CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203858Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW
MEMORANDUM
(Addendum to the original review dated November 5, 2012)

NDA	203-858; N-000, N-012, N-014, N-015, N-024, N-029
Submission Date	February 29, 2012
Brand Name	To be determined
Generic Name	Lomitapide mesylate
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Immo Zadezensky, Ph.D.
Division Director	Chandrahas Sahajwalla, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Aegerion Pharmaceuticals
Formulation; Strength	Oral immediate release capsule: 5, 10, and 20 mg
Relevant IND	50,820
Indication	Treatment of homozygous familial hypercholesterolemia

Background

Refer to Clinical Pharmacology review dated November 5, 2012 in DARRTS for the Clinical Pharmacology information of lomitapide. The purpose of this addendum is to summarize the Clinical Pharmacology related post marketing study requirement.

Phase IV Requirements

Severe Renal Impairment Study

Lomitapide is mainly cleared via metabolism from the body. For drugs that are mainly metabolized, a study in all categories of renal impairment such as mild, moderate, severe, and end-stage renal disease (ESRD) for these drugs is generally not conducted but a Reduced Pharmacokinetic Study Design in ESRD patients **not yet on** dialysis as the "worst case" is acceptable. Data shows that the exposure increase of a drug that is mainly cleared via nonrenal route is higher in patients with severe renal impairment than ESRD patients receiving chronic hemodialysis (Zhang et al. *J Clin Pharmacol* 2012;52:79S-90S).

The sponsor conducted the renal impairment study (AEGR-733-021) in patients with ESRD **receiving** hemodialysis treatment, such patients may not represent the "worst case" of renal impairment, since the clearance of lomitapide may have been altered as the chronic and predose hemodialysis may remove uremic inhibitors that are important for lomitapide metabolism and transporters (Nolin et al. *Clin Pharmacol Ther* 2008;83:898-903; Dreisbach & Lertora *Expert Opin Drug Metab Toxicol* 2008;4:1065-74). Thus, patients with severe renal impairment may represent the "worst case" of renal impairment.

In Study AEGR-733-021, lomitapide $AUC_{0\text{-}inf}$ and C_{max} of ESRD patients receiving hemodialysis treatment increased 40% and 50%, respectively, as compared to those of healthy participants. The potential lomitapide exposure increase in patients with severe renal impairment as compared to ESRD patients receiving hemodialysis may pose a safety concern since the use of lomitapide was associated with elevated transaminases even at low

doses, such as 2.5 mg lomitapide daily (FDA Briefing Document for the Lomitapide Advisory Committee Briefing Document, Pages 56 – 57). The exposure of a lomitapide metabolite, M1, is also significantly increased in ESRD patients receiving hemodialysis but the extent of M1 increase in severe renal impairment is unknown for toxicological assessment.

Since the clearance of lomitapide decreased in patients with ESRD receiving hemodialysis (assuming no change in oral bioavailability) and such decrease is not generally expected of a drug mainly cleared via metabolism, we are requesting the Postmarketing Requirement. The sponsor should conduct a comparative study between patients with severe renal impairment and healthy volunteers with normal renal function to assess the effect of extreme renal impairment on lomitapide and M1's exposures as a Postmarketing Requirement. The results of this study will help guide the dosing of lomitapide in the renally impaired patients with homozygous familial hypercholesterolemia.

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

/s/

SZE W LAU
11/08/2012

IMMO ZADEZENSKY
11/09/2012

CHANDRAHAS G SAHAJWALLA
11/09/2012

CLINICAL PHARMACOLOGY REVIEW

NDA	203-858; N-000, N-012, N-014, N-015, N-024, N-029
Submission Dates	February 29, 2012, June 18, 2012, June 27, 2012, July 2, 2012, September 7, 2012, October 1, 2012
Brand Name	To be determined
Generic Name	Lomitapide mesylate
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Immo Zadezensky, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Aegerion Pharmaceuticals
Formulation; Strength	Oral immediate release capsule: 5, 10, and 20 mg
Relevant IND	50,820
Indication	Treatment of homozygous familial hypercholesterolemia

Table of Contents **Page**

1 Executive Summary

Lomitapide mesylate is a new molecular entity and is the first in the class of microsomal triglyceride transfer protein inhibitor. The sponsor seeks approval for NDA 203-858 with the once daily oral administration of a 5, 10, 20, (b) (4) mg lomitapide dose as an adjunct therapy to a low-fat diet and other lipid-lowering drugs with or without low density lipoprotein apheresis to treat homozygous familial hypercholesterolemia. The Office of Orphan Products Development granted the orphan-drug designation for lomitapide to treat homozygous familial hypercholesterolemia on October 23, 2007 (designation request number 07-2359).

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 203-858's Clinical Pharmacology data, and finds it acceptable.

1.2 Post Marketing Requirement

Severe Renal Impairment Study

The draft renal impairment guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf) recommends the Reduced Pharmacokinetic Design to be conducted in patients with end-stage renal disease (ESRD) **not yet on** dialysis to assess the "worst case" of renal impairment effect on drug pharmacokinetics. However, the sponsor conducted the renal impairment study (AEGR-733-021) in patients with ESRD **receiving** hemodialysis treatment, such patients may not represent the "worst case" of renal impairment since the chronic and predose hemodialysis may remove uremic inhibitors that are important for lomitapide metabolism and transporters (Nolin et al. *Clin Pharmacol Ther* 2008;83:898-903; Dreisbach & Lertora *Expert Opin Drug Metab Toxicol* 2008;4:1065-74). The sponsor should conduct a comparative study between patients with severe renal impairment and healthy volunteers with normal renal function to assess the effect of extreme renal impairment on lomitapide and M1 metabolite's exposures as a Postmarketing Requirement.

1.3 Summary of Important Clinical Pharmacology Findings

Pharmacokinetics (PK)

Absorption

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

Distribution

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

Metabolism

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

Excretion

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

Dose-Response Relationships

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

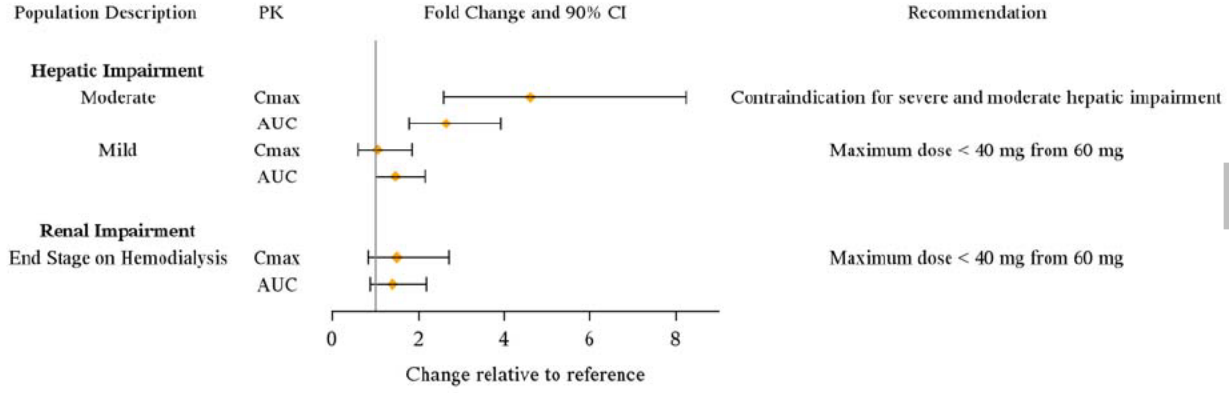
performed because doses were escalated from 5 mg to an individually determined maximum tolerated dose up to 60 mg.

QT Prolongation
A thorough QT study does not detect the single doses of 75 and 200 mg lomitapide as well as single dose of 75 mg lomitapide and 200 mg ketoconazole twice daily have significant QT prolongation effect.

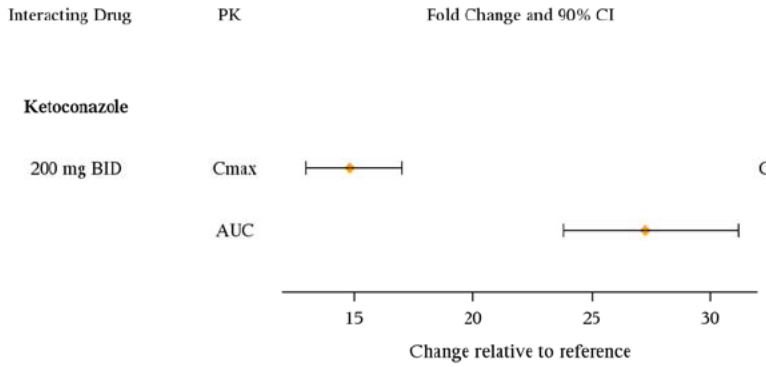
Pharmacogenomics
This submission does not contain any pharmacogenomic data.

Intrinsic Factors
When compared with matching healthy volunteers, moderate hepatically impaired patients' lomitapide $AUC_{0\text{-}inf}$ and C_{max} increased 164% and 361%, respectively, whereas mild hepatically impaired patients' lomitapide $AUC_{0\text{-}inf}$ and C_{max} increased 47% and 4%, respectively. When compared with matching healthy volunteers, moderate hepatically impaired patients' M1 $AUC_{0\text{-}inf}$ and C_{max} increased 39% and 27%, respectively, whereas mild hepatically impaired patients' M1 $AUC_{0\text{-}inf}$ and C_{max} increased 22% and 17%, respectively. When compared with matching healthy volunteers, moderate hepatically impaired patients' M3 $AUC_{0\text{-}inf}$ and C_{max} decreased 19% and 4%, respectively, whereas mild hepatically impaired patients' M3 $AUC_{0\text{-}inf}$ and C_{max} decreased 25% and 4%, respectively. These observations are consistent that metabolism of lomitapide decreases as liver disease worsens. Per these data, lomitapide should be contraindicated from use in patients with moderate **and** severe hepatic impairment. The dose for patients with mild hepatic impairment should not exceed 40 mg lomitapide.

When compared with matching healthy volunteers, lomitapide $AUC_{0\text{-}inf}$ and C_{max} of patients with end stage renal disease (ESRD) receiving hemodialysis increased 40% and 50%, respectively, whereas M3 exposure of ESRD patients on hemodialysis is comparable to that of healthy volunteers. However, M1 $AUC_{0\text{-}inf}$ and C_{max} of ESRD patients on hemodialysis increased about 200% and 108%, respectively, as compared to those of healthy volunteers. The 200% increase in M1 exposure does not appear to pose safety issue. The dose for patients with ESRD receiving dialysis treatment should not exceed 40 mg lomitapide.



Extrinsic Factors
Effect of other drug on lomitapide exposure
In the presence of ketoconazole, lomitapide C_{max} and AUC_{inf} increased 1382% and 2625%, respectively. Therefore, concomitant administration of lomitapide with strong CYP3A inhibitors should be contraindicated. Concomitant use of moderate CYP3A inhibitors with lomitapide should be avoided. When concomitantly used with weak CYP3A inhibitors, lomitapide dosage should not exceed 30 mg daily since lomitapide exposure approximately doubled in the presence of oral contraceptives (weak CYP3A inhibitors) via cross-study comparison. OCP encouraged the sponsor to model the effect of weak and moderate CYP3A inhibitors on lomitapide exposure in the pre-NDA meeting. However, the sponsor did not submit such modeling data in NDA 203-858.

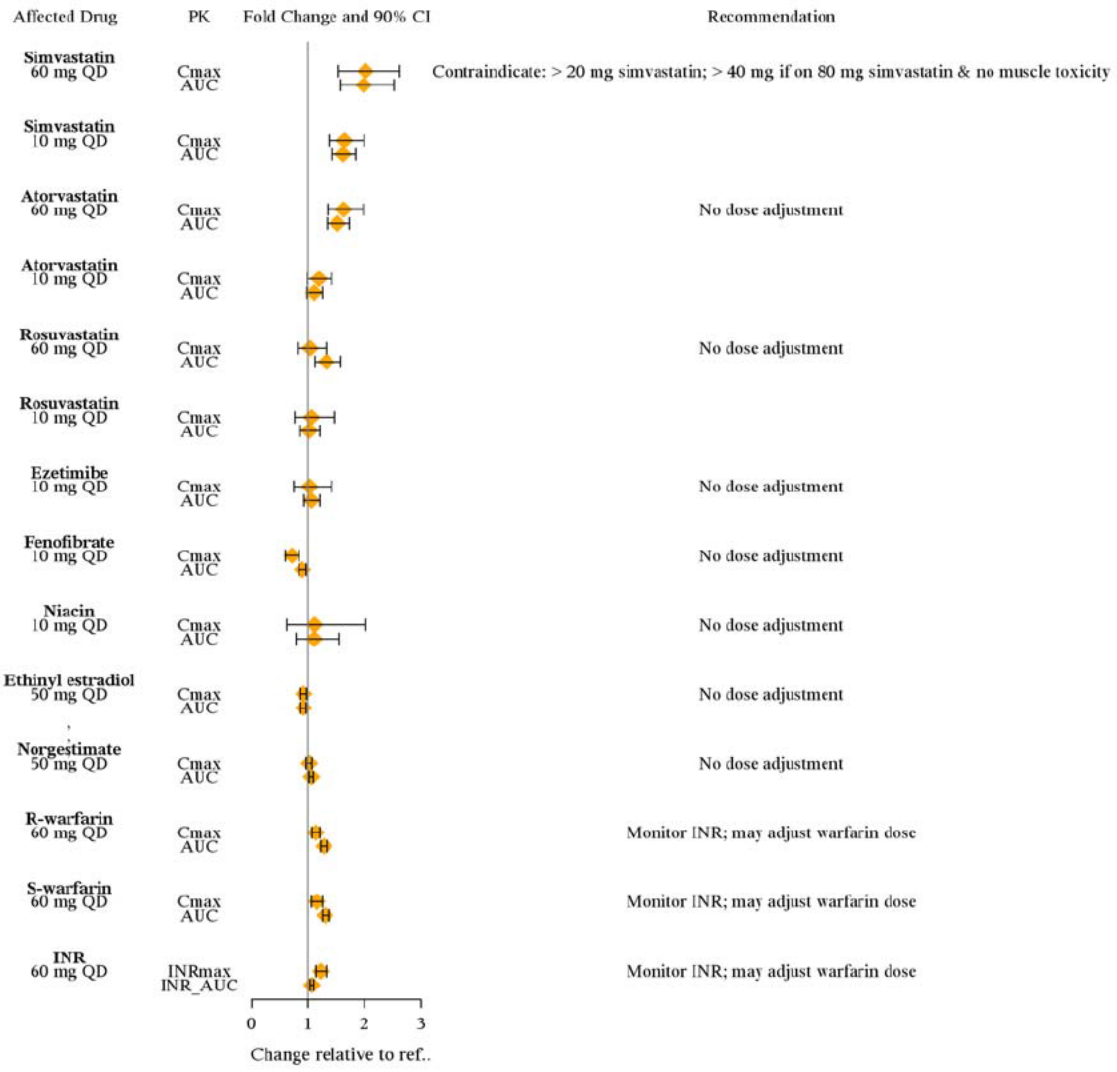


Best Available Copy

Effect of lomitapide on other drugs' exposure

The following highlights the significant drug-drug interaction. See the remainder in the chart below. The dosing regimen under the affected drug is the lomitapide dosing regimen.

Both simvastatin C_{max} and AUC_{inf} doubled in the presence of lomitapide. The approved maximum daily simvastatin dose has been lowered to 40 mg. However, the approved maximum daily simvastatin dose is 80 mg for patients who have been taking 80 mg simvastatin for 1 year without evidence of muscle toxicity. With concomitant use of lomitapide, the maximum daily simvastatin dose should not exceed 20 mg and should not exceed 40 mg for patients who have been taking 80 mg simvastatin for 1 year without evidence of muscle toxicity.



Lomitapide mesylate shows pH-dependent solubility. However, acid-reducing agents such as proton pump inhibitor may have minimal effect on lomitapide exposure since the highest lomitapide mesylate dose of 60 mg will be soluble in 250 mL of water from pH 1.3 – 6.

Biopharmaceutics
Lomitapide mesylate's Biopharmaceutics Classification System class status is unkown.

Formulation
The clinically-tested formulations (5 and 20 mg lomitapide capsules) are identical to the to-be-marketed formulations.

_____
S.W. Johnny Lau, R.Ph., Ph.D.
OCP/DCP2

FT signed by, Immo Zadezensky, Ph.D., Team Leader 11/ /12

An Office Level Clinical Pharmacology Briefing for NDA 203-858 was conducted on October 19, 2012; participants included K. Burkhart, D. Abernethy, S. Doddapaneni, Y. Xu, A. Mushtaq, G. Ngo, K. Estes, M. Pacanowski, K. Reynolds, D. Bashaw, Y. Ren, S. Chung, C. Sahajwalla, I. Zadezensky, and J. Lau in person; E. Chikale, J. Vaidyanathan, and L. Zhang via Adobe Connect.

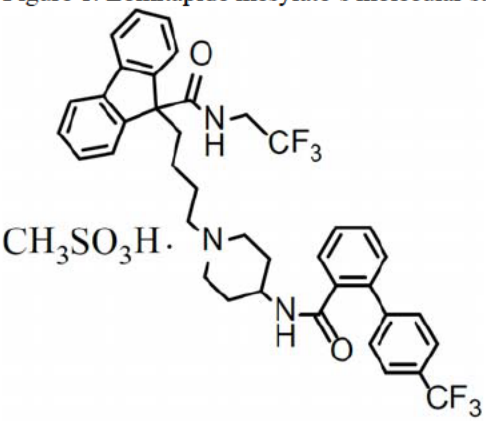
2 Question-Based Review

This review will frequently refer to the draft Guidance for Industry Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf). This review refers such guidance as the draft drug interaction guidance for simplicity.

2.1 General Attributes

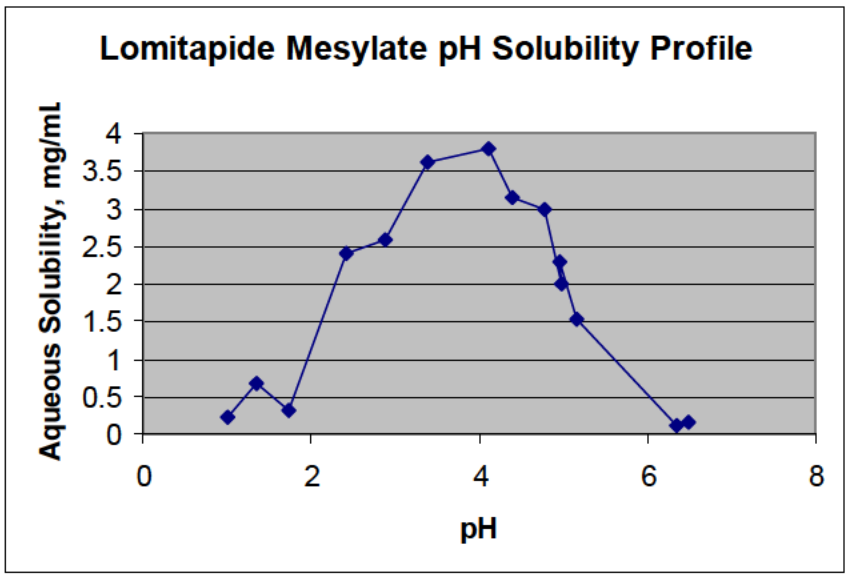
2.1.1 What are lomitapide mesylate's key physicochemical properties?

Figure 1. Lomitapide mesylate's molecular structure. Source: M3.2.S.1.2



Lomitapide mesylate has a molecular weight of 789.8 amu, empirical formula of $C_{39}H_{37}F_6N_3O_2 \bullet CH_4O_3S$ (molecular weight of the lomitapide moiety is 693.8 amu), and is freely soluble in methanol, acetone, and ethanol; soluble in methylene chloride, 2-butanol, and acetonitrile; sparingly soluble in 1-octanol and 2-propanol; slightly soluble in ethyl acetate; and insoluble in heptane. Lomitapide mesylate has the following pH solubility profile as shown in Figure 2.

Figure 2. Lomitapide mesylate's pH solubility profile. Source: Data from M3.2.S.3.1 page 28 of 51.



Lomitapide has a pK_a value of about 8.2. The apparent 1-octanol:water distribution coefficient of lomitapide is 45.7 – 27.4 for pH 3.07 – 4.21, respectively, with a maximum value of 169 at pH 5.48 and decreasing to 66.8 at pH 6.46. Lomitapide is achiral.

2.1.2 What is the formulation for the to-be-marketed oral lomitapide mesylate?

Tables 1 – 3 show the to-be-marketed formulations for 5, 10, and 20 mg lomitapide mesylate capsules.

Table 1. Composition of the 5 mg lomitapide capsule formulation. Source: M3.2.P.1

COMPONENT	FUNCTION	GRADE	BMS CAPSULE FORMULA	AEGERION CAPSULE CLINICAL FORMULA	AEGERION CAPSULE COMMERCIAL FORMULA
Lomitapide mesylate[1]	Active ingredient	In house	5.69 mg (5.00 mg free base)	5.69 mg (5.00 mg free base)	5.69 mg (5.00 mg free base)
Pregelatinised starch	(b) (4)	NF, Ph.Eur.	(b) (4)		(b) (4)
Microcrystalline cellulose		NF, Ph.Eur.			
Lactose[2,3]		NF, Ph.Eur.			
Sodium starch glycolate		NF, Ph.Eur.			
(b) (4)					(b) (4)
Colloidal silicon dioxide	(b) (4)	USP, Ph.Eur.	(b) (4)		(b) (4)
Magnesium stearate		NF, Ph.Eur.			
Total amount			250.00 mg	100.00 mg	100.00 mg

Table 2. Composition of the 10 mg lomitapide capsule formulation. Source: M3.2.P.1

COMPONENT	FUNCTION	GRADE	BMS CAPSULE FORMULA[1]	AEGERION CAPSULE CLINICAL FORMULA[2]	AEGERION CAPSULE COMMERCIAL FORMULA
Lomitapide mesylate[3]	Active ingredient	In house	---	---	11.39 mg (10.00 mg free base)
Pregelatinised starch	(b) (4)	NF, Ph.Eur.	---	---	(b) (4)
Microcrystalline cellulose		NF, Ph.Eur.	---	---	
Lactose[4,5]		NF, Ph.Eur.	---	---	
Sodium starch glycolate		NF, Ph.Eur.	---	---	
(b) (4)					(b) (4)
Colloidal silicon dioxide	(b) (4)	USP, Ph.Eur.	---	---	(b) (4)
Magnesium stearate		NF, Ph.Eur.	---	---	
Total amount			---	---	200.00 mg

Table 3. Composition of the 20 mg lomitapide capsule formulation. Source: M3.2.P.1

COMPONENT	FUNCTION	GRADE	BMS CAPSULE FORMULA[1]	AEGERION CAPSULE CLINICAL FORMULA	AEGERION CAPSULE COMMERCIAL FORMULA
Lomitapide mesylate[2]	Active ingredient	In house	---	22.77 mg (20.00 mg free base)	22.77 mg (20.00 mg free base)
Pregelatinised starch	(b) (4)	NF, Ph.Eur.	---	(b) (4)	
Microcrystalline cellulose		NF, Ph.Eur.	---		
Lactose[3,4]		NF, Ph.Eur.	---		
Sodium starch glycolate		NF, Ph.Eur.	---		
(b) (4)					
Colloidal silicon dioxide	(b) (4)	USP, Ph.Eur.	---	(b) (4)	
Magnesium stearate		NF, Ph.Eur.	---		
Total amount			---	200.00 mg	200.00 mg

The sponsor studied the 5 and 20 mg lomitapide capsules in the clinical efficacy and safety study. However, there is no comparable clinical dosage unit for the 10 mg lomitapide capsule. The 10 mg lomitapide capsule is (b) (4) to the 5 mg lomitapide. The sponsor seeks in vivo bioavailability study waiver for the 10 mg lomitapide capsule. The Office of New Drugs, Quality Assurance, Biopharmaceutics is responsible to review this waiver. Also, the sponsor does not intend to market the 50 mg lomitapide capsule (Table 4) and the sponsor did not study this strength of capsule in the clinical efficacy and safety study. However, the sponsor used the 50 mg lomitapide capsule to conduct the food-effect study (CV145-005), oral single-dose study (CV145-001), oral multiple-dose study (CV145-002), and absolute bioavailability study (CV145-003). The 50 mg lomitapide capsule's formulation is (b) (4) the other 3 strengths of to-be-be-marketed lomitapide capsules.

Table 4. Composition of the 50 mg lomitapide capsule formulation. Source: Sponsor's July 2, 2012 response to information request

INGREDIENT	GRADE	RATIONALE FOR USE	AMOUNT (MG/CAPSULE
Lomitapide mesylate		Active ingredient	56.926[a]
Lactose, (b) (4)	NF	(b) (4)	
Microcrystalline cellulose	NF		
Pregelatinized starch	NF		
Sodium starch glycolate	NF		
Colloidal silicon dioxide	NF		
Magnesium stearate	NF		
(b) (4)			
(b) (4)			One capsule
		Total fill weight	250.00

2.1.3 How does lomitapide work to reduce blood cholesterol?

Lomitapide is a microsomal transfer protein (MTP) inhibitor. MTP transfers triglyceride (TG) to nascent apolipoprotein B (apo B), aiding the formation of TG-rich lipoproteins, namely chylomicrons and very low density lipoprotein (VLDL) in enterocytes and hepatocytes, respectively. Thus, MTP inhibition would lead to decreases in chylomicrons and VLDL. Since LDL is formed from VLDL, MTP inhibitors would decrease plasma LDL-C concentrations (T.R. Joy. *Pharmacol Ther* 2012;135:31-43).

2.1.4 What are the sponsor's proposed indication and dosage regimen for lomitapide mesylate?

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

The proposed starting daily dose is 5 mg lomitapide. After 2 weeks, the daily dose may be increased, based on acceptable safety and tolerability to 10 mg lomitapide and then, at a minimum of 4-week intervals, to 20, 40, and 60 mg lomitapide (maximum proposed dose).

2.2 General Clinical Pharmacology

2.2.1 What is lomitapide's clinical pharmacokinetic (PK) characteristics?

Absorption

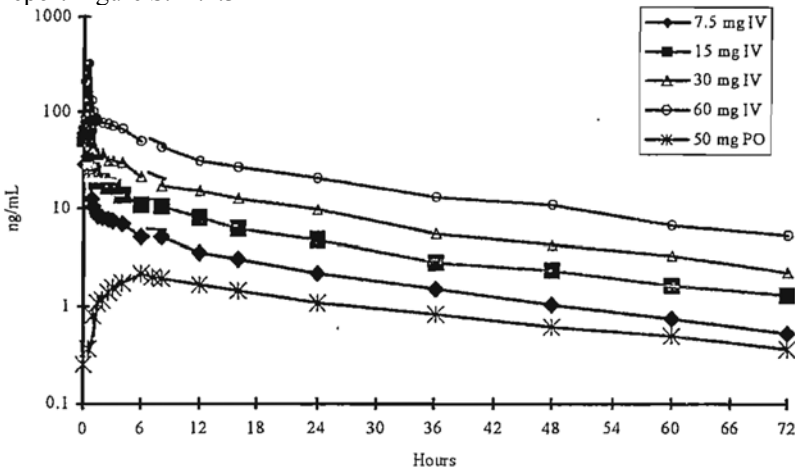
Study CV145-003 is an ascending dose, parallel group, placebo-controlled study. Thirty two randomized healthy men received 0, 7.5, 15, 30, or 60 mg lomitapide as a 30-minute intravenous (IV) infusion after an overnight fast. After a washout of ≥ 7 days, those participants who received the 30 mg lomitapide IV infusion also orally (PO) received a 50 mg lomitapide capsule after an overnight fast. Serial plasma samples were collected for 72 hours postdose to determine lomitapide, M1, M2, and M3 concentrations via validated bioanalytical methods. M1, M2, and M3 are lomitapide metabolites; see the "Metabolism and Excretion" section below for details.

Table 5. Mean (SD) lomitapide PK parameters upon IV and PO administration. Source: Study CV145-003's report Table 11.1.3

Treatment	C_{max}, ng/mL	AUC_{inf}, ng·hr/mL	V_{ss}, L	CL, mL/hr	$t_{½}$, hr
7.5 mg IV	36.8 (11.2)	192.9 (20.2)	1075.3 (120.8)	39269.6 (4574.9)	24.7 (6.1)
15 mg IV	71.4 (21.7)	422.6 (51.4)	1126.2 (131.0)	35891.8 (3936.3)	29.5 (5.4)
30 mg IV	177.3 (65.1)	837.9 (72.4)	1292.0 (744.5)	36039.6 (3407.2)	37.5 (21.5)
60 mg IV	350.7 (100.9)	1776.5 (200.9)	985.1 (210.6)	34160.7 (4139.0)	24.8 (6.9)
50 mg PO	2.2 (0.8)	96.7 (35.6)	NA	*573465.6 (188810.1)	43.6 (24.3)

*CL/F

Figure 3. Mean plasma lomitapide concentrations versus time profiles upon IV and PO administration. Source: Study CV145-003's report Figure S.11.1.3



The mean (SD) lomitapide absolute oral bioavailability is 7.1 (2.4) between PO 50 mg lomitapide and IV 30 mg lomitapide.

Distribution
Per Study CV145-003, the mean lomitapide volume of distribution at steady state is 985.1 – 1292.0 L.

Study BMS-910060036 examined the in vitro binding of [^{14}C]lomitapide in pooled human plasma. The spiked samples were dialyzed against Trizma NaCl buffer for 16 hours at 37°C. The mean percent bound is 99.8% and is independent of the lomitapide concentrations over the range of 250 – 5000 ng/mL.

Study AEGR-733PC0025 showed that the mean (SD) lomitapide apical to basolateral membrane permeability is 8.57 (2.24) x 10^{-6}, 20.5 (3.41) x 10^{-6}, and 11.3 (8.90) x 10^{-6} cm/sec, respectively, for 1, 3.5, and 8 μM lomitapide and the basolateral to apical membrane permeability is 11.9 (1.87) x 10^{-6}, 7.5 (1.19) x 10^{-6}, and 8.04 (2.34) x 10^{-6} cm/sec, respectively, for 1, 3.5, and 8 μM lomitapide in in vitro Caco-2 experimental cell systems. The mean (SD) digoxin apical to basolateral membrane permeability is 1.18 (0.08) x 10^{-6} cm/sec and the basolateral to apical membrane permeability is 17.0 (1.66) x 10^{-6} cm/sec; the bidirectional digoxin permeability (efflux ratio) is 14.4. Digoxin is a known P-gp substrate (positive control) and these observations suggest that the Caco-2 system functions as expected. The bidirectional lomitapide permeability (net efflux ratio) is 1.4, 0.4, and 0.7 for 1, 3.5, and 8 μM lomitapide, respectively. Since the net efflux ratios for lomitapide are < 2, lomitapide is either a poor or non P-gp substrate per the decision tree in Figure A1 of the draft drug interaction guidance. When compared with digoxin's net efflux ratio, lomitapide is a non-P-gp substrate. The sponsor also claimed that lomitapide is a high permeability compound; see further discussion in Question 2.5.1 below.

Study AEGR-733PC0023 showed that the net efflux ratios of lomitapide decreases with increasing lomitapide concentration. Thus, lomitapide probably is a P-gp inhibitor. Study AEGR-733PC0023 showed that 6 μg/mL lomitapide inhibited digoxin efflux mediated by P-gp expressed in Caco-2 cells in a concentration dependent manner. The lomitapide IC_{50} per the corrected efflux ratios of digoxin was 0.49 μg/mL or 0.62 μM. The lomitapide $[I]_1/IC_{50}$ value is 0.035 (17.3 ng/mL/0.49 μg/mL; $[I]_1$ = 17.3 ng/mL and is the C_{max} upon single dose of 200 mg lomitapide oral administration). The guidance recommends lomitapide C_{max} (1.23 ng/mL) upon single dose of 60 mg lomitapide (the highest dose). The lomitapide $[I]_1/IC_{50}$ value is 0.0025 (1.23 ng/mL/0.49 μg/mL). This reviewer erred on the side of being conservative to use the highest oral dose studied, 200 mg lomitapide. The lomitapide $[I]_2/IC_{50}$ value is 490.1 (molecular weight of lomitapide mesylate is 789.8; highest daily oral dose = 60 mg; $[I]_2$ = 60000/789.8 μMoles in 250 mL; IC_{50} is 0.62/(1000/250) μMole in 250 mL). Even though lomitapide's $[I]_2/IC_{50}$ value is > 10, the draft drug interaction guidance recommends an in vivo drug interaction study between lomitapide and a P-gp substrate. Since lomitapide's label will recommend that dose adjustment of P-gp substrate may be necessary when lomitapide is concomitantly administered with P-gp substrate, the sponsor may not need to conduct the in vivo interaction study between a P-gp substrate and lomitapide.

Study AEGR-733PC0023 also examined the inhibition of BCRP function (cladribine bidirectional transport) by 6 μg/mL lomitapide in CPT-P1 cell monolayers with 10 μM cladribine as the BCRP probe substrate. Ko143 (10 μM; positive control) reduced the cladribine efflux ratio from 12 to 0.9 (corrected efflux ratio [C_{ER}] from 11 to 0) indicating the CPT-P1 cells had appropriate BCRP function. The efflux cladribine ratio (9.9) in the presence of 6 μg/mL lomitapide was not significantly different from the control value of 12. Thus, lomitapide at 6 μg/mL did not inhibit BCRP and IC_{50} determination may not be necessary.

Study AEGR-733PC0023 also examined the in vitro inhibition of hepatic uptake transporters, OATP1B1 and OATP1B3 (transfected and vector control-transfected cells) as well as OCT1 (transfected and parental cells) by 40 ng/mL lomitapide. It also examined the in vitro inhibition of renal uptake transporters, OAT1, OAT3, and OCT2 (all transfected and parental cells) by 40 ng/mL lomitapide. Lomitapide at 40 ng/mL did not inhibit

OATP1B1, OATP1B3, OCT1, OAT1, OAT3, and OCT2. The unbound C_{max}/IC_{50}s of lomitapide for OAT1, OAT3, and OCT2 will be at least 0.0009, which is 111 times less than the cutoff value of 0.1 as recommended by the draft drug interaction guidance (Figure A6). This reviewer calculated the unbound C_{max}/IC_{50}s of 0.0009 as [0.002 X 17.3 ng/mL]/40 ng/mL (0.2% is the unbound fraction since lomitapide is 99.8% plasma protein bound). Thus, the sponsor does not need to determine the IC_{50}s of lomitapide for OAT1, OAT3, and OCT2 in vitro. The draft drug interaction guidance does not provide recommendation to assess the potential of a investigational drug's potential to inhibit OCT1.

