30 May 2013
EMA/CHMP/274464/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lojuxta

International non-proprietary name: Lomitapide

Procedure No. EMEA/H/C/002578/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

List of abbreviations

ABL	Abetalipoproteinaemia
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
apo B	Apolipoprotein B
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical, therapeutic, chemical (class)
AUC	Area under the curve
BLQ	Below the limit of quantification
BMI	Body mass index
CHD	Coronary heart disease
Cmax	Maximum plasma concentration
CNS	Central nervous system
CPK	Creatine phosphokinase
CV(S)	Cardiovascular
CVD	Cardiovascular disease
DDI	Drug-drug interaction
ECG	Electrocardiogram
ED50	50% effective dose
ELF	Enhanced Liver Fibrosis
ER	Endoplasmic reticulum
ESRD	End-stage renal disease
GGT	Gamma glutamyl transpeptidase
GI	Gastrointestinal
GLP	Good laboratory practice
hERG	Human ether-a-go-go-related gene
HA	Hyaluronic acid
HDL	High density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HoFH	Homozygous familial hypercholesterolemia
IC50	50% inhibitory concentration
INR	International normalized ratio
IV	Intravenous
LDL	Low density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDL-R	Low-density lipoprotein receptor
LFT	Liver function test
LLT	Lipid-lowering therapy
MedDRA	Medical Dictionary for Regulatory Activities
MOA	Mechanism of action
MRI	Magnetic resonance imaging
MTP	Microsomal triglyceride transfer protein
MTP-I	Microsomal triglyceride transfer protein inhibitor
NASH	Nonalcoholic steatohepatitis
NMRS	Nuclear magnetic resonance spectroscopy
NOAEL	No observed adverse effect level
NOEL	No observed effect level
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	Per os
PT	Prothrombin time
SNP	Single nucleotide polymorphisms
SUV	Small unilamellar vesicles

QD	Once daily
SAE	Serious adverse event
SD	Standard deviation
SOC	System organ class
TEAE	Treatment-emergent adverse event
TEM	Transmission electron microscopy
Tmax	Time of maximum plasma concentration
UGT	Uridinediphosphate-glucuronosyltransferase
ULN	Upper limit of normal
VLDL	Very-low-density lipoprotein
WBC	White blood cell (count)
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Aegerion Pharmaceuticals submitted on 1 March 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Lojuxta (originally under the name Lomitapide Aegerion), through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 May 2011.

The applicant applied for the following indication:

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

The effect of Lomitapide Aegerion on cardiovascular morbidity and mortality has not been determined.

The legal basis for this application refers to Article 8(3) of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/306/2011 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/306/2011 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Marketing Authorisation under exceptional circumstances

The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004 based on the following claim:

The applicant claimed that he is unable to provide comprehensive clinical data on the efficacy and safety of the medicinal product under normal conditions of use, as the indication for which the product in question is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence.

According to Article 14(8) of Regulation (EC) No 726/2004, marketing authorisations under exceptional circumstances may be granted subject to certain specific obligations. Continuation of the marketing authorisation shall be linked to the annual reassessment of these conditions.

The applicant proposed the following obligations and conditions:

— the applicant will have to conduct a prospective observational cohort study (registry) to further assess the safety of lomitapide in the treatment of patients with HoFH and to further assess the long-term effectiveness of lomitapide in usual care.

— the medicinal product in question may be supplied on restricted medical prescription only

— the package leaflet and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

In addition, risk minimisation measures will be set up by the applicant as agreed with the Agency and detailed in the product's RMP and the conditions for the safe and effective use of the product.

New active Substance status

The applicant requested the active substance lomitapide contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice / Protocol Assistance

The applicant received Scientific Advice from the CHMP on 18 February 2010. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

Lojuxta has been given a Marketing Authorisation in the USA on 21 December 2012.

A new application was filed in the following countries: Canada, Brazil.

1.2. Manufacturers

Manufacturer responsible for import and batch release in the European Economic Area

Catalent Pharma Solutions
Wingates Industrial Park
Lancaster Way

Westhoughton
Bolton, Lancashire BL5 3XX
United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Robert James Hemmings

- The application was received by the EMA on 1 March 2012.
- The procedure started on 21 March 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 June 2012.
- During the meeting on 19 July 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The consolidated List of Questions was sent to the applicant on 20 July 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 November 2012.
- The summary report of the inspection carried out on 25 February 2013 was issued on 12 April 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 22 January 2013.
- During the CHMP meeting on 21 February 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 March 2013.
- During an ad-hoc Expert group meeting of on 9 April 2013, experts addressed the questions raised by the CHMP with respect to safety and efficacy of lomitapide.
- During the PRAC meeting on 11 April 2013, the PRAC issued the PRAC advice on the submitted RMP.
- During the CHMP meeting on 25 April 2013, the CHMP agreed on a second List of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the second List of Outstanding Issues on 29 April 2013.
- During the PRAC meeting on 16 May 2013, the PRAC issued the PRAC advice on the updated submitted RMP.
- During the meeting on 30 May 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a

Marketing Authorisation under exceptional circumstances for Lojuxta.

2. Scientific discussion

2.1. Introduction

Homozygous familial hypercholesterolemia (HoFH) is a rare, life-threatening autosomal dominant genetic disease characterised by marked elevations in low-density lipoprotein cholesterol (LDL-C). The disease is typically caused by homozygosity or heterozygosity for mutations in the LDL receptor (LDL-R) gene leading to impairment of LDL-R function. Phenotype copies result from mutations in other genes, including apo B, proprotein convertase subtilisin/kexin type 9 (PCSK9), and the autosomal recessive hypercholesterolemia (ARH) LDL-R adapter protein, which alter the function or expression of LDL-R or adversely affect LDL binding to LDL-R interactions. The prevalence of defects in both alleles of the LDL-R (homozygous) has been calculated to occur in approximately 1 in 1 million persons, based on the estimated prevalence of 1 in 500 for the more common heterozygous FH, which is characterised by less severe hypercholesterolemia. The prevalence of HoFH has been reported to be higher in certain populations with a presumed founder effect. The frequency of HoFH exceeds 0.2% in Ashkenazi Jews of Lithuanian descendent, Afrikaners, French Canadians, Christian Lebanese, Druze, Sephardic Jews and Finns.

Early onset of atherosclerosis is generally accompanied by accelerated disease progression, even in the early teenage years. If untreated, most subjects do not survive past age 30 due to sudden death from acute myocardial infarction (MI) or acute coronary insufficiency. Early initiation of aggressive treatment for these subjects is therefore essential. In terms of clinical management of these patients, statins are the treatment of choice for hypercholesterolemia due to their LDL C-lowering potency and well-documented benefits in terms of CVS morbidity and mortality. However, these therapies are not always adequate in patients with HoFH, due to the dependence of statin efficacy on up-regulation of a functional LDL-R.

Lomitapide is an oral small molecule inhibitor of microsomal triglyceride transfer protein (MTP). MTP is an intracellular lipid-transfer protein responsible for transferring triglycerides and cholesterol esters onto apolipoprotein B (apo B) in the assembly of both very low density lipoprotein (VLDL) in the liver (the precursor to low density lipoprotein [LDL]) and chylomicrons in the intestine. Inhibition of MTP activity has been shown to reduce hepatic VLDL and intestinal chylomicron secretion, and consequently to lower plasma lipids of both hepatic and intestinal origin. The proposed and recommended dose range for lomitapide is 5 mg to 60 mg given orally once daily.

The clinical programme of lomitapide consisted of a total of 24 studies, including phase 1, 2, and 3 studies conducted in healthy adults, adults with HoFH, adults with elevated LDL-C levels (without HoFH), adults with hepatic impairment, and adults with end-stage renal disease on hemodialysis. Across these studies, a total of 1145 patients and subjects were treated, including 943 who received lomitapide, either as monotherapy or coadministered with another lipid lowering therapy. One pivotal single-arm open label study in the targeted population of 29 patients with HoFH has been conducted.

The proposed indication for lomitapide was:

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

The effect of lomitapide Aegerion on cardiovascular morbidity and mortality has not been determined.

Lomitapide was proposed as a product for restricted medicinal prescription.

2.2. Quality aspects

2.2.1. Introduction

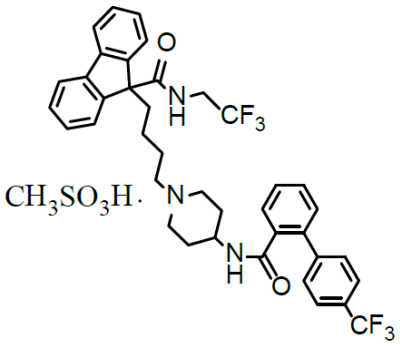
Lojuxta is presented as hard capsules containing 5 mg, 10 mg and 20 mg of lomitapide mesylate as active substance.

Other ingredients are: pregelatinized starch, sodium starch glycolate, microcrystalline cellulose, lactose monohydrate, silica, colloidal anhydrous, magnesium stearate, gelatin, titanium dioxide (E171), red iron oxide (capsule shell 5 mg and 20 mg only), and shellac, black iron oxide, propylene glycol in the printing ink.

The product is available in high density polyethylene bottles with an induction seal and fitted with a 38-mm twist off closure.

2.2.2. Active substance

The chemical name of lomitapide mesylate is N-(2,2,2-trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl] amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, methanesulfonate salt and has the following structure:



The structure of lomitapide mesylate has been derived from the route of synthesis and was further elucidated satisfactorily by elemental analysis, IR, UV, 1H-NMR, 13C-NMR, MS.

Lomitapide mesylate is a white to off-white powder, moderately hygroscopic and slightly soluble in water.

Lomitapide mesylate has a non-chiral molecular structure.

Polymorphism has been observed for lomitapide mesylate. Of the different solid-state forms, hydrates, and solvates identified in the polymorph studies, only 2 desolvated solid-state forms, Form I and Form II, were identified in batches after drying to final drug substance. The polymorphism will be controlled and limited according to batches used in the clinical studies.

Manufacture

Lomitapide mesylate is synthesized in several steps using well defined starting materials with acceptable specifications. The final particle size distribution is controlled during the crystallisation step. The specification of the active substance includes satisfactory limits for particle size distribution based on biobatch data.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well characterised and discussed with regards to their origin.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for appearance, identification (FT-IR, HPLC), assay (HPLC), related substances (HPLC), residual solvents (GC), water content (KF), heavy metals, particle size, polymorphism and water content.

The analytical methods used have been adequately described. Compendial and in-house methods are appropriately validated in accordance with ICH guidelines.

Batch analysis data of the active substance are provided. The results are within the specifications and consistent from batch to batch.

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. Additional specifications have been set for particle size and polymorphism for the reasons exposed above.

Stability

Stability data from the manufacturer stored in the intended commercial package for 49 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed. Results on stress conditions (heat, acid, alkaline, oxidative) were also provided.

The following parameters were tested: appearance, identification, assay, related substances, polymorphism, particle size and water content. The analytical methods used were the same as for release and were stability indicating.

The stability results support the retest period of 12 months when stored below 25 °C in double LDPE bags with desiccant between the bags, placed in a fibre tube.

2.2.3. Finished medicinal product

Lojuxta is available in three strengths: 5 mg, 10 mg and 20 mg of lomitapide, as mesylate

Pharmaceutical development

The manufacture of lomitapide was transferred to Aegerion during nonclinical and clinical development. The synthesis of the active substance remained unchanged. The finished product formulation and manufacturing processes have had minor changes from the original processes. All changes introduced have been satisfactorily supported with regards quality aspects as well as the performance of the product *in vivo*.

The 10 mg strength has not been used in clinical trials. However, it is considered that a bioavailability study was not necessary as the 10 mg strength complies with the waiver criteria for an additional strength according to Guideline on the Investigation of Bioequivalence.

The impact of the active substance particle size and polymorphism was considered during pharmaceutical development and satisfactory studies were submitted supporting the limits in the specification of the active substance.

The excipients used in the lomitapide drug product are typical excipients found in hard-shell gelatin capsule solid oral dosage forms. The compatibility of the drug substance with excipients has been demonstrated through the stability data.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included above and in section 6.1 of the SmPC.

The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is high density polyethylene bottles with an induction seal and fitted with a 38-mm twist off closure. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

Lactose monohydrate and the gelatin capsule shells are the only two materials of animal origin.

It is confirmed that the lactose monohydrate is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

There are no novel excipients used in the manufacture of Lojuxta.

Manufacture of the product

The manufacturing process for the production of Lojuxta capsules is a conventional method and has been sufficiently described.

The processes for the manufacture of Lojuxta 5 mg, 10 mg, and 20 mg capsules will be validated post-authorisation in accordance with EMEA guidance CPMP/QWP/848/96 EMEA/CVMP/598/99, Note for Guidance on Process Validation, March 2001.

The in-process controls have been evaluated and justified with results from pilot scale manufacturing and are adequate for a standard manufacturing process of this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (HPLC, MS), assay (HPLC), related substances (HPLC), dissolution, uniformity of dosage units (HPLC), water content and microbiological quality.

Batch analysis results are provided for each strength at different manufacturing sites confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The analytical methods used have been adequately described. Compendial and in-house methods are appropriately validated in accordance with ICH guidelines.

Stability of the product

Stability data of finished product stored under long term conditions for 24 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided for all three strengths. The batches of medicinal product are manufactured according to the initial and proposed for marketing manufacturing process, packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, related substances, dissolution, water content and biological quality.

Results on stress conditions (heat, acid, alkaline, oxidative) were provided. The analytical procedures used are confirmed as stability indicating.

As the active substance is not photosensitive, it was found acceptable not to submit photostability studies with the finished product.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

2.3.1. Introduction

Lomitapide was proposed for use as an adjunct to diet and other lipid-lowering drugs with or without low-density lipoprotein (LDL) apheresis in patients with homozygous familial hypercholesterolaemia (HoFH) and is proposed as a chronic treatment at a dose of 5mg to 60mg, given once daily. A dose escalation approach was suggested in order to achieve the optimal individualised dose to maximise efficacy and minimise gastrointestinal effects and transaminase elevations. Lomitapide represents a proposed new class of drugs with a mechanism of action that differs from those of other classes of lipid lowering agents. It is an orally bioavailable small molecule that inhibits microsomal triglyceride transfer protein (MTP), which plays a key role in the assembly of lipoproteins in the liver and intestines. MTP is found in the lumen of the endoplasmic reticulum and is responsible for binding and shuttling individual lipid molecules between membranes. Lomitapide inhibits MTP, thereby reducing lipoprotein release and circulating concentrations of lipoprotein-borne lipids including cholesterol and triglycerides in the blood stream. Lomitapide has a mechanism of action that differs from those of other classes of lipid lowering agents.

Patients with homozygous familial hypercholesterolemia have severely elevated lipid concentrations, causing patients to develop cardiovascular disease mostly before age 30. Lomitapide was developed because currently available drug therapies fail to adequately reduce LDL cholesterol levels in these patients and the only alternative treatment is plasma apheresis, a mechanical filtration used to remove lipids from the blood.

All toxicity and safety pharmacology studies that were considered pivotal for the human safety assessment were conducted in compliance with Good Laboratory Practice (GLP) regulations.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies

In vitro and *in situ* studies based on previously reported methods were used to demonstrate the effects of lomitapide on microsomal triglyceride transfer protein (MTP) activity. The MTP binds to and transfers lipid molecules from the site of lipid synthesis to apolipoprotein B (apo B)-containing lipoproteins in both, enterocytes and hepatocytes. Inhibition of MTP prevents the assembly of apo B-containing lipoproteins, thus reducing their release into the systemic circulation. Lomitapide treatment is intended to reduce total cholesterol (total C), LDL-C, triglycerides, and apo B in patients with homozygous familial hypercholesterolemia (HoFH).

Lomitapide was shown to inhibit recombinant human MTP-mediated transport of several neutral lipid substrates. In an assay that selectively assessed lipid substrate transfer between donor and acceptor small uni-lamellar vesicles (SUV, a type of liposome), triglyceride and cholesteryl ester (CE) transfers were equivalently inhibited with an approximate IC_{50} of 0.5 nM. The IC_{50} for triglyceride transport was 1.2 nM. In contrast, the transfer of phosphatidylcholine (PC) was weakly inhibited (IC_{50} >100 nM; maximum decrease of 18%). The MTP has a specific preference for binding and transporting nonpolar lipids (e.g., triglycerides) compared with phospholipids. In a competitive assay when human MTP was incubated with a photoactivatable analogue that binds to MTP in the absence or presence of lomitapide the binding of the analogue was reduced by 15% and 69% in the presence of 10 and 100 nM lomitapide, indicating that lomitapide binds directly to MTP. A similar competitive assay was performed in human hepatoblastoma cells (HepG2) cells. The amount of triglyceride bound to MTP was reduced in a dose-dependent manner with an IC_{50} of 1.2 nM. Furthermore, lomitapide potently inhibited triglyceride transport of rat, hamster, and human MTP, with IC_{50} values between 5 and 7 nM.

With respect to the possible pharmacological activity of the metabolites, the major lomitapide metabolite, M3, was about 400-fold less active than lomitapide as an inhibitor of triglyceride transfer activity of bovine MTP. Another important metabolite of lomitapide, M1, had no significant inhibitory activity.

Overall, the CHMP noted that the studies showed that lomitapide is active in inhibiting lipid transfer, confirming its proposed mechanism of action. *In vitro* activity of lomitapide in lipid transfer assays seems to differ more between studies than between species.

In vivo studies

The primary pharmacodynamic actions of lomitapide *in vivo* were characterised using rodent (mouse, rat, and hamster) and nonrodent (rabbit and monkey) models.

Rats: A rat Triton model was used to evaluate the effects of lomitapide-mediated inhibition of MTP on very low density lipoprotein (VLDL) secretion in fasted versus fed rats (VLDL is the lipoprotein that contains the highest amount of triglycerides). Triton blocks the clearance of plasma triglyceride-rich lipoproteins, which are secreted from the liver and intestine. Pre-

treatment of fasted or fed rats with lomitapide inhibited the Triton-induced accumulation of plasma triglycerides. The ED_{50} values of 0.19 or 0.15 mg/kg were obtained following oral or intravenous administration of lomitapide to fasted rats and the ED_{50} following oral administration to fed rats was 0.15 mg/kg (IV administration not determined in fed rats). Approximate equivalent potency was thus observed in both fasted and fed states, indicating that VLDL secretion from both intestine and liver are inhibited by lomitapide. No elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were observed at 3.5 h following lomitapide administration.

Oral administration of lomitapide to rats once daily for 3 days resulted in a dose-dependent lowering of total cholesterol; the oral ED_{50} was 2.5 mg/kg; VLDL/LDL as well as HDL-cholesterol were lowered equivalently at all doses (0.3, 1, 3 and 10 mg/kg). Plasma triglyceride levels were reduced by 36% and 63% compared to controls at 3 and 10 mg/kg doses, respectively. No changes in plasma levels of ALT or AST were observed.

Hamsters: Hamsters have proved to be a useful model of human lipoprotein metabolism, since hamster LDL-cholesterol responds to changes in dietary lipid intake in a manner that is essentially identical to that in humans and the kinetics of LDL-cholesterol have been worked out in detail in this species. Oral administration of lomitapide to hamsters (4-5 per treatment group) once daily for 3 days resulted in dose-dependent reductions in total cholesterol, VLDL+LDL-C, and HDL-C. The ED_{50} for total cholesterol reduction was 2.0 mg/kg. At 10 mg/kg, the highest dose tested the plasma triglyceride levels were also significantly reduced (by 26%). A slight increase in plasma AST was also observed at 10 mg/kg (<2× control value).

To explore the effects of extended inhibition of MTP, hamsters on standard or high-fat diets received lomitapide orally at daily doses of 1, 3, and 6 mg/kg for up to 3 weeks. Hamsters on the high fat diet developed a stable hyperlipidemic state after 5 days of this diet. Lomitapide resulted in a significant dose-dependent lowering of plasma total cholesterol after 1 to 3 weeks of dosing for both diets. However, ED_{50} values for total-C reduction in hamsters fed a high-fat diet were approximately 50% lower than those for hamsters on the standard diet at all 3 time intervals. Tissue triglyceride levels were determined in liver and small intestine. A dose dependent elevation in tissue triglyceride levels was observed (up to 6.5-fold in small intestine and up to 3-fold in liver; no increase was observed over the weeks). The decreases in HDL-C were unlikely to be due to a direct effect on HDL production given that the ED_{50} for inhibition of secretion of apo A1 in HepG2 cells was about 8000× higher than the ED_{50} for inhibition of secretion of apo B. Hamsters (4 per treatment group) were dosed with lomitapide at 0 or 10 mg/kg once daily for 7 days. Groups of hamsters were sacrificed at various days following the cessation of treatment, up to 6 days after treatment. Plasma total cholesterol and triglycerides were lowered by >85% compared to controls after 3 or 7 days of dosing. Recovery of both parameters occurred 48 hours or 72 hours post-dose, respectively. After treatment, triglycerides at first rose to levels higher than control levels, but they stabilized to control levels at 72 h post-dose. At Days 3 and 7, tissue levels of triglycerides were increased approximately 3-fold (hepatic). The CHMP noted that after the cessation of treatment in hamsters, a rebound effect seemed to occur on plasma triglycerides, but not on cholesterol.

Rabbits: Homozygous Watanabe-heritable hyperlipidaemic (WHHL) rabbits have hepatic LDL receptor activity <5% that of normal rabbits, which results in dramatically elevated levels of apo B-containing lipoproteins. For this reason, WHHL rabbits are a good model for human HoFH.

The lomitapide ED_{50} for total-C lowering in these rabbits (n=5) was 1.9 mg/kg after 14 days of dosing; triglyceride levels were lowered in parallel. At a dosage of 10 mg/kg given daily for 14 days, plasma total-C and triglyceride levels were reduced 84% to 92% and 60% to 90%, respectively.

Mice: Lomitapide was administered orally by gavage at 1 mg/kg for 4 days to wild-type mice (C57BL6) and to knockout mice (a humanized LDL-receptor-deficient mouse model, LAHB mouse transduced with cholesteryl ester transferase protein and human apo A1). Lomitapide reduced plasma lipids in both mouse models: reductions in plasma total cholesterol, triglycerides, HDL-C, and/or apo B were approximately 75% at 1.5 or 3 mg/kg and 50% at 1 mg/kg, respectively. Apo A1 was not decreased. Hepatic triglyceride levels were increased 3-fold to 5-fold compared to controls at doses from 0.5 to 3 mg/kg in LAHB mice and wild type mice; hepatic levels of total cholesterol were not increased.

Cynomolgus monkeys: In cynomolgus monkeys (5 per treatment group) fed a standard diet, lomitapide administered orally once daily for 14 days at doses of 0, 1.25, 2.5, or 5 mg/kg significantly reduced plasma total cholesterol at all 3 dose levels on treatment Days 7 (by 35.3%, 64.6% and 81.0% resp.) and 14 (by 31.1%, 59.2% and 74.8% resp.). The ED_{50} was 2.1 mg/kg. Significant dose-dependent reductions in plasma levels of VLDL+LDL-C and HDL-C also were observed. Lomitapide clearly decreased plasma cholesterol in cynomolgus monkeys. Triglycerides were decreased significantly at day 7 of treatment. At day 14 of treatment, the control value was very low and therefore no significant decrease in plasma triglycerides could be found at that time point. Changes in creatine kinase levels were not statistically significant either. Another study was conducted in cynomolgus monkeys on a high-fat/high-cholesterol diet. Cynomolgus monkeys adapted for 4 weeks to a high-fat/high-cholesterol diet had 2-fold to 3-fold increases in total-C and VLDL+LDL-C, but no increases in HDL-C and triglycerides, compared to monkeys fed a standard diet. Following oral administration of lomitapide at 5 mg once daily for 14 days, significant reductions were observed on Days 7 and 14 for plasma total cholesterol, VLDL+LDL-C, and HDL-C, but not for triglycerides. Again, variability in the control group may have contributed to a lack of effect on triglycerides. Creatine kinase was not significantly changed.

