar for the other lipid parameters.

Figure 6: Geometric Mean Percent Change from Baseline in LDL-C following Multiple Doses of Lomitapide and Placebo, Study CV145-002 (Pharmacokinetic Population, N=54)



Note: The dotted line represents LDL-C levels off treatment as dosing in the 100 mg group was halted on Day 8 due to GI AEs.
Note: N=5 in the 25 mg group on Days 8, 11 and 14/15

Consistent dose response results were observed in the Phase 2 studies in which polygenic hypercholesterolemic subjects were evaluated; the efficacy of the 5 mg dose was generally between 14 to 19% reduction from baseline. The 10 mg dose achieved a 30 to 37% reduction, and the 25 mg dose provided a 64% reduction. An additive reduction in LDL-C also was observed when lomitapide was co-administered with other LLDs (Table 5).

Table 5: Efficacy of Lomitapide (LDL-C reduction) from Phase 2 Studies in Subjects with Elevated LDL-C and Other Cardiovascular Risk Factors

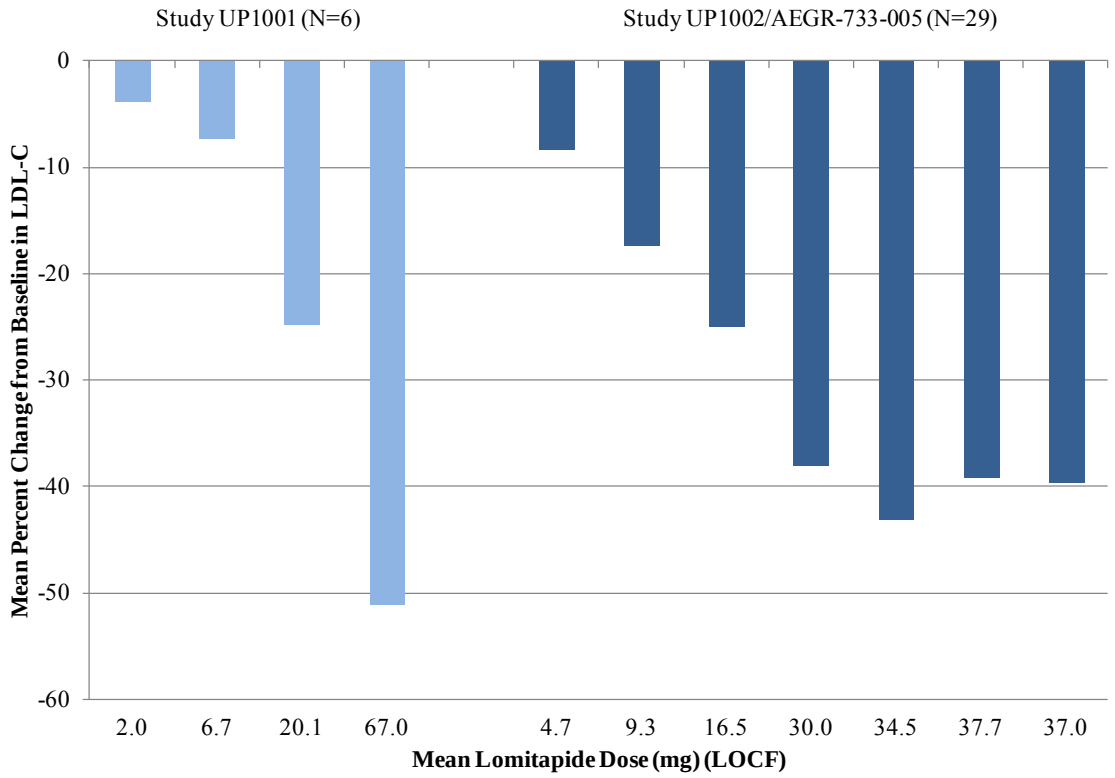
LOMITAPIDE DOSE (MG)	LDL-C CHANGE (% FROM BASELINE)	STUDY
Placebo	-6% to +7%	733-003b, 733-004, CV145-009
5 mg	-14% to -19%	733-001, 733-003b, 733-004
10 mg	-30% to -37%	733-001, 733-003b, 733-004
5 mg + atorvastatin 20 mg	- 47% to -56%	733-003b, 733-004, 733-006
10 mg + atorvastatin 20 mg	-50%	733-003b
5 mg + ezetimibe 10 mg	-34% to -35%	733-001, 733-004
10 mg + ezetimibe 10 mg	-46%	733-001
25 mg	-64%	CV145-009

Based on these data, a dose escalation regimen with a low starting dose was proposed for subjects with HoFH. The purpose of dose escalation, as opposed to a fixed dosing approach, was to allow GI tolerability and hepatic safety to be established at each dose level before moving to the next dose level.

In the Phase 2 HoFH study, the mean doses administered every 4 weeks were 2.0, 6.7, 20.1, and 67.0 mg/day. Safety and tolerability were assessed following 1, 2 and 4 weeks of treatment at each dose level. The lipid-lowering effect was minimal after the first 4 weeks at a mean dose of 2 mg and the dose was well tolerated. Thus, the starting dose for the Phase 3 HoFH trial was 5 mg. It was thought that at this low dose, minimal GI side effects would be observed in most subjects, so the initial dosing period at 5 mg was 2 weeks, with all subsequent escalations conducted at 4-week intervals consistent with Study UP1001.

As can be seen from Figure 7, a dose-response relationship is evident in both HoFH studies. Subjects in Study UP1001 were removed from all background lipid-lowering treatment within 4 weeks prior to starting lomitapide monotherapy. As a result, mean baseline LDL-C was much higher (614 mg/dL) than that observed in the Phase 3 trial (336 mg/dL), and the magnitude of percent changes from baseline in LDL-C would be expected to be greater.

Figure 7: Dose Response: Mean Percent Change from Baseline in LDL-C by Mean Lomitapide Dose Level in the HoFH Studies



Note: mean percent changes from baseline in LDL-C are based on a last observation carried forward (LOCF) method for subjects who discontinued early.

4 OVERVIEW OF STUDY DESIGNS FOR THE PIVOTAL AND SUPPORTIVE STUDIES

This section reviews the key design features of the pivotal Phase 3 study in subjects with HoFH and the supportive Phase 2 proof-of-concept study conducted in this population. A brief summary of the design features of other Phase 2 studies conducted in subjects with polygenic hypercholesterolemia that are used to support the lipid-lowering effects of lomitapide and provide additional safety data is also included.

4.1 Key Design Features of the Pivotal Phase 3 Study UP1002/AEGR-733-005 in Subjects with HoFH

4.1.1 Overview

Study UP1002/AEGR-733-005 was a multinational, multicenter, open-label, single-arm, 78-week clinical trial designed to evaluate both the efficacy and long-term safety of lomitapide in subjects with HoFH at an individually-defined maximum tolerated dose. The primary objective of the study was to evaluate the efficacy of lomitapide coadministered with other LLTs, including drugs and apheresis, as defined by percent change from baseline in LDL-C after 26 weeks of treatment (see Section 5.2). Secondary efficacy objectives were evaluation of percent changes from baseline in total cholesterol, apo B, non-HDL-C, triglycerides, VLDL-C, Lp(a), HDL-C, and apo AI.

The protocol for the Phase 3 HoFH trial was designed as a single-arm study in order to maximize the number of subjects exposed to long-term active treatment in this rare disease. The single-arm (baseline-controlled) design in this population is considered appropriate for several reasons:

- The study's primary endpoint is an objective lipid measurement obtained at a central laboratory, thus eliminating any bias inherent in determination of the endpoint.
- Strong measures of control were included in the design of the study in order to avoid potential confounding due to the effects of background LLTs or other factors:
    - A minimum 6-week Run-in Phase was incorporated to stabilize concomitant LLTs, including drugs and apheresis and to institute the low-fat diet.
    - Two separate baseline measurements of lipid levels obtained at least 4 weeks after standardization of LLTs were used to calculate a mean baseline value for comparison to on-treatment measurements to ensure a stable, well-characterized baseline. Establishing a stable LDL-C baseline permitted a clear elucidation of the pharmacologic effect during the treatment phase of the trial.
    - Background therapies, including apheresis, were to remain unchanged through Week 26 (the primary efficacy endpoint). For subjects receiving apheresis, efficacy was consistently evaluated using pre-apheresis lipid levels.

- LDL-C reductions in the 50% range, which were observed in the Phase 2 study UP1001 (see Section 5.6.1), were considered to be easily discernible from baseline measurements in this conservatively powered Phase 3 study.
- The rapid reduction in LDL-C following initiation of treatment (see Figure 9), the magnitude of the reduction that could not have occurred spontaneously in this population given that in the absence of effective treatment, LDL-C levels are known to deteriorate in HoFH subjects over time, and the rebound following cessation of treatment (see Figure 10) make a baseline-controlled design reasonable (ICH E10, Choice of Control Group and Related Issues in Clinical Trials, May 2001).

4.1.2 Study Design

Subjects were selected for inclusion in the Phase 3 study based on accepted diagnostic criteria from international expert organizations. Although clinical diagnostic criteria for HoFH are not uniform, several groups have developed tools for use in familial hypercholesterolemia. These include the Dutch Lipid Clinics Network criteria (Fouchier, 2001), the MedPed criteria (Williams, 1993) and the Simon Broome Registry criteria (Simon Broome Register Group, 1991). The inclusion criteria for the Phase 3 study were consistent with these recommendations.

Men and women 18 years of age or older with a diagnosis of functional HoFH by at least one of the following clinical criteria were eligible for the study:

a) Documented functional mutation(s) in both LDL-R alleles or alleles known to affect LDL-R functionality, OR

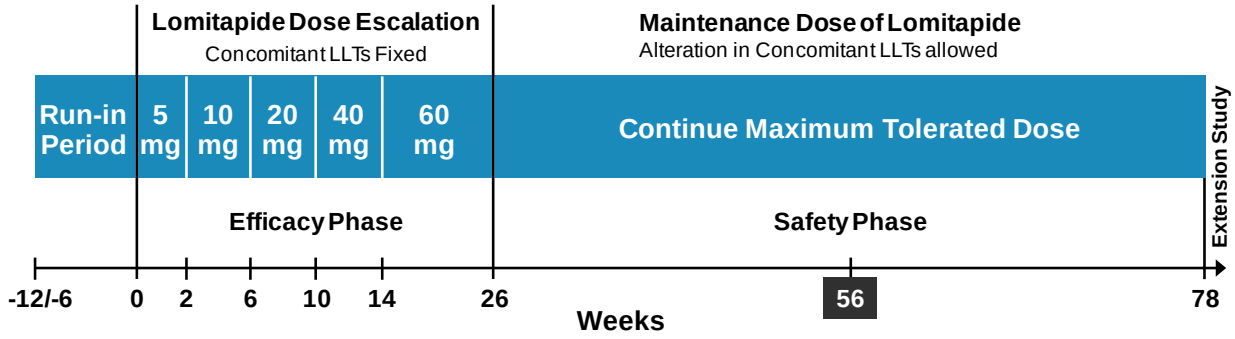
b) Skin fibroblast LDL-R activity < 20% normal, OR

c) Untreated total cholesterol >500 mg/dL and triglycerides < 300 mg/dL and both parents with documented untreated total cholesterol >250 mg/dL.

Key exclusion criteria included uncontrolled hypertension, chronic renal insufficiency, biopsy-proven cirrhosis, chronic hepatitis B or C, ALT or AST >2×ULN and/or total bilirubin >1.5 mg/dL (in the absence of diagnosed Gilbert's syndrome), other significant liver disease (e.g., NASH, alcoholic liver disease), New York Heart Association (NYHA) Class III or IV cardiac insufficiency, significant pulmonary disease (e.g., idiopathic pulmonary fibrosis), and known significant GI bowel disease or malabsorption.

An overview of the Phase 3 study design is provided in Figure 8.

Figure 8: Overview of Study Design, Study UP1002/AEGR-733-005



Eligible subjects entered a minimum 6-week Run-in Phase during which they were maintained on a stable regimen of their ongoing LLTs, including oral medications and apheresis, and were instructed on how to follow a diet supplying < 20% energy from fat. The low-fat diet was instituted during the Run-in phase and continued throughout the study to improve GI tolerability during lomitapide treatment based on the results of early Phase 1 and 2 studies, including the Phase 2 study UP1001, in which subjects were able to consume, on average, 17% energy from fat and exhibited a better tolerability profile. Based on the results of the Phase 2 HoFH study which showed a decline in vitamin E levels and essential fatty acid levels, subjects were provided with dietary supplements of 400 IU of vitamin E and approximately 200 mg linoleic acid, 110 mg EPA, 220 mg ALA and 80 mg DHA per day; supplements were provided by the Sponsor. Subjects also were counseled to limit alcohol intake.

Following the Run-in Phase, subjects entered a 26-week Efficacy Phase to reach their maximum tolerated dose of lomitapide. Study drug was initiated at 5 mg/day for 2 weeks, and then escalated to 10 mg/day for 4 weeks, followed by escalations to 20, 40, and 60 mg/day at 4-week intervals unless dose modification rules applied. Subjects who met strict safety and efficacy criteria could have their dose escalated to 80 mg/day during the Efficacy Phase. Criteria were established related to liver function tests to direct escalation of the dose as well as dose reduction and treatment discontinuation (see Section 8) thus, allowing subjects to achieve an individualized maximum tolerated dose. The 26-week efficacy assessment was timed to allow each subject to establish their maximum tolerated dose before the primary assessment of efficacy.

Subjects were instructed that all concomitant LLTs, including oral medications and apheresis, should not change for ≥6 weeks prior to the start of lomitapide treatment through the Week 26 on-treatment assessments. The timing of the fasting lipid profile relative to apheresis was specifically outlined in the protocol. Apheresis treatment causes a sharp drop in LDL-C, followed by a rebound phase, and therefore it was important that lipid parameters were evaluated at a time that was as close as possible to, and before, the next scheduled apheresis treatment, i.e., when lipid levels would be maximally elevated. Once established, this time point for lipid

assessments was to be maintained, relative to the previous apheresis visit, so that lipid assessments were always performed at the same point on the individual subjects' LDL rebound curve.

Following completion of the 26-week Efficacy Phase, subjects entered the 52-week Safety Phase during which they received their maximum tolerated dose of lomitapide defined at Week 26. During the Safety Phase, study drug dose could be reduced if specific dose modification rules applied, but could not be increased above the highest dose administered to the subject during the Efficacy Phase. In addition, in subjects who met specific protocol criteria, background LLTs (oral medications and frequency of apheresis) could be altered.

Fasting lipid panels were obtained at Screening and 2 weeks prior to and on the day of the first dose of lomitapide (prior to dosing); the latter 2 assessments were averaged and used as the subject's baseline assessment. Fasting lipid panels were repeated at the end of each dose escalation period (Weeks 2, 6, 10, 14 and 26) as well as at Weeks 18 and 22 during the Efficacy Phase and at Weeks 36, 46, 56, 66 and 78 during the Safety Phase (and Week 84 for subjects not enrolling into the extension study). For consistency across study sites, all lipid measurements were determined at a central laboratory.

The safety of treatment with lomitapide was carefully evaluated. An independent DSMB met regularly during the conduct of the study to review safety data and made recommendations to ensure subject safety. Thorough safety assessments were conducted throughout the study, with particular emphasis on known and potential risks of lomitapide treatment based on its mechanism of action and data across the lomitapide program. Standard safety evaluations, including monitoring for AEs, clinical laboratory evaluations, electrocardiograms (ECGs), vital signs, and physical examinations, were conducted at baseline and throughout treatment. Liver function tests, including AST, ALT, total bilirubin, and alkaline phosphatase, were assessed every 4 to 5 weeks. Based on its known mechanism of action related to increased hepatic triglyceride levels and results from Phase 2 studies, percent hepatic fat was assessed by NMRS/MRI at baseline and approximately every 6 months on treatment. As subjects were on a low-fat diet, and based on results from the Phase 2 HoFH study, fat-soluble nutrient levels were monitored. Based on nonclinical data (see Section 6.1), pulmonary function tests (PFTs), including forced expiratory volume in 1 minute (FEV_1) and forced vital capacity (FVC), were monitored.

4.2 Key Design Features of the Proof-of-Concept Phase 2 Study UP1001 in Subjects with HoFH

The proof-of-concept Phase 2 Study UP1001 was an open-label, single-arm clinical trial designed to evaluate the safety and lipid-lowering effect of lomitapide in subjects with HoFH.

In this study, men and women 13 years of age or older were eligible; however, none of the subjects enrolled was younger than 17 years. The diagnosis of functional HoFH used for this Phase 2 study was identical to that used in the Phase 3 study. Key exclusion criteria were also similar to the Phase 3 study and included uncontrolled hypertension, cardiac insufficiency (NYHA Class III or Class IV), serum creatinine >2.5 mg/dL, and LFTs >3×ULN.

The primary efficacy variable was the percent change from baseline in LDL-C. Other lipid and lipoprotein parameters, including total cholesterol, triglycerides, VLDL-C and HDL-C, as well as plasma lipoproteins (e.g., apo B, apo AI) and Lp(a) also were evaluated.

Subjects were required to stop all LLTs, including oral medications and apheresis, within 4 weeks prior to baseline and remain off these therapies throughout the study until completion of the 4-week follow-up assessment. Study UP1001 required subjects to follow a rigorous low-fat diet (<10% of energy from total dietary fat) starting at the Screening assessment. Subjects were provided a standard multivitamin supplying 100% of the current dietary reference intake for all essential vitamins and minerals and instructed on how to include 2% of energy from essential fatty acids.

The initial starting dose was 0.03 mg/kg daily for 4 weeks. Intra-subject dose escalation to 0.1 mg/kg, 0.3 mg/kg/day and 1.0 mg/kg/day occurred every 4 weeks if specific protocol-defined dose modification rules did not apply.

Fasting lipid panels were obtained at baseline (i.e., after subjects were off all lipid-lowering therapies for at least 4 weeks), at the end of each dose escalation period (i.e., at Weeks 4, 8, 12 and 16), and 4 weeks post-treatment.

The Phase 2 study also included a comprehensive safety evaluation, including monitoring for AEs; clinical laboratory evaluations, including LFTs and fat soluble nutrients; ECGs; vital signs, including weight; physical examinations; hepatic fat assessment by NMRS/MRI; and PFTs. Importantly, hepatic fat was assessed at baseline, after each dose titration, and after the 4-week washout period.

4.3 Key Design Features of the Supportive Phase 1 and 2 Studies in Subjects with Elevated LDL-C and Other Cardiovascular Risk Factors used to Support the Efficacy and Safety of Lomitapide

The lomitapide clinical development program also includes a series of 6 randomized, double-blind, placebo- and/or active-controlled Phase 2 studies with lomitapide at doses ranging from 2.5 to 25 mg daily administered as monotherapy and/or coadministered with other LLTs over 4 to 12 weeks in subjects with elevated LDL-C and other CV risk factors. These studies followed standard study designs, including a thorough evaluation of lomitapide safety. All 6 studies included fasting lipid assessments at baseline and during and/or at the end of the treatment phase allowing for assessment of the lipid-lowering effect of lomitapide.

Based on its mechanism of action, the effect of lomitapide to lower LDL-C is expected to be the same regardless of the severity or the etiology of the LDL-C elevations. Therefore, these Phase 2 studies, which included both placebo- and active-control arms, provide important additional efficacy data substantiating lomitapide as a potent lipid-lowering therapy. In addition, the safety experience from these studies is relevant to and supportive of the safety in the proposed indication as the AE profile was consistent with that in the HoFH population. Results of these studies also provide evidence of a dose response in the lipid-lowering effect of lomitapide across a range of lomitapide doses.

Two Phase 1 randomized, double-blind, placebo-controlled studies conducted in healthy volunteers with elevated total cholesterol which evaluated fixed doses of lomitapide ranging from 10 to 100 mg over 2 weeks provide additional safety data.

5 OVERVIEW OF CLINICAL EFFICACY

5.1 Overview of Efficacy Data Presentation and Pooling

The focus of the integrated efficacy analyses is on the primary indication for registration, subjects with HoFH, including data from the Phase 3 pivotal Study UP1002/AEGR-733-005 with supportive data from the Phase 2 Study UP1001. Given the differences in study designs, data from Study UP1001 are not pooled with data from Study UP1002/AEGR-733-005. The NDA includes efficacy results from the Phase 3 study through Week 56 of the trial, i.e., it includes a final evaluation of the primary efficacy endpoint of percent change from baseline to Week 26 in LDL-C and more than 1-year of lomitapide treatment for continued evaluation of the persistence of effect.

Data from Phase 2 studies conducted in a total of 622 subjects with elevated LDL-C or other CV risk factors support the lipid-lowering effect of lomitapide observed in the HoFH population. The larger sample size from this pool of studies that include both placebo- and active-control arms allows for robust conclusions of effectiveness and support the efficacy observed in the HoFH population. Data for this study pool are summarized for subjects who received lomitapide monotherapy (across low [2.5, 5 and 7.5 mg], mid [10 mg], high [25 mg] and escalated [2.5 to 5 mg and 5 to 10 mg] dose groups), subjects who received lomitapide in combination with other LLTs, subjects who received placebo, and subjects who received active control treatments (atorvastatin and ezetimibe). Taken together, these data provide compelling evidence of the efficacy of lomitapide in lowering LDL-C and other atherogenic lipoproteins.

5.2 Choice of the Primary Endpoint

In view of the central causal role of LDL-C in CVD risk (see Section 2.1.2) and given the mechanism of action of lomitapide, mean percent change from baseline in LDL-C was the primary efficacy endpoint for the Phase 2 and Phase 3 HoFH studies. The secondary endpoints, total cholesterol, triglycerides, non-HDL-C, and apo B, are also clinically relevant as elevated levels of these lipids also are associated with CVD risk and represent additional therapeutic targets (Sniderman, 2011). In view of their association with CVD, other variables of interest include VLDL-C, HDL-C and the intrinsic apolipoprotein of HDL-C, apo AI, and Lp(a).

5.3 Statistical Methodology

Standard statistical testing was performed for the efficacy analyses. For both study pools, paired t-tests were used to test the hypothesis of no percent change from baseline within each treatment group. For the Elevated LDL-C and Other CV Risk Factors Study Pool, an analysis of covariance (ANCOVA) model with treatment group as the main effect and a covariate of baseline LDL-C was used to assess any difference in percent change across treatment groups; treatment group least square means (LSMs) and standard error of the means (SEMs); 95%

confidence intervals (CIs) for the LSM, and p-values comparing individual treatment groups to placebo also are presented from this model. Mean absolute change from baseline in LDL-C was evaluated in a manner similar to percent change.

Missing data due to subject withdrawal was imputed using a LOCF method to the primary endpoint. Sensitivity analyses were conducted on the primary endpoint using other methods, including baseline observation carried forward (BOCF), worst observation carried forward (WOCF), area under the curve (AUC), and nonparametric analyses. In addition, a mixed-models repeated-measures regression analysis for overall percent change from baseline in LDL-C was conducted for the HoFH studies and for the pool of studies in subjects with elevated LDL-C. The models included treatment, baseline LDL-C level, and week of lipid assessment as covariates.

Analyses in both study pools are based on all subjects who received at least one dose of lomitapide, placebo, or active treatment and had a baseline and at least one post-baseline efficacy assessment. Note that all subjects who were treated in both HoFH studies had a baseline and at least 1 post-baseline lipid assessment and therefore were included in these analyses.

5.4 Subject Disposition

5.4.1 Subject Disposition: HoFH Studies

Subject disposition in the HoFH studies is summarized in Table 6.

All 6 subjects enrolled and treated in Study UP1001 completed the study as planned. Note that 4 of the 6 subjects treated in Study UP1001 also were enrolled and treated in the Phase 3 HoFH study.

In Study UP1002/AEGR-733-005, 6 (21%) of the 29 subjects who entered the Efficacy Phase discontinued the study during that phase (i.e., prior to Week 26), primarily due to AEs (see Section 6.9.2.1). Note that all 23 subjects who completed the Efficacy Phase of Study UP1002/AEGR-733-005 entered the Safety Phase and completed the study.