The total C_{max}/IC_{50}s of lomitapide for OATP1B1 and OATP1B3 will be at least 0.43. This reviewer calculated the total C_{max}/IC_{50}s of 0.43 as (17.3 ng/mL/40 ng/mL). The IC_{50}s of lomitapide for OATP1B1 and OATP1B3 will be > 40 ng/mL. Rosuvastatin C_{max} and AUC_{0-t} increased 4% and 32%, respectively, in the presence of lomitapide (see Section 2.4.2.4 below). CYPs 2C9 and 2C19 metabolize rosuvastatin (Neuvonen et al. *Clin Pharmacol Ther* 2006;80:565-81). Rosuvastatin is a substrate of OATP1B1, OATP1B3, and BCRP but is not a substrate of P-gp. Lomitapide does not inhibit CYPs 2C9 and 2C19 (see Section 2.2.1's Metabolism and Excretion). Lomitapide does not inhibit BCRP (see Section 2.2.1's Distribution). The increase in rousuvastatin exposure may reflect the effect of lomitapide on OATP1B1 and OATP1B3, which are not extensive (32%). Thus, the sponsor may not need to determine the IC_{50} of lomitapide for OATP1B1 and OATP1B3.

The sponsor did not assess the substrate statuses of lomitapide for BCRP, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, and OCT2. The draft drug interaction guidance (page 48) recommends the routine evaluation of an investigational drug's role in BCRP, OATP, OATs, and OCTs. However, lomitapide was not detectable in the urine (see Study AEGR-733-010's discussion in the Metabolism and Excretion section below) and OATs and OCTs are primarily renal transporters. Thus, the sponsor may not need to study the substrate statuses of lomitapide for OCT1, OAT1, OAT3, and OCT2. The sponsor used the in vitro Caco-2 cells to determine the substrate status of P-gp (Study AEGR-733PC0025) and the bidirectional lomitapide permeability (net efflux ratio) is 1.4, 0.4, and 0.7 for 1, 3.5, and 8 μM lomitapide, respectively. There is evidence that Caco-2 cell based bidirectional efflux ratio of ≤ 2 suggests that the drug is not an efflux transporter substrate such as P-gp and BCRP (Mease et al. *J Pharm Sci* 2012;101:1888-97). Thus, the sponsor may not need to study the substrate statuses of lomitapide for BCRP. Per the draft drug interaction guidance, atazanavir, cyclosporine, eltrombopag, gemfibrozil, lopinavir, rifampin, ritonavir, saquinavir, and tipranavir are in vivo OATP1B1 and OATP1B3 inhibitors. Most of such inhibitors (atazanavir, cyclosporine [weak CYP3A inhibitor], lopinavir, ritonavir, saquinavir, and tipranavir [weak CYP3A inhibitor]) are also strong or moderate CYP3A inhibitors, which are contraindicated with concomitant use of lomitapide. Thus, the sponsor may not need to study the substrate statuses of lomitapide for OATP1B1 and OATP1B3 since most of the in vivo OATP1B1 and OATP1B3 inhibitors are contraindicated. However, the sponsor needs to study the substrate statuses of lomitapide or its congener for BCRP, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, and OCT2 should they develop lomitapide or its congener for a wider patient population beyond HoFH.

The sponsor did not assess the induction potential of lomitapide for P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OAT1, OAT3, and OCT2. Since Study AEGR-733PC0022 showed that lomitapide does not induce CYP3A4 in vitro, thus no further tests of CYP3A and P-gp induction in vivo are necessary per the draft drug interaction guidance (page 51). Because of the lack of a validated in vitro system to study transporter induction, the definitive determination of induction potential of lomitapide on transporters is per in vivo induction studies.

Metabolism and Excretion

The sponsor conducted 2 lomitapide mass balance studies in humans:

- Study CV145-006 characterized lomitapide and its 3 metabolites in plasma with 3 metabolites uncharacterized.
- Study AEGR-733-010 completes the characterization of lomitapide and its metabolites.

Study CV145-006 examined the mass balance of a single oral administration of 50 mg lomitapide (80.3 μCi; fluorine carboxamide carbonyl-^{14}C lomitapide and biphenyl carboxamide carbonyl-^{14}C lomitapide) solution in 6 healthy men (5 white and 1 black). It collected serial blood samples for 120 hours postdose and collected urine and feces for 360 hours postdose to determine lomitapide and its metabolites (M1, M3, and M2) in plasma via validated LC/MS/MS method. It used liquid scintillation counting to measure total radioactivity in blood, plasma, urine, and fecal samples.

Figure 4. Mean (SD) plasma concentration-time profile of lomitapide, M1, M3, M2, and total radioactivity upon PO administration in Study CV145-006 (Concentration of radioactivity expressed as ng equivalent of lomitapide/mL). Source: Modified from Study CV145-006's report Figure 11.6.1

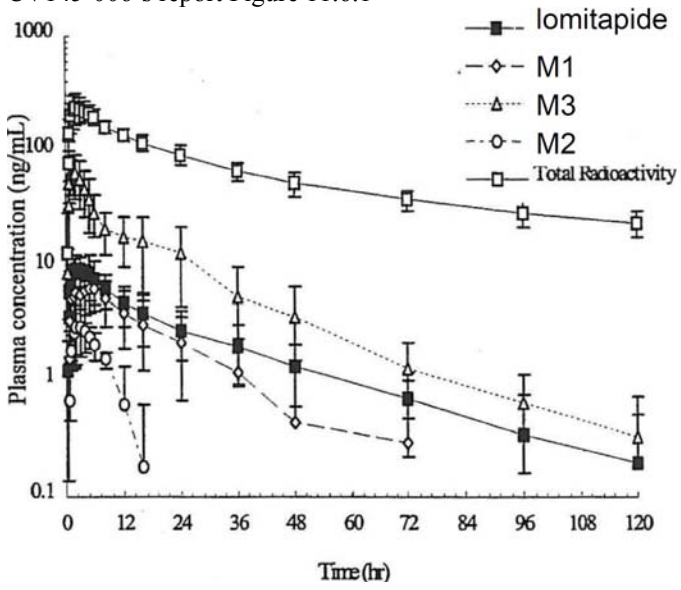


Table 6. Mean (SD) PK parameters of lomitapide, M1, M3, and M2 in plasma as well as recoveries. Source: Modified from Study CV145-006's report Table 11.6.1

Parameter	Lomitapide	M1	M3	M2	Total Radioactivity
C_{max} (ng/mL)	10.7 (3.33)	7.44 (3.70)	68.9 (26.3)	3.29 (1.38)	251 (71.1)[a]
$AUC_{(0-t)}$ (ng·hr/mL)	216 (99.9)	128 (88.2)	847 (448)	21.0 (10.6)	7649 (1415)[b]
$AUC_{(inf)}$ (ng·hr/mL)	236 (114)	165 (120)	868 (460)	32.3 (12.3)	-
t_{max} (hr)	2.00 (2.0, 5.0)	5.5 (2.9, 6.0)	1.5 (1.0, 3.0)	2.5 (1.5, 4.0)	2.5 (1.5, 5.0)
$t_{½}$ (hr)	29.2 (13.0)	-	-	-	-
Urinary Recovery (%)	-	-	-	-	33.4 (4.0)
Fecal Recovery (%)	-	-	-	-	59.5 (4.7)
Total Recovery (%)	-	-	-	-	93.0 (3.15)

[a] C_{max} values for total radioactivity are expressed in terms of ng equivalents of lomitapide/mL.
[b] $AUC_{(0-t)}$ values for total radioactivity are expressed in terms of ng equivalents of lomitapide·hr/mL.

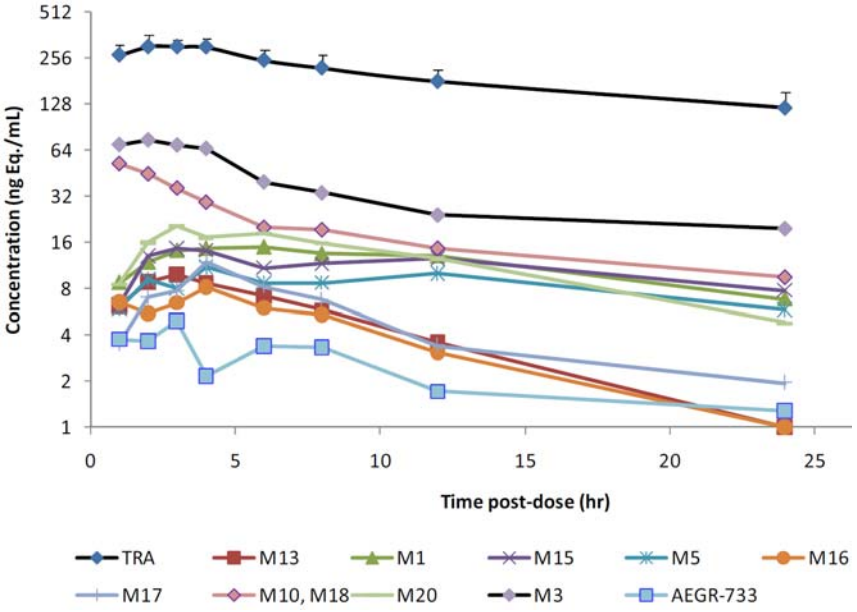
In general, plasma M1 concentrations were similar to or slightly lower than those of plasma lomitapide concentrations. Plasma M3 concentrations were about 4-fold that of plasma lomitapide concentrations, while plasma M2 concentrations were about one-tenth that of plasma lomitpapide concentrations. The value of lomitapide AUC was about 3% that of the administered total radioactivity AUC, suggesting that most of the radioactivity was due to circulating metabolites.

Mean recovery of total radioactivity from the participants was 93.0%. A mean of 59.5% radioactivity (range: 53.4 – 61.6%) was in the feces and a mean of 33.4% (range: 30.1 – 40.1%) was in the urine. Per the mean recovery of the total radioactivity in urine, at least 33.4% of the drug-related radioactivity was absorbed upon oral administration of ^{14}C-lomitapide.

Study AEGR-733-010 examined the mass balance of a single oral administration of 55 mg lomitapide (about 100 μCi; fluorine carboxamide carbonyl-^{14}C lomitapide and biphenyl carboxamide carbonyl-^{14}C lomitapide) in a 50 mL solution in 6 healthy men (5 white and 1 black). It collected serial plasma samples for 120 hours postdose to determine lomitapide and its metabolites via validated LC/MS/MS method. It collected urine and feces for 6 days and 7 days (24 hours fecal sample), respectively, postdose for metabolic profiling (quantitative and qualitative) via HPLC and radio-chromatography. Selected samples or isolated metabolites were also subjected to LC/MS and LC/MS/MS analyses in conjunction with radioactivity detection for characterization and/or identification of metabolites.

Mean total recovery of radioactivity was 88.0%, with a mean of 52.9% of the dose recovered in feces and 35.1% recovered in urine. Figure 5 shows the mean (SD) concentrations of lomitapide, its metabolites, total radioactivity (TRA) in plasma. Figure 6 shows the proposed human metabolic pathways of lomitapide and its metabolites with relative abundance in plasma, urine, and feces.

Figure 5. Mean (SD) plasma concentrations of radiolabeled lomitapide, radiolabeled lomitapide metabolites, and TRA following a single oral dose of 55 mg [^{14}C]-lomitapide in Study AEGR-733-010 (For display, the vertical axis is not linear in scale). Source: Modified from Study AEGR-733-010's report Figure 11-4



Lomitapide was a minor circulating metabolite in plasma. Of the more than 10 circulating metabolites, only M3 exceeded 10% of the plasma radioactivity (mean = 17.3%). Other prominent metabolites in plasma were M1, M5, M10+M18 (co-eluting; M10 being a minor component), M15, and M20, each accounting for 5.75%, 4.26%, 9.67% (combined), 5.60%, and 5.98% of the total radioactivity in 0 – 24 hours plasma samples, respectively. Additional minor metabolites, M2, M13, M14, M16, and M17, each accounted for less than 3% of the total radioactivity in 0 – 24 hours plasma samples. For reference, the sponsor monitored plasma M2 concentrations in early clinical pharmacology studies (study number with CV-145 prefix). M2 is an N-dealkylated metabolite of lomitapide and M1. The sponsor did not monitor M2 in latter clinical studies (with AEGR-733 prefix).

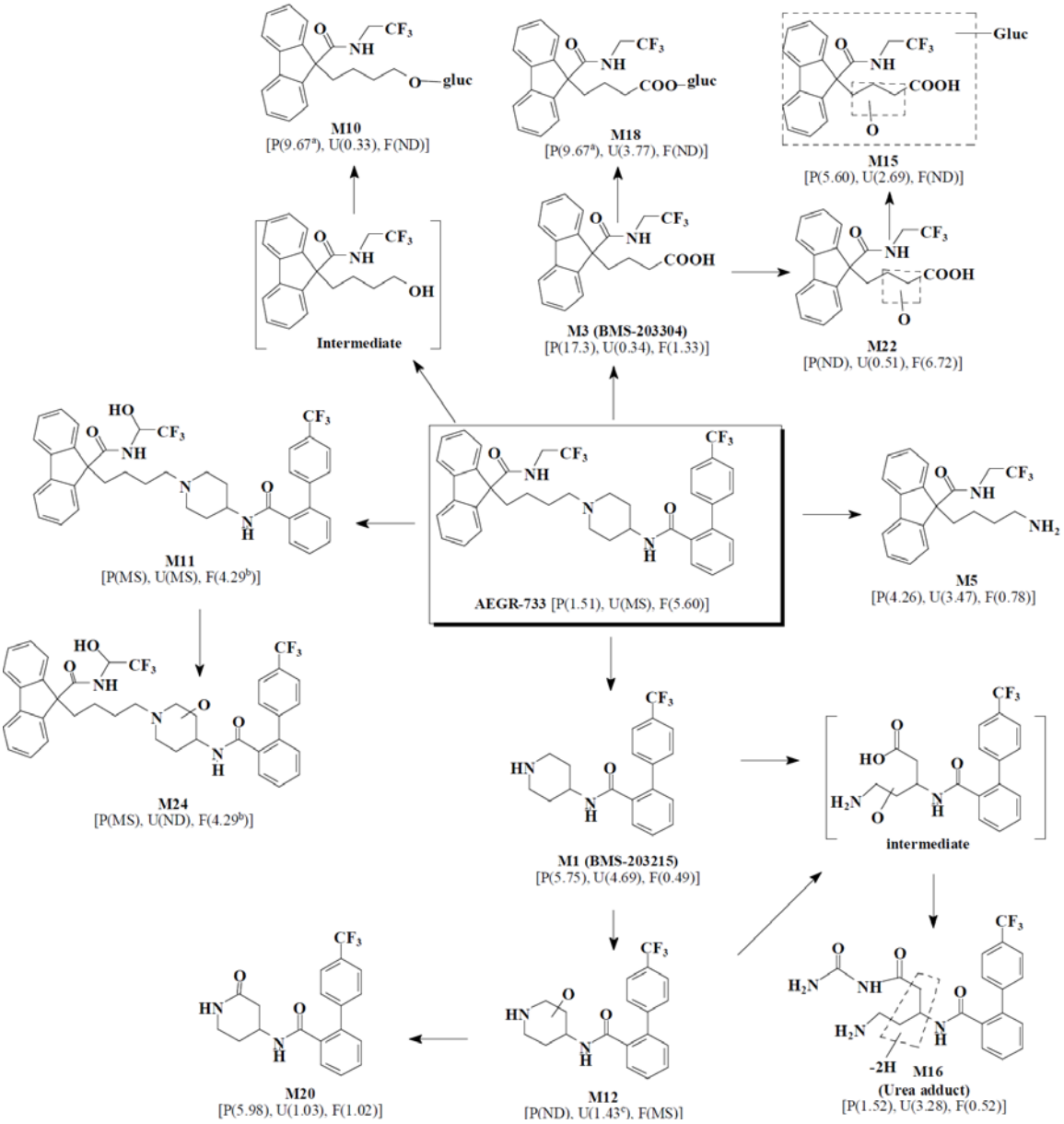
Lomitapide was not detectable in urine samples via radioprofiling due to its trace amount (<0.05% of dose). Metabolites M1, M5, M15, M16, and M18 were the prominent urinary metabolites, representing the mean (SD) of 4.69% (1.23%), 3.41% (0.37%), 2.69% (0.31%), 3.28% (0.74%), and 3.77% (1.15%) of the dose in the 0 – 96 hours urine samples, respectively. M3, M10, M12, M13, M14, M17, M19, M20, and M22 are minor urine metabolites that each accounted for < 2% of the dose in the 0 – 96 hours urine samples.

Approximately 44.9% (mean) of the administered radioactivity was recovered in 0 – 96 hours feces. Unchanged lomitapide was a major radioactive component, accounting for 4.04 – 7.73% (mean = 5.60%) of the administered dose in the pooled 0 – 96 hours feces. Metabolites M11+M24 (co-eluting) and M22 were the major fecal metabolites, representing mean (SD) 4.29% (0.58%) and 6.72% (2.00%) of the dose in the 0 – 96 hours feces, respectively. Additional minor metabolites were M1, M3, M5, M8, M16, M20, M21, M23, M25, and M26 each accounting for less than 2% of the dose in the 0 – 96 hours feces.

The metabolic pathways include oxidation (M8, M11, M23, M24, M25), oxidative N-dealkylation (M1, M2, M3, M5), followed by oxidation (M12, M13, M20, M21, M22, M26), glucuronide conjugation (M10, M14, M15, M17, M18), and piperidine ring opening (M16, M19).

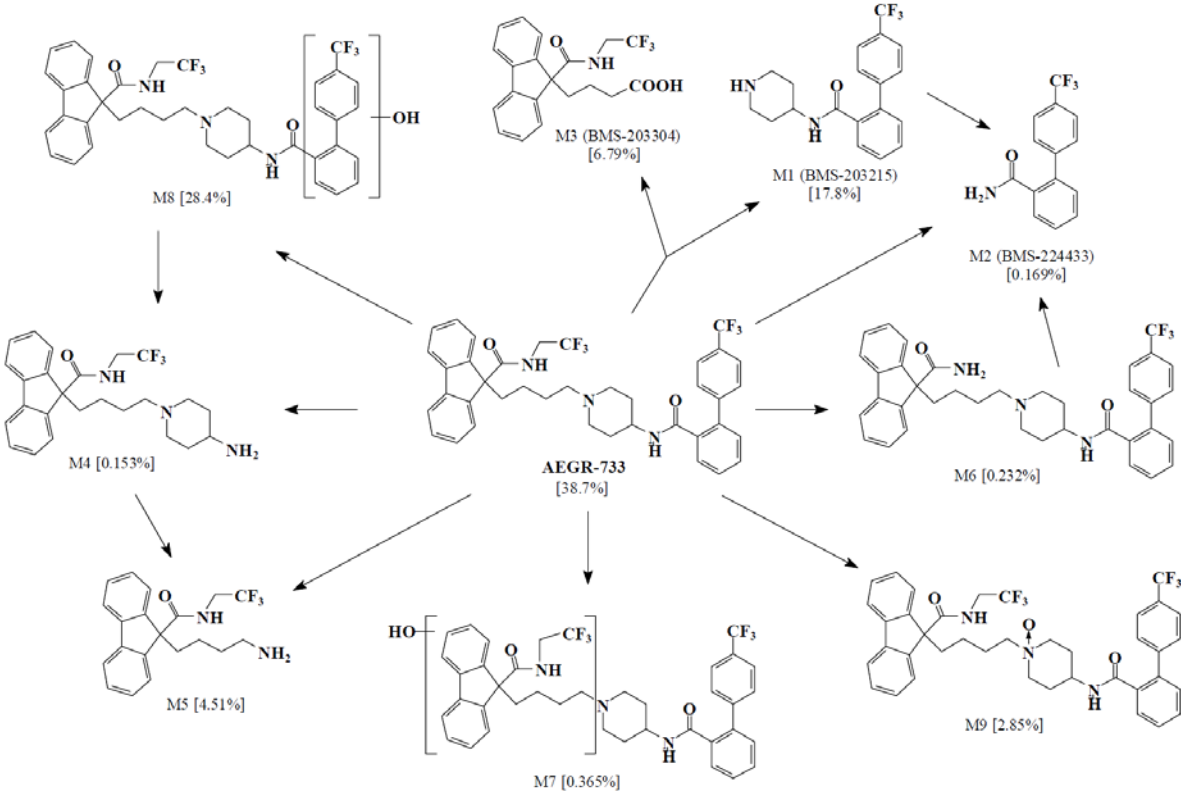
Since Study CV145-006 had samples with large proportion of radioactivity remained associated with the plasma protein pellets, one of Study AEGR-733-010's objectives is to examine the radioactivity associated with the plasma protein pellet following extraction of radioactivity from plasma. Study AEGR-733-010 showed that recovery of radioactivity from plasma following a single methanol extraction ranged 80.3 – 96.5%. Reextraction of the protein pellets showed complete recovery of total plasma radioactivity, which suggests that covalent binding of lomitapide or its metabolites may not be likely.

Figure 6. Proposed lomitapide metabolic pathways in humans. Source: Study AEGR-733-010's report Figure 11-3



Study AEGR 744PC005 examined the stability of lomitapide and the identity of prominent lomitapide metabolites in in vitro human liver microsomes via LC/MS. Lomitapide at 1 and 10 µM in 0.1 M potassium phosphate buffer (pH 7.4), was separately incubated with human liver microsomes in the presence of 1 mM NADPH and 2 mM $MgCl_2$ for 0, 0.5 and 1 hr. Figure 7 shows lomitapide and its metabolites with their relative abundance. M1, M3, M5, M8, and M9 appeared to be the most prominent metabolites per the mass ion intensity. In vivo Study AEGR-733-010 identified the metabolites, M1, M3, and M5 but showed that M8 is a minor fecal metabolite and did not identify M9.

Figure 7. Proposed lomitapide metabolic pathway in human liver microsomes. Source: Study AEGR 733PC0005's report Figure 57



Study AEGR 733PC0006 showed the P450 mediated metabolism of lomitapide in human liver microsomes and in recombinant CYP enzymes via monitoring the formation of 5 prominent in vitro metabolites (M1, M3, M5, M8, and M9) with and without selective P450 chemical inhibitors. The results indicate that CYP3A4 plays a major role in the phase I metabolism of lomitapide. In addition, CYP2E1 played a lesser role, specifically in the formation of metabolite M9. CYPs 1A2, 2B6, 2C8, and 2C19 may metabolize lomitapide to a small extent to M1, which is 1 of the 2 major metabolites in plasma. See Figure 8 and Table 7.

Figure 8. P450 mediated metabolism of lomitapide in human liver microsomes. Source: Study AEGR 733PC0006's report page 12 of 76

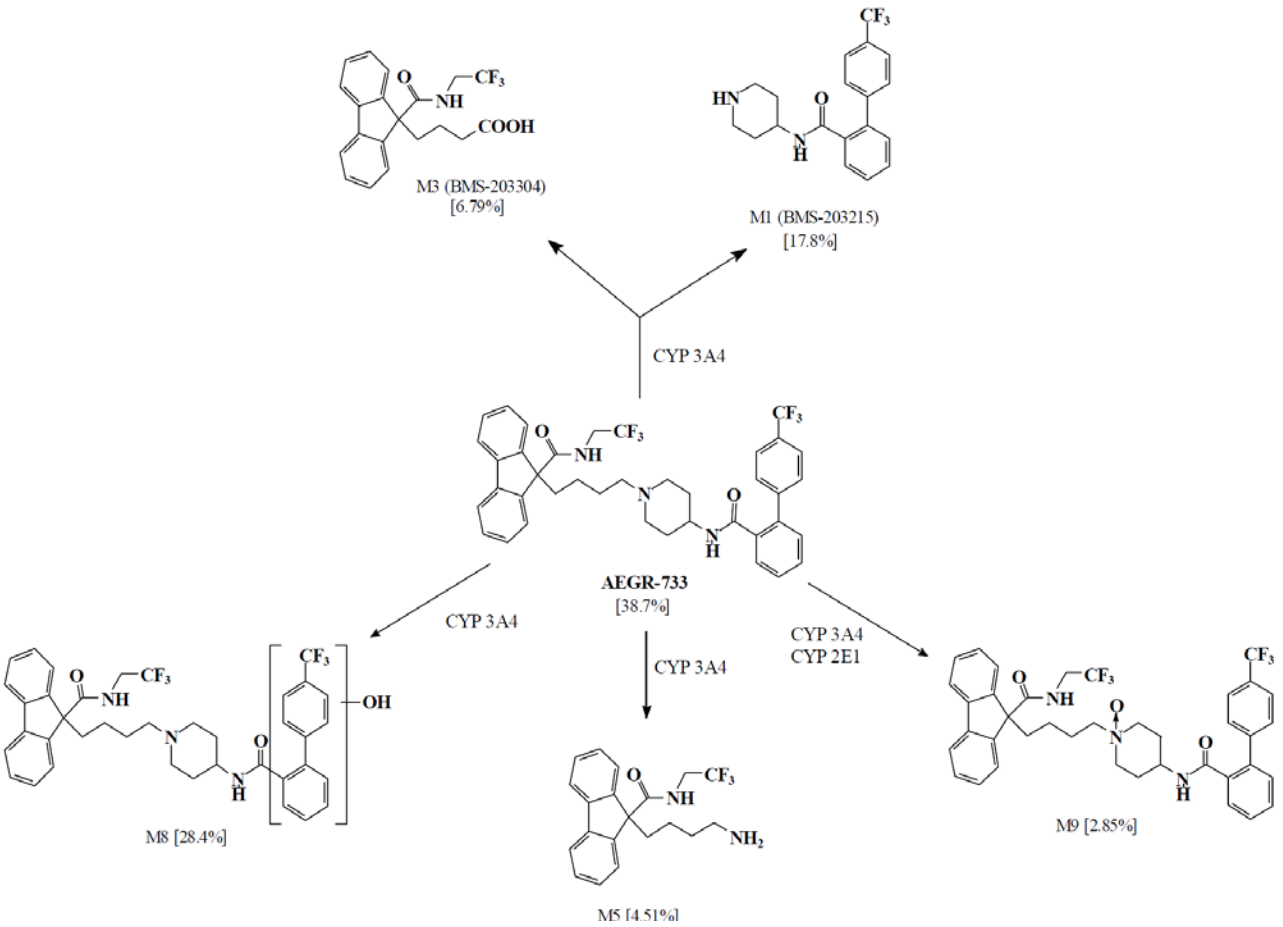


Table 7. Percentage inhibition and formation of lomitapide metabolites; M1, M3, M5, M8, and M9 in human liver microsomes and rCYP isoforms. Source: Study AEGR-733PC0006's report

CYP Isoform	Metabolite M1		Metabolite M3		Metabolite M5		Metabolite M8		Metabolite M9	
	% CI[a]	rCYP[b]	% CI[a]	rCYP[b]	% CI[a]	rCYP[b]	% CI[a]	rCYP[b]	% CI[a]	rCYP[b]
1A2	32	Low	41	ND	16	ND	7	ND	11	ND
2B6	35	Low	59	ND	52	ND	40	ND	38	ND
2C8	38	Low	68	ND	52	ND	38	ND	38	ND
2C9	ND	Low	17	ND	10	ND	5	ND	ND	ND
2C19	24	Low	31	ND	18	ND	12	ND	ND	ND
2D6	ND	ND	ND	ND	ND	ND	None	ND	ND	ND
CYP2E1	39	ND	72	ND	44	ND	44	ND	30	High
3A4/5[C]	98	High	100	High	100	High	99	High	100	High
3A4/5[d]	98	High	100	High	100	High	99	High	100	High

a Percent inhibition of formation of AEGR-733 metabolites by isoform-selective chemical inhibitor compared to no-inhibitor control in human liver microsomes.
b Formation of AEGR-733 metabolites by recombinant human cytochrome P450 isoform.
c Inhibition of formation of AEGR-733 metabolites by 1'hydroxy-midazolam.
d Inhibition of formation of AEGR-733 metabolites by 6β-hydroxy-testosterone.
ND: Not detected.

The formation of M2 did not follow Michaelis-Menten kinetics thru the entire tested lomitapide concentration range and the K_m value could not be estimateable. In addition, none of the rCYP enzymes were capable of forming M2 to a significant extent, suggesting that the formation of M2 may not depend on a human liver CYP.

Study AEGR-733PC0022 examined lomitapide, M1, and M3's induction potential of CYP1A2, CYP3A4, and CYP2B6 in cryopreserved plateable human hepatocytes. The following are the inducer and marker substrate pair:

- omeprazole (50 μM) and phenacetin (50 μM) for CYP1A2
- rifampin (25 μM) and testosterone (50 μM) for CYP3A4
- phenobarbital (750 μM) and bupropion (100 μM) for CYP2B6

Lomitapide at concentrations up to 20 ng/mL, M1 at concentrations up to 50 ng/mL, and M3 at concentrations up to 600 ng/mL showed no induction potential for CYP1A2, CYP3A4, and CYP2B6 activities, respectively. Respective positive controls under the same conditions showed significant induction relative to untreated hepatocytes.

Study AEGR-733PC-007 examined lomitapide's inhibition potential of 7 CYPs (1A2, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4) in human liver microsomes. CYP-dependent activities were determined via monitoring the enzyme specific metabolite formation of individual marker substrates. For each CYP isozyme, formation of the metabolite of the marker substrate in the presence (0.1, 1, 10, 50, and 100 μM) and absence (vehicle control) of lomitapide mesylate were measured in triplicate. Incubations with a selective inhibitor for each isozyme, at a concentration above the established IC_{50} were conducted concurrently of each other for confirmation of enzymatic activity and comparison of inhibitory potential.

Time-dependent inhibition studies were carried out in the same way as the direct inhibition study with the following exception, lomitapide mesylate was allowed to incubate with the microsomes for 30 min in the presence of the NADPH regenerating system prior to the addition of marker substrates. CYP-dependent activities were then determined by monitoring the enzyme specific metabolite formation of individual marker substrates. Table 8 shows the lomitapide IC_{50}s for direct and time-dependent inhibitions of specific CYP isozymes.

Table 8. Lomitapide IC_{50}s for direct and time-dependent inhibitions of CYP isozymes. Source: Study AEGR-733PC-007 report

CYPs	Marker Substrate (μM)[a]	Isoform-Catalyzed Reaction	Direct Inhibition (IC_{50})	Time-dependent Inhibition (IC_{50})
1A2	Phenacetin (50 μM)	*O*-dealkylation	NA[b]	NA[b]
2B6	Bupropion (100 μM)	2'-hydroxylation	35 μM	10 μM
2C9	Diclofenac (10 μM)	4'-hydroxylation	68 μM	55 μM
2C19	(*S*)-mephenytoin (50 μM)	4'-hydroxylation	62 μM	64 μM
2D6	Bufuralol (10 μM)	1'-hydroxylation	6 μM	10 μM
2E1	Chlorzoxazone (50 μM)	6'-hydroxylation	NA[b]	NA[b]
3A4 (m)	Midazolam (5 μM)	1'-hydroxylation	11 μM	7 μM
3A4 (t)	Testosterone (30 μM)	6-hydroxylation	8 μM	4 μM

[a] Incubation concentration of marker substrates at or near their established Km

[b] Not estimateable in the tested concentration range

Lomitapide does not inhibit CYPs 1A2 and 2E1 via direct or time-dependent inhibition since the respective IC_{50} is not estimateable in the tested concentration range. Lomitapide is not a time-dependent inhibitor of CYPs 2C19 and 2D6 since the respective IC_{50}s for time-dependent inhibitor is larger than direct inhibitor. Lomitapide may have time-dependent inhibition potential for CYPs 2B6, 2C9, and 3A4. However, Study AEGR-733PC-

007 did not report k_{deg} and k_{obs} values. Thus, this reviewer cannot calculate R_2 for lomitapide per the draft drug interaction guidance.

For the direct inhibition potential of lomitapide, CYP2D6 has the smallest IC_{50} value of 6 μM. Thus, this reviewer used it to estimate the direct inhibition potential for CYPs 2B6, 2C9, 2C19, 2D6, and 3A4. [I] is 17.3 ng/mL, which is the C_{max} upon single dose of 200 mg lomitapide oral administration. The guidance recommends C_{max} upon single dose of 60 mg lomitapide (the highest dose). This reviewer erred on the side of being conservative to use the highest oral dose studied, 200 mg lomitapide. The smallest K_i is 3 μM ($IC_{50}/2$). The $R_1 = 1 + [I]/K_i$ value is 1.0073. Thus, lomitapide is not a direct inhibitor for CYPs 2B6, 2C9, 2C19, and 2D6 ($R_1 < 1.1$). For lomitapide's inhibition of CYP3A4 via oral administration, $R_{alternate} = 1 + I_{gut}/K_i$. I_{gut} is 60000/789.8 moles/250 mL. K_i = 4 μM (8 μM/2). Lomitapide $R_{alternate}$ for CYP3A4 is 76.97 ($R_{alternate} > 11$) . Thus, lomitapide is likely a CYP3A4 direct inhibitor per the draft drug interaction guidance. See Sections 2.4.2.4 and 2.4.2.5 for in vivo drug interactions for lomitapide.

Studies BMS-910055194 assessed lomitapide mesylate's potential to inhibit CYP3A4 via the model substrate testosterone and cDNA-derived CYP3A4 in microsomes prepared from a human lymphoblasted cell line. The lomitapide K_i value for CYP3A4 is 0.42 μM, which is not consistent with Study AEGR-733PC-007's results (IC_{50} of 8 and 11 μM). Anyhow, lomitapide $R_{alternate}$ for CYP3A4 is 724.42 per the K_i value of 0.42 μM. Thus, lomitapide is likely a CYP3A4 direct inhibitor per the draft drug interaction guidance.

Studies BMS-910055193 assessed lomitapide mesylate's potential to inhibit CYP2D6 via the model substrate bufuralol and cDNA-derived CYP2D6 in microsomes prepared from a human lymphoblasted cell line. The lomitapide Ki value for CYP2D6 is 2.57 μM, which is consistent with Study AEGR-733PC-007's results.

Study AEGR-733PC-007 also examined lomitapide's inhibition potential on warfarin and estimated IC_{50} values of lomitapide to inhibit warfarin (2 μM) metabolism as determined via the formation of 2 hydroxylated metabolites of warfarin were 97 μM for warfarin-OH-1 and 32 μM for warfarin-OH-2, respectively.

Study AEGR-733PC0021 examined M1 and M3's (tested separately) CYP inhibition potential of 9 CYPs (1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) in human liver microsomes. CYP-dependent activities were determined by monitoring the enzyme specific metabolite formation of individual marker substrates. For each CYP isozyme, formation of the metabolite of the marker substrate in the presence (0, 0.01, 0.1, 1, 10, and 30 μM) and absence (vehicle control) of M1 and M3 were measured in triplicate. Incubations with a selective inhibitor for each isozyme, at a concentration above the reported IC_{50}, were conducted concurrently of each other for confirmation of enzymatic activity and comparison of inhibitory potential.

Time-dependent inhibition studies were carried out similarly as the direct inhibition study with the following exception, M1 and M3 were allowed to incubate with the microsomes for 30 min in the presence of the NADPH regenerating system prior to the addition of marker substrates. CYP-dependent activities were then determined by monitoring the enzyme specific metabolite formation of individual marker substrates. Table 9 shows the M1 and M3 IC_{50}s for direct and time-dependent inhibitions.