To further understand the variable effects of lomitapide on plasma triglycerides in monkeys, another study was conducted in monkeys fed with a standard diet. Lomitapide 2.5 and 5 mg/kg was given for 7 consecutive days and plasma triglycerides and cholesterol were determined at 10 and 24 h after the last treatment. At 10 hours postdose on Day 7, significant reductions were observed in plasma triglyceride levels at daily doses of 2.5 mg/kg (153%) and 5 mg/kg daily (171%). However, at 24 hours post dose, there was no effect on plasma triglycerides. The CHMP noted that lomitapide actually prevented the postprandial increase of triglycerides in monkeys, instead of lowering the baseline value, whereas for cholesterol, baseline values were decreased. *In vitro* studies also showed that lomitapide inhibited transfer of triglycerides and cholesteryl esters in small, unilamellar vesicles. The studies indicate that lomitapide binds directly to MTP and the IC_{50} values of inhibition of MTP of different species in studies with small unilamellar vesicles varied between 0.5 and 15.5 nM. In HepG2 cells, lomitapide potently inhibited apo B secretion, while apo A1 secretion was only weakly inhibited. These data thus confirm the proposed mechanism of action. Furthermore, lomitapide significantly reduced plasma total cholesterol, VLDL/LDL-cholesterol and HDL-cholesterol in rats with triton-induced accumulation of

plasma triglycerides, hamsters, hyperlipidaemic rabbits, humanized LDL-receptor deficient mice and cynomolgus monkeys.

Nevertheless, evidence of lipid accumulation in liver and small intestine was observed in hamsters and mice. Lipid accumulation was also observed in toxicology studies in mice, rats and dogs. Lipid accumulation in liver and small intestine is consistent with the mechanism of action: since transport of lipids to the blood is inhibited, liver remains at the site of synthesis or absorption.

Secondary pharmacodynamic studies

In previous rat studies, lomitapide caused effects on coagulation and in high doses and patients with abetalipoproteinemia demonstrated in some cases a deficiency of fat-soluble vitamins vitamin K and vitamin E. In order to investigate the role of vitamin K in lomitapide-induced toxicity, rats were treated with 0, 125 or 250 mg/kg p.o. for 14 days with or without vitamin K supplementation. Without supplementation, both doses resulted in toxic effects, including reduced body weight gain and prolonged clotting times compared to controls. Supplementation with vitamin K completely reversed the prolongation of both prothrombin time (PT) and activated partial thromboplastin time (APTT), but did not reverse the lack of body weight gain. The effect of fat-soluble vitamin K is likely related to the impact of MTP inhibition on chylomicron formation. It is likely that vitamin K absorption is inhibited by lomitapide.

Results from a battery of *in vitro* and *in vivo* general pharmacology studies were also described (non-GLP). In mice and rats, effects on CNS, gastrointestinal motility and urinalysis were investigated at doses 0, 3, 10, 30 or 100 mg/kg. No behavioural effects were observed except for dose-related transient reductions in locomotor activity and reductions in the incidence of writhing to pain stimuli in mice at 30 and 100 mg/kg. In mice, gastrointestinal motility was suppressed at 100 mg/kg, but not at 30 mg/kg. Urinary excretion of Na^+ and K^+ (µEq/6 h) was decreased in rats at doses ≥ 10 mg/kg and urinary volume was decreased at doses ≥ 30 mg/kg. At 100 mg/kg, protein was found in the urine of all rats. Effects on gastrointestinal motility were further investigated in isolated rabbit ileum and in guinea pig isolated ileum with contractions induced by various agonists. No adverse effects were observed on contraction or motility at concentrations as high as 60 ng/mL (about 10× higher than the predicted steady-state C_{max} in humans at 60 mg) in isolated ileum preparations from rabbits and guinea pigs. Respiratory evaluations, blood pressure, heart rate and ECG were measured in dogs dosed intravenously with 0, 0.8, 1.8, 4 or 20 mg/kg. Intravenous administration of 20 mg/kg lomitapide produced generally transient effects including increased respiratory rate; decreased blood pressure, heart rate, and femoral arterial blood flow. No effects were observed following single intravenous doses of 0.8, 1.8, or 4 mg/kg.

The CHMP noted that no significant effects on general activity and behaviour were observed except for a transient reduction in locomotor activity in mice. Decreased blood pressure, heart rate, and femoral arterial blood flow and increased respiratory rate were observed in dogs only at high exposures. Similarly, at high doses, urinary volume was decreased and protein was found in urine of rats. The cause of these effects is not identified, however they are not expected to be clinically relevant since they were observed mainly at very high doses and furthermore, no kidney toxicity was observed in toxicology studies.

Safety pharmacology programme

The ICH S7A core battery of GLP safety pharmacology studies was not conducted with lomitapide. Several non-GLP safety pharmacology studies and GLP-compliant CNS and hERG safety pharmacology studies were carried out. Regarding studies for CNS effects, non-GLP studies as well as GLP studies were performed. A non-GLP cardiovascular study in dogs as well as a GLP hERG assay was conducted, and ECG measurements in dogs were performed in GLP repeated dose studies. Only in case of the tests on potential effects of lomitapide on respiration, a non-GLP study was available, but there does not seem to be a signal that lomitapide causes adverse effect on respiration. The increased respiration rate in dogs occurred at high exposures only, and was associated with a decrease in blood pressure. The CHMP noted that not all safety pharmacology studies were performed in compliance with GLP. However, overall, the pivotal components were in compliance with GLP. Thus, the CHMP considered the quality of the safety pharmacology studies sufficiently guaranteed.

In vitro evaluation of the effects of lomitapide on receptor and ion-channel ligand binding demonstrated significant levels of inhibition of radio-ligand binding to serotonin 5HT1 and 5HT2 receptors, the sigma receptor, and the type 2 sodium channel. Relative to the predicted human C_{max} at 60 mg, these IC_{50} values are at least 44 times higher, and thus, not expected to be clinically relevant.

A study examining the effects of lomitapide on general behavioural in male rats showed that one hour following oral administration of 150 mg/kg or vehicle, no adverse effects were observed. No significant effects on mean arterial pressure of normotensive rats were observed. A mild decrease (18% compared to controls) in heart rate was observed after 24 hours. The GLP-compliant safety pharmacology study conducted in female rats in order to assess the effects of lomitapide on gross behavioural and physiological status revealed that no major adverse effects were observed following any of the lomitapide doses. Rats treated with chlorpromazine exhibited effects consistent with it's pharmacology, including catalepsy and decreased motor activity and alertness. In a hERG assay, inhibition of IKR by lomitapide and by metabolite M1 was observed at concentrations at least 250 times the human C_{max}. In dogs, no effects on ECG were observed.

Pharmacodynamic drug interactions

No nonclinical pharmacodynamic drug interaction studies were conducted with lomitapide and a justification was put forward based on the fact that markedly hyperlipidaemic animal models would be needed to carry out meaningful pharmacodynamic drug interaction studies with lomitapide. The applicant considered that it might be therefore more appropriate to obtain this data in humans and avoid the unnecessary use of animals which supports the 3Rs principles in accordance with ICH Topic M3 (3Rs). The principles of the 3Rs as quoted in the ICH guidance [CPMP/ICH/286/95] is endorsed by the CHMP.

2.3.3. Pharmacokinetics

Pharmacokinetic- and toxicokinetic parameters of lomitapide and its metabolites M1, M2 and M3 were determined in mice, rats, dogs and monkeys given lomitapide orally and/or intravenously. Plasma-protein binding was assessed *in vitro* across species, including humans. Biliary excretion was studied in bile-duct cannulated rats. Metabolism of lomitapide was assessed *in vitro* in hepatocytes from mice, rats, dogs and humans, and *in vivo* in rats and dogs. The lomitapide metabolite M3 was approximately 400x less active than lomitapide and M1 had no activity.

Therefore, it was concluded that M1 and M3, as well as metabolites of M1 and M3, did not exhibit pharmacologic activity at therapeutic doses in humans. All single-dose studies were conducted without using a validated method of analysis. The toxicokinetics of lomitapide investigated in the repeated-dose studies on the other hand were determined by validated LC/MS/MS methods.

The CHMP noted that two different salts were used in the pharmacokinetic studies: hydrochloride (HCl) and mesylate. Lomitapide mesylate is the active substance in the proposed product and this salt was used in the dog pharmacokinetic studies while the HCl salt was used in rats and monkeys. It was, however, acknowledged that toxicokinetic data in rats with the mesylate salt existed as well and the CMP asked for a comparison of the pharmacokinetic profiles of the two different salts and the possible impact on interpretation of the pharmacokinetic data. In response, an overview and discussion on the early pre-clinical studies using the HCl salt was provided. None of these suggest any impact on the safety margins generated between animals and humans and thus, the change in salt during development is not considered to have any significant impact on the safety data.

Lomitapide has a low and variable oral bioavailability of approximately 7-54% in humans and the non-clinical species, which is caused by a large first-pass effect. Dose-normalised systemic exposure values for lomitapide after a single dose were found in the following order: dog > rat > monkey, which is consistent with the observed bio-availabilities in these species. The time to reach maximum plasma concentrations was found to be dependent on the formulation used, i.e. oral administration of lomitapide in gelatine capsules led to higher T_{max} values than in solution. In all three non-clinical species, the volume of distribution is high, varying between approximately 3 and 38 L/kg, with the largest volume of distribution found in monkeys and the smallest in dogs. Plasma half-lives were comparable in the non-clinical species: approximately 11-14 hours in rat and dog after oral dosing and around 12 hours after IV dosing. Repeated oral administration of lomitapide generally led to plasma accumulation up to approximately 4-fold in rat and dog. The C_{max} and AUC values generally increased in a dose-proportional manner, but were more than dose-proportional in mice. Only at the highest tested dose of 80 mg/kg, the increase in dose was accompanied by a less than dose-proportional increase in lomitapide exposure. However, for the other two non-clinical species, rat and dog, lomitapide exposure could increase in proportion linear to the dose.

Based on AUC_{0-24h} metabolite-to-parent ratios, systemic exposure to lomitapide and its metabolites occurred in the following order in the pre-clinical species: M3>lomitapide>M1>M2 in mice; M2≥M3>lomitapide>M1 in rats; and lomitapide>M1>M3>M2 in dogs. The metabolites were not pharmacologically active at clinically relevant concentrations and no *in vivo* toxicity was observed.

Lomitapide is extensively bound to plasma proteins in the non-clinical species and in humans (>99.4%). Due to the high plasma protein binding of lomitapide, interactions with other drugs may occur. Furthermore, changes in the health status of patients may result in differences in free fraction and consequently different systemic plasma exposures. As plasma protein binding was determined at much higher concentrations than the clinical C_{max} due to technical difficulties, the CHMP considered this to be an uncertainty for the interpretation of adverse effects found in animal studies for relevance for humans. These uncertainties are addressed in the clinical part of this report and reflected in the clinical major objection that the CHMP rose during the evaluation.

The observed blood-to-plasma ratio indicates that either lomitapide slowly binds to erythrocytes, or that metabolites bind to erythrocytes.

Consistent with its high volume of distribution, lomitapide is widely distributed in various tissues with the highest overall cumulative radioactivity exposure. The target organ, the liver, was well exposed after oral administration in both rats and dogs, with lomitapide concentrations several hundred fold higher than plasma levels. Radioactivity concentrations declined in rats in all tissues but were still higher than the blood/plasma concentrations at 24 and 48 hours, except for the eyes and brain. This indicates that with repeated dosing tissue accumulation cannot be ruled out (see section on Repeat Dose Toxicity). Lomitapide does not readily cross the blood-brain or the blood-testes barrier as concentrations in the blood and in the testes were almost consistently lower than those in plasma.

At clinical concentrations, lomitapide is extensively metabolised. The major metabolic routes are mono-oxidation and N-dealkylation, followed by further oxidation and/or glucuronidation. The CYP3A4/5 was found to be the enzyme responsible for most of lomitapide's metabolism. In addition, CYP2E1 may play a role, especially in the formation of M9 metabolite. Metabolite M2 is most likely formed by other systems than the human liver CYPs and related to the formation of M1. Metabolism in mouse, rat and dog hepatocytes was less extensive than in human hepatocytes with unchanged lomitapide as the major component (~45-68%). However, all human metabolites were also observed in hepatocytes of at least two animal species. The *in vivo* metabolite profiles differed from the *in vitro* profiles and differed across species. More metabolites were observed *in vivo* than *in vitro*.

Excretion *via* faeces is the major excretion pathway in all species after oral administration of lomitapide. Secretion into bile constitutes another possible excretion pathway. Urinary excretion is only a very minor route in rat, but accounts for the excretion of about a third of the dose in humans. Excretion via urine might be an important elimination route also for dogs, but the data should be interpreted with caution due to low total recovery. No data on the excretion of lomitapide in milk has been provided. It is of note that the complete excretion will most likely take longer than 24 hours. Therefore, once-daily repeated dosing with lomitapide may result in accumulation of lomitapide in the body. Transport of lomitapide via p-glycoprotein is probably limited. However, the results could not be readily interpreted as the recoveries from the experiments were very low, which was caused by non-specific binding and cellular accumulation. Lomitapide was found to be an inhibitor of p-glycoprotein, however, not at clinically relevant levels. Transport *via* the transporters BCRP, OATP1B3, OCT1, OAT1, OAT3 and OCT2 was not inhibited by lomitapide. Lomitapide was not proven to be an inhibitor of CYP1A2 and 2E1 activities. In addition, at clinically relevant plasma concentrations, lomitapide is not an inhibitor of CYPs 2B6, 2C9, 2C19, 2D6 and 3A4. However, since lomitapide is subject to a large first pass effect and the gut concentrations will be much higher than the plasma concentrations, interactions with other drugs may occur in the gastrointestinal tract. This issue is addressed in the clinical section of this report. The metabolites of lomitapide, M1 and M3, were not found to inhibit CYP iso-enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 directly or time-dependently at clinical relevant concentrations. Lomitapide nor its metabolites M1 and M3 induced CYP1A2, 3A4 or 2B6 activities.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies were performed in CD-1 mice, SD rats and beagle dogs. Effects of lomitapide mesylate were investigated on body weight, clinical assessment, physical examinations, gross pathology, and histopathology of organs with gross pathology lesions. In dogs, also food consumption, ECG, blood pressure measurements and ophthalmoscopy were performed (see table below).

Single dose toxicity studies

Study ID	Species/ Sex/Number/ Group	Dose/Route (mg/kg)	Approx. lethal dose / observed max non-lethal dose	Major findings
BMS-96011	Mouse 5/sex/gp	0, 300, 600, 1200, 2400 Oral gavage	2400 / 1200	**2400**: Decreased activity, death (1M/ 1F)
BMS-96035	Mouse 5/sex/gp	0, 12.5, 25, 50 IV	50 / 25	**50**: Convulsions, death (all animals)
BMS-96010	Rat 7/sex/gp	0, 0.1, 1, 10, 100, 300, 600, 1200, 2400 Oral gavage	1200 / 600	**≥1200**: mortality (1F at 1200, 2M/1F at 2400)
BMS-96036	Rat 5/sex/gp	0, 12.5, 25, 35, 50 IV	50 / 35	**≥25**: ataxia, convulsions, lipid accumulation liver, injection site irritation **50**: lipid accumulation jejunum, mortality (5M/1F)
BMS-96041	Dog 2/sex/gp	0, 0.05, 0.5, 5 IV	>5 / 5	**≥0.5**: emesis, head shaking, decreased activity **5**: ataxia, decreased blood pressure

The mice that died within 1 day in study BMS-96011 had a moderate distention of the stomach with fluid, but no microscopic findings were observed. Mice dosed IV at 50 mg/kg died within 2 minutes of dosing in study BMS-96035. In orally dosed rats, cases of mortality occurred at 8 – 12 days after dosing. Rats dosed IV at high dose died within 30 minutes of dosing. Clinical signs in the dogs such as head shaking, emesis, decreased activity and ataxia were ascribed to the presence of Tween-80 in the vehicle. In general, lethal doses after oral administration were at least 1000 times higher than the maximally recommended human dose of 60 mg/day.

Repeat dose toxicity

Repeated-dose toxicokinetics of lomitapide were investigated in oral repeated-dose toxicity studies (see overview table below).

Repeat-dose toxicity studies

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg/day)	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
Pivotal studies					

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg/day)	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
BMS-96003	Rat 15/sex/gp	0, 0.5, 5, 50 Oral gavage	1 month + 1 month recovery	< 0.5	**≥0.5**: liver lipid vacuolation **≥5**: small intestine lipid vacuolation **50**: fc ↓, mortality (15M/13F), Hb+Ht+RBC ↓, anisocytosis, neutrophils ↑, BUN ↑, ALT ↑, AST ↑, creatine kinase ↑, eyes thin retinal vessels, liver centrilob.necrosis, spleen extramedull. haemotopoiesis, haemorrhage many organs, M: bw ↓, platelets ↑, bilirubin ↑, K ↑, F: urine vol ↑
BMS-96024	Rat 10/sex/gp	0, 0.02, 0.2, 2, 20 Half of each gp + vit A, D, E, K Oral gavage	6 months	M: NOEL 0.02 F: < 0.02	**≥0.02**: F: liver lipid vacuolation **≥0.2**: poikilocytosis, liver subacute inflammation and single cell necrosis, M: liver lipid vacuolation **≥2**: leukocytes ↑, reticulocytes ↑, ALP ↑, ALT ↑, AST ↑, total protein ↓, small intestine lipid vacuolation, F: lymphocytes ↑ **20**: lung histiocytosis, pulmonary phospholipidosis **20 without vitamins**: haemorrhages, mortality (10M/10F)
BMS-96209	Rat 10/sex/gp	0, 0.1, 1, 10 IV	2 weeks	< 0.1	**≥0.1**: liver lipid vacuolation **≥1**: ALP ↑, small intestine lipid vacuolation, injection site irritation **10**: Hb+Ht+RBC ↓, reticulocytes ↑, lymphocytes ↑, neutrophils ↑, monocytes ↑, APTT ↑, bilirubin ↑, M: bw ↓
BMS-96004	Dog 3/sex/gp	0, 0.02, 0.2, 2, 20 Oral capsules	1 month	NOEL 0.02	**≥0.2**: RBC ↓, total protein ↓, small intestine lipid vacuolation **≥2**: fc ↓, bw ↓, water consumption ↓, heart rate ↓, poikilocytosis, MCV+MCH↑, ALT ↑, AST ↑, urine pH ↓, M: liver single cell necrosis, F: liver lipid deposition **20**: blood pressure ↓, monocytes ↑, APTT ↓, BUN ↑, urine volume ↓, spec. gravity urine ↑
BMS-96025	Dog 4/sex/gp	0, 0.01, 0.1, 1, 10 Half of each gp + vit A, D, E, K Oral	6 months	NOEL 0.01	**≥0.1**: small intestine lipid vacuolation **≥1**: bw ↓, platelets ↑, poikilocytosis, urine pH ↓ liver lipid vacuolation **10**: heart rate ↓, Hb+Ht+RBC ↓, plasma fibrinogen ↑, anisocytosis, PT ↑, total protein ↓, ALT ↑, M: testes tubular degeneration **10 plus vitamins**: fc ↓, blood pressure ↓, fibrinogen ↑, AST ↑

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg/day)	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
BMS-97057	Dog 4/sex/gp	0, 0.05, 0.5, 5 Oral capsules	1 year	NOAEL 0.05	**≥0.05**: ocular clear discharge **≥0.5**: white material in faeces, total protein ↓, small intestine lipid vacuolation **5**: bw loss or decreased bw gain, decreased activity, Hb+Ht+RBC ↓, platelets ↑, M: fc ↑, F: reticulocytes ↑
BMS-96331	Dog 2/sex/gp	0, 0.05, 0.5, 5 IV	2 weeks	M: < 0.05 F: NOEL 0.05	**≥0.05:** M: water consumption ↓ **≥0.5**: QT-prolongation, poikilocytosis, pH urine ↓ small intestine vacuolation, M: fc ↓ **5**: injection site irritation, F: fc ↓, water consumption
Non-pivotal studies					
BMS-96042	Mouse 6/sex/gp	0, 50, 100, 200, 250 + vitamin K Oral diet	2 weeks	< 50	**≥50**: fc ↓, bw ↓ **≥200**: mortality (3M/1F at 200, all animals at 250)
BMS-96056	Mouse 5/sex/gp	0, 4, 25, 100, 400 Oral gavage	3 weeks	NOEL 25	**≥100**: fc ↓, bw ↓, mortality (3M/1F at 100, 5M/4F at 400) **400**: inactivity
BMS-96042	Mouse 5/sex/gp	0, 4, 10, 25 Oral diet	1 month	NOEL 4	**≥10**: fc ↓, M: bw ↓
BMS-96057	Mouse 10/sex/gp + 18/sex/gp for TK	0, 1.5, 5, 15, 45 Oral diet	3 months	< 1.5	**≥1.5:** lipid accumulation small intestine **≥5**: lipid accumulation liver, pulmonary histiocytosis **≥15**: RBC ↑, neutrophils ↓, total protein ↓
BMS-99008	Mouse 10/sex/gp + 18/sex/gp for TK	0, 1.25, 5, 20, 80 Oral gavage	3 months	< 1.25	**≥1.25**: lipid vacuolation liver and small intestine **≥20**: M: neutrophils ↑, F: bw ↑ **80**: total protein ↓, M: bw ↓, F: fc ↑, RBC ↑, neutrophils ↑, BUN ↑
BMS-96043	Rat 6/sex/gp	0, 25, 50, 100, 200 + vitamin K Oral diet	2 weeks	M: <25 F: NOEL 100	**≥25**: M: fc ↓, bw ↓ **200**: F: fc ↓, bw ↓
BMS-95051	Rat 5/sex/gp	0, 4, 20, 100 Oral gavage	2 weeks	< 4	**≥4**: lipid accumulation liver and small intestine **≥20**: poikilocytosis **100**: mortality (3M/5F), decreased activity, bw loss, platelets ↓, neutrophils ↑, multifocal haemorrhage, M: RBC+Hb+ Ht ↓, BUN ↑
BMS-96016	Rat 15/sex/gp	0, 50 + or – vit K Oral gavage	1 month Interim sacrifice 2 weeks		**50:** bw ↓, neutrophils ↑, lymphocytes ↑, poikilocytosis, total protein ↓, ALT ↑, AST ↑, ALP ↑, lipid accumulation liver and small intestine, M: fc ↓ **50 without vit K:** mortality (8M/10F), PT ↑, APTT ↑, M: platelets ↑, F: RBC+Hb+Ht ↓, BUN ↑, creatine kinase ↑, multifocal haemorrhage

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg/day)	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
BMS-96058	Rat 10/sex/gp	0, 1, 5, 10, 15 Oral diet	3 months	< 1	**≥1**: AST ↑, ALP ↑, lipid accumulation in liver and small intestine, lungs histiocytosis, F: fc ↑ **≥5**: neutrophils ↑, lymphocytes ↑, PT ↑, APTT ↑, M: bw ↓, platelets ↑, mortality associated with haemorrhage (1M) **≥10**: mortality associated with multifocal haemorrhage, poikilocytosis, liver single cell necrosis, M: RBC+Hb+ Ht ↓

Fc=food consumption; bw= body weight; gp=group; TK=toxicokinetics; RBC=red blood cells; Hb= haemoglobin; Ht=haematocrit; PT=prothrombin time

Repeated dose studies were performed in rats, dogs and mice. In the repeated dose studies, the most important observed effect was lipid accumulation in the liver and small intestine as a consequence of the pharmacological effect. This was observed at doses comparable to the ED_{50} and at exposures comparable to the human therapeutic exposure. Accumulation does not seem to increase with time of treatment and evidence of reversibility was shown after cessation of treatment in a mechanistic study in rats. However, fat accumulation remains to be present during long-term treatment and this involves a risk of adverse effects such as liver toxicity and perhaps also liver carcinogenicity. In the liver, besides fat accumulation, single cell necrosis and increases in ALT, AST and ALP were observed at exposures comparable to or lower than the human exposure (rat) or at exposures from 20 times the human exposure (dogs) based on AUC. Furthermore, in the rat carcinogenicity study, besides lipid vacuolation also fibrosis and, in males, cystic degeneration were observed in the liver. In clinical studies, hepatic fat accumulation and transaminase elevations were observed. Liver toxicity is further discussed in the clinical section of the report. In the small intestine, no damage was observed besides fat accumulation.