Table 6: Subject Disposition in the HoFH Studies

DISPOSITION	TOTAL UP1001 (N=6)	TOTAL UP1002/ AEGR-733-005 (N=29)
Treated, Lomitapide Alone, N	6	29
Prematurely Discontinued Study Medication, n (%)	0	6 (20.7)
Reason for Early Discontinuation of Study Medication, n (%):		
Adverse Event	0	4 (13.8)
Withdrawal by Subject	0	1 (3.4)
Non-compliance with Study Protocol	0	1 (3.4)
Death	0	0

Maximum tolerated dose achieved at Week 26 in the Phase 3 study was 60 mg in 10 subjects, 40 mg in 7 subjects, 20 mg in 6 subjects, 10 mg in 2 subjects and 5 mg in 3 subjects. One subject was receiving 80 mg at Week 26; however, the subject had not met the strict criteria for escalation to this dose as she had lost >5% of body weight (from 56 to 52 kg); dose was reduced to 40 mg during the Safety Phase.

5.4.2 Subject Disposition: Elevated LDL-C and Other Cardiovascular Risk Factors Studies

Disposition for subjects in the Elevated LDL-C and Other CV Risk Factors Study Pool is provided in Table 7. This pool of studies includes a total of 622 subjects who received treatment with lomitapide alone (255 subjects, 41%), lomitapide coadministered with another lipid-lowering therapy (191 subjects, 31%), placebo (98 subjects, 16%), or active comparator (78 subjects, 13%). The majority of these subjects (481 of 622, 77%) completed the studies as planned; 23% prematurely discontinued from study treatment, primarily due to GI AEs.

Table 7: Subject Disposition in the Elevated LDL-C and Other Cardiovascular Risk Factors Studies

DISPOSITION	ELEVATED LDL-C AND OTHER RISK FACTORS[A]
Treated, N	622
Received at Least One Dose of: (n, %)	
Lomitapide Alone	255 (41.0)
Lomitapide + Active Drug	191 (30.7)
Placebo	98 (15.8)
Active Control Alone	78 (12.5)
Included in Full Analysis Set[b]	612 (98.4)
Prematurely Discontinued Study Medication, n (%)	141 (22.7)
Reason for Early Discontinuation of Study Medication, n (%):	
Adverse Event	120 (19.3)
Withdrawal by Subject	14 (2.3)
Lost to Follow-up	2 (0.3)
Death	0
Other	5 (0.8)

[a] Studies AEGR-733-001, AEGR-733-003b, AEGR-733-004, AEGR-733-006, and CV145-009
[b] Had baseline and at least 1 post-baseline assessment for evaluation of efficacy

5.5 Demographics and Baseline Characteristics

5.5.1 Demographics and Baseline Characteristics: HoFH Studies

The demographic characteristics of the HoFH population were similar in the Phase 2 and Phase 3 studies (Table 8). All 35 subjects had genetically confirmed HoFH. In the Phase 3 study, 28 of 29 subjects had documented defects in the *LDLR* gene and 1 subject had documented ARH, which is attributed to defects in the LDL receptor adaptor protein.

Mean baseline LDL-C for the 6 subjects in Study UP1001 was markedly elevated at 614 mg/dL as these subjects were required to be off all LLTs within 4 weeks of study entry. In Study UP1002/AEGR-733-005, where subjects were required to be on a stable regimen of their LLTs, mean baseline LDL-C also was elevated at 336 mg/dL despite their standard of care therapies.

Table 8: Demographics and Baseline Characteristics, HoFH Studies

CHARACTERISTIC	STUDY UP1001 (N=6)	STUDY UP1002/ AEGR-733-005 (N=29)
Age (years)		
Mean (SD)	25.0 (9.19)	30.7 (10.64)
Median	21	30
Minimum, Maximum	17, 39	18, 55
Sex, n (%)		
Male	3 (50.0)	16 (55.2)
Female	3 (50.0)	13 (44.8)
Race, n (%)		
Caucasian	3 (50.0)	25 (86.2)
Asian	1 (16.7)	2 (6.9)
Black	0	1 (3.4)
Other	2 (33.3)	1 (3.4)
BMI (kg/m^2), n (%)		
<30	5 (83.3)	25 (86.2)
≥30	1 (16.7)	4 (13.8)
Baseline LDL-C (mg/dL)		
Mean (SD)	614.2 (105.85)[a]	336.4 (113.54)
Median	622.5	356.5
Minimum, Maximum	480, 789	152, 564

[a] Subjects were required to be off all lipid-lowering therapies within 4 weeks of study entry.

LDL-C levels were stable during the Run-in Phase of the Phase 3 study.

Comparison of the Screening and Day 0 (first dosing day) LDL-C levels in the Phase 3 study after stabilization of LLTs and establishment of the low-fat diet during the minimum 6-week Run-in Phase indicated minimal change over this pre-dosing time period. Mean percent change from Screening to Day 0 in LDL-C was -1.2%.

Subjects entered the Phase 3 study with significant underlying cardiovascular disease.

Subjects who entered the Phase 3 trial had evidence of significant CV morbidity with 27 (93%) of the 29 subjects having underlying cardiovascular or cerebrovascular disease prior to study entry. Ten (35%) of the 29 subjects had undergone CABG surgery prior to study entry; 5 of these subjects were ≤ 21 years of age, including 3 under the age of 8 at the time of open-heart surgery. Three subjects had undergone multiple CABG procedures. Coronary angioplasty had been performed in 3 subjects (10%), including 1 who required 3 procedures at the ages of 20, 21 and 22. Aortic valve replacement had been performed in 3 subjects (10%), and mitral valve replacement or repair in 3 subjects (10%). Cerebrovascular disease was also evident, with 3 subjects (10%) having suffered a transient ischemic attack, and 2 subjects (7%) having

undergone carotid endarterectomy. Arterial stenosis, including the aortic, carotid, and coronary arteries, was reported at study entry in 8 (28%) of the 29 subjects.

Subjects entered the Phase 3 study on optimized doses of statins.

Overall, 27 (93%) of the 29 subjects in the Phase 3 study were on HMG-CoA reductase inhibitors (statins) at study entry, primarily rosuvastatin (45%) and atorvastatin (31%); 17% of subjects were receiving simvastatin (Table 9). Eighteen subjects (62%) were undergoing apheresis. As expected, the majority of the 29 subjects were receiving maximum approved doses of statins. Most subjects receiving rosuvastatin were on the 40 mg dose (11 of 13) and most receiving atorvastatin were on the 80 mg dose (8 of 9); the dose of simvastatin was 160 mg in 1 subject, 80 mg in 1 subject, 40 mg in 1 subject, and 20 mg in 2 subjects.

As detailed above, all 6 subjects in Study UP1001 were required to be off all LLTs.

Table 9: Concomitant Lipid-Lowering Therapies, Study UP1002/AEGR-733-005

LIPID-LOWERING THERAPY	STUDY UP1002/AEGR-733-005 (N=29)
HMG-CoA Reductase Inhibitors (Statins)	27 (93.1)
Rosuvastatin/Rosuvastatin Calcium	13 (44.8)
Atorvastatin/Atorvastatin Calcium	9 (31.0)
Simvastatin	5 (17.2)
Ezetimibe	22 (75.9)
Bile acid Sequestrants, Colesevelam Hydrochloride	1 (3.4)
Nicotinic Acid	3 (10.3)
Receiving Apheresis	18 (62.1)

5.5.2 Demographics and Baseline Characteristics: Elevated LDL-C and Other Cardiovascular Risk Factors Studies

As expected based on protocol entry criteria and the population studied, mean age of the subjects in the Elevated LDL-C and Other CV Risk Factors Study Pool group ranged from 51.0 years in the placebo and lomitapide high-dose groups to 57.5 years in the lomitapide escalated dose group. A total of 49% of subjects who received lomitapide were male as were 54% of subjects who received placebo and 40% of subjects who received active control. Most subjects in all treatment groups in this Study Pool were Caucasian. Mean baseline LDL-C ranged from 148.9 mg/dL in the lomitapide low dose group to 185.9 mg/dL in the lomitapide high dose group.

5.6 Results for the Primary Efficacy Endpoint: Change From Baseline in LDL-C

5.6.1 Change from Baseline in LDL-C: HoFH Studies

Treatment with lomitapide significantly reduced LDL-C levels in subjects with HoFH. The reductions were observed early in the treatment course and the effect was maintained over 1 year of treatment.

Table 10 summarizes the results of the primary efficacy variable of percent change from baseline in LDL-C at the primary time point for each HoFH study: Week 16 in the Phase 2 Study UP1001 and Week 26 in Phase 3 Study UP1002/AEGR-733-005. Results are based on LOCF methods. Changes from baseline are analyzed using paired t-tests.

In Study UP1001, in which all subjects were required to be off all LLTs, including oral medications and apheresis, mean LDL-C at baseline was extremely elevated at 614 mg/dL. Following 16 weeks of treatment with lomitapide using dose escalation, mean LDL-C levels had decreased to 303 mg/dL, a mean observed change of -311.2 mg/dL. The mean percent change from baseline to Week 16 of -51% was both statistically significant ($p<0.001$) and clinically meaningful.

In Study UP1002/AEGR-733-005, LDL-C was elevated at baseline despite standard of care therapy with a mean level of 336 mg/dL. By Week 26, following dose escalation to each individual subject's maximum tolerated dose, mean LDL-C was 190 mg/dL, a mean observed change from baseline of -146.9 mg/dL. This study confirmed the significant lipid-lowering effect of lomitapide in HoFH subjects who were receiving standard of care therapy with a statistically significant ($p<0.001$) and clinically meaningful mean percent change from baseline to Week 26/LOCF of -40%.

Table 10: Summary of Results of the Primary Efficacy Endpoint, Change from Baseline in LDL-C using LOCF Methods, HoFH Studies (ITT Population)

ASSESSMENT STATISTIC	STUDY UP1001 (N=6)	STUDY UP1002/AEGR-733-005 (N=29)
Observed Value at Baseline, n	6	29
Mean (SD)	614.2 (105.85)	336.4 (113.54)
95% CI	503.09, 725.25	293.3, 379.6
Median	622.5	356.5
Minimum, Maximum	480.0, 789.0	152.0, 564.0
Observed Value at Primary Endpoint[a], n	6	29
Mean (SD)	303.0 (81.31)	189.6 (104.24)
95% CI	217.67, 388.33	149.9, 229.2
Median	303.5	169.0
Minimum, Maximum	201.0, 403.0	28.0, 442.0
Mean Observed Change at Primary Endpoint[a], n	6	29
Mean (SD)	-311.2 (70.06)	-146.9 (127.11)
95% CI	-384.69, -237.64	-195.2, -98.5
Median	-331.5	-107.0
Minimum, Maximum	-406.0, -206.0	-350.5, 49.0
p-value[b]	<0.001	<0.001
Mean Percent Change at Primary Endpoint[a] n	6	29
Mean (SD)	-50.9 (9.31)	-40.1 (31.25)
95% CI	-60.71, -41.16	-51.9, -28.2
Median	-52.3	-49.5
Minimum, Maximum	-62.4, -33.8	-92.6, 20.4
p-value[b]	<0.001	<0.001

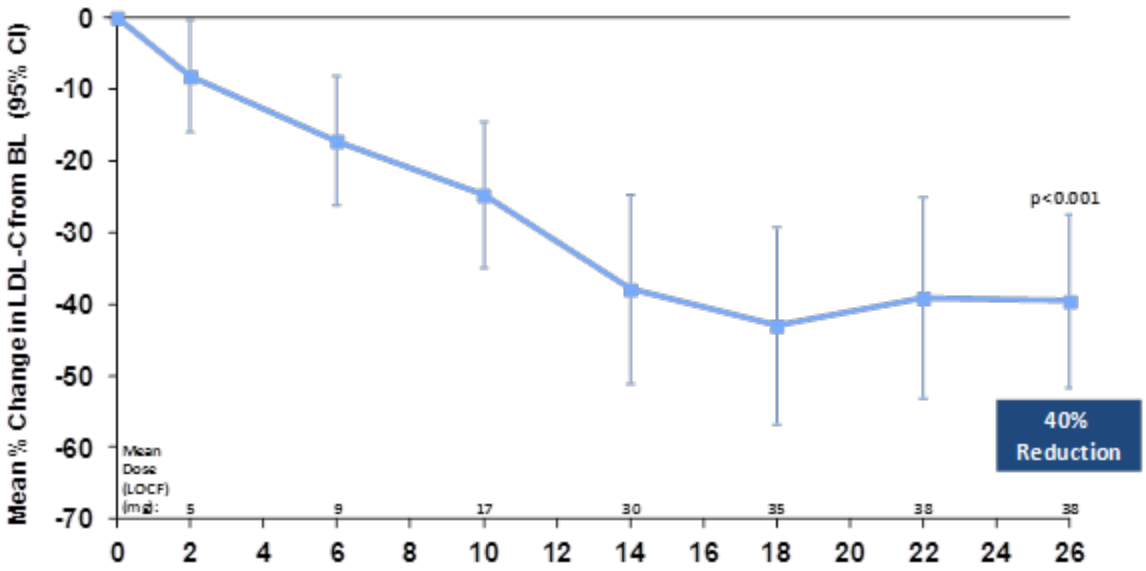
Note: subjects on Study UP1001 were required to be off all lipid-lowering therapies; subjects on Study UP1002/AEGR-733-005 were receiving standard of care lipid-lowering therapies.

[a] Data are from Week 16 for Study UP1001 and from Week 26 for Study UP1002/AEGR-733-005

[b] p-value based on paired t-test

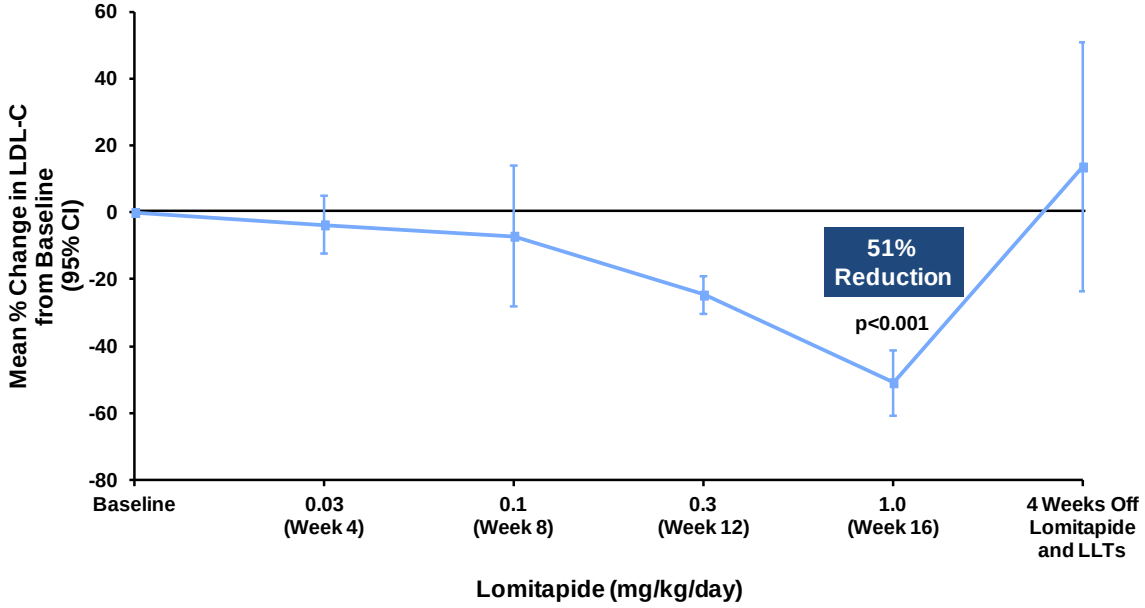
In the Phase 3 study, mean LDL-C levels decreased significantly after 2 weeks on lomitapide with a mean percent change from baseline of -8% (p=0.0396) (Figure 9). Furthermore, a dose response was evident as the dose was escalated through the planned doses of 10, 20, and 40 mg with LDL-C levels showing significant decreases from baseline with mean percent changes of -17%, -25% and -38% at Weeks 6, 10 and 14 ($p \leq 0.0005$) based on LOCF. The mean percent changes from baseline in LDL-C plateaued during Weeks 18, 22 and 26 (-43%, -39% and -40%, respectively; $p < 0.0001$), consistent with a plateau in the mean dose of lomitapide administered across these visits.

Figure 9: Mean (95% CI) Percent Changes from Baseline in LDL-C in the Phase 3 Study UP1002/AEGR-733-005 through the Primary Endpoint of Week 26 using LOCF to Each Assessment (ITT Population, N=29)



A similar rapid decline in LDL-C was observed in the Phase 2 study UP1001 (Figure 10). By Week 8 of treatment at a mean dose of 7 mg, LDL-C had decreased by a mean of 7% from baseline (similar to the Week 2 time point in the Phase 3 study) with a mean decrease of 25% observed at Week 12 when the mean lomitapide dose was 20 mg. At Week 16, when the mean dose of lomitapide was 67 mg, LDL-C had decreased a mean of 51% from baseline. Notably, once subjects were off treatment, including lomitapide and all LLTs, the LDL-C levels rose rapidly and were above baseline levels by the assessment conducted 4 weeks post-treatment, clearly indicating the effect of lomitapide on LDL-C.

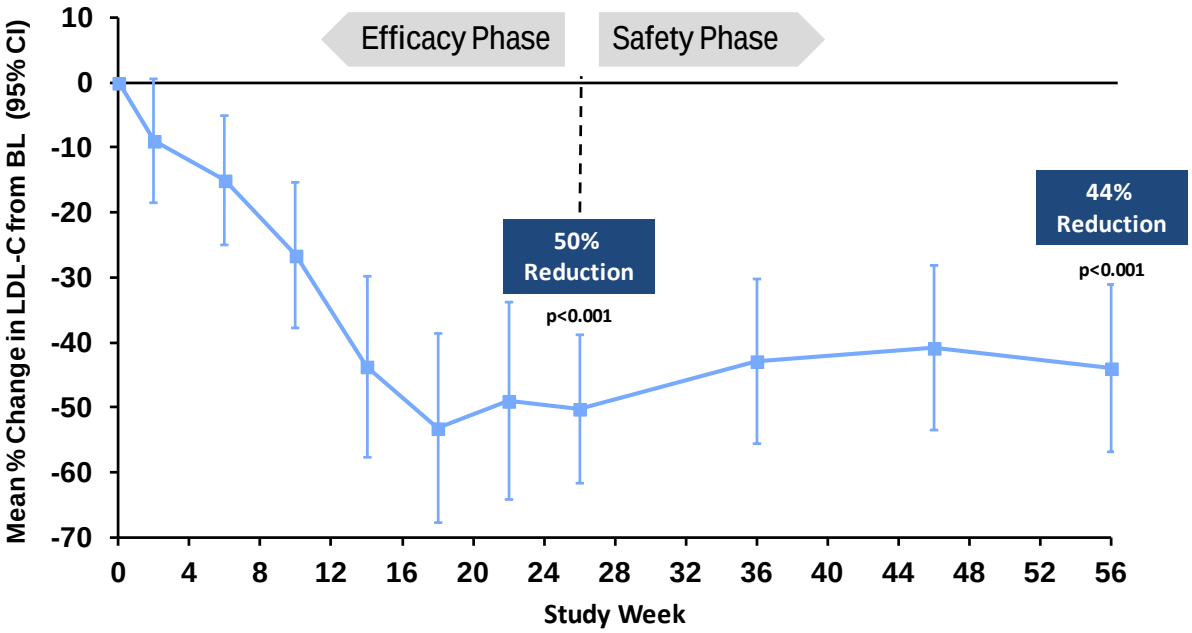
Figure 10: Mean (95% CI) Percent Changes from Baseline in LDL-C in the Phase 2 Study UP1001 (ITT Population, N=6)



The reductions in LDL-C were maintained over 1 year of treatment.

Figure 11 displays mean percent change in LDL-C through Week 56 of treatment for the Phase 3 HoFH study. The figure includes results for the 23 subjects who completed the Efficacy Phase through Week 26 and entered the Safety Phase; all of these subjects had data at Week 56 and completed the study. As shown, persistence of the lipid-lowering effect was observed through Week 56 of treatment during the time when subjects were permitted to modify their background lipid-lowering therapies. At Week 56, the mean percent change from baseline in LDL-C was -44%.

Figure 11: Mean (95% CI) Percent Change from Baseline in LDL-C Over Time during the Efficacy and Safety Phases, Study UP1002/AEGR-733-005 (Subjects who Completed the Efficacy Phase, N=23)



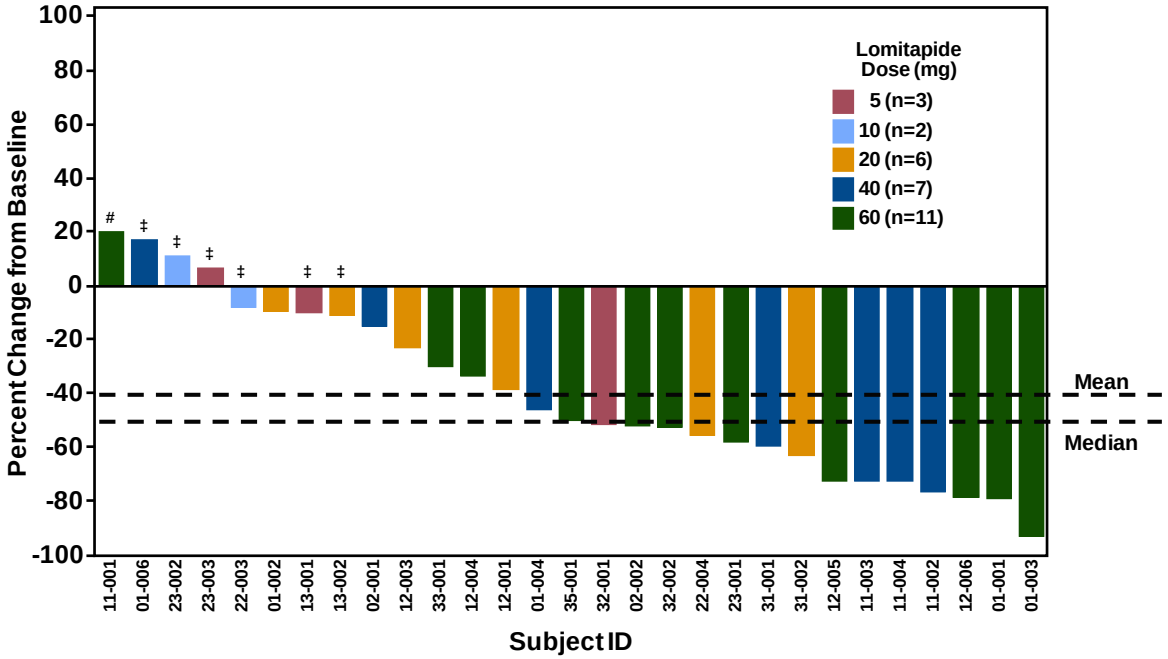
A repeated measures regression analysis model for overall percent change from baseline in LDL-C was conducted for the HoFH studies. The model included treatment, baseline LDL-C level, and week of lipid assessment as covariates. The LSM percent changes (decreases) from baseline in LDL-C were statistically significant in both Study UP1001 (p=0.0007) and in Study UP1002/AEGR-733-005 (p<0.0001). The only other significant factor in the model was study week (p<0.0001) controlling for baseline and dose level. Other sensitivity analyses conducted on percent change from baseline in LDL-C (see Section 5.3) gave consistent results showing statistically significant reductions to Week 26.

5.6.2 Responder Analyses Based on Change from Baseline in LDL-C: Phase 3 HoFH Study

The majority of subjects in the Phase 3 study achieved substantial reductions in LDL-C levels by Week 26, including those who did not escalate to the maximum dose.

Figure 12 presents a waterfall plot of percent change from baseline in LDL-C to Week 26 or the last assessment for subjects who discontinued prior to that time point. Overall, 16 (55%) of the 29 subjects had a reduction in LDL-C of >40% at Week 26 with 15 (52%) achieving a ≥50% reduction. Eight of these 15 subjects had escalated to the 60 mg dose of lomitapide, 4 were on the 40 mg dose, 2 were receiving 20 mg and 1 was receiving 5 mg at Week 26.

Figure 12: Waterfall Plot of Percent Change from Baseline in LDL-C at Week 26/LOCF by Subject, Study UP1002/AEGR-733-005 (ITT Population, N=29)



Subject was a responder after Week 26
‡ Subject discontinued from treatment prior to Week 26
Note: Dose is the final titrated dose administered at Week 26
Note: One subject (Subject 33-001), who is depicted as receiving 60 mg, received a maximum dose of 80 mg at Week 26 outside of protocol required criteria.