Table 9. M1 and M3 IC_{50}s for direct and time-dependent inhibitions of CYP isozymes. Source: Study AEGR-733PC0021 report

CYPs	Marker Substrate (Conc.)[a]	Isoform-Catalyzed Reaction	M1		M3	
			Direct Inhibition (IC_{50}[b]) μM	Time-dependent Inhibition (IC_{50}[b]) μM	Direct Inhibition (IC_{50}[b]) μM	Time-dependent Inhibition (IC_{50}[b]) μM
1A2	Phenacetin (10 μM)	*O*-dealkylation	N/A[c]	>30	N/A	N/A
2A6	Coumarin (1 μM)	7-hydroxylation	N/A	N/A	N/A	N/A
2B6	Bupropion (50 μM)	hydroxylation	N/A	N/A	N/A	N/A
2C8	Paclitaxel (5 μM)	6-hydroxylation	N/A	N/A	N/A	>30
2C9	Diclofenac (5 μM)	4'-hydroxylation	N/A	N/A	N/A	N/A
2C19	(*S*)-mephenytoin (10 μM)	4'-hydroxylation	>30	>30	N/A	N/A
2D6	Bufuralol (10 μM)	1'-hydroxylation	15.4	>30	N/A	N/A
2E1	Chlorzoxazone (40 μM)	6-hydroxylation	N/A	N/A	N/A	N/A
3A4 (m)	Midazolam (1 μM)	1'-hydroxylation	N/A	N/A	N/A	N/A
3A4 (t)	Testosterone (50 μM)	6β-hydroxylation	N/A	N/A	N/A	N/A

M1 did not show any direct or time-dependent inhibition for CYPs 2A6, 2B6, 2C8, 2C9, 2E1, and 3A4 within the studied concentrations. M1 did not show direct inhibition for CYP1A2 but showed a time-dependent inhibition with an estimated IC_{50} > 30 μM. M1 showed both direct and time-dependent CYP2C19 inhibition with estimated IC_{50} values > 30 μM. M1 also showed both direct and time-dependent CYP2D6 inhibition with estimated IC_{50} values of 15.4 μM and > 30 μM, respectively. The R_1 ($1 + [I]/K_i$) value for CYP2D6 is 1.0135 for M1 ([I] = 36.3 ng/mL, which is the C_{max} upon single dose of 200 mg lomitapide oral administration; Ki is 15.4/2). Thus, M1 is not a direct inhibitor for CYPs 2D6 and 2C19. Study AEGR-733PC-0021 did not report k_{deg} and k_{obs} values. Thus, this reviewer cannot calculate R_2 for M1 per the draft drug interaction guidance.

M3 did not show any direct or time-dependent inhibition on the 9 studied CYP isozymes with the only exception of CYP2C8. The time-dependent inhibition IC_{50} for CYP2C8 by M3 was > 30 μM.

Metabolites' Pharmacological Activities

Study AEGR-733PC0024 examined the MTP inhibition potential of lomitapide and its prominent metabolites, M1 and M3. Vesicles of the fluorescent-labeled triglyceride transfer assay kit were added to a fluorescence microtiter plate with water, buffer, increasing concentrations of lomitapide, M1, or M3 and incubated for 30 minutes. If the test substance inhibits MTP, the amount of fluorescence compared to control would decrease. The IC_{50}s for inhibiting triglyceride transfer are 15.5 nM, 6.3 μM, and > 300 μM, respectively, for lomitapide, M3, and M1. When compared with lomitapide's IC_{50}, M1 and M3 do not likely inhibit MTP at the clinically achievable concentrations.

Chiral Conversion

Lomitapide is achiral and does not have the chiral inversion issue.

2.2.2 Is lomitapide PK dose-proportional upon intravenous and oral administrations?

Per the power model to assess dose-proportionality (C_{max} or $AUC_{0\text{-}inf} = \alpha \bullet [\text{Intravenous or Oral Dose}]^{\beta}$; α depends on the participant and error; β is the dose-proportionality factor; after transformation, ln C_{max} or ln

$AUC_{0\text{-}inf} = \ln \alpha + \beta \bullet \ln$ Intravenous or Oral Dose; $\beta = 1$ when dose-proportional; Gough et al. *Drug Information Journal* 1995;29:1039-48), this reviewer performed the power model analyses for the following studies:

Study CV145-003 (see Question 2.2.1 for experimental details) had the IV 0, 7.5, 15, 30, or 60 mg lomitapide dose groups. The slope, β (95% CI), for lomitapide ln AUC_t vs. ln IV Dose plot and ln C_{max} vs. ln IV Dose plot was 1.03 (0.89 – 1.16) and 1.10 (0.93 – 1.28), respectively. Since the β values are close to 1 and the 95% CIs include 1, lomitapide PK is approximately dose-proportional for IV lomitapide doses from 7.5 to 60 mg.

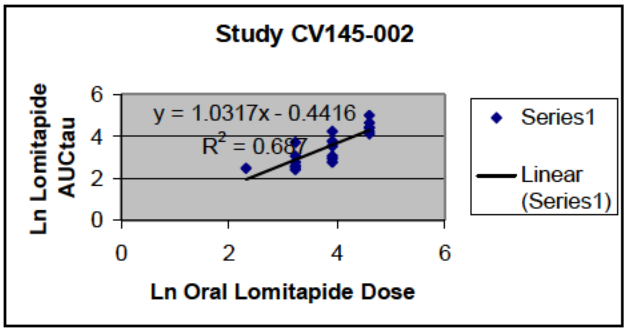
Study CV145-001 is an oral single-dose (0, 1, 5, 25, 50, 100, or 200 mg lomitapide), parallel groups study to assess the PK of lomitapide and its metabolites in healthy men. Serial plasma samples were collected predose and 72 hours postdose to determine lomitapide and its metabolites via validated bioanalytical methods. The 1 and 5 mg dose groups did not result in high enough plasma lomitapide concentrations to allow C_{max} and AUC determinations. The slope of 25 to 200 mg lomitapide, β (95% CI), for lomitapide ln AUC_{inf} vs. ln Oral Dose plot and ln C_{max} vs. ln Oral Dose plot was 1.32 (1.05 – 1.59) and 1.37 (1.09 – 1.64), respectively. Since the β values do not equal to 1 and the 95% CIs do not include 1, lomitapide PK is not dose-proportional for oral single doses from 25 to 200 mg. However, for the dose range of 25 to **100** mg lomitapide, the β (95% CI) for lomitapide ln AUC_{inf} vs. ln Oral Dose plot and ln C_{max} vs. ln Oral Dose plot was 1.32 (0.92 – 1.72) and 1.27 (0.82 – 1.72), respectively. Since the 95% CIs include 1 even the β values do not equal to 1, lomitapide PK may be dose-proportional for oral single doses from 25 to 100 mg.

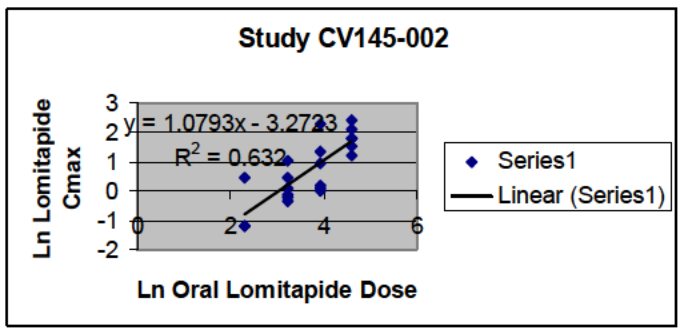
Study CV145-002 is an oral multiple-dose (0, 10, 25, 50, 100, or 200 mg lomitapide once daily for 14 days), parallel groups study to assess the PK of lomitapide and its metabolites in healthy men. Serial plasma samples were collected predose and 72 hours postdose to determine lomitapide and its metabolites via validated bioanalytical methods. The slope, β (95% CI), for lomitapide ln AUC_{tau} vs. ln Oral Dose plot and ln C_{max} vs. ln Oral Dose plot was 1.03 (0.68 – 1.39) and 1.08 (0.68 – 1.47), respectively, for oral single doses from 10 – 100 mg (Day 1). Since the β values are close to 1 and the 95% CIs include 1, lomitapide PK is approximately dose-proportional for oral single doses from 10 – 100 mg. The slope, β (95% CI), for lomitapide ln AUC_{tau} vs. ln Oral Dose plot and ln C_{max} vs. ln Oral Dose plot was 0.93 (0.44 – 1.42) and 0.94 (0.44 – 1.43), respectively, for oral multiple doses from 10 – 50 mg (Day 14). Since the β values are close to 1 and the 95% CIs include 1, lomitapide PK is approximately dose-proportional for oral multiple doses from 10 – 50 mg. Due to safety considerations, the sponsor did **not**:

- study the 200 mg lomitapide dose group
- complete the 100 mg lomitapide dose group in the multiple dosing part of the study

Overall, lomitapide PK is approximately dose-proportional for intravenous doses from 7.5 – 60 mg lomitapide. Lomitapide PK is approximately dose-proportional for oral doses from 10 – 100 mg.

Figures 9 (left) and 10 (right). Lomitapide ln AUC_{tau} or ln C_{max} vs. ln Dose plots for single doses, respectively, for demonstration.





2.2.3 Does chronic oral dosing alter lomitapide PK?

Per Study CV145-002 in Question 2.2.2 above, the observed mean (SD) accumulation index for lomitapide ($AUC_{tau,\ Day\ 14}/AUC_{tau,\ Day\ 1}$) was 2.7 (1.3) and 3.9 (2.1) for 25 and 50 mg lomitapide daily, respectively. Per this [$Accumulation = \frac{1}{(1-e^{-(k\tau)})}$] relationship, k= $\frac{0.693}{39.7}$ hr^{-1}, and τ = 24 hours. Thus, the estimated accumulation factor is 2.92. Study CV145-002's 10 mg daily dose group only had 1 evaluable accumulation index of 2.7 since the other 5 AUC_{tau}s for the 10 mg daily dose group at Day 1 were not evaluable. Thus, this reviewer did not accept the observed accumulation index value of 2.7 for the 10 mg dose group.

Study CV145-010 was a double blind, placebo controlled, parallel groups study in 18 healthy women. Randomized participants orally received the following treatments daily for 14 days:

- 10 mg lomitapide
- 25 mg lomitapide, or
- matching placebo

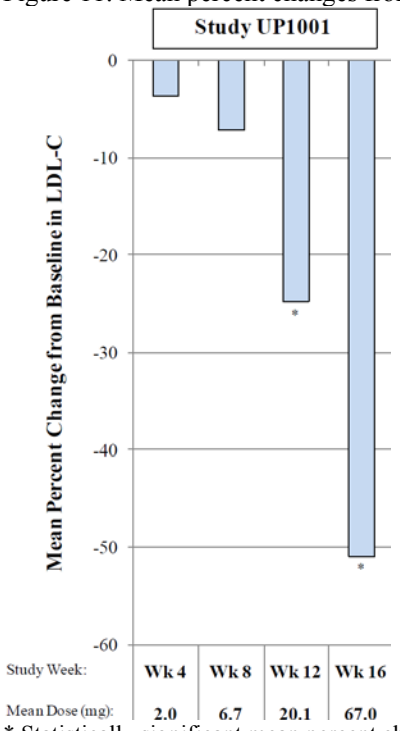
Serial plasma samples were collected to determine lomitapide, M1, and M3 at predose and 24 hours postdose.

Lomitapide C_{min} values on Days 5, 6, 7, 12, 13, and 14 were generally similar suggesting that plasma lomitapide concentrations were at steady state on Day 14. Study CV145-0010's mean (SD) lomitapide accumulation index is 4.3 (2.0) for the 25 mg lomitapide daily dose group. The lomitapide AUC_{tau} at Day 1 was all not evaluable for the 10 mg daily dose group. Thus, mean accumulation index value for Studies CV145-002 and CV145-010 is 3.63.

2.2.4 How is the proposed daily oral lomitapide mesylate dosing regimens determined?

The dose regimen selected for the pivotal Study AEGR-733-005, including the starting dose and the escalation steps, as well as the interval between escalations were per the results of Study UP1001 (Phase 2 study). Study UP1001 used the weight-based dosing approach from 0.03 mg/kg and escalated by ½ log units every 4 weeks to the maximum dose of 1.0 mg/kg. The mean doses administered every 4 weeks were 2.0, 6.7, 20.1, and 67.0 mg/day. Figure 11 shows the mean percent changes from baseline in LDL-C for Study UP1001.

Figure 11. Mean percent changes from baseline in LDL-C for Study UP1001. Source: M2.5 Figure 7



* Statistically significant mean percent change from Baseline, paired t-test

Baseline LDL-C in Study UP1001 was 614 mg/dL (15.9 mmol/L) in which subjects were **off all** lipid lowering treatments..

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 Study UP1002/AEGR-733-005 was 5 mg. The sponsor expected minimal GI side effects at this low dose in most patients, so the initial dosing period at 5 mg was 2 weeks, with all subsequent escalations conducted at 4-week intervals consistent with Study UP1001.

The dosing approach used in this pivotal Phase 3 study did not incorporate adjustment for body weight since PK analyses did not identify body weight as an important co-factor influencing drug exposure. Due to the small size and the dose titration scheme of the pivotal Phase 3 study, the sponsor did not conduct population PK analysis for Study AEGR-733-005 yet. The sponsor proposed to conduct a population PK analysis later in development via combining the data from pediatric studies during the pre-NDA meeting on June 15, 2011 and the Division of Metabolism and Endocrinology Products agreed (see July 5, 2011's meeting minutes).

2.2.5 Exposure-Response

2.2.5.1 Is there evidence of dose-response for effectiveness?

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

2.2.5.2 Is there evidence of a dose-response relationship for safety?

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

2.2.6 What would be the recommended optimal oral lomitapide mesylate dosing regimen to reduce blood cholesterol?

The sponsor's proposed lomitapide dosing regimen seems reasonable since it is a dose titration approach to balance efficacy and adverse events.

2.2.7 Does lomitapide mesylate prolong the QT or QTc interval?

Study AEGR-733-011 examined lomitapide's QT prolongation potential in 50 healthy participants. This was a single-center, randomized, 6-treatment, 5-period, crossover study. The 6 study drug treatments were oral lomitapide solution (single 75 and 200 mg doses sequentially and 75 mg co-administered with ketoconazole), placebo, ketoconazole alone, and moxifloxacin (positive control). The study was double-blinded with regard to the lomitapide and placebo treatments, and open-label for the ketoconazole and moxifloxacin treatments. The cardiologist responsible for over-reading the ECGs was blinded to all study treatments and sequences. Continuous ECG recordings were performed up to 24 hours postdose on Days 1 and 3 of each period. Plasma samples for the measurement of lomitapide, M1, and M3, and ketoconazole concentrations were collected up to 24 hours postdose on Days 1 and 3 of each period.

See the QT-Interdisciplinary Review Team's (QT-IRT) reviews dated July 9, 2012 and August 8, 2012 in DARRTS.

Figure 12 (left). Scatterplot of placebo- or ketoconazole-corrected change from baseline in qtci (ΔΔQTcI) versus observed lomitapide concentration following dosing with 75 mg lomitapide, 200 mg lomitapide, and 75 mg lomitapide co-administered with ketoconazole Source: IRT review
Figure 13 (right). Scatterplot of placebo- or ketoconazole-corrected change from baseline in qtci (ΔΔQTcI) versus observed ketoconazole concentration following dosing with 75 mg lomitapide, 200 mg lomitapide, and 75 mg lomitapide co-administered with ketoconazole Source: IRT review

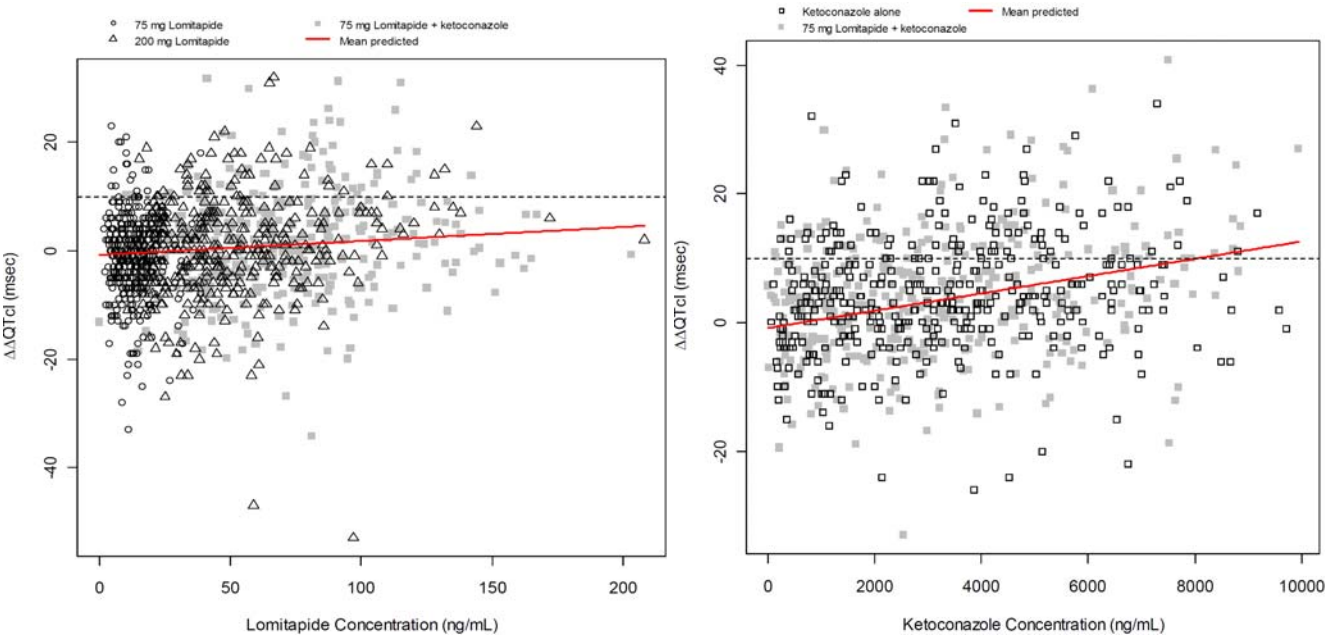


Table 10. Exposure-response analysis of plasma concentrations of lomitapide and ketoconazole and placebo-corrected change from baseline in QTcI (ΔΔQTcI). Source: IRT review

Parameter	Estimate (90% CI)	P-Value	Between-Subject Variation
Intercept (ms)	-0.82 (-1.99, 0.35)	0.2504	4.43
Slope for lomitapide (ms per ng/mL)	0.0258 (0.0018, 0.050)	0.0771	0.0795
Slope for ketoconazole (ms per ng/mL)	0.0013 (0.0010, 0.0017)	< 0.0001	0.0012
Slope for lomitapide-ketoconazole interaction (ms per square ng/mL)	-0.000006 (-0.000011, -0.000001)	0.0378	0.000010
Residual variability (ms)	7.03	--	--

Per the QT-IRT analysis, QT-IRT concludes that the relationship between ΔΔQTcI and lomitapide was not significant upon correcting for the effects of placebo and the effects of ketoconazole, analyzed separately. However, the QT-IRT does not believe assay sensitivity was successfully demonstrated in the study. Even though the largest lower bound of the two-sided 90% CI for the ΔΔQTc for moxifloxacin was greater than 5 ms, the moxifloxacin profile was not consistent with expectation.

Table 11. Point estimates and the 90% CIs for 75 mg lomitapide, 200 mg lomitapide, 75 mg lomitapide + ketoconazole, moxifloxacin and ketoconazole (QT-IRT analysis) Source: IRT review

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
75 mg Lomitapide	24	1.1	(-0.8, 3.1)
200 mg Lomitapide	12	2.8	(0.3, 5.4)
75 mg Lomitapide + Ketoconazole*	24	2.7	(0.2, 5.3)
Moxifloxacin 400 mg**	1	12.5	(9.8, 15.2)
Ketoconazole	3	6.4	(3.7, 9.2)

* Ketoconazole-corrected change from baseline in QTcI.
** Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 8.8 ms.

2.2.8 What is the difference of lomitapide PK between homozygous familial hypercholesterolemic patients and healthy volunteers?

No data yet. The sponsor conducted sparse sampling for the population PK analysis of the pivotal Phase 3 study (AEGR-733-005). Due to the small size of the Phase 3 study (29 patients) and the titration dosing scheme, the sponsor proposed the conduct of a population PK analysis later via combining data from pediatric studies. The Agency agreed to the sponsor's proposal per meeting minutes of July 5, 2011.

2.3 Intrinsic Factors

2.3.1 How does hepatic impairment affect lomitapide PK?

Study AEGR-733-017 examined the effect of hepatic impairment on lomitapide PK. Each of the following participants orally received 60 mg lomitapide (3 x 20 mg capsules) after an 8-hour fast:

- 8 patients with mild hepatic impairment (Child-Pugh score of 5 – 6)
- 8 matched healthy participants to patients with mild hepatic impairment
- 8 patients with moderate hepatic impairment (Child-Pugh score of 7 – 9)
- 8 matched healthy participants to patients with moderate hepatic impairment

Serial plasma samples were collected predose and 216 hours postdose to determine lomitapide, M1, and M3 via validated LC/MS/MS assays. Plasma protein binding for ^{14}C-lomitapide was measured via equilibrium dialysis with participants' predose plasma samples.

Figures 14 - 19 show the plasma drug concentration-time profiles of lomitapide, M1, and M3. Tables 12 – 14 show the PK parameters of lomitapide, M1, and M3.

Figure 14 (left). Geometric mean plasma lomitapide concentration-time profiles (mild hepatic impairment). Figure 15 (right) Geometric mean plasma lomitapide concentration-time profiles (moderate hepatic impairment). For both figures, solid circles represent hepatic impairment and open circles represent healthy participants. Source: Study AEGR-733-017's report Figures 11-1 and 11.2

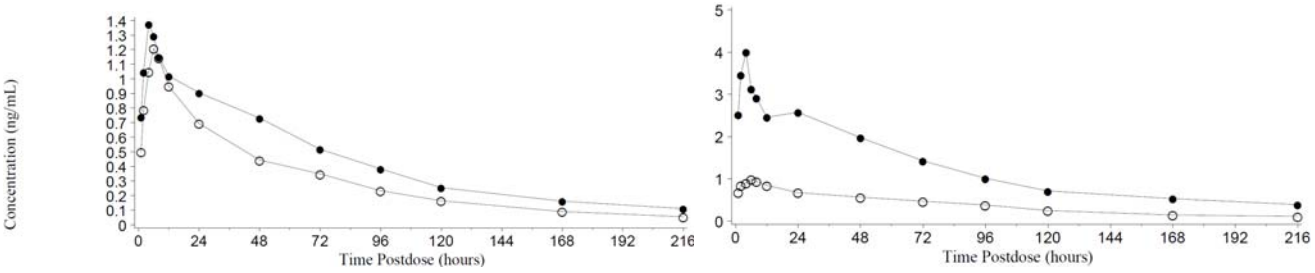


Figure 16 (left). Geometric mean plasma M1 concentration-time profiles (mild hepatic impairment). Figure 17 (right) Geometric mean plasma lomitapide concentration-time profiles (moderate hepatic impairment). For both figures, solid circles represent hepatic impairment and open circles represent healthy participants. Source: Study AEGR-733-017's report Figures 11-3 and 11-4

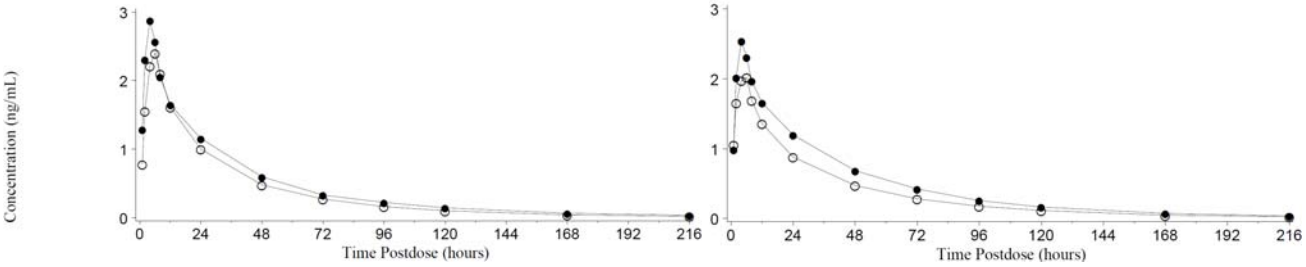


Figure 18 (left). Geometric mean plasma M3 concentration-time profiles (mild hepatic impairment). Figure 19 (right) Geometric mean plasma lomitapide concentration-time profiles (moderate hepatic impairment). For both figures, solid circles represent hepatic impairment and open circles represent healthy participants. Source: Study AEGR-733-017's report Figures 11-5 and 11-6

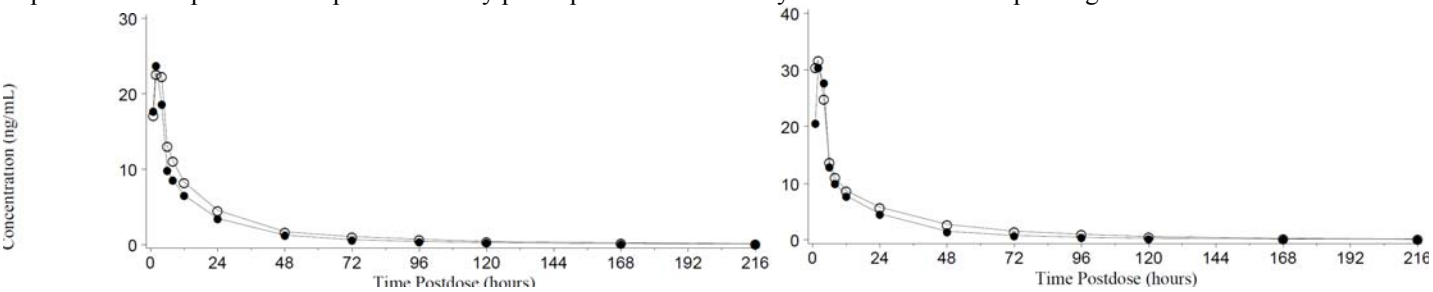


Table 12. Lomitapide PK parameters for groups of varying hepatic function. Source: Study AEGR-733-017's report Table 11-5

Comparison	Parameter	Units	Reference N	Reference Mean	Test N	Test Mean	Test/Reference (%)	90% Confidence Interval
Mild Impairment vs. Matched Normal	C_{max}	ng/mL	8	1.45	8	1.50	104	(58 , 185)
	AUC_{0-t}	ng·hr/mL	8	67.2	8	95.4	142	(86 , 234)
	AUC_{0-inf}	ng·hr/mL	8	74.3	8	109	147	(100 , 216)
Moderate Impairment vs. Matched Normal	C_{max}	ng/mL	8	1.05	8	4.83	461	(258 , 823)
	AUC_{0-t}	ng·hr/mL	8	80.9	8	279	345	(209 , 570)
	AUC_{0-inf}	ng·hr/mL	8	92.9	7	245	264	(178 , 392)

Table 13. M1 PK parameters for groups of varying hepatic function. Source: Study AEGR-733-017's report Table 11-7

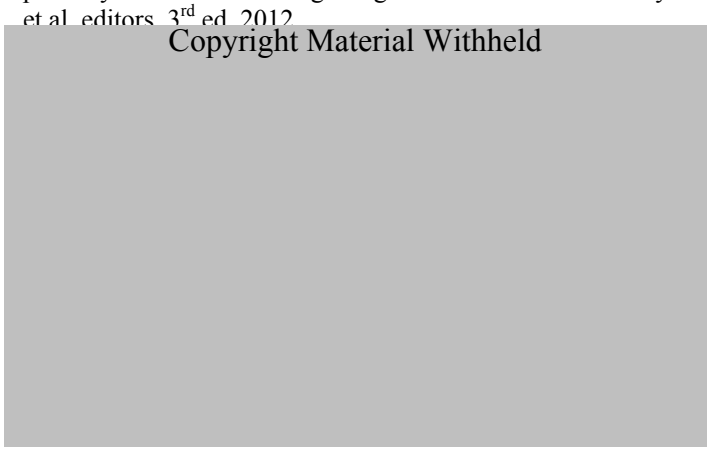
Comparison	Parameter	Units	Reference N	Reference Mean	Test N	Test Mean	Test/Reference (%)	90% Confidence Interval
Mild Impairment vs. Matched Healthy	C_{max}	ng/mL	8	2.52	8	2.94	117	(86 , 159)
	AUC_{0-t}	ng·hr/mL	8	76.3	8	91.8	120	(80 , 180)
	AUC_{0-inf}	ng·hr/mL	8	78.5	8	95.9	122	(81 , 184)
Moderate Impairment vs. Matched Healthy	C_{max}	ng/mL	8	2.14	8	2.70	127	(93 , 172)
	AUC_{0-t}	ng·hr/mL	8	72.7	8	99.9	137	(92 , 205)
	AUC_{0-inf}	ng·hr/mL	8	75.4	8	105	139	(92 , 209)
Moderate Impairment vs. Mild Impairment	C_{max}	ng/mL	8	2.94	8	2.70	91.8	(67 , 126)
	AUC_{0-t}	ng·hr/mL	8	91.8	8	99.9	109	(73 , 163)
	AUC_{0-inf}	ng·hr/mL	8	95.9	8	105	109	(73 , 162)

Table 14. M3 PK parameters for groups of varying hepatic function. Source: Study AEGR-733-017's report Table 11-9

Comparison	Parameter	Units	Reference N	Reference Mean	Test N	Test Mean	Test/Reference (%)	90% Confidence Interval
Mild Impairment vs. Matched Healthy	C_{max}	ng/mL	8	28.5	8	27.2	95.5	(69 , 132)
	AUC_{0-t}	ng·hr/mL	8	431	8	326	75.7	(51 , 112)
	AUC_{0-inf}	ng·hr/mL	8	447	8	334	74.7	(50 , 110)
Moderate Impairment vs. Matched Healthy	C_{max}	ng/mL	8	34.9	8	33.4	95.7	(69 , 132)
	AUC_{0-t}	ng·hr/mL	8	531	8	439	82.7	(56 , 123)
	AUC_{0-inf}	ng·hr/mL	8	548	7	442	80.7	(54 , 121)
Moderate Impairment vs. Mild Impairment	C_{max}	ng/mL	8	27.2	8	33.4	123	(89 , 169)
	AUC_{0-t}	ng·hr/mL	8	326	8	439	135	(91 , 200)
	AUC_{0-inf}	ng·hr/mL	8	334	7	442	132	(88 , 199)

There is a trend that intrinsic clearance of CYP3A substrate decreases with increasing severity of liver disease, Figure 20 (Susla and Lertora. Chapter 7, *Principles of Clinical Pharmacology*, A.J. Atkinson et al. editors, 3rd ed, 2012).

Figure 20. Schematic diagram showing the relationship between the intrinsic clearance of drugs mediated by specific CYP metabolic pathways and the Child-Pugh stages of liver disease severity. Source: Chapter 7, *Principles of Clinical Pharmacology*, A.J. Atkinson et al. editors, 3rd ed, 2012



Moderate hepatically impaired patients' M1 AUC_{0-inf} and C_{max} increased 39% and 27%, respectively, as compared to those of healthy participants. Mild hepatically impaired patients' M1 AUC_{0-inf} and C_{max} increased 22% and 17%, respectively, as compared to those of healthy participants. Moderate hepatically impaired patients' M3 AUC_{0-inf} and C_{max} decreased 19% and 4%, respectively, as compared to those of healthy participants. Mild hepatically impaired patients' M3 AUC_{0-inf} and C_{max} decreased 25% and 4%, respectively, as compared to those of healthy participants. These observations are consistent that metabolism of lomitapide decreases as liver disease worsens.

Moderate hepatically impaired patients' lomitapide AUC_{0-inf} and C_{max} increased 164% and 361%, respectively, as compared to those of healthy participants. Liver extensively metabolizes lomitapide. The mean unbound fraction of lomitapide decreased in moderate hepatic impairment patients when compared with matching healthy participants (0.078% vs. 0.168%, respectively) with excluding samples of low precision (standard deviation of measurement is anomalously high). Plasma protein binding usually decreases (increase in unbound

fraction) because of the reduction of plasma albumin and α_1–acid glycoprotein concentrations in liver impairment (McLean and Morgan. *Clin Pharmacokinet* 1991;21:42-69). Also affinity of α_1–acid glycoprotein for drugs is also lower in cirrhosis. With the inclusion of samples of low precision samples, there is no significant difference in lomitapide plasma protein binding between moderate hepatic impairment and matching healthy participants. Safety issues precluded dose adjustment for patients with moderate hepatic impairment per discussion with the clinical reviewer. Per these data, lomitapide should be contraindicated from use in patients with moderate **and** severe hepatic impairment.

Mild hepatically impaired patients' lomitapide $AUC_{0\text{-inf}}$ and C_{max} increased 47% and 4%, respectively, as compared to those of healthy participants. Liver extensively metabolizes lomitapide. There is no significant difference in lomitapide plasma protein binding between mild hepatic impairment and matching healthy participants with excluding samples of low precision (standard deviation of measurement is anomalously high). With the inclusion of samples of low precision samples, there is no significant difference in lomitapide plasma protein binding between mild hepatic impairment and matching healthy participants. Per these data, the dose for patients with mild hepatic impairment should not exceed 40 mg lomitapide.

2.3.2 How does renal impairment affect lomitapide PK?

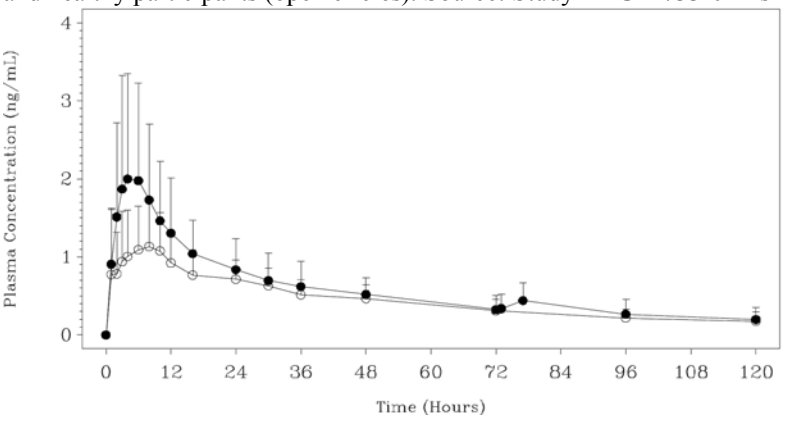
Study AEGR-733-021examined the effect of ESRD on lomitapide PK. Each of the following participants orally received 60 mg lomitapide (3 x 20 mg capsules) after an overnight fast:

- 6 patients with ESRD received the lomitapide dose within 2 hours of completing hemodialysis and the next hemodialysis about 3 days postdose
- 7 healthy volunteers with Cockcroft-Gault creatinine clearance ≥ 80 mL/min matched to patients with ESRD

Serial plasma samples were collected predose and for 120 hours postdose to assess lomitapide, M1, and M3. Plasma concentrations of lomitapide, M1, and M3 were determined via LC/MS/MS assays. Plasma protein binding for ^{14}C-lomitapide was measured via equilibrium dialysis with participants' predose plasma samples.

Figures 21 - 23 show the plasma drug concentration-time profiles of lomitapide, M1, and M3. Tables 15 – 17 show the PK parameters of lomitapide, M1, and M3.