Multifocal haemorrhages and extramedullar haematopoiesis, as well as increases in APTT and PT, were observed in rats. This was most likely caused by vitamin K deficiency due to inhibited absorption of fat-soluble vitamins, since no haemorrhages were observed in vitamin-supplemented animals. Decreased red blood cell parameters, poikilocytosis and/or anisocytosis were also observed in animal studies and the CHMP requested an explanation of their mechanism and clinical relevance. It was argued that the abnormal red blood cell morphology can be ascribed to abnormalities in cell membrane lipid structure secondary to low cholesterol levels due to the pharmacological effect. The CHMP considered this a plausible explanation; however, decreases in red blood cell parameters, although mostly observed at high exposures in animals, cannot be completely excluded. Therefore, anaemia is included as side effect in section 4.8 of the SmPC.

Decreased food consumption and decreased body weight compared to controls was observed in several studies in rats, dogs and mice. In rats and mouse, decreased body weight was only observed in males. In the 6-month dog study, tubular degeneration in the testes occurred, however the exposure was very high compared to humans (205 times based on AUC of 69.5 ng.hr/mL in humans at 60 mg). In the lungs of rats, mild histiocytosis was detected following 3

months administration of lomitapide and was reversible from 4 months after treatment. There was no evidence of phospholipidosis or structural damage to the lungs.

Genotoxicity

A standard package of genotoxicity assays was conducted. Lomitapide concluded to be negative for mutagenic potential in the bacterial reverse mutation assay and for the induction of structural and numerical chromosome aberrations in human peripheral blood lymphocytes. Lomitapide was shown not to be genotoxic in a rat micronucleus study.

Carcinogenicity

The following carcinogenicity studies were performed with lomitapide:

Study ID	Dose / Route	Exposure (AUC)	Species / No. of animals / Group	Major findings
AEGR-733PC0003	0 0.3 1.5 7.5 15 45 mg/kg/day Oral, diet	<1x/<1x 2x/2x 11x/9x 26x/22x 77x/77x (M/F) that in humans at 60 mg daily At NOEL <1x(M)/2x(F)	Mice/CD-1 60M+60F (main) & 24M+24F (TK)	Hepatocellular tumours in males ≥ 1.5 mg/kg/day and in females ≥ 7.5 mg/kg/day. Tumours of the small intestine in males ≥ 15 mg/kg/day and in females at 15 mg/kg/day. Intestinal tumours were seen in 1 or 2 males at 0.3, 1.5 and 7.5 mg/kg/day and in 3 females at 45 mg/kg/day.
AEGR-733PC0002	M/F 0/0 0.25/0.03 1.7/0.35 7.5/2.0 mg/kg/day Oral, gavage	 <1, 2x, 6x (M) <1, 2x, 8x (F) that in humans at 60mg daily	Rats/SD 60M+60F (main) & 12M+12F (TK)	No significantly increased tumour incidences. Benign pancreatic adenomas were increased in males at 7.5 mg/kg/day with systemic exposure to lomitapide at 6x that of humans at 60mg.

In the mouse carcinogenicity study, occurrence of hepatocellular adenoma and carcinoma were observed, but no apparent large scale lipid accumulation in the liver. In the small intestine of mice, lipid vacuolation was observed as well as increased epithelial carcinoma. In the rat carcinogenicity study, there was no clear increase in occurrence of liver tumours, but at the high dose, there was a tendency to an increase when adenoma and carcinoma of males and females were summarised. In the small intestine, lipid vacuolation was observed but without an increase in the number of tumours. In rats, lipid vacuolation was observed in the acinar pancreas. Overall, the date could indicate an association between lipid accumulation as a consequence of the pharmacological action of lomitapide and the development of tumours in liver, small intestine and, after long-term exposure in rats, also in the pancreas. Therefore, the CHMP requested information on whether the accumulation of lipids in liver, small intestine and pancreas could possibly lead to tumour development, as well as estimation and monitoring of this risk in humans. The applicant provided further reassurance that the available data indicating occurrence of tumours in liver, small intestine and pancreas do not seem to be directly related to lipid vacuolation in these organs. Since the risk of tumour development cannot be completely excluded, further monitoring of tumours in a prospective observational cohort study, with emphasis on small bowel, hepatic and colorectal tumours was proposed. The CHMP agreed and

requested that the pancreas tumours are monitored as well. This is sufficient considering the claimed indication in the small patient population. The prospective observational cohort study is included in the Risk Management Plan and an adequate statement regarding pancreatic tumour findings is present in section 5.3 of the SmPC.

Small increases in thyroid follicular cell adenoma, adrenal medulla hyperplasia, and pituitary adenoma in rats were observed more in animals at scheduled sacrifice than in animals that died or were sacrificed prematurely. However, this seems to be due to the increased survival in high dose animals.

Reproduction Toxicity

A complete battery of reproductive toxicity studies was conducted with lomitapide. All pivotal studies were conducted in compliance with GLP regulations, were adequately designed, and met ICH guidelines (ICH S5[R2], Detection of Toxicity to Reproduction for Medicinal Products and Toxicity to Male Fertility, November 2005). Dose/exposure multiples relative to a 60-mg dose in humans were estimated using either existing data from toxicology studies in non-pregnant rats or calculated using body-surface area in rabbits.

Overall, there were no major effects on fertility in male or female rats treated with lomitapide. In rats, malformations were observed in various organs, also at lower doses than the maternally toxic dose. There is no safety margin for teratogenicity in rats. Supplementation with fat-soluble vitamins did not protect against this teratogenic effect, and a decrease in these vitamins in treated animals can therefore not be seen as the cause of malformations. The mechanism behind this teratogenicity and therefore its relevance for humans is not known. However, the CHMP noted that there are adequate warnings in the SmPC not to use lomitapide during pregnancy and this was considered satisfactory for the use of lomitapide in the rare HoFH population.

In rabbits, no embryo-foetal toxicity was seen in the pivotal study. Since no toxicokinetic data were available in rabbits, it is difficult to conclude whether in this study, rabbits were sufficiently exposed to lomitapide. In a preceding, range-finding study, increased resorption was observed at doses exceeding those tested in the pivotal study. In ferrets, maternal and embryo-foetal toxicity was observed, and was accompanied by increases in malformations in various organs. Due to maternal toxicity, the relevance of this finding is difficult to interpret. The teratogenic effects are not to be disregarded and appropriate contraindication for the use of lomitapide during pregnancy was therefore introduced. The exposure to lomitapide in ferrets is unknown.

In the pre- and postnatal studies in rats with doses up to 1 mg/kg/day, a similar pattern regarding maternal toxicity and decrease litter sizes was observed as in the rat embryo-foetal study. Additional findings include a very slight increased duration of gestation, increased pup mortality and decreased viability index, and decreased pup weight. There is no safety margin for these effects. Maturation of the surviving offspring was not affected. No off-spring studies were conducted with lomitapide because the target indication for this MAA is limited to the adult patient population. However, as agreed in the Paediatric Investigation Plan (PIP), a juvenile toxicity study in rats prior to the implementation of a planned paediatric study will be conducted.

Toxicokinetic data

No separate toxicokinetic studies were performed in animals, but the toxicokinetic profile of lomitapide was investigated as part of the repeat-dose toxicity studies.

Local Tolerance

Local tolerance studies were not performed, since lomitapide is intended for oral administration.

Other toxicity studies

Several additional toxicity studies were conducted with lomitapide including examination of antigenicity, immunotoxicity, and the toxicological profile of lomitapide's metabolites and impurities. Lomitapide was not antigenic in guinea pigs. No direct evidence of immunotoxicity was observed in the repeated dose studies or in the carcinogenicity studies. No adverse effect on phagocytic activity was observed in macrophages obtained by bronchoalveolar lavage of lungs from rats treated with lomitapide for three months, with exposures up to approximately 20 times higher than the human exposure. Two drug substance impurities are specified above the qualification limit. These impurities are sufficiently qualified. Phototoxicity was not investigated and although some absorption takes place above 290 nm, this is considered minor and no relevant phototoxicity is expected.

2.3.5. Ecotoxicity / environmental risk assessment

Summary of main study results

Substance (INN / Invented Name): lomitapide / Lojuxta			
CAS-number (if available): 202914-84-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		3.67	Potential PBT No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.67m	B/not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default PEC $_{surfacewater}$, refined PEC $_{surfacewater}$, corrected for metabolism	0.3 (Fpen 0.01) 0.09 (Fpen 0.000003) 5.4	µg/L ng/L pg/L	> 0.01µg/L threshold No (for refined value)
Other concerns (e.g. chemical class)			No

The CHMP noted that the initially provided data were not entirely sufficient and thus, did not allow for a definitive conclusion on the potential risk of lomitapide to the environment. Upon CHMP's request a study was performed to determine the log K_{ow} for lomitapide; however, this study did not meet the criteria of the OECD guidelines. The CHMP recommended that the applicant provides the results and study report on the determination of the log K_{ow} of lomitapide according to OECD guidelines during the post-phase. Considering the refined Fpen, it is observed that the $PEC_{surfacewater}$ is below the action limit. Epidemiological data have been provided to support the refinement of Fpen. Further environmental risk assessment of this issue is not necessary.

2.3.6. Discussion on non-clinical aspects

Lomitapide is a new lipid lowering agent that significantly reduces plasma cholesterol and triglycerides in several animal species. Forthcoming from the mechanism of action, which is inhibition of the assembly of lipoproteins and their release into the circulation, lipid accumulation is observed in liver, small intestine and pancreas, as well as evidence of liver toxicity. Liver toxicity remains an issue of concern. Additional non-clinical data are however not expected to add relevant information to what is already known. Clinical monitoring will be of importance (see section Clinical aspects).

In the animal studies, no correlation was observed between lipid accumulation and tumour formation. Potential other causes of the observed tumours or their clinical relevance were not discussed and this is accepted by the CHMP in view of the limited current indication to the small patient population (patients with HoFH). Lomitapide showed potential teratogenic effects in two out of three tested animal species; however, sufficient exposure in the species in which no teratogenicity was found could not be obtained. The mechanism behind this teratogenicity and therefore its relevance for humans is not known and therefore, no firm conclusions can be made. The risk of teratogenicity observed in the nonclinical setting has been reflected in the RMP and in the Educational material for prescribers and the use of lomitapide in pregnancy is contraindicated. Overall, the CHMP considered the non-clinical profile of Lojuxta to be well characterised considering the indication for the restricted rare indication in HoFH patients in the EU. A post-authorisation commitment in the area of eco-toxicity has been acknowledged and agreed by the CHMP.

2.3.7. Conclusion on the non-clinical aspects

The CHMP considered that in general, the non-clinical studies conducted with Lojuxta were sufficient and provide a good overview of the product's non-clinical profile. All CHMP's questions raised during the assessment were addressed either by means of submitting additional data, proposing risk minimisation measures, or agreeing to post-authorisation measures, e.g. conduct of addition eco-toxicity testing. Thus, the CHMP considered the non-clinical development satisfactory.

2.4. Clinical aspects

2.4.1. Introduction

The clinical programme for Lojuxta included fifteen phase 1 studies, seven phase 2 studies and three phase 3 studies (see table below). Of these, two studies are still on-going. In total, 1145 healthy subjects and patients were treated, including 943 who received lomitapide, either as monotherapy or co-administered with other lipid lowering therapy. The majority of subjects (959 out of 1145) were enrolled in placebo and/or active-controlled trials.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID	Population studied	Objectives	N Total (N lomitapide)
Phase I			
CV145-005	HV	Safety and PK, effect of food (fasted, low- and high-fat diet)	25 (25)
CV145-001	Male HV with TC ≥195 mg/dL	Safety, PK, PD	55 (37)
CV145-002	HV with TC ≥200 mg/dL	Safety, PK, PD	36 (24)
CV145-003	HV with TC ≥200 mg/dL	Safety, PK, PD, bioavailability	32 (24)
CV145-006	HV	PK, Safety, ADME	6 (6)
CV145-010	HV females with TC ≥200 mg/dL	Safety, PK, PD	18 (12)
AEGR- 733-010	HV, male	Safety, AME, PK	6 (6)
AEGR- 733-017	HV and mild to moderate hepatic impairment	Safety, PK	32 (32)
AEGR- 733-021	HV and renal impairment	Safety, PK	14 (14)
AEGR- 733-002	HV	Safety, PK, PD, DDI with LLT3 and dextromethorphan	1293 (107)
AEGR- 733-013	HV, male	Safety, PK DDI with warfarin, PD (INR/PT)	16 (16)
AEGR- 733-015	HV, female	Safety, PK DDI with Ortho- Cyclen	28 (27)
AEGR- 733-018	HV	Safety, PK DDI with ketoconazole	30 (30)
AEGR- 733-019	HV	Safety, PK DDI with simvastatin	16 (16)
AEGR- 733-011	HV	Safety, PK, PD TQTc study	56 (56)
AEGR- 733PC0028	Population PK study	Investigate linearity, incluence of covariates and bridging between healty subjects and HoFH population	66*
AEGR- 733PC0029	PBPK study	Predict the Interaction with an array of CYP3A4 inhibitors	
Phase II			
CV145-009	LDL-C ≥160 mg/dL mean TG ≤500 mg/dL	Safety, PD, effect on hepatic fat	76 (38)
AEGR- 733-003a7	LDL-C >1305 and <250 mg/dL TG ≤400 mg/dL	Safety, Efficacy	1136 (826)
AEGR- 733-003b7	LDL-C >1305 and <250 mg/dL TG ≤400 mg/dL	Safety, Efficacy	157 (104)
AEGR- 733-001	LDL-C >1305 and <250 mg/dL TG ≤400 mg/dL	Safety, Efficacy	85 (56)
AEGR- 733-004	LDL-C >100 and ≤190 mg/dL	Safety, PD, effect on hepatic fat	260 (193)
AEGR- 733-006	LDL-C >1305 and <250 mg/dL TG ≤400 mg/dL	Safety, Efficacy	44 (21)
UP1001	HoFH	Safety, Efficacy	6 (6)
Phase III			
UP1002/ AEGR-733-005	HoFH	Efficacy, Safety	29 (29)
AEGR- 733-012	HoFH	Efficacy, Safety	18 (18)
AEGR- 733-005	HoFH	Liver safety (Sub-study of UP1002 AEGR-733-005)	29 (29)

**PK data from study CV145-001 (N=24), CV145-002(N=16), CV145-003 (N=24) were used.*

In support of the clinical studies in man, the marketing authorisation application also includes twelve *in vitro* studies using human samples or human cell material. These studies are summarised in the following table.

Study	Objectives	lomitapide concentration
BMS-910060036	Plasma protein binding in samples from several animal species, as well as humans	N/A
AEGR-733-017	Plasma protein binding in samples obtained from subjects with hepatic impairment	N/A
AEGR-733-021	Plasma protein binding in samples obtained from subjects with renal impairment	N/A
AEGR-733PC0005	Stability of lomitapide in human liver microsomes. Identification of metabolites.	1, 10 and 50 μM
AEGR- 733PC0006	To determine the human cytochrome P450 enzymes responsible for the formation of prominent metabolites of lomitapide	0.01-25 μM
AEGR- 733PC0007	Investigation of inhibitory potential of lomitapide on CYP enzymes (1A2, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4) and on warfarin in human liver microsomes	0.1, 1, 10, 50 and 100 μM
BMS- 910055193	To determine inhibitory activity of lomitapide on CYP2D6	0-300 μM
BMS- 910055194	To determine inhibitory activity of lomitapide on CYP3A4	0-300 μM
AEGR- 733PC0022	To determine induction potential of lomitapide, M1 and M3 on CYP1A2 CYP3A4, CYP2B6	0.2- 20 ng/mL M1: 0.5- 50 ng/mL M3: 6.0-600 ng/mL
AEGR- 733PC0021	To determine inhibitory activity of M1 and M3 against 9 human CYP P450s using pooled human liver microsomes	M1 and M3 concentrations: 0, 0.01, 0.1, 1, 10, and 30 μM
AEGR- 733PC0023	To evaluate the inhibition potential of lomitapide on efflux transporters P-gp and BCRP, hepatic uptake transporters OATP1B1, OATP1B3, and OCT1 andrenal transporters. OAT3, OAT1 and OCT2	Efflux transporters: 0.19-6 μg/mL, Hepatic and renal uptake transporters: 40 ng/mL
AEGR- 733PC0025	In vitro P-gp substrate assessment of lomitapide in a Caco-2 cell monolayer system	1, 3.5, and 8 μM
AEGR- 733PC0026	To evaluate the inhibition potential of lomitapide onCYP2C8	0.3, 1, 3, 10, 30 and 100 μM
AEGR-733PC0032	To evaluate if lomitapide is a substrate for the hepatic uptake transporters OATP1B1, OATP1B3 and OCT1	40, 100, 400, and 4000 ng/mL

The pharmacokinetics/pharmacodynamic (PK/PD) of lomitapide was initially investigated in single and multiple fixed dose monotherapy studies. Subsequently, in five phase II studies, dose finding was performed when lomitapide was administered concomitantly with other lipid lowering agents (atorvastatin or ezetimibe) in hypercholesterolemic patients (also the LDL-C elevated and other CV risk factor study pool). Dose escalation was tested in a proof of concept study in six HoFH patients. Subsequently, a pivotal study in HoFH patients (n=29) was performed.

2.4.2. Pharmacokinetics

The PK of lomitapide was evaluated in individual studies using non-compartmental methods. In selected studies, preliminary PK/PD analyses were completed. The analytical methods in PK studies were sufficiently validated and are consistent with the current regulatory recommendations.

Absorption

After oral administration, lomitapide has an absolute bioavailability of 7%. The concentrations of its metabolites were lower following IV administration than following oral administration. The permeability tests with Caco-2 cell monolayers indicate that lomitapide can be classified as having a high absorption potential. An important food effect was also observed, since both, the low- and high-fat breakfasts produced statistically significant increases in Cmax and AUC0-t of lomitapide when compared to the fasted group. However, food intake did not affect the tmax values. After a low fat breakfast, the bioavailability and Cmax of lomitapide were increased by 30% and 70% respectively and after a high fat breakfast by 60% and 80% respectively.

The qualitative composition of lomitapide was not changed during the course of development. However, the formulations varied with respect to micronisation grade and percentage of polymorphous forms. The commercial available lomitapide 10mg capsules were not studied in the clinical trials. A justification was provided and was based on comparative dissolution of the 5 mg and 20 mg capsules. This is in line with the requirements for biowaivers as per the CHMP guideline on the investigation of bioequivalence.

Distribution

Lomitapide has a high volume of distribution of approximately 1300 litre and a high degree of protein binding (>99.5%). In the ADME trial, no covalent binding of lomitapide or its metabolites to plasma proteins was observed. Lomitapide appears to be loosely bound to plasma proteins and this protein binding does not affect its distribution. Protein binding was unchanged in plasma samples from subjects with end stage renal disease (ESRD). Small but significant differences in protein binding were noted between matched controls and subjects with moderately impaired hepatic function, but these do not appear to be of clinical significance.

Elimination

The apparent elimination half-life of lomitapide following IV administration was 24 hours, following oral administration about 49 hours. In the ADME studies it was shown that approximately 35% of the total lomitapide dose is excreted via urine and 60% via faeces. Approximately 5% of the administered dose of lomitapide was excreted unchanged with the faeces, no unchanged lomitapide was detected via radio profiling in the urine samples. Metabolism of lomitapide was evaluated in two in vitro studies and two human ADME studies. In vitro data showed that lomitapide is primarily metabolised by CYP3A4, but also by CYP2E1. Other CYP enzymes are also involved. Several metabolites have been identified in human plasma. Of these, BMS-203215 (M1), BMS-203304 (M3) and BMS-224433 (M2) have been determined in most pharmacokinetic trials. The M3 is the most abundant metabolite; its plasma concentration is approximately 15–fold higher than that of the parent drug. The metabolic activity of M3 was estimated to be several hundred times less than of lomitapide. The IC_{50} for lomitapide was determined to be 15.5 nM compared to 6.3 µM for M3. Nevertheless, the potential role of this major circulating metabolite M3 in the pharmacological effect of lomitapide is not clear because its plasma protein binding is unknown and the potential for accumulation of M3 in the liver is not understood.

Dose proportionality and time dependencies

As determined in two dose-ranging studies, lomitapide displays linear PK in the dose range of 10-50mg. At higher dose levels (100mg and 200mg), a more than proportional increase of lomitapide and a less than proportional increase of the metabolite M1 were observed. At steady state, the accumulation of lomitapide was 2.7 for the 25mg dose and 3.9 for the 50mg dose. A dose proportional reduction in LDL-C levels was also observed after multiple dosing. Lomitapide has an inter-individual variability of approximately 50% PK in the target population.

Special populations

The exposure to lomitapide is increased by approximately 40% in subjects with end stage renal disease (ESRD) on haemodialysis. No full renal impairment study was conducted; subjects with mild and moderate renal impairment were excluded from clinical trials. The exposure to lomitapide in subjects with mild hepatic impairment was somewhat higher (40%) than in the matched healthy subjects, and was approximately 3-fold increased in subjects with moderate hepatic impairment compared to matched controls.

A dedicated PK population study was not conducted, but a population PK analysis (AEGR-733PC0028) limited to covariates of race, body mass index (BMI), gender, weight, and age, was performed. For the development of the a PK population model, PK results of study CV145-001, CV145-002 and CV145-003, and PK data of 66 healthy subjects were included. All subjects received a single dose of lomitapide IV 7.5, 15, 30, and 60 mg and/or lomitapide oral 25, 50, 100, and 200 mg. A non-linear mixed effect modelling approach was applied. The final PK model was a three compartment model, based on which it can be concluded that lomitapide displays linear pharmacokinetics in the dose range of 10-50 mg after oral administration. The linear model underestimates the bioavailability of higher doses (100 and 200mg) of lomitapide. Although the studied covariates do not appear to affect the PK of lomitapide, only a limited analysis of the influence of these variables on the PK of lomitapide was conducted, mainly focusing on the influence of age, weight and race on the PD parameters such as changes of LDL-C by patient subgroups. At the 10 mg daily dose level there were no differences between males and females, at the 25 mg daily dose level, females had 1.9-fold higher AUC values for lomitapide as compared to males.

No elderly subjects aged >75 were included in any study. A limited number of patients (N=97) of ≥ 65-74 were included in the phase 2 trials, however, no elderly HoFH patients were included.

Pharmacokinetic interaction studies

The potential for drug interactions was evaluated in seven in vitro studies and five *in vivo* studies.

In vitro studies

In vitro tests showed that CYP3A4 plays a major role in phase I metabolism of lomitapide. In addition, CYP2E1 might also contribute to a smaller degree. Lomitapide is a direct inhibitor of CYPs 2B6, 2C9, 2C19, 2D6 and 3A4 with IC50 values of 24.3 µg/mL, 47.2 µg/mL, 43.0 µg/mL, 4.16 µg/mL and 7.63/5.55 µg/mL, respectively. Time-dependent inhibition by lomitapide was found for these CYPs with IC50 values of 6.94 µg/mL, 38.1 µg/mL, 44.4 µg/mL, 6.94µg/mL and 4.86/2.77 µg/mL, respectively. The CYP1A2 , CYP2E1 and CYP2C8 activities were not inhibited. Further investigations of the CYP 2D6 and 3A4 inhibition showed that at higher lomitapide concentrations the inhibition was greater than predicted on the inhibition observed at lower

concentrations, indicating a non-linear inhibition. Based on these in vitro results, no direct problems would be expected after the first pass effect as all IC50 values are much higher than the clinical steady-state Cmax (5.5 ng/mL) when the extensive protein binding (> 99%) is taken into account. Lomitapide showed no induction potential for CYP1A2, CYP3A4, and CYP2B6 activities.