HoFH subjects receiving lomitapide in the Phase 3 study were able to achieve recognized target goals for LDL-C levels (>50% reduction, < 100 and < 70 mg/dL) that are known to reduce cardiovascular risk. This is rarely seen in clinical experience in patients with HoFH.

The NCEP-ATP III has recommended an LDL-C treatment target of <100 mg/dL for subjects at high-risk (NCEP, 2001) and a target of <70 mg/dL for subjects at very high-risk, which often requires >50% reduction in LDL-C levels (Grundy, 2004).

As a measure of clinical benefit, the proportions of subjects in the Phase 3 study who achieved a >50% reduction in LDL-C or who achieved LDL-C levels <100 or <70 mg/dL at 1 or more time points were assessed (Table 11). Overall, 72% (21 of 29) of subjects were able to achieve a >50% reduction in LDL-C at one or more time points through Week 56.

More than half (55%, 16 of 29) of the subjects were able to achieve an LDL-C level <100 mg/dL, including 9 (31%) with LDL-C <70 mg/dL at one or more time points through Week 56. Achievement of these target goals (<100 and <70 mg/dL) is rarely seen in clinical practice in subjects with HoFH.

Table 11: Proportion of LDL-C Responders, Study UP1002/AEGR-733-005 (ITT Population)

	TOTAL SUBJECTS (N=29)	
RESPONSE CATEGORY[a]:	N (%)	95% CI
>50% Reduction in LDL-C	21 (72.4)	52.8, 87.3
LDL-C <100 mg/dL	16 (55.2)	35.7, 73.6
LDL-C <70 mg/dL	9 (31.0)	15.3, 50.8

[a] Subjects were required to achieve the response at 1 or more time points on or after Week 8 of treatment.

As evidence of the lipid-lowering effect of lomitapide, some subjects on the study stopped or permanently reduced the frequency of apheresis after Week 26.

A review of all subjects who were on apheresis was conducted to assess if these subjects were able to stop apheresis or prolong the interval between apheresis treatments and maintain efficacy based on continued reduction in LDL-C levels from baseline. Note that subjects were not to stop or alter the intervals between apheresis treatments during the Efficacy Phase. Overall, 13 subjects who entered the Safety Phase were on apheresis. Among these 13 subjects, 4 (31%) either stopped (n=3) or permanently increased (n=1) the interval between apheresis treatments by Week 56. Of note, 2 additional subjects were able to permanently increase the interval between apheresis sessions between Weeks 56 and 78 of the study and 1 additional subject was able to permanently discontinue apheresis during the extension study AEGR-733-012.

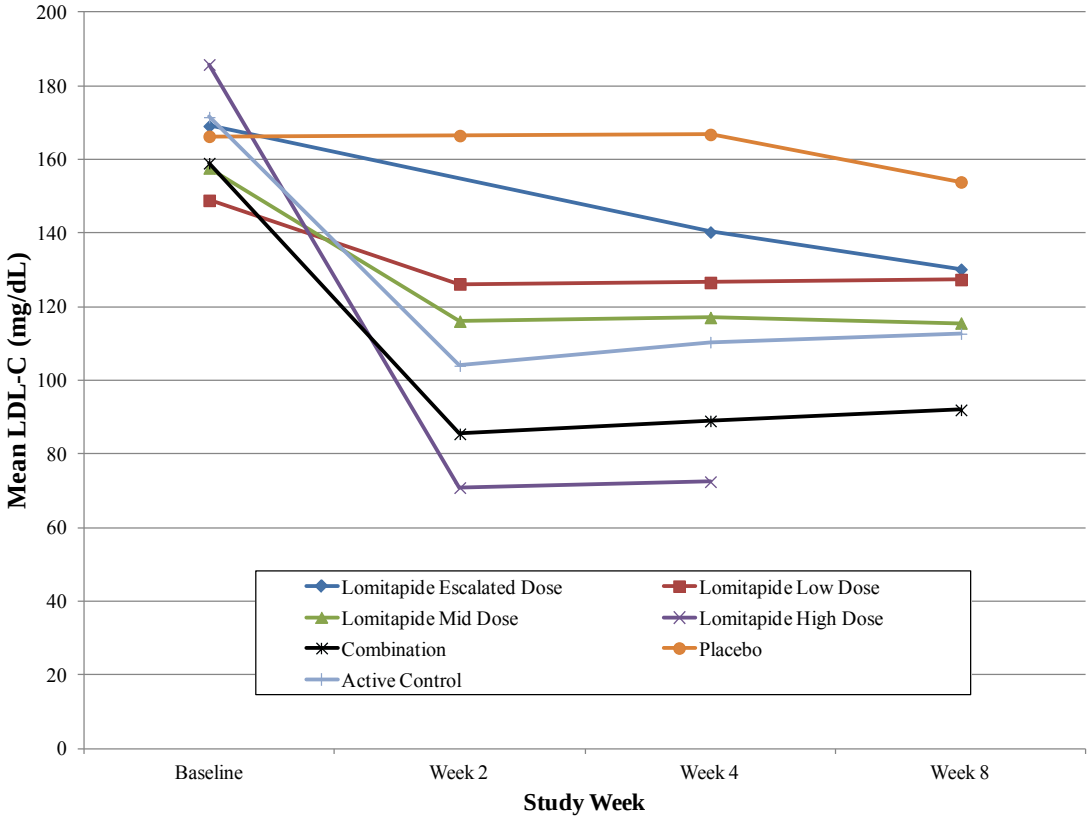
5.6.3 Change from Baseline in LDL-C: Elevated LDL-C and Other Cardiovascular Risk Factors Study Pool

Results of the Phase 2 studies in subjects with elevated LDL-C and other CV risk factors confirmed the significant LDL-C lowering effect observed in the HoFH studies.

Figure 13 displays mean LDL-C levels over time on study by treatment group in the Elevated LDL-C and Other CV Risk Factors Study Pool using LOCF methodology.

Consistent with the results in the HoFH population, mean LDL-C decreased rapidly in all active treatment groups in subjects with elevated LDL-C; the mean changes from baseline to Weeks 2, 4, and 8 using LOCF were statistically significant for all active treatment groups ($p<0.0001$) (see Appendix Table 23). Mean changes from baseline in the placebo group were not statistically significant at any study week. Results of the ANCOVA model indicated that all comparisons of active treatment to placebo were statistically significant at Weeks 2, 4 and 8 ($p<0.0001$) and that the difference across treatment groups also was significant ($p<0.0001$) (see Appendix Table 23).

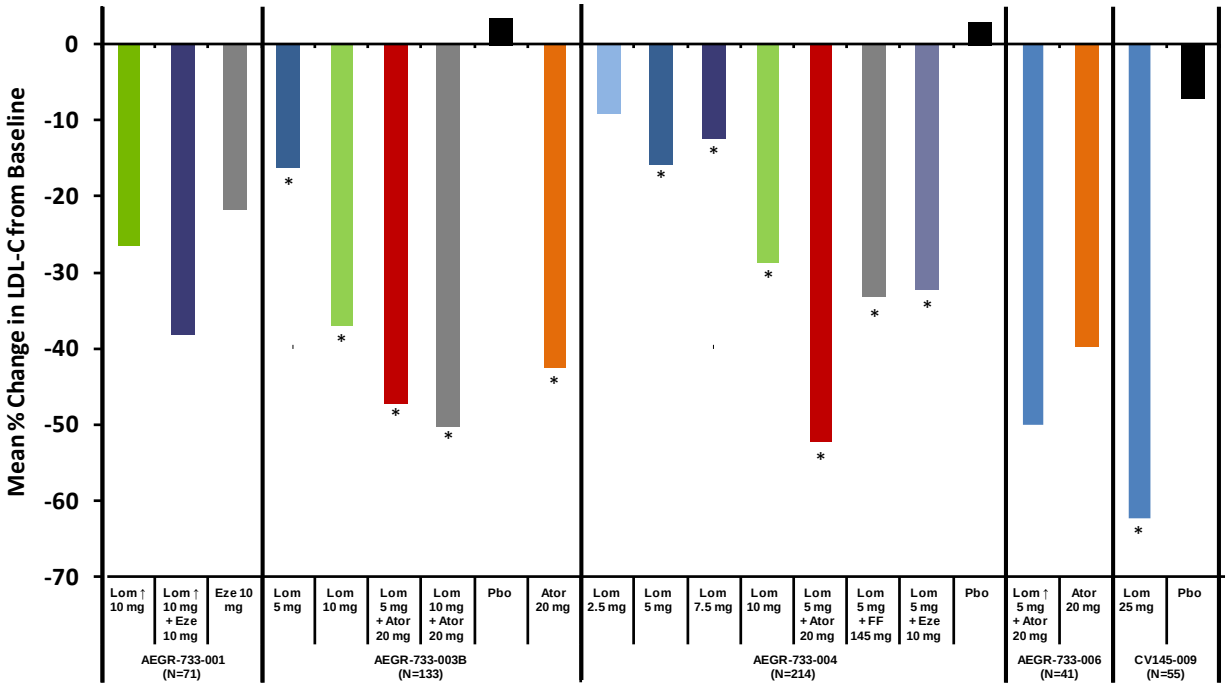
Figure 13: Mean LDL-C Levels by Study Week and Treatment Group Using LOCF, Phase 2 Studies in Subjects with Elevated LDL-C and Other Cardiovascular Risk Factors (Full Analysis Set)



Note: the lomitapide high-dose study (CV145-009) was a 4-week study

Figure 14 displays mean percent changes from baseline in LDL-C to Week 8 across the Phase 2 studies conducted in subjects with elevated LDL-C and other CV risk factors by dose level and combination therapy. As shown, lomitapide at doses ranging from 5 to 25 mg led to significant reductions relative to placebo in LDL-C across these studies. Co-administration of lomitapide with other LLTs led to incremental improvements in efficacy, in particular with atorvastatin. In those studies in which a placebo-control was included, the mean changes from baseline in LDL-C for subjects who received placebo were small (~ ±5%).

Figure 14: Mean Percent Changes from Baseline to Week 8[a] in LDL-C by Treatment Group and Study, Phase 2 Studies in Subjects with Elevated LDL-C and Other Cardiovascular Risk Factors



Abbreviations: Ator = atorvastatin, Eze = ezetimibe, FF = micronized fenofibrate, Lom = lomitapide, Lom ↑= lomitapide escalated doing, Pbo = placebo

* $p<0.05$ compared to placebo

[a] Data are at Week 4 for Study CV145-009 as this was a 4-week study.

5.7 Secondary Efficacy Variables

5.7.1 Change from Baseline in Total Cholesterol, Apo B, Non-HDL-C, and Triglycerides: HoFH Studies

Consistent with its mechanism of action (MOA) and the results observed with LDL-C, treatment with lomitapide led to significant and durable reductions in other atherogenic apo B containing lipoproteins.

Results for changes from baseline in the secondary efficacy endpoints of total cholesterol, non-HDL-C, apo B, and triglycerides were consistent with the primary endpoint of LDL-C for both Study UP1001 and Study UP1002/AEGR-733-005 showing the significant lipid-lowering effects of lomitapide in subjects with HoFH. Table 12 summarizes percent changes from baseline for these efficacy parameters to the primary time point of Week 16 in Study UP1001 and Week 26/LOCF in Study UP1002/AEGR-733-005, including results of the statistical analyses. As shown, mean percent changes from baseline to the Week 16 and Week 26/LOCF

assessments in the 2 studies, respectively, were statistically significant with clinically meaningful changes noted for all lipid parameters.

Table 12: Summary of Results of the Secondary Efficacy Variables, Percent Change from Baseline to Week 16 in Study UP1001 and Week 26/LOCF in Study UP1002/AEGR-733-005 (ITT Population)

EFFICACY VARIABLE STATISTIC	STUDY UP1001 (N=6)	STUDY UP1002/AEGR-733-005 (N=29)
Total Cholesterol, n	6	29
Mean (SD)	-58.4 (8.60)	-36.4 (28.2)
95% CI	-67.4, -49.4	-47.1, -25.7
Median	-56.7	-40.0
Minimum, Maximum	-68.7, -50.3	-81.4, 14.8
p-value[a]	<0.001	<0.001
Apo B, n	6	29
Mean (SD)	-55.6 (13.49)	-39.4 (30.01)
95% CI	-69.7, -41.4	-50.8, -28.0
Median	-57.0	-46.2
Minimum, Maximum	-70.0, -36.8	-90.4, 19.0
p-value[a]	<0.001	<0.001
Non-HDL-C, n	6	29
Mean (SD)	-60.1 (8.86)	-40.0 (29.66)
95% CI	-69.4, -50.8	-51.3, -28.8
Median	-58.7	-47.7
Minimum, Maximum	-70.5, -52.1	-89.7, 15.7
p-value[a]	<0.001	<0.001
Triglycerides, n	6	29
Mean (SD)	-65.2 (13.26)	-29.0 (55.72
95% CI	-79.1, -51.3	-50.2, -7.8
Median	-68.2	-44.6
Minimum, Maximum	-82.1, -43.9	-87.4, 168.8
p-value[a]	<0.001	0.009

Note: subjects on Study UP1001 were required to be off all LLTs; subjects on Study UP1002/AEGR-733-005 were receiving standard of care LLTs.

[a] p-value based on paired t-test

Consistent with the results for changes from baseline in LDL-C, there was a rapid and steady decline in total cholesterol, apo B, non-HDL-C, and triglyceride levels as the lomitapide dose was escalated in both the Phase 3 study UP1002/AEGR-733-005 and the Phase 2 study UP1001 (Figure 15 and Figure 16, respectively).

Stabilization in levels of these lipids and apo B was observed after ~Week 18 through Week 56 in Study UP1002/AEGR-733-005 as the mean dose of lomitapide stabilized. Triglyceride levels decreased through Week 18 with a small increase toward baseline by Week 26/LOCF and a

further small increase to Week 56; at Week 56 the median percent change from baseline in triglyceride levels was -33%.

Figure 15: Mean (95% CI) Percent Change from Baseline in Total Cholesterol, Apo B, non-HDL-C and Triglycerides in the Phase 3 Study UP1002/AEGR-733-005 Over Time During the Efficacy and Safety Phases (Subjects who Completed the Efficacy Phase, N=23)

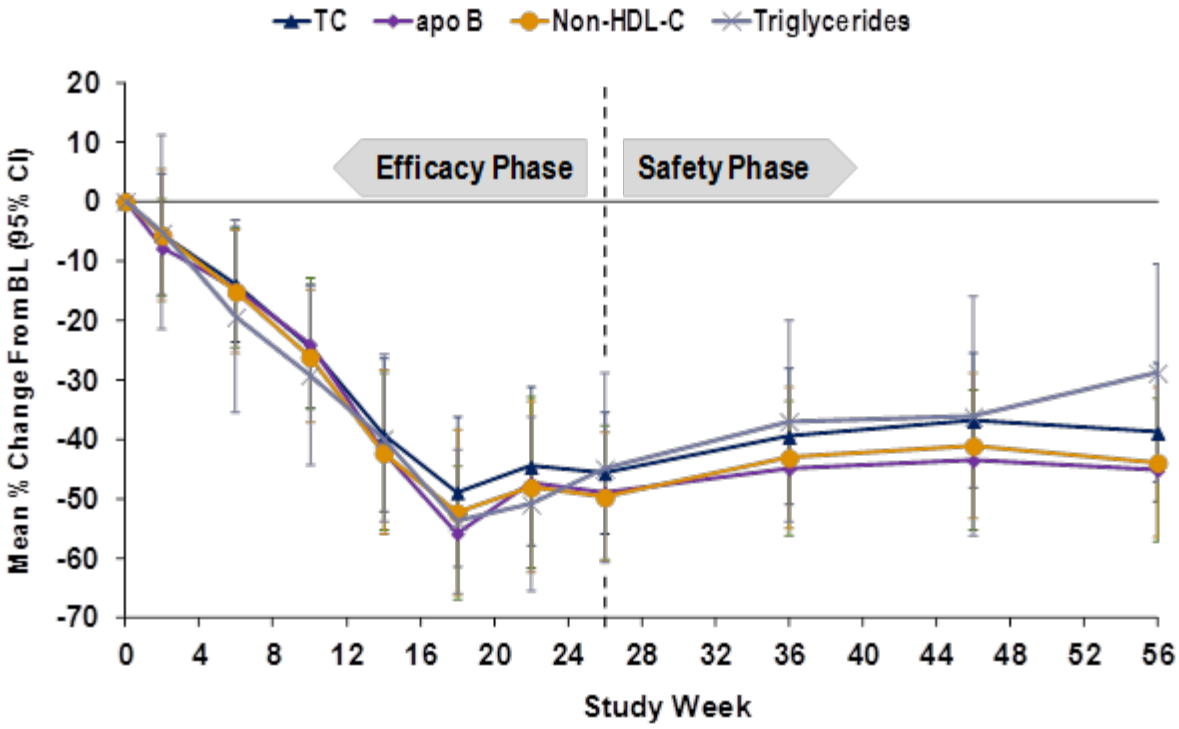
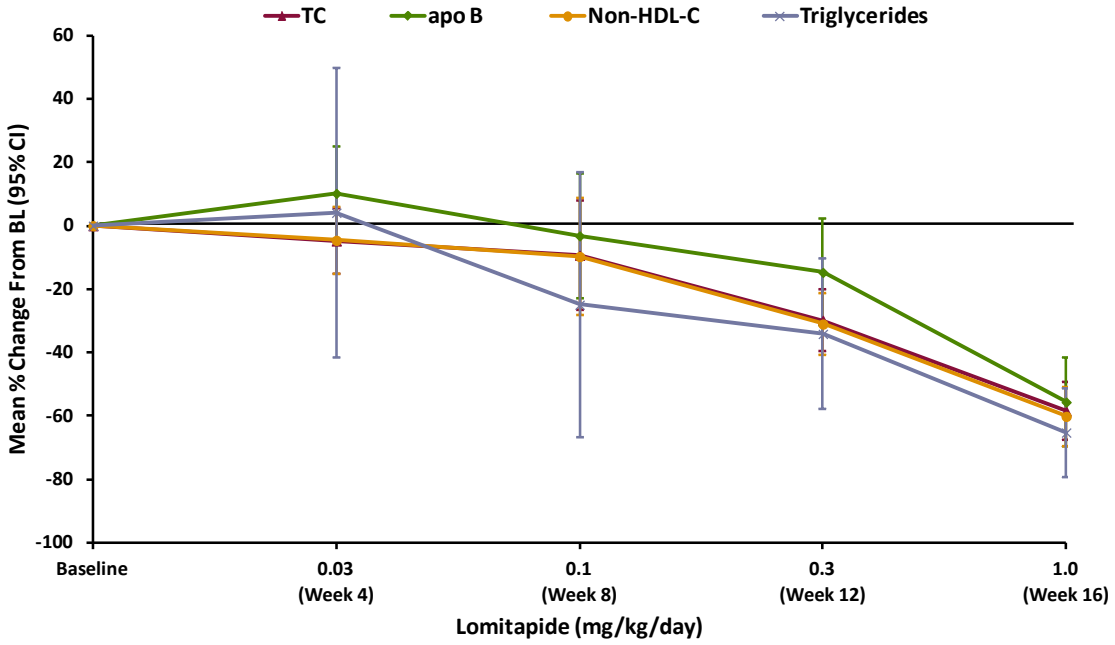


Figure 16: Mean (95% CI) Percent Change from Baseline in Total Cholesterol, Apo B, non-HDL-C and Triglycerides in the Phase 2 Study UP1001 Over Time (ITT Population, N=6)



5.7.2 Change from Baseline in Total Cholesterol, Non-HDL-C, Apo B and Triglycerides: Elevated LDL-C and Other Cardiovascular Risk Factors Study Pool

Results for analysis of the secondary efficacy endpoints of total cholesterol, non-HDL-C, apo B and triglycerides in subjects in the Elevated LDL-C and Other CV Risk Factors Study Pool were consistent with the results observed with LDL-C in this group and with the results observed in the HoFH studies (see Appendix Table 24). Treatment with lomitapide led to clinically meaningful and statistically significant decreases in all atherogenic apo B-containing lipoproteins.

5.8 Other Efficacy Variables

5.8.1 Change from Baseline in VLDL-C, HDL-C, Apo AI, Total Cholesterol/HDL-C Ratio, and Lp(a): HoFH Studies

Lomitapide treatment resulted in reductions in VLDL-C and Lp(a) and a reversible decrease in HDL-C.

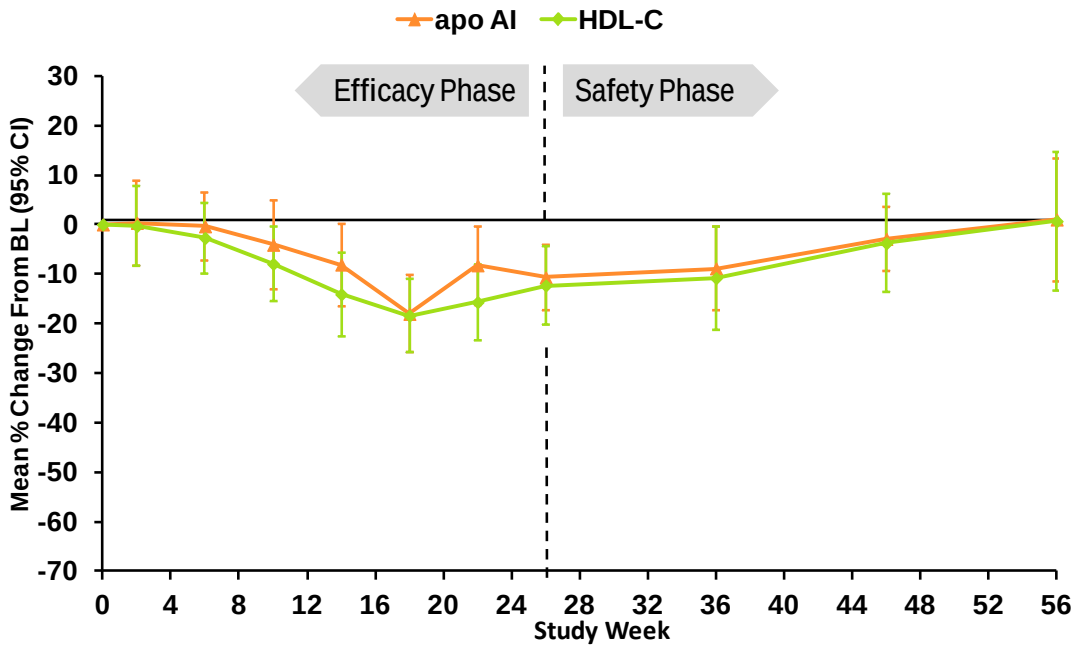
Consistent with its mechanism of action, treatment with lomitapide led to statistically significant mean percent decreases from baseline in VLDL-C to the primary efficacy time point of Week 16 in the Phase 2 study and to Week 26/LOCF in the Phase 3 study. Mean percent decreases from baseline were observed for Lp(a); however, the results were not statistically significant at Week 16 in UP1001 or Week 26 in UP1002/AEGR-733-005. By Week 56 in the Phase 3 study, the mean percent change from baseline in Lp(a) of -21% was statistically significant (p=0.0003).

Mean percent changes from baseline in HDL-C was -2% at Week 16 in the Phase 2 study and was -7% at Week 26/LOCF for the ITT population (N=29) in the Phase 3 study; similar results were observed for apo AI.

These lipid parameters were also evaluated over time through Week 56 for those 23 subjects who completed the Efficacy Phase of the Phase 3 study (Figure 17). Mean apo AI and HDL-C levels initially declined but by Week 56, mean levels were at baseline with a mean percent change from baseline of 1%.

Importantly, there was improvement in the total cholesterol/HDL-C ratio in both studies due to the substantial decrease in total cholesterol observed during treatment with lomitapide.

Figure 17: Mean (95% CI) Change from Baseline in HDL-C and Apo AI in the Phase 3 Study UP1002/AEGR-733-005 Over Time During the Efficacy and Safety Phases (Subjects who Completed the Efficacy Phase, N=23)



5.8.2 Change from Baseline in VLDL-C, HDL-C, Apo AI, Total Cholesterol/HDL-C Ratio, and Lp(a): Elevated LDL-C and Other Cardiovascular Risk Factors Study Pool

In general, the results of the analysis of VLDL-C, Lp(a), HDL-C, apo AI, and the total cholesterol/HDL-C ratio in subjects in the elevated LDL-C and other CV risk factors study pool were consistent with the results observed in the HoFH population. Statistically significant decreases were observed to Week 4 in VLDL-C for the higher lomitapide dose groups and the group that evaluated lomitapide coadministered with other LLTs. Percent changes from baseline to Week 4 were statistically significant in all active treatment groups for apo AI and HDL-C. As was observed in the HoFH studies, the total cholesterol/HDL-C ratio improved by Week 4 in all

active treatment groups and the changes were statistically significant for the low, mid and high dose lomitapide monotherapy groups and for lomitapide coadministered with other LLTs.