Figure 21. Mean (SD) plasma lomitapide concentration-time profiles between ESRD patients on hemodialysis treatment (solid circles) and healthy participants (open circles). Source: Study AEGR-733-021's report Figure 11-1



Best Available Copy

Figure 22 (left). Mean (SD) plasma M1 concentration-time profiles between ESRD patients on hemodialysis treatment (solid circles) and healthy participants (open circles). Figure 23 (left). Mean (SD) plasma M3 concentration-time profiles between ESRD patients on hemodialysis treatment (solid circles) and healthy participants (open circles). Source: Study AEGR-733-021's report Figures 11-2 and 11-3

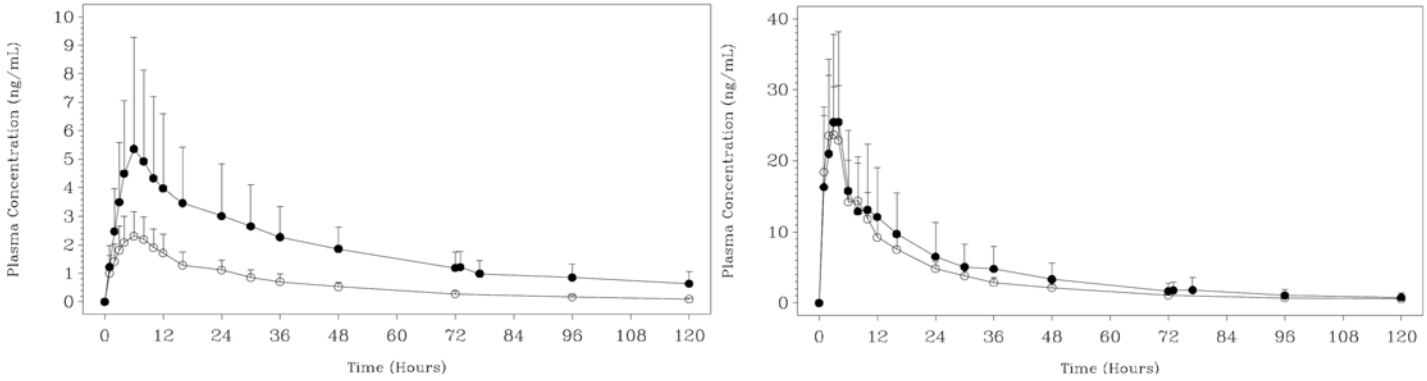


Table 15. Lomitapide PK parameters for ESRD patients on hemodialysis treatment and healthy participants. Source: Study AEGR-733-021's report Table 11-6

Parameter (Unit)	Group	N	Mean	Ratio of Geometric LS Means (ESRD/Normal)	90% CI of the Ratio
AUC_{0-t} (ng•hr/mL)	Healthy Participants	7	51.944	–	–
	ESRD Patients	6	69.757	1.343	(0.955, 1.888)
AUC_{0-inf} (ng•hr/mL)	Healthy Participants	4	52.680	–	–
	ESRD Patients	4	73.388	1.393	(0.882, 2.201)
AUC_{0-72} (ng•hr/mL)	Healthy Participants	7	41.557	–	–
	ESRD Patients	6	58.012	1.396	(1.002, 1.944)
C_{max} (ng/mL)	Healthy Participants	7	1.258	–	–
	ESRD Patients	7	1.892	1.505	(0.838, 2.703)

Table 16. M1 PK parameters for ESRD patients on hemodialysis treatment and healthy participants. Source: Study AEGR-733-021's report Table 11-4

Parameter	Healthy Participants Mean (CV), N = 7	ESRD Patients Mean (CV), N = 7
AUC_{0-t} (ng•hr/mL)	69.93 (32)	210.97 (42)
AUC_{0-inf} (ng•hr/mL)	73.90 (32)	221.11 (50)
AUC_{0-72} (ng•hr/mL)	61.85 (33)	170.56 (48)
C_{max} (ng/mL)	2.26 (36)	4.69 (70)
T_{max} (hr)	6.00 (3.00, 6.00)	6.00 (4.00, 8.00)
$t_{1/2}$ (hr)	28.74 (12)	38.19 (41)

Table 17. M3 PK parameters for ESRD patients on hemodialysis treatment and healthy participants. Source: Study AEGR-733-021's report Table 11-5

Parameter	Healthy Participants Mean (CV), N = 7	ESRD Patients Mean (CV), N = 7
AUC_{0-t} (ng•hr/mL)	413.70 (21)	456.89 (62)
AUC_{0-inf} (ng•hr/mL)	441.58 (21)	490.49 (62)
AUC_{0-72} (ng•hr/mL)	377.08 (22)	408.97 (61)
C_{max} (ng/mL)	25.72 (25)	26.56 (41)
T_{max} (hr)	3.00 (1.00, 4.00)	3.00 (2.00, 4.00)
$t_{1/2}$ (hr)	32.92 (9)	32.29 (28)

M3 exposure of ESRD patients on hemodialysis treatment is comparable to that of healthy participants (Table 17). However, M1 AUC_{0-inf} and C_{max} of ESRD patients on hemodialysis treatment increased about 200% and 108%, respectively, as compared to those of healthy participants (Table 16). M1 is the most prominent urinary metabolite of lomitapide (see Study AEGR-733-010's discussion above). Thus, it is consistent that M1 will

accumulate in renal impairment. Per the Pharmacology/Toxicology reviewer, majority of the non-clinical lomitapide toxicology findings appear to be pharmacologically mediated and M1 has much less MTP inhibitory activity compared with lomitapide. Thus, it would seem that a 200% increase in M1 exposure would not pose a significant safety risk.

The sponsor seemed to use the "Reduced PK Study Design" approach of the draft renal guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf) to address the effect of renal impairment on lomitapide PK. Such approach is reasonable because lomitapide is mainly cleared via metabolism (see Section 2.2.1's Metabolism and Excretion). However, the guidance recommends, in such design, the study of investigational drug between ESRD patients **not yet on** dialysis and participants with normal renal function to compare the PK at the extremes of renal function. Study AEGR-733-021 assessed ESRD patients **receiving** hemodialysis, such patients may not represent the extreme ("worst case") of renal impairment since the chronic and predose hemodialysis may remove uremic inhibitors that are important for lomitapide metabolism and transporters (Nolin et al. *Clin Pharmacol Ther* 2008;83:898-903; Dreisbach & Lertora *Expert Opin Drug Metab Toxicol* 2008;4:1065-74). Data show that the exposure increase of a drug that is mainly cleared via nonrenal route is higher in patients with severe renal impairment than ESRD patients receiving chronic hemodialysis (Zhang et al. *J Clin Pharmacol* 2012;52:79S-90S). Thus, patients with severe renal impairment may represent the "worst case" of renal impairment better than ESRD patients receiving hemodialysis for lomitapide.

The potential lomitapide exposure increase in patients with severe renal impairment as compared to ESRD patients receiving hemodialysis may pose safety concern since the use of lomitapide was associated with elevated transaminases even at low doses such as 2.5 mg lomitapide daily (FDA Briefing Document for the Lomitapide Advisory Committee Briefing Document, Pages 56 – 57). M1 exposure is also significantly increased in ESRD patients receiving hemodialysis but the extent of M1 increase in severe renal impairment is unknown for toxicological assessment.

M3 is a minor urine metabolite (see Study AEGR-733-010's discussion above). Severe renal impairment may alter the metabolism/transport of M3. However, M3 exposure is comparable between ESRD patients on hemodialysis and healthy volunteers. Thus, it is likely that severe renal impairment may not alter M3 exposure as compared to healthy volunteers. The sponsor should conduct a comparative study between patients with severe renal impairment and healthy volunteers with normal renal function to assess the effect of severe renal impairment on lomitapide and its M1 metabolite's exposures as a Postmarketing Requirement. A separate Postmarketing Requirement memo for the severe renal impairment study will follow this review.

Lomitapide $AUC_{0\text{-}inf}$ and C_{max} of ESRD patients receiving hemodialysis treatment increased 40% and 50%, respectively, as compared to those of healthy participants. The in vitro determination showed no significant difference of unbounded ^{14}C-lomitapide between plasma from ESRD patients on hemodialysis treatment and plasma from healthy participants. Per these data, the dose for patients with ESRD receiving dialysis should not exceed 40 mg lomitapide.

2.3.3 Do the intrinsic factors such as age, body mass index, gender, and race affect lomitapide PK?

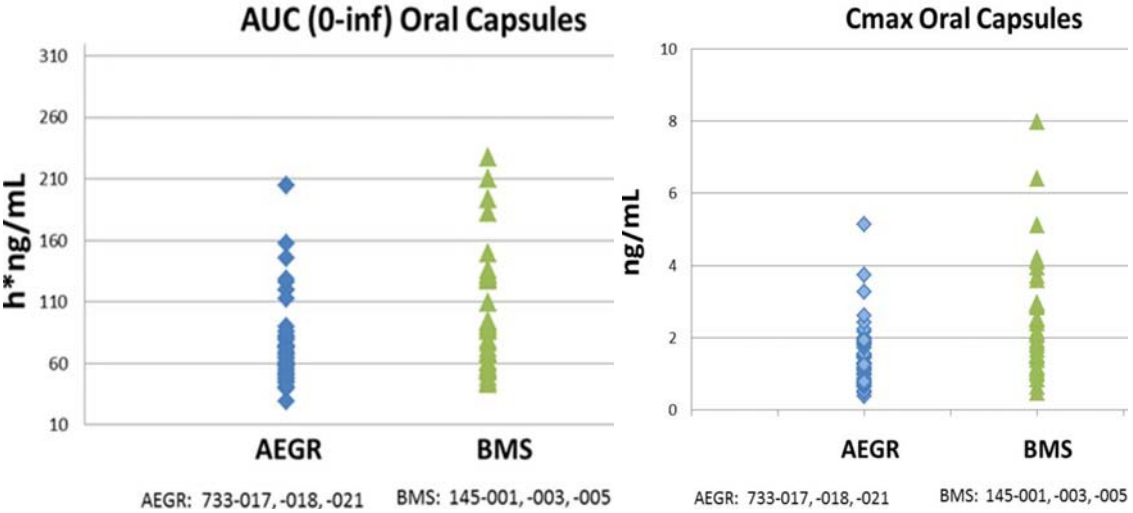
The sponsor did not conduct any dedicated analysis to address the issue whether intrinsic factors such as age, body mass index, gender, and race will affect lomitapide PK. The sponsor collected sparse samples for plasma lomitapide concentration determination from the pivotal clinical Study AEGR-733-005. Due to the small size (29 patients) and the dose titration scheme of the Phase 3 study, the sponsor did not conduct population PK analysis for Study AEGR-733-005. The sponsor proposed to conduct a population PK analysis later in development via combining the data from pediatric studies during the pre-NDA meeting on June 15, 2011 and the Division of Metabolism and Endocrinology Products agreed (see July 5, 2011's meeting minutes).

In the October 1, 2012 response to FDA Information request, the sponsor used Studies CV145-010 and AEGR-733-015's results to compare with Study CV145-002's results to address the potential difference in lomitapide PK between female and male, respectively. The sponsor claimed that "The Mean C_{max} and AUC_{tau} in these female subjects (Study AEGR-733-015) when compared to historical male data (CV145-002) indicated no

difference in the PK between male and females." without providing the details. The mean (SD) lomitapide C_{max} and AUC_{tau} of the participants (female) for Study AEGR-733-015 are 7.45 (3.63) ng/mL and 108 (55.3) ng·hr/mL, respectively, upon coadministration of 50 mg (2 X 20 and 2 X 5) lomitapide and 0.035 mg ethinyl estradiol and 0.25 mg norgestimate on Day 21. The mean (SD) lomitapide C_{max} and AUC_{tau} of the participants (male) for Study CV145-002 are 8.5 (7.8) ng/mL and 132.6 (122.5) ng·hr/mL, respectively, upon multiple dose administration of 50 mg (1 X 50) lomitapide on Day 14. The cross-study comparison between Study AEGR-733-015 and CV145-002 is not acceptable because of the following 2 issues:

- Oral contraceptive may confound the lomitapide PK parameters for Study AEGR-733-015 since oral contraceptives are weak CYP3A inhibitors per the draft drug interaction guidance and lomitapide is a CYP3A substrate.
- Study CV145-002 used the 50 mg (1 X 50 BMS) lomitapide formulation, whereas Study AEGR-733-015 used the 50 (2 X 5 and 2 X 20 AGER) mg lomitapide formulations. The 50 mg BMS formulation tends to yield higher lomitapide exposure than the 60 mg (3 X 20 AEGR) formulation as shown in Figures 24 and 25 despite the dose for the BMS formulation is 10 mg less than the AEGR formulation. Studies CV145-001, CV145-003, and CV145-005 examined the 50 (1 X 50) mg lomitapide dose. Studies AEGR-733-017, AEGR-733-018, and AEGR-733-021 examined the 60 (3 X 20) mg lomitapide dose. See Section 2.4.2.6 for Study AEGR-733-015's details.

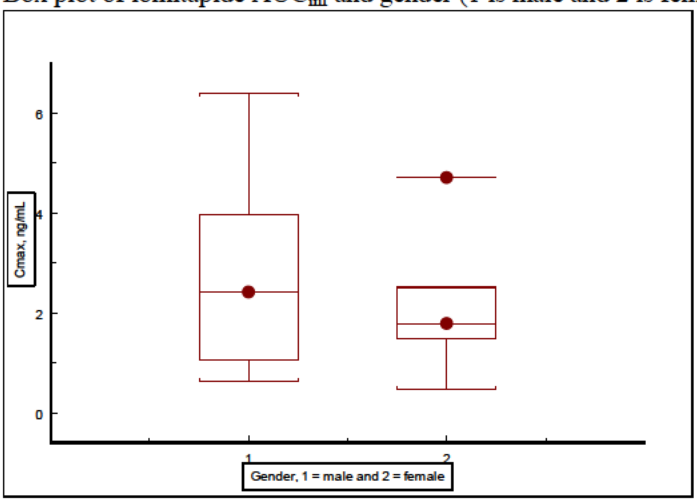
Figure 24 (left panel). Scattergram of lomitapide AUC_{inf} from BMS and Aegerion Phase 1 studies upon oral administration of lomitapide capsule. Figure 25 (right panel). Scattergram of lomitapide C_{max} from BMS and Aegerion Phase 1 studies upon oral administration of lomitapide capsule. Source: Module M2.7.2 Figures 4 and 5.

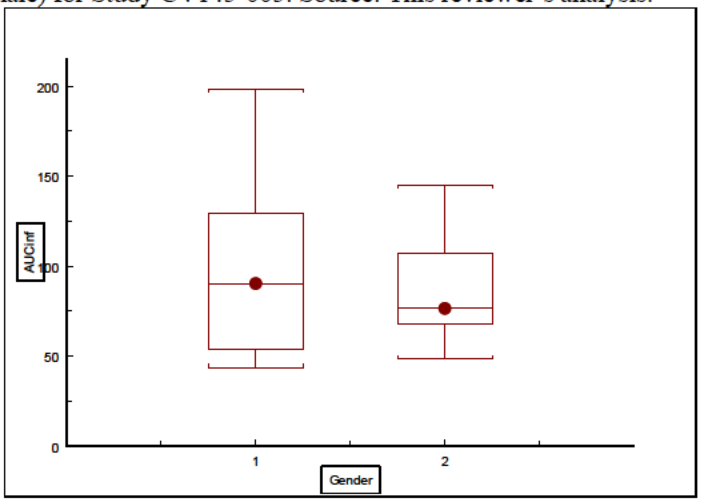


Both Studies CV145-010 and CV145-002 for the cross-study comparison of lomitapide PK between female and male, respectively, have the 10 mg and 25 mg lomitapide dose groups administered for 14 days. Both studies used the multiples of 5 mg lomitapide capsule to administer the 10 mg and 25 mg lomitapide daily doses. Since Studies CV145-010 and CV145-002 have the similar design and used the same formulation of lomitapide capsule, comparison of lomitapide PK results of these 2 studies are appropriate. There was no difference between female and male for the lomitapide C_{max} and AUC_{tau} at Day 14 for the 10 mg lomitapide dose group. Three of the 6 female participants had lomitapide C_{max} and AUC_{tau} values similar to those of the male. However, another 3 female participants have lomitapide C_{max} and AUC_{tau} values there were 2 – 3 times to those of the male.

Since the comparison of Studies CV145-010 and CV145-002 is cross-study in nature, this reviewer compared the female and male lomitapide C_{max} and AUC_{inf} values for the single dose of 50 mg lomitapide within Study CV145-005. Figures 26 and 27 show the box plots of the comparison between male and female of Study CV145-005. It seems that there is no difference between female and male lomitapide C_{max} and AUC_{inf} values.

Figure 26 (left panel) Box plot of lomitapide C_{max} and gender (1 is male and 2 is female) for Study CV145-005. Figure 27 (right panel) Box plot of lomitapide AUC_{inf} and gender (1 is male and 2 is female) for Study CV145-005. Source: This reviewer's analysis.





The assessment of gender effect on lomitapide PK is not conclusive via cross-study comparison and within study comparison. Thus, population PK analysis which will be submitted at a later time will be helpful to assess gender as a covariate of lomitapide PK.

2.3.4 What pharmacogenomic information is in the application?

Pharmacogenomic information is not available in this submission.

2.4 Extrinsic Factors

2.4.1 How does food affect lomitapide's bioavailability (BA)?

Study CV145-005 examined the effect of food on lomitapide bioavailability. This was a 3-treatment, 3-period, 6-sequence (4 randomized healthy volunteers each) crossover study. Each participant orally received a 50 mg lomitapide capsule after 1 of the following treatments in 3 different treatment periods:

- A: 10 hours overnight fast,
- B: completion of a low-fat breakfast, or
- C: completion of a high-fat breakfast

Each participant ate the breakfast in 15 minutes and then received the dose 5 minutes after the breakfast. Participants received each dose with 150 mL room temperature tap water and fasted for another 4 hours postdose.

Each low- and high-fat breakfast consisted of about 750 calories and contained about 9 and 37 g of fat, respectively. A washout of at least 7 days separated each dose. Serial plasma samples were collected predose and 120 hours postdose to determine lomitapide, M1, M2, and M3.

Figure 28. Mean plasma lomitapide concentration vs. time profiles.

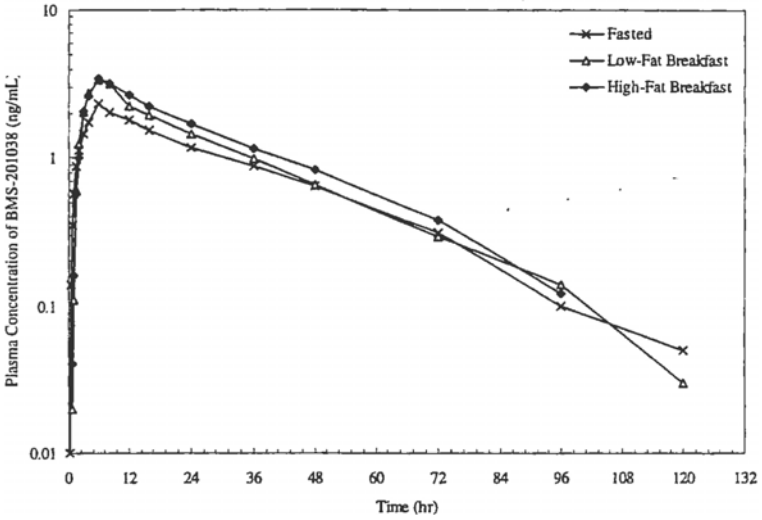


Table 18. Effect of high- and low-fat breakfast on lomitapide C_{max} and $AUC_{(0-t)}$. Source: Study CV145-005's report Table 11.6.1

		Geometric Means		Ratio of Means	
Treatment	Parameter	Test	Reference	Point Estimate	90% CI
High Fat vs. Fasted	C_{max} (ng/mL)	3.55	2.01	1.77	1.46 – 2.16
	$AUC_{(0-t)}$ (ng.h/mL)	94.27	59.82	1.58	1.33 – 1.87
Low Fat vs. Fasted	C_{max} (ng/mL)	3.40	2.01	1.70	1.39 – 2.07
	$AUC_{(0-t)}$ (ng.h/mL)	76.24	59.82	1.28	1.08 – 1.51
High Fat vs. Low Fat	C_{max} (ng/mL)	3.55	3.40	1.05	0.86 – 1.27
	$AUC_{(0-t)}$ (ng.h/mL)	94.27	76.24	1.24	1.04 – 1.46

After a high fat meal, lomitapide C_{max} and $AUC_{(0-t)}$ increased 77% and 58%, respectively, as compared to those under fasting. After a low fat meal, lomitapide C_{max} and $AUC_{(0-t)}$ increased 70% and 28%, respectively, as compared to those under fasting.

Study CV145-005 has the following issues:

- The sponsor did not study the 50 mg lomitapide capsule in the clinical efficacy and safety study and does not plan to market the 50 mg lomitapide capsules. The 50 mg lomitapide capsule is (b) (4) from the proposed to-be-marketed (b) (, 10, and 20 mg capsules (see Section 2.1.2).
- There is a significant period effect of all lomitapide PK parameters. However, the period effect is unlikely due to carryover of prior treatment because all the predose plasma lomitapide concentrations were zero and no statistically significant carryover effects for any of the PK parameters exist. Since the analysis of variance model for the calculation of the point estimate for the test/reference ratio and 90% confidence interval (CI) took into consideration for the period and carryover effects, the results for the point estimate and 90% CI appear valid.
- The high fat breakfast is slightly different from that of the food effect guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070241.pdf). See Table 19 for the difference between the tested high fat breakfast and the food effect guidance's recommended high fat meal. The fat content is 37 g for the tested breakfast, whereas the food effect guidance recommends 500 – 600 calories. One gram of fat would generate 9 calories. Thus the test high fat meal would yield 333 calories, which is lower than the recommendation of the food effect guidance.

Table 19. Comparison of the tested high fat meal and recommended high fat meal. Source: Study CV145-005's report Section 5.8.2 and food effect guidance

Study CV145-005	Food Effect Guidance
2 scrambled eggs	2 eggs fried in butter
2 stripes of bacon	2 strips of bacon
2 slices of toasted white bread	2 slices of toast with butter
4 ounces of has brown	4 ounces of hash brown
8 ounces of whole milk	8 ounces of whole milk

The sponsor proposed the following labeling statements pertaining to administration of lomitapide:

(b) (4)

GI events were the commonest adverse events upon administering with the high-fat breakfast. The extent of reported GI events were 33%, 36%, and 67% for participants who fasted, received a low-fat breakfast, and received a high-fat breakfast, respectively (Table 20).

Table 20. Gastrointestinal adverse events of Study CV145-005. Source: Study CV145-005's report Appendix 12.1.3

Primary Term	Fasted (n=24)	Low-fat (n=25)	High-fat (n=24)
Abdominal pain	2 (8%)	1 (4%)	2 (8%)
Decreased appetite	0	0	1 (4%)
Dental abnormal	0	0	1 (4%)
Diarrhea	2 (8%)	5 (20%)	12 (50%)
Distention abdomen	0	2 (8%)	1 (4%)
Dry mouth	1 (4%)	0	0
Dyspepsia/heartburn	2 (8%)	1 (4%)	2 (8%)
Epigastric pain	0	0	1 (4%)
Flatulence	2 (8%)	4 (16%)	4 (17%)
Nausea/vomiting	3 (13%)	1 (4%)	10 (42%)
Total Events	12	14	34
Total Participants	8 (33%)	9 (36%)	16 (67%)

The pivotal Phase 3 study's (UP1002/AEGR-733-005) protocol did not specify when the participants should receive lomitapide and with regard to meals. In the September 7, 2012 response to an FDA Information Request, the sponsor stated that participants in the pivotal study were advised to take the drug in the evening at least 2 hours after dinner; this instruction was provided with guidelines to each participant at the start of the study. Per the pivotal study's PK concentration dataset, which includes time-of-last-dose prior to each clinic visit, approximately 80% of records (excluding observations with missing time of last dose) indicated that the study drug was taken between 6 PM and 11 M. Per these data, lomitapide should be taken at least 2 hours after dinner in the evening.

2.4.2 What are the potential drug-drug interactions for lomitapide?

Coadministered drugs' effect on lomitapide PK:

2.4.2.1 Ketoconazole

Study AEGR-733-018 examined the effect of multiple dose ketoconazole on the single dose of lomitapide in 30 healthy men and women. All participants received the following:

- 60 mg lomitapide (3 X 20 mg capsules) on Day 1
- 200 mg ketoconazole every 12 hours (BID) on Days 7 – 9
- 200 mg ketoconazole BID and 60 mg lomitapide on Day 10
- 200 mg ketoconazole BID on Days 11 – 15

Doses of lomitapide (Days 1 and 10) were preceded by an overnight fast (8 hours). Morning doses of ketoconazole on Days 7 – 9 and Days 11 – 15 were preceded by an overnight fast. Serial plasma samples were collected predose and 196 hours postdose to determine lomitapide via validated LC/MS/MS assays.

Figure 29. Geometric mean plasma lomitapide concentrations following single oral doses of 60 mg lomitapide on Day 1 and 60 mg lomitapide co-administered with 200 mg bid ketoconazole on Day 10. Source: Study AEGR-733-018's report Figure 11-1

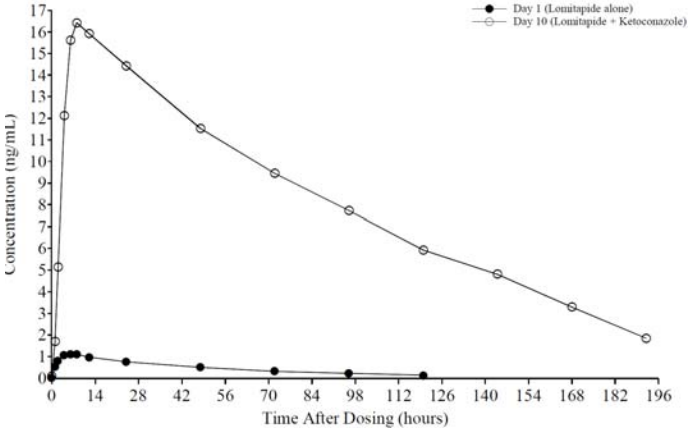


Table 21. Comparison of lomitapide PK parameters between the presence and absence of ketoconazole. Source: Study AEGR-733-018's report Table 11-2

Parameter	N	Test Mean (Combination)	N	Reference Mean (Lomitapide)	Test/Reference (%)	90% Confidence Interval (%)
C_{max} (ng/mL)	28	18.2	30	1.23	1482	(1293 , 1698)
AUC_{0-t} (ng·hr/mL)	28	1566	30	56.8	2757	(2430 , 3128)
AUC_{inf} (ng·hr/mL)	28	1772	30	65.0	2725	(2380, 3119)

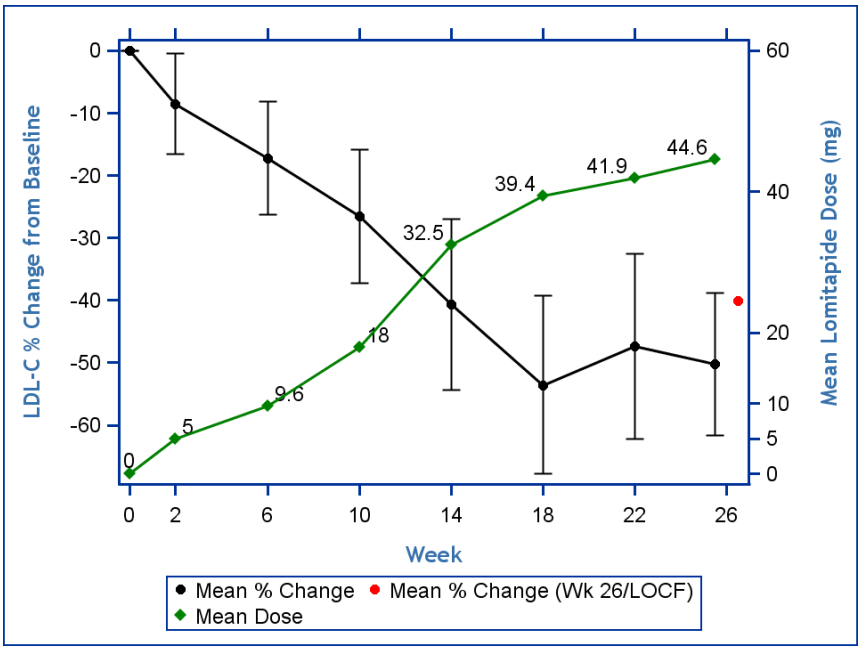
Lomitapide AUC_{inf} and C_{max} increased 2625% and 1382%, respectively, in the presence of ketoconazole. Per the lomitpapide exposure increase, concomitant administration of lomitapide with strong CYP3A inhibitors should be contraindicated since the clinical data do not cover this much of lomitapide exposure increase. Ketoconazole is a strong CYP3A inhibitor per the draft drug interaction guidance. Concomitant use of moderate CYP3A inhibitors with lomitapide should be avoided since such use has not been studied.

The sponsor did not conduct any study to assess the concomitant administration of lomitapide with weak CYP 3A inhibitors. This reviewer used the cross-study comparison approach to assess the effect of weak CYP3A inhibitors on lomitapide exposure at steady state since oral contraceptives are in vivo weak CYP3A inhibitors per the draft drug interaction guidance. The mean lomitapide AUC_{0-t} is 98 ng·hr/mL upon daily dosing of 50 mg lomitapide in the presence of oral contraceptives (Study AEGR-733-015's report Page 45 of 316). Since the last quantifiable concentration is at 24 hours, the mean lomitapide AUC_{tau} is 98 ng·hr/mL upon daily dosing to steady state at Day 21. To correct for the dose difference, the mean lomitapide AUC_{tau} will be 117.6 (98 X 60/50) ng·hr/mL for a 60 mg lomitapide daily dose at Day 21. Since a drug's AUC_{0-inf} after a single dose can be used to approximate a drug's AUC_{tau} at steady state when the drug shows linear PK, the mean lomitapide AUC_{0-inf} of healthy volunteers in the hepatic impairment study (AEGR-733-017) and renal impairment study (AEGR-733-021) can be used to approximate the mean lomitapide AUC_{tau} if these healthy volunteers were to take 60 mg lomitapide to steady state at Day 21. Studies AEGR-733-015, AEGR-733-017, and AEGR-733-021 used the to-be-marketed 5 and 20 mg lomitapide capsules; thus, formulation effect is minimized. The mean lomitapide AUC_{0-inf} for the healthy volunteers in the hepatic impairment study is 74.3 ng·hr/mL and 92.9 ng·hr/mL upon a single oral dose of 60 mg lomitapide (Study AEGR-733-017's report Page 45 of 313). The mean lomitapide AUC_{0-inf} for the healthy volunteers in the renal impairment study is 52.68 ng·hr/mL upon a single oral dose of 60 mg lomitapide (Study AEGR-733-021's report Page 65). The ratio of lomitapide AUC_{tau}

to lomitapide $AUC_{0\text{-}inf}$ is 1.27 (117.6/92.9), 1.58 (117.6/74.3), and 2.23 (117.6/52.7). Thus, lomitapide exposure increased about 2-fold in the presence of oral contraceptive.

To err on the side of being conservative to account for other in vivo weak CYP3A inhibitors that may have more CYP3A inhibitory effect than oral contraceptives, this reviewer recommends the maximum dose of lomitapide should be 30 mg daily when concomitantly administered with weak CYP3A inhibitors. The mean lomitapide dose of 30 mg daily would result in about 40% decrease of LDL-C from baseline (See Figure 30). No severe adverse events occurred upon multiple-dosing in Study AEGR-733-015 and nausea incidence is higher for the lomitapide with oral contraceptive dosing (11.1%) than the placebo with oral contraceptive dosing (3.8%).

Figure 30. LDL-C lowering for lomitapide in the pivotal clinical trail. Source: FDA presentation slide #19 for the lomitapide advisory committee meeting.



2.4.2.2 Grapefruit Juice

The sponsor did not conduct any study to evaluate the interaction between grapefruit juice. The draft drug interaction guidance classifies grapefruit juice as moderate CYP3A inhibitor and even strong CYP3A inhibitor for certain preparation (double strength). Thus, the concomitant use of grapefruit juice and lomitapide should be contraindicated.

2.4.2.3 Acid-reducing Agents

Clinically used acid-reducing agents include proton pump inhibitor (PPI), H_2-receptor antagonist, and antiacid. This reviewer only discusses PPI since it is the most potent agent and has the longest duration of action for acid lowering effect.

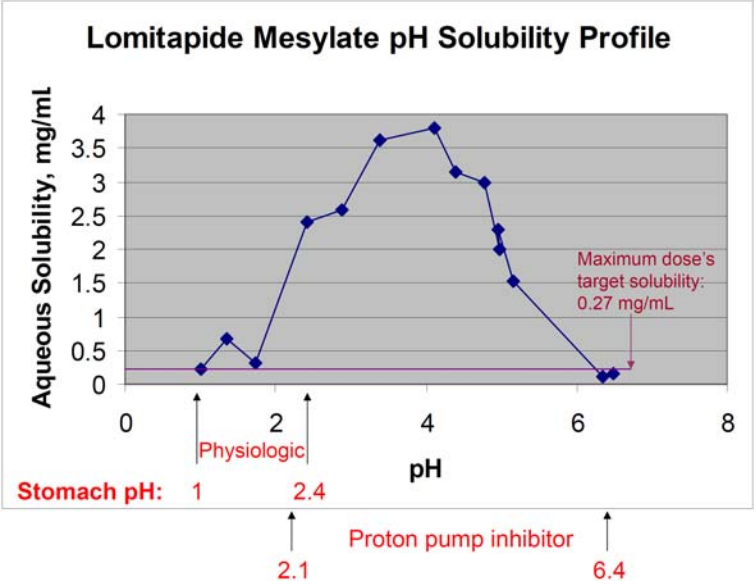
Lomitapide is a basic drug and lomitapide mesylate shows pH-dependent solubility. There may be a potential on the interaction of lomitapide absorption between PPI and lomitapide as PPI raises the stomach pH that can affect lomitapide mesylate solubility and in turn affects lomitapide exposure. Budha et al. suggested the following 2 criteria for a basic drug that the impact of pH on drug exposure is most prominent when (*Clin Pharmacol Ther* 2012;92:203-13):

- A drug shows exponentially **de**creasing solubility in the pH range 1 – 4.
- The drug's maximum dose strength is not soluble in 250 mL of water at pH above stomach pH.

Lomitapide mesylate's solubility is exponentially **in**creasing in the pH range 1 – 4. Lomitapide mesylate's **maximum dose strength** solubility needs to be 0.091 mg/mL (22.77/250) and, thus, lomitapide mesylate will

be soluble from pH 1 – 6.48 per the lomitapide mesylate pH-solubility profile. See Figure 31, which shows lomitapide mesylate's solubility, physiologic stomach pH, and stomach pH upon PPI administration.