The metabolite M1 had no inhibitory potential for CYP2A6, 2B6, 2C8, 2C9, 2E1 or 3A4 and a modest inhibition was observed on CYP2C19 and CYP2D6. Metabolite M3 showed some time dependent inhibition of CYP2C8. Both, M1, and M3, showed no induction potential for CYP1A2, CYP3A4, and CYP2B6 activities.

In vitro tests showed that lomitapide is an inhibitor of the P-gp function at the high concentration tested (6 µg/mL). No inhibition of the efflux transporter BCRP was also observed. No inhibition of the hepatic uptake transporters OATP1B1, OATP1B3 and OCT1 and the renal transporters OAT3, OAT1 and OCT2 was detected.

In vivo studies

The *in vivo* interaction study with the strong CyP3A4 inhibitor ketoconazole (200 mg twice daily for 5 days) and lomitapide (single dose) showed that lomitapide Cmax and AUC were increased by 15-fold and 27-fold, respectively. Lomitapide had no effect on the PK of ethinyl estradiol and norgestimate, the components of a typical oestrogen-containing oral contraceptive Orthocyclen. The weak-CYP3A4 inhibitor ethinyl estradiol did not affect the lomitapide PK.

The physiologically-based pharmacokinetic (PBPK) model to predict the impact of an array of CYP3A4 inhibitors on the concentration time profile of lomitapide was used to predict the impact of weak, moderate, and strong CYP3A4 inhibitors on lomitapide's PK. Both, strong and moderate CYP3A4 inhibitors, are predicted to have a substantial impact on lomitapide's PK (mean AUC ratios >5). The weak inhibitors used in the simulations had no major effect on the lomitapide PK, although the model was insufficiently validated for definitive conclusions.

When 60 mg lomitapide was administered for five days prior to simvastatin 40 mg, simvastatin acid AUC and Cmax increased by 71% and 57%, respectively. The effect of the weak CYP3A4 inhibitor simvastatin on the PK of lomitapide was not evaluated in an interaction study. When 60 mg lomitapide was administered for five days prior to atorvastatin 20 mg, atorvastatin acid AUC and Cmax increased with 49% and 38%, respectively. When 60 mg lomitapide was administered for five days prior to rosuvastatin 20 mg, a modest change in rosuvastatin PK parameters was observed, although rosuvastatin is not metabolized by CYP3A4. Rosuvastatin tmax increased from 1 to 4 hours, AUC increased 45%, but Cmax was unchanged. The PK of other cholesterol-lowering drugs not metabolised by CYP3A4 were generally unaffected by lomitapide. No drug interaction study of lomitapide with bile acid sequestrants was performed.

Pharmacokinetics using human biomaterials

Several *in vitro* studies were conducted using human biomaterial and their results are described in above sections.

2.4.3. Pharmacodynamics

Mechanism of action

Lomitapide has a novel mechanism of action, targeting microsomal triglyceride transfer protein (MTP), which is involved in the assembly of triglyceride-rich lipoproteins such as chylomicrons in the intestine and VLDL in the liver. Deficiency of MTP has been reported to be associated with very low levels of LDL-C. Therefore, inhibiting MTP is considered a valid target to effectively lower LDL-C, which has been implicated in the pathogenesis of atherosclerosis and is accepted as a major risk factor for cardiovascular disease. Of note, the mechanism of action of lomitapide is independent from the function of LDL receptor, which is defective in HoFH patients.

Primary and Secondary pharmacology

Lomitapide is an MTP inhibitor targeting apolipoprotein B synthesis. In humans, apo B-100 is the principal apolipoprotein associated with VLDL, IDL and LDL. The PD of lomitapide was evaluated as part of four PK/tolerability studies in healthy volunteers and one drug-drug interaction study. A thorough QT study was also conducted in order to assess the effect of lomitapide on QT interval. Lomitapide primary PD assessment concerns its effect on lipid parameters such as LDL-C and total cholesterol (TC), HDL-C, VLDL-C, triglycerides and apo B.

In the first-in-man study BMS-CV145-001, single doses ranging from 1 to 200 mg showed a dose response for percent change in LDL-C from baseline at doses of 50 mg and higher; the LDL-C decreased in 24 hours and the effect was maintained through to 72 hours. TC and apo B showed a similar pattern. At doses of ≥25 mg there were dose-related decreases in triglycerides, with a maximal effect generally seen at 8 hours. Study BMS-CV145-003 single IV doses of lomitapide of 7.5, 15, 30, or 60 mg showed a transient increase in total cholesterol, HDL-C and LDL-C following the intravenous doses for a 12-hour period after which the plasma concentrations decreased. By 48 hours, there was a profound cholesterol-lowering effect apparent at the highest dose that persisted throughout the 72-hour sampling period and a corresponding decrease in the apo B levels. There was a significant triglyceride-lowering effect that persisted post-dose for at least 4 hours, and at the highest dose, this persisted to at least 48 hours post-dose. In study BMS-CV145-002 lomitapide doses of 10, 25, 50 and 100 lomitapide or placebo were administered once daily for 14 days in hypercholesterolaemic males. Subjects in the 10, 25, and 50 mg dose cohorts received 14 days of dosing as planned; dosing in the 100 mg dose group was stopped after Day 7 in all subjects due to GI AEs and an initially planned 200 mg dose level was not evaluated. Decreases from baseline in LDL-C were dose dependent with maximal decreases noted between Days 8 and 11. The patterns were similar for the other lipid parameters.

In the BMS-CV145-010 trial, healthy female subjects were randomised to 10 mg or 25 mg of lomitapide daily or matched placebo for 14 days. Fasting triglycerides on day 14 decreased by almost 50% in comparison to baseline on 25 mg and 18% on 10 mg QD (placebo -10%). Following a 2 week treatment, the mean LDL-C at 10 mg dose was -41% and at 25 mg -78% (placebo -3%). These decreases remained relatively stable throughout the 24 hr sampling time at the end of the study. The decreases in lipid values in females at the 25 mg dose were generally higher than those seen in males receiving 25 mg in clinical study BMS-CV145-002.

In the AEGR-733-002 drug-drug interaction study 10 and 60 mg lomitapide was co-administered with other lipid-lowering drugs. Although in the absence of a lomitapide only arm the assessment of PD is not feasible, the comparison of the possible additive effects of lomitapide 10mg vs 60mg in those groups of patients who received it over 20mg atorvastatin or 20mg rosuvastatin

suggests a dose dependent effect. For LDL-C, after 8 days of treatment with 60 mg lomitapide, co-administration of 20 mg atorvastatin or 20 mg rosuvastatin achieved a mean percent reduction from baseline of -66.02% and -63.20%, respectively whereas the 10 mg dose with the same amount of atorvastatin or rosuvastatin achieved a mean percent reduction of -30.99% and -41.74% respectively. Apo B and total cholesterol changes from baseline showed a similar pattern. The effect was less clear for triglycerides and VLDL. HDL-C showed a consistent decrease from baseline with both low and high lomitapide doses.

The proof-of-concept UP1001 Phase 2 single-arm, open-label study without background lipid lowering therapy conducted in 6 patients with HoFH showed LDL-C reduction after 16 weeks of dose-escalating lomitapide treatment. Other lipid and lipoprotein parameters, including TC, triglycerides, and VLDL-C concentrations, as well as changes from baseline in plasma lipoproteins were also evaluated. Subjects followed a rigorous low-fat diet (<10% of energy from total dietary fat) and were provided a standard multivitamin supplement. A dose dependent reduction in LDL-C was observed (see table below). This was also shown for TC, TG, apoB, non-HDL, but not for the other parameters VLDL-C, Lp(a), HDL-C and apo A1. After 4 weeks dose withdrawal, LDL-C levels returned to baseline.

Mean (sd) percent change from baseline in lipids following 28 days of dosing at 0.03, 0.1, 0.3 and 1.0 mg/kg lomitapide (n=6)

Lipid Parameter	Lomitapide Dose[1]			
	0.03 mg/kg (Visit 5)	0.1 mg/kg (Visit 8)	0.3 mg/kg (Visit 11)	1.0 mg/kg (Visit 14)
LDL-C (direct)	-3.74 (8.294)	-7.14 (20.047)	-24.71 (5.321)****	-50.94 (9.311)****
TC	-4.82 (9.926)	-9.31 (16.596)	-29.78 (9.241)***	-58.37 (8.597)****
apo B	+10.22 (13.966)	-3.16 (18.829)	-14.66 (16.026)	-55.57 (13.494)***
Triglycerides	+4.06 (43.524)	-24.93 (39.707)	-34.07 (22.779)*	-65.18 (13.261)****
Non-HDL-C	-4.63 (10.132)	-9.71 (17.518)	-30.99 (9.319)***	-60.12 (8.858)****
VLDL-C	+34.42 (103.395)	-42.28 (142.462)	+3.27 (103.746)	-78.74 (23.095)***
Lp(a)	+1.04 (34.552)	+6.02 (22.938)	-18.69 (16.629)*	-10.54 (20.475)
HDL-C	-10.35 (8.972)*	+9.90 (25.625)	+11.61 (43.451)	-2.23 (18.024)
apo AI	+34.23 (90.931)	+22.41 (61.540)	+38.67 (86.204)	-6.14 (26.434)

Secondary pharmacology was investigated in one study AEGR-733-011, a thorough QT study that examined the effect of single 75 and 200 mg doses of lomitapide (in solution) alone, as well as 75 mg lomitapide (in solution) co-administered with ketoconazole 200mg twice daily, in order to achieve supratherapeutic exposure on QT interval in 56 healthy male and female subjects. Moxifloxacin 400mg was used as a positive control for the QT assessment. The C_{max} and AUC_{0-t} values increased in a greater than dose proportional manner, co-administration of 75 mg lomitapide with ketoconazole markedly increased exposure to lomitapide. Lomitapide did not affect heart rate, but single doses of 75 and 200 mg caused minor changes from baseline in the QT interval corrected for heart rate using the individualized formula (ΔQTcI), whereas moxifloxacin and ketoconazole (alone or co-administered with lomitapide) caused an increase of ΔQTcI with a peak effect at 3 hours post-dose. The largest mean placebo-corrected ΔQTcI (ΔΔQTcI) following administration of 75 or 200 mg lomitapide alone did not exceed 3ms at any

time point, thus an effect exceeding 4.7 ms could be confidently excluded. When adjusted for the effect of ketoconazole, 75 mg lomitapide caused a maximum mean ΔΔQTcI effect of 2.3 ms, and the upper bound of the 90% CI did not exceed 4.4 ms. The ΔΔQTcI after administration of 400 mg moxifloxacin was up to 12.4 ms, confirming the study's ability to detect a small QTc effect. The analysis of Fridericia corrected QT (QTcF) was entirely consistent with that of QTcI. The concentration effect analysis demonstrated a significant, very shallow slope for the relation between lomitapide plasma levels and ΔΔQTcI.

2.4.4. Discussion on clinical pharmacology

Lomitapide has a low absolute bioavailability of 7% after oral administration. The low bioavailability is at least partly due to a high first-pass effect and not to poor intrinsic absorption. Lomitapide is extensively and primarily metabolised by CYP3A4, but CYP2E1 and other CYP enzymes are also involved. In an interaction study with the strong CYP3A4 inhibitor ketoconazole a 27-fold increase of the lomitapide exposure was found. Based on *in vitro* findings and the ketoconazole drug-drug interaction study concomitant use of strong CYP3A4 inhibitors is contraindicated. *In vivo* interaction studies with mild or moderate CYP 3A4 inhibitors were not conducted. Based on the magnitude of the interaction with the strong CYP3A4 inhibitor ketoconazole, other strong and moderate CYP3A4 inhibitors are expected to have a substantial impact on lomitapide's PK. Therefore, the use of moderate and strong CYP 3A4 inhibitors such as itraconazole, fluconazole, ketoconazole, voriconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, diltiazem or verapamil, is contraindicated, as adequately reflected in the SmPC.

Weak CYP3A4 inhibitors are predicted to have a substantial impact on lomitapide's PK. A 4-10 fold increase of lomitapide exposure can be expected based on the results of the study with the strong CYP3A4 inhibitor ketoconazole and on historical data for the model CYP3A4 probe midazolam. As lomitapide is likely to be co-administered with weak CYP3A inhibitors, such as simvastatin, atorvastatin or oral contraceptives, the CHMP considered necessary that the SmPC contains an adequate advice the treating physicians on their concomitant use with lomitapide. In case of a 5 mg starting dose, a careful up-titration of lomitapide is recommended when it is added to a weak CYP 3A4 inhibitor. When a weak CYP 3A4 inhibitor is added to lomitapide, dose reduction of lomitapide is recommended, followed by careful up-titration, to assure the safe use of lomitapide. In addition, the applicant committed to conduct post-approval drug-drug interaction studies with the weak CYP3A4 inhibitors (atorvastatin and oral contraceptive containing ethinyl estradiol and norgestimate). The study with atorvastatine will be conducted at the highest approved dose atorvastatine to mimic the worst case clinical situation. Dose spacing in time will also be evaluated. The concomitant use of compounds that induce CYP3A4 and inhibit or induce CYP2E1 may lead to drug-drug interactions with lomitapide, as they will influence the metabolism of lomitapide.

The PBPK model was considered by the CHMP to be insufficiently validated at present to predict the impact of other weak, moderate, and strong CYP3A4 inhibitors on lomitapide's PK, but the model will be updated with the additional interaction study data. As the model is updated, the CHMP advised the applicant to take into account the correct computation of the fraction of the dose of the capsule formulation that is absorbed into enterocytes, explanation of equation 7 and origin of data included in the computation, method of estimation of and estimated parameter

values for drug distribution, justification and/or sensitivity analysis for assumed B/P ratio of 1, justification of use of Ki in place of Km, given the multiple active binding sites of CYP3A4, method of active uptake into hepatocytes in the model, consideration of gut metabolism in the model.

Lomitapide exhibits a significant food effect. The presence of fat in the food increases lomitapide exposure and decreases the gastrointestinal tolerability. In the pivotal trial UP1002, patients were to take lomitapide at bedtime with a glass of water, in order to separate the administration of lomitapide from the presence of food in the gastrointestinal tract. The CHMP considered this to be an adequate SmPC recommendation for timing relative to meals.

The distribution and protein binding of lomitapide were sufficiently characterised. Lomitapide has a high volume of distribution of approximately 1300 L and a high degree of protein binding >99.5%. In animal studies, lomitapide was shown to be highly concentrated (200-fold) in the liver and as the main site of action is in the liver , it is viewed as important to understand if the drug is also concentrated in the liver in humans. Thus, the applicant will conduct *in vitro* investigations to evaluate if lomitapide is actively or passively transported into the liver. Lomitapide also seems to be loosely bound to the plasma proteins and protein binding does not affect the distribution of lomitapide. Several metabolites were identified in human plasma, i.e. M1, M2 and M3. The M3 metabolite is most abundant, with plasma concentration approximately 15–fold higher than that of the parent drug. Although the metabolic activity of M3 was estimated to be considerably lower than that of lomitapide, its potential role in the pharmacological effect of lomitapide is not defined and further investigations are considered necessary by the CHMP. Thus, *in vitro* studies will be conducted in the post-authorisation phase. The elimination of lomitapide is sufficiently characterised. Lomitapide has a half-life of approximately 49 hours following oral administration; approximately 35% of the total lomitapide dose was excreted in the urine and 60% in faeces. Around 5% of the lomitapide dose was excreted unchanged via the faeces, no unchanged lomitapide was found in the urine.

Based on the results of two dose ranging studies it can be concluded that lomitapide displays linear PK in the dose range of 10-50 mg. At higher dose levels (100 and 200mg) a more than proportional increase of lomitapide and a less than proportional increase of the metabolite M1 and M3 were observed. Although 60 mg is above the linear range, it is only slightly higher and patients will be titrated to this dose; thus linearity can be accepted above the linear dose range. Lomitapide has an inter-individual variability of approximately 50%. Based on the currently available data, the intra-individual variability cannot be estimated and this is considered acceptable. Sparse PK data in the HoFH patients were collected and included in a population PK analysis. It was possible to predict the lomitapide trough concentrations in the HoFH patient population reasonably well. Simulation slightly underestimated the observed trough concentrations by a factor of about 1.3. This underestimation is attributed to the differences in the BMI between healthy volunteers and HoFH patients and the fact that concentrations obtained from the sparse sampling in the Phase III study were not real trough concentrations.

The exposure to lomitapide is increased by approximately 40% in subjects with ESRD on haemodialysis. Although the SmPC recommends adjusting the lomitapide dose over time, the CHMP considered it necessary that patients with ESRD receiving dialysis should not exceed 40 mg daily. An adequate advice was included in the SmPC. The exposure to lomitapide was increased by 40% in subjects with mild hepatic impairment and a 3-fold increase was found in in subjects with moderate hepatic impairment. Irrespective of the PK data, lomitapide is

contraindicated in patients with moderate or severe hepatic impairment due to safety reasons; therefore no additional data are required in this sub-population.

The influence of age, weight and race on the PK of lomitapide were evaluated in a population PK analysis using the PK results of three phase 1 studies. The population PK database was small (66 subjects) and homogenous due to the in- and exclusion criteria of the studies. A full set of demographic data in the population PK study was not provided and the covariate model building steps were not justified. Therefore, the CHMP recommended a conduct of a more extensive population PK analysis, which takes other variables into account. This will be provided post-authorisation.

In the *in vitro* tests lomitapide slightly inhibited CYP 3A4 and several other CYP enzymes. Based on these results, no direct consequences would be expected after the first pass effect, since all IC_{50} values were much higher than the clinical steady-state. The interaction of lomitapide and statins was evaluated and a significant interaction with simvastatine (a CYP3A4 substrate) during concomitant use. Considerable increase of atorvastatin and a modest increase of rosuvastatin exposure were observed after concomitant administration with lomitapide. Although the mechanism of interaction with statins is not entirely clear at the time, it can be adequately managed by taking into account the CHMP recommendations in the SmPC, i.e. contraindication of the 80mg dose of simvastatin, and warning that lomitapide can increase plasma concentrations of statins and patients receiving this combination should be monitored for adverse events (including the muscular and liver adverse events). The PK of other cholesterol-lowering drugs not metabolised by CYP3A4 was generally unaffected by co-administration of lomitapide.

The results of *in vitro* tests also showed that lomitapide is an inhibitor of the P-gp function and thus, may potentially cause a drug interaction with P-gp substrates. An *in vivo* drug interaction study was not conducted. Since the most relevant P-gp substrates will rarely be used in the relatively young HoFH population, the CHMP considered it sufficient to inform the treating physician of this potential interaction *via* the SmPC. The interaction with Pgp-substrates is also addressed in the risk management plan. Lomitapide had no effect on the PK of the components of an oestrogen-containing oral contraceptive. Lomitapide increased warfarin INR_{max} and the exposure to warfarin. This interaction is sufficiently reflected in the SmPC, since a recommendation to monitor the INR before starting lomitapide and regularly after the treatment start is included in the SmPC. As per the CHMP request, this was extended to all coumarin based anticoagulants.

Regarding the PD investigations, reduction in LDL-C concentrations was clearly demonstrated in hypercholesterolemic patients after single and multiple dose. Although data of the proof-of-concept study in HoFH (n=6) are not easy to interpret due to the very low number of patients, open-label nature and non-placebo controlled data, they can be further supported by the dose finding and main pivotal studies.

2.4.5. Conclusions on clinical pharmacology

Lomitapide is a new compound with a novel mechanism of action. It is well absorbed but with low bioavailability due to extensive first pass metabolism, highly bound to human plasma proteins, eliminated mainly by metabolism, and potential for significant drug interactions. Although the available data allow for understanding of the main pharmacokinetic

characteristics, there are a number of issues that require further investigations. Therefore, the CHMP considered the following measures necessary to address the clinical pharmacology of lomitapide:

- Conduct of clinical studies to further investigate the drug-drug interactions between lomitapide and the two weak CYP3A4 inhibitors, atorvastatin and oral contraceptives. The studies should evaluate the effect when co-administered (worst case) and when dosing is spaced in time.
- Validation of the mechanistic (PBPK) model to predict lomitapide interactions with CYP3A4 inhibitors using the data from the above studies and the interaction with ketoconazole.
- Depending on the results of the clinical studies and the reliability of the mechanistic (PBPK) model of lomitapide, further clinical drug-drug interaction studies for commonly co-administered drugs (potentially including co-administration of two weak CYP3A4 inhibitors) or further modelling work may be needed.
- Conduct of *in vitro* studies to determine whether lomitapide and its active metabolite M3 are transported into the liver and if so, to identify the hepatic uptake transporters involved using clinically relevant concentrations of lomitapide and M3 (also taking into account protein binding).
- A more extensive population PK analysis to study the other potentially relevant covariates, such as gender is needed.

The applicant committed to conduct the above investigations in the post-authorisation phase.

2.5. Clinical efficacy

The clinical trials of lomitapide were initiated with early clinical development focusing on treatment of hypercholesterolaemia with lomitapide monotherapy administered at fixed daily doses. Study UP1001, a phase 2 single-arm study in HoFH patients was the first study using dose escalation, i.e. initiating lomitapide at a low dose (0.03 mg/kg) with escalation to higher doses every 4 weeks (0.1 mg/kg, 0.3 mg/kg and 1.0 mg/kg, respectively). This study also introduced a rigorous low-fat diet (containing <10% energy from fat), which resulted in a substantially improved tolerability profile. Based on the results observed in study UP1001, a Phase 3 study UP1002 was initiated aiming to confirm the efficacy and safety of lomitapide in HoFH. Additional sites of this study were opened outside the US under protocol AEGR-733-005. Thus, UP1002/AEGR-733-005 is the pivotal study for the proposed indication in HoFH.

The clinical development programme also includes four randomised, double blind, placebo- and/or active-controlled (AEGR-733-001, AEGR-733- 003b, AEGR-733-004 and AEGR- 733-006) studies with lomitapide at doses ranging from 2.5 to 10 mg daily administered as monotherapy and/or co-administered with other lipid-lowering therapies in subjects with elevated LDL-C. Phase 2 study BMS-CV145-009 evaluating the safety and pharmacodynamics of lomitapide administered at a dose of 25 mg once daily for 4 weeks in subjects with elevated LDL-C was also conducted. The on-going study AEGR-733-012 is an extension of the pivotal UP1002/AEGR-733-005 trial and evaluates the long-term efficacy and safety of lomitapide at the maximum tolerated

dose established during study UP1002/AEGR-733-005 in HoFH patients. The below table provides an overview of these clinical trials as submitted for the originally applied indication for lomitapide:

Lomitapide is indicated as an adjunct to a low-fat diet and other lipid-lowering drugs with or without LDL apheresis to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B) and triglycerides (TG) in patients with homozygous familial hypercholesterolemia (HoFH). The effect of lomitapide on cardiovascular morbidity and mortality has not been determined.