5.9 Analysis of Efficacy Results in Subgroups

Use of apheresis during the Phase 3 HoFH study did not impact the lipid-lowering effect of lomitapide.

For the Phase 3 study UP1002/AEGR-733-005, a planned subgroup analysis was conducted on changes from baseline in LDL-C based on subjects who were and were not receiving apheresis during the study. Based on the results of this analysis, a post-hoc analysis using a mixed-model repeated-regression analysis, accounting for multiple observations per subject, was conducted to assess potential differences in percent change from baseline to Week 26 in lipid parameters for subjects who did and who did not receive apheresis. The model included treatment with apheresis (yes, no), baseline lipid level, and categorical study week as fixed parameters and a study week-by-apheresis interaction. A t-test was applied to assess the differences in least square means for percent change from baseline to Week 26 across the 2 subgroups.

There were no significant differences noted for any lipid parameter for percent change from baseline to Week 26, including LDL-C, total cholesterol, apo B, triglycerides, non-HDL-C, VLDL, HDL-C, apo AI or Lp(a) for subjects receiving or not receiving apheresis.

Table 13: Estimated Differences in Percent Change from Baseline in Lipid and Lipoprotein Levels for Subjects Receiving and Not Receiving Apheresis, Study UP1002/AEGR-733-005 (ITT Population, N=29)

Lipid Parameter	Did not Receive Apheresis (N=11) LSM (SD)	Received Apheresis (N=18) LSM (SD)	Estimated Difference (SD) (Apheresis vs. No apheresis)	p-value
LDL-C	-55.09 (8.94)	-47.99 (7.51)	7.10 (11.70)	0.5448
Total Cholesterol	-49.81 (8.15)	-43.81 (6.86)	6.00 (10.68)	0.5753
apo B	-53.20 (8.22)	-47.88 (6.92)	5.31 (10.83)	0.6246
Non-HDL-C	-54.16 (8.89)	-48.25 (7.47)	5.90 (11.65)	0.6132
Triglycerides	-41.24 (10.63)	-45.20 (9.03)	-3.96 (13.97)	0.7772
VLDL-C	-41.32 (10.67)	-45.21 (9.06)	-3.89 (14.03)	0.7820
HDL-C	-12.40 (5.34)	-10.25 (4.59)	2.16 (7.04)	0.7598
TC/HDL-C	-43.15 (7.88)	-37.09 (6.64)	6.07 (10.35)	0.5587
apo A1	-9.23 (4.54)	-11.31 (3.91)	-2.07 (5.99)	0.7302
Lp(a)	-23.13 (9.99)	-12.80 (8.56)	10.33 (13.24)	0.4364

Results from a mixed-model repeated-measures analysis; p-value based on t test.

Changes from Baseline in LDL-C also were examined across subgroups in the Elevated LDL-C and Other CV Risk Factors Study Pool as this pool included a large enough sample size to assess results across smaller subgroups. Subgroups assessed included age, gender, race, BMI, smoking status, and baseline LDL-C.

There were no clinically meaningful or consistent differences in mean percent changes from baseline to Weeks 4 or 8 in LDL-C by age (<65 and ≥65 years), gender, race (Caucasian and non-Caucasian), BMI (<30 and ≥30 kg/m^2), or smoking status. When mean percent changes from baseline in LDL-C were analyzed by baseline LDL-C level (tertiles: ≤146, 147 to 173, and ≥174 mg/dL), subjects with higher baseline LDL-C tended to have a greater mean decrease from baseline following active treatment than subjects with lower baseline LDL-C.

5.10 Efficacy Conclusions

The significant reduction in LDL-C and other apo B-containing lipoproteins observed in subjects with HoFH in the Phase 3 study reflect the pharmacodynamic effect of lomitapide based on the following factors:

- The design of the Phase 3 study included elements to control potential confounding factors, including: 1) a Run-in Phase for stabilization of background LLTs and the low fat diet; 2) determination of baseline LDL-C based on an average of 2 measures (Week -2 and Day 0); and 3) a requirement that all LLTs remain stable prior to determination of the primary endpoint at Week 26.
- There was minimal change in LDL-C levels during the Run-in Phase of the study indicating that stabilization of LLTs and the institution of the low-fat diet during this phase had no meaningful impact on lowering LDL-C levels in these subjects.
- Following initiation of lomitapide treatment, there was a rapid and significant reduction in LDL-C by Week 2. The reduction continued as the dose was escalated. The magnitude of the reduction at Week 26, following escalation to each subject's maximum tolerated dose, was substantial with a mean percent change in LDL-C using LOCF methods of -40%.

Furthermore, the significant reduction in LDL-C and other apo B-containing lipoproteins observed in subjects with HoFH in the Phase 3 study is supported by data from Phase 2 studies:

- In the Phase 2 HoFH study that evaluated lomitapide monotherapy, a mean reduction of 51% was observed after 16 weeks on lomitapide. Notably, there was a rapid return to baseline levels following discontinuation of lomitapide.
- In Phase 2 studies conducted in subjects with elevated LDL-C and other CV risk factors, statistically significant reductions in LDL-C were observed relative to placebo. The demonstration of efficacy in subjects with hypercholesterolemia would be expected to predict response in subjects with HoFH as the mechanism of action of lomitapide is independent of LDL receptor function.

Given the fact that elevations in LDL-C causally mediate CVD in HoFH patients, reduction of LDL-C in these patients is expected to confer clinical benefit.

6 OVERVIEW OF SAFETY

6.1 Nonclinical Findings

6.1.1 General and Safety Pharmacology

The effects of lomitapide on the central nervous system and other organ systems (i.e., GI, respiratory, cardiovascular and renal) were evaluated in a battery of *in vitro* and *in vivo* general and safety pharmacology studies. The results did not reveal any important safety issues for humans administered lomitapide at the recommended doses of 5 to 60 mg/day.

6.1.2 Repeat-Dose Toxicity: Target Organs

Pivotal repeat-dose studies in the primary toxicology species were conducted for 1 to 6 months in rats and 1, 6 and 12 months in dogs. Doses up to 50 mg/kg in rats and 20 mg/kg in dogs were evaluated in these studies. These doses corresponded to systemic exposures (area under the curve [AUC]) to lomitapide up to approximately 6000 ng•hr/mL in rats and 20000 ng•hr/mL in dogs; for reference, the AUC in humans at 60 mg is about 70 ng•hr/mL. Common target organs in these studies were the liver and small intestine (also pharmacologic target organs). The lung was also a target organ in rodents (mostly rats) and the testis was a target organ in dogs at high systemic exposures to lomitapide and the M1, M2, and M3 metabolites. Changes related to the liver, lung, and small intestine were shown to be reversible in rats (dog studies did not include reversibility). As previously mentioned, M1 and M3 are the primary metabolites in humans; they have no pharmacologic activity at clinically relevant levels. M2 is a very minor metabolite in humans.

Liver

Drug-related increases in serum ALT, AST, and ALP were observed in rats and increases in serum ALT and AST were observed in dogs. In 1- and 6-month studies in rats, the increases were modest (i.e., mean values ≤ 3× control means) even at overtly toxic doses. In dogs, substantive increases in serum ALT were observed in 1- and 6-month studies (i.e., mean values ≤7× and <5× control means; individual values up to 25× and 14× control means). In these studies serum AST increases were modest (mean values ≤3× and individual values ≤5× control means). In a 1-year study in dogs, only serum AST was minimally increased (<2× control mean) in females. The primary microscopic finding in the liver was lipid vacuolation. As previously discussed, this is secondary to the MOA of lomitapide. The vacuolation was greater in rats (minimal to marked) compared to dogs (not present to minimal), even at higher systemic exposures to lomitapide and its metabolites. Higher levels of lomitapide in the liver of rats compared to dogs may have played a role in the increased severity of this change in rats. Increased liver weights (≤90% in rats and ≤30% in dogs relative to controls) often accompanied the lipid vacuolation. Subacute inflammation (minimal to moderate) and single-cell necrosis

(minimal to mild) were observed in rats in a 6-month study. Subacute inflammation in the liver appears to be specific to rats because it was not a drug-related finding in 3-month studies in mice or in 1-, 6-, and 12-month studies in dogs at plasma and/or liver exposures to lomitapide and the M1, M2, and M3 metabolites higher than those at the threshold dose for this change in rats. Thus the relevance of this finding for humans is questionable. Single-cell necrosis (minimal) in the liver was a drug-related finding in a 1-month study in dogs, but not in 6- and 12-month studies in dogs or in a 2-year study in rats in which plasma and/or liver exposures to lomitapide and the M1, M2, and M3 metabolites exceeded those at the threshold dose for this change in rats. Thus, the relevance of this finding for humans given lomitapide on a chronic basis is unclear. In general, with the exception of the 1-month study in dogs, in which there appeared to be an association between serum ALT values and single-cell necrosis (minimal), there was no apparent association between increases in serum transaminases /ALP and the observed microscopic changes in the liver. Increased serum transaminases associated with MTP inhibition are not unexpected with lomitapide as they are often observed in patients with abetalipoproteinemia (Kane and Havel, 2001; Zamel, 2008).

In a lifetime study in rats (discussed below), there were increased incidences of focal/multifocal fibrosis (mostly minimal to slight) and cystic degeneration (males only; mostly minimal) in the liver. Both were primarily observed late in the study. Fibrosis was random and non-connecting; the majority of the liver was unaffected by fibrosis. Increased incidences of cystic degeneration were not observed in females despite a higher exposure to lomitapide compared to males.

Small Intestine

Changes in the small intestine were limited to lipid vacuolation of absorptive epithelial cells across species (i.e., consistent with the MOA of lomitapide). Minimal to severe and minimal to moderate vacuolation was observed in rats and dogs.

Lung

Pulmonary histiocytosis (minimal to marked) was a drug-related finding in a 6-month study in rats. It was also a drug-related change in a 3-month dietary study in mice; however, the severity was much less than that in rats (i.e., trace to minimal). Pulmonary histiocytosis was not a drug-related finding in repeat-dose studies in dogs. Pulmonary phospholipidosis was ruled out based on an evaluation of numerous rodent lungs using transmission electron microscopy. It was concluded that the histiocytosis noted by light microscopy reflected the excessive accumulation of neutral lipids in the cytoplasm of alveolar macrophages, which is consistent with the MOA of lomitapide. The histiocytosis was not associated with any adverse effects on alveolar macrophage function. Overall, this appears to be a drug-related change specific to rodents (mostly rats).

Testis

Testicular degeneration was observed in a 6-month study in dogs at high mean systemic exposures (AUC) to lomitapide (approximately 205×) and its metabolites relative to those in humans at 60 mg. It was not observed in the 1-year study in dogs in which lomitapide AUC values were ≤64× higher than in humans at 60 mg. Thus, it was concluded that testicular degeneration is not an important safety issue for humans.

6.1.3 Genotoxicity

Lomitapide was not mutagenic in the Ames assay or a cytogenetics study in human lymphocytes. Lomitapide was not clastogenic in an oral micronucleus study in rats at doses ranging from 10 to 1000 mg/kg daily for 3 days. Thus, lomitapide poses no genotoxic risk to humans.

6.1.4 Carcinogenicity

In a 2-year study in mice, lomitapide was administered at doses of 0.3, 1.5, 7.5, 15, and 45 mg/kg/day. There were statistically significant increases in the incidences of hepatocellular adenomas and carcinomas at doses ≥1.5 mg/kg/day in males and ≥7.5 mg/kg/day in females (≥2× and ≥9×, respectively, the human exposure at 60 mg based on AUC). There were also statistically significant increases in the incidences of small intestinal carcinomas at doses ≥15 mg/kg/day in males and combined adenomas and carcinomas at 15 mg/kg/day in females (≥26× and 22× the human exposure at 60 mg based on AUC). Although not statistically significant, tumors in the small intestine were also observed in a total of 5 of 179 males at 0.3, 1.5, and 7.5 mg/kg/day (AUCs <1× to 11× that in humans at 60 mg). Three of the tumors were adenomas that did not result in moribundity or mortality and two were carcinomas, only one of which was deemed to be fatal (mouse at 7.5 mg/kg after 98 weeks of dosing). Thus, at exposures up to 11× that in humans at 60 mg, only 1 of 179 mice had a fatal tumor that occurred after 98 weeks of dosing (equivalent to about 70 years in humans). With regard to the liver, it is the most common target organ for tumors in chronic rodent bioassays and the mouse is the most sensitive species (Holsapple, 2006). Thus, it is not surprising that increased incidences of liver tumors have been observed with a number of marketed drugs, including the statins (Brambilla, 2012). For example, simvastatin caused up to a 90% incidence of hepatocellular carcinomas in mice at 4× the exposure in humans at 80 mg . It is also important to note that lomitapide showed no evidence of genotoxicity or immunotoxicity, and no cellular injury in the liver and small intestine was observed in mice (i.e., tumorigenic mechanisms that could be relevant to humans). In addition, the historic difficulty in extrapolating tumor findings in animals to predict risk in humans is well known (i.e., a number of marketed drugs are rodent carcinogens but those with definitive evidence of carcinogenicity in humans are predominately chemotherapeutic and immunosuppressant agents) (Peto, 1980; Brambilla, 2012).

In a 2-year oral study in rats, lomitapide was administered at doses of 0.25, 1.7 and 7.5 mg/kg/day in males and 0.03, 0.35, and 2.0 mg/kg/day in females. There were no statistically significant increases in tumor incidences; exposures to lomitapide were 6× and 8× the human exposure at 60 mg based on AUC, respectively. There was an increased incidence of pancreatic acinar-cell adenomas in males at 7.5 mg/kg that was considered to be treatment-related; this is a common spontaneous tumor in male rats. There were no pancreatic acinar-cell carcinomas and the majority of tumors were observed at terminal sacrifice; importantly, none were associated with moribundity or mortality. At the highest doses in males and females, 1 of 120 rats had a small intestinal carcinoma.

Although it is not possible to state unequivocally that the tumor findings in rodents do not pose any risk to humans, based on a weight of evidence approach, it was concluded that the risk of this theoretical concern is outweighed by the benefits to patients associated with LDL-C reduction achieved with lomitapide.

6.1.5 Reproductive and Developmental Toxicity

Lomitapide demonstrated selective developmental toxicity in rats at a clinically relevant exposure. Reduced lipophilic nutrient transfer may be responsible for this toxicity as robust MTP messenger ribonucleic acid (mRNA) expression and activity have been identified in the murine inverted yolk sac which encapsulates the embryo/fetus; rats and rabbits, but not humans, share a similar yolk sac structure (Slentrol [EPAR] 2007). Thus, the embryo-fetal toxicity observed in rats may not be relevant for humans. However, because there are no adequate and well-controlled studies of lomitapide in pregnant women, the Sponsor is recommending that lomitapide not be administered to pregnant women or women of reproductive potential without adequate use of contraception.

6.2 Safety Monitoring in Clinical Trials

Lomitapide is a first-in-class MTP inhibitor and based on its known mechanism of action and results of nonclinical studies, it was anticipated that the primary adverse effects of lomitapide would be related to lomitapide's site of action, the liver and small intestine.

All studies included in the lomitapide development program included a thorough evaluation of the safety of treatment. Standard safety evaluations conducted in all studies included physical examinations; vital signs and weight assessments; clinical laboratory assessments, including hematology, chemistry, LFTs and pregnancy tests (as applicable); and 12-lead ECGs; as well as monitoring for AEs and concomitant medication usage.

In addition, based on the known mechanism of action, nonclinical data and information obtained in early phase studies, the Phase 2 and 3 studies conducted with lomitapide included special approaches to subject safety during the conduct of the clinical trials as outlined below.

Liver functions tests, including ALT, AST, alkaline phosphatase and bilirubin, were monitored in all trials. In the HoFH studies, algorithms were provided that detailed dose modification, including reduction and treatment discontinuation, in the event of elevations in these parameters.

Both the Phase 2 and Phase 3 studies in HoFH and 3 of the Phase 2 studies conducted in subjects with elevated LDL-C and other CV risk factors included an evaluation of triglyceride content in the liver. The studies included NMRS and/or MRI of the liver at baseline and over time on treatment. Two of the studies also evaluated changes in hepatic fat percent after subjects were off lomitapide to assess reversibility of hepatic fat accumulation. NMRS of the liver with the use of chemical-shift techniques has been shown to evaluate fat content of the liver accurately and is considered to be the state of the art measurement for quantitative hepatic fat assessments (Rinella, 2003; Fishbein, 2005).

It is known that patients with the autosomal recessive disorder abetalipoproteinemia, which is a condition resulting from inhibition of assembly of apo B-containing lipoproteins (Stein, 2009) and is characterized by very low levels of plasma cholesterol and triglycerides and a virtually complete absence of plasma apo B (Benayoun, 2007), have deficiencies in fat-soluble vitamins, particularly vitamin E. Given this fact and as subjects in both HoFH studies were placed on strict low-fat diets to improve GI tolerability, fat-soluble nutrients, including vitamins and fatty acids, were monitored in both HoFH studies; weight was also carefully monitored. Further, subjects were provided dietary supplements and dietary counseling in both studies. In Study UP1001, subjects were provided a standard multivitamin supplying 100% of the current dietary reference intake for all essential vitamins and minerals and instructed on how to consume 2% of energy from essential fatty acids. However, it was noted that fatty acid levels declined in the subjects enrolled in this Phase 2 study. Therefore, in the Phase 3 study subjects were instructed to take dietary supplements of 400 IU of vitamin E and approximately 200 mg linoleic acid, 110 mg EPA, 220 mg ALA and 80 mg DHA per day (supplied by the Sponsor). As detailed earlier, the dose escalation regimen and appropriate instruction to follow a low-fat diet were introduced into the Phase 2 and 3 study designs to reduce GI side effects.

In Study UP1001, 2 subjects who were receiving warfarin concomitantly with lomitapide required warfarin dose adjustments based on INR levels. Therefore, for the Phase 3 trial, subjects receiving concomitant warfarin were to be monitored closely and the warfarin dose adjusted as necessary guided by frequent INR results that were obtained at each site's local laboratory. The interaction with warfarin has since been investigated and confirmed (AEGR-733-013).

Based on the nonclinical data showing excessive accumulation of neutral lipids leading to histiocytosis, several of the Phase 2 studies and both studies conducted in subjects with HoFH included PFTs, including FVC, FEV_1, forced expiratory flow (25% - 75%) (FEF_{25-75}), and carbon monoxide lung diffusion (DLCO) parameters.

Aegerion has also conducted a thorough QT study to assess the potential for lomitapide to prolong the QTc interval (see Section 6.16).

6.3 Pooling of Data for Analyses of Safety

The primary data to support the safety of lomitapide in patients with HoFH are derived from the HoFH studies, which includes data from both the Phase 2 study UP1001 and the Phase 3 study UP1002/AEGR-733-005. Additional safety data are available from the Phase 3 extension study AEGR-733-012 through a data cut-off of 31 December 2011.

The largest pool of data for summary safety presentations included in the NDA is the Elevated LDL-C and Other CV Risk Factors Study Pool, which includes 676 subjects treated in 7 placebo- and/or active-controlled Phase 1 and 2 studies conducted in adults with elevated LDL-C and other CV risk factors. Note that this study pool differs from the pool presented for efficacy results by the inclusion of 2 Phase 1 studies. This pool of studies includes subjects that received treatment from 2 to 12 weeks, either lomitapide monotherapy, lomitapide coadministered with other LLDs, placebo, or active control. Tabulations from this pool also were produced for studies that evaluated lomitapide monotherapy; a total of 462 subjects are included in these tabulations. Data for the Elevated LDL-C and Other CV Risk Factors Study Pool are summarized for subjects who received lomitapide monotherapy (across low [2.5, 5 and 7.5 mg], mid [10 mg], high [25, 50 and 100 mg] and escalated [2.5 to 7.5 and 5 to 10 mg] dose groups), subjects who received lomitapide in combination with other LLDs, subjects who received placebo, and subjects who received active control treatments.

The integrated safety summary included in the NDA also provided summaries of safety data from 5 single-dose studies conducted in healthy volunteers, 6 drug-drug interaction studies, and studies conducted in subjects with renal and hepatic impairment, which are not summarized here as these are single-dose studies or cross-over studies of limited duration. The PK results of the drug-drug interaction studies and the studies conducted in subjects with renal and hepatic impairment are summarized in Section 3.

Note that the safety data presented in the NDA for the Phase 3 HoFH study were based on results through the Week 56 assessment; since that time the study has completed and final safety results were provided to the agency in the 4-Month Safety Update Report submitted on June 27, 2012. In addition, the 4-Month Safety Update Report also included safety data from the ongoing Phase 3 extension study to the pivotal study, AEGR-733-012. Safety results presented in this document are based on the final data from the Phase 3 study (i.e., through Week 78) and where applicable, data from the ongoing extension study are summarized.

6.4 Disposition and Exposure for Subjects in the Safety Population

6.4.1 Disposition and Exposure: HoFH Studies

Subject disposition in the HoFH Studies UP1001 and UP1002/AEGR-733-005 is presented in Section 5.4.1, Table 6. All 6 subjects treated in Study UP1001 completed the study through the Week 20 follow-up assessment. In the Phase 3 study, 23 of the 29 subjects treated completed the study through Week 78. Among the 23 subjects who completed the Phase 3 study through Week 78, 19 were enrolled in the extension study AEGR-733-012 for continued treatment with lomitapide. Among the 19 subjects enrolled, 16 remained on treatment as of the data cut-off date of 31 December 2011 for reporting in the 4-month Safety Update Report and 3 (17%) had discontinued. One subject was removed from the study based on noncompliance with study procedures, 1 subject discontinued because of a planned pregnancy, and 1 subject was terminated from the study by the Sponsor because of transaminase elevations >5×ULN and non-compliance with instruction to limit alcohol intake. The subject who discontinued due to a planned pregnancy has since re-entered the study.

In Study UP1001, median total dose of lomitapide administered was 2491 mg over a median duration of treatment of 115 days (16.4 weeks). In this study, subjects received treatment for a duration ranging from 112 to 148 days.

Table 14 summarizes exposure to lomitapide for studies UP1002/AEGR-733-005 and the extension study AEGR-733-012. Median duration of treatment for the 29 subjects across the 2 studies was 736 days (2.0 years). Twenty-three of the 29 subjects had received lomitapide for more than 1 year with 15 exposed for 2 years or more as of the 31 December 2011 data cut-off.

Compliance with the low-fat diet was assessed during the Phase 3 study by use of dietary records. During the study, mean percent energy from dietary fat ranged from 24 to 27%.

Table 14: Summary of Exposure to Lomitapide in Studies UP1002/AEGR-733-005 and AEGR-733-012, and Overall (Safety Populations)

EXPOSURE PARAMETER	UP1002/AEGR-733-005 (N=29)	AEGR-733-012[a] (N=18)	OVERALL[b] UP1002/AEGR-733-005 & AEGR-733-012 (N=29)
Total Dose (mg), n	28[3]	18	28[c]
Mean (SD)	15214.3 (10083.46)	14691.9 (10447.83)	24659.1 (18999.57)
Median	17485.0	10700.0	26555.0
Minimum, Maximum	20, 28870	3240, 40080	20, 68770
Duration of Treatment (days), n	29	18	29
Mean (SD)	443.9 (193.42)	370.0 (187.98)	673.6 (374.15)
Median	539.0	381.5	736.0
Minimum, Maximum	4, 560	84, 728	4, 1274
Duration of Treatment (days), n (%)			
1-30	1 (3.4)	0	1 (3.4)
31-91	3 (10.3)	2 (11.1)	3 (10.3)
92-182	2 (6.9)	1 (5.6)	2 (6.9)
183-365	0	5 (27.8)	0
366-545	13 (44.8)	5 (27.8)	4 (13.8)
546-730	10 (34.5)	5 (27.8)	4 (13.8)
731-1096	0	0	10 (34.5)
1097-1461	0	0	5 (17.2)

[a] Data for Study AEGR-733-012 are as of the cut-off of 31 December 2011
[b] Includes data through the final visit Week 78/84 from Study UP1002/AEGR-733-005 pooled with data through 31 December 2011 for Study AEGR-733-012.
[c] For one subject, total dose could not be determined as the subject was not compliant with dosing.