Figure 31. Lomitapide mesylate solubility and the ranges of stomach pH under physiologic condition and upon PPI administration
Source: This reviewer's analysis



This reviewer took a more conservative approach and determined that lomitapide mesylate's **maximum dose** solubility needs to be 0.273 mg/mL (3 x 22.77/250). With this target solubility, lomitapide mesylate will be soluble from between pH 1 and pH 1.35 to about pH 6 per the lomitapide mesylate pH-solubility profile. The physiologic stomach pH range is 1 – 2.4 (Evans et al. *Gut* 1988;29:1035-41). The median 24 h stomach pH upon PPI administration ranges from 2.1 – 6.4, which depends on the particular PPI and dosing regimen (Stedman & Barclay *Aliment Pharmacol Ther* 2000;14:963-78). PPIs rarely raise stomach pH to > 6. Thus, the effect of stomach acid lowering by PPI on lomitapide exposure may be minimal.

Lomitapide's effect on coadministered drugs' PK:

2.4.2.4 Atorvastatin, Rousuvastatin, Simvastatin, Fenofibrate, Ezetimibe, Niacin, and Dextromethorphan.

Study AEGR-733-002 assessed the PK interaction of 10 and 60 mg lomitapide on 6 lipid-lowering drugs and dextromethorphan in 129 healthy participants. Each participant belonged to 1 of the following 9 dose groups:

- A: 20 mg atorvastatin with 10 mg lomitapide (15 participants)
- B: 20 mg simvastatin with 10 mg lomitapide (15 participants)
- C: 10 mg ezetimibe with 10 mg lomitapide (10 participants)
- D: 20 mg rosuvastatin with 10 mg lomitapide (10 participants)
- E: 145 mg micronized fenofibrate with 10 mg lomitapide (10 participants)
- F: 20 mg atorvastatin with 60 mg lomitapide (15 participants)
- G: 20 mg rosuvastatin with 60 mg lomitapide (18 participants)
- H: 30 mg dextromethorphan with 60 mg lomitapide (15 participants)
- I: 1000 mg extended-release (ER) niacin with 10 mg lomitapide (20 participants)

Each participant orally received 1 of the 7 drugs (besides lomitapide) on Day 1. Prior to discharge on Day 2, participants received a lomitapide dose. On Days 3 – 7, each participant orally received the assigned lomitapide dose (10 or 60 mg) once daily. On Day 8, each participant received the 2nd oral dose of the same drug that they received on the Day 1 and the last lomitapide dose. Serial plasma samples were collected to predose and 24 hours postdose to determine the plasma drug and metabolites concentrations from Dose Groups A thru G and I on Day 1 and Day 8 via validated assays. Urine samples were collected predose and for 8 hours post dose for

Dose Group H to determine dextromethorphan and dextorphan via validated assays. Urine samples were collected predose predose and at 6 hours intervals postdose to 24 hours to determine nicotinic acid and metabolites via validated assays.

Atorvastatin

Figure 32 (left panel). Mean plasma atorvastatin concentration- time profile for Dose Group A. Figure 33 (right panel). Mean plasma 2-hydroxy atorvastatin concentration- time profile for Dose Group A. Source: Study AEGR-733-002' report Figure 11.4.1.1:1 and 11.4.1.1:2

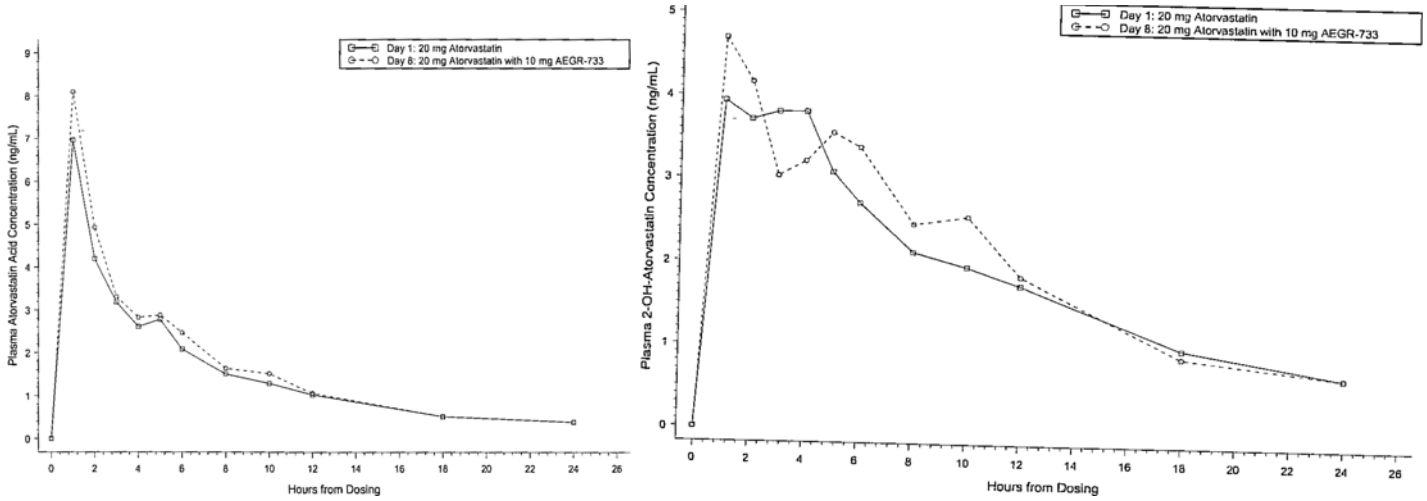


Figure 34. Mean plasma 4-hydroxy atorvastatin concentration- time profile for Dose Group A. Source: Study AEGR-733-002' report Figure 11.4.1.1:3

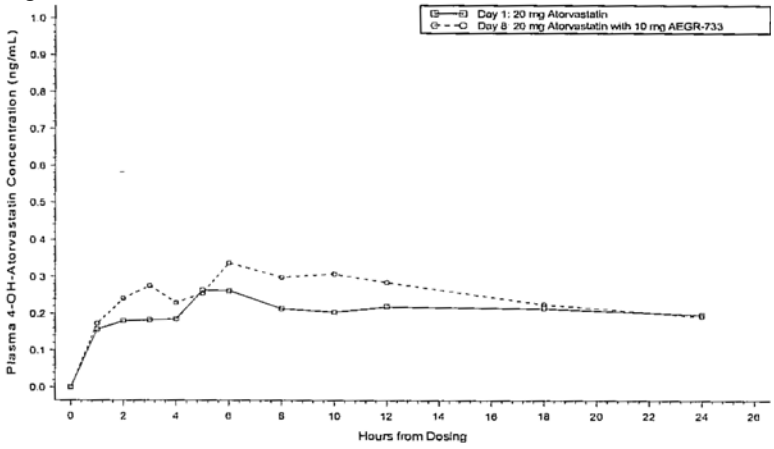


Table 22. Comparison of atorvastatin and metabolites PK parameters in the presence and absence of lomitapide for Group A. Source: Study AEGR-733-002' report Tables 11.4.1.1:1, 11.4.1.1:2, and 11.4.1.1:3

	Atorvastatin			2-OH Atorvastatin			4-OH Atorvastatin		
	Day 8	Day 1	Day 8/Day1 (90% CI)	Day 8	Day 1	Day 8/Day1 (90% CI)	Day 8	Day 1	Day 8/Day1 (90% CI)
Parameters	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
C_{max} (ng/mL)	8.24 (4.43)	6.96 (3.7)	119.2 (99.89, 142.2)	5.87 (5.57)	5.1 (3.29)	101.6 (76.13, 135.5)	0.383 (0.323)	0.341 (0.24)	97.43 (75.94, 125.02)
AUC_{0-t} (ng·hr/mL)	40.43 (20.44)	36.75 (19.36)	110.97 (98.42, 125.1)	48.57 (28.69)	45.41 (19.61)	100.8 (87.27, 116.43)	4.77 (4.26)	3.757 (3.279)	140.76 (106.28, 186.43)

Figure 35 (left panel). Mean plasma atorvastatin concentration- time profile for Dose Group F. Figure 36 (right panel). Mean plasma 2-hydroxy atorvastatin concentration- time profile for Dose Group F. Source: Study AEGR-733-002' report Figure 11.4.1.2:1 and 11.4.1.2:2

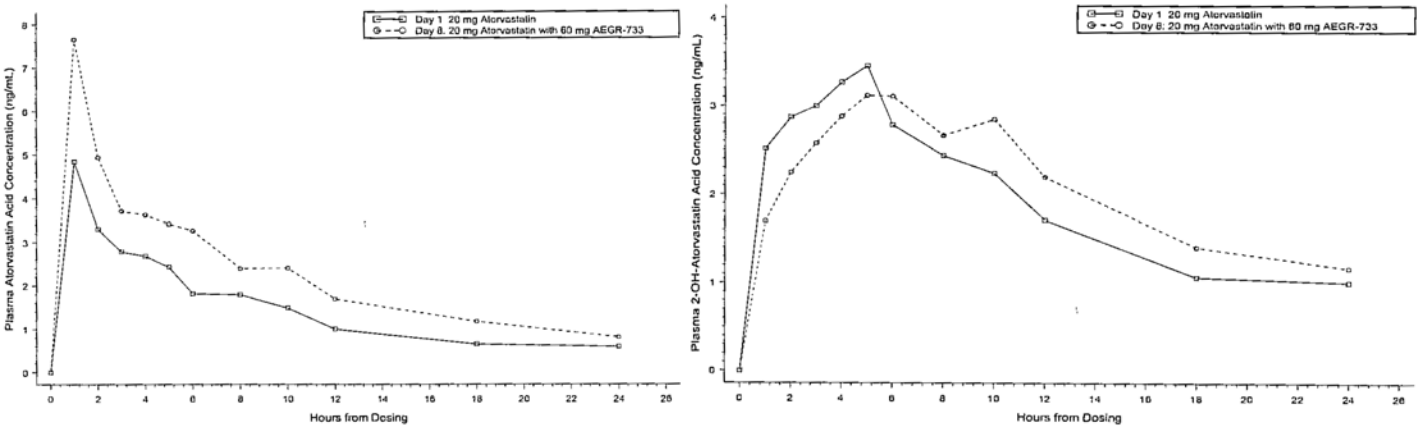
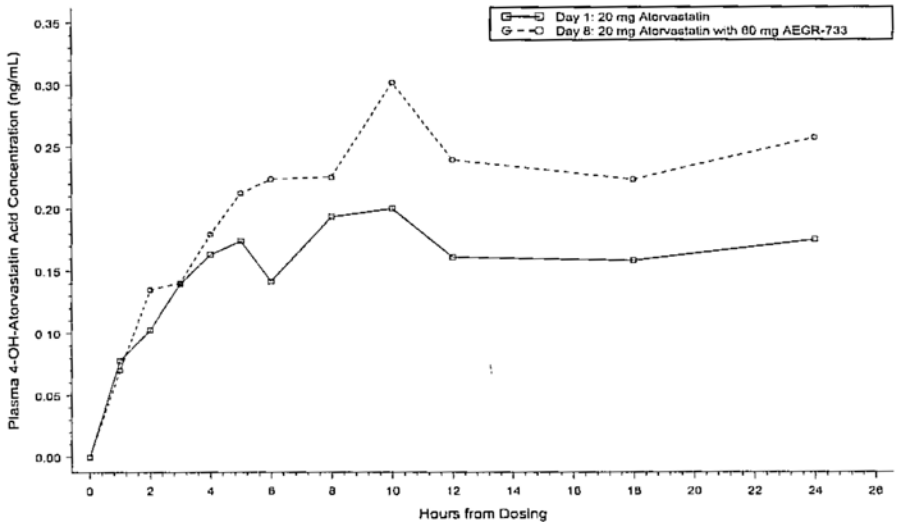


Figure 37. Mean plasma 4-hydroxy atorvastatin concentration- time profile for Dose Group F. Source: Study AEGR-733-002' report Figure 11.4.1.2:3



Best Available Copy

Table 23. Comparison of atorvastatin and metabolites PK parameters in the presence and absence of lomitapide for Group F. Source: Study AEGR-733-002' report Tables 11.4.1.2:1, 11.4.1.2:2, and 11.4.1.2:3

	Atorvastatin			2-OH Atorvastatin			4-OH Atorvastatin		
	Day 8	Day 1	Day 8/Day1 (90% CI)	Day 8	Day 1	Day 8/Day1 (90% CI)	Day 8	Day 1	Day 8/Day1 (90% CI)
Parameters	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
C_{max} (ng/mL)	8.07 (3.73)	4.84 (2.14)	163.2 (134.5, 198.2)	4.02 (1.81)	3.87 (1.68)	101.4 (86.12, 119.4)	0.34 (0.136)	0.237 (0.12)	138.5 (116.7, 164.32)
AUC_{0-t} (ng·hr/mL)	54.09 (26.31)	34.97 (16.43)	152.32 (133.8, 173.5)	48.9 (20.11)	44.8 (16.7)	107.3 (97.2, 118.4)	4.91 (2.55)	3.51 (1.853)	149.1 (106.7, 208.2)

Atorvastatin C_{max} and AUC_{0-t} increased 63% and 52%, respectively, and 4-hydroxy atorvastatin C_{max} and AUC_{0-t} increased 38% and 49%, respectively, in the presence of 60 mg lomitapide. There is no need to adjust the atorvastatin dose with concomitant use of lomitapide since diltiazem increased atorvastatin AUC 51% and the atorvastatin label does not recommend atorvastatin dose adjustment.

Rosuvastatin

Figure 38 (left panel). Mean plasma rosuvastatin concentration-time profile for Dose Group D. Figure 39 (right panel). Mean plasma rosuvastatin concentration-time profile for Dose Group G. Source: Study AEGR-733-002' report Figure 11.4.1.5:1 and 11.4.1.5:2

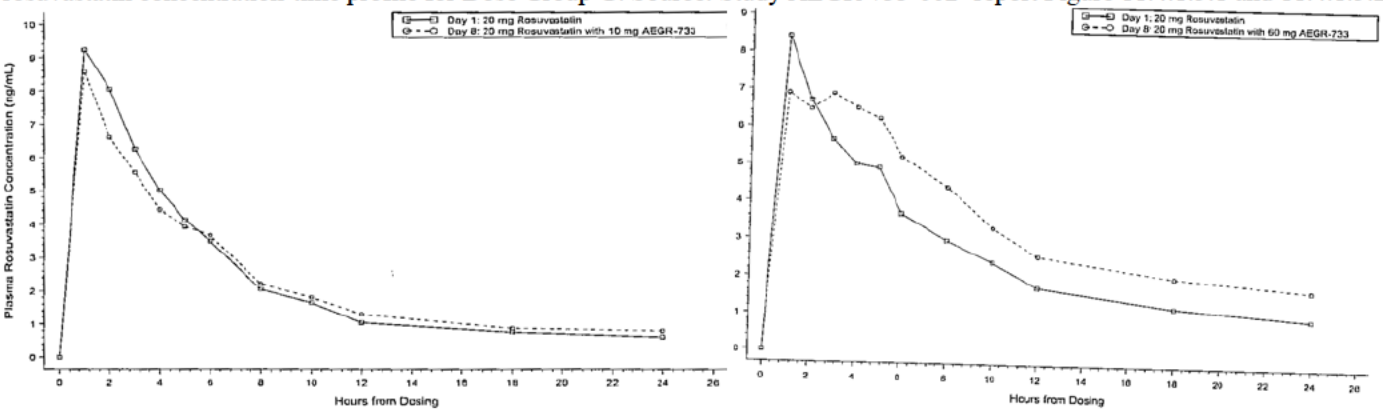


Table 24. Comparison of rosuvastatin PK parameters in the presence and absence of lomitapide for Groups D and G. Source: Study AEGR-733-002' report Tables 11.4.1.5:1, 11.4.1.2:2, and 11.4.1.5:2

	Rosuvastatin, Group D			Rosuvastatin, Group G		
	Day 8	Day 1	Day 8/Day1 (90% CI)	Day 8	Day 1	Day 8/Day1 (90% CI)
Parameters						
C_{max} (ng/mL)	8.91 (7.03)	9.32 (10.6)	106.13 (76.0, 148.2)	9.06 (6.52)	8.94 (6.47)	103.8 (81.57, 132.1)
AUC_{0-t} (ng·hr/mL)	55.42 (39.34)	55.14 (43.45)	102.1 (86.0, 121.1)	84.68 (35.83)	64.85 (31.46)	132.2 (111.6, 156.7)

Rosuvastatin C_{max} and AUC_{0-t} increased 4% and 32%, respectively, in the presence of 60 mg lomitapide. The approved maximum daily rosuvastatin dose is 40 mg. There is no need to adjust the rosuvastatin dose with concomitant use of lomitapide since tipranavir/ritonavir increased rosuvastatin AUC and C_{max} 26% and 100%, respectively, the rosuvastatin label does not recommend rosuvastatin dose adjustment.

Simvastatin

Figure 40 (left panel). Mean plasma simvastatin concentration- time profile for Dose Group B. Figure 41 (right panel). Mean plasma simvastatin acid concentration- time profile for Dose Group B. Source: Study AEGR-733-002' report Figure 11.4.1.3:2 and 11.4.1.3:1

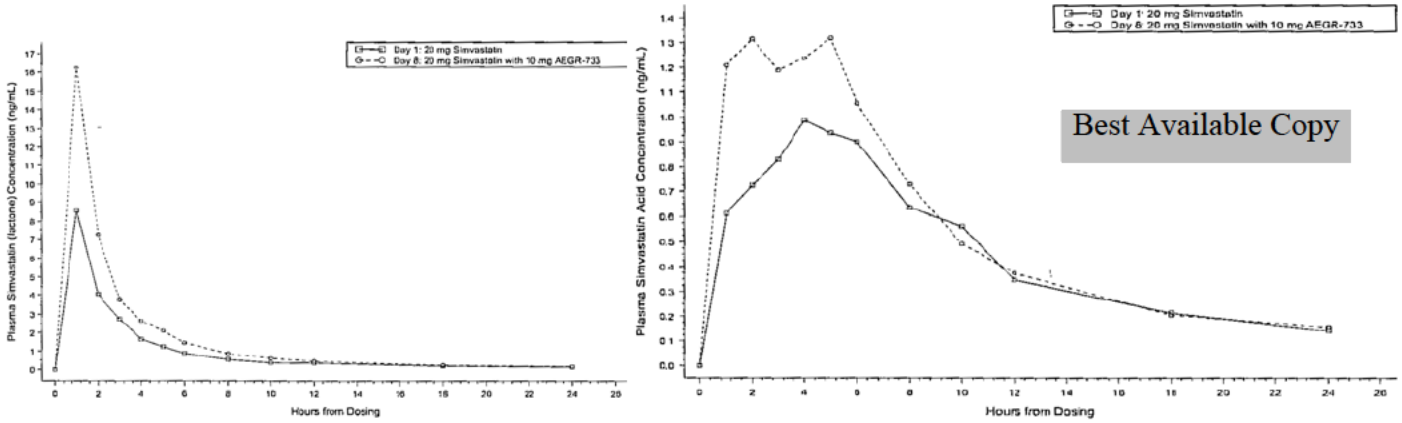


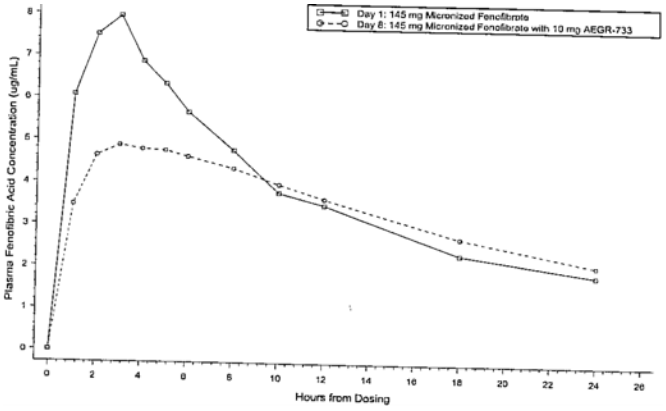
Table 25. Comparison of simvastatin and simvastatin acid PK parameters in the presence and absence of lomitapide for Groups B. Source: Study AEGR-733-002' report Tables 11.4.1.3:2 and 11.4.1.3:1

	Simvastatin			Simvastatin Acid		
	Day 8	Day 1	Day 8/Day1 (90% CI)	Day 8	Day 1	Day 8/Day1 (90% CI)
Parameters						
C_{max} (ng/mL)	16.4 (17.1)	9.14 (8.51)	165.15 (136.7, 199.6)	1.62 (1.24)	1.27 (1.01)	134.95 (111.3, 163.6)
AUC_{0-t} (ng·hr/mL)	38.74 (42.88)	22.36 (20.41)	162.3 (143.2, 183.9)	11.82 (10.35)	8.73 (6.55)	138.8 (109.7, 175.6)

Simvastatin C_{max} and AUC_{0-t} increased 65% and 62%, respectively, in the presence of 60 mg lomitapide. Simvastatin acid C_{max} and AUC_{0-t} increased 35% and 39%, respectively, in the presence of 60 mg lomitapide. See Section 2.4.2.5 for further discussion.

Fenofibrate

Figure 42. Mean plasma fenofibric acid concentration- time profile for Dose Group E. Source: Study AEGR-733-002' report Figure 11.4.1.6:1



Best Available Copy

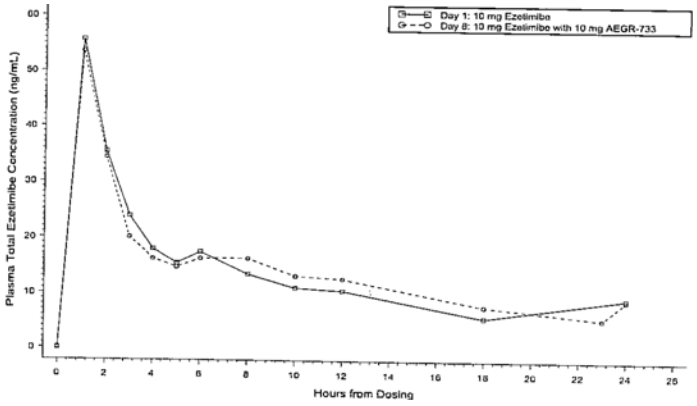
Table 26. Comparison fenofibric acid PK parameters in the presence and absence of lomitapide for Groups E. Source: Study AEGR-733-002' report Table 11.4.1.6:1

	Fenofibric Acid		
	Day 8	Day 1	Day 8/Day1 (90% CI)
Parameters			
C_{max} (ng/mL)	6.05 (1.17)	8.6 (1.97)	70.64 (59.64, 83.65)
AUC_{0-t} (ng·hr/mL)	83.11 (13.53)	93.95 (22.3)	89.62 (82.76, 97.04)

Fenofibric acid C_{max} and AUC_{0-t} decreased 29% and 10%, respectively, in the presence of 10 mg lomitapide.

Ezetimibe

Figure 43 (left panel). Mean plasma total ezetimibe concentration- time profile for Dose Group C. Figure 44 (right panel). Mean plasma unconjugated ezetimibe concentration- time profile for Dose Group C. Source: Study AEGR-733-002' report Figure 11.4.1.4:1 and 11.4.1.4:2



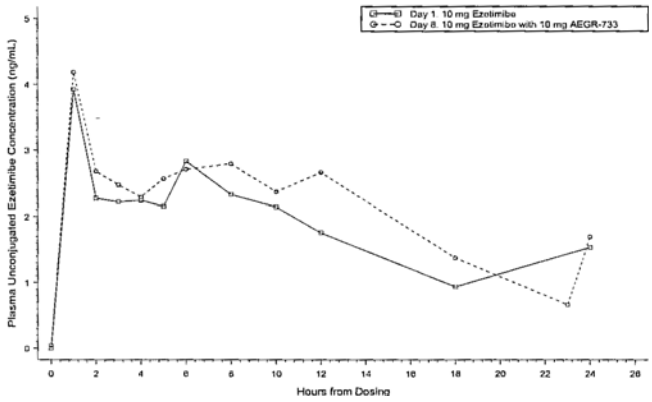
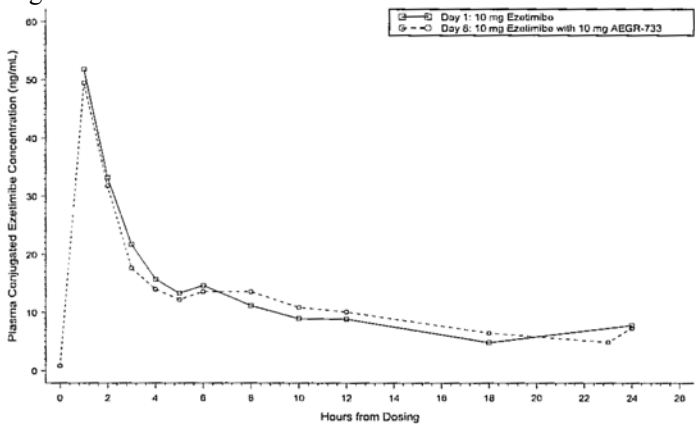


Figure 45. Mean plasma conjugated ezetimibe concentration- time profile for Dose Group C. Source: Study AEGR-733-002' report Figure 11.4.1.4:3



Best Available Copy

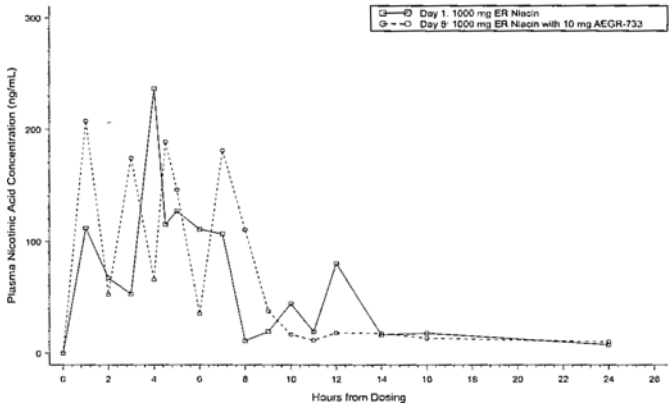
Table 27. Comparison of ezetimibe and metabolites PK parameters in the presence and absence of lomitapide for Group C. Source: Study AEGR-733-002' report Tables 11.4.1.4:1, 11.4.1.4:2, and 11.4.1.4:3

	Total Ezetimibe			Unconjugated Ezetimibe			Conjugated Ezetimibe		
	Day 8	Day 1	Day 8/Day1 (90% CI)	Day 8	Day 1	Day 8/Day1 (90% CI)	Day 8	Day 1	Day 8/Day1 (90% CI)
Parameters	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)	
C_{max} (ng/mL)	61.4 (21.3)	60.7 (21.8)	102.7 (74.1, 142.34)	5.813 (2.49)	4.82 (3.22)	107.78 (75.85, 153.14)	56.63 (20.0)	56.3 (19.8)	102.74 (73.45, 143.72)
AUC_{0-t} (ng·hr/mL)	347.7 (118.4)	327.9 (115.1)	105.71 (92.62, 120.66)	52.51 (23.9) (28.69)	43.12 (18.73)	118.33 (95.9, 146.01)	295.2 (106.5)	284.8 (112.2)	104.08 (92.26, 117.43)

Total ezetimibe C_{max} and AUC_{0-t} increased 2% and 5%, respectively, in the presence of 10 mg lomitapide. Unconjugated ezetimibe C_{max} and AUC_{0-t} increased 8% and 18%, respectively, in the presence of 10 mg lomitapide. Conjugated ezetimibe C_{max} and AUC_{0-t} increased 2% and 4%, respectively, in the presence of 10 mg lomitapide.

Niacin

Figure 46 (left panel). Mean plasma nicotinic acid concentration- time profile for Dose Group I. Figure 47 (right panel). Mean plasma nicotinuric acid concentration- time profile for Dose Group I. Source: Study AEGR-733-002' report Figure 11.4.1.8:1 and 11.4.1.8:2



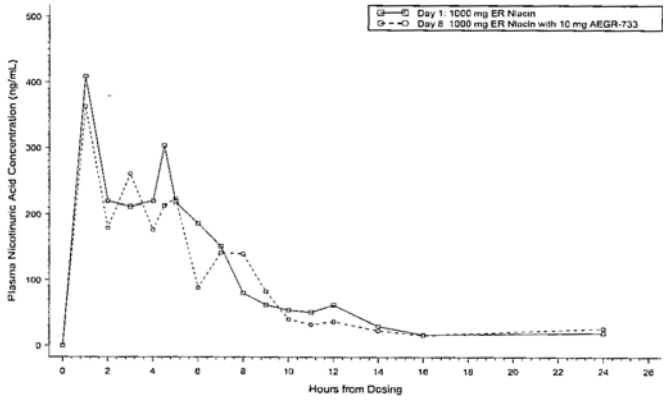


Table 28. Comparison of nicotinic acid and nicotinuric acid PK parameters in the presence and absence of lomitapide for Groups I. Source: Study AEGR-733-002' report Tables 11.4.1.8:1 and 11.4.1.8:2

	Nicotinic Acid			Nicotinuric Acid		
	Day 8	Day 1	Day 8/Day1 (90% CI)	Day 8	Day 1	Day 8/Day1 (90% CI)
Parameters						
C_{max} (ng/mL)	637 (686)	482 (477)	111.24 (61.17, 202.29)	637 (364)	700 (312)	85.04 (65.06, 111.16)
AUC_{0-t} (ng·hr/mL)	1091 (1218)	877.1 (750.5)	110.22 (78.2, 155.18)	1781 (1252)	1993 (940.9)	79.15 (59.82, 104.72)

Nicotinic acid C_{max} and AUC_{0-t} increased 11% and 10%, respectively, in the presence of 10 mg lomitapide. Nicotinuric acid C_{max} and AUC_{0-t} decreased 15% and 21%, respectively, in the presence of 10 mg lomitapide.

Figure 48 (left panel). Mean plasma N-methyl-2Pyridone-5-carboxamide (2PY) concentration- time profile for Dose Group I. Figure 49 (right panel). Mean plasma N-methylnicotinamide (MNA) concentration- time profile for Dose Group I. Source: Study AEGR-733-002' report Figure 11.4.1.8:3 and 11.4.1.8:4

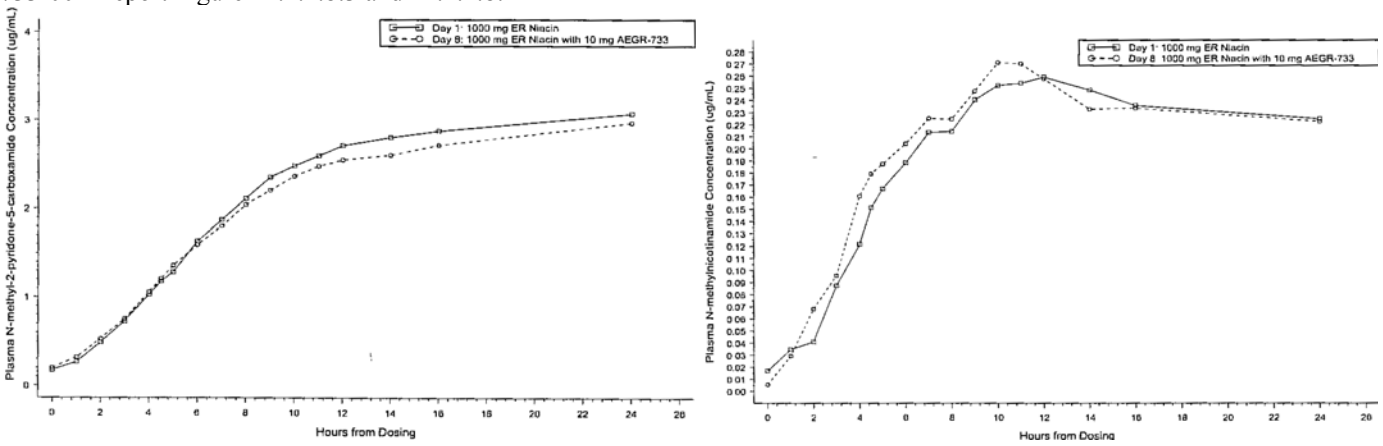


Table 29. Comparison of 2PY and MNA PK parameters in the presence and absence of lomitapide for Groups I. Source: Study AEGR-733-002' report Tables 11.4.1.8:1 and 11.4.1.8:2

	N-methyl-2Pyridone-5-carboxamide (2PY)			N-methylnicotinamide (MNA)		
	Day 8	Day 1	Day 8/Day1 (90% CI)	Day 8	Day 1	Day 8/Day1 (90% CI)
Parameters						
C_{max} (ng/mL)	3.2 (0.87)	3.28 (0.967)	98.28 (88.28, 109.42)	0.307 (0.176)	2.88 (0.154)	105.01 (92.9, 118.69)
AUC_{0-t} (ng·hr/mL)	51.12 (13.28)	53.27 (13.2)	96.1 (86.51, 106.76)	4.736 (2.425)	4.001 (2.644)	135.84 (110.52, 166.97)

2 PY C_{max} and AUC_{0-t} decreased 2% and 4%, respectively, in the presence of 10 mg lomitapide. MNA C_{max} and AUC_{0-t} increased 5% and 35%, respectively, in the presence of 10 mg lomitapide.

Table 30. Summary of 24-hour urinary excretion of NA and metabolites. Source: AEGR-733-002' report Tables 11.4.1.9:1

	Ae_{0-24} (mg)		
	Day 8	Day 1	
Analyte	Mean ± SD (N)	Mean ± SD (N)	p-value
NA	5.13 ± 5.13	4.74 ± 4.19	0.8154
	(20)	(20)	
NUA	53.81 ± 53.81	61.98 ± 23.72	0.3100
	(20)	(20)	
2PY	208.27 ± 208.27	214.05 ± 67.25	0.7327
	(20)	(20)	
MNA	119.10 ± 119.10	94.25 ± 41.06	0.1647
	(20)	(20)	

Urinary excretion of NA and its metabolites did not show significant difference between Day 8 and Day 1 in the presence of 10 mg lomitapide.

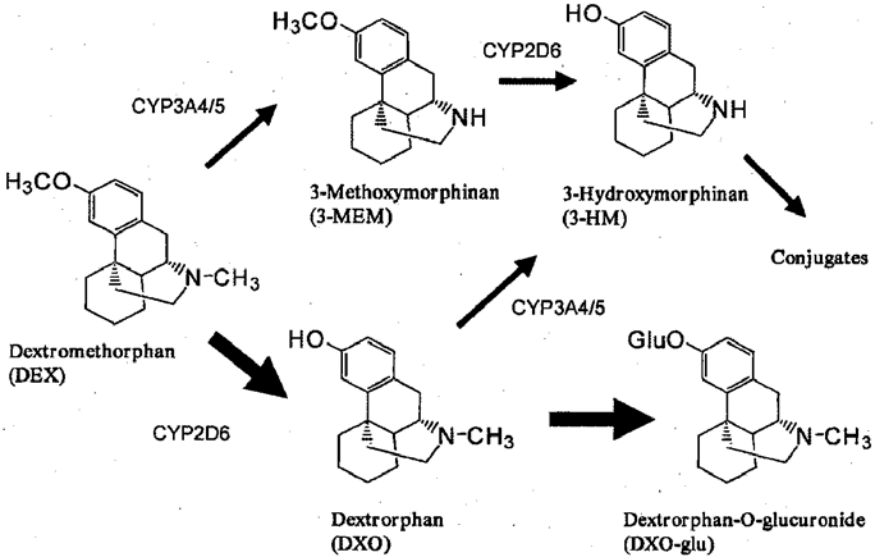
Dextromethorphan

The mean (SD) urinary dextromethorphan to dextrorphan ratio is 0.055 (0.071) and 0.076 (0.120) on Day 1 and Day 8, respectively. The paired t-test yielded a p-value of 0.2093 for the comparison of ratios between Day 1 and Day 8. Thus, there is no significant difference for urinary dextromethorphan to dextrorphan ratios between Day 1 and Day 8. Interpretation of urinary dextromethorphan to dextrorphan ratio is difficult because:

- CYP3A4 also contributes to the metabolism of dextromethorphan besides CYP2D6. Figure 50 shows the interconnections of dextromethorphan metabolic pathways via CYPs 2D6 and 3A4.
- Urinary drug exposures are more variable than plasma drug exposures. The changes in urinary drug ratios are hard to relate to the actual fold change in enzyme activities.
- The ratio needs the assumption that renal clearances of dextromethorphan and dextrorphan are unchanged in the presence and absence of lomitapide (no implication that lomitapide will alter the renal clearances of dextromethorphan and dextrorphan).