Overview of Clinical Studies with Lomitapide

PROTOCOL PHASE	**POPULATION PRIMARY INCLUSION**	**STUDY DESIGN**	**DOSE REGIMEN/ DURATION**	**NUMBER OF SUBJECTS TREATED/COMPLETED:**				**PRIMARY EFFICACY ENDPOINT**
				LOM Alone	**LOM + LLT**	**Control**	**Total (mean age)**	
UP1002/ AEGR-733-005 Phase 3 **Pivotal**	HoFH	MD, OL, 6-wk run-in, 26 wk dose escalation, 52-wk long-term treatment; low fat diet and standard of care	QD x 78 wks 5 mg x 2wk 10 mg x 4wk 20 mg x 4wk 40 mg x 4wk 60 mg x 4wk (as tolerated)	29/23[1]	0	0	29/23[1] (30.7)	%change in LDL-C after 26 weeks of treatment
UP1001 Phase 2	HoFH	MD, OL, low-fat diet, no concurrent lipid-lowering therapy	QD x 16 wks 0.03 mg/kg x 4 wk 0.10 mg/kg x 4 wk 0.3 mg/kg x 4 wk 1.0 mg/kg x 4 wk	6/6	0	0	6/6 (25.7)	% change in LDL-C after 16 weeks of treatment
AEGR-733-001 Phase 2	LDL-C >130[2] & <250 mg/dL TG ≤400 mg/dL	R, MD, DB, active-control; low-fat diet (monotherapy & +EZET)	QD x 12wks 5mg x 4wk 7.5mg x 4wk 10mg x 4wk (as tolerated)	28/19	28/24 LOM +EZET	29/24 EZET	85/67 (56)	%change in LDL-C after 12 weeks of treatment.
AEGR-733-003b Phase 2	LDL-C >130[2] & <250 mg/dL TG ≤400 mg/dL	R, MD, DB, PC, active-control; low-fat diet (monotherapy/ & +ATOR)	QD x 8 wks 5 or 10 mg	52/27	52/26 LOM +ATOR	27/26 PBO, 26/25 ATOR	157/104 (54)	%change in LDL-C after 8 weeks of treatment
AEGR-733-004 Phase 2	LDL-C >100 & ≤190 mg/dL	R, MD, DB, PC, low-fat diet (monotherapy & + LLT)	QD x 12 wk 2.5, 5, 7.5, 10 mg QD alone 5 mg in combination	137/99	28/23 LOM +ATOR 33/28 LOM +FENO 29/25 LOM +EZET	33/31 PBO	260/206 (47.8-54.0)	%change in LDL-C, non-HDL-C, TC, VLDL-C, TG, apo B and apo AI, and change in hsCRP[3]
AEGR-733-006 Phase 2	LDL-C >130[2] & <250 mg/dL TG ≤400 mg/dL	R, MD, DB, active-control; low-fat diet (+ATOR)	QD x 8 wk 2.5mg x 4wk to 5mg x 4wk	0	21/19 LOM+ATOR	23/22 ATOR	44/41 (58.3)	%change in LDL-C after 4 and 8 weeks of treatment
CV145-009 Phase 2	LDL-C ≥160 mg/dL TG ≤500 mg/dL	R, MD, DB, PC, low-fat diet	25 mg QD x 4 wk	38/26	0	38/37 PBO	76/63 (51.6)	Evaluation of the lipid profile: LDL-C, TC, TG, apo B, VLDL-C, Lp(a), and HDL-C[4]

Key: ATOR=atorvastatin, DB=double-blind, EZET=ezetimibe, F=female, FENO=fenofibrate, HoFH=homozygous familial hypercholesterolemia, LDL-C=low density lipoprotein cholesterol, LLT=lipid-lowering therapies, LOM=lomitapide, M=male, MD=multiple dose, MRI=magnetic resonance imaging, NMRS=nuclear magnetic resonance spectroscopy, OL=open-label, PC=placebo controlled, PBO=placebo, QD=once daily; wk=week, R=randomised, TG=triglycerides.
1 Includes 4 subjects who also received lomitapide in Study UP1001
2 LDL-C >130 and <250 mg/dL for subjects with 2 or more National Cholesterol Education Program (NCEP) risk factors and >160 and <250 mg/dL for subjects with 0 or1 risk factor.
3 The primary endpoint of the study was safety/pharmacodynamic based: percent change in hepatic fat content at 12 weeks as measured by MRS compared to placebo
4 The primary endpoint of the study was safety/pharmacodynamic based: reversibility of fat accumulation in the liver based on MRS/MRI at Baseline, End of Treatment and 6 weeks after drug discontinuation
NOTE: For TC or LDL-C, to convert from mg/dL of to mmol/L, divide by 38.67; For TG, to convert from mg/dL to mmol/L divide by 88.57

2.5.1. Dose response studies

No specific dose response study was conducted. In phase 2 studies, the dose response of lomitapide as a mono-component or combined with other lipid lowering therapy (placebo controlled) was evaluated as shown in the table below after 8 weeks of treatment. The following phase 2 studies were randomised, double-blind, active-controlled, parallel-group studies in patients with moderate hypercholesterolemia, excluding HoFH patients: Study AEGR-733-001 (lomitapide+ezetimibe vs lomitapide), study AEGR-733-003 (lomitapide+atorvastatin 20 mg vs monotherapy), and study AEGR-733-006 (lomitapide+atorvastatin 20 mg vs atorvastatin).

Adding atorvastatin or ezetimibe to lomitapide resulted in further reduction of LDL-C with, no difference between adding atorvastatin to the lower and higher lomitapide dose, as shown in the table below.

In Phase 2 study UP1001 in HoFH patients, escalating dose titration was used based primarily on the observed poor GI tolerability in the hypercholesterolemic patient population. The mean doses administered every 4 weeks were 2.0, 6.7, 20.1, and 67.0 mg/day. The lipid-lowering effect was minimal after the first 4 weeks at a mean dose of 2 mg and the dose was well tolerated. Thus, the starting dose for the subsequent Phase 3 trial UP1002/AEGR-733-005 was decided to be 5 mg for the first two weeks and this was expected to lead to reduced GI side effects.

Efficacy of Lomitapide (LDL-C reduction after 8 weeks) from Phase 2 studies (excluding UP1001 in HoFH patients)

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

2.5.2. Main study

Title of Study

Study UP1002/AEGR-733-005: A Phase III Study of Microsomal Triglyceride Transfer Protein (MTP) Inhibitor AEGR-733 in Patients with Homozygous Familial Hypercholesterolemia on Current Lipid-lowering Therapy.

The clinical trial UP1002/AEGR-733-005 is considered the main pivotal study supporting the claimed indication for lomitapide.

Methods

Study Participants

In the study UP1002/AEGR-733-005, men and women 18 years of age or older with a diagnosis of functional HoFH by at least one of the following genetic or clinical criteria were eligible:

- Documented functional mutation(s) in both LDL-R alleles or alleles known to affect LDL-R functionality, or
- Skin fibroblast LDL-R activity <20% normal, or
- Untreated TC >500 mg/dL and triglycerides <300 mg/dL and both parents with documented untreated TC >250 mg/dL.

Genetic information was available for all 29 subjects in the trial. Twenty-eight of 29 patients had defects in the LDLR gene and 1 patient had ARH, which is attributed to defects in the LDLR adaptor protein. Seven subjects also had skin fibroblast LDL-R activity <20% of normal and 11 had evidence of untreated TC >500 mg/dL and triglycerides <300 mg/dL with both parents having documented untreated TC >250 mg/dL. Twenty five patients had documented mutations in each of 2 alleles, consistent with the diagnosis of HoFH. Among the 25 patients with 2 mutant LDLR alleles listed, 7 were “true” homozygotes, i.e. exhibiting the same mutation in each LDLR allele, and 18 were “compound” heterozygotes, i.e. exhibiting 2 different mutations at the LDLR locus.

Main exclusion criteria included:

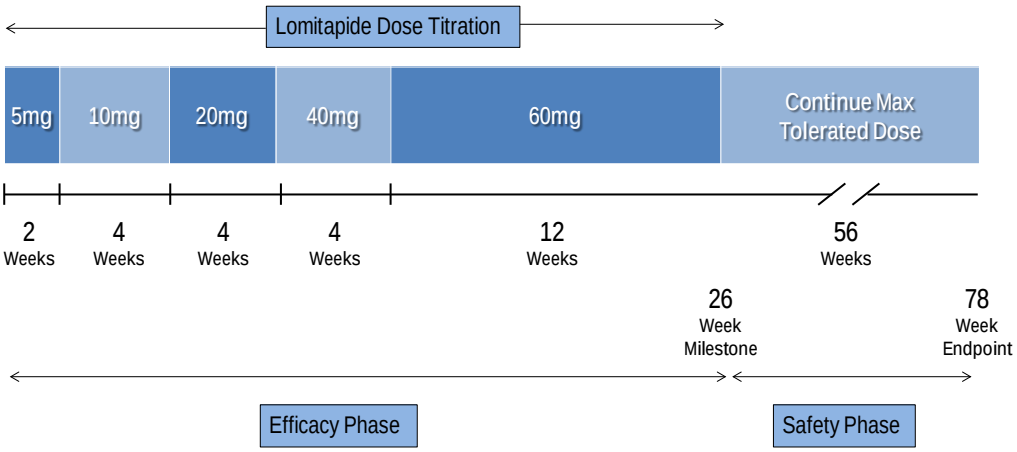
- Several types of liver diseases
- History of biopsy-proven cirrhosis or abnormal liver function tests (LFTs) at screening (AST or ALT >2 x upper limit of normal and/or total bilirubin of >1.5 mg/dL (25.7 µmol/L) unless patient has unconjugated hyperbilirubinemia due to Gilbert’s syndrome).
- Male subjects reporting more than 2 drinks per day or females reporting more than 1 drink per day (1 drink = 12 oz beer, 1 oz hard liquor, 5 oz wine).
- Chronic hepatitis B or C
- Known significant GI bowel disease or malabsorption such as inflammatory bowel disease or chronic pancreatitis requiring use of daily pancreatic enzymes.
- Uncontrolled hypertension
- History of chronic renal insufficiency

The CHMP considered the inclusion and exclusion criteria acceptable.

Treatments

In study UP1002/AEGR-733-005, a dose escalating scheme with 4 weeks intervals was used for optimal efficacy and tolerability of lomitapide, especially with respect to the GI events. Dose definition in the study was based on the efficacy and tolerability experience obtained from the small phase 2 study in HoFH patients. Background therapy should have been stable during 6 weeks prior to start of therapy and during the remainder of the 26 weeks until primary endpoint. Furthermore, patients should be on optimal background therapy. This is considered appropriate. Subjects were also counselled to follow a diet supplying <20% energy from fat and were instructed to take dietary supplements of vitamin E and fatty acids throughout the study. A schematic of the dosing regimen is provided in the figure below.

Schematic of Phase 3 Study UP1002/AEGR-733-005 Study Design



Objectives

The main objective of the study UP1002/AEGR-733-005 was to evaluate the efficacy of lomitapide co-administered with other LLTs as defined by percent change from baseline in LDL-C after 26 weeks of treatment. Furthermore, percent changes from baseline of other lipid parameters, such as TC, non-HDL-C, HDL-C, triglycerides, VLDL-C, Lp(a), HDL-C, apo AI, and hsCRP were also determined in order to assess the lipid-lowering activity of lomitapide. The efficacy objectives are considered appropriate by the CHMP, since after 26 weeks, the effect of lomitapide would have been established.

Outcomes/endpoints

The primary endpoint was the percent change from baseline in directly measured LDL-C at 26 weeks. This was calculated for each individual patient as [100 x (week 26 LDLC- baseline LDL-C)/baseline LDL-C]. For patients receiving aphaeresis, only pre-aphaeresis LDL-C levels were used in the analyses. For the baseline value LDL-C levels from visits 2 and 3 (Week -2 and Week 0), obtained before initiation of the therapy, were averaged.

Secondary endpoints was the mean percent change of TC, non-HDL, ApoB, TG, VLDL-C, and Lp(a) at 26 weeks. Exploratory efficacy variables included the mean percent change of the calculated LDL-C values at each visit, HSL-C, TC/HDL-C ratio, hs-CRP and ApoAI.

Sample size

The assumptions of 25% change in LDL-C with a 30% standard deviation and 15% dropout rate were used to calculate the sample size in study UP1002/AEGR-733-005. Applying an alpha value of 0.05 with intended 90% study power, 20 subjects were needed. In order to adequately assess safety, up to 25 subjects were to be enrolled. Eventually 29 patients were included in the pivotal study.

Randomisation

There was no randomisation in study UP1002/AEGR-733-005 since this was a single arm study and all patients who met entry criteria were assigned to receive lomitapide.

Blinding (masking)

The pivotal study UP1002/AEGR-733-005 was an open-label study, no blinding was carried out.

Statistical methods

Efficacy was assessed primarily in the intent-to-treat (ITT) population, which included all subjects who received at least 1 dose of lomitapide and had at least 1 post-baseline lipid profile. Secondary populations for evaluation of efficacy included 2 Completer analysis sets, defined as all subjects who completed the study through week 26 and through week 56, respectively. The primary efficacy endpoint of the study was the percent change from baseline in LDL-C at the end of the efficacy phase (week 26) for the ITT population. Missing data at week 26 were imputed using the last observation obtained during the efficacy phase. The key secondary efficacy parameters were TC, apo B, and triglycerides. These were statistically evaluated separately in a sequential fashion at alfa=0.05, where significance was claimed for an endpoint only when the previous parameter was significant. The additional secondary parameters of non-HDL-C, VLDL-C and Lp(a) were analysed in a similar fashion, separately from the first 3 parameters. Assessment of treatment group differences in continuous demographic variables was conducted using an ANOVA model with a term for treatment group using the F-test. For the categorical variables, comparisons across treatment groups were performed using a chi-square test. The statistical methods applied are considered appropriate for an uncontrolled trial. However, it must be remembered that a statistically significant change from baseline in an uncontrolled trial is not proof of benefit.

Results

Participant flow

The participant flow in the pivotal study UP1002/AEGR-733-005 is described in the below table.

Subject disposition by study pool

DISPOSITION PARAMETER	HOFH INDICATION N(%)	HYPERCHOLESTEROLEMIA N(%)
Received at Least One Dose of Study Medication	35	676
Prematurely Discontinued Study Medication	6 (17.1)	151 (22.3)
Reason for Early Discontinuation of Study Medication:		
Adverse Event	4 (11.4)	128 (18.9)
Withdrawal by Subject	1 (2.9)	14 (2.1)
Lost to Follow-up	0	2 (0.3)
Non-compliance with Study Drug	1 (2.9)	0
Death	0	0
Other	0	7 (1.0)

All 29 patients who completed the run-in phase entered the efficacy phase with 23 (79%) of these completing the efficacy phase through week 26. Six patients (21%) discontinued during the efficacy phase; 4 patients discontinued because of adverse events (3 patients with GI events. One patient discontinued because of unstable prothrombin index, however, also had GI events contributing to withdrawal. And one patient withdrew due to non-compliance.

Recruitment

Study UP1002/AEGR-733-005 was conducted between December 2007 and February 2010 at 11 study sites in the US (2), Canada (2), South Africa (3), and Italy (4).

Conduct of the study

The original protocol under which the first patients were enrolled in 2007 at US study sites was Protocol UP1002, Version 5. The protocol was amended on 8 January 2008 to Version 6 and on 20 May 2008 to Version 7, which was the protocol that was also initiated as Version 2 for AEGR-733-005 at sites in South Africa, Canada, and Italy. There were 2 additional protocol amendments (Versions 8 and 9 to UP1002 and Versions 3 and 4 for AEGR-733-005, which remained identical protocols). In addition, there was 1 regional amendment for sites in Canada. These amendments did not significantly impact the overall study conduct.

Overall, 27 (93%) of the 29 patients were taking concomitant HMG CoA reductase inhibitors (statins), primarily rosuvastatin and atorvastatin, and 22 (76%) were taking ezetimibe, all in combination with a statin. Three patients (10%) were using niacin and one (3%) was using a bile acid sequestrant. The majority of patients was receiving maximal approved doses of HMG CoA reductase inhibitors. Eighteen patients were on apheresis. The patients were instructed to adhere to a strict low-fat diet (i.e., averaged <20% of calories from fat) and approximately 400 IU vitamin E daily. Patients also had to take approximately 200 mg linoleic acid, 110 mg EPA, 220 mg ALA and 80 mg DHA per day.

Stopping rules for treatment were: ALT or AST ≥10.0 x upper limit of normal (ULN) or ≥200 U/L on 2 separate occasions at least 7 days apart; ALT or AST >20.0 x ULN at a single time point; ALT >5 x ULN AND total bilirubin >2 x ULN on 2 separate occasions at least 7 days apart; Alkaline phosphatase >5 x ULN on 2 separate occasions at least 7 days apart; Total bilirubin ≥3.0 mg/dL in the absence of Gilbert's syndrome or hemolysis; or Grade 3 or 4 hepatobiliary AE.

Dose reduction rules were: two occasions separated by at least 7 days with ALT or AST between 5.0 and 9.9 x ULN or >100 U/L but < 200 U/L levels, or decrease by ≥20% at any repeat visit after drug dose had been reduced.

An independent Data Safety Monitoring Board (DSMB) met regularly during the conduct of the study to review safety data and assure patients' safety.

Baseline data

The baseline data in the pivotal study are shown in the below table.

Demographics and Baseline Characteristics, HoFH Study Pool (Full Analysis Set)

CHARACTERISTIC	STUDY UP1001 (N=6)	STUDY UP1002/ 733-005 (N=29)
Age (years) Mean (SD) Minimum, Maximum	 25.0 (9.19) 17, 39	 30.7 (10.56) 18, 55
Number (%) Male	3 (50.0)	16 (55.2)
Number (%) Caucasian	3 (50.0)	25 (86.2)
BMI (kg/m^2), n (%) <30 ≥30	 5 (83.3) 1 (16.7)	 25 (86.2) 4 (13.8)
Baseline LDL-C (mg/dL) Mean (SD) Minimum, Maximum	 614.2 (105.85)[1] 480, 789	 337.0 (113.75) 152, 565
Baseline LDL-C (mmol/L) Mean (SD) Minimum, Maximum	 15.9 (2.74)[1] 12, 20	 8.7 (2.94) 4, 15

Baseline data are reflecting of a relative young population (18 top 55 years of age) with high levels of LDL-C at baseline. Several patients were already suffering from CV disease at a young age. Patients had appropriate background therapy at the study start as 27 of the 29 patients were optimally treated with statins, in 76% of the cases with additional ezetimibe, and some with niacin or bile sequestrant.

Numbers analysed

A summary of the data sets used for the analysis of efficacy and safety is provided in table below.

Patient Populations Used for Analysis (All Patients Treated)

ANALYSIS DATA SET	ALL PATIENTS N (%)
ITT Population	29 (100.0)
Safety Population	29 (100.0)
Per Protocol Population	19 (65.5)
Completers Populations Week 26 Completers Week 56 Completers	 23 (79.3) 23 (79.3)

All 29 patients who entered the efficacy phase of study UP1002/AEGR-733-005 received at least one dose of lomitapide and had at least one post-baseline efficacy assessment and therefore were included in the ITT and safety populations for analysis of efficacy and safety data, respectively. The per protocol population included 19 (66%) of the 29 patients; 10 patients were excluded from this population, primarily related to changes in their aphaeresis schedule during the efficacy phase or <80% or >120% compliance with study drug. A total of 23

patients completed both the week 26 and week 56 visits and were included in the Completers populations for these time points.

Outcomes and estimation

Primary Efficacy Endpoint: Percent Change in LDL-C to Week 26

Lomitapide, added to each subject's maximum tolerated dose of concurrently administered other lipid-lowering therapies and a low-fat diet for 26 weeks, significantly reduced the LDL-C levels. In the ITT population, mean LDL-C decreased from 8.7 mmol/L at baseline to 4.9 mmol/L at the end of the efficacy phase (week 26/LOCF), which represented a mean change of -3.8 mmol/L and a clinically meaningful, statistically significant mean percent change from baseline of -40% (p< 0.001) as summarised in the table below.

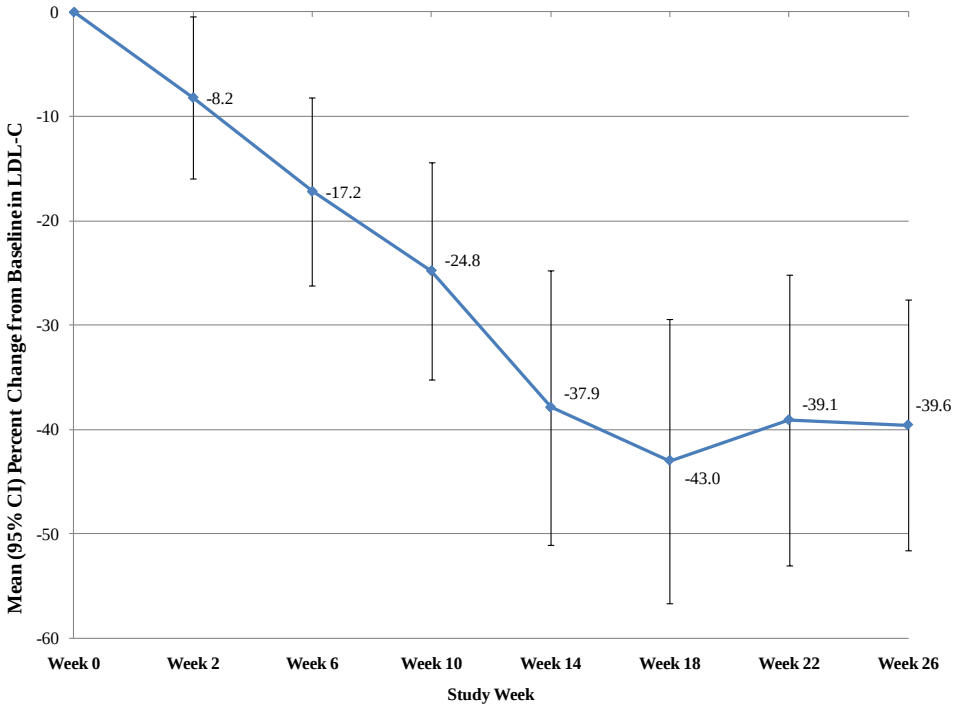
Primary Efficacy Endpoint: LDL-C at Baseline and Week 26/LOCF (ITT Population)

TIME POINT STATISTIC	OBSERVED VALUE (mmol/L)	OBSERVED CHANGE (mmol/L)	PERCENT CHANGE (%)	P-VALUE[1]
Baseline		NA	NA	NA
N	29			
Mean (SD)	8.7 (2.9)			
Median	9.2			
Minimum, Maximum	3.9, 14.6			
[95% CI]	[7.6, 9.8]			
Week 26/LOCF				
N	29	29	29	< 0.001
Mean (SD)	4.9 (4.4)	-3.8 (3.3)	-40.1 (31.25)	
Median	4.4	-2.8	-49.5	
Minimum, Maximum	0.7, 11.4	-9.0, 1.3	-92.6, 20.4	
[95% CI]	[3.9, 5.9]	[-5.0, -2.5]	[-51.9, -28.2]	

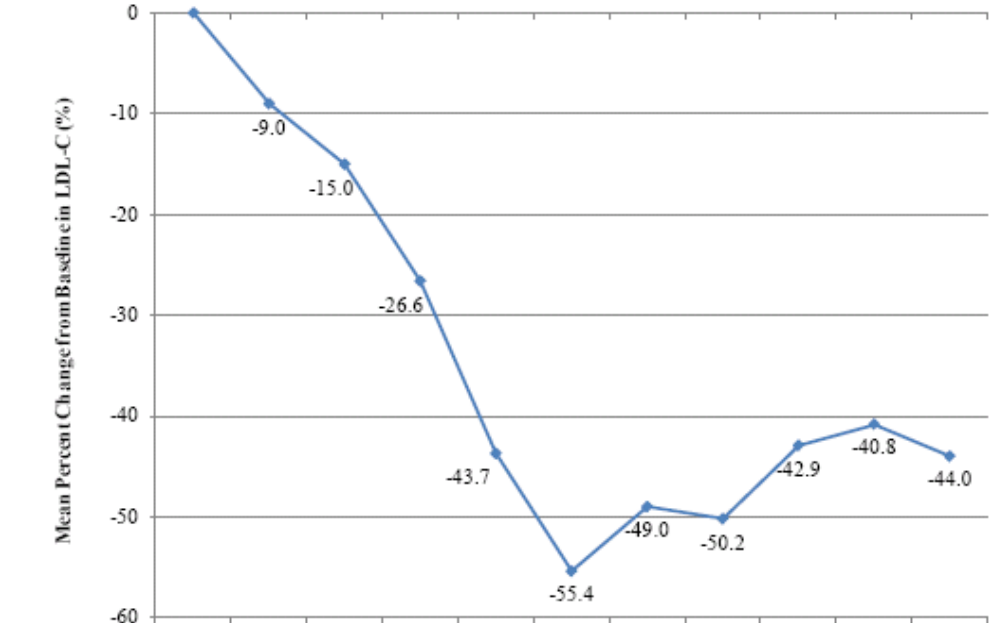
[1] *p-value on the mean percent change from baseline based on paired t-test.*

Mean LDL-C levels decreased significantly after 2 weeks of treatment with lomitapide at a mean dose of 5 mg, with mean percent change of -9% from baseline. A dose response was evident, as the dose was escalated through the planned doses of 10, 20, and 40 mg, with LDL-C levels showing decreases from baseline with mean percent changes of -17%, -27% and -41% at weeks 6, 10 and 14 (p< 0.001), respectively. Changes over time for LDL-C for the 23 patients who completed the 26-week efficacy phase were similar to those reported for the ITT population, see figure below. During the safety phase from week 26 through week 56 there, was a slight increase toward baseline in LDL-C levels; however, the mean percent change from baseline at week 56 was statistically significant at -44% (p< 0.001).