6.4.2 Disposition and Exposure: Elevated LDL-C and Other CV Risk Factors Study Pool

An overview of subject disposition in the Elevated LDL-C and Other CV Risk Factors Study Pool is provided in Table 15. A total of 676 subjects are included in this pool, of whom 482 were treated with lomitapide and 194 received either placebo or active control. Across these studies, 151 (22%) of the 676 subjects discontinued from treatment prematurely, primarily due to GI AEs.

Table 15: Subject Disposition, Elevated LDL-C and Other Cardiovascular Risk Factors Study Pool

DISPOSITION PARAMETER	ELEVATED LDL-C AND OTHER RISK FACTORS[A]
Received at Least One Dose of Study Medication	676
Prematurely Discontinued Study Medication	151 (22.3)
Reason for Early Discontinuation of Study Medication:	
Adverse Event	128 (18.9)
Withdrawal by Subject	14 (2.1)
Lost to Follow-up	2 (0.3)
Non-compliance with Study Drug	0
Death	0
Other	7 (1.0)

[a] Studies AEGR-733-001, AEGR-733-003b, AEGR-733-004, AEGR-733-006, CV145-002, CV145-009 and CV145-010

Across lomitapide dose groups in the Elevated LDL-C and Other Risk CV Factors Study Pool, median total lomitapide exposure was 613 mg in the escalated-dose group (n=77), 408 mg in the low-dose group (n=244), 370 mg in the mid-dose group (n=99), and 700 mg in the high-dose group (n=62). The median durations of treatment were comparable in the lomitapide escalated-dose (82 days) and low-dose (83 days) groups, and were lower in the mid-dose (37 days) and high-dose (17 days) groups. Median durations of treatment were 52 and 57 days in the placebo and active control groups, respectively. Note that the differences observed in treatment duration are related to both study design (studies varied in duration from 2 to 12 weeks) as well as early discontinuations from treatment.

6.5 Demographic and Baseline Characteristics of the Safety Population

Demographic and baseline characteristics for subjects enrolled in the HoFH studies UP1001 and UP1002/AEGR-733-005 are provided in Section 5.5.1. Subjects who were enrolled in the extension study AEGR-733-012 had previously participated in the Study UP1002/AEGR-733-005, and thus, the demographic characteristics of the 19 subjects enrolled in the extension study AEGR-733-012 were similar to those in Study UP1002/AEGR-733-005.

As shown in Table 16, the demographic characteristics were generally comparable across treatment groups for the Elevated LDL-C and Other CV Risk Factors Study Pool.

Table 16: Summary of Demographic Characteristics: Elevated LDL-C and Other Cardiovascular Risk Factors Study Pool (Safety Population)

PARAMETER	LOMITAPIDE DOSE GROUP[a]				COMPARATOR	
	Escalated (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)
Age (years), n	77	244	99	62	115	78
Mean (SD)	56.6 (6.96)	52.0 (10.80)	51.8 (11.62)	46.2 (10.60)	49.0 (12.17)	56.2 (8.13)
Minimum, Maximum	40, 71	20, 70	21, 70	26, 65	22, 69	34, 71
Number (%) Male	39 (50.6)	121 (49.6)	41 (41.4)	42 (67.7)	64 (55.2)	31 (39.7)
Number (%) ≥65 years	9 (11.7)	28 (11.5)	17 (17.2)	1 (1.6)	10 (8.7)	13 (16.7)
Number (%) Caucasian	60 (77.9)	177 (72.5)	71 (71.7)	42 (67.7)	90 (77.6)	65 (83.3)
BMI, n (%)						
<30 kg/m²	47 (61.0)	174 (71.6)[c]	73 (73.7)	51 (82.3)	86 (74.1)	53 (67.9)
≥30 kg/m²	30 (39.0)	69 (28.4)[c]	26 (26.3)	11 (17.7)	30 (25.9)	25 (32.1)
Family History of Coronary Heart Disease - n (%)[b]	22 (28.6)	30 (12.3)	22 (25.3)	NA	11 (18.3)	23 (29.5)
History of Hypertension - n (%)[b]	32 (41.6)	59 (24.2)	24 (27.6)	NA	14 (23.3)	25 (32.1)
Current Smoker - n (%)[b]	17 (22.1)	24 (9.8)	14 (16.1)	NA	10 (16.7)	18 (23.1)

[a] Includes subjects who received lomitapide alone and coadministered with other lipid-lowering drugs.
[b] Data were not reported for Studies CV145-002, CV145-009, and CV145-010; i.e., data were not reported for 12 subjects in the mid dose group, all 62 subjects in the high dose group, and 56 subjects in the placebo group. Therefore the denominators in these groups for these parameters were 87, 0, and 60, respectively.
[c] BMI was missing for one subject in this dose group.

6.6 Common Adverse Events

Consistent with the mechanism of action of lomitapide and nonclinical studies, the safety profile was characterized principally by GI disturbances and elevations in liver transaminase levels, both of which were managed by dose reduction or interruption.

6.6.1 Common Adverse Events: HoFH Studies

Table 17 summarizes the most commonly reported TEAEs, i.e., those reported in 10% or more of subjects in Study UP1002/AEGR-733-005. The table presents results by Medical Dictionary for Regulatory Authorities (MedDRA) preferred term. Note that TEAE reports related to laboratory abnormalities (e.g., ALT increased) are abnormalities that investigators considered clinically significant and therefore reported as AEs; as such, not all laboratory abnormalities are reported. As well, the severity of a specific AE was also determined by the investigator and may not correspond to changes in laboratory parameters of a specific magnitude. A discussion of abnormalities based on review of laboratory data is provided in Section 6.10.

Overall, the most commonly reported TEAEs in the Phase 3 HoFH study were GI events, including diarrhea (79%), nausea (66%), dyspepsia and vomiting (35% each), abdominal discomfort (31%), abdominal pain (28%), and constipation and flatulence (21% each). The only other TEAEs occurring in ≥20% of subjects with HoFH were chest pain and weight decreased (24% each) and influenza (21%).

When the AE data were reviewed across Study UP1002/AEGR-733-005 and the extension study AEGR-733-012, there were no clinically meaningful differences in the profile of the most common TEAEs reported. In general, the TEAEs that were reported at the highest incidence in the overall pool of data across both studies UP1002/AEGR-733-005 and AEGR-733-012 were the same as those reported in Study UP1002/AEGR-733-005 through Week 78. Further, a review of TEAE incidence per person years of exposure for the pooled results across the 2 studies showed no clinically meaningful increases in the incidence of any of the commonly reported TEAEs compared with results reported through Week 78 of Study UP1002/AEGR-733-005 despite a 47% increase in person years of exposure, suggesting no apparent cumulative toxicity with extended lomitapide treatment (Table 18).

The most commonly reported AEs among the 6 subjects treated in the Phase 2 HoFH study were diarrhea (5 subjects), oropharyngeal pain (4 subjects), and ALT increased and headache (3 subjects each).

Table 17: Treatment-Emergent Adverse Events Reported in ≥10% of Subjects in Studies UP1002/AEGR-733-005 and AEGR-733-012 (Safety Population)

MEDDRA PREFERRED TERM	END OF STUDY, WEEK 78 N (%) (N=29)
At least one TEAE	***27 (93.1)***
Diarrhea	23 (79.3)
Nausea	19 (65.5)
Dyspepsia	10 (34.5)
Vomiting	10 (34.5)
Abdominal Discomfort	9 (31.0)
Abdominal Pain	8 (27.6)
Chest Pain	7 (24.1)
Weight Decreased	7 (24.1)
Constipation	6 (20.7)
Flatulence	6 (20.7)
Influenza	6 (20.7)
Abdominal Distension	5 (17.2)
Abdominal Pain Upper	5 (17.2)
Alanine Aminotransferase Increased	5 (17.2)
Fatigue	5 (17.2)
Nasopharyngitis	5 (17.2)
Back Pain	4 (13.8)
Gastroenteritis	4 (13.8)
Oropharyngeal Pain	4 (13.8)
Angina Pectoris	3 (10.3)
Dizziness	3 (10.3)
Headache	3 (10.3)
Nasal Congestion	3 (10.3)
Palpitations	3 (10.3)
Pyrexia	3 (10.3)
Rectal Tenesmus	3 (10.3)

Table 18: Incidence per Subject Exposure Years of Common[a] Treatment-Emergent Adverse Events in Study UP1002/AEGR-733-005 and Overall (Safety Population)

MEDDRA PREFERRED TERM	UP1002/ AEGR-733-005 THROUGH WEEK 78 (N=29) N (PER PEY)	OVERALL[b] UP1002/AEGR-733-005 AND AEGR-733-012 (N=29) N (PER PEY)
Person Exposure Years	38.51	56.64
Diarrhea	23 (2.38)	23 (1.70)
Nausea	19 (1.33)	20 (1.05)
Dyspepsia	10 (0.36)	11 (0.30)
Vomiting	10 (0.39)	11 (0.31)
Abdominal Discomfort	9 (0.32)	9 (0.22)
Abdominal Pain	8 (0.28)	8 (0.19)
Chest Pain	7 (0.21)	8 (0.17)
Flatulence	6 (0.19)	7 (0.15)
Weight Decreased	7 (0.22)	7 (0.15)
Alanine Aminotransferase Increased	5 (0.16)	6 (0.13)
Constipation	6 (0.20)	6 (0.13)
Headache	3 (0.08)	6 (0.12)
Influenza	6 (0.18)	6 (0.13)
Abdominal Distension	5 (0.16)	5 (0.11)
Abdominal Pain Upper	5 (0.15)	5 (0.10)
Back Pain	4 (0.11)	5 (0.10)
Fatigue	5 (0.14)	5 (0.10)
Nasopharyngitis	5 (0.16)	5 (0.11)

[a] TEAEs that occurred in 5 or more subjects overall.
[b] Includes data through the final visit Week 78/84 from Study UP1002/AEGR-733-005 pooled with data through 31 December 2011 for Study AEGR-733-012.

6.6.2 Common Adverse Events: Elevated LDL-C and Other Cardiovascular Risk Factors Study Pool

In order to evaluate possible differences in the AE profile of lomitapide administered as monotherapy compared with placebo and active control, TEAEs reported in 5% of more of subjects who received lomitapide alone, placebo, or active control in studies that evaluated lomitapide monotherapy in the Elevated LDL-C and Other CV Risk Factors Study Pool were tabulated; results are provided in Table 19. A tabulation of the most commonly reported TEAEs across all subjects in the Elevated LDL-C and Other CV Risk Factors Study Pool is presented by MedDRA preferred term in Appendix Table 25. The table presents results across the lomitapide dose groups, including both lomitapide monotherapy and lomitapide coadministered with other lipid-lowering therapies, as well as the placebo and active control groups.

Table 19: Treatment-Emergent Adverse Events Reported in ≥5% of Subjects in a Treatment Group: Studies that Evaluated Lomitapide Monotherapy in the Elevated LDL-C and Other Cardiovascular Risk Factors Study Pool[a] (Safety Population)

MedDRA Preferred Term	Lomitapide Monotherapy (N=291) n (%)	Placebo (N=116) n (%)	Active Control (N=55) n (%)
Diarrhea	163 (56.0)	13 (11.2)	4 (7.3)
Nausea	68 (23.4)	4 (3.4)	3 (5.5)
Flatulence	32 (11.0)	7 (6.0)	0
Headache	27 (9.3)	13 (11.2)	2 (3.6)
Abdominal Pain Upper	25 (8.6)	4 (3.4)	0
Abdominal Distension	24 (8.2)	4 (3.4)	3 (5.5)
Abdominal Pain	23 (7.9)	2 (1.7)	2 (3.6)
Alanine Aminotransferase Increased	22 (7.6)	1 (0.9)	1 (1.8)
Fatigue	21 (7.2)	3 (2.6)	0
Vomiting	20 (6.9)	3 (2.6)	0
Aspartate Aminotransferase Increased	19 (6.5)	1 (0.9)	1 (1.8)
Dyspepsia	15 (5.2)	3 (2.6)	4 (7.3)
Back Pain	11 (3.8)	6 (5.2)	2 (3.6)
Nasopharyngitis	5 (1.7)	6 (5.2)	4 (7.3)

[a] Excludes Study AEGR-733-006, which did not evaluate lomitapide monotherapy

Similar to what was observed in the HoFH studies, the most commonly reported TEAE across the lomitapide dose groups in this pool of studies was diarrhea (Appendix Table 25). The incidence of diarrhea was lowest (39%) in the lomitapide escalated-dose group compared with 50% in the low-dose, 64% in the mid-dose, and 74% in the high-dose groups. The incidence of diarrhea was lower in the placebo and active control groups (11% and 9%, respectively). In studies that evaluated lomitapide monotherapy, the incidence of diarrhea was 56% for lomitapide compared with 11% and 7% for placebo and active control, respectively (Table 19).

Similar to the HoFH studies, other GI events that were among the most commonly reported TEAEs in the lomitapide groups in this study pool included nausea, flatulence, abdominal distension, vomiting, dyspepsia, abdominal pain, upper abdominal pain, constipation, abdominal discomfort, decreased appetite, and eructation (Appendix Table 25). In general, the incidence of these other commonly reported GI events was lower in the comparator groups than in the lomitapide groups.

Non-GI events that were among the most commonly reported TEAEs in the Elevated LDL-C and Other CV Risk Factors Study Pool included headache, dizziness, ALT increased, AST increased, fatigue, asthenia, back pain, and nasopharyngitis (Appendix Table 25). Increases in ALT and AST reported as TEAEs were most common in the lomitapide escalated-dose group. In this group, ALT increased was reported for 22% of subjects and AST increased was reported for 14%

of subjects. Importantly, all reports of ALT and AST increased in the escalated-dose group were assessed as mild to moderate in severity; there were no severe increases reported. Across the other lomitapide dose groups, ALT increased and AST increased were reported for 3% to 5% of subjects. The incidence of ALT and AST increased reported as TEAEs was low in the placebo and active control groups, with approximately 1% of subjects reporting each of these events. In studies that evaluated lomitapide monotherapy, the incidence of ALT and AST increased was 8% and 7%, respectively, among subjects who received lomitapide compared with 1% of subjects who received placebo and 2% of subjects who received active control (Table 19).

6.6.3 Treatment-Related Adverse Events

The most commonly reported treatment-related events in the Phase 3 HoFH study were GI disturbances, including diarrhea (79%), nausea (62%), abdominal discomfort and vomiting (31% each), and dyspepsia and abdominal pain (24% each).

Among those subjects who received lomitapide monotherapy in the Elevated LDL-C and Other CV Risk Factors Study Pool, the most commonly reported treatment-related AEs were diarrhea (53%), nausea (22%), and flatulence (11%).

6.7 Other Adverse Events of Interest

As a component of the analysis of safety, adverse events of special interest were identified and tabulated based on Standardized MedDRA Queries (SMQs) and MedDRA preferred terms. These categories of events were selected based on 1) events that may have occurred as a result of the sites of action of lomitapide, specifically GI tract and liver; 2) systems affected by the target disease (HoFH), i.e., cardiovascular-specific to atherosclerosis/coronary heart disease (CHD); 3) AEs associated with statins (e.g., rhabdomyolysis); 4) AEs indicative of warfarin interaction (e.g., changes in INR or PT); and 5) AEs expected to occur based on findings in animal studies (e.g., phospholipidosis/ neutralipidosis of the lungs). A brief review of key findings follows.

6.7.1 Ischemic Heart Disease

HoFH Studies

Review for TEAEs categorized as ischemic heart disease showed that 5 (14%) of 35 subjects in the Phase 2 and Phase 3 HoFH studies experienced at least 1 such event, including angina pectoris in 3 subjects, and 1 subject each with acute coronary syndrome, coronary artery arteriosclerosis, and blood creatine phosphokinase increased; 1 subject with angina pectoris also had acute coronary syndrome reported. In all 5 subjects, the ischemic heart disease events were assessed as unrelated to study treatment. The ischemic heart disease event was considered serious for 2 of these 5 subjects, including angina pectoris and severe acute coronary syndrome for 1 subject and coronary artery arteriosclerosis for 1 subject. No other events considered

representative of ischemic heart disease were severe or serious and none led to treatment discontinuation.

Elevated LDL-C and Other CV Risk Factors Study Pool

Review for TEAEs categorized as ischemic heart disease for the Elevated LDL-C and Other CV Risk Factors Study Pool showed that 3 subjects experienced at least 1 such event. Across lomitapide dose groups, the incidence of ischemic heart disease events was low: 1%, <1%, 1%, and 0% in the escalated-, low-, mid-, and high-dose groups, respectively. As detailed in Section 6.8.3, 1 of these 3 subjects experienced a fatal MI; this event was considered unrelated to study drug. Other ischemic heart disease events included MI and CAD experienced in a subject who received lomitapide 5 mg and MI experienced by a subject who received lomitapide 10 mg. For both subjects, MI was considered serious, unrelated to study treatment, and led to study drug discontinuation.

6.7.2 Myopathy Events

There were no reports of rhabdomyolysis in any subject treated in the lomitapide program.

HoFH Studies

Five (14%) of 35 subjects in the Phase 2 and Phase 3 HoFH studies experienced musculoskeletal system events or events potentially associated with rhabdomyolysis including myalgia (3 subjects); musculoskeletal pain (2 subjects), blood creatine phosphokinase increased and transient acute renal failure (1 subject each). All of these events were mild or moderate in severity, non-serious, and assessed as unrelated to study drug; none led to study drug discontinuation. Four of the subjects were receiving a statin at the time of the event and did not change their statin treatment because of the event.

Elevated LDL-C and Other CV Risk Factors Study Pool

TEAEs experienced by subjects in the Elevated LDL-C and Other CV Risk Factors Study Pool that were categorized under rhabdomyolysis / myopathy included blood creatinine increased (not associated with rhabdomyolysis or myopathy), myalgia, muscular weakness, and musculoskeletal pain. Across dose groups, the incidence of such events was 3%, 5%, 0%, and 0% in the lomitapide escalated, low-, mid-, and high-dose groups and 1% and 3% in the placebo and active control groups, respectively. Severe myalgia was reported for 1 (<1%) subject in the lomitapide low-dose group and 1 (1%) subject in the active control group. Myalgia led to study drug discontinuation for the subject in the active control group.

Importantly, review for TEAEs categorized as rhabdomyolysis / myopathy among subjects who received lomitapide monotherapy or coadministered with a statin or who received placebo showed that the incidence of such events was the same among subjects who received lomitapide

monotherapy (4%) and in those who received lomitapide + statin (4%). The incidence of such events among placebo-treated subjects was lower (1%).

6.7.3 Asthma/Bronchospasm

HoFH Studies

Review for TEAEs categorized as asthma or bronchospasm showed that 1 (3%) of 35 subjects in the Phase 2 and Phase 3 HoFH studies experienced wheezing (concurrent with sore throat, cough, nasal congestion and conjunctivitis). The event was mild, unlikely related to study drug, non-serious and did not require study drug modification or discontinuation.

Elevated LDL-C and Other CV Risk Factors Study Pool

Review for TEAEs categorized as asthma or bronchospasm showed that 3 subjects in the Elevated LDL-C and Other CV Risk Factors Study Pool experienced 1 such event, including 1 subject in the lomitapide escalated dose group who experienced wheezing and 2 subjects, one in the low-dose group and one in the mid-dose group, who experienced asthma. The events were mild to moderate in severity and assessed as unrelated to study treatment.

6.8 Deaths and Other Serious Adverse Events

The incidence of SAEs was low across the lomitapide program. The majority of SAEs reported were related to the subjects' underlying conditions, and were primarily cardiac-related events.

6.8.1 Deaths and Other Serious Adverse Events: HoFH Studies

There have been no deaths reported during the HoFH studies, including the Phase 2 study UP1001, the Phase 3 Study UP1002/AEGR-733-005, and the Phase 3 extension study AEGR-733-012.

During the Study UP1001, 1 of the 6 subjects experienced an SAE. The subject developed a post-operative seroma following cardiac surgery that had been conducted pre-study; the seroma required surgical drainage. The event was assessed as unrelated to study treatment and did not lead to treatment discontinuation.

In Study UP1002/AEGR-733-005, 3 (10%) of the 29 subjects experienced an SAE. In 2 subjects, these events were related to the subject's underlying CVD, including acute coronary syndrome and angina pectoris in 1 subject (who also experienced a lower respiratory tract infection) and coronary artery arteriosclerosis in the other. One subject with a history of menorrhagia required a hysterectomy. All SAEs were assessed as unrelated to treatment with lomitapide and none led to treatment discontinuation.

During the ongoing Phase 3 extension study AEGR-733-012, 4 of 19 subjects experienced SAEs through the data cut-off of 31 December 2011. The SAEs reported in these subjects were hepatotoxicity; hospitalization for transfusion and hypovolemic shock and hospitalization for anticoagulation; arteriovenous fistula and lower respiratory tract infection; and reflux esophagitis. With the exception of report of hepatotoxicity (elevations in liver transaminase levels), all other SAEs were assessed as unrelated to study treatment. The case reported as 'hepatotoxicity' occurred following administration of 2 concomitant medications known to be associated with liver injury (agomelatine and clarithromycin). Lomitapide and both of these agents were discontinued and aminotransferase levels returned rapidly towards normal levels. Since histology from a liver biopsy that was obtained approximately 2 months later in this subject demonstrated the presence of mild steatosis without significant inflammation or fibrosis, lomitapide treatment was re-started without clinical consequence.

6.8.2 Major Adverse Cardiac Events: HoFH Subjects

Treatment-emergent AEs reported during Study UP1002/AEGR-733-005 were reviewed and classified as MACE or not, based on the nature of the event and the investigator determination of seriousness. Overall, there were 3 subjects with MACE events, including angina pectoris with acute coronary syndrome, coronary artery arteriosclerosis, and transient ischemic attack. The per-subject incidence of MACE in Study UP1002/AEGR-733-005, which was conducted over an 18-month period, was 10.3% (3 of 29 subjects).

Since the pivotal study UP1002/AEGR-733-005 did not include a control group, published information for the rates of MACE from a large retrospective cohort study was used (Raal, 2011). In this study, data across approximately 9 years (1990 to 1999) from 113 HoFH subjects who were on maximal statin therapy were evaluated. In this cohort, 44 subjects had at least one MACE in the 9-year period, resulting in approximately 7.3 subjects [(1.5/9.0)×(44)] expected to have MACE in an 18-month period, giving a per-subject rate of 6.5% (7.3/113), assuming a uniform probability of MACE over time.

The Fisher's Exact Test p-value for a difference in these rates (10.3% versus 6.5%) was not significant (p=0.4266) and the relative risk of MACE for subjects receiving lomitapide versus subjects in the Raal cohort was 1.67, with 95% CI of (0.46, 6.06).

The comparison of event rates that occurred in Study UP1002/AEGR-733-005 with those reported in the Raal cohort has several limitations. Subjects in the Raal cohort were not treated contemporaneously with those in the Phase 3 study. Further, the number of events that occurred in the Phase 3 study were few due to the small size of the study and the relatively short duration of follow-up. However, within the limitations of this analysis, the relative risk of MACE in the UP1002/AEGR-733-005 study compared to an external historical control group of subjects with

HoFH has wide 95% CI that includes 1; therefore, there is no evidence of a higher than expected MACE rate in subjects treated with lomitapide.

6.8.3 Deaths and Other Serious Adverse Events: Elevated LDL-C and Other Cardiovascular Risk Factors Study Pool

Across the lomitapide clinical program, 1 death, assessed as unrelated to study treatment, was reported in a subject who received lomitapide in a Phase 2 study in the Elevated LDL-C and Other CV Risk Factors Study Pool. The subject was a 54-year-old Caucasian male with medical history significant for deep vein thrombosis, peptic ulcer, Factor V Leiden, and hypertension. He received lomitapide for 12 weeks. One week post-treatment, while at work, the subject developed nausea and diaphoresis. Upon arrival of the emergency medical response service, the subject was in ventricular fibrillation. He was intubated and treated with multiple doses of epinephrine and Amiodarone and defibrillated. He arrived at the emergency room (ER) in ventricular fibrillation, unresponsive and receiving cardiopulmonary resuscitation. He was cyanotic and on auscultation had no cardiac activity. He expired in the ER.

Serious AEs were reported for a total of 6 subjects in this Study Pool, including 1 (1%), 2 (1%) and 3 (3%) subjects in the lomitapide escalated, low- and mid-dose groups, respectively. No subject in the lomitapide high-dose group, the placebo group, or the active control group experienced an SAE. All SAEs in this Study Pool were assessed as unrelated to study treatment.