Thus, the lack of a difference for urinary dextromethorphan to dextrorphan ratios between Day 1 and Day 8 may not substantiate that lomitapide does not have impact on CYP2D6. Anyhow, the in vitro Study AEGR-733PC-007 showed that lomitapide is not a CYP2D6 inhibitor. Thus, no further in vivo study is necessary per the draft drug interaction guidance.

Figure 50. Metabolic pathways of dextromethorphan in humans [Takasima et al. *Drug Metab Pharmacokinet* 2005;20:177-82].



Per the urinary dextromethorphan to dextrorphan ratio on Day 1, all 12 participants are extensive CYP2D6 metabolizers since all of their ratios are < 0.3 (Gupta et al. *J Clin Pharmacol* 2004;44:1252-9). The urinary dextromethorphan to dextrorphan ratio is appropriate for the screening of polymorphic CYP2D6 phenotype since CYP3A4 is not polymorphic.

It is unclear the dosage form of dextromethorphan used in Study AEGR-773-002. Study AEGR-773-002's report on Page 6 states that "Dose Group H: 30 mg/**15 mL** Dextromethorphan **tablets**" and on Page 48 (Table 9.4.2) "Dextromethorphan 30 mg/**15 mg tablets**."

2.4.2.5 Simvastatin

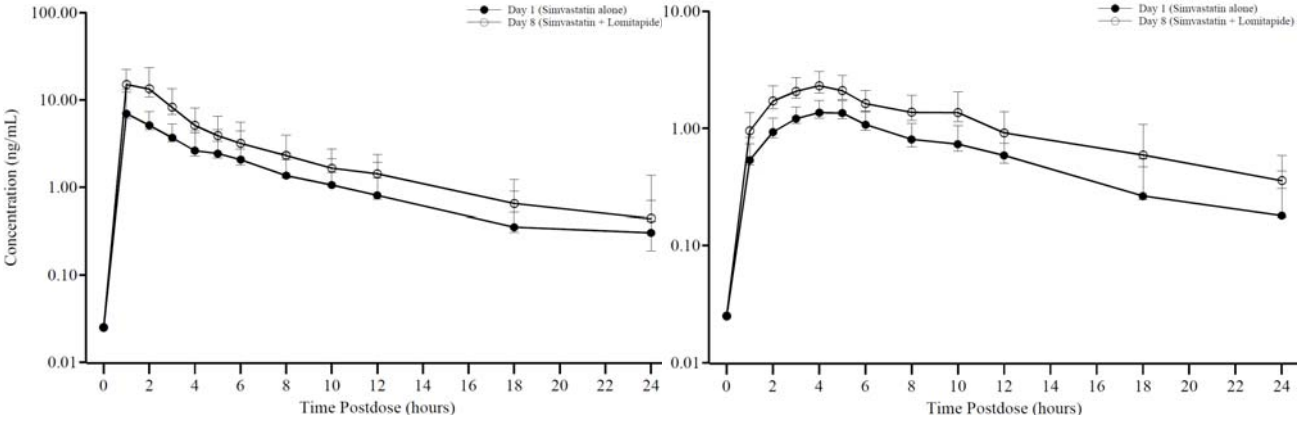
Study AEGR-773-019 assessed the effect of lomitapide on simvastatin PK in 16 healthy men and women. Each overnight fasted (8 hours) participant orally received:

- a 40 mg (1 X 40) simvastatin dose on Day 1
- a daily 60 mg (3 X 20) lomitapide dose from Days 2 – 7
- a 40 mg (1 X 40) simvastatin dose and 60 mg (3 X 20) lomitapide dose on Day 8

Serial plasma samples were collected predose and 24 hours postdose for the determination of simvastatin and simvastatin acid via validated assays.

Figures 51 and 52 show the geometric mean plasma simvastatin and simvastatin acid concentration – time profiles, respectively, upon single oral dose of 40 mg simvastatin on Day 1 and 40 mg simvastatin and 60 mg lomitapide on Day 8.

Figure 51 (left panel). Geometric mean plasma simvastatin concentration-time profiles. Source: Study AEGR-733-019's report Figure 11-1. Figure 52 (right panel). Geometric mean plasma simvastatin acid concentration-time profiles. Source: Study AEGR-733-019's report Figure 11-2.



Best Available Copy

Table 31 . Statistical comparison of simvastatin PK Parameters. Source: Study AEGR-733-019's report Table 11-2.

Parameter	N	Test Mean (Combination)	N	Reference Mean (Simvastatin)	Test/Reference (%)	90% Confidence Interval (%)
C_{max} (ng/mL)	15	18.5	16	9.16	202	(154.91 , 262.87)
AUC_{0-t} (ng·hr/mL)	15	76.9	16	41.6	185	(152.21 , 224.46)
AUC_{inf} (ng·hr/mL)	11	84.0	12	42.1	199	(158.01 , 251.56)

Simvastatin C_{max} and AUC_{inf} increased 102% and 99%, respectively, in the presence of lomitapide.

Table 32. Statistical comparison of simvastatin acid PK Parameters. Source: Study AEGR-733-019's report Table 11-4.

Parameter	N	Test Mean (Combination)	N	Reference Mean (Simvastatin)	Test/Reference (%)	90% Confidence Interval (%)
C_{max} (ng/mL)	15	2.37	16	1.51	157	(132.51 , 186.25)
AUC_{0-t} (ng·hr/mL)	15	26.0	16	15.5	168	(139.17 , 202.81)
AUC_{inf} (ng*hr/mL)	14	30.5	14	17.9	171	(140.04 , 208.68)

Simvastatin acid C_{max} and AUC_{inf} increased 57% and 71%, respectively, in the presence of lomitapide.

Simvastatin C_{max} and AUC_{inf} both about doubled in the presence of lomitapide. The approved maximum daily simvastatin dose has been lowered to 40 mg. However, the approved maximum daily simvastatin dose is 80 mg for patients who have been taking 80 mg simvastatin for 1 year without evidence of muscle toxicity. With concomitant use of lomitapide, the maximum daily simvastatin dose should not exceed 20 mg and should not exceed 40 mg for patients who have been taking 80 mg simvastatin for 1 year without evidence of muscle toxicity. Patients who are currently tolerating the concomitant use of the daily dose of 40 mg simvastatin and lomitapide who need to be initiated on an interacting drug that is contraindicated or is associated with a dose cap for simvastatin should be switched to an alternative statin with less potential for the drug-drug interaction. These recommendations are consistent with current simvastatin label in that diltiazem increase simvastatin exposure 3.1 – 4.6 fold and patients should avoid taking > 10 mg simvastatin. When amiodarone, amlodipine, and ranolazine increase simvastatin exposure from 1.58 – 1.86 fold, patients should avoid taking > 20 mg simvastatin.

Simvastatin is a sensitive in vivo CYP3A substrate per the draft drug interaction guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf), which also defines a weak inhibitor for a specific CYP as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold. With reference to the simvastatin exposure increase, lomitapide is a weak CYP3A inhibitor per the draft drug interaction guidance.

The sponsor did not conduct clinical study to assess the potential interaction between lovastatin and lomitapide. The parent lovastatin and simvastatin are either oxidized by CYP3A4 (and by CYP3A5) in the intestinal wall and liver to several metabolites, or hydrolyzed to their active ring-opened acids (lovastatin acid and simvastatin acid) (Neuvonen et al. *Clin Pharmacokinet* 2008;47:463-74). CYP3A and CYP2C8 further metabolize lovastatin acid and simvastatin acid. Lovastatin and simvastatin have similar profiles for transporters as substrate and inhibitor. Thus, concomitant use of lovastatin and lomitapide should be monitored for muscle adverse effects and dose reduction may be necessary for lovastatin.

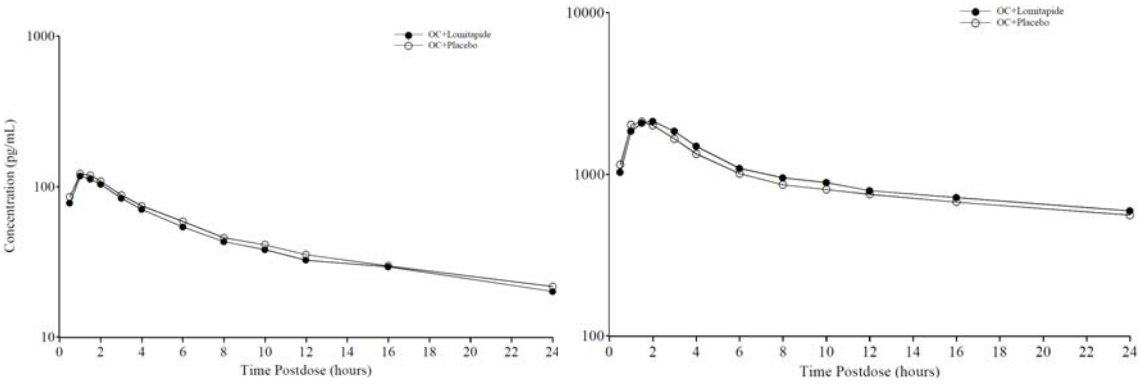
2.4.2.6 Ethinyl Estradiol and Norgestimate

Study AEGR-773-015 is a randomized, 3-period, double-blind, 2–way crossover study to assess the effect of lomitapide at steady state on multiple-dose 0.035 mg ethinyl estradiol and 0.25 mg norgestimate at steady state in 25 healthy women. Participants received the oral contraceptive for 3 periods of 28 days per period. On Days 14 – 21 of the 2nd period, participants received an oral 50 mg lomitapide (2 X 20 and 2 X 5) or matching placebo dose daily for a total of 8 doses. Participants received all doses of oral contraceptive and lomitapide/matching placebo on Days 14 – 21 following an overnight fast of at least 8 hours. Participant received the oral contraceptive dose within 15 minutes prior to the lomitapide or placebo dose. During Days 14 – 21 of the 3rd period, participants received the alternate treatment to that received in the 2nd period. On Days 19 – 21 of Periods 2 and 3, trough plasma samples for determination of ethinyl estradiol and 17-deacetyl norgestimate (metabolite of norgestimate) were collected prior to dosing. Serial plasma samples were collected on Day 21 predose and 24 hours postdose to determine ethinyl estradiol, 17-deacetyl norgestimate, lomitapide, M1, and M3 via validated assays.

The trough plasma concentrations for ethinyl estradiol, 17-deacetyl norgestimate, lomitapide, M1, and M3 from Days 19 – 21 indicated that steady state were achieved for ethinyl estradiol, 17-deacetyl norgestimate, lomitapide, M1, and M3.

Figures 53 and 54 show the geometric mean plasma ethinyl estradiol and 17-deacetyl norgestimate concentration-time profiles following multiple doses of oral contraceptive co-administered with 50 mg lomitapide daily or matching placebo daily dosed to steady state on Day 21.

Figure 53 (left panel). Geometric mean plasma ethinyl estradiol concentration-time profiles. Source: Study AEGR-733-015's report Figure 11-1 Figure 54 (right panel). Geometric mean plasma 17-deacetyl norgestimate concentration-time profiles. Source: Study AEGR-733-015's report Figure 11-2



Best Available Copy

Table 33. Comparison of ethinyl estradiol PK parameters in the presence and absence of lomitapide. Source: Study AEGR-733-015's report Table 11.3.

			Reference (OC with Placebo)		Test (OC with Lomitapide)		Ratio	
Analyte	Parameters	Units	N	Mean	N	Mean	Test/Reference (%)	90% Confidence Interval (%)
EE	C_{max}	pg/mL	25	129	25	119	91.9	(86.4, 97.7)
	AUC_{0-t}	pg·hr/mL	25	1118	25	1027	91.8	(87.0, 96.9)

The 90% CI of mean ratios (presence/absence of lomitapide) for ethinyl estradiol C_{max} and AUC_{0-t} were within the 80 – 125% bioequivalence goalpost. Thus, lomitapide did not significantly affect the ethinyl estradiol exposure upon coadministration with ethinyl estradiol.

Table 34. Comparison of 17-deacetyl norgestimate PK parameters in the presence and absence of lomitapide. Source: Study AEGR-733-015's report Table 11.6.

			Reference (OC with Placebo)		Test (OC with Lomitapide)		Ratio	
Analyte	Parameters	Units	N	Mean	N	Mean	Test/Reference (%)	90% Confidence Interval (%)
17-DNE	C_{max}	pg/mL	25	2252	25	2286	102	(96.6, 107)
	AUC_{0-t}	pg·hr/mL	25	21815	25	23042	106	(102, 109)

The 90% CI of mean ratios (presence/absence of lomitapide) for 17-deacetyl norgestimate C_{max} and AUC_{0-t} were within the 80 – 125% bioequivalence goalpost. Thus, lomitapide did not significantly affect the 17-deacetyl norgestimate exposure upon coadministration with norgestimate.

The plasma C_{trough} lomitapide concentrations were similar among Days 19 – 21. This observation also happened to plasma C_{trough} concentrations for M1 and M3. Thus, lomitapide reached steady state on Day 21.

The sponsor proposed the labeling statement [redacted] (b) (4)

[redacted] Per the Ogestrel label, the 8 point of Precaution section states "Diarrhea and/or vomiting may reduce hormone absorption." The 1st part of the sponsor's statement is per OGESTREL label. However, we should use the newer combined oral contraceptive label such as NATAZIA label's section 2.3 that "In case of severe vomiting or diarrhea, absorption may not be complete and additional contraceptive measures should be taken."

2.4.2.7 Warfarin

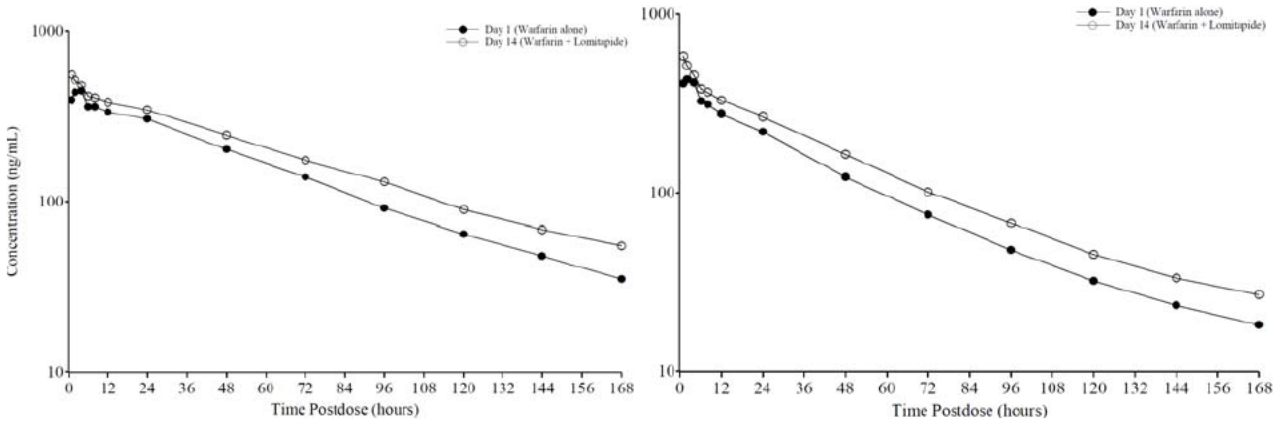
Study AEGR-773-013 assessed the effect of multiple-dose lomitapide on the single-dose of warfarin PK and PD in 16 healthy men. Each participant orally received the following treatments:

- A: a single oral dose of 10 mg warfarin sodium on Day 1 after an 8 hour overnight fast
- B: 60 mg of lomitapide (3 x 20 mg capsules) daily for 12 days beginning on Day 9 with one 10 mg single oral dose of warfarin co-administered on Day 14. The single oral dose of 10 mg warfarin sodium and 60 mg lomitapide (3 x 20 mg capsules) on Day 14 were co-administered after an 8-hour fast.

Serial plasma samples were collected predose and 168 hours postdose to determine warfarin R(+) and warfarin S(-) via validated assay. Serial blood samples were collected predose and 168 hours postdose to determine prothrombin time (PT) and international normalization ratio (INR).

Figures and show the geometric mean plasma concentrations of warfarin R(+) and warfarin S(-), respectively, following a single oral dose of 10 mg warfarin on day 1, and 10 mg warfarin co-administered with daily 60 mg lomitapide dosed to steady state on day 14.

Figure 55 (left panel). Geometric mean plasma warfarin R(+) concentration-time profile. Source: Study AEGR-733-013's report Figure 11-1 Figure 56 (right panel). Geometric mean plasma warfarin S(-) concentration-time profile. Source: Study AEGR-733-013's report Figure 11-2



Best Available Copy

Table 35. Comparison of warfarin R(+) PK parameters in the presence of lomitapide. Study AEGR-733-013's report Table 11-2

Parameter	N	Test Mean (Combination)	N	Reference Mean (Warfarin)	Test/Reference (%)	90% Confidence Interval (%)
C_{max} (ng/mL)	16	589	16	517	114	(107.16 , 121.11)
AUC_{0-t} (ng·hr/mL)	16	31177	16	25367	123	(118.09 , 127.91)
AUC_{inf} (ng·hr/mL)	16	36213	16	28336	128	(122.18 , 133.68)

Warfarin R(+) C_{max} and AUC_{inf} increased 14 and 28%, respectively, in the presence of lomitapide.

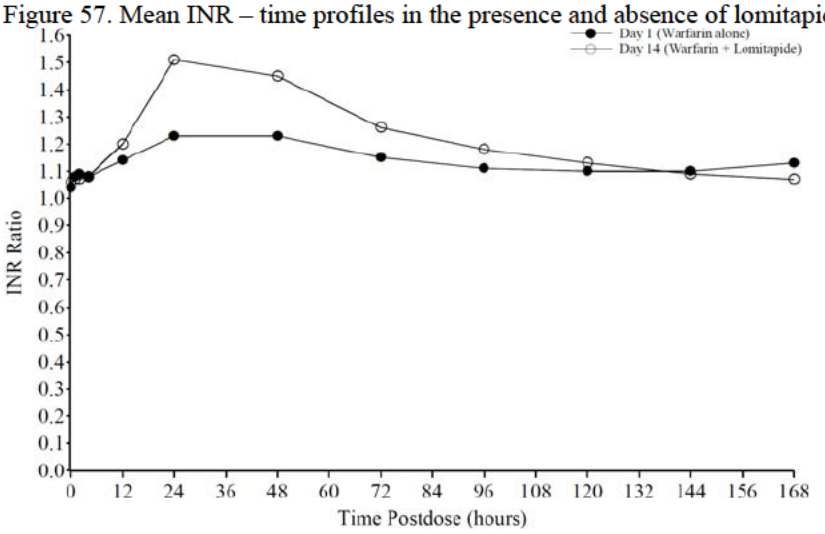
Table 36. Comparison of warfarin S(-) PK parameters in the presence of lomitapide. Study AEGR-733-013's report Table 11-3

Parameter	N	Test Mean (Combination)	N	Reference Mean (Warfarin)	Test/Reference (%)	90% Confidence Interval (%)
C_{max} (ng/mL)	16	603	16	524	115	(105.59 , 125.38)
AUC_{0-t} (ng·hr/mL)	16	21760	16	17088	127	(122.85 , 131.99)
AUC_{inf} (ng·hr/mL)	16	24371	16	18722	130	(124.64 , 135.95)

Warfarin S(-) C_{max} and AUC_{inf} increased 15 and 30%, respectively, in the presence of lomitapide.

These increase in warfarin exposure is consistent with the in vitro Study AEGR-733PC0007 that lomitapide inhibits warfarin metabolism.

Figure 57. Mean INR – time profiles in the presence and absence of lomitapide. Source: Study AEGR-733-013's report Figure 11-4.



Best Available Copy

Table 37. Comparison of warfarin PD parameters in the presence and absence of lomitapide. Source: Study AEGR-733-013's report Table 11-5.

Parameter	N	Test Mean (Combination)	N	Reference Mean (Warfarin)	Test/Reference (%)	90% Confidence Interval (%)
AUC_{INR} (hr)	16	205	16	192	107	(104.30 , 110.11)
INR_{max}	16	1.51	16	1.24	122	(113.88 , 131.59)

The AUC_{INR} and INR_{max} increased 7 and 22%, respectively, in the presence of lomitapide. In addition, lomitapide may reduce the absorption of fat-soluble vitamins such as vitamin K, warfarin is a vitamin K antagonist. Thus, patients who receive concomitant administration of lomitapide and warfarin should be monitored closely via INR measurements, especially for changes of lomitapide doses.

The sponsor proposed the labeling statement: (b) (4)

[redacted] (b) (4)

.

2.4.2.8 Fat Soluble Vitamins

The sponsor did not conduct dedicated clinical pharmacology study for the effect of lomitapide on exposure of vitamins and nutrients. Per the clinical efficacy study, the sponsor made labeling statement in the Dosage and Administration section concerning fat soluble vitamin: [redacted] (b) (4)

Clinical Pharmacology will defer to the Clinical reviewers to comment on this labeling proposal.

2.5 General Biopharmaceutics

2.5.1 What biopharmaceutics classification system (BCS) class does lomitapide mesylate belong?

The sponsor did not propose the BCS class for lomitapide. Clinical Pharmacology defers to OND QA Biopharmaceutics for the determination of BCS solubility status. Since Study AEGR-733PC0025 did not demonstrate suitability of the in vitro method via permeability model drugs per the biopharmaceutics classification system guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070246.pdf), the sponsor's claim that lomitapide is a high permeability drug is not acceptable per the BCS perspective.

2.5.2 Does difference exist between the to-be-marketed lomitapide mesylate formulations and the clinically-studied lomitapide mesylate formulations? If so, has the sponsor addressed it satisfactorily?

No. The clinically-tested formulations (5 and 20 mg lomitapide capsules) are identical to the to-be-marketed formulations (see Questions 2.1.2).

2.6 Bioanalytical

2.6.1 Are the bioanalytical methods properly validated?

Table 38 (in 4 parts). Validation of LC/MS/MS bioanalytical assays for lomitapide, M1, M2, M3, and analytes for drug interaction studies. Source: M.27.1 Table 7.

Validation Report No.	Study No.	Matrix	Compound	Linear Dynamic Range of Assay (ng/mL)	Assay Characteristics				Comments
					Accuracy	Precision	LLQ (ng/mL)	Selectivity	
(b) (4)96-009	BMS-CV145-001	Human plasma	Lomitapide	0.25-500	<14%	≤9.1%	0.25		Assay developed by (b) (4) (b) (4) Low recovery of M2 precluded its reproducible quantitation. Data source: Appendix 11.1 of BMS CV145-001
			M3	1.0-500	<14%	<10%	1.0		
(b) (4)96-032 (lomitapide, M3 and M1) and (b) (4) 97-004 (M2) [BMS Accession No. 910061694 and 910062132]	BMS-CV145-002, BMS-CV145-003, BMS-CV145-005, BMS-CV145-010	Human plasma	Lomitapide	0.25-500	<12%	<10%	0.25		
			M3	0.25-500	<12%	<10%	0.25		
			M1	1-500	<16%	<11%	1.0		
			M2	1-500	<12%	<10%	1.0		
AEGHPP (b) (4)7781-114	AEGR-733-011, AEGR-733-018, AEGR-733-017, AEGR-733-021	Human plasma	Lomitapide, M1	0.025-500	<85-115%	≤15%	0.025		Assay developed by (b) (4) (b) (4) 2010
			M3	0.025-500			0.025		

Validation Report No.	Study No.	Matrix	Compound	Linear Dynamic Range of Assay (ng/mL)	Assay Characteristics				Comments
					Accuracy	Precision	LLQ (ng/mL)	Selectivity	
(b) (4) 2100-823	AEGR-733-019-	Human plasma	Simvastatin	0.05-50	85%-107% for both analytes	<5%	0.05 for both analytes	No interfering peaks were found in the areas of interest that were determined to significantly impact the data	Assay developed by (b) (4) (b) (4)
			Simvastatin acid	0.05-10		<5%			
WENHPC (b) (4) 2100-829	AEGR-733-013	Human plasma	R(-) and S(+) warfarin	5-1500	85%-115% for both analytes	≤15%	5 for both analytes	No interfering peaks were found in the areas of interest that were determined to significantly impact the data	Assay developed by (b) (4) (b) (4)
NEEHPC (b) (4) 2100-808	AEGR-733-015	Human plasma	Ethinyl estradiol	0.005-0.125	85%-115%	<15%	0.005	No interfering peaks were found in the areas of interest that were determined to significantly impact the data	Assay developed by (b) (4) (b) (4)
			Norelgestromin	0.050-25	85%-115%	<15%	0.050		
KZHP (b) (4) 2100-331	AEGR-733-011	Human plasma	Ketoconazole	5-1000	85%-115%	<15%	5	No interfering peaks were found in the areas of interest that were determined to significantly impact the data	Assay developed by (b) (4) (b) (4)

Validation Report No.	Study No.	Matrix	Compound	Linear Dynamic Range of Assay (ng/mL)	Assay Characteristics				Comments
					Accuracy	Precision	LLQ (ng/mL)	Selectivity	
(b) (4) 99333 (LKR-MKR)	AEGR-733-002	Human plasma	Total ezetimibe	1-500	11%	<9%	1.0	No significant interference was observed greater than ~20% of the LOQ	Assay developed by (b) (4) (b) (4)
(b) (4) 99332 (LKR-MKR)	AEGR-733-002	Human plasma	Unconjugated ezetimibe	0.2-100	4%	6%	0.200	No significant interference was observed greater than ~20% of the LOQ	Assay developed by (b) (4)
LCMS 120 (b) (4) (MZP / MZP2)	AEGR-733-002	Human plasma	Atorvastatin (AT), ortho-hydroxy AT (o-AT), para-hydroxy AT (p-AT)	AT: 0.0790-79.0 o-AT: 0.0750-75.0 p-AT: 0.0808-80.8	AT: 7% o-AT: 4% p-AT: 7%	AT: 12% o-AT: 11% p-AT: 8%	AT: 0.0790 o-AT: 0.0750 p-AT: 0.0808	No interfering peaks were found in the areas of interest that were determined to significantly impact the data	Assay developed and validated by (b) (4)
LCMSC 367 (b) (4) (NZP)	AEGR-733-002	Human plasma	Simvastatin (S) Simvastatin acid (SA)	0.100-50.0	S:6% SA:10%	S: 12% SA:10%	0.100	No interfering peaks were found in the areas of interest that were determined to significantly impact the data. Interconversion S to SA: 2.0%-3.5% SA to S: 0.4%-1.2%	Assay developed and validated by (b) (4)

Validation Report No.	Study No.	Matrix	Compound	Linear Dynamic Range of Assay (ng/mL)	Assay Characteristics				Comments
					Accuracy	Precision	LLQ (ng/mL)	Selectivity	
LCMSB 264 Version 4 (b) (4) (ODS)	AEGR-733-002	Human plasma	Niacin (N) Nicotinuric acid (NA)	5-2000	N: 7% NA: 4%	N: 10% NA: 5%	5.0	LLOQ raised to 5.0 ng/mL to account for endogenous N & NA present in samples	Assay developed and validated by (b) (4)
LCMSB 235 (b) (4) (PZP2)	AEGR-733-002	Human plasma	Fenofibric acid	0.0500-30.0	10%	12%	0.0500	No interfering peaks were found in the areas of interest that were determined to significantly impact the data.	Assay developed and validated by (b) (4)
LCMSC 393 (b) (4) (QHR)	AEGR-733-002	Human plasma	Rosuvastatin	0.100-100	11%	4%	0.100	No interfering peaks were found in the areas of interest that were determined to significantly impact the data.	Assay developed and validated by (b) (4)
P600 (b) (4) (AEIH / ACPC)	AEGR-733-002	Human urine	Dextrometh-orphan Dextrorphan 3-methoxy-morphinan 3-hydroxy-morphinan	1.00-1,000 20.0-20,000 1.00-1,000 10.0-10,000	10% 6% 5% 8%	7% 6% 10% 6%	1.00 20.0 1.00 10.0	Conversion of dextrophan to 3-hydroxymorphinan occurred at a significant level	Assay developed and validated by (b) (4)

All validations for the LC/MS/MS bioanalytical methods appear acceptable with reasonable precision and accuracy.

Labeling Recommendations

Strikethrough text means deletion of the sponsor's proposed text. Underscored text means recommended addition. *Italicized text means internal notes and not to be communicated with the sponsor.*

---------- *INDICATIONS AND USAGE*----------

(b) (4)

33 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

SZE W LAU
11/05/2012

IMMO ZADEZENSKY
11/05/2012

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 203858	**Reviewer:** Elsbeth Chikhale, PhD	
Submission Date:	February 29, 2012		
Division:	Division of Metabolism and Endocrinology Products	**Acting Team Leader:** John Duan, PhD	
Applicant:	Aegerion Pharmaceuticals, Inc.		
Trade Name:	TBD	**Date Assigned:**	March 1, 2012
Generic Name:	Lomitapide mesylate	**Date of Review:**	October 26, 2012
Indication:	Treatment of homozygous familial hypercholesterolemia when used as an adjunct to a low-fat diet and other lipid-lowering therapies	**Type of Submission:** 505(b)(1) Original New Drug Application	
Formulation/ strengths	Capsule/ 5, 10, and 20 mg/capsule		
Route of Administration	Oral		

SUBMISSION:

This 505(b)(1) New Drug Application is for an immediate release capsule, containing 5, 10, or 20 mg of lomitapide as the active ingredients, indicated for the treatment of homozygous familial hypercholesterolemia when used as an adjunct to a low-fat diet and other lipid-lowering therapies. Lomitapide is a potent, selective microsomal triglyceride transfer protein (MTP) inhibitor. MTP is an intracellular lipid-transfer protein that is found in the lumen of the endoplasmic reticulum and is responsible for binding and shuttling individual lipid molecules between membranes. Through this activity, MTP plays a key role in the assembly of lipoproteins in the liver and intestines. Lomitapide inhibits MTP thereby reducing lipoprotein release and circulating concentrations of lipoprotein-borne lipids including cholesterol and triglycerides in the blood stream.

BIOPHARMACEUTICS INFORMATION:

The Biopharmaceutics review for this NDA will be focused on the evaluation and acceptability of
1) the proposed dissolution methodology,
2) dissolution acceptance criteria,
3) the biowaiver request for the 10 mg strength, and
4) comparative dissolution data to support minor changes made between the clinical drug product and the to be marketed (commercial) drug product.

In addition, this review will evaluate the Applicants responses to several Biopharmaceutics related information requests.

The drug substance is present in the drug product [redacted] (b) (4) have different melting points, dissolution rates, and solubility. [redacted] (b) (4) The Applicant stated that the drug substance was [redacted] (b) (4) Data provided upon request show that most drug substance batches used for the manufacturing of the clinical drug product batches containe [redacted] (b) (4) The Applicant claims that since lomitapide is BCS 1 (high solubility, high permeability), the impact of [redacted] (b) (4) should be negligible. Although the NDA does not contain sufficient permeability data, the solubility data provided in the response to information request (see section "Information requests and responses", page 21 of this review) support this claim. The drug substance particle size distribution is critical to the dissolution of the drug product, therefore, drug substance particle size distribution is controlled as part of the drug substance specifications. The clinical tested formulation is identical (except for the color of and printing on the capsule) to the to-be marketed formulation for the 5 mg and 20 mg strength capsules. Clinical studies were conducted using 5 mg and 20 mg capsules only. Per Agency's request, the NDA Applicant has introduced a 10 mg capsule (in addition to the 5 mg and 20 mg capsules), for which a biowaiver is requested.