Mean (95% CI) Percent Changes from Baseline in LDL-C in study UP1002/AEGR-733-005 through the Primary Endpoint of Week 26 using LOCF to each assessment (full analysis set, N=29)



Mean Percent Change from Baseline in LDL-C Levels Over Time during the Efficacy and Safety Phases (Completers Population, N=23)



Study Week:	Baseline	Week 2	Week 6	Week 10	Week 14	Week 18	Week 22	Week 26	Week 36	Week 46	Week 56
Mean Dose (mg):	0 mg	5.0 mg	10.0 mg	18.0 mg	32.8 mg	40.2 mg	42.8 mg	44.6 mg	38.9 mg	40.9 mg	40.2 mg

Secondary Efficacy Endpoints

Results for the secondary efficacy endpoints of TC, apo B, and triglycerides, non-HDL-C and VLDL-C were generally consistent with the values obtained for the primary endpoint LDL-C. The percent decrease in Lp(a) was smaller than for the other apo B containing lipoproteins, with a median percent change of -13% from baseline to week 26; this difference was not statistically significant, as depicted in the summary table below.

Change from baseline to week 26/LOCF for secondary efficacy parameters (ITT, N=29)

EFFICACY VARIABLE	BASELINE VALUE Mean (SD)	OBSERVED VALUE Mean (SD)	OBSERVED CHANGE Mean (SD)	PERCENT CHANGE (%)	P-VALUE[1]
Total Cholesterol (mmol/L)	11.1 (3.50)	6.7 (3.0)	-4.4 (3.8)	-36.4 (28.2)	< 0.001
Apo B (g/L)	2.6 g/L	1.48 (0.74)	-1.11 (0.96)	-39.4 (30.01)	< 0.001
Triglycerides (mmol/L)	1.2 (0.54)	0.72 (0.5)	-0.4 (0.6)	-29.0 (55.72)	0.009
Non-HDL-C (mmol/L)	10.1 (3.41)	5.6 (2.9)	-4.7 (3.7)	-40.0 (29.66)	< 0.001
VLDL-C (mmol/L)	0.5 (0.25)	0.3 (0.2)	-0.2 (0.3)	-28.6 (57.45)	0.012
Lp(a) (mmol/L)	77.9 (64.41)	62.0 (41.37)	-15.9 (36.13)	-11.0 (34.04)	0.094

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

Tertiary endpoints

Mean percent changes from baseline in apo AI were -6.1% and -6.5% at week 16 in the phase 2 study and at week 26/LOCF in the phase 3 study, respectively. By week 56, mean apo AI levels had increased to baseline levels and the mean percent change from baseline to this time point was 1%. A small mean percent change from baseline in HDL-C to the primary time point was observed in both studies, which was not statistically significant in either study.

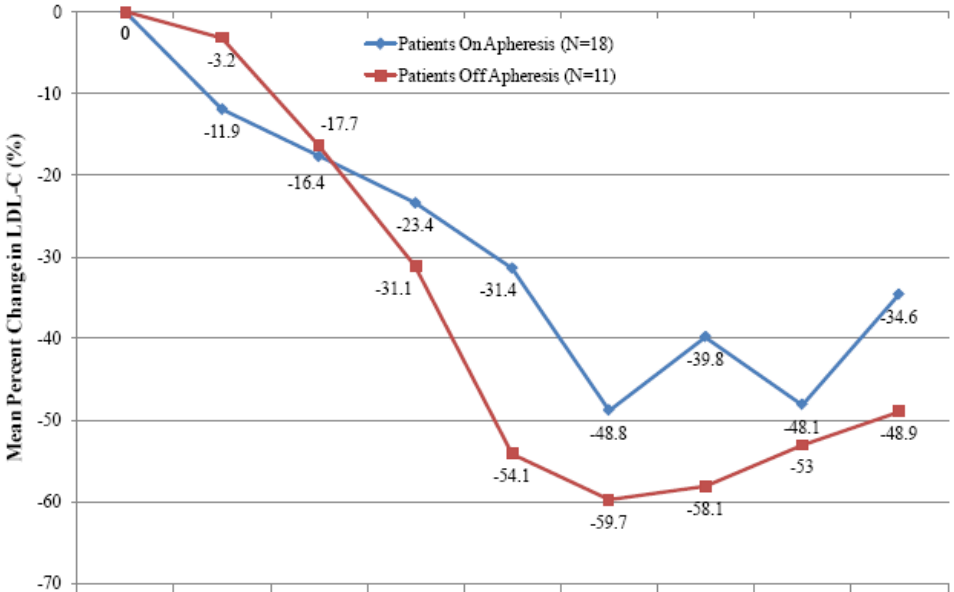
Overall, the pivotal study showed that patients were on a considerable duration of time on lomitapide treatment (mean 322 days) and this treatment indicated a significant reduction of LDL-C of almost 40% (39.6%) with 72% showing more than 50% reduction in LDL-C. Secondary response parameters of cholesterol lowering are consistent with the primary endpoint. TC, non-HDL-C, Apo-B, and TG all showed a significant reduction. However, no significant change was found for levels of ApoA1 and HDL-C at 26 weeks of treatment. Results of the small UP1001 sUP1002/AEGR-733-005 study, with patients not on background lipid lowering therapy, showed consistent results with the pivotal study.

Ancillary analyses

Twenty seven of 29 (93%) of the patients had a CV history (35% CABG, 10% coronary angioplasty, 10% aortic valve replacement, 10% cerebrovascular disease, 3% carotid endarterectomy). Furthermore, 55% of patients were male, 86% Caucasian, and 86% had a BMI <30 kg/m2. Only six (20%) of the 29 subjects were compliant over their treatment course with the strict low-fat diet (averaged <20% of calories from fat).

Subgroup analyses were only performed in the hypercholesterolemic studies, as only in this population sufficient data were available. In general, no obvious differences in efficacy were observed across patient subgroups with respect to age, gender, race, BMI and whether patients were on apheresis or not. Some observed differences were noted, but due to the lack of power, no meaningful conclusions can be drawn. The figure below demonstrates the treatment effects for the subgroups of patients on apheresis, currently the most effective treatment for HoFH, versus those who are not.

Mean percent change from baseline over time in LDL-C levels for patients who did and did not receive apheresis, efficacy phase based on available data at each assessment and at week 26/LOCF.



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

In the ITT population (n=29), mean LDL-C decreased from 336 mg/dL (8.7 mmol/L) at baseline to 190 mg/dL (4.9 mmol/L) at the end of the efficacy phase (week 26/LOCF), a mean change of -146.9 mg/dL (3.8 mmol/L), with a mean percent change from baseline of -40% [95%CI: -51.9, -28.2; p< 0.001]. In the PP analysis (n=19), this was -52% for LDL-C. At week 56, the mean percent change from baseline in LDL-C in this study was -44% for the 23 subjects who were on treatment from study from week 26 to week 56 (no discontinuations during this period).

Ten patients did not meet the PP protocol analysis due to an adjustment in their apheresis schedule or because they were non-compliant to study drug. Eight patients missed an apheresis treatment or modified the time between treatments more than two days (deviated from the protocol-specified requirement of maintaining the interval within ±1 day). Four (31%) were able to completely stop (three patients) or permanently increase (one patient) the interval between apheresis treatments and maintain low LDL-C levels through Week 56.

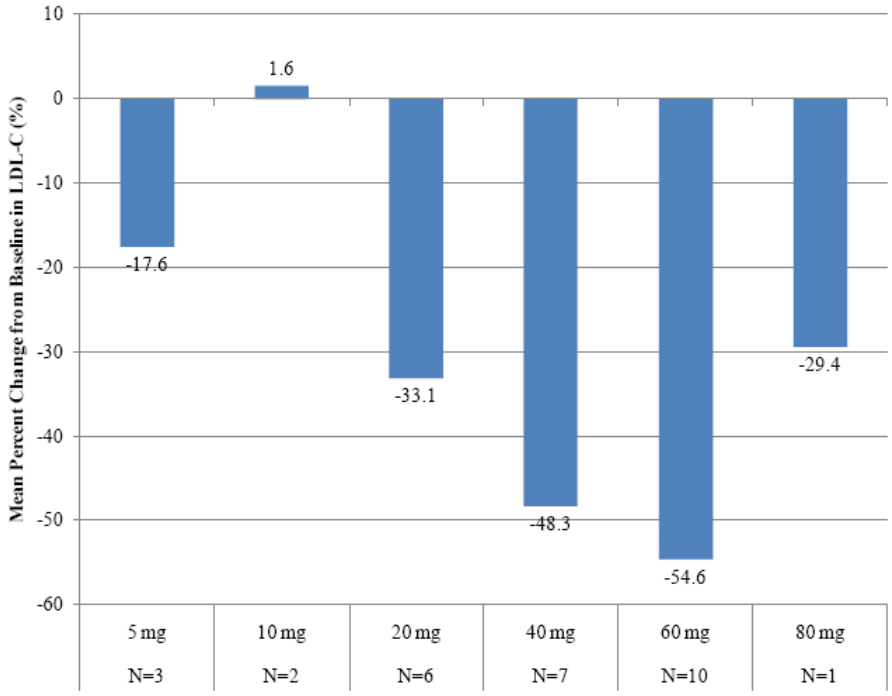
In a responder analysis 21 (72%) of patients had a 50% or greater reduction in LDL-C from baseline. Treatment goals of LDL<2.6mmol/L and <1.8 mmol/L were achieved in 55% and 31% of HoFH patients respectively.

Proportion of LDL-C responders, HoFH study pool (full analysis set)

Response Category: Statistic	**Study UP1001 (N=6)**	**Study UP1002/733-005 (N=29)**
>15% Response Category		
N (%)	6 (100.0)	25 (86.2)
95% CI	54.1, 100.0	68.3, 96.1
>25% Response Category		
N (%)	6 (100.0)	23 (79.3)
95% CI	54.1, 100.0	60.3, 92.0
>50% Response Category		
N (%)	5 (83.3)	21 (72.4)
95% CI	35.9, 99.6	52.8, 87.3
LDL-C <100 mg/dL (<2.6 mmol/L)		
N (%)	0	16 (55.2)
95% CI	0.0, 45.9	35.7, 73.6
LDL-C <70 mg/dL (<1.8 mmol/L)		
N (%)	0	9 (31.0)
95% CI	0.0, 45.9	15.3, 50.8

The dose escalation demonstrated that higher lomitapide doses were associated with greater reductions in LDL-C up to 60 mg. Data from patients treated with 80 mg of lomitapide are inconclusive as only one patient achieved to attain this dose. The overall evidence suggests that generally a dose proportional response is likely across the recommended range.

Mean percent change from baseline to week 26/LOCF in LDL-C by maximum tolerated dose (ITT, n=29)



Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial UP1002/AEGR-733-005

Title: A Phase III Study of Microsomal Triglyceride Transfer Protein (MTP) Inhibitor AEGR-733 in Patients with Homozygous Familial Hypercholesterolemia on Current Lipid-lowering Therapy		
Study identifier	UP1002/AEGR-733-005	
Design	Phase 3 open-label, single-arm clinical trial designed	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	26 weeks 6 weeks 50 weeks
Hypothesis	Superiority in LDL-C reduction on top of existing lipid lowering medication (statins) of lomitapide in subjects with HoFH at an individually-defined maximum tolerated dose.	
Treatments groups	lomitapide	5, 10, 20, 40 , 60, (and 80 mg)
Endpoints and definitions	LDL-C	Difference from baseline at 26 weeks
	TC, non-HDL-C, APO-B and TG	Subsequent analyses of secondary endpoints

	HDL-C, VLDL-C, Lp(a), APO-A1, hsCRP	Tertiary endpoints			
Database lock	12 April 2011				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat at 26 weeks with LOCF				
Descriptive statistics and estimate variability	Treatment group	lomitapide			
	Number of subjects	29			
	Statistical method	ANOVA (F-test)			
Effect estimate per comparison	Primary endpoint	LDL-C reduction at week 26 versus baseline			
		-39.6% versus baseline			
		95%CI [-51.9, -28.2]			
		P-value <0.001			

Analysis performed across trials (pooled analyses and meta-analysis)

Two sets of pooled analyses were carried out. The first focused on the primary indication i.e. patients with HoFH, including data from the phase 3 pivotal study UP1002/AEGR-733- 005 and the phase 2 supportive study, UP1001. Four subjects who were treated in Study UP1001 were also treated in Study UP1002/AEGR-733-005. These subjects were included in both UP1001 and UP1002/AEGR-733-005 since there was a long duration of "washout" between studies and the study design was different. The second pooled analysis includes 5 studies conducted in subjects with elevated LDL-C or other risk factors (AEGR-733-001, AEGR-733-003b, AEGR-733-004, AEGR-733-006 and CV145-009) used to support the lipid-lowering effect of lomitapide. With regard to the lipid endpoints, these analyses, especially in HoFH patients, provide only limited additional information on efficacy over what was shown for the individual studies due to the limited size of the population. Overall, there were no clear clinically relevant or consistent differences in mean percent changes from baseline to weeks 4 or 8 for subjects by age, race, BMI or smoking status. Subjects with higher baseline LDL-C tended to have a greater mean decrease from baseline following active treatment than subjects with lower baseline LDL-C.

Clinical studies in special populations

No special populations were examined in the efficacy studies.

Supportive studies

Results of the following randomized, double-blind, active-controlled, parallel-group phase 2 studies concerning patients with moderate hypercholesterolemia were discussed in the dose-response section:

Study AEGR-733-001: A Randomized, Double-Blind, Active-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of the Combination AEGR-733 and Ezetimibe vs. Monotherapy in Subjects with Moderate Hypercholesterolemia.

This study assessed the efficacy and safety of the co-administration of lomitapide plus ezetimibe versus monotherapy with either compound. The study consisted of 2 periods, a 1- to 2-week screening period where baseline lipids and other characteristics were evaluated to determine study eligibility and a 12-week treatment period with interim visits at weeks 4 and 8. A low-fat diet (<20% energy from fat) throughout the study was recommended. Subjects who received lomitapide + ezetimibe achieved a mean LDL-C percent change of -46.2% after 12 weeks of therapy; the lomitapide monotherapy group had a mean percent change of -29.9%; and the ezetimibe monotherapy group had a mean percent change of -19.6%. Similar results were noted for the secondary efficacy parameters of TC, apo B and non- HDL-C.

Study AEGR-733-003: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of the Combination of AEGR-733 (Formerly BMS-201038) and Atorvastatin 20 mg vs Monotherapy in Subjects with Moderate Hypercholesterolemia.

This Phase 2 was a continuation of the terminated study AEGR-733-003a and restarted with a new drug product as a 6-arm, double-blind, placebo-controlled, parallel, randomised clinical trial to assess the efficacy of 5 mg and 10 mg of lomitapide alone and in combination with atorvastatin 20 mg on LDL-C and other lipid parameters. Comparisons were made to a placebo arm and to atorvastatin 20 mg monotherapy. A total of 157 subjects were randomized. A low-fat/low cholesterol diet supplying <30% kcal as fat, <7% kcal as saturated fatty acid and <200 mg dietary cholesterol was recommended. Overall, 53 (34%) of the 157 subjects withdrew prematurely from the study, including 4%, 4%, 35%, 62%, 31%, and 69% of subjects in the placebo, atorvastatin 20 mg, lomitapide 5 mg, lomitapide 10 mg, lomitapide 5 mg + atorvastatin 20 mg and lomitapide 10 mg + atorvastatin 20 mg groups, respectively. The most common reason for premature withdrawal from the study was adverse event. Mean percent changes in LDL-C from baseline to week 8 were 2% in the placebo group; -42% in the atorvastatin monotherapy group; -16% and -37% in the lomitapide 5 and 10 mg monotherapy groups, respectively; and -47% and -50% in the lomitapide 5 mg + atorvastatin and lomitapide 10 mg + atorvastatin groups, respectively. All 5 active treatments had a statistically significant decrease in LDL-C from baseline to week 8 as compared to placebo ($p < 0.0019$). LDL-C reductions with the lomitapide atorvastatin + combinations were statistically significant also when compared to lomitapide 5 mg but not against the other treatments.

Study AEGR-733-004: Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate Low Doses of the MTP-Inhibitor AEGR-733 [lomitapide] on Hepatic Fat Accumulation as Measured by Magnetic Resonance Spectroscopy.

This was primarily a safety study but lipid parameters were also measured. It was designed as an 8 arm, multicentre, randomised, double-blind, placebo-controlled phase 2 study in order to assess the effect of lomitapide 2.5, 5, 7.5 and 10 mg alone and lomitapide 5 mg with atorvastatin 20 mg, micronized fenofibrate 145 mg or ezetimibe 10 mg on hepatic fat accumulation as measured by magnetic resonance spectroscopy (MRS)/MRI. The results were generally consistent with the findings of the previous studies.

Study AEGR-733-006: A Randomized Double Blind Comparator-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of the Combination of AEGR-733 and Atorvastatin 20 mg vs Atorvastatin Monotherapy in Subjects with Moderate Hypercholesterolemia.

This was a 2 arm, randomised, double-blind, active-comparator, phase 2 study designed to assess the efficacy and safety of lomitapide dose escalated from 2.5 to 5 mg with atorvastatin compared with atorvastatin alone. Subjects who met entry criteria were to discontinue any current lipid-lowering medications and to follow a low-fat, low cholesterol diet supplying <30% kcal as fat for a 35-day period. A total of 44 subjects were randomised into this study. The addition of lomitapide to atorvastatin 20 mg resulted in statistically significant reductions in serum LDL-C compared with atorvastatin 20 mg monotherapy over an 8-week treatment period. Results for the majority of secondary lipid efficacy endpoints were consistent with results observed in LDL-C.

The high discontinuation rate in some studies, reaching more than the third of the study population in AEGR-733-003 was noted by the CHMP. This issue is further discussed in the safety section. Overall, the findings of the supportive studies are consistent with the pivotal trial.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In terms of the dose finding studies, the doses below 10mg/day, including the proposed starting dose of 5 mg, would be expected to have a minimal effect on lipids but they appear to be necessary as a first step in a dose escalation regimen aiming at attenuating the GI adverse effects. Doses 10 mg and higher appear to have a significant and proportionally increasing effect. However, there is some uncertainty, especially about the upper bound of the proposed range, as it is not possible to properly evaluate a dose response in a clinical trial with a single arm forced titration design, as opposed to a trial where patients are randomised to the different doses. Nevertheless, clinical evidence supports the theory that patients reaching the highest dose experience the greatest benefits.

The main clinical programme for lomitapide consisted of two studies performed in 29 and 6 HoFH patients, respectively, and five studies performed in hypercholesterolemic (elevated LDL-C pool) patients. The elevated LDL-C pool patients supplies additional efficacy and safety data in a different, but related population. Both, the HoFH studies and the supportive studies, provide efficacy and safety data for use of lomitapide monotherapy, as well as on top of existing lipid lowering therapy. However, the clinical programme is very limited, especially with regards to the target population included in the proposed indication. This is due to the very low prevalence (and availability) of these types of patients. The duration of the supportive studies is 8 to 12 weeks only and therefore limits evaluation of maintenance of effect, tolerability and long-term safety.

There was a single pivotal study to demonstrate the efficacy of lomitapide in patients with HoFH. A dose escalating scheme was used to minimise the significant gastrointestinal and hepatic events based on the efficacy and tolerability experience in the limited phase 2 study in HoFH patients.

In this pivotal study, on top of lipid lowering background therapy, a dose level of 39.4 mg was the average dose reached with only one patient achieving 80 mg. Based on these data, the

recommended dose range for lomitapide was 5 mg to 60 mg given orally once daily. The inclusion and exclusion criteria of the HoFH population in the pivotal study were thought to be appropriate by the CHMP. Background therapy would have been stabilised during the 6 week period prior to start of lomitapide administration and during the remainder of the 26 weeks until the primary endpoint. Almost all patients were on an optimal dose of statin therapy. This was considered appropriate.

The pivotal study is limited, mainly due to the single arm open-label design, where both, patients and investigators were clearly not blinded to study treatment allocation. However, the very prominent gastrointestinal adverse events, warranting a dose titration based on gastrointestinal tolerability and the rarity of the condition, provide sufficient rationale for the chosen study design. The CHMP considere re-assuring that a Data Safety Monitoring Board assessed the validity and integrity of the safety data, including clinical laboratory testing. Objective assessment of the primary outcome measure, the LDL-C level, was further secured by measurement of lipid levels at a central laboratory. In addition, the supportive studies provide additional placebo and active controlled information.

The primary and secondary efficacy objectives were considered adequate by the CHMP. Lipid levels were regularly assessed throughout the study. This was necessary in order to achieve a good understanding on how lipid levels develop during the study. The primary evaluation of efficacy was at 26 weeks. Nevertheless, the extension of the pivotal study until up to 78 weeks of follow-up for safety results allows for further evaluation of maintenance of the lomitapide's effect on LDL-C levels. The statistics applied involve the standard methods and are considered appropriate. Similarly, the sample size calculation appeared to be adequate. Stopping rules regarding the liver toxicity were applied during the study and are considered adequate by the CHMP; namely the SmPC requires the treating physicians to stop lomitapide treatment if the LDL-C levels do not drop by 15%.

Overall, the CHMP agreed that the efficacy data from the pivotal clinical trials were supportive of the claimed indication for lomitapide. However, the CHMP also noted that the assumed clinical benefit of lomitapide is based on a surrogate endpoint (lowering of LDL-C levels) and this would have to be confirmed in clinical practice *via* a post-marketing clinical study assessing the CVS benefits of the treatment. As this long-term outcome is considered key to the benefit risk, the CHMP agreed with the applicant that this study would be imposed as a condition to the marketing authorisation.

Furthermore, given the safety profile of this product, the CHMP was of the opinion that it is critical to ensure that only HoFH patients will receive lomitapide. Thus, the originally proposed indication was requested to be further restricted (see Clinical Safety section).

Efficacy data and additional analyses

All supportive studies provide evidence of a dose response relationship to the lomitapide treatment. Doses 5 to 25 mg were investigated in the hypercholesterolemic patient population either alone or on top of existing lipid lowering therapy (atorvastatin or ezetimibe). The obtained data showed that a maximum lipid lowering effect was achieved after 2 weeks of the fixed dosing and remained almost stable, with slight diminishing of the effect until week 8. These studies also demonstrated significant reduction in secondary endpoints of total cholesterol, apo B, non-HDL, and triglycerides levels.

Concerning the subsequent pivotal HoFH study, the reasons for inclusion and exclusion of patients in and from the study are justified. A substantial part of the HoFH patients (17%, n=6) discontinued the study. This percentage was higher in the phase 2 studies with hypecholesterolemic patients (22%), where lower maximal but fixed doses were used. The primary reason was adverse events; 5 of 6 patients discontinuing due to GI adverse events, indicating a low tolerability level of lomitapide. Furthermore, during the conduct of the trial, a poor compliance with regard to diet was observed. Although the data are limited when subdividing the patient population according to their fat intake, there is no indication of a substantial difference in lipid lowering efficacy between patients with a high or low fat consumption. In this HoFH pivotal study, baseline data were reflective of a relative young population (18 to 55 years of age) with high levels of LDL-C at baseline. Twenty seven (93%) of the 29 patients had a cardiovascular disease history (e.g. 8 (27.6%) angina pectoris, 5 (17.2%) MI, 10 (34.5) coronary artery bypass) at the start of the study.