Myocardial infarction was the most common SAE in the Elevated LDL-C and Other CV Risk Factors Study Pool, reported in 3 subjects overall, including 1 subject each in the lomitapide escalated-, low-, and mid-dose groups. As noted above, 1 subject died as a result of this event. All other SAEs were reported in 1 subject each and included chest pain in the lomitapide low-dose group and ankle fracture and inflammatory bowel disease in the lomitapide mid-dose group.

6.9 Other Significant Adverse Events

Across the lomitapide program, most reported events were mild to moderate in severity. The most commonly reported events of severe intensity were GI disorders, primarily reports of diarrhea, which were noted more commonly at higher doses of lomitapide. Diarrhea was a dose limiting-toxicity in early Phase 2 studies leading to treatment discontinuation in more than 20% of subjects at fixed doses of 10 mg or higher. In the Phase 3 HoFH study, diarrhea was severe in intensity in 4 subjects (14%) and led to treatment discontinuation in 2 (7%).

6.9.1 Adverse Events of Severe Intensity

6.9.1.1 Adverse Events of Severe Intensity: HoFH Studies

A total of 8 (28%) of the 29 subjects in the Phase 3 HoFH study experienced events of severe intensity. The most common severe TEAEs among these 29 subjects were diarrhea (4 subjects;

11%), vomiting (3 subjects; 10%) and ALT increased (2 subjects; 7%). All other severe TEAEs in this study were reported in 1 subject. During the extension study, 2 additional subjects experienced severe events, including ALT increased, AST increased, and hypovolemic shock in 1 subject, and dyspepsia in 1 subject.

In the Phase 2 HoFH study UP1001, the most common events of severe intensity were ALT and AST increased (3 of 6 subjects).

Use of the dose-escalation scheme used in the HoFH studies led to a reduction in the severity of GI AEs compared to fixed-dose studies. In the BMS-sponsored study CV145-009, which evaluated a fixed dose of 25 mg lomitapide administered for 4 weeks, the proportions of GI events that were assessed as mild, moderate and severe were 31%, 54% and 15%, respectively. In the 16-week Phase 2 HoFH study, which was the first to utilize the dose-escalation regimen, all GI AEs reported during the study were mild to moderate in severity; no events of severe intensity were reported. During the 78-week Phase 3 HoFH study, the proportion of GI AEs that were assessed as severe in intensity was low. In this study the proportions of GI events that were assessed as mild, moderate and severe were 53%, 41% and 6%, respectively.

6.9.1.2 Adverse Events of Severe Intensity: Elevated LDL-C and Other Cardiovascular Risk Factors Study Pool

GI disorders were the most commonly reported types of severe events in the Elevated LDL-C and Other CV Risk Factors Study Pool. Severe diarrhea was reported by 8%, 10%, 26%, and 11% of subjects in the escalated-, low-, mid-, and high-dose lomitapide groups, respectively. No subjects in the placebo or active control groups experienced severe diarrhea. Severe nausea was reported in 0%, 2%, 8% and 3% of subjects in the escalated-, low-, mid-, and high-dose lomitapide groups, respectively, and 1% of subjects in the active control group. Other than diarrhea and nausea, all severe TEAEs were reported for <5% of subjects in any treatment group. Severe ALT increased and AST increased were each reported for 1 (1%) subject in the mid-dose lomitapide group and no subjects in any other treatment group.

6.9.2 Adverse Events Leading to Treatment Modification

6.9.2.1 Adverse Events Leading to Treatment Modification: HoFH Studies

Four (14%) of the 29 subjects in Study UP1002/AEGR-733-005 experienced TEAEs leading to treatment discontinuation. All but 1 of the discontinuations due to TEAEs was related to a GI disorder. One subject discontinued because of abdominal pain, nausea, and diarrhea; and 1 subject each discontinued because of diarrhea, gastroenteritis, and headache.

During the extension study AEGR-733-012, as detailed above 1 subject temporarily discontinued treatment due to a serious event related to elevations in liver transaminase levels (reported as hepatoxicity); the subject was later restarted on lomitapide. One additional subject was

terminated by the Sponsor during the extension study due to continued aminotransaminase elevations > 5×ULN, which may have been complicated by continued excessive alcohol intake.

Overall, 17 of the 29 subjects in the Phase 3 study had at least 1 dose reduction or a dose interruption of 3 or more days; 7 of these subjects had both a reduction and an interruption, 9 had only a reduction, and 1 had only an interruption. In most subjects (13 of 17) the reductions or interruptions were due to GI AEs; 5 subjects had a dose reduction (N=5) or interruption (N=1) due to elevations in transaminase levels.

None of the subjects in Study UP1001 discontinued treatment. Dose interruptions or reductions were reported in 3 of the 6 subjects in this study, 1 due to GI AEs, 1 due to transaminase elevations and 1 due to an SAE requiring surgical intervention for a seroma.

6.9.2.2 Adverse Events Leading to Treatment Discontinuation: Elevated LDL-C and Other Cardiovascular Risk Factors Study Pool

Overall, the majority of discontinuations due to TEAEs in the Elevated LDL-C and Other CV Risk Factors Study Pool were related to GI disorders. In the low-, mid-, and high-dose lomitapide groups, diarrhea was the most commonly reported TEAE leading to discontinuation, with 14%, 26%, and 21% of subjects, respectively, discontinuing because of this event. The incidence of discontinuation due to diarrhea was low in the lomitapide escalated-dose group (4%). Nausea was also among the most commonly reported TEAEs leading to discontinuation in the lomitapide mid-dose group (15% of subjects) and high-dose group (10% of subjects); none of the subjects in the escalated-dose group discontinued treatment due to nausea.

In the lomitapide escalated-dose group, LFT abnormalities were the most common TEAEs leading to discontinuation. In this dose group, 13% of subjects discontinued treatment because of LFT AEs, specifically ALT increased (8%), AST increased (3%), hepatic enzymes increased (3%), and LFT abnormal (3%). Liver function test abnormalities leading to discontinuation were reported at lower incidences in the other lomitapide dose groups (≤3%) and by none of the subjects in the placebo or active control groups.

6.10 Clinical Laboratory Results

Results of a thorough evaluation of clinical laboratory data indicate that treatment with lomitapide is associated with transient and reversible increases in transaminase levels, including elevations >5×ULN, without clinically meaningful concomitant increases in serum bilirubin or alkaline phosphatase and with no associated symptoms. None of the subjects in any of the lomitapide clinical studies had an ALT or AST elevation to >3×ULN with a corresponding total bilirubin value that was >2×ULN (i.e., no subject met Hy's Law criteria).

6.10.1 Hematology and Clinical Chemistry

A thorough review of hematology, renal function, electrolytes, serum protein and creatine phosphokinase data, including descriptive statistics over time, shift analyses and assessment of clinically significant changes from baseline, showed no effect of lomitapide on any of these parameters.

6.10.2 Coagulation Parameters

Coadministration of lomitapide with warfarin has been shown to prolong INR related to an increase in exposure (AUC and maximum plasma concentration [C_{max}]) to warfarin. During the Phase 2 study UP1001, it was noted that 2 subjects, both of whom had elevated INR levels at baseline due to concomitant treatment with warfarin, had further increases in INR during treatment with lomitapide requiring warfarin dose modifications. Both subjects completed study treatment and no bleeding events were noted. In the Phase 3 study, 5 subjects received warfarin concomitant with lomitapide. All 5 subjects were carefully monitored and had warfarin dose adjustments as required. Three of the 5 subjects completed the study through Week 78 and 2 discontinued during the Efficacy Phase. One subject discontinued due to GI AEs and 1 withdrew consent as the GI side effects were no longer tolerable; the latter subject had unstable INR levels reported at the time of discontinuation. No serious bleeding events were reported through Week 78.

One subject enrolled in the extension study, AEGR-733-012, required hospitalization for anticoagulation due to low INR levels. This subject, with aortic and mitral valve replacements, atrial fibrillation, and previous history of transient ischemic attack (TIA), was receiving warfarin and had been previously hospitalized for hypovolemic shock related to severe menorrhagia requiring transfusion. This subject also required hospitalization for left cranial nerve VII palsy with nystagmus; her INR had not been monitored for more than 6 weeks and was found to be 5.7 on admission. She was hospitalized for adjustment of warfarin levels. MRI showed small subdural hemorrhages. The subject's symptoms improved 3 days later and she remains on lomitapide at this time.

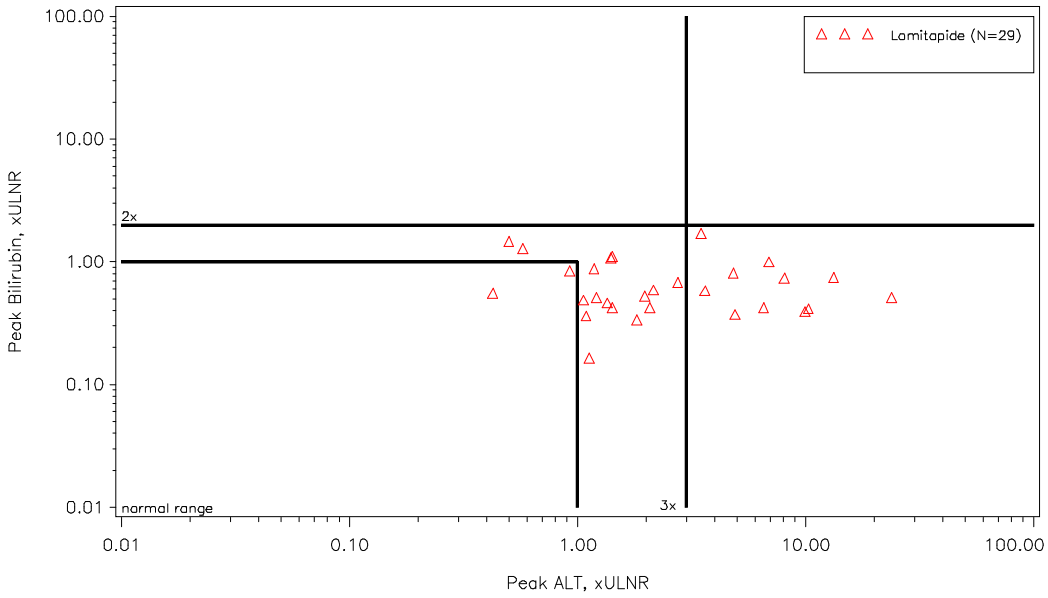
6.10.3 Liver Function Tests

6.10.3.1 Liver Function Tests: HoFH Studies

Peak ALT values with corresponding total bilirubin values for subjects in the Phase 3 Study UP1002/AEGR-733-005 and its extension Study AEGR-733-012 are presented in eDISH (evaluation of drug-induced serious hepatotoxicity) plots in Figure 18. As shown, none of the these 29 HoFH subjects, including 23 who had received at least 2 years of treatment with lomitapide, had an ALT elevation to >3×ULN with a corresponding total bilirubin elevation that was >2×ULN (i.e., no subject met Hy's Law) (Zimmerman, 1978). In addition, none of the 6

subjects in Study UP1001 had an ALT or AST elevation to >3×ULN with a corresponding total bilirubin elevation that was >2×ULN. Similar results were observed for AST.

Figure 18: Peak ALT and Corresponding Total Bilirubin Levels during Studies UP1002/AEGR-733-005 and AEGR-733-012 (Safety Population)



Note: ULNR=upper limit of normal range.
Note: Peak ALT is plotted with peak bilirubin obtained within ±7 days of the peak ALT

The highest post-baseline LFT values for subjects in the HoFH studies are summarized in Table 20; the table presents results relative to the upper limit of the normal range for Study UP1001, Study UP1002/AEGR-733-005 through Week 78, and overall (i.e., across all lomitapide treatment in Study UP1002/AEGR-733-005 and its extension study AEGR-733-012).

Maximum elevations in ALT of >5×ULN were observed for 3 of 6 subjects in the Phase 2 Study UP1001 and in 4 of 29 subjects during the Phase 3 study UP1002/AEGR-733-005 through Week 78. One subject who participated in both studies experienced maximum elevations >10×ULN in each study; these elevations were just above 10×ULN (10.2 and 10.6×ULN, respectively) with corresponding AST elevations of 7.4×ULN and 4.8×ULN, respectively. The corresponding bilirubin levels for this subject were within the normal range. Both elevations to 10×ULN were transient.

During the extension study, 3 additional subjects had maximum ALT elevations >5×ULN, including 1 subject with an elevation to 10.3×ULN and 1 with an elevation to 23.9×ULN; corresponding AST elevations in these 2 subjects were 16.9×ULN and 13.1×ULN, respectively. Both of these elevations were transient. Brief narratives follow:

The subject with ALT of 10.3×ULN during the extension study had elevated ALT (412 U/L) and AST (674 U/L) identified through routine local laboratory work; bilirubin was in the normal range. At that time, the subject had received lomitapide for ~2 years and was at a current dose of 60 mg. During Study UP1002/AEGR-733-005, AST and ALT were within normal range or slightly elevated, never exceeding 2.3×ULN. At the time of the >10×ULN elevation, the subject had been taking cold medicine (Motrin, Mucinex, Robitussin and Nyquil [includes acetaminophen]) for the previous 2 months. Lomitapide and the concomitant medications were stopped and LFTs measured 2 weeks later (first assessment) showed improvement (ALT, 186 U/L and AST, 147 U/L). Three weeks later further improvement was noted with ALT of 103 U/L and AST of 83 U/L. Lomitapide was reintroduced at 40 mg and later titrated back to 60 mg with stable LFTs.

The subject with the ALT elevation >20×ULN during the extension study had ALT and AST of 954 and 565 U/L, respectively. The corresponding bilirubin was in the normal range. As noted in Section 6.8.1, this subject had elevated ALT and AST levels at baseline (Study UP1002/AEGR-733-005) that were 5.8 and 2.3×ULN, respectively, with maximum ALT during Study UP1002/AEGR-733-005 of 4.9×ULN. An SAE of hepatotoxicity that was confounded by concomitant medication use (agomelatine and clarithromycin) was reported for this subject.

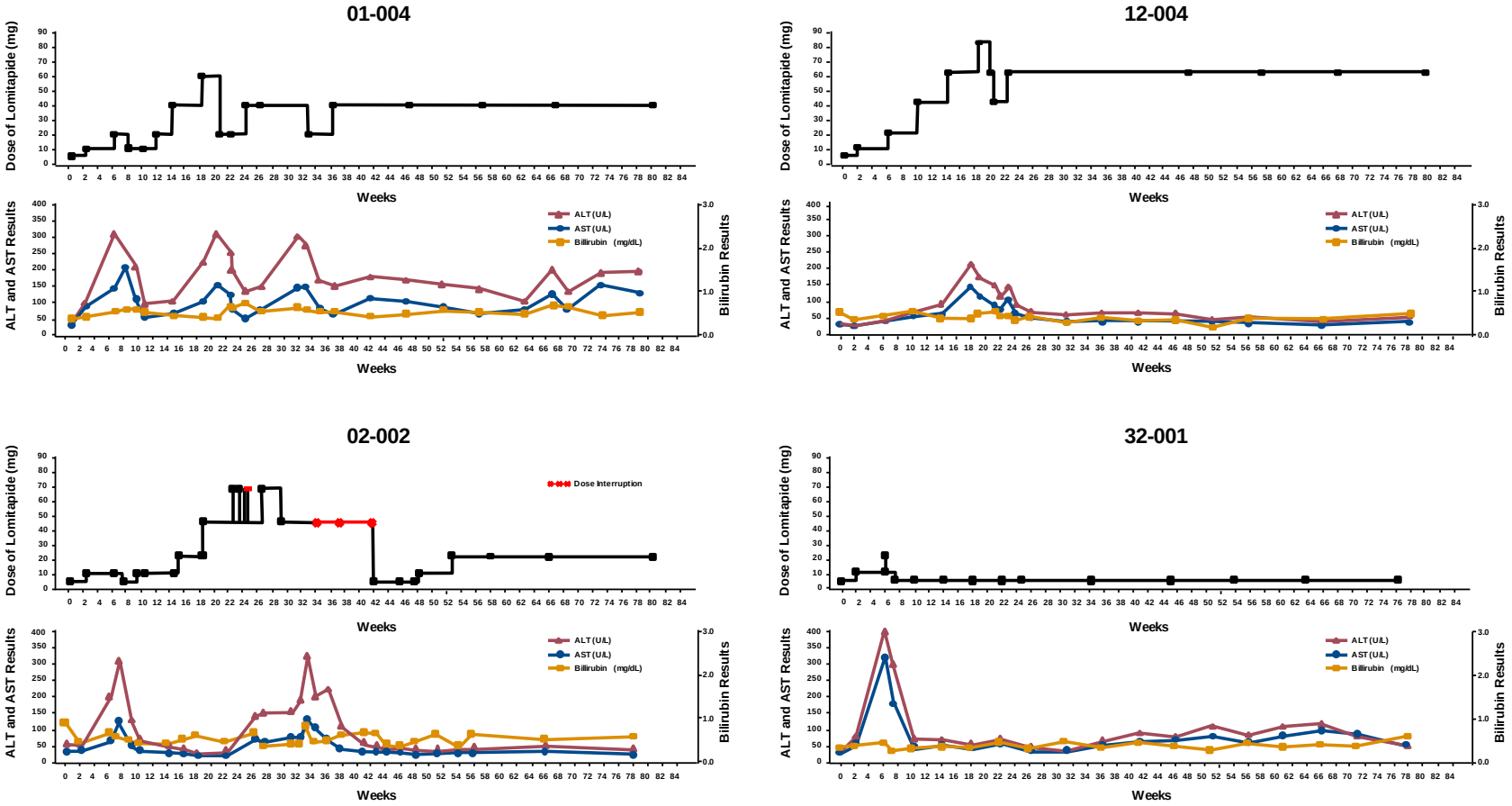
In all subjects with elevations >5×ULN, dose reductions and/or interruptions led to a rapid decrease in the transaminase levels. This is shown graphically in Figure 19 for the 4 subjects in Study UP1002/AEGR-733-005 with elevations >5×ULN.

Table 20: Maximum Abnormal Liver Function Test Results Post First Dose: HoFH Indication (Safety Population)

ALT AND/OR AST:[a]	STUDY UP1001 (N=6) N (%)	STUDY UP1002/AEGR-733-005 (N=29) N (%)	OVERALL UP1002/AEGR-733-005 AND AEGR-733-012 (N=29) N (%)
≤2×ULN	3 (50.0)	15 (51.7)	14 (48.3)
>2 to ≤3×ULN	0	4 (13.8)	4 (13.8)
>3 to ≤5×ULN	0	6 (20.7)	4 (13.8)
>5 to ≤10×ULN	2 (33.3)	3 (10.3)	4 (13.8)
>10 to ≤20×ULN	1 (16.7)	1 (3.4)	2 (6.9)
>20×ULN	0	0	1 (3.4)

[a] Only values greater than the Baseline value were considered.

Figure 19: Subjects with ALT and/or AST Elevations >5×ULN during Study UP1002/AEGR-733-005

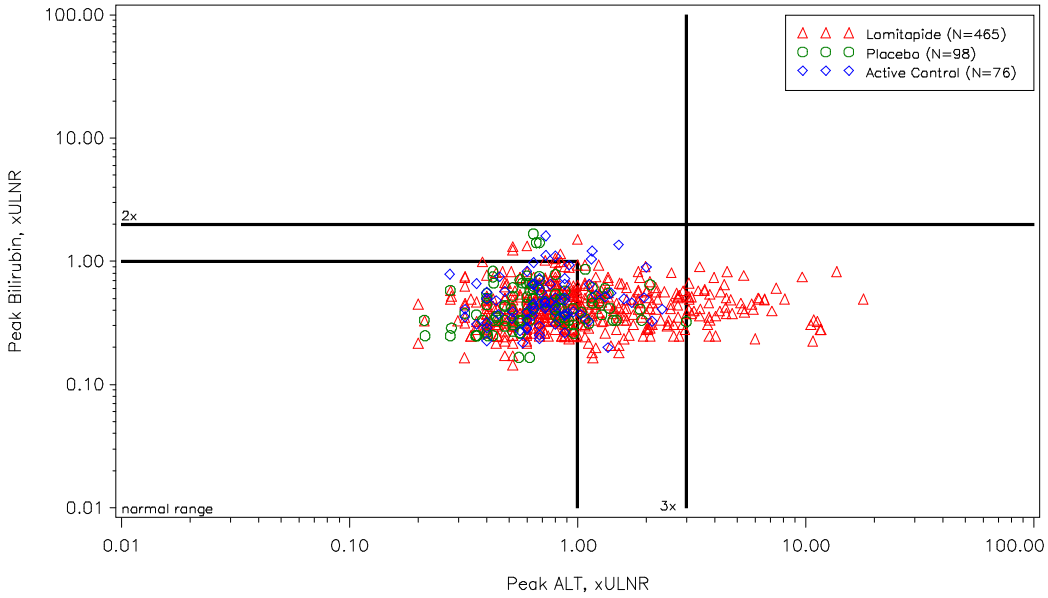


Median time to ALT or AST >3×ULN for subjects who experienced this laboratory abnormality was 55 days in Study UP1001 and 112 days in Study UP1002/AEGR/733-005. Median duration of the abnormal transaminase elevation (time from onset of abnormality >3×ULN to return to the normal range) was 36 days in Study UP1001 and 29 days in Study UP1002/AEGR-733-005.

6.10.3.2 Liver Function Tests: Elevated LDL-C and Other Cardiovascular Risk Factors Study Pool

As was observed in the HoFH Study Pool, none of the subjects in the larger Elevated LDL-C and Other CV Risk Factors Study Pool developed acute hepatoxicity. Subjects' peak ALT values with corresponding total bilirubin values are presented in an eDISH plot in Figure 20. As shown, the majority of subjects in these studies had ALT and bilirubin levels within the normal range. Similar results were noted for AST. None of the subjects in the Elevated LDL-C and Other CV Risk Factors Study Pool had an ALT or AST elevation to >3×ULN with a corresponding total bilirubin value that was >2×ULN, i.e., no subject met Hy's Law (Zimmerman, 1978).

Figure 20: Peak ALT and Corresponding Total Bilirubin Levels by Treatment Group: Elevated LDL-C and Other Cardiovascular Risk Factors Study Pool (Safety Population)



Note: ULNR=upper limit of normal range.
Note: Peak ALT is plotted with peak bilirubin obtained within ±7 days of the peak ALT

6.11 Hepatic Fat

Consistent with the mechanism of action of lomitapide, increases in hepatic triglyceride content were observed. The levels decreased spontaneously during continued treatment in some subjects, but remained elevated in most during the treatment period. Rapid reversal of hepatic fat accumulation was observed when subjects discontinued lomitapide.

6.11.1 Hepatic Fat: HoFH Studies

Table 21 presents the baseline value and mean absolute change in hepatic fat percent from baseline as assessed by NMRS for the HoFH studies.

In Study UP1001, a mean absolute increase in hepatic fat percent of 19% was observed from a baseline value of 3%. Four weeks after completion of dosing (last assessment), the mean absolute change in hepatic fat percent from baseline was 5% indicating rapid reversibility of hepatic fat content in the liver after discontinuation of lomitapide.

In Study UP1001/AEGR-733-005, there was a mean absolute change in hepatic fat percent of 8% at the Week 26 assessment. At Week 78, the mean absolute change from baseline was similar to Week 26 at 7%. Similar results were also observed during the extension study with mean absolute changes from baseline in hepatic fat percent of 8% at Weeks 102 and 126 of treatment.