DISSOLUTION METHOD:

The proposed dissolution method is:

USP Apparatus II (paddle)
Volume: 500 mL (5 mg strength) or 1000 mL (10 and 20 mg strength)
Dissolution medium: 0.001 N HCl containing 0.1% Tween 80
Temperature: 37 °C
Rotation speed: 50 rpm

Key findings from the dissolution method development (justification) report (submitted in the original NDA section M.1.12.15 and 3.2.P.2 and NDA amendment dated 8/31/12) are as follows:

The selection of medium pH:

[redacted] (b) (4)

(b) (4)

Selection of surfactant:

(b) (4)

(b) (4)

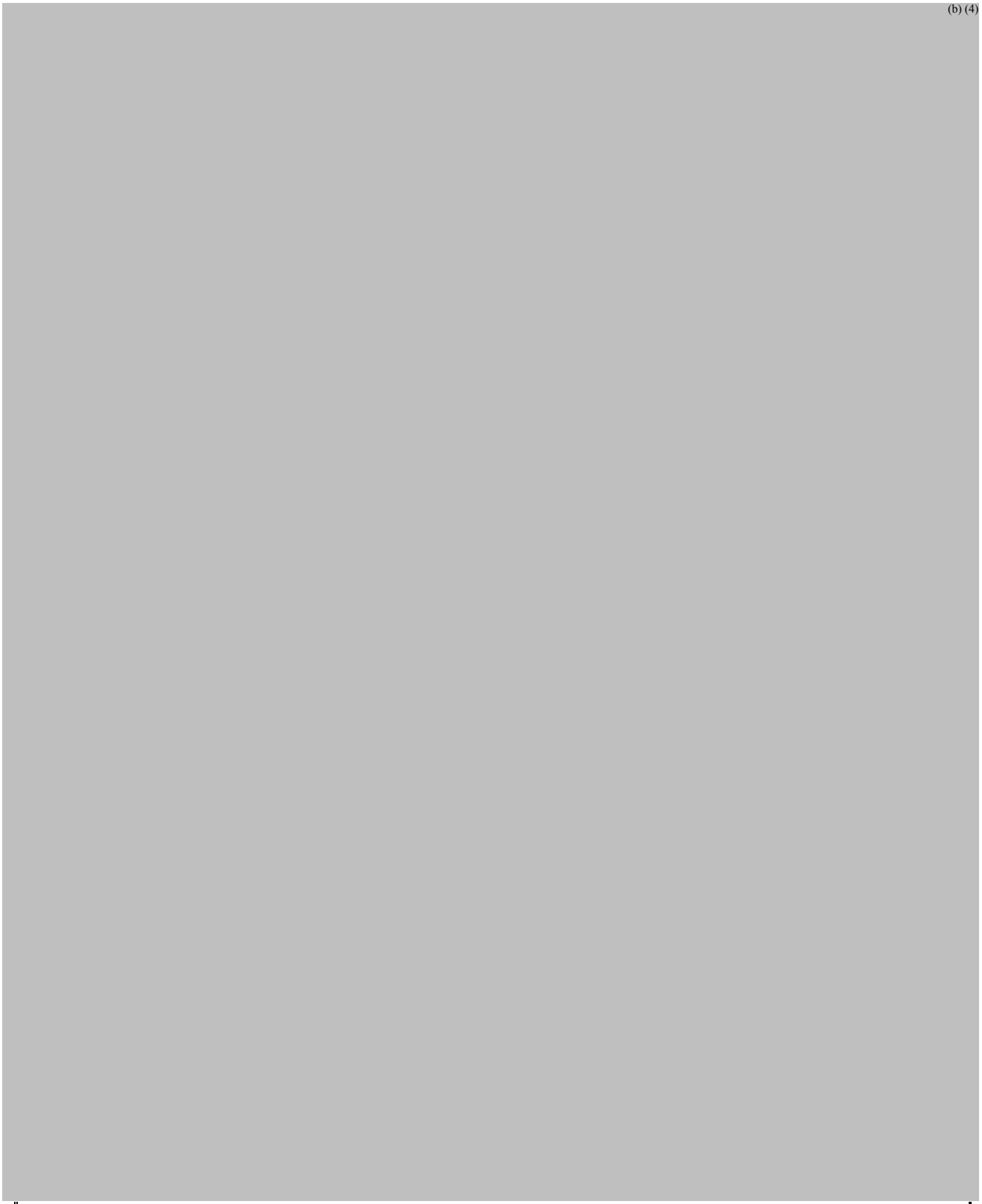
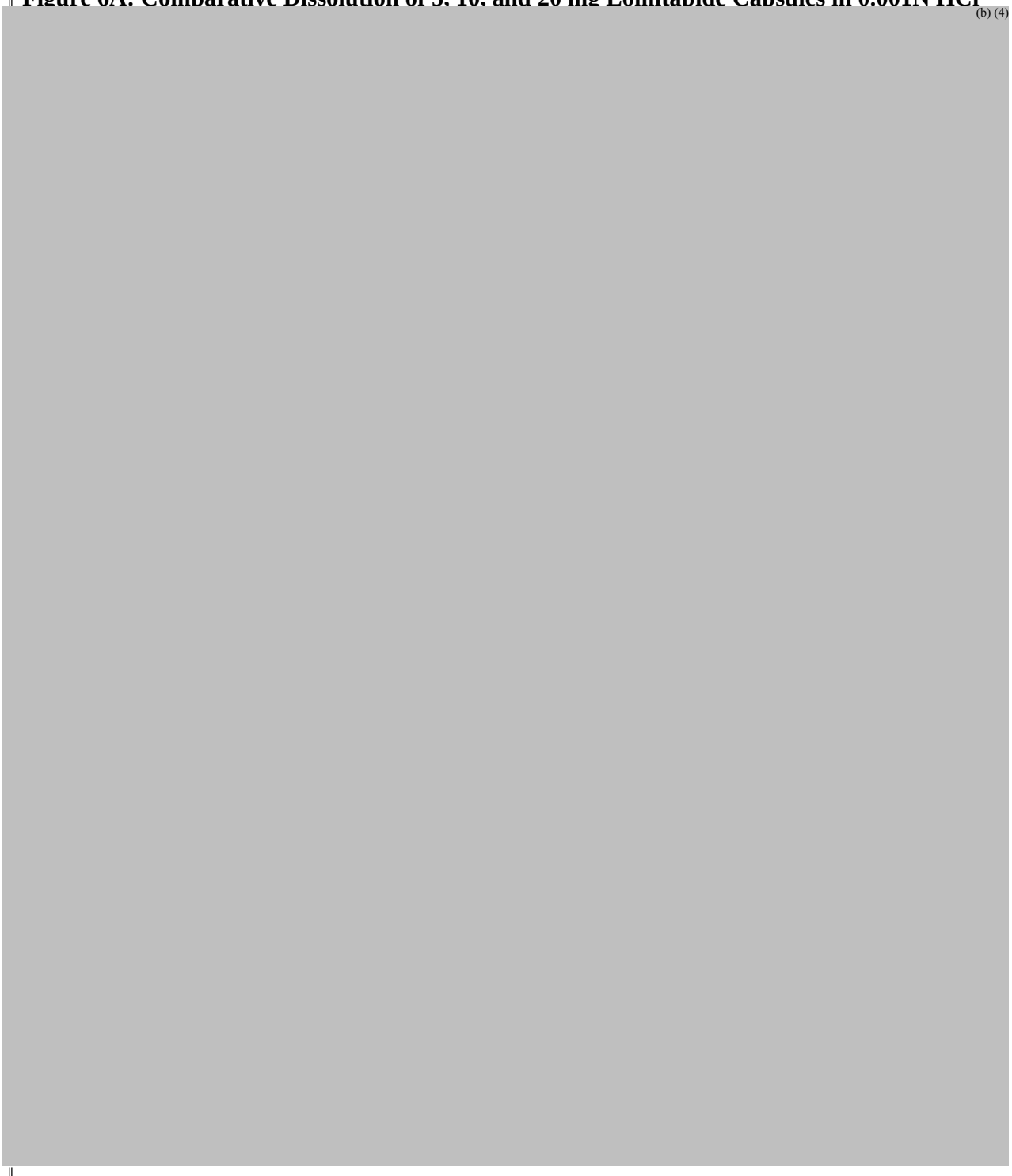


Figure 6A: Comparative Dissolution of 5, 10, and 20 mg Lomitapide Capsules in 0.001N HCl

(b) (4)



Selection of paddle rotation speed:
(For different batches of 5 mg and 20 mg drug product)

Figure 7: Paddle Speed Evaluation for the 5 mg Capsules

(b) (4)

Figure 8: Paddle Speed Evaluation for the 20 mg Capsules

(b) (4)

Figure 9: Paddle Speed Evaluation for the 5 mg Capsules

Figure 10: Paddle Speed Evaluation for the 20 mg Capsules

Discriminating power:

The discriminatory power of the proposed dissolution method was not discussed in the dissolution method development report (called dissolution method justification report in the NDA). However, in section 3.2.P.2 in the "drug product" folder in the original NDA, the dissolution properties of 3 drug product lots with the following particle size distribution data are provided:

Drug Substance Batch No.	(b) (4)	20 mg Drug Product Lot No.
1713-1713-07-001		L0306299
1713-1713-11-001H		A13669-5
1713-1713-11-002H[a]		A13669-11

[a] This lot contains slightly more Form II than the other 2 lots.

Using these 3 drug products lots, the following two dissolution profile figures were provided:

Figure 15: Comparative Dissolution of 20 mg Drug Product in 0.001N HCl + 0.1% Polysorbate 80 Made from Drug Substance Batches with Different Particle Size Distributions

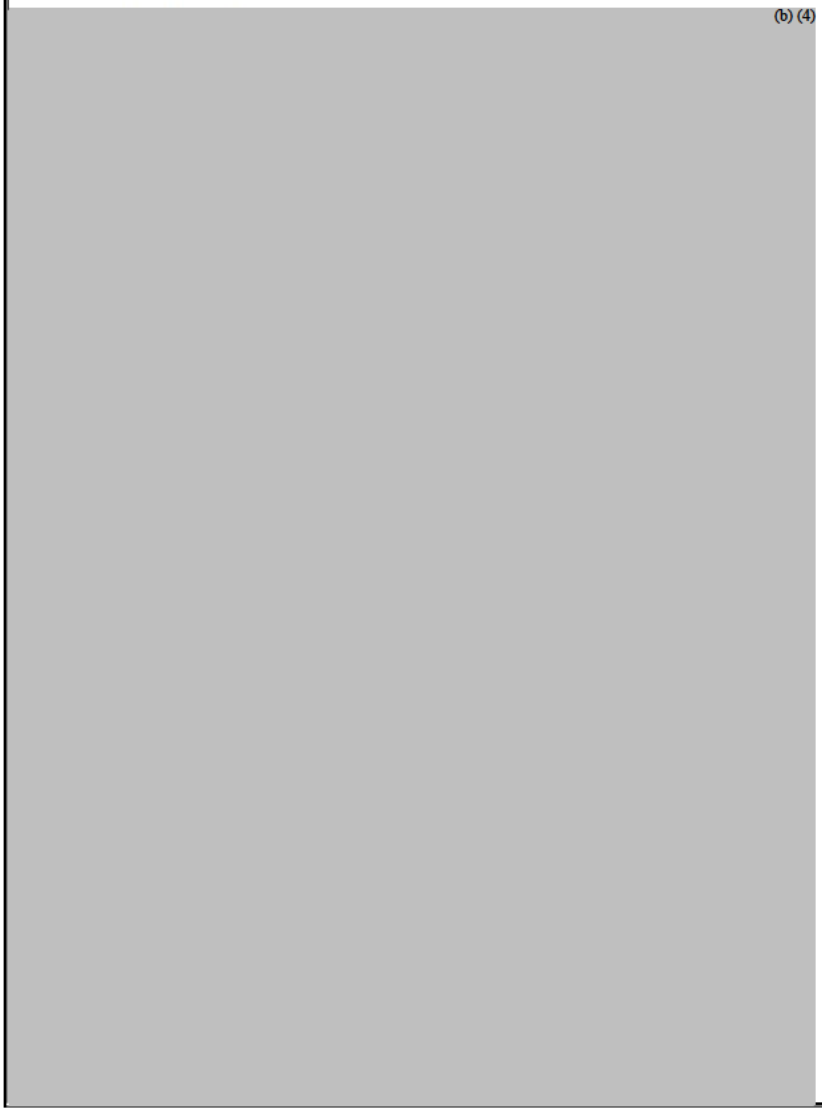


Table 11: Similarity Factor Comparison of 20 mg Drug Product Lots Made from Drug Substance Batches with Different Particle Size Distributions

TEST LOT NO.	REFERENCE LOT NO.	MEDIA	f_2
A136669-5 (11-001H)	L0306299 (07-001)	0.001N HCl + 0.1% PS80	44
A13669-11 (11-002H)	L0306299 (07-001)	0.001N HCl + 0.1% PS80	56
A136669-5 (11-001H)	L0306299 (07-001)	(b) (4)	37
A13669-11 (11-002H)	L0306299 (07-001)		44

(b) (4) The Applicant pointed out that due to the rapid dissolution in 0.001 N HCl + 0.1 % tween 80, only 1 or 2 points were included in the calculation of f_2 in that media. The Applicant had earlier concluded that (b) (4) Therefore the 0.001 N HCl + 0.1% tween medium was chosen as the final dissolution medium. The drug substance particle size distribution is critical to the dissolution of the drug product, therefore, drug substance particle size distribution is controlled as part of the drug substance specifications (see CMC review by Xavier Ysern, Ph.D., dated 9/21/12).

Dissolution method validation report (Section 1.12.15):
The validation of the dissolution method and the analytical method (HPLC with UV detection at 215 nm) can be summarized as follows:

(b) (4)

Specificity:

Linearity:

Accuracy:

Instrument Precision:

Repeatability:

Filter Study:	(b) (4)
Solution Stability:	
Issue Date:	

Evaluation of the proposed dissolution method:

The Applicant's proposed dissolution method is found acceptable based on the data in their dissolution method development report (discussed above).

DISSOLUTION DATA AND PROPOSED DISSOLUTION ACCEPTANCE CRITERION:

The statistical analysis of the dissolution data can be summarized as follows:

Table 7: 5 mg Statistical Worksheet for Dissolution (All Dissolution Data)

(b) (4)

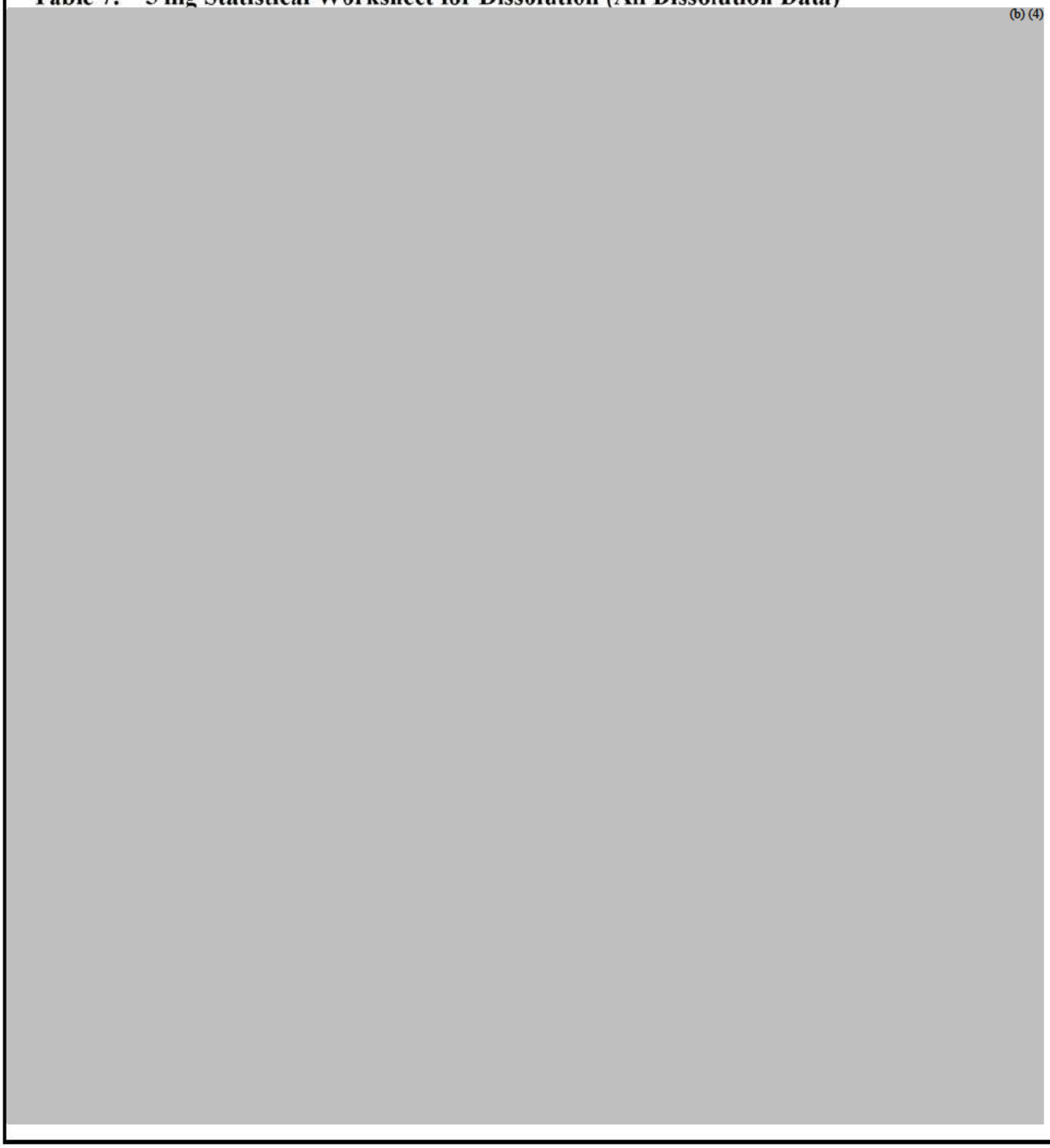


Table 10: 20 mg Statistical Worksheet for Dissolution (All Dissolution Data)

(b) (4)

[redacted]

The proposed dissolution acceptance criterion is:

Dissolution (Apparatus 2)[a]	QM3216 Harmonised USP<711> Ph.Eur. 2.9.3	Q= (b) (4) at 60 minutes

[a] Indicates tests that will be conducted on stability.

Evaluation of the proposed dissolution acceptance criterion:
Based on the provided data, and with the goal to set the acceptance criterion in a way to ensure consistent drug product performance from lot to lot and to prevent release of any drug product lot with dissolution profiles outside those that were clinically tested, the revised dissolution acceptance criterion of Q (b) (4) at 45 minutes for all 3 strengths is recommended.

Based on the provided dissolution data and per FDA request dated 7/13/12, the dissolution specification was revised as follows:

Dissolution (Apparatus 2)[a]	QM3216 Harmonised USP<711> Ph.Eur. 2.9.3	Q= (b) (4) at 45 minutes

[a] Indicates tests that will be conducted on stability.

The revised acceptance criterion of Q= (b) (4) at 45 minutes is acceptable.

BIOWAIVER REQUEST:
The Applicant is requesting a waiver from the requirement to demonstrate in vivo BA for the 10 mg strength, based on 21 CFR 320.22(d)(2):

In support of this waiver request, the Applicant provided:
1) the comparative quantitative compositions of the proposed capsule strengths,
2) lomitapide's pharmacokinetics information, and
3) *in vitro* dissolution data comparing the 5, 10 and 20 mg capsule strengths in various dissolution media.

1) the comparative quantitative compositions of the proposed capsule strengths are:

COMPONENT	FUNCTION	SPECIFICATION	AMOUNT 5 MG CAPSULE	%*	AMOUNT 10 MG CAPSULE	%*	AMOUNT 20 MG CAPSULE	%*
(b) (4)								
Lomitapide mesylate [a]	Active Ingredient	In-house	5.69 mg (5.00 mg free base)	5.69	11.39 mg (10.00 mg free base)	5.69	22.77 mg (20.00 mg free base)	11.39
Pregelatinized Starch	(b) (4)	NF, Ph.Eur.						(b) (4)
Microcrystalline Cellulose		NF, Ph.Eur.						
Lactose Monohydrate[b]		NF, Ph.Eur.						
Sodium Starch Glycolate		NF, Ph.Eur.						
								(b) (4)
Colloidal Silicon Dioxide (b) (4)	(b) (4)	USP, Ph.Eur						(b) (4)
Magnesium Stearate		NF, Ph.Eur.						
Sodium Starch Glycolate		NF, Ph.Eur.						
Total Amount			100 mg	100	200 mg	100	200 mg	100

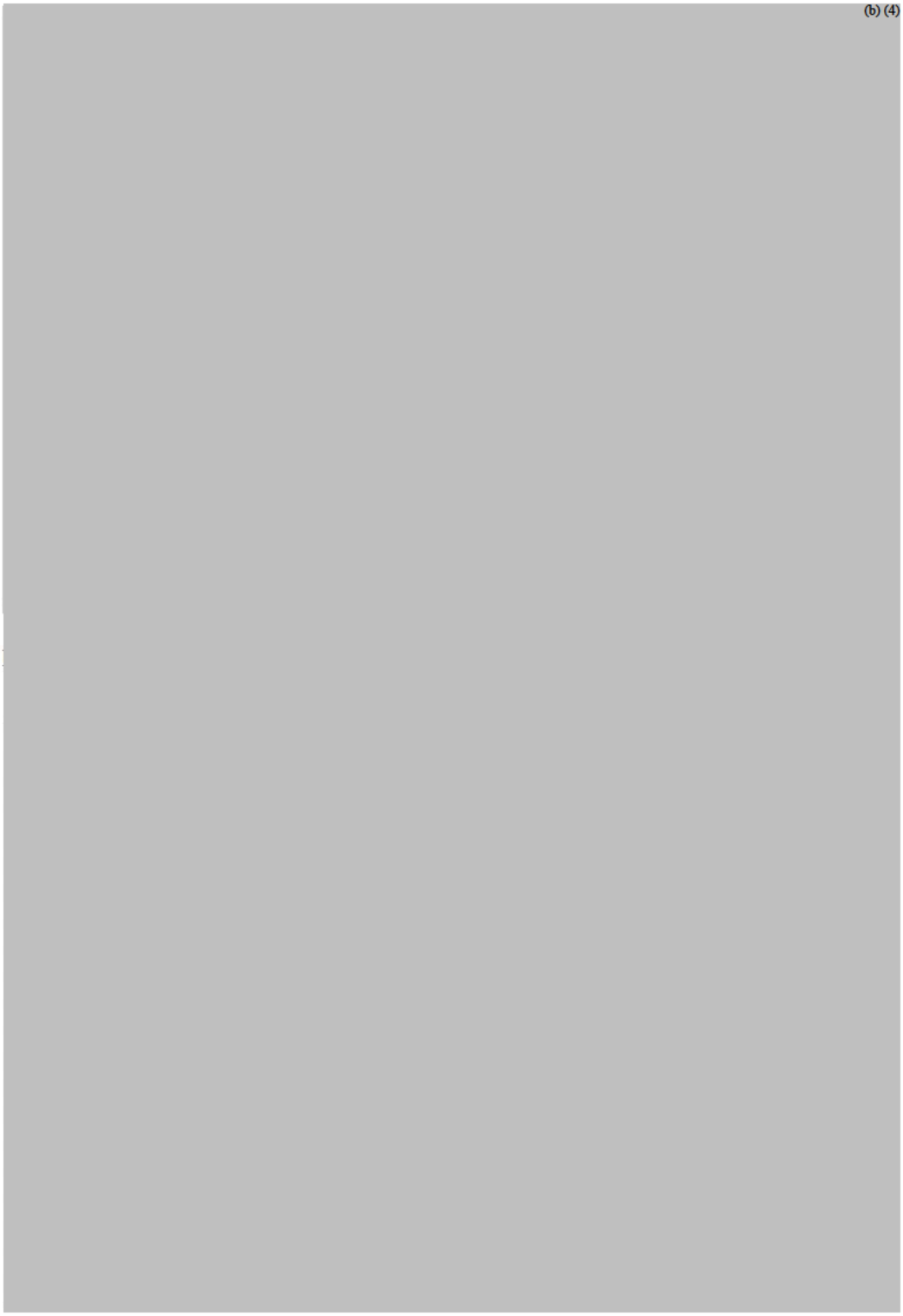
2) lomitapide's pharmacokinetics information

The pharmacokinetic proportionality with respect to dose between doses of 5, 10 and 20 mg has been discussed in the Clinical Pharmacology review by Johnny Lau, Ph.D. His review concludes that the proposed drug product exhibit approximately dose-proportional pharmacokinetics.

3) comparative dissolution profile data:

The applicant provided the following dissolution data and summary of f_2 comparisons:

Figure 1: Comparative Dissolution of 5, 10, and 20 mg Lomitapide Capsules in 0.001N HCl



(b) (4)

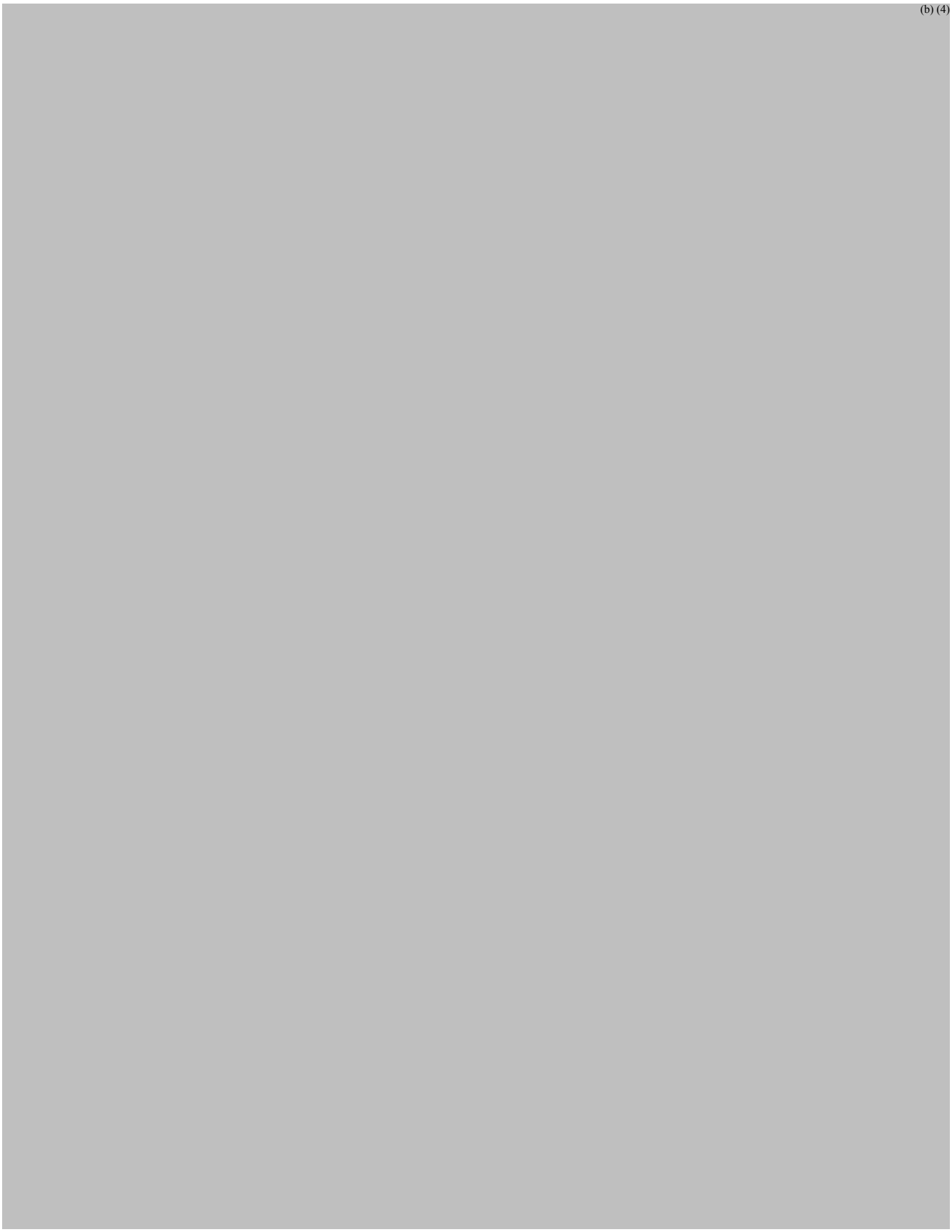


Figure 5: Comparative Dissolution of 5, 10, and 20 mg Lomitapide Capsules in 0.001N HCl with 0.1% Polysorbate 80 (Release Testing Dissolution Medium)

Assessment of the biowaiver request for the 10 mg capsule:

The 10 mg lomitapide mesylate capsule is in the same dosage form (capsule) and is (b) (4) . All the f_2 values were > 50, indicating that the dissolution profiles of the 10 mg capsule is highly similar to the dissolution profile of the 5 mg and the 20 mg capsules. Based on the provided data, a waiver for the requirement to conduct BA/BE studies for the 10 mg capsule strength is granted.

COMPARATIVE DISSOLUTION DATA TO SUPPORT MINOR DRUG PRODUCT CHANGES BETWEEN THE CLINICAL AND TO BE MARKETED DRUG PRODUCT:

The capsule shell color will be different (removal of colorant) in the commercial 20 mg drug product compared to that used in the clinical studies and primary stability studies. Additionally, all commercial capsules will bear an ink imprint, unlike those used in the clinical and primary stability studies. These changes are being introduced to allow for product differentiation and branding. There have been no other changes to the drug product manufacturing process.

	PRIMARY STABILITY/CLINICAL LOTS	BRIDGING (COMMERCIAL) LOTS
Capsule size		
5 mg	Size 1	Size 1
10 mg	Not produced	Size 1
20 mg	Size 1	Size 1
Capsule colour		
5 mg	Swedish orange[1] body & cap	Swedish orange body and cap
10 mg	Not produced	White[2] body, Swedish orange cap
20 mg	Swedish orange body & cap	White[2] body & cap
Capsule imprint	None	Edible black ink stripe

[1] Swedish orange capsules contain titanium dioxide and red iron oxide
[2] White capsules contain titanium dioxide

Dissolution profiles have been generated for the bridging (commercial) lots and clinical/primary stability lots for both the 5 mg and the 20 mg capsules. The following drug product lots were used for the comparative studies, followed by the dissolution profiles and f_2 values:

Table 2: 5 mg Lomitapide Drug Product Comparative Dissolution Testing Summary

LOT NO.	DATE OF MANUFAC.	LOT SIZE	SITE OF MANUFAC.	BATCH NO. OF DRUG SUBSTANCE	USE SUMMARY
L0306297	17 Aug 2011	(b) (4)		1713-1713-07-001	Bridging, stability supplies, named patient supplies
L0302138	14 Jun 2010			1713-1713-07-001	UP1002/AEGR-005, AEGR-733-015, AEGR-733-012
L0206440	19 Feb 2009			1713-1713-07-001	UP1002/AEGR-733-005
L0109391	13 Dec 2007			1713-1713-07-001	UP1002/AEGR-733-005

(b) (4)

Figure 6: 5 mg Drug Product Comparative Dissolution Profiles in 0.001N HCl + 0.1% Polysorbate 80

Table 3: Comparison of Dissolution Profile f_2 for 5 mg Bridging and Clinical Lomitapide Drug Product in 0.001N HCl with 0.1% Polysorbate 80

COMPARISON LOT NO.	REFERENCE LOT NO.	f_2
L0302138	L0306297	73
L0206440	L0306297	74
L0109391	L0306297	61

Table 5: 20 mg Lomitapide Drug Product Comparative Dissolution Testing Summary

LOT NO.	DATE OF MANUFAC.	LOT SIZE	BATCH NO. OF DRUG SUBSTANCE	USE SUMMARY
L0306299	17 Aug 2011	(b) (4)	1713-1713-07-001	Bridging, stability supplies, named patient supplies
L0302139	15 Jun 2010		1713-1713-07-001	AEGR-733-012, AEGR-733PC0020
L0206441	20 Feb 2009		1713-1713-07-001	UP1002/AEGR-733-005, AEGR-733-015, AEGR-733-018, AEGR-733-019, AEGR-733-021
L0203329	19 May 2008		1713-1713-07-001	UP1002/AEGR-733-005
L0109390	18 Dec 2007		1713-1713-07-001	UP1002/AEGR-733-005

Figure 8: 20 mg Drug Product Comparative Dissolution Profiles in 0.001N HCl + 0.1% Polysorbate 80

Table 6: Comparison of Dissolution Profile f_2 for 20 mg Bridging and Clinical Lomitapide Drug Product in 0.001N HCl with 0.1% Polysorbate 80

COMPARISON LOT NO.	REFERENCE LOT NO.	f_2
L0302139	L0306299	77
L0206441	L0306299	82
L0203329	L0306299	84
L0109390	L0306299	82

Evaluation of comparative dissolution profiles:

All the f_2 values were > 50, indicating that the dissolution profiles of the clinical/primary stability lots are highly similar to the dissolution profile of the bridging (commercial) lots for both the 5 mg and the 20 mg capsules, thereby providing an acceptable bridge.

Information requests and responses:
In the 74 day letter dated May 8, 2012, the following information requests were sent to the sponsor, followed by the Applicant's responses:

Question 2: You have not provided adequate information to show (b) (4) the product safety or efficacy. Propose and justify acceptance criteria for (b) (4) in the drug substance specification. In addition, justify the (b) (4) in the product stability specification given that the limited data in the NDA (b) (4)

Applicant's Response (7/23/12): *Differences in ratios (b) (4) are not expected to result in clinically meaningful differences in product safety or efficacy (see discussion in M2.7.1, Section 1.1.3). Under the acidic conditions of the stomach (Evans, 1988 Gut) lomitapide has a solubility of 2 to 3.6 mg/mL, and a rapid dissolution profile (b) (4) Therefore, even in circumstances of more rapid gastric emptying, as observed following administration of oral solution (Tmax 2hrs), lomitapide will be fully solubilized prior to entry into the proximal small intestine, where it should be rapidly absorbed due to its high permeability.*

Evaluation of response:
Solubility data for drug substance (b) (4) are provided in the response to question 4 below. Drug product dissolution profiles for drug products made using drug substance (b) (4) are provided in response to question 7 below. Dissolution profiles for drug product lots made using drug substance (b) (4) , have similar dissolution profiles, supporting the Applicants claim that drug products made using (b) (4) the drug substance have the same clinical efficacy and safety. The drug permeability data provided in the NDA were insufficient to conclude that the drug has a high permeability (see the Clinical Pharmacology review by Johnny Lau, Ph.D.). The drug substance specifications for the physical form require that the drug substance consist of (b) (4) This acceptance criterion is found acceptable by the CMC reviewer, Xavier Ysern, Ph.D. in his review (pg. 57/137) dated 9/21/12, based on solubility, dissolution, and permeability. The same CMC review also indicated that (b) (4) See also response and evaluation of question 7 below.

Question 4: Provide drug substance solubility (over pH range) (b) (4)

Applicant's Response (6/19/12): *This information is presented in section 3.2.S.3.1 of the NDA. Specifically, Table 11 presents (b) (4) .*

(b) (4)

Question 5: Submit permeability data for (b) (4)

Applicant's Response (6/19/12): *Permeability data on lomitapide were provided in the NDA (see M2.7.2, AEGR-733PC0025). Permeability studies are solution-phase in-vitro assays, run using dilute solutions of the drug substance.* (b) (4)

Evaluation of response:
The response is acceptable.

Question 6: Submit ratio information for (b) (4) **in the clinical drug product batch(es).**

Applicant's Response (7/23/12): *Development of a quantitative method for assessing the* (b) (4) *drug product has not been possible for two reasons:*

1. (b) (4)

2 (b) (4)

(b) (4) *Seven clinical lomitapide drug product lots were analyzed using x-ray powder diffraction (XRPD) to determine the relative change* (b) (4) *present in lots of drug product as compared to that seen in the source drug substance batch (see Table 1). Eleven other drug product lots that were used in the clinical development program were not analyzed, because no retain samples were available at time of analysis. The lots not tested are presented in Table 2 for reference. Table 2* (b) (4) *present in the drug substance used to produce the drug product lots.*

Table 1: Estimation of the Amount of Solid State (b) (4) **in Lomitapide Drug Product Lots by XRPD**

CLINICAL DRUG PRODUCT LOT NUMBER	STRENGTH	CLINICAL STUDIES	DRUG SUBSTANCE BATCH USED	(b) (4) PRESENT IN THE DRUG SUBSTANCE*	(b) (4) ESTIMATED IN DRUG PRODUCT
L0105923	5 mg	AEGR-733-003a	N010A (L0106206)		(b) (4)
L0108401	5 mg	AEGR-733-002 AEGR-733-003b AEGR-733-004 AEGR-733-006	N009A (L0107803)		
L0109390	20 mg	UP1002/AEGR-733-005	1713-1713-07-001		
L0109391	5 mg	UP1002/AEGR-733-005	1713-1713-07-001		
L0206440	5 mg	UP1002/AEGR-733-005	1713-1713-07-001		
L0302138	5 mg	AEGR-733-015 UP1002/AEGR-733-005 AEGR-733-012	1713-1713-07-001		
L0302139	20 mg	AEGR-733-011 AEGR-733-015 AEGR-733-017 AEGR-733-018 AEGR-733-019 AEGR-733-021 UP1002/AEGR-733-005 AEGR-733-012	1713-1713-07-001		

(b) (4)

Table 2: Clinical Drug Product Lots Not Analyzed (b) (4)

LOT NUMBER	STRENGTH	DRUG SUBSTANCE BATCH USED	(b) (4) PRESENT IN THE DRUG SUBSTANCE	CLINICAL STUDIES
N96070	5 mg	R005A	(b) (4)	CV145-001 CV145-002 CV145-010
N96074	50 mg	R005A		CV145-001 CV145-002 CV145-003 CV145-005
N97101	200 mg/vial powder for reconstitution	N009A / 001 / 001		CV145-006
N97018	25 mg	N009A		CV145-009
I60307A	5 mg	N009A (L0107803)		AEGR-733-001
I60307B	7.5 mg	N009A (L0107803)		AEGR-733-001
I60214B	10 mg	N009A (L0107803)		AEGR-733-001 AEGR-733-002
7030202	10 mg	N009A (L0107803)		AEGR-733-002
L0105924	2.5	N010A (L0106206)		AEGR-733-003a
L0108400	2.5 mg	N009A (L0107803)		AEGR-733-003b AEGR-733-004 AEGR-733-006
L0206441	20 mg	1713-1713-07-001		UP1002/AEGR-733-005

*Batch R005A was an earlier BMS batch and is no longer available for testing with the quantitative method. (b) (4)
(b) (4)

Evaluation of response:
Drug product lots made with a range of drug substance (b) (4) ratios were used in the clinical studies. The drug substance specifications for the physical form require that the drug substance consist of (b) (4).
This acceptance criterion is found acceptable by the CMC reviewer, Xavier Ysern, Ph.D. in his review (pg. 57/137) dated 9/21/12, based on solubility, dissolution, and permeability. The same CMC review also indicated that (b) (4) See also response and evaluation of question 7.