Patients had appropriate background therapy at start of study; 27 of the 29 patients were optimally treated with statins, in 76% of the cases with additional ezetimibe, and some with niacin or bile acid sequestrants. Eighteen patients were on apheresis.

Ultimately, in the pivotal study patients were able to continue on lomitapide therapy for a considerable duration of time (mean 322 days) with 23 out of 29 patients for more than 365 days. No patients discontinued from week 26 to 56. Lomitapide showed a clear significant reduction of LDL-C of almost 40% (39.6%), with 72% of the subjects showing more than 50% reduction in LDL-C. However, after 18 weeks of treatment the effect slightly diminished. Secondary lipid outcome parameters were consistent with the effect observed on the primary endpoint. TC, non-HDL-C, Apo-B, and TG all showed a significant reduction. However, no significant change was found for ApoA1 and HDL-C at 26 weeks of treatment. Although the Per Protocol population differs substantially from the ITT population (19 versus 29 patients), the overall results of LDL-C lowering (50% instead of 40% LDL-C lowering) are approximately similar and therefore did not substantially impact the results. When data are presented according to LDL-C lowering with regard to maximum tolerated dose, a dose from 20 mg to 60 mg showed a dose dependent reduction in LDL-C while this association could not be found for the other doses, mainly because of discontinuations due to safety. Although protocol deviations were found because of apheresis, this did not substantially impact the results. For patients treated until 56 weeks (n=23), LDL-C reduction was essentially similar with the ITT population with a 50% reduction at 26 weeks and 44% reduction at 56 weeks.

Results of the small UP1001 proof of concept study (n=6), with HoFH patients not on background lipid lowering therapy, showed consistent results with the pivotal study. The baseline characteristics of the hypercholesterolemic patients in the supportive phase 2 studies are, as expected, different from the HoFH patients, mainly in the sense that the patients are older. However, these studies are meaningful in the way that they provide substantially more information on placebo-controlled and active-controlled treatment effect of lomitapide, albeit in a different patient population and for a short-term period of time (8 to 12 weeks).

Subgroup analyses were only performed in the hypercholesterolemic studies, as only in this population sufficient data were available. Subgroup analyses were performed with respect to age, gender, BMI, region, race and baseline LDL-C level. In general, no substantial differences could

be observed, but no definite conclusions on subgroups could be made due to the low patient numbers.

Additional expert consultation

The CHMP requested the opinion of additional experts on the uncertainties identified during the assessment of lomitapide's efficacy and safety profile in the HoFH patients. Due to the fact that majority of these concerns relate to safety and the adverse profile of this product, the details of the experts' consultation and its outcome are summarised in the Clinical Safety section.

Assessment of paediatric data on clinical efficacy

The safety and efficacy of Lojuxta in children below 18 years of age have not been established and the use of this medicinal product in children is therefore not recommended. No paediatric data are available. The agreed Paediatric Investigation Plan (PIP) for lomitapide includes:

- Waiver in all subsets of the HoFH paediatric population from birth to less than 8 years of age and a deferral of the study in children from 8 to less than 18 years of age;
- Waiver in patients with HeFH of all age subsets of the paediatric population from birth to less than 18 years of age;

The PDCO agreed a single-arm, open-label trial in paediatric patients with HoFH on stable lipid-lowering therapy. However, due to the unknown clinical relevance of the risk for tumour formation (i.e. hepatocellular adenomas/carcinomas and dermal/epithelial hyperplasia), the PDCO requested that this study must not be initiated before the CHMP concludes on a positive benefit/risk balance of lomitapide in HoFH adults, and before the PDCO re-discusses and evaluates the potential significant therapeutic benefit and need for paediatric studies for lomitapide.

The CHMP recommends that in the light of their positive benefit/risk balance conclusion in adult patients, the applicant initiates the above described dialogue with the PDCO at the earliest possibility with a view to agree on the final PIP.

Additional efficacy data needed in the context of an MA under exceptional circumstances

The applicant did not provide results from a full clinical development with lomitapide and the CHMP agreed with the applicant's argument that the patient population of lomitapide is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive clinical data on the safety and efficacy of this medicinal product. As a consequence, the applicant will be obliged to provide further evidence as specific obligations relating in particular to the safety and efficacy as follows:

The applicant shall set up a long term prospective observational study to systematically collect information on the safety and effectiveness outcomes of patients treated with lomitapide.

The objectives of the study are:
- To evaluate the occurrence of the following in patients treated with lomitapide:
  - Hepatic events
  - Gastrointestinal events
  - Small bowel, hepatic, colorectal and pancreatic tumours
  - Events associated with coagulopathy
  - Major Adverse Cardiovascular Events (MACE) events

- Death, including cause of death

• To evaluate the occurrence and outcomes of pregnancy in females of reproductive potential treated with lomitapide who decide to continue the pregnancy following advice from a teratologist.
• To evaluate the long-term effectiveness of lomitapide in maintaining control of serum lipid levels in clinical practice.
• To evaluate whether prescribers of lomitapide are following the screening and monitoring recommendations as specified in the product information and the educational materials.

These specific obligations shall be annually reassessed.

2.5.4. Conclusions on the clinical efficacy

The efficacy of lomitapide to lower LDL-C in a HoFH population was demonstrated in a very limited dataset, mainly due to the rarity of the disease, and using a suboptimal study design. These were supported by short-term efficacy data in hypercholesterolemic patients. As per the CHMP guideline EMA/CPMP/3020/2003, lowering of the LDL-C level is considered an appropriate surrogate endpoint of lipid lowering agents aiming at lowering the cardiovascular risk in the affected patients. However, the absolute long term effect remains to be evaluated. Therefore, the CHMP was of the opinion that the originally proposed indication for lomitapide would need to be restricted further, in order to guarantee that only those patients are treated, who can truly benefit from this medicinal product. The revised and agreed indication for Lojuxta is:

Lojuxta is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).

Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolemia (e.g. nephrotic syndrome, hypothyroidism) must be excluded.

The CHMP agreed with the applicant's argument that the patient population of lomitapide is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive clinical data on the safety and efficacy of this medicinal product. As a consequence, the applicant will be obliged to provide further evidence as specific obligations relating in particular to the safety and efficacy as follows:

The applicant shall set up a long term prospective observational study to systematically collect information on the safety and effectiveness outcomes of patients treated with lomitapide.

The objectives of the study are:
• To evaluate the occurrence of the following in patients treated with lomitapide:
  - Hepatic events
  - Gastrointestinal events
  - Small bowel, hepatic, colorectal and pancreatic tumours
  - Events associated with coagulopathy
  - Major Adverse Cardiovascular Events (MACE) events
  - Death, including cause of death

• To evaluate the occurrence and outcomes of pregnancy in females of reproductive potential treated with lomitapide who decide to continue the pregnancy following advice from a teratologist.
• To evaluate the long-term effectiveness of lomitapide in maintaining control of serum lipid levels in clinical practice.

• To evaluate whether prescribers of lomitapide are following the screening and monitoring recommendations as specified in the product information and the educational materials.

These specific obligations shall be annually reassessed.

2.6. Clinical safety

Patient exposure

The exposure according to study type is displayed in the below table.

Overview of subjects with safety data evaluated by study phase and type, treatment and data summarization

STUDY PHASE STUDY TYPE	TREATMENT LOMITAPIDE	 ACTIVE CONTROL	 PLACEBO	 TOTAL
DATA INCLUDED IN THE POOLED ANALYSES				
Phase 1				
Single Dose Studies	87	--	26	113
Multiple Dose Studies	150	16	44	168
TOTAL Phase 1	**237**	**16**	**70**	**281**
Phase 2 (Multiple Dose Studies)				
Controlled Studies	446	78	98	622
Fixed Dose	369	26	98	493
Escalated Dose	77	52	0	129
Uncontrolled Studies	133	0	0	133
Fixed Dose	127	0	0	127
Escalated Dose	6	0	0	6
TOTAL Phase 2	**579**	**78**	**98**	**755**
Phase 3				
Single-arm, Escalated Dose	**29**	**0**	**0**	**29**
TOTAL for Studies in Pooled Analyses	**845**	**94**	**168**	**1065**

Data from 20 of the 24 lomitapide studies were pooled for analysis based on the population treated and the study design. The relevant study pools are:

- HoFH: Studies UP1001 (16 weeks) and UP1002/AEGR-733-005 (56 weeks).
- Hypercholesterolemic population (elevated LDL-C and other risk factors; 8-12 weeks): Studies AEGR-733-001, AEGR-733-003b, AEGR-733-004, AEGR-733-006, CV145-002, CV145-009, CV145-010

Adverse events

The safety review includes data from 1145 patients and healthy subjects (out of these 845 were patients) treated with lomitapide and/or a comparator agent across the phase 1, 2, and 3 clinical programme. The table below provides the data on adverse events in the pivotal study according to dose in the HoFH pivotal study.

Overall summary of TEAEs for the pivotal study.

NUMBER OF SUBJECTS WITH:	DOSE OF LOMITAPIDE AT THE TIME OF ONSET OF THE TEAE						ALL PATIENTS
	5 MG	10 MG	20 MG	40 MG	60 MG	80 MG	
Efficacy Phase							
Number of Patients who Received the Dose	29	27	26	21	13	2	29
TEAE	18 (62.1)	20 (74.1)	19 (73.1)	18 (85.7)	11 (84.6)	1 (50.0)	27 (93.1)
Related TEAE	12 (41.4)	15 (55.6)	12 (46.2)	13 (61.9)	8 (61.5)	0	25 (86.2)
Severe TEAE	0	1 (3.7)	5 (19.2)	3 (14.3)	3 (23.1)	1 (50.0)	8 (27.6)
Deaths due to TEAE	0	0	0	0	0	0	0
SAE	1 (3.4)	0	1 (3.8)	1 (4.8)	1 (7.7)	0	3 (10.3)
Discontinued treatment due to TEAE	1 (3.4)	2 (7.4)	0	1 (4.8)	0	0	4 (13.8)
Interruption or dose reduction due to TEAE	4 (13.8)	2 (7.4)	4 (15.4)	5 (23.8)	4 (30.8)	1 (50.0)	12 (41.4)
Safety Phase							
Number of Patients who Received the Dose	2	1	9	10	11	1	23
TEAE	2 (100.0)	1 (100.0)	7 (77.8)	7 (70.0)	9 (81.8)	1 (100.0)	19 (82.6)
Related TEAE	1 (50.0)	1 (100.0)	6 (66.7)	7 (70.0)	4 (36.4)	1 (100.0)	15 (65.2)
Severe TEAE	0	0	2 (22.2)	2 (20.0)	2 (18.2)	1 (100.0)	5 (21.7)
Deaths due to TEAE	0	0	0	0	0	0	0
SAE	0	0	0	0	0	0	0
Discontinued treatment due to TEAE	0	0	0	0	0	0	0
Interruption or dose reduction due to TEAE	0	0	3 (33.3)	2 (20.0)	2 (18.2)	1 (100.0)	6 (26.1)

Gastrointestinal adverse events: The following were the most commonly reported TEAE among HoFH patients: diarrhoea (80%), nausea (60%), vomiting (34%), dyspepsia (31%), abdominal discomfort (26%), abdominal pain (23%), upper abdominal pain, and constipation (20%) (see table below). The mean and median time to a first GI event in the 27 patients experiencing them was 9.1 days and 5.0 days, respectively, and ranged from 1 to 39 days. In the pivotal study, the incidence of diarrhoea decreased from 79% to 35% from the 26 week phase to the 56 week phase, respectively. Overall, 6 (20%) of 29 HoFH subjects experienced a severe GI event, of which all but one were considered to be drug-related, including diarrhoea (14%), vomiting (7%) and single cases of abdominal discomfort, abdominal distension, abdominal pain, constipation, dyspepsia, food poisoning, and gastric dilatation (3%). Five (17%) subjects discontinued study treatment because of GI symptoms. Around 41% patients had dose reductions and/or dose interruptions, duration of which were short with a median of 5 days and occurred during the first 26 weeks. GI symptoms were the main cause for patients not reaching the highest dose.

Gastrointestinal Disorders reported in ≥5% of subjects in either study: HoFH study pool

MedDRA SOC Preferred Term	UP1001 (N=6) n (%)	Final Escalated Dose Level at Week 26, UP1002/AEGR-733-005 5 mg (N=3) n (%)	10 mg (N=2) n (%)	20 mg (N=6) n (%)	40 mg (N=7) n (%)	60 mg (N=11) n (%)	Total (N=29) n (%)
Gastrointestinal Disorders	**5 (83.3)**	**2 (66.7)**	**2 (100.0)**	**6 (100.0)**	**7 (100.0)**	**10 (90.9)**	**27 (93.1)**
Diarrhoea	5 (83.3)	1 (33.3)	2 (100.0)	5 (83.3)	7 (100.0)	8 (72.7)	23 (79.3)
Nausea	2 (33.3)	1 (33.3)	1 (50.0)	5 (83.3)	5 (71.4)	7 (63.6)	19 (65.5)
Dyspepsia	1 (16.7)	1 (33.3)	0	3 (50.0)	4 (57.1)	2 (18.2)	10 (34.5)
Vomiting	2 (33.3)	0	0	2 (33.3)	3 (42.9)	5 (45.5)	10 (34.5)
Abdominal Discomfort	0	2 (66.7)	0	2 (33.3)	2 (28.6)	3 (27.3)	9 (31.0)
Abdominal Pain	0	1 (33.3)	1 (50.0)	1 (16.7)	3 (42.9)	2 (18.2)	8 (27.6)
Constipation	1 (16.7)	0	0	1 (16.7)	1 (14.3)	4 (36.4)	6 (20.7)
Flatulence	0	0	0	1 (16.7)	3 (42.9)	2 (18.2)	6 (20.7)
Abdominal Distension	0	1 (33.3)	0	0	3 (42.9)	1 (9.1)	5 (17.2)
Abdominal Pain Upper	2 (33.3)	1 (33.3)	0	1 (16.7)	1 (14.3)	2 (18.2)	5 (17.2)
Rectal Tenesmus	0	0	0	1 (16.7)	1 (14.3)	1 (9.1)	3 (10.3)
Defaecation Urgency	0	0	0	0	1 (14.3)	1 (9.1)	2 (6.9)
Eructation	0	0	0	0	0	2 (18.2)	2 (6.9)
Gastritis	0	0	0	0	0	2 (18.2)	2 (6.9)
Gastrooesophageal Reflux Disease	0	0	0	0	0	2 (18.2)	2 (6.9)

In the supportive studies in hypercholesterolemic patients, the GI adverse events seemed dose-dependent. In the escalated dose group, the dose was up-titrated based on tolerability. The maximal dose level reached was 10 mg. Gastrointestinal disorders of severe intensity, most commonly diarrhoea, were reported in 9%, 12%, 28% and 13% of subjects in the escalated-, low-, mid-, and high-dose lomitapide groups, respectively. Diarrhoea was the most commonly reported TEAE leading to discontinuation. Nausea was also among the most commonly reported TEAEs leading to discontinuation.

Hepatic adverse events: In the HoFH population, twelve (34%) of 35 subjects experienced at least one AE classified as a hepatic disorder; the most common were elevations in transaminase levels, of which most were considered to be related to treatment. Six subjects experienced serious hepatic disorders including increased ALT (5 subjects), increased AST (3 subjects), and hepatic steatosis, hepatic toxicity, and prothrombin time prolonged (1 subject each), as summarised in the table below. For two of the three patients with ALT elevation >5x ULN and hepatic fat levels >20% during lomitapide treatment, hepatic steatosis was reported and this required a dose modification. None of the reported hepatic disorders were severe or resulted in study drug discontinuation in the HoFH population.

Treatment emergent hepatic disorders reported as adverse events, HoFH indication.

MEDDRA PREFERRED TERM	UP1001 (N=6) N (%)	FINAL ESCALATED DOSE LEVEL AT WEEK 26, UP1002/AEGR-733-005					
		5 MG (N=3) N (%)	10 MG (N=2) N (%)	20 MG (N=6) N (%)	40 MG (N=7) N (%)	60 MG[1] (N=11) N (%)	TOTAL (N=29) N (%)
AT LEAST 1 HEPATIC DISORDER:	4 (66.7)	1 (33.3)	0	3 (50.0)	3 (42.9)	1 (9.1)	8 (27.6)
Alanine Aminotransferase Increased	3 (50.0)	0	0	2 (33.3)	2 (28.6)	1 (9.1)	5 (17.2)
Aspartate Aminotransferase Increased	3 (50.0)	0	0	1 (16.7)	1 (14.3)	0	2 (6.9)
Hepatic Steatosis	0	1 (33.3)	0	0	0	1 (9.1)	2 (6.9)
Transaminases Increased	0	1 (33.3)	0	0	1 (14.3)	0	2 (6.9)
International Normalised Ratio Abnormal	0	0	0	1 (16.7)	0	0	1 (3.4)
Hepatotoxicity	0	0	0	0	0	1 (9.1)	1 (3.4)
Blood Alkaline Phosphatase Increased	0	0	0	1 (16.7)	0	0	1 (3.4)
International Normalised Ratio Increased	2 (33.3)	0	0	0	0	0	0
Prothrombin Time Prolonged	1 (16.7)	0	0	0	0	0	0

The incidence of hepatic disorders, majority of which were drug related, in the hypercholesterolemic population was 29%, 7%, 9%, and 10% in the escalated-, low-, mid-, and high-dose groups, respectively. Twenty subjects, discontinued study drug because of a hepatic disorder (13%, <1%, 5%, and 5% in the escalated-, low-, mid-, and high-dose groups, respectively).

Treatment emergent hepatic disorders reported as adverse events, hypercholesterolemic study pool.

MEDDRA PREFERRED TERM	LOMITAPIDE[1]				PLACEBO (N=116) N (%)	ACTIVE CONTROL (N=78) N (%)
	ESCALATED (5-10 MG) (N=77) N (%)	LOW DOSE (2.5-7.5 MG) (N=244) N (%)	MID DOSE (10 MG) (N=99) N (%)	HIGH DOSE (25-100 MG) (N=62) N (%)		
AT LEAST ONE HEPATIC DISORDER	22 (28.6)	18 (7.4)	9 (9.1)	6 (9.7)	2 (1.7)	2 (2.6)
Alanine Aminotransferase Increased	17 (22.1)	13 (5.3)	3 (3.0)	3 (4.8)	1 (0.9)	1 (1.3)
Aspartate Aminotransferase Increased	11 (14.3)	12 (4.9)	3 (3.0)	2 (3.2)	1 (0.9)	1 (1.3)
Liver Function Test Abnormal	3 (3.9)	0	2 (2.0)	3 (4.8)	0	0
Hepatic Enzyme Increased	2 (2.6)	1 (0.4)	3 (3.0)	0	0	0
Prothrombin Time Prolonged	0	1 (0.4)	2 (2.0)	0	1 (0.9)	1 (1.3)
International Normalised Ratio Increased	0	2 (0.8)	0	0	1 (0.9)	0
Hepatomegaly	0	0	0	1 (1.6)	0	0
Blood Bilirubin Increased	0	1 (0.4)	0	0	0	0
Transaminases Increased	0	0	1 (1.0)	0	0	0
Gamma-Glutamyltransferase Increased	0	0	0	1 (1.6)	0	0
Blood Alkaline Phosphatase Increased	0	0	0	0	0	1 (1.3)

Accumulation of fat in the liver: Analyses of hepatic fat by imaging procedures NMRS and MRI were performed in the HoFH studies. Consistent with the mechanism of action of lomitapide, increases in hepatic triglyceride content were observed. The levels decreased spontaneously during continued treatment in some subjects, but remained elevated in most during the treatment period. Reversal of the hepatic fat accumulation was observed when subjects discontinued lomitapide. A mean absolute change in hepatic fat percent of 8% at the week 26 and 6% at week 56 was observed in the pivotal study. The majority of patients (13 of 23, 57%) with hepatic fat assessments had maximal hepatic fat percentages <10% during the 78-week phase 3 study. The hepatic fat percentage was >20% in three patients and all three subjects also had ALT levels >5x ULN during lomitapide treatment. In two of these, fat levels decreased to <20% at the next assessment during continued treatment with lomitapide. In one case, on-treatment hepatic fat levels continued to increase to a maximum level of 44% reported at week 61. This patient completed the study through Week 78. At the post-treatment assessment (week 84; six weeks off treatment), a computed tomography scan revealed significantly decreased hepatic fat content to 7-15%.

In the supportive HoFH study UP1001 (n=6), a mean absolute increase in hepatic fat percent of 19% was observed from a baseline value of 3%. At 4 weeks after completion of dosing, the mean absolute change in hepatic fat percent from baseline was 5% indicating reversibility of hepatic fat content in the liver.

Maximum categorical change in hepatic fat percent: HoFH indication (study UP1001 and UP1002/AEGR-733-005).

Maximum Increase	UP1001 (N = 6)	Final Escalated Dose of Lomitapide at Week 26, UP1002/AEGR-733-005					
		5 mg (N = 3)	10 mg (N = 2)	20 mg (N = 6)	40 mg (N = 7)	60 mg (N = 11)	Total (N = 29)
Number of Subjects[1]	6	1	0	5	5	11	22
≤5%	1 (16.7)	0	0	2 (40.0)	1 (20.0)	2 (18.2)	5 (22.7)
>5% to ≤10%	1 (16.7)	0	0	3 (60.0)	2 (40.0)	5 (45.5)	10 (45.5)
>10% to ≤15%	0	0	0	0	1 (20.0)	2 (18.2)	3 (13.6)
>15% to ≤20%	1 (16.7)	0	0	0	1 (20.0)	0	1 (4.5)
>20% to ≤25%	1 (16.7)	0	0	0	0	1 (9.1)	1 (4.5)
>25%	2 (33.3)	1 (100.0)	0	0	0	1 (9.1)	2 (9.1)

Hepatic fat content in the liver was also measured by MRI in studies AEGR-733-002 (2 weeks, healthy volunteers), AEGR-733-004 (measured at week 12) and CV145-009 (measured at week 4, and again 6 weeks after withdrawing treatment). In Study CV145-009, the extent of reversibility of hepatic fat increases was assessed in 76 (63 completed) subjects with LDL-C ≥160 mg/dL and TG <500 mg/dL. Liver MRI/NMRS imaging was performed at baseline, end of treatment (25 mg lomitapide or matched for 4 weeks) and 6 weeks after drug discontinuation. Lomitapide treatment resulted in hepatic fat accumulation (11.03% hepatic fat content at baseline increased to 31.65% by the end of treatment) and this effect was almost fully reversed after 6 weeks off treatment. The mean absolute increase in percent hepatic fat content of 20.88% at the end of 4 weeks of treatment decreased to 4.02% by the end of 6 weeks off treatment. Subjects in the placebo group showed essentially no change in mean percent hepatic fat content. The difference in change in percent hepatic fat between lomitapide

and placebo was statistically significant between baseline and the end of 4 weeks of treatment (p<.0001) but not after 6 weeks off the drug (p=0.13).

Cardiovascular adverse events: Five (14%) of 35 subjects with HoFH experienced at least one cardiovascular event (2 serious) unrelated to study drug: angina pectoris in 3 subjects, and 1 subject each with acute coronary syndrome, coronary artery arteriosclerosis, and blood creatine phosphokinase increased; 1 subject with angina pectoris also had acute coronary syndrome reported. Three subjects experienced at least 1 CV event (one fatal MI, unrelated) in the hypercholesterolemic population.