Table 21: Baseline Value and Absolute Change from Baseline in Hepatic Fat Percent Based on NMRS[a] HoFH Studies (Safety Population)

VISIT STATISTIC	STUDY UP1001 (N=6)	STUDY UP1002/AEGR-733-005 (N=29)
Baseline – n[b]	6	23
Mean (SD)	3.42 (2.200)	0.87 (0.959)
Minimum, Maximum	2.00, 6.50	0.00, 3.79
Δ from BL to Wk 16/Wk 26[c]– n[2b]	6	22
Mean (SD)	19.25 (12.922)	8.06 (7.460)
Minimum, Maximum	3.00, 37.50	0.35, 29.85
Δ from BL to Wk 56 – n[b]	Not	21
Mean (SD)	Assessed	6.44 (7.955)
Minimum, Maximum		-0.47, 35.05
Δ from BL to Wk 78 – n[b]	Not	21
Mean (SD)	Assessed	7.37 (5.411)
Minimum, Maximum		0.01, 18.33
Δ from BL to Wk 102[d]– n[b]	Not	14
Mean (SD)	Assessed	8.36 (6.846)
Minimum, Maximum		0.20, 22.52
Δ from BL to Wk 126[d] – n[b]	Not	9
Mean (SD)	Assessed	7.78 (6.793)
Minimum, Maximum		1.17, 21.99
Δ from BL to Last[e] – n[b]	6	23
Mean (SD)	4.92 (12.257)	8.74 (9.756)
Minimum, Maximum	-4.00, 29.50	-1.78, 41.63

Note: BL = baseline
[a] Per the SAP, if NMRS data were not available, MRI data were used.
[b] Only subjects who had the parameter assessed at baseline and at least one follow-up are included.
[c] Hepatic fat evaluated at Week 16 in UP1001 and at Week 26 in UP1002/AEGR-733-005.
[d] Visits conducted during the extension study AEGR-733-012
[e] Last value for UP1001 is Week 20, which is 4 weeks after the last study drug administration. Last value for UP1002/AEGR-733-005 is last value obtained on Study UP1002/AEGR-733-005 or Study AEGR-733-012, whichever was later.

In Study UP1002/AEGR-733-005, 3 subjects had a maximum absolute increase in hepatic fat percent from baseline of >20%, including 2 subjects with an increase >25%. One additional subject, had an increase in hepatic fat to >20% during Study AEGR-733-012. Three of these 4 subjects also had maximum ALT elevation >5×ULN during the treatment period and 1 subject had maximum ALT of 3.2×ULN.

6.11.2 Hepatic Fat: Elevated LDL-C and Other Cardiovascular Risk Factors Study Pool

Three of the studies in the Elevated LDL-C and Other CV Risk Factors Study Pool assessed hepatic fat levels. At baseline, mean absolute hepatic fat percent levels were 2%, 2%, and 8% in the lomitapide low-dose, mid-dose, and high-dose groups, respectively, and 5% in the placebo group. At the Week 4/5 assessment, mean absolute increases in hepatic fat percent of 5%, 8%,

and 21% were observed in the lomitapide low-dose, mid-dose, and high-dose groups, respectively. At the Week 8 assessment, mean absolute hepatic fat percent values were similar to the Week 4/5 values in the lomitapide low- and mid-dose groups; no data were available at Week 8 for the lomitapide high-dose group as the study was only 4 weeks in duration. The mean absolute changes in hepatic fat percent were <1% at all assessment times in the placebo group.

The extent of reversibility of hepatic fat increases was assessed in a Phase 2 study conducted in subjects with elevated LDL-C and other CV risk factors. In this study, subjects treated with lomitapide 25 mg once daily for 4 weeks had a mean absolute increase of 21% in hepatic fat percent content from baseline. Six weeks after discontinuation of dosing, the change from baseline in mean absolute hepatic fat content was 4%, demonstrating that the increase in hepatic fat content observed during treatment with lomitapide in this study reversed to near baseline levels after 6 weeks off treatment.

6.11.3 Potential for Insulin Resistance

The possibility that hepatic steatosis related to lomitapide exposure might predispose subjects to the development of insulin resistance was examined in a Phase 2 placebo-controlled study of subjects with hypercholesterolemia that evaluated lomitapide doses of 2.5 to 10 mg administered for 12 weeks (Study AEGR-733-004). Insulin levels were within reference range (2.0 – 30 µIU/mL) for all treatment groups at baseline and each subsequent time point. In addition, homeostasis model assessment-insulin resistance (HOMA-IR) values calculated for subjects who received low (2.5 to 7.5 mg) or mid (10 mg) dose lomitapide or placebo did not suggest any differences in insulin resistance between lomitapide-treated subjects and placebo controls.

An analysis was conducted to assess the possible correlation of HOMA-IR and changes in percent hepatic fat over time on study based on the data from Study AEGR-733-004. There were no significant correlations noted in the pooled lomitapide group (2.5, 5, 7.5, and 10 mg) between these 2 parameters ($p \geq 0.1642$).

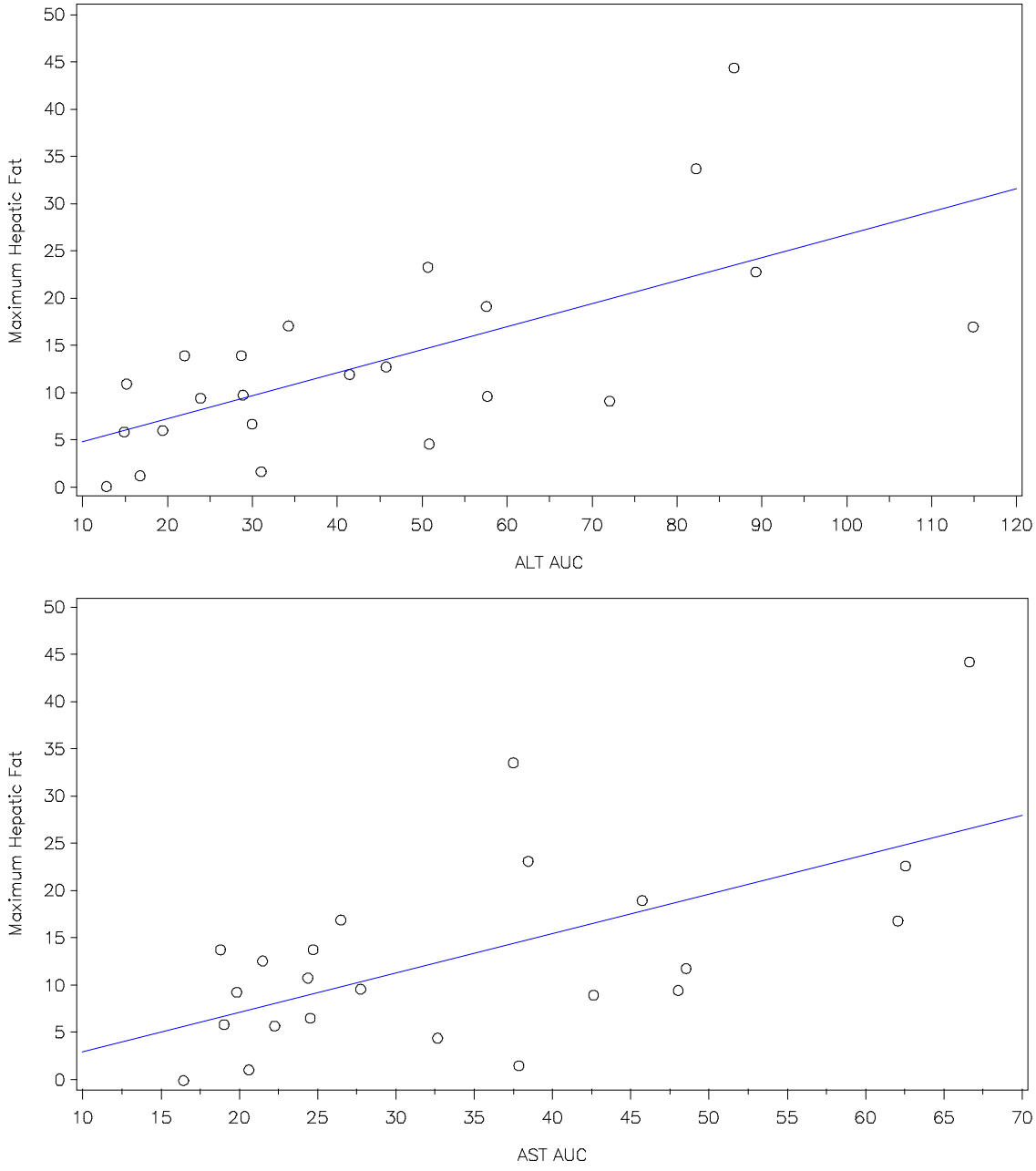
Non-clinical in vivo data also suggest that hepatic fat accumulation and insulin resistance are not causally related. In a study of high-fat fed rats, hepatic insulin action was sustained despite a sevenfold elevation of hepatic triglyceride (Buettner, 2004). Furthermore in a Zucker rat model of hypertriglyceridemia, in which all animals had substantially elevated levels of hepatic fat, administration of lomitapide was associated with improved insulin sensitivity and glucose metabolism, possibly related to decreased weight gain and hyperphagia compared to control animals (Dhote, 2011).

6.12 Analyses of Changes in Transaminase Levels with Changes in Lipids and Hepatic Fat

A regression analysis of the relationship between time-averaged AUC for ALT and AST up to the date of the maximum hepatic fat measurement and the maximum hepatic fat measurement

was conducted. Results are depicted graphically in Figure 21. These results showed that both AUC of ALT and AST were significantly related to maximum hepatic fat (p=0.0006 and p=0.0018, respectively) with r-square values of 0.433 and 0.377, respectively.

Figure 21: Regression Analysis of Time-Averaged[a] AUC for ALT and AST and Maximum Hepatic Fat Measurement, Phase 3 HoFH Study



[a] AUC through maximum hepatic fat elevation
Regression equation: Maximum hepatic fat = 2.298997 + 0.243477× ALT AUC
Regression equation: Maximum hepatic fat = -1.17958 + 0.418299×AST AUC

In addition to the regression analysis, correlation analyses based on Spearman rank-correlation statistic were conducted on data from the Phase 3 HoFH study for changes in ALT and AST to Weeks 26 and 56 with changes triglycerides, LDL-C, and percent hepatic fat to the same time points.

As expected, changes in ALT to Weeks 26 and 56 were significantly correlated with changes in AST to those time points ($p<0.0001$) with a correlation coefficient r of 0.9713 at Week 26 and 0.9188 at Week 56. Changes in ALT were significantly ($p\leq0.0158$) correlated with changes in hepatic fat at Weeks 26 and 56 ($r = 0.6203$ and $r = 0.5145$, respectively); there was also a significant correlation for AST and hepatic fat changes at Week 26 ($p<0.0001$, $r = 0.7202$) but not at Week 56 ($p=0.0634$, $r = 0.4117$).

Statistically significant ($p\leq0.0212$) correlations were noted for changes in ALT and in AST with changes in LDL-C to Week 26 ($r = -0.6194$ and $r = -0.6457$, respectively) and to Week 56 ($r = -0.5012$ and $r = -0.4740$, respectively). For the correlation of changes in transaminases with change in triglycerides, the results were not statistically significant for Week 26 for either ALT or AST; significant ($p\leq0.0062$) correlations were observed between change in ALT and AST and change in triglycerides to Week 56 ($r = -0.5731$ and $r = -0.5161$, respectively).

Changes in LDL-C at Weeks 26 and 56 were significantly correlated with changes in percent hepatic fat at those time points ($p = 0.0125$ and $p = 0.0085$, respectively) with correlation coefficients r of -0.5178 at Week 26 and -0.5515 at Week 56.

6.13 Liver Histology Data

To date, 2 subjects receiving lomitapide have undergone post-baseline liver biopsies, including the 1 HoFH subject described above who developed ALT >20×ULN during the Phase 3 extension study that was confounded by concurrent treatment with agomelatine and clarithromycin and 1 subject with familial chylomicronemia (FC) who has been receiving lomitapide for over 13 years under a compassionate use protocol.

In the HoFH subject, who had been receiving lomitapide for more than 2 years at the time of the transaminase elevations, ALT and AST levels were below baseline levels within 2 weeks following discontinuation of lomitapide and the 2 concomitant medications. Histology from liver biopsy conducted 2 months off treatment demonstrated the presence of mild steatosis without significant inflammation or fibrosis. This subject has re-started lomitapide treatment without clinical consequence.

The FC subject was placed on lomitapide over 13 years ago after a near fatal bout of pancreatitis with severe triglyceridemia (>2000 mg/dL) despite maximal dietary (<7% total fat) and drug treatment (gemfibrozil 1200 mg/day and atorvastatin 80 mg/day). She initiated treatment with lomitapide at 12.5 mg and was escalated to 25 mg to improve response; after 6 weeks at this dose her triglyceride levels were 253 mg/dL. During the course of treatment with lomitapide, her

triglyceride levels improved markedly associated with a reduction in the incidence and severity of pancreatitis episodes. Serial ultrasound of the liver showed severe fatty liver at baseline with no progression observed over the course of lomitapide treatment. Liver biopsies performed 1.5, 2.5 and 5 years after initiating lomitapide showed marked steatosis but no hepatocyte necrosis, inflammation or fibrosis. A biopsy after 9 years on treatment demonstrated marked, predominantly macrovesicular, steatosis and mild steatohepatitis but no significant fibrosis. Hepatic transaminase levels were stable during this time remaining <2×ULN. Recently, her ALT and AST values increased, peaking at ~4×ULN. From a clinical perspective the subject had been doing well, with no episodes of pancreatitis and no GI symptoms. As a result of the elevation in aminotransferases, a liver biopsy was performed in June 2012. The results of this biopsy are consistent with the development of NASH. There is clear evidence of progression relative to her last biopsy. Since the subject appears to have had long-standing steatosis that is likely related to her underlying condition, the extent to which the recent progression may have been precipitated by hepatic fat accumulation due to lomitapide is unclear. The subject remains on lomitapide at this time.

6.14 Fat Soluble Nutrients

As vitamin E is primarily transported to the peripheral tissues via the LDL particle, and due to the profound LDL-C lowering effect observed during treatment with lomitapide, it is not unexpected that the mean levels of vitamin E decreased from baseline. Importantly, the ratio of vitamin E:total lipids (total cholesterol + triglycerides) remained relatively stable through Week 78 of the Phase 3 study and during the extension study; mean changes from baseline to Week 78 and Week 138 in the ratio were -0.2 and -0.1, respectively. Also, none of the subjects had a vitamin E:total lipids ratio <1 at any time on either Study UP1002/AEGR-733-005 or AEGR-733-012 (Horwitt, 1972).

There were no notable changes over time on treatment in other fat-soluble compounds, including vitamins A, D and K, as well as beta carotene.

Mean levels of fatty acids decreased over time compared to baseline in the Phase 3 HoFH study. However, the majority of subjects did not have fatty acid levels shift into the low range during treatment with lomitapide. Shifts from normal or elevated levels at baseline to values below the normal range were observed most commonly for ALA and linoleic acid. Importantly, levels of both omega-3 and omega-6 fatty acids needed to produce eicosanoids (EPA, DHA and arachidonic acid) remained stable during 78 weeks of treatment. Thus, dietary supplementation with essential fatty acids in the amounts provided in the Phase 3 trial was important for maintaining adequate levels of fatty acids.

6.15 Vital Signs, Weight, Body Mass Index and Pulmonary Function Tests

Thorough review of vital signs parameters, including systolic and diastolic blood pressure, heart rate, and respiratory rate, showed no effect of lomitapide on any of these parameters. Weight loss was observed in some subjects on lomitapide treatment. Decreased weight was reported as a TEAE in 7 (24%) of the 29 subjects across Studies UP1002/AEGR-733-005 and AEGR-012.

Across the 29 subjects in Study UP1002/AEGR-733-005, mean change in BMI from baseline to the final visit was -0.8 kg/m^2 a -2.9% decrease. At the last visit across both the Phase 3 study and its extension, the mean change in BMI from baseline was -0.5 kg/m^2, or -1.4%. None of the subjects had BMI < 18.5 kg/m^2 at any time on either study, indicating that the weight loss observed did not reach levels of clinical concern for any subject.

There were no clinically meaningful changes from baseline over time on treatment for any PFTs in the HoFH studies or the Elevated LDL-C and Other CV Risk Factors Study Pool.

6.16 Electrocardiograms

A thorough QT study was performed to determine that single 75 and 200 mg oral solution doses of lomitapide, and 75 mg (in solution) coadministered with ketoconazole (when adjusted for the effects of ketoconazole administration alone), do not differ from placebo in mean change from baseline in 12-lead ECG QTc interval measurements. This study also evaluated the relationship between plasma lomitapide and ketoconazole concentrations and QTc interval and further evaluated the safety and tolerability of lomitapide when given as single therapeutic and supra-therapeutic doses of 75 and 200 mg, respectively, and 75 mg coadministered with ketoconazole. A total of 56 healthy subjects aged between 18 and 55 years were enrolled and 50 subjects completed the study.

The results of this study clearly demonstrated that lomitapide at doses producing therapeutic and supra-therapeutic plasma levels does not have an effect on the QTc interval or heart rate. In addition, the study did not find evidence of any effect of the primary metabolites (M1 and M3) on QTc intervals when lomitapide was administered at therapeutic and supra-therapeutic levels.

6.17 Safety of Lomitapide in Subgroups

There were no clinically meaningful or consistent differences across lomitapide dose groups in the incidence of the most common TEAEs for subgroups based on age, gender, race, BMI, baseline lipid levels, or risks for CHD in the Elevated LDL-C and Other CV Risk Factors Study Pool. In addition, no clinically meaningful differences were observed in the incidence of elevations in LFTs for subgroups based on age, gender, race, BMI, baseline lipid levels or baseline hepatic fat content in the Elevated LDL-C and Other CV Risk Factors Study Pool.

Further, based on the results of the Phase 2 studies conducted to assess safety and PK in subjects with hepatic dysfunction and renal dysfunction, there were no differences in the safety profile of

lomitapide when administered to subjects with mild hepatic impairment and those with ESRD on hemodialysis compared with healthy volunteers.

7 SUMMARY OF THE SPONSOR'S PROPOSED RISK MITIGATION PLAN

The Sponsor is committed to ensure safe and appropriate use of lomitapide by the implementation of risk mitigation activities as part of a proposed REMS plan that was submitted in the NDA.

The goals of the lomitapide REMS are:

- 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.

The REMS will include the following elements to ensure safe use:

1. HCPs who prescribe lomitapide will be required to be specially certified.

   In order for HCPs to be certified, they must undergo an educational program and enroll in the lomitapide REMS program by acknowledging an understanding of the risks of lomitapide therapy; the need to monitor hepatic transaminases during treatment; and the indication for use. They must also agree to counsel patients about the risk of hepatotoxicity, the need to have regular blood tests performed to monitor for evidence of liver injury or dysfunction, and to attest that the patient is an appropriate candidate for lomitapide therapy prior to prescribing lomitapide.

2. Lomitapide will be dispensed by a limited number of specialty pharmacy providers that are certified and that agree to follow the REMS requirements.

   Certified pharmacies will need to have systems in place to ensure that only certified prescribers prescribe lomitapide to patients in whom therapy with lomitapide is medically appropriate.

3. Lomitapide will be dispensed only to patients with evidence or other documentation of safe-use conditions.

   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 sponsor will also implement a communication plan to include the following:

- Full Product Information (FPI; approved prescribing information);
- A "Dear Doctor" letter distributed to HCPs and to the leadership of specific professional societies (e.g., National Lipid Association, The Endocrine Society, American Heart Association, etc.).
- A Prescriber's Guide to Important Safety Information about Lomitapide
- A Lomitapide Web Site

7.1 Future Clinical Development Plans

In order to continue to collect information on identified and potential risks of lomitapide treatment, the Sponsor will conduct a prospective observational cohort study (Registry) focused on hepatic safety, pregnancy outcomes (if use in pregnancy occurs despite safe use advice), malignancies of the liver and small intestine, and other safety variables in order to continue to collect information on identified and potential risks of lomitapide treatment. This activity will supplement routine pharmacovigilance monitoring provided by spontaneous reporting and safety data from ongoing clinical trials.

In addition, the Sponsor plans to conduct a clinical trial in pediatric subjects with HoFH (age 8 to 17 inclusive) following approval of lomitapide in the adult HoFH patient population. The details of this proposed clinical trial protocol will be discussed and agreed with the FDA prior to initiation of the study.

8 BENEFITS AND RISKS CONCLUSIONS

The only defect in patients with HoFH as a result of LDL receptor deficiency is a severely elevated LDL-C. This places these patients at high risk of premature death and CV events. Existing therapies do not adequately control LDL-C in these patients.

Patients with HoFH are minimally responsive or unresponsive to conventional drug therapy and thus there are limited treatment options. Specifically, treatment with statins, which reduce LDL-C by inhibiting cholesterol synthesis and up-regulating the hepatic LDL receptor, has negligible effects in HoFH patients whose LDL receptors are non-existent or defective. As a result, patients with this disease continue to have elevated levels of LDL-C and suffer major adverse CV events such as MI, stroke, heart failure, and premature death. This is exemplified by the medical history of the subjects who participated in the Phase 3 trial (UP1002/AEGR-733-005), in which the mean baseline LDL-C was 336 mg/dL despite maximal LLTs, including LDL apheresis in most subjects.

LDL-C is a central risk factor in CVD and is a validated therapeutic target

The central role of LDL-C in the pathophysiology of arterial atherosclerosis is well established. Epidemiological evidence places LDL-C high on the list of important and modifiable risk factors for CVD (The Lipid Research Clinic1984a; Neaton and Wentworth, 1992). There is now a large body of prospective clinical evidence demonstrating the benefit of LDL-C reduction in the modification of clinical outcomes (NCEP, 2001; Grundy, 2004; Baigent, 2005; Baigent, 2010). A reduction in LDL-C by approximately 38 mg/dL with statin therapy is estimated to reduce the 5-year incidence of major coronary events, coronary revascularization, and stroke by about one fifth (Baigent, 2005). In HoFH, LDL-C is clearly causal in the generation of markedly premature CVD. HoFH patients who are 'receptor-defective' and who have lower LDL-C levels (400 to 600 mg/dL) have delayed development of CVD compared with HoFH patients who are 'receptor-negative' and have LDL-C levels often >750 mg/dL. Thus, a reduction of 40 to 50% in LDL-C in HoFH would be expected to substantially reduce the risk of developing CVD.

The use of LDL-C as a primary efficacy variable and surrogate for CV outcomes has been accepted by health authorities when there is epidemiologic, therapeutic, and pathophysiologic evidence to predict benefit. All of these circumstances clearly apply in the setting of hypercholesterolemia and CVD.

Lomitapide is a novel, first-in-class, oral therapy that has demonstrated dramatic reductions in LDL-C

Lomitapide has been developed as adjunctive therapy for a rare and serious lipid disorder, HoFH, and is the first in a novel class of lipid-lowering agents (MTP inhibitors) that functions independently of the LDL receptor. MTP is a logical target to effect significant reduction in

LDL-C due to its essential role in the assembly of chylomicrons (in the small intestine) and VLDL (in the liver). Nonclinical and clinical data demonstrate a clear pharmacodynamic effect of lomitapide that results in a broad and substantial reduction in LDL-C and other atherogenic lipoproteins.

Lomitapide produced significant reductions in LDL-C and other atherogenic lipoproteins in clinical trials

The efficacy of lomitapide to reduce plasma levels of LDL-C was consistently observed in all clinical studies regardless of population. The observed effect remained consistent in sub-population analyses, although, as expected, subjects with higher baseline LDL-C levels tended to demonstrate larger reductions with lomitapide treatment.

This magnitude of LDL-C reduction is rarely seen in clinical experience within the HoFH population, in whom LDL-C levels have largely proven refractory to oral therapy, necessitating use of regular plasma apheresis to effect further reductions. The observed percent decreases in mean LDL-C from baseline following escalation to an individual maximum tolerated dose resulted in a mean decrease of 40% after 26 weeks of treatment in the ITT population and 50% in the completer population. This level of reduction was maintained at 56 weeks (-44%), despite a decrease in background LLTs in some subjects.

Of note, 74% of HoFH subjects in the Phase 2 and Phase 3 studies were able to achieve a >50% reduction in LDL-C from baseline. Among the 29 HoFH subjects who received lomitapide concurrent with standard of care LLTs, 55% were able to achieve an LDL-C level <100 mg/dL, including 9 subjects (31%) with LDL-C <70 mg/dL, at one or more assessments. It is also noted that 3 subjects were able to discontinue apheresis during the trial, and 3 subjects were able to increase the interval between apheresis sessions by Week 78.

For the first time, it is now feasible for some subjects with HoFH to reach target LDL-C goals and to maintain these levels during chronic treatment.

Elevations in hepatic aminotransferases associated with lomitapide exposure were manageable with dose adjustment or interruption in treatment in the Phase 3 trial

Elevations of hepatic aminotransferases ≥3×ULN on one or more occasion occurred in 11 (38%) of 29 subjects in the Phase 3 HoFH trial of lomitapide and its extension study. On no occasion was any elevation above 3×ULN temporally associated with an increase in bilirubin or alkaline phosphatase; consequently there were no cases that satisfied Hy's Law criteria in the clinical development program for lomitapide.