Question 7: Provide dissolution data for drug product having the minimum and maximum extremes of observed ratios (b) (4)

Applicant's Response (7/23/12): *An experimental batch of lomitapide drug substance, DP12-026-29-15, was produced in the laboratory* (b) (4)

(b) (4)

the particle size distribution data are shown in Table 3.

(b) (4)

Table 3: (b) (4) Drug Substance Batches

BATCH IDENTITY	SOURCE	(b) (4)	PARTICLE SIZE DISTRIBUTION (µM) (b) (4)
DP12-026-29-15			
4791-72-01	DP-12-026-29-15		
124019	DP-12-026-29-15		

(b) (4)

Table 4: 20 mg (b) (4) Drug Product Lots

LOT IDENTITY	DRUG SUBSTANCE LOT	SOLID STATE FORM (b) (4)
A13669-19	124019	
A13669-20	4791-72-01	
A13669-22	(b) (4)	

Drug Product Dissolution in 0.001N HCl + 0.1% PS80

(b) (4)

(b) (4)

The in vitro dissolution profiles for drug product made from the two solid state forms of lomitapide are very similar. Similarity factors were not calculated due to the rapid dissolution of all three drug product lots, which was due to the fact that the particle size distributions were (b) (4)

Evaluation of response:
Dissolution profiles for drug product lots made using drug substance (b) (4) have practically identical dissolution profiles, supporting the Applicant's claim that drug products made (b) (4) of the drug substance have the same clinical efficacy and safety.

On July 13, 2012, the following information requests to the sponsor were sent, followed by the Applicant's responses:
Question 1: Please submit dissolution profile figures (with error bars) for the following dissolution data:
Medium selection:
• Figure 1: For the 5 mg tablets: Dissolution data in Tables: 6,7,10,11,14,15,18,19,22,23
• Figure 2: For the 20 mg tablets: Dissolution data in Tables: 5,8,9,12,13,16,17,20,21,24,25
Surfactant Study:
• Figure 3: For the 5 mg tablets: Dissolution data in Tables: 26,27,30,31,34,35
• Figure 4: For the 20 mg tablets: Dissolution data in Tables: 28,29,32,33,36,37
• Figure 5: For the 5 mg tablets: Dissolution data in Tables: 38,39,42,43,46,47
• Figure 6: For the 20 mg tablets: Dissolution data in Tables: 40,41,44,45,48,49
Paddle speed:
• Figure 7: For the 5 mg tablets: Dissolution data in Tables: 38,39,50,51
• Figure 8: For the 20 mg tablets: Dissolution data in Tables: 46,47,52,53
• Figure 9: For the 5 mg tablets: Dissolution data in Tables: 40,41,54,55
• Figure 10: For the 20 mg tablets: Dissolution data in Tables: 48,49,56,57

Applicant's Response (8/31/12): *The requested figures are provided (and incorporated in this review as part of the review of the dissolution method development). Figures pertaining to selection of media are provided as Figure 1 and Figure 2. Figures related to the surfactant study*

are provided in Figure 3 through Figure 6. Figures related to selection of paddle speed are provided in Figure 7 through Figure 10.

Evaluation of response:
The response is acceptable. The provided figures were used in the review of the dissolution method development.

Question 2: The provided dissolution data in M3.2.P.5.6. Tables 7 and 8 support a (b) (4) acceptance criterion for your product. Please implement a dissolution acceptance criterion of Q = (b) (4) at 45 minutes for your product at release and on stability. Revise the dissolution acceptance criterion accordingly and submit the updated specifications table for the drug product.

Applicant's Response (8/31/12): *As requested, the dissolution specification has been (b) (4) from Q = (b) (4) at 60 minutes to Q = (b) (4) at 45 minutes. An updated M3.2.P.5.1 is provided to reflect this change.*

Evaluation of response:
The response is acceptable.

RECOMMENDATION:

- The applicant's dissolution methodology, as summarized below is acceptable by the Agency:
  USP Apparatus II (paddle)
  Volume: 500 mL (5 mg strength) or 1000 mL (10 and 20 mg strength)
  Dissolution medium: 0.001 N HCl containing 0.1% Tween 80
  Temperature: 37 °C
  Rotation speed: 50 rpm

- The following drug product dissolution acceptance criterion is acceptable by the Agency:

Dissolution (Apparatus 2)[a]	QM3216 Harmonised USP<711> Ph.Eur. 2.9.3	Q= (b) (4) at 45 minutes

[a] Indicates tests that will be conducted on stability.

- A waiver for the requirement to conduct BA/BE studies for the 10 mg capsule strength is granted.

- From the Biopharmaceutics perspective, NDA 203858 for lomitapide mesylate capsules 5, 10, and 20 mg/capsule is recommended for APPROVAL.

Elsbeth Chikhale, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

John Duan, Ph.D.
Acting Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

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

/s/

ELSBETH G CHIKHALE
10/26/2012

JOHN Z DUAN
10/26/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 203-858

NDA Number: 203-858 **Applicant: Aegerion Pharmaceuticals** **Stamp Date: March 1, 2012**

Drug Name: Lomitapide **NDA Type: Standard**

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			Not applicable since the sponsor did not change the formulation
2	Has the applicant provided metabolism and drug-drug interaction information?	Yes		
Criteria for Assessing Quality of an NDA				
	Data			
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?	Yes		
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		No	The sponsor did not submit pharmacogenomic data nor propose pharmacogenomic claim in the labeling.
	Studies and Analyses			
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	Yes		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?	Yes		
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			Not applicable
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	Yes		Contraindicate use of lomitapide in moderate and severe hepatic impairment patients due to increased lomitapide exposure
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		No	There are no adequate and well-controlled studies investigating the safety and efficacy of lomitapide in the pediatric population.
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		No	
11	Is the appropriate pharmacokinetic information submitted?	Yes		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology	Yes		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 203-858

	section of the label?			
	General			
13	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?	Yes		
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	Yes		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	Yes		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Yes		
17	Was the translation from another language important or needed for publication?		No	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILABLE?
___Yes_____

If the NDA/BLA is not filable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

S. W. Johnny Lau, R.Ph., Ph.D.

Reviewing Pharmacologist Date

Jaya Vaidyanathan, Ph.D.

Acting Team Leader/Supervisor Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 203-858

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA	203-858	Brand Name	To be determined
OCP Division	2	Generic Name	Lomitapide
Medical Division	DMEP	Drug Class	Microsomal triglyceride transfer protein inhibitor
OCP Reviewer	S.W. Johnny Lau	Indication(s)	Treat homozygous familial hypercholesterolemia
OCP Team Leader (Acting)	Jaya Vaidyanathan	Dosage Form	Immediate release capsule (5, 10 , and 20 mg)
Date of Submission	1-MAR-2012	Dosing Regimen	5, 10, 20, 40, and 60 mg/day with 2 – 4 week intervals to titrate up the next dose
Estimated Due Date of OCP Review	31-OCT-2012	Route of Administration	Oral
PDUFA Due Date	10-DEC-2012	Sponsor	Aegerion Pharmaceuticals
Division Due Date	9-NOV-2012	Priority Classification	Standard

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Comments (Study number)
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
In vivo mass balance:	X	2		CV145-006; AEGR-733-010
In vitro isozyme characterization	X	1		AEGR-733PC0006
In vitro metabolite Identity	X	1		AEGR-733PC0005
In vitro metabolism inhibition	X	4		AEGR-733PC0007; BMS-910055193; BMS-910055194; AEGR-733PC0021
In vitro metabolism induction	X	1		AEGR-733PC0022
In vitro efflux and uptake transporters inhibition:	X	1		AEGR-733PC0023
P-gp substrate assessment	X	1		AEGR-733PC0025
In vitro mechanism of uptake in human liver				
In vitro plasma protein binding:	X	1		BMS-910060036
Blood/plasma ratio:				
Pharmacokinetics (e.g., Phase I) -				
Dose proportionality, healthy volunteers – fasting & non-fasting single and multiple doses:	X	3		CV145-001 (single ascending dose); CV145-002 (multiple ascending dose); CV145-010 (multiple dose)
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	1		AEGR-733-018
In-vivo effects of primary drug:	X	4		AEGR-733-002; AEGR-733-013; AEGR-733-015; AEGR-733-019
In-vitro:				
Subpopulation studies -				
ethnicity:				
pediatrics:				
gender & geriatrics:				
renal impairment:	X	1		AEGR-733-021
hepatic impairment:	X	1		AEGR-733-017
PD:				
Phase 1:				
Phase 3:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 203-858

PK/PD:				
Phase 2, dose ranging studies:				
Phase 3 clinical STUDIES (placebo controlled):				
Phase 3 clinical STUDIES (active controlled):				
Population Analyses -				
Meta-analysis:				
NONMEM:	X	(1)		Noted in Integrated Summary of Efficacy but not submitted
II. Biopharmaceutics				
Absolute bioavailability:	X	1		CV145-003
Bioequivalence studies – traditional design				
Relative bioavailability				
alternate formulation as reference:				
Food-drug interaction studies:	X	1		CV145-005
Absorption site				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Phenotype studies:				
Chronopharmacodynamics				
Pediatric development plan				
Literature References				
QT prolongation assessment	X	1		AEGR-733-011
Total Number of Studies		25		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING CHECKLIST FOR NDA 203-858

Filability and QBR comments				
	"X" if yes	**Comments**		
Application filable?	**X**			
Comments to be sent to firm?	**X**	**Please advise when you will submit the lomitapide population pharmacokinetic data. The following are the general expectations for submitting future population pharmacokinetic datasets and models:** **All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been *excluded from the analysis* should be flagged and maintained in the datasets.** **Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).** **A model development decision tree and/or table which gives an overview of modeling steps.** **For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.**		
QBR questions (key issues to be considered)	• **What is the difference of lomitapide PK between HoFH patients and healthy volunteers?** • **What is the exposure-efficacy and safety relationships for lomitapide/metabolites in HoFH patients?** • **What will the effect of coadministration of moderate and mild CYP inhibitors on lomitapide exposure?** • **What are the covariates effects on population PK of lomitapide?** • **What are the effects of hepatic and renal impairment on the exposure of lomitapide, M3, and M1?** • **Will the food effect study be valid since they studied the 50 mg capsule that is not the highest to-be-marketed strength and did not study in the pivotal clinical trial?** • **What is the potential for interaction between lomitapide and fat soluble vitamins?**			
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 203-858

Filing Memo

CLINICAL PHARMACOLOGY	
NDA:	**203-858**
Compound:	Lomitapide (Trade name to be determined)
Sponsor:	Aegerion Pharmaceuticals
Submission Date:	March 1, 2012
Relevant IND:	50,820
From:	S.W. Johnny Lau, R.Ph., Ph.D.

Background

The sponsor submits NDA 203-858 to seek marketing approval for the 5, 10, and 20 mg lomitapide oral immediate release capsules 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 patients with homozygous familial hypercholesterolemia.

Findings

To support NDA 203-858's Clinical Pharmacology and Biopharmaceutics sections, the sponsor submitted studies' results as indicated in the table above. Findings' highlights follow:

- The clinically-tested formulation is identical to the to-be-marketed formulation for the 5 and 20 mg strength immediate release capsules. The sponsor requested a biowaiver for the 10 mg strength. Also, the particle size (b) (4) of lomitapide may be different between the clinically-tested and to-be-marketed lomitapide drug substance. This reviewer notified ONDQA and ONDQA Biopharmaceutics reviewers for the drug substance issues.
- 25 Clinical Pharmacology studies (see Attachment for details):
  - 10 in vitro human biomaterial studies
  - 1 absolute bioavailabiliy study
  - 2 mass balance studies
  - 1 food effect study
  - 3 pharmacokinetic studies
    - 1 single ascending dose
    - 2 multiple ascending dose
  - 5 in vivo drug interaction studies
  - 2 specific population studies (renal and hepatic impairment)
  - 1 dedicated QT prolongation study

The sponsor provided:

- Annotated label for review and the submitted information appears to be adequate to review the proposed labeling.
- Electronic data files for further review

The sponsor did not provide:

- Simulation results of interaction between lomitapide and mild as well as moderate cytochrome P450 inhibitors as recommended in the preNDA meeting.
- Population pharmacokinetic analysis – which is acceptable per the preNDA meeting agreement that given the small size of the Phase 3 trial as well as the titration scheme used, a population PK analysis will not provide useful information. The sponsor will conduct a population PK analysis later in development combining data from pediatric studies.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 203-858

Attachment starts here.

Type of Study (Phase)	Protocol ID (Sponsor)	Location of Study Report	Study Status (Dates); Type Of Report	Population Studied	Objectives	Study Design	Lomitapide Dose/Regimen	Number of Subjects		
								Total Enrolled	Lomitapide	Control
5.3.1 Reports of Biopharmaceutic Studies										
5.3.1.1 Bioavailability (BA) Study Reports										
BA (Ph 1)	CV145-005 (BMS)	5.3.1.1	Complete (Oct 97 - Dec 97) Full CSR	HV	Safety and PK, effect of food (fasted, low- and high-fat diet)	R, SD, OL, 3-period CO	Single oral dose 50 mg	25	25	None
5.3.1.2 Comparative BA and Bioequivalence Reports (N/A)										
5.3.1.3 In Vitro – In Vivo Correlation Study Reports (N/A)										
5.3.1.4 Reports of Bioanalytical Methods for Human Studies										
Analytical method validation	BMS-910061694 (BMS)	5.3.1.4	Method used in studies: CV145-002; CV145-003; CV145-005; CV145-006; and CV145-010							
Analytical method validation	7881-114 (b) (4)	5.3.1.4	Method used in studies: AEGR733-010 and AEGR733-018							
Analytical method validation	BMS-910062132 (BMS)	5.3.1.4	Method used in studies: CV145-002; CV145-003; CV145-005; CV145-006; and CV145-010							

Type of Study (Phase)	Protocol ID (Sponsor)	Location of Study Report	Study Status (Dates); Type Of Report	Population Studied	Objectives	Study Design	Lomitapide Dose/Regimen	Number of Subjects		
								Total Enrolled	Lomitapide	Control
5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials										
5.3.2.1 Plasma Protein Binding Study Reports										
Plasma protein binding was evaluated in Study BMS-910060036, which included samples from several animal species, as well as humans; therefore, the report is provided in M4.2.2.3. Additionally, plasma protein binding was assessed in samples obtained in studies conducted in subjects with hepatic impairment (AEGR-733-017) and renal impairment (AEGR-733-021); please refer to M5.3.3.3 for details on these studies.										
5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies										
In vitro metabolism	AEGR-733PC0005 (Aegerion)	5.3.2.2	Complete (Jul 07 – Sep 07) Non-GLP report	N/A – in vitro	Stability of lomitapide in human liver microsomes Identification of metabolites	*In vitro*	lomitapide: 1, 10 and 50 µM	N/A		
In vitro metabolism	AEGR-733PC0006 (Aegerion)	5.3.2.2	Complete (Nov 07 – Jan 08) Non-GLP report	N/A – in vitro	To determine the human cytochrome P450 enzymes responsible for the formation of prominent metabolites of lomitapide	*In vitro*	0.01-25 µM	N/A		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 203-858

Type of Study (Phase)	Protocol ID (Sponsor)	Location of Study Report	Study Status (Dates); Type Of Report	Population Studied	Objectives	Study Design	Lomitapide Dose/Regimen	Number of Subjects		
								Total Enrolled	Lomitapide	Control
In vitro metabolism	AEGR-733PC0007 (Aegerion)	5.3.2.2	Complete (Aug 07 – Dec 08) Non-GLP report	N/A – in vitro	Investigation of inhibitory potential of lomitapide on CYP enzymes and on warfarin in human liver microsomes	*In vitro*	0.1, 1, 10, 50 and 100 µM	N/A		
5.3.2.3 Reports of Studies Using Other Human Biomaterials										
In vitro metabolism	BMS-910055193 (BMS)	5.3.2.3	Complete (Apr 96) Non-GLP report	N/A – in vitro	To determine inhibitory activity of lomitapide on CYP P450 2D6	*In vitro*	0-300 µM	N/A		
In vitro metabolism	BMS-910055194 (BMS)	5.3.2.3	Complete (Apr 96) Non-GLP report	N/A – in vitro	To determine inhibitory activity of lomitapide on CYP P450 3A4	*In vitro*	0-300 µM	N/A		
Type of Study (Phase)	**Protocol ID (Sponsor)**	**Location of Study Report**	**Study Status (Dates); Type Of Report**	**Population Studied**	**Objectives**	**Study Design**	**Lomitapide Dose/Regimen**	**Number of Subjects**		
								Total Enrolled	**Lomitapide**	**Control**
In vitro metabolism	AEGR-733PC0022 (Aegerion)	5.3.2.3	Complete (Nov 11) Non-GLP report	N/A – in vitro	To determine induction potential of lomitapide, M1 and M3 on CYP1A2 CYP3A4, CYP2B6	*In vitro*	Concentrations: lomitapide: 0.2-20 ng/mL M1: 0.5- 50 ng/mL M3: 6.0-600 ng/mL	N/A		
In vitro metabolism	AEGR-733PC0021 (Aegerion)	5.3.2.3	Complete (Nov 11) Non-GLP report	N/A – in vitro	To determine inhibitory activity of M1 and M3 against 9 human CYP P450s using pooled human liver microsomes	*In vitro*	M1 and M3 concentrations: 0, 0.01, 0.1, 1, 10, and 30 µM	N/A		
In vitro metabolism	AEGR-733PC0023 (Aegerion)	5.3.2.3	Complete (Dec 11) Non-GLP report	N/A – in vitro	To evaluate the inhibition potential of lomitapide on efflux and uptake transporters.	*In vitro*	Efflux transporters: 0.19-6 µg/mL, Hepatic and renal uptake transporters: 40 ng/mL	N/A		

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 203-858

Type of Study (Phase)	Protocol ID (Sponsor)	Location of Study Report	Study Status (Dates); Type Of Report	Population Studied	Objectives	Study Design	Lomitapide Dose/Regimen	Number of Subjects		
								Total Enrolled	Lomitapide	Control
In vitro metabolism	AEGR-733PC0025 (Aegerion)	5.3.2.3	Complete (Dec 11) Non-GLP report	N/A – in vitro	P-gp substrate assessment of lomitapide in a Caco-2 cell monolayer system	*In vitro*	1, 3.5, and 8 µM	N/A		
5.3.3 Reports of Human Pharmacokinetic (PK) Studies										
5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports										
PK/PD (Ph 1)	CV145-001 (BMS)	5.3.3.1	Complete (Jul 96 - Sep 96) Full Report	Male HV with TC ≥195 mg/dL	Safety, PK, PD	R, SD, DB, PC, dose escalation	Single oral dose 1, 5, 25, 50, 100 or 200 mg	55	37 1, 5, 25, 50 and 200 mg (each, n=6) 100 mg n=7	Placebo: 18
PK/PD (Ph 1)	CV145-002 (BMS)	5.3.3.1	Complete (Jul 96 - Sep 96) Full Report	HV with TC ≥200 mg/dL	Safety, PK, PD	R, MD, DB, PC, dose escalation low-fat diet	Multiple oral dose 10, 25, 50, 100[1] mg QD x 14 d	36	24 10, 25, 50 and 100 mg (each, n=6)	Placebo: 12
PK/PD/BA (Ph 1)	CV145-003 (BMS)	5.3.3.1	Complete (Jan 96 - Feb 96) Full Report	HV with TC ≥200 mg/dL	Safety, PK, PD, bio-availability	R, SD, DB, PC, dose escalation low-fat diet	Single IV dose 7.5, 15, 30, or 60 mg Single oral dose 50 mg[2]	32	24	Placebo: 8
PK (Ph 1)	CV145-006 (BMS)	5.3.3.1	Complete (Aug 97 - Sep 97) Full Report	HV	Safety, ADME	SD, OL	Single oral solution [^{14}C] 50 mg (100 µCi)	6	6	None
Type of Study (Phase)	**Protocol ID (Sponsor)**	**Location of Study Report**	**Study Status (Dates); Type Of Report**	**Population Studied**	**Objectives**	**Study Design**	**Lomitapide Dose/Regimen**	**Number of Subjects**		
								Total Enrolled	**Lomitapide**	**Control**
PK/PD (Ph 1)	CV145-010 (BMS)	5.3.3.1	Complete (Nov 97 - Jan 98) Full Report	HV females with TC ≥200 mg/dL	Safety, PK, PD	R, MD, DB, PC, low-fat diet	Multiple oral dose 10 or 25 mg QD x 14 d	18	10 mg: 6 25 mg: 6	Placebo: 6
PK (Ph 1)	AEGR-733-010 (Aegerion)	5.3.3.1	Complete (Dec 10 - Dec 10) Full Report	HV, male	Safety, AME	SD, OL	Single oral solution [^{14}C] 50 mg	6	6	None
5.3.3.2 Patient PK and Initial Tolerability reports (N/A)										
5.3.3.3 Intrinsic Factor PK Study Reports										
PK (Ph 1)	AEGR-733-017 (Aegerion)	5.3.3.3	Complete (Feb 2011 - Apr 11) Full Report	HV and mild to moderate hepatic impairment	Safety, PK	SD, OL	Single oral dose 60 mg	32	32	None
PK (Ph 1)	AEGR-733-021 (Aegerion)	5.3.3.3	Complete (Jul 11- Aug 11) Full Report	HV and renal impairment	Safety, PK	SD, OL	Single oral dose 60 mg	14	14	None

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 203-858

Type of Study (Phase)	Protocol ID (Sponsor)	Location of Study Report	Study Status (Dates); Type Of Report	Population Studied	Objectives	Study Design	Lomitapide Dose/Regimen	Number of Subjects		
								Total Enrolled	Lomitapide	Control
5.3.3.4 Extrinsic Factor PK Study Reports										
PK/DDI (Ph 1)	AEGR-733-002 (Aegerion)	5.3.3.4	Complete (May 06 - Nov 07) Full Report	HV	Safety, PK, PD, DDI with LLT[3] and dextro-methorphan	R, MD, OL	Multiple oral dose 10 mg QD x 7 d 60 mg QD x 7 d	129[3]	10 mg: 80 60 mg: 47	None
PK/DDI (Ph 1)	AEGR-733-013 (Aegerion)	5.3.3.4	Complete (Dec 10 – Dec 10) Full Report	HV, male	Safety, PK DDI with warfarin, PD (INR/PT)	MD, OL, 2-period	Multiple oral doses 60 mg QD x 12 d	16	16	None
PK/DDI (Ph 1)	AEGR-733-015 (Aegerion)	5.3.3.4	Complete (Feb 11 - Jun 11) Full Report	HV, female	Safety, PK DDI with Ortho-Cyclen	R, MD, DB, PC, 2-period CO	Multiple oral doses 50 mg QD x 8 d	28	27[4]	Placebo: 27[4]
PK/DDI (Ph 1)	AEGR-733-018 (Aegerion)	5.3.3.4	Complete (Nov 10 – Dec 10) Full Report	HV	Safety, PK DDI with keto-conazole	SD, OL, 2-period low-fat diet	Single oral dose 60 mg (x 2)	30	30	None
PK/DDI (Ph 1)	AEGR-733-019 (Aegerion)	5.3.3.4	Complete (Dec 10 – Dec 10) Full Report	HV	Safety, PK DDI with simvastatin	MD, OL	Multiple oral dose 60 mg QD x 6 d	16	16	None
5.3.3.5 Population PK Study Reports (N/A)										
Type of Study (Phase)	**Protocol ID (Sponsor)**	**Location of Study Report**	**Study Status (Dates); Type Of Report**	**Population Studied**	**Objectives**	**Study Design**	**Lomitapide Dose/Regimen**	**Number of Subjects**		
								Total Enrolled	**Lomitapide**	**Control**
5.3.4 Reports of Human Pharmacodynamic (PD) Studies (N/A)										
Pharmacodynamics was evaluated as part of 4 of the healthy subject PK/tolerability studies and 2 of the drug-drug interaction studies (please refer to Section 5.3.3.1 and 5.3.3.4, above). Specifically, PD was evaluated as part of the following studies: CV145-001, CV145-002, CV145-005, CV145-010, AEGR-733-002, and AEGR-733-013. Dose response evaluation is based on the pharmacodynamics assessments cited previously, as well as Study UP1001 (Ph 2).										
5.3.4.1 Healthy Subject PD and PK/PD Study Reports (N/A)										
5.3.4.2 Patient PD and PK/PD Study Reports (N/A)										
5.3.5 Reports of Efficacy and Safety Studies										
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication										
PK/TQT (Ph 1)	AEGR-733-011 (Aegerion)	5.3.5.1	Complete (May 11 – Sep 11) Full Report	HV	Safety, PK, PD TQTc study	R, SD, PC, 5-period CO	Single oral doses 25 (combination with keto-conazole), 75 and 200 mg	56	Lomitapide 75 mg: 56 Lomitapide 200 mg: 53	Placebo: 56 Keto-conazole: 200 mg: 55 Moxi-floxacin 400 mg: 53
PD/Safety (Ph 2)	CV145-009 (BMS)	5.3.5.1	Complete (Jan 99 - Dec 99) Abbreviated Report	LDL-C ≥160 mg/dL mean TG ≤500 mg/dL	Safety, PD, effect on hepatic fat	R, MD, DB, PC, low-fat diet	Multiple oral dose 25 mg QD x 4wk	76	38	Placebo: 38
Efficacy (Ph 2)	AEGR-733-003a[7] (Aegerion)	5.3.5.1	Complete (May 07 - Sep 07) Abbreviated Report	LDL-C ≥130[5] and <250 mg/dL TG ≤400 mg/dL	Safety, Efficacy	R, MD, DB, PC, active-control; low-fat diet (mono-therapy/ & combination w/atorva-statin)	Multiple oral dose 2.5, 5, 7.5 and 10 mg x 8 wk alone and in combination	113[6]	Total: 82[6]	Total: 31[6]

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 203-858

Type of Study (Phase)	Protocol ID (Sponsor)	Location of Study Report	Study Status (Dates); Type Of Report	Population Studied	Objectives	Study Design	Lomitapide Dose/Regimen	Number of Subjects		
								Total Enrolled	Lomitapide	Control
Efficacy (Ph 2)	AEGR-733-003b[7] (Aegerion)	5.3.5.1	Complete (Nov 07 - Aug 08) Full Report	LDL-C ≥130[5] and <250 mg/dL TG ≤400 mg/dL	Safety, Efficacy	R, MD, DB, PC, active-control; low-fat diet (mono-therapy/ & combination w/atorva-statin)	Multiple oral dose 5, 10 mg x 8 wk alone and in combination	157	Total: 104 5 mg alone: 26 5 mg + A: 26 10mg alone: 26 10 mg + A: 26	Total: 53 Placebo: 27 Atorva-statin alone 20 mg: 26
Efficacy (Ph 2)	AEGR-733-001 (Aegerion)	5.3.5.1	Complete (Jun 06 to Dec 06) Full Report	LDL-C ≥130[5] and <250 mg/dL TG ≤400 mg/dL	Safety, Efficacy	R, MD, DB, active-control; low-fat diet (mono-therapy & combination w/ ezetimibe)	Multiple oral dose QD x 12 wk 5 mg x 4 wk to 7.5 mg x 4 wk to 10 mg x 4 wk (as tolerated)	85	Total: 56 Lomitapide alone: 28 Lomitapide +Ezetimibe: 28	Ezetimibe alone 10 mg: 29
PD/Safety (Ph 2)	AEGR-733-004 (Aegerion)	5.3.5.1	Complete (Sep 07 - Sep 08) Full Report	LDL-C >100 and ≤190 mg/dL	Safety, PD, effect on hepatic fat	R, MD, DB, PC, low-fat diet (mono-therapy & combination with LLT)	Multiple oral dose 2.5, 5, 7.5, 10 mg QD x 12 wk alone 5 mg QD x 12 wk in combination	260	2.5 mg: 34 5 mg: 34 7.5 mg 34 10 mg: 35 5 mg in combination: with: Atorvastatin 20 mg: 28 Fenofibrate 145 mg: 33 Ezetimibe 10 mg: 29	Placebo: 33
Efficacy (Ph 2)	AEGR-733-006 (Aegerion)	5.3.5.1	Complete (May 08 - Aug 08) Full Report	LDL-C ≥130[5] and <250 mg/dL TG ≤400 mg/dL	Safety, Efficacy	R, MD, DB, active-control; low-fat diet (combi-nation w/atorva-statin)	Multiple oral dose QD x 8 wk 2.5 mg x 4 wk to 5 mg x 4 wk	44	Lomitapide + Atorvastatin 20 mg: 21	Atorva-statin 20 mg alone: 23
Efficacy (Ph 2)	UP1001 (U Penn)	5.3.5.1	Complete (Jun 03 - Feb 04) Full Report	HoFH	Safety, Efficacy	MD, OL, low-fat diet	Multiple oral dose QD x16 wk 0.03mg/kg x 4wk 0.10mg/kg x 4wk 0.3mg/kg x 4wk 1.0mg/kg x 4 wk	6	6	None
Efficacy (Ph 3)	UP1002/ AEGR-733-005 (Aegerion)	5.3.5.1	Complete (Dec 07 – Oct 11) Full report through Week 56; Week 78 data being analyzed	HoFH	Efficacy, Safety	MD, OL, 6-wk run-in, 26 wk dose escalation, 52-wk long-term treatment; low fat diet and standard of care	Multiple oral dose x 78 wk 5 to 60 mg QD escalated to MTD	29	29	None

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING CHECKLIST FOR NDA 203-858

Type of Study (Phase)	Protocol ID (Sponsor)	Location of Study Report	Study Status (Dates); Type Of Report	Population Studied	Objectives	Study Design	Lomitapide Dose/Regimen	Number of Subjects		
								Total Enrolled	Lomitapide	Control
Efficacy (Ph 3) (Extension for patients in UP1002/AEGR-733-005)	AEGR-733-012 (Aegerion)	5.3.5.3 (provided with ISS)	Ongoing (Start: Oct 09) Tables only (through cut-off date of 08Sept2011) *Placeholder for the future study report*	HoFH	Efficacy, Safety	MD, OL, long-term follow-on treatment; low fat diet and standard of care	MTD from AEGR-733-005	18	18	None
5.3.5.2 Study Reports of Uncontrolled Clinical Studies										
5.3.5.3 Reports of Analyses of Data from More than One Study										
ISE	Integrated Summary of Efficacy	5.3.5.3 Tables only (narrative in 2.7.3)	Integrated Summary	N/A						
ISS	Integrated Summary of Safety	5.3.5.3	Integrated Summary	N/A						
5.3.5.4 Other Study Reports										
Compassionate Use	Investigator Sponsored	5.3.5.4	Ongoing compassionate use program under Investigator Sponsored INDs	HoFH; FC	N/A	N/A	Individualized	3	3	None
Hepatic Biomarkers	Data from UP1002/AEGR-733-005 (Aegerion)	5.3.5.4	Sub-study of UP1002/AEGR-733-005 (Interim Report)	HoFH	Liver safety	MD, OL, 6-wk run-in, 26 wk dose escalation, 52-wk long-term treatment; low fat diet and standard of care	Multiple oral dose x 78 wk 5 to 60 mg QD escalated to MTD	29	29	None
5.3.6 Reports of Post-Marketing Experience (N/A)										
5.3.7 Case Report Forms and Individual Patient Listings – Provided within Each Individual Study Report (US NDA); Available Upon Request (EU MAA)										

Abbreviations : A=atorvastatin, ADME=absorption/distribution/metabolism/excretion, CO=crossover, d=day, DB=double-blind, DDI=drug-drug interaction, HV=healthy volunteers, L=lomitapide, LLT=lipid-lowering agents, MD=multiple dose, MTD = maximum tolerated dose, N/A=not applicable, OL=open-label, PC=placebo-controlled, PK=pharmacokinetic, PD=pharmacodynamic, QD=once daily, R=randomized, SD=single-dose, TC=total cholesterol, TG=triglyceride, wk=week

[1] Due to GI adverse events, subjects in the 100 mg group were discontinued on Day 8

[2] Patients who received 30 mg IV also received a single oral dose of 50 mg for a preliminary assessment of bioavailability.

[3] Lipid lowering therapies included in Study AEGR-733-002 included: Atorvastatin, simvastatin, rosuvastatin, fenofibrate, ezetimibe, extended-release niacin; three subjects were withdrawn prior to receiving lomitapide in the study; therefore, they received LLT only (1: Atorva 20 mg and 1: Rosuva 20 mg)

[4] One subject withdrew consent prior to the Check-in visit for Study Period 2 after completing Study Period 1; therefore, 28 subjects were enrolled and received Ortho-cyclen during Study Phase 1; however, they did not enter the lomitapide/placebo periods (period 2 and 3)

[5] LDL-C >130 and <250 mg/dL for patients with 2 or more National Cholesterol Education Program (NCEP) risk factors and >160 and <250 mg/dL for patients with 0 or 1 risk factor.

[6] Dose groups: lomitapide alone: 2.5 mg (n=7), 5 mg (n=10), 7.5 mg (n=10), 10 mg (n=12); lomitapide + atorvastatin 20 mg: 2.5 mg (n=11), 5 mg (n=11), 7.5 mg (n=12), 10 mg (n=9); placebo (n=13); atorvastatin 20 mg (n=11); and atorvastatin 80 mg (n=7)

[7] The first study conducted under protocol AEGR-733-003 is referred to as AEGR-733-003a and the second study conducted under protocol AEGR-733-003 after the study had been halted prematurely and restarted under an amended protocol with a different design as protocol 733-003b. The two studies reported under Protocol 733-003 have been summarized in separate clinical study reports.

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

/s/

SZE W LAU
05/07/2012

JAYABHARATHI VAIDYANATHAN
05/07/2012