Management of elevated hepatic aminotransferases was carefully specified by an algorithm in the protocols for the HoFH trials. In addition, an independent DSMB (including a hepatologist), provided oversight of patient safety. For most subjects with elevated aminotransferase levels,

dose adjustment or temporary interruption in lomitapide treatment resulted in rapid improvement of liver aminotransferase levels, thereby allowing continued participation and dosing with lomitapide. In general liver enzyme elevations were apparent during the dose escalation phase; however, there were cases of elevation during maintenance on a constant dose. One subject was discontinued from therapy during the extension study AEGR-733-012 due to aminotransferase elevations. This subject had ALT elevations that persisted after down titrating to the lowest dose of 5 mg. Continued excessive alcohol intake may have contributed to this subject's aminotransferase elevations. One other subject in this study developed transient ALT elevations >20×ULN in the setting of concomitant medications known to cause liver injury; this subject was discontinued from the study but has since been restarted on lomitapide and the subject's clinical course has been uneventful. There was no consistent dose-response relationship that predicted onset of liver enzyme elevation; however, decreasing or interrupting the dose resulted in predictable reductions in hepatic aminotransferases. Several subjects demonstrated improvement in aminotransferase levels over time with maintenance of the same dose of lomitapide. Detailed recommendations for dose adjustment, interruption, or permanent discontinuation in the event of hepatic aminotransferase elevations >3×ULN are provided in the proposed prescribing information (see Table 22).

Due to the potential for lomitapide to cause elevations in aminotransferase levels, caution should be exercised when lomitapide is co-administered with agents known to be hepatotoxic and is contraindicated in patients with moderate to severe hepatic impairment and those with active liver disease, including patients with unexplained persistent abnormal LFTs.

Hepatic imaging revealed asymptomatic steatosis in most subjects treated with lomitapide

Consistent with the mechanism of action of lomitapide, most treated subjects exhibited increases in hepatic triglyceride content. In the Phase 3 study, there was an increase from a baseline hepatic fat value of <1% to 8% after 26 weeks of treatment and 7% at the Week 78 assessment; similar mean percent changes were noted over continued treatment during the extension study. Clinical data suggest that hepatic fat accumulation is reversible within 4 to 6 weeks after stopping treatment with lomitapide.

The long-term consequences of steatosis in association with lomitapide treatment are unknown. It is reassuring to note, however, that in a recent prospective observational cohort study in 11,371 US adults followed for a median of 14.5 years, NAFLD was not associated with an increased risk of death from all causes, CVD, cancer, or liver disease (Lazo, 2011).

Gastrointestinal symptoms were commonly associated with lomitapide but manageable with a low-fat diet and dose modification

The most common AEs in the Phase 3 trial were GI symptoms, primarily diarrhea. This pattern of GI symptoms also was consistently observed in Phase 1 and 2 trials. This finding is expected

since MTP inhibition is known to cause fat malabsorption and steatorrhea. There was convincing evidence of a dose-response relationship for most of the GI AEs reported in the pool of Phase 2 studies in which subjects with elevated LDL-C were randomized to different doses of lomitapide. This relationship became less clear in the Phase 3 HoFH study, probably due to the ability to modify dosing according to tolerability and the low fat diet. While it is not feasible to quantify the relative importance of a low-fat diet and dose escalation over time, it is highly likely that both aspects of this modified dosing regimen are important to achieve satisfactory GI tolerability and compliance with lomitapide treatment.

Modest weight loss may occur in some subjects treated with lomitapide over time.

In the Phase 3 HoFH trial and its extension, decreased body weight was reported as an AE in 7 (24%) of 29 subjects. All cases were assessed as mild to moderate in severity and non-serious and none led to study drug discontinuation. The combination of GI symptoms (e.g. diarrhea, nausea), fat malabsorption, and adherence to a strict fat-restricted diet, may result in a calorie deficit relative to daily requirements. Appropriate dietary supervision and monitoring is an important component to improved GI tolerability and the maintenance of an adequate diet to avoid unintended weight loss. The results of the Phase 3 study in HoFH provide evidence that such dietary supervision may be used successfully to maintain subjects on lomitapide treatment.

Dietary supplementation with vitamin E and essential fatty acids prevents deficiency of these nutrients.

Patients with abetalipoproteinemia are known to experience fat malabsorption and deficiency of fat soluble vitamins, particularly vitamin E. It may be expected, therefore, that MTP inhibition with lomitapide is likely to cause a less severe but potentially important deficiency in these essential nutritional elements over time with prolonged dosing. All subjects with HoFH in the Phase 3 trial had dietary supplementation with 400 IU vitamin E, and approximately 200 mg linoleic acid, 110 mg EPA, 220 mg ALA and 80 mg DHA per day. Mean decreases from baseline to Week 78 were observed across all fatty acid parameters. Importantly, there were no shifts from normal to below normal levels of fatty acids needed to produce eicosanoids (EPA, DHA, and arachidonic acid). In addition, despite a fall in vitamin E levels (expected as a result of LDL-C reduction), the ratio of vitamin E:total lipids (total cholesterol + triglycerides), which is the clinical standard for assessing nutritional status, did not reach levels indicating a nutritional inadequacy in any subjects across the lomitapide program (Horwitt, 1972).

The proposed label for lomitapide includes recommendations for dietary counseling and supplementation with vitamin E and fatty acids.

Lomitapide was associated with rodent tumors and was a selective development toxicant in rats

Significantly increased incidences of liver and small intestine tumors were observed in a lifetime dosing study in mice. These findings were not noted in clinical trials, and a variety of factors

suggest that they may not be expected to occur in clinical use. Most importantly, lomitapide showed no evidence of genotoxicity or immunotoxicity, and no cellular injury in the liver and small intestine was observed in mice (i.e., tumorigenic mechanisms that could be relevant to humans). Further, liver tumors, which are common spontaneous tumors in mice (Holsapple, 2006), have been observed with a number of marketed drugs, including the statins, in carcinogenicity studies in mice (e.g., simvastatin caused up to a 90% increased in the incidence of hepatocellular carcinomas in mice at ≥4× the drug exposure in humans at 80 mg) (Zocor [Package Insert] 2012; Brambilla, 2012). In addition, the historic difficulty in extrapolating tumor findings in animals to predict risk in humans is well known (i.e., a number of marketed drugs are rodent carcinogens but those with strong evidence of carcinogenicity in humans are predominately chemotherapeutic and immunosuppressant agents) (Peto, 1980; Brambilla, 2012).

To evaluate this potential risk, the Sponsor proposes to conduct a prospective observational cohort study in the post-approval setting that will include collection of incidence information for all malignancies with follow-up for a minimum period of 5 years.

Lomitapide demonstrated selective developmental toxicity in rats. Consequently, the Sponsor is recommending that lomitapide not be given to pregnant women or women of reproductive potential without adequate use of contraception (i.e., same labeling as statins).

Key areas of the proposed prescribing information specify measures to minimize risk and optimize benefit

The proposed prescribing information provides guidance in key areas to minimize risk to patients during treatment with lomitapide. Use of lomitapide in patients with moderate or severe hepatic impairment, or active liver disease is contraindicated. Contraindications also include co-administration with strong or moderate inhibitors of CYP3A4, co-administration with doses of simvastatin ≥80 mg, and use of lomitapide in pregnancy. Use in patients with known significant or chronic bowel disease is also contraindicated since MTP inhibition is known to cause fat malabsorption and steatorrhea. Hepatic aminotransferase levels must be determined prior to initiating therapy, and then monitored prior to each dose escalation, and regularly during treatment. In the event that hepatic aminotransferases become elevated, a detailed algorithm for dose adjustment or treatment discontinuation is provided (Table 22). This algorithm is based on the approach agreed with the DSMB hepatologist that was used successfully in the Phase 3 HoFH study and is consistent with the FDA's draft guidance, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, October 2007.

Table 22: Dosage Adjustment and Monitoring in Patients Developing Liver Aminotransferase Elevations >3×ULN

ALT/AST LEVELS	TREATMENT AND MONITORING RECOMMENDATIONS
>3 and ≤5×ULN	Confirm with another aminotransferase test. If the elevation is confirmed then continue to monitor aminotransferase levels at least every 2 weeks to establish no further increase on at least 2 successive occasions. A decision may be made to continue on the same dose of lomitapide, or to reduce the dose if aminotransferase levels continue to rise.
>5 and ≤10×ULN	Confirm with another aminotransferase test. If the elevation is confirmed, then reduce the dose of lomitapide to the previous dose level. Continue to monitor aminotransferase levels at least every 2 weeks until levels fall below 5×ULN. If levels remain above 5×ULN the dose should be reduced again. If levels fall below 3×ULN, an increase in dose to the next level may be considered on an individualized patient basis.
>10×ULN	Confirm with another aminotransferase test. If the elevation is confirmed, stop treatment with lomitapide and continue to monitor aminotransferase levels at least every 2 weeks. Reintroduction of lomitapide at the recommended starting dose may be considered once aminotransferase levels fall below 5×ULN. If aminotransferase levels remain elevated >10×ULN, seek a consult from a hepatologist.

If liver aminotransferase elevations are accompanied by clinical symptoms of liver injury (e.g., nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms) or increases in bilirubin ≥2×ULN, lomitapide is to be discontinued and advice sought from a hepatologist. Reintroduction of treatment with lomitapide may be considered if the benefits are considered to outweigh the risks associated with potential liver injury.

Dietary advice, including fat content and supplementation with vitamin E and essential fatty acids, is also specified in the proposed prescribing information, and dosing is escalated gradually to minimize GI side effects and allow for regular hepatic aminotransferase determination. These elements of prescribing advice and safety monitoring are designed to allow the optimum individualized dose to be selected for each patient in order to maximize the benefit of LDL-C reduction, ensure compliance with treatment, and minimize adverse effects.

Risk mitigation activities essential to ensure safe and appropriate use of lomitapide

Lomitapide treatment must be prescribed by appropriately trained physicians in a setting that will allow for close supervision of liver safety and nutritional status. The Sponsor is committed to ensure safe and appropriate use of lomitapide by the implementation of risk mitigation activities as part of a comprehensive risk management plan.

A risk mitigation program will be established by the Sponsor and implemented according to applicable national regulatory requirements. Specialized physicians will be educated on all important safety issues. Critical safety information provided in the prescribing information, particularly in relation to liver safety and the use of the drug during pregnancy, will be

emphasized. Baseline liver aminotransferase levels and the absence of pregnancy (when relevant) will be checked prior to lomitapide treatment.

Lomitapide will be dispensed by a limited number of designated pharmacies that are under contract with the Sponsor.

Finally, in order to continue to collect information on identified and potential risks of lomitapide treatment, the Sponsor will conduct a prospective observational cohort study (Registry) focused on hepatic safety, pregnancy outcomes (if use in pregnancy occurs despite safe use advice), malignancies of the liver and small intestine, and other safety variables. This activity will supplement routine pharmacovigilance monitoring provided by spontaneous reporting and safety data from ongoing clinical trials.

Conclusions

Hypercholesterolemia caused by HoFH is difficult to treat, and currently available options are inadequate as evidenced by the unsatisfactory baseline situation observed in the lomitapide clinical trials and reports in the clinical literature. Despite pharmacological intervention (including maximally tolerated doses of statins), and the addition of frequent LDL apheresis, HoFH patients entered the clinical program with average LDL-C levels well above consensus targets. The lack of adequate treatment options for HoFH means patients continue to be exposed to elevated levels of LDL-C resulting in a high risk for serious or fatal CV events such as MI and/or stroke. Furthermore, many of these young patients have already experienced these events, and undergone CV interventions including coronary angioplasty, stenting, and coronary bypass surgery. The highly unsatisfactory and perilous situation in which these patients find themselves demands the addition of further intervention to reduce LDL-C levels.

Patients with HoFH deal with a life-threatening disease every day as a consequence of severely elevated LDL-C despite aggressive use of currently available therapies. Lomitapide treatment reduced mean LDL-C levels in the Phase 3 study by 40% in the ITT population and 50% in the completer population. With appropriate information on safe and appropriate use, the physicians who manage these patients are well positioned to optimize the benefit that can be derived from the dramatic reductions in LDL-C achievable with lomitapide treatment while closely monitoring safety and tolerability as part of the Sponsor's risk mitigation plan. In this context, lomitapide represents a potential major advancement in the treatment of a devastating disease through modification of a risk factor that is currently uncontrolled by available treatment interventions, supporting a favorable benefit-risk assessment for its use in this high-risk patient population.

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10 APPENDICES

10.1 Appendix Tables

Table 23: Percent Change from Baseline in LDL-C using LOCF, Elevated LDL-C Study Pool (Full Analysis Set)

Study Week Statistic	Lomitapide Alone: Escalated (5 to 10 mg) (N=28)	Lomitapide Alone: Low Dose (2.5-7.5 mg) (N=127)	Lomitapide Alone: Mid Dose (10 mg) (N=61)	Lomitapide Alone: High Dose (25 mg) (N=33)	Lomitapide Combined with Active Treatments (N=190)	Placebo (N=97)	Active Control (N=76)	p-value[4]
Week 4								
N	28	127	61	33	190	97	76	<0.0001
Mean (SD)	-15.9 (16.6)	-13.9 (17.7)	-25.6 (25.4)	-59.7 (26.5)	-42.5 (22.9)	1.6 (15.9)	-34.8 (15.5)	
[95% CI]	[-22.4, -9.5]	[-17.0, -10.8]	[-32.1, -19.1]	[-69.1, -50.3]	[-45.8, -39.2]	[-1.6, 4.8]	[-38.3, -31.2]	
p-value[1]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.3329	<0.0001	
LSM (SEM)[2]	-14.56 (3.69)	-16.11 (1.76)	-26.29 (2.50)	-55.32 (3.45)	-42.93 (1.42)	2.45 (1.98)	-32.95 (2.25)	
[95% CI]	[-21.80, -7.31]	[-19.56, -12.66]	[-31.20, -21.39]	[-62.10, -48.55]	[-45.71, -40.15]	[-1.44, 6.35]	[-37.37, -28.53]	
p-value[3]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001		<0.0001	
Week 8								
N	28	127	61	Not conducted	190	60	76	<0.0001
Mean (SD)	-22.5 (15.4)	-13.3 (17.9)	-26.3 (23.1)		-40.3 (24.2)	3.0 (14.9)	-33.7 (17.1)	
[95% CI]	[28.4, -16.5]	[-16.4, -10.2]	[-32.3, -20.4]		[-43.8, -36.8]	[-0.9, 6.8]	[-37.6, -29.8]	
p-value[1]	<00001	<00001	<00001		<00001	0.1251	<00001	
LSM (SEM)[2]	-20.33 (3.72)	-14.98 (1.76)	-26.37 (2.51)		-40.08 (1.42)	1.58 (2.54)	-31.10 (2.28)	
[95% CI]	[27.63, -13.03]	[-18.43, -11.53]	[-31.30, -21.44]		[-42.87, -37.28]	[-3.41, 6.56]	[-35.58, -26.62]	
p-value[3]	<00001	<00001	<00001		<00001		<00001	

Abbreviations: CI=confidence intervals; LSM=least square mean; SD=standard deviation; SEM=standard error of the mean.
Includes Studies AEGR-733-001, AEGR-733-003b, AEGR-733-004, AEGR-733-006, and CV145-009

1 p-value from paired t-test assessing change from Baseline
2 LSM and SEM from analysis of covariance (ANCOVA) model with treatment group and Baseline LDL-C as covariates
3 p-value from ANCOVA model comparing treatment to placebo
4 p-value from F-test of overall treatment group differences from ANCOVA model

Table 24: Percent Change from Baseline to Week 4 in Total Cholesterol, Non-HDL-C, Apo B and Triglycerides Based on LOCF, Elevated LDL-C Study Pool (Full Analysis Set)

Efficacy Variable Statistic	Lomitapide Alone: Escalated (5 to 10 mg) (N=28)	Lomitapide Alone: Low Dose (2.5-7.5 mg) (N=127)	Lomitapide Alone: Mid Dose (10 mg) (N=61)	Lomitapide Alone: High Dose (25 mg) (N=33)	Lomitapide Combined with Active Treatments (N=190)	Placebo (N=97)	Active Control (N=76)	p-value[4]
TC								
N	28	127	61	33	190	97	76	<0.0001
Mean (SD)	-12.8 (12.5)	-11.8 (13.3)	-22.6 (19.4)	-49.5 (19.6)	-32.0 (18.5)	1.7 (11.0)	-24.8 (12.5)	
[95% CI]	[-17.7, -8.0]	[-14.2, -9.5]	[-27.5, -17.6]	[-56.4, -42.5]	[-34.7, -29.4]	[-0.5, 4.0]	[-27.7, -21.9]	
p-value[1]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.1235	<0.0001	
LSM (SEM)[2]	-11.78 (2.86)	-13.36 (1.36)	-22.86 (1.94)	-46.37 (2.67)	-32.50 (1.10)	2.31 (1.54)	-23.34 (1.75)	
[95% CI]	[-17.41, -6.16]	[-16.03, -10.68]	[-26.66, -19.05]	[-51.62, -41.12]	[-34.66, -30.34]	[-0.71, 5.33]	[-26.78, -19.91]	
p-value[3]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001		<0.0001	
Non-HDL-C								
N	28	127	61	33	190	97	76	<0.0001
Mean (SD)	-13.9 (13.5)	-13.0 (15.5)	-25.0 (23.9)	-55.8 (21.9)	-39.3 (21.5)	1.7 (13.5)	-31.8 (15.1)	
[95% CI]	[-19.2, -8.7]	[-15.7, -10.3]	[-31.1, -18.9]	[-63.5, -48.0]	[-42.4, -36.2]	[-1.0, 4.4]	[-35.3, -28.4]	
p-value[1]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.2167	<0.0001	
LSM (SEM)[2]	-12.39 (3.36)	-15.12 (1.60)	-25.55 (2.27)	-51.54 (3.14)	-39.94 (1.29)	2.60 (1.80)	-29.71 (2.05)	
[95% CI]	[-18.99, -5.80]	[-18.26, -11.98]	[-30.01, -21.08]	[-57.70, -45.37]	[-42.48, -37.41]	[-0.94, 6.15]	[-33.75, -25.68]	
p-value[3]	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001		<0.0001	
Apo B								
N	28	127	61	33	189	97	75	<0.0001
Mean (SD)	-9.8 (12.5)	-11.1 (14.4)	-24.6 (22.3)	-53.9 (19.6)	-33.9 (20.0)	2.3 (14.3)	-26.5 (14.3)	
[95% CI]	[-14.6, -5.0]	[-13.6, -8.5]	[-30.3, -18.9]	[-60.9, -47.0]	[-36.8, -31.0]	[-0.6, 5.2]	[-29.8, -23.3]	
p-value[1]	0.0003	<0.0001	<0.0001	<0.0001	<0.0001	0.1130	<0.0001	
LSM (SEM)[2]	-7.46 (3.24)	-12.65 (1.54)	-24.84 (2.18)	-51.00 (3.01)	-34.40 (1.24)	2.44 (1.73)	-24.70 (1.99)	
[95% CI]	[-13.83, -1.10]	[-15.67, -9.63]	[-29.11, -20.57]	[-56.91, -45.10]	[-36.84, -31.97]	[-0.95, 5.83]	[-28.61, -20.79]	
p-value[3]	0.0071	<0.0001	<0.0001	<0.0001	<0.0001		<0.0001	

Efficacy Variable Statistic	Lomitapide Alone: Escalated (5 to 10 mg) (N=28)	Lomitapide Alone: Low Dose (2.5-7.5 mg) (N=127)	Lomitapide Alone: Mid Dose (10 mg) (N=61)	Lomitapide Alone: High Dose (25 mg) (N=33)	Lomitapide Combined with Active Treatments (N=190)	Placebo (N=97)	Active Control (N=76)	p-value[4]
Triglycerides								
N	28	127	61	33	190	97	76	<0.0001
Mean (SD)	3.1 (29.3)	4.1 (49.8)	-14.3 (42.3)	-31.3 (35.8)	-14.8 (31.6)	9.3 (40.8)	-14.0 (24.1)	
[95% CI]	[-8.3, 14.4]	[-4.7, 12.8]	[-25.1, -3.5]	[-43.9, -18.6]	[-19.3, -10.3]	[1.1, 17.5]	[-19.5, -8.5]	
p-value[1]	0.5823	0.3580	0.0106	<0.0001	<0.0001	0.0275	<0.0001	
LSM (SEM)[2]	5.38 (6.73)	2.21 (3.16)	-14.52 (4.55)	-27.06 (6.21)	-16.63 (2.59)	10.65 (3.61)	-10.55 (4.10)	
[95% CI]	[-7.83, 18.59]	[-4.00, 8.42]	[-23.46, -5.58]	[-39.25, -14.87]	[-21.71, -11.55]	[3.56, 17.75]	[-18.60, -2.51]	
p-value[3]	0.4898	0.0796	<0.0001	<0.0001	<0.0001		0.0001	

Abbreviations: Apo B=apolipoprotein B; CI=confidence intervals; HDL-C=high-density lipoprotein cholesterol; LSM=least square mean; SD=standard deviation; SEM=standard error of the mean; TC=total cholesterol.
Includes Studies AEGR-733-001, AEGR-733-003b, AEGR-733-004, AEGR-733-006, and CV145-009
1 p-value from paired t-test assessing change from Baseline
2 LSM and SEM from analysis of covariance (ANCOVA) model with treatment group and Baseline lipid parameter as covariates
3 p-value from ANCOVA model comparing treatment to placebo
4 p-value from F-test of overall treatment group differences from ANCOVA model

Table 25: Treatment-Emergent Adverse Events Reported in 5% or More of Subjects in a Treatment Group: Elevated LDL-C and Other Cardiovascular Risk Factors Study Pool (Safety Population)

	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 (%)
Diarrhea	30 (39.0)	122 (50.0)	63 (63.6)	46 (74.2)	13 (11.2)	7 (9.0)
Nausea	9 (11.7)	46 (18.9)	36 (36.4)	19 (30.6)	4 (3.4)	5 (6.4)
Flatulence	9 (11.7)	27 (11.1)	9 (9.1)	12 (19.4)	7 (6.0)	2 (2.6)
Headache	4 (5.2)	28 (11.5)	4 (4.0)	7 (11.3)	13 (11.2)	4 (5.1)
Abdominal distension	4 (5.2)	19 (7.8)	8 (8.1)	8 (12.9)	4 (3.4)	6 (7.7)
Vomiting	6 (7.8)	15 (6.1)	8 (8.1)	7 (11.3)	3 (2.6)	0
Alanine aminotransferase increased	17 (22.1)	13 (5.3)	3 (3.0)	3 (4.8)	1 (0.9)	1 (1.3)
Dyspepsia	8 (10.4)	16 (6.6)	6 (6.1)	1 (1.6)	3 (2.6)	4 (5.1)
Abdominal pain upper	2 (2.6)	17 (7.0)	9 (9.1)	4 (6.5)	4 (3.4)	0
Abdominal pain	4 (5.2)	10 (4.1)	7 (7.1)	9 (14.5)	2 (1.7)	3 (3.8)
Fatigue	2 (2.6)	17 (7.0)	4 (4.0)	5 (8.1)	3 (2.6)	0
Aspartate aminotransferase increased	11 (14.3)	12 (4.9)	3 (3.0)	2 (3.2)	1 (0.9)	1 (1.3)
Constipation	5 (6.5)	12 (4.9)	0	1 (1.6)	4 (3.4)	3 (3.8)
Back pain	1 (1.3)	9 (3.7)	2 (2.0)	4 (6.5)	6 (5.2)	3 (3.8)
Nasopharyngitis	0	11 (4.5)	2 (2.0)	1 (1.6)	6 (5.2)	4 (5.1)
Abdominal discomfort	5 (6.5)	4 (1.6)	5 (5.1)	4 (6.5)	1 (0.9)	2 (2.6)
Decreased appetite	1 (1.3)	4 (1.6)	7 (7.1)	4 (6.5)	0	0
Dizziness	0	4 (1.6)	2 (2.0)	4 (6.5)	3 (2.6)	2 (2.6)
Eructation	4 (5.2)	0	4 (4.0)	2 (3.2)	1 (0.9)	0
Asthenia	0	4 (1.6)	1 (1.0)	4 (6.5)	0	0

1 Includes subjects who received lomitapide alone and coadministered with other lipid-lowering drugs.