Musculoskeletal adverse events: There were no reports of rhabdomyolysis in the lomitapide programme. Four (11%) of 35 HoFH subjects experienced musculoskeletal system events or events potentially associated with rhabdomyolysis (myalgia; musculoskeletal pain, blood creatine phosphokinase increased, and transient acute renal failure). These were considered unrelated to study drug. As described in the individual study report, nine (31%) of the 29 patients had a musculoskeletal disorder reported during the study. The incidence was highest during dosing with 60 mg lomitapide with incidences of 7%, 7%, 8%, 5%, 23% and 0% during dosing with 5, 10, 20, 40, 60 and 80 mg, respectively. None led to study drug discontinuation. A mean maximum increase of 163 IU/L was observed for CPK, from a baseline value of 135 IU/L; this was related to one subject who had a maximum increase of 1540 U/L receiving rosuvastatin 40 mg and ezetimibe 10 mg during lomitapide treatment, and continued treatment. No musculoskeletal symptoms were reported in this subject.

In the hypercholesterolemic population, the incidence of musculoskeletal events was 3%, 5%, 0%, and 0% in the escalated, low-, mid-, and high-dose groups and 1% and 3% in the placebo and active control groups, respectively. Severe myalgia was reported for 1 (<1%) subject in the lomitapide low-dose group and 1 (1%) subject in the active control group (discontinued). There was no difference in maximum mean change in CPK for the placebo group versus lomitapide with one subject each with Grade 3 or 4 increased CPK.

Pulmonary function: One (3%) of 35 subjects with HoFH experienced wheezing. Respiratory disorders were reported in six (21%) of the 29 patients; of nasal congestion and pharyngolaryngeal pain, each reported in three patients (10%) assessed as unrelated to study treatment. Three subjects in the hypercholesterolemic population experienced one (unrelated) event of asthma or bronchospasm (escalated, low-dose and mid-dose group).

Weight loss: Six (21%) of 29 subjects with HoFH experienced at least one weight loss event and this event was considered drug-related for four of six subjects. At Weeks 26 and 56, weight had decreased a mean of 3.4 (-4.7%) and 2.4 kg (-3.5%) from baseline. All weight loss events were assessed as mild to moderate in severity, non-serious and none led to study drug discontinuation. There were no significant correlations between change in weight and number of diarrhoea events at any time point. In the hypercholesterolemic population two subjects (high-dose) experienced weight loss (one discontinued).

Serious adverse event / deaths / other significant events

One (17%) of six subjects in the 16-week HoFH supportive study and three (10%) of 29 subjects in the 56 weeks pivotal study experienced a serious adverse event. According to the applicant, no events were related to study treatment, but most to the subject's underlying CV disease

(acute coronary syndrome and angina pectoris, or coronary artery arteriosclerosis), or the event was related to prior cardiac surgery (post-operative seroma, breast mass). One subject with a history of menorrhagia required a hysterectomy. Lower respiratory tract infection was also reported as an SAE in the subject with acute coronary syndrome and angina pectoris. There were six subjects in the hypercholesterolemic population, who experienced a serious AE, including 1 (1%), 2 (1%) and 3 (3%) in the escalated, low- and mid-dose groups, respectively. One subject each in the escalated low-, and mid-dose groups experienced a myocardial infarction. One subject in the escalated-dose group (AEGR-733-001) died as a result of this MI. All other SAEs were reported in 1 subject each and included chest pain in the lomitapide low-dose group and ankle fracture and inflammatory bowel disease in the lomitapide mid-dose group.

There were no deaths reported during either HoFH studies. As stated above, 1 death (unrelated) occurred in the hypercholesterolemic population. The subject was a 54-year-old Caucasian male with medical history significant for deep vein thrombosis, peptic ulcer, Factor V Leiden, and hypertension, who received lomitapide for 12 weeks. The subject developed nausea and diaphoresis and ventricular fibrillation, and received cardiopulmonary resuscitation. He was cyanotic without cardiac activity and died.

There have been no reports of malignancies across the lomitapide clinical programme, which is reassuring. However, in non-clinical studies, long-term fat accumulation as well as an increased number of tumours was observed in liver, small intestine and pancreas. Fatty liver in itself might be a risk factor for hepatocellular carcinoma.

In the pivotal study with HoFH patients, infections were reported in 17 (59%) of the 29 patients, with the highest incidence observed with 60 mg lomitapide (seven of 13 patients, 54%). The incidence at the other dose levels were 10%, 4%, 27%, 19% and 0% at doses of 5, 10, 20, 40 and 80 mg, respectively. The types of infections reported in 10% or more of the 29 patients were nasopharyngitis (17%), gastroenteritis (14%), and influenza (14%). Two patients experienced gastroenteritis that was assessed as treatment-related; all other infections were reported as unrelated to lomitapide treatment. With the exception of 1 report of lower respiratory tract infection, which was assessed as severe in intensity, all other infections were reported as mild to moderate in intensity.

Laboratory findings

Liver function tests: Elevations of ALT >3 to ≤5×ULN were observed in five (14%) of 35 subjects in the HoFH pool and elevations >5 to ≤10×ULN were observed for five (14%) subjects. One subject in study UP1001 had a transient elevation in ALT >10 to ≤20×ULN. This subject was subsequently enrolled in the pivotal study, and again experienced a transient elevation in ALT >10 to ≤20×ULN. Furthermore, one patient experienced an ALT > 20x ULN. Median time to ALT or AST >3×ULN was 55 days in study UP1001 and 112 days in the pivotal study. Median duration of the abnormal transaminase elevation (time from onset of abnormality >3×ULN to return to within the normal range) was 36 days in study UP1001 and 29 days in the pivotal study.

Statistically significant ($p \leq 0.0212$) correlations were noted for changes in ALT and in AST with changes in LDL-C at week 26 ($r=-0.6194$ and $r=-0.6457$, respectively) and at week 56 ($r=-0.5012$ and $r=-0.4740$, respectively). Changes in ALT and AST were also significantly ($p \leq 0.0158$) correlated with changes in hepatic fat at weeks 26 and 56 (ALT: $r=0.6203$ and $r=0.5145$, respectively; AST $p<0.0001$, $r=0.7202$; but not at week 56 time point: $p=0.0634$, $r = 0.4117$).

None of the subjects in the HoFH study pool developed acute hepatotoxicity. No subject had an ALT elevation to >3xULN with a corresponding total bilirubin elevation that was >2xULN, i.e., no subject met Hy's Law (ALT>3ULN and Bili>2 ULN). Similar results were observed for AST.

Maximum Abnormal Liver Function Test Results Post First Dose: HoFH Indication (safety population)

PARAMETER / ABNORMALITY[1]	STUDY UP1001 (N=6) N (%)	STUDY UP1002 / AEGR-733-005 (N=29) N (%)
ALT		
>3 to ≤5 x ULN	0	5 (17.2)
>5 to ≤10 x ULN	2 (33.3)	3 (10.3)
>10 to ≤20 x ULN	1 (16.7)	1 (3.4)
>20 x ULN	0	0
AST		
>3 to ≤5 x ULN	0	5 (17.2)
>5 to ≤10 x ULN	3 (50.0)	1 (3.4)
>10 to ≤20 x ULN	0	0
>20 x ULN	0	0
Bilirubin		
>ULN to ≤1.5 x ULN	2 (33.3)	3 (10.3)
>1.5 to ≤2 x ULN	0	2 (6.9)
>2 x ULN	0	1 (3.4)
Alkaline phosphatase		
>1.5 x ULN	1 (16.7)	2 (6.9)

In the hypercholesterolemic population elevations in ALT >3 to ≤5×ULN were observed in 14%, 2%, 7% and 15% of subjects in the escalated-, low-, mid-, and high-dose groups, respectively and elevations >5 to ≤10×ULN were observed in 10%, 1%, 2% and 3%, respectively. Eight lomitapide-treated subjects had ALT elevations >10 to ≤20×ULN (0%, 1%, 5% and 2%, respectively). Elevations in AST >3 to ≤5×ULN were observed in 10%, 2%, 7% and 3% of subjects in the escalated-, low-, mid-, and high-dose groups, respectively, and elevations >5 to ≤10×ULN were observed in 1%, 1%, 2% and 2%, respectively. Elevations >10 to ≤20×ULN were observed in 2 subjects, including 1%, 0%, 1% and 0% of subjects in the escalated-, low-, mid-, and high-dose groups, respectively. The median times to onset for subjects with ALT or AST >3×ULN were 58, 53, 30 and 22 days in escalated-, low-, mid-, and high-dose groups, respectively. Median durations of the abnormal transaminase elevation (time from onset of abnormality >3×ULN to return to the normal range) were estimated at 27, 15, 24.5 and 49 days in lomitapide escalated-, low-, mid- and high-dose groups respectively.

None of the subjects developed acute hepatoxicity or had an ALT or AST elevation to >3×ULN with a corresponding total bilirubin value that was >2×ULN, thus, no subject met Hy's Law.

Maximum Abnormal Liver Function Test Results Post First Dose: hypercholesterolemic Study Pool (safety population)

	LOMITAPIDE DOSE GROUP[1]				COMPARATOR	
PARAMETER ABNORMALITY[2]	ESCALATED (5-10 MG) (N=77) N (%)	LOW DOSE (2.5-7.5 MG) (N=244) N (%)	MID DOSE (10 MG) (N=99) N (%)	HIGH DOSE (25-100 MG) (N=62) N (%)	PLACEBO (N=116) N (%)	ACTIVE CONTROL (N=78) N (%)

ALT	77	243	98	61	116	76
>3 to ≤5 x ULN	11 (14.3)	6 (2.5)	7 (7.1)	9 (14.8)	0	0
>5 to ≤10 x ULN	8 (10.4)	3 (1.2)	2 (2.0)	2 (3.3)	0	0
>10 to ≤20 x ULN	0	2 (0.8)	5 (5.1)	1 (1.6)	0	0
>20 x ULN	0	0	0	0	0	0
AST	77	243	98	61	116	76
>3 to ≤5 x ULN	8 (10.4)	5 (2.1)	7 (7.1)	2 (3.3)	1 (0.9)	0
>5 to ≤10 x ULN	1 (1.3)	2 (0.8)	2 (2.0)	1 (1.6)	0	0
>10 to ≤20 x ULN	1 (1.3)	0	1 (1.0)	0	0	0
>20 x ULN	0	0	0	0	0	0
Bilirubin	77	243	98	61	116	76
>ULN to ≤1.5xULN	0	7 (2.9)	4 (4.1)	1 (1.6)	3 (2.6)	5 (6.6)
>1.5 to ≤2 x ULN	0	1 (0.4)	2 (2.0)	0	1 (0.9)	1 (1.3)
>2 x ULN	0	0	0	0	0	1 (1.3)
Alkaline phosphatase	77	243	98	61	116	76
>1.5 x ULN	1 (1.3)	2 (0.8)	1 (1.0)	0	0	1 (1.3)

Five subjects received warfarin concomitant with lomitapide in HoFH patients. All five subjects were carefully monitored and had warfarin doses adjusted as required. Three of the five subjects completed the study through week 56, but two discontinued during the efficacy phase (unrelated to INR levels). No serious bleeding events were reported. One subject developed ecchymosis at the time of elevated INR; the event was assessed as mild in intensity and possibly treatment related. Increases in INR were reported in three (9%) of the 35 HoFH subjects. All three subjects were receiving concomitant warfarin.

Vitamins levels: In the pivotal study, the majority of subjects did not have shifts from baseline to weeks 26 or 56 in the levels of vitamins A, D or E, beta carotene, or un-carboxylated osteocalcin (as a measure of vitamin K) mainly because they received vitamin supplements. Since vitamin E is transported to the peripheral tissues *via* the LDL particle, and due to the LDL-C lowering effect of lomitapide, it is not unexpected to observe the mean levels of vitamin E decreasing from baseline to weeks 26 and 56. However, this decreased did not occur in any patient below normal levels. In study UP1001, one (17%) subject had a shift in the level of vitamin D from normal at baseline to below normal at week 16. Vitamin E levels were also evaluated in the hypercholesterolemic population of study CV145-009. Mean vitamin E values decreased during 4 weeks of treatment but returned to near baseline levels after 6 weeks off the drug, however, without a ratio below 1 for vitamin E to total lipid (vitamine E is transported by lipid particles). In study AEGR-733-004, dose-related decreases in vitamin E were observed in the lomitapide monotherapy groups, however, without a ratio below 1 for vitamin E to total lipid.

Fatty acid levels: In HoFH patients, mean decreases from Baseline to Week 56 also were observed across all fatty acid parameters, with mean percent changes of -25% for alpha linolenic acid, -42% for arachidonic acid, -35% for docosahexaenoic acid, -41% for eicosatrienoic acid, -51% for eicosapentaenoic acid, and -6% for linoleic acid.

Safety in special populations

Due to the small number of patients in the HoFH studies, a specific analysis of safety in sub-populations was note feasible.

Nevertheless, the majority (88%) of subjects in the hypercholesterolemic population were <65 years of age, with only 55 subjects being ≥65 years of age. In the lomitapide escalated-dose group, dyspepsia was reported by 12% of subjects <65 years of age *vs* 0% of subjects who were

≥65 years. In the lomitapide low-dose group, nausea was reported for 21% of subjects <65 years of age *vs* 7% of subjects who were ≥65 years. In the lomitapide mid-dose group, diarrhoea was reported by 66% of subjects <65 years of age *vs* 53% of subjects ≥65 years of age and back pain was reported by 12% *vs* 0%.

There was no notable increase in the incidence of any adverse event for subjects who had a renal impairment (32%) compared with subjects with normal renal function. In the phase 1 parallel-group studies it was shown that a single oral 60 mg dose was well tolerated by subjects with ESRD on haemodialysis and matched healthy subjects. Three healthy subjects (43%) reported TEAEs of headache, nausea, and rash and 1 subject (14%) with ESRD on haemodialysis reported a TEAE of orthostatic hypertension.

Safety related to drug-drug interactions and other interactions

The relevant discussion on drug-drug investigations between lomitapide and other medicinal products are presented in the Clinical Pharmacology section, where the agreed post-marketing investigations needed for established of lomitapide's interaction profile are described.

Discontinuation due to adverse events

Diarrhoea was identified as the main dose limiting adverse event in phase 2 studies and lead to treatment discontinuation in more than 20% of subjects on lomitapide doses 10 mg or higher.

Four of the HoFH subjects experienced TEAEs (three GI disorders) that resulted in treatment discontinuation. One subject discontinued because of abdominal pain, nausea, and diarrhoea, and 1 subject each discontinued because of diarrhoea, gastroenteritis, and headache. In the hypercholesterolemic population, diarrhoea was the most commonly reported TEAE leading to discontinuation in 14%, 26%, and 21% of subjects in the low-, mid-, and high-dose lomitapide groups, respectively. The incidence of discontinuation due to diarrhoea was low in the lomitapide escalated-dose group (4%). Nausea was also among the most commonly reported TEAEs leading to discontinuation in the lomitapide mid-dose group (15%) and high-dose group (10%); but none in the escalated-dose. In the escalated-dose group, liver function test abnormalities were the most common TEAEs leading to discontinuation (13%); specifically ALT increased (8%), AST increased (3%), hepatic enzymes increased (3%), and liver function test abnormal (3%).

Post marketing experience

There is currently no post-marketing experience with lomitapide since the product was not marketed at the time of CHMP evaluation.

2.6.1. Discussion on clinical safety

Clinical safety data for lomitapide were provided for both, the HoFH and the hypercholesterolemic population subsets. The first group are patients targeted by the proposed indication and the second subset provides further safety data due to the additional number of patients exposed to lomitapide. For the proposed target group of HoFH patients, only a limited number of patients were treated up to 78 weeks. In hypercholesterolemic patients, exposure was limited to maximum 8 weeks of treatment. Overall, the CHMP considered this a rather limited safety package, which is, however, justified mainly due to the rarity of the HoFH condition.

Gastrointestinal adverse events were the most frequently occurring adverse events in patients treated with lomitapide. These include diarrhoea, nausea, vomiting, dyspepsia, abdominal discomfort, abdominal pain, upper abdominal pain or constipation. Almost all patients experienced a GI AE, which generally started within a month after first dosing. Nearly all were considered treatment related. In 20% (n=6) of the HoFH patients these events were classified as severe. Severe GI adverse events were also common in the hypercholesterolemic patients (9-28%). Although the clinical study investigators were aware of the GI adverse effects of lomitapide, due to which a dose escalation approach in the study design had been used, still 5 out of 6 patients discontinued treatment with lomitapide in the HoFH studies because of GI AE experience. Furthermore, dose reductions and/or dose interruptions because of GI events were applied in case of twelve out of 29 patients (41%), which is indicative of the severity of these symptoms that interfered with optimal dosing. However, six out of ten patients with dose reductions could be successfully re-challenged to their previous dose before the GI adverse events occurred and five out of six patients with dose interruptions could reinstate the therapy. In general, the GI events therefore did not diminish the overall efficacy on LDL-C levels to an important extent, since most patients maintained a similar effective dose as before the GI event occurred. Dose escalation is favourable over a fixed dose design. Fewer hypercholesterolemic patients discontinued treatment (4%) in the dose escalation study than in the other studies (14-21%) due to GI disorders; especially diarrhoea. Still, the CHMP considered the GI side effects an important limitation of lomitapide treatment; in particular for clinical practice where less intensive monitoring can be expected. It is also recognised that not all patients could be up-titrated to the maximum 60 mg dose, after dose limiting adverse events have subsided, which was related to the occurrence of GI events.

Therefore, in view of the missing data, the CHMP agreed a specific obligation that the applicant will conduct of a long term prospective observational study to systematically collect information on the demographics, safety and effectiveness outcomes of patients treated with lomitapide, including gastrointestinal events.

Hepatic adverse events: Lomitapide has a considerable impact on liver function tests as determined in both, the HoFH and the hypercholesterolemic patient studies. Increases of ALT >3 to ≤5×ULN were observed for 5 (14%) of 35 subjects in the HoFH pool and elevations >5 to ≤10×ULN were observed for 5 (14%) HoFH subjects. One patient had an ALT >20X ULN. In the hypercholesterolemic study pool, ALT >3 to ≤5×ULN were observed in 14%, 2%, 7% and 15% of subjects in the escalated-, low-, mid-, and high-dose groups, respectively, and elevations >5 to ≤10×ULN were observed in 10%, 1%, 2% and 3%, respectively. It is important to note that eight lomitapide-treated subjects in this study pool had ALT elevations >10 to ≤20×ULN. Results on AST were approximately similar. These observations were associated with the LDL-C level reduction and therefore suggest a response-driven effect. This is strengthened by the reversibility of the effect upon treatment cessation. Although no patients discontinued due to liver adverse events in the HoFH population, 13% of the hypercholesterolemic patients discontinued treatment because of liver test elevations.

The CHMP also noted that the observed persistent elevation in hepatic transaminases across the studied populations and lomitapide doses is associated with hepatic fat accumulation in a considerable number of patients (8-19% in the HoFH population and 5-21% in the hypercholesterolemic population) without any sign of diminishing effect on liver fat over

treatment time (e.g. one HoFH patient showed increases up to 44%), except that fat fraction seems to decrease on treatment discontinuation. Furthermore, the elevations seem to be more prominent in the higher dose groups. Still, no patient exposed met the criterion of Hy's law of ALT>3ULN and bilirubin> 2ULN, which is considered reassuring in terms of toxic effects. Although until now only sporadic signs of hepatotoxicity have been observed (one case), the CHMP also acknowledged that this could be due to the limited safety database in terms of patient numbers, and the limited duration of exposure for most of the treated patients. Therefore, the impact of these hepatic safety findings for the development and occurrence of steatohepatitis or a possible further development of hepatic fibrosis remains unclear. One case of hepatosteatosis was observed in the HoFH patient population; the liver biopsy, although obtained approximately 2 months after drug discontinuation, demonstrated the presence of mild steatosis without inflammatory activity or fibrosis. The patient was re-entered into the study: ALT remained ≤2x ULN and AST and bilirubin were in the normal range. Another patient with severe hypertriglyceridemia was placed on lomitapide over 13 years ago after a near fatal bout of pancreatitis. After several biopsies during these years, only the most recent biopsy was consistent with the development of NASH. However, even in this case of NASH and elevated liver enzyme levels, the investigator considered the benefit risk to be positive as the patient was still treated with lomitapide at the time of MAA submission.

In conclusion, the CHMP agrees that the effects of lomitapide on liver, including increase in liver enzymes and in particular steatosis, are related to the mechanism of action of the drug and generally show reversible characteristics after discontinuation of the drug. The pattern of the adverse liver effects resembles that of benign steatosis as seen in familial hypobetalipoproteinemia (FHBL), a genetic condition with alterations in apoB coding that results in low apo B/LDL-C associated with moderate to severe steatosis, but not cirrhosis or altered morbidity/ mortality. However, on the basis of the current data it cannot be ruled out completely, whether an individual patient might still develop non alcoholic steatohepatitis, which could in the long term result in fibrosis and cirrhosis. The interpretation of the findings remains limited since only few biopsies were performed. Liver biopsies are considered the single decisive diagnostic tool for detection of liver toxicity. The clinical laboratory parameters and imaging data can only suggest the presence of potential hepatotoxicity but lack both, sensitivity and specificity. Furthermore, the lack of elevated liver enzymes cannot guarantee the absence of liver inflammatory disease. Therefore, when lomitapide is used in clinical practice, the CHMP strongly recommends a close collaboration and involvement of hepatologists. New exploring ways to possible detect any progression of liver disease such as non-invasive elastography are supported in order to further aid the hepatology specialist in hepatic risk assessment. Further detailing of liver safety monitoring based on biomarkers suggestive of inflammatory liver disease (γGT, albumin, and validated marker combinations such as Enhanced Liver Fibrosis test, ELF) in addition to non-specific markers such as CRP has been included in the SmPC. The CHMP also recommended clear criteria for monitoring of liver enzymes elevations and these are detailed in the SmPC. Patients who do not achieve the needed benefit with lomitapide (15% decrease of LDL-C) should stop taking the medicinal product. As described above, the CHMP a specific obligation to conduct a long term prospective observational study that would collect safety and efficacy data from patients on lomitapide and this will include monitoring of the hepatic events as well.

Cardiovascular adverse events: In the clinical trials with lomitapide several patients experienced a CV event (5 of 35 patients in HoFH and 3 patients in the hypercholesterolemic patient group). However, association with the drug is difficult to assume, mainly due to the low numbers of events occurring, short follow-up and the single arm design. Nevertheless, the typical HoFH patient's characteristics with a high risk for CV mortality are likely responsible for the occurrence of CV events. It is somewhat reassuring that the rate of the events seen with lomitapide is generally within the expected range for this population. Nevertheless, any conclusion towards a either a beneficial or a detrimental effect on CV outcome would not be appropriate given the uncontrolled and very limited data available.

The CHMP agreed a specific obligation to conduct a post-approval an observational cohort study with independent adjudication of CV (MACE) events, amongst others, and compare this to historical data. This is considered an acceptable approach as long as this information is obtained in a structured and predefined manner. The study is expected to increase the knowledge on the CV effect of lomitapide.

*Musculoskeletal events o*ccurred in a considerable proportion of patients (31%; n=7) in the HoFH group. Although a dose related incidence of adverse events in the Musculoskeletal and Connective Tissue Disorders category was observed, only 4 adverse events were specifically related to muscle pain. This number is far too low to conclude on any dose related trend. Moreover, the description of these events did not really confirm a relation with lomitapide, as background therapy could also have been the cause of muscle pain as these patients were on maximum background statin therapy. Nevertheless, a warning statement in the SmPC has been included as lomitapide increases exposure of statins. Reassuringly, CPK levels were not systematically increased.

Pulmonary adverse events: Asthma and bronchospasm occurred infrequent in both, the HoFH and hypercholesterolemic population. However, respiratory disorders were reported for six (21%) of the 29 HoFH patients; nasal congestion and pharyngolaryngeal pain were also noted, but these were assessed as unrelated to study drug. Negative effect on accumulation of neutral lipids in lung tissue was not demonstrated in rat studies based on macrophage function. Phagocytosis in lung-tissue was not observed. Clinical data on long term lung function tests do not indicate any substantial changes either. Therefore, it is not expected that lomitapide has an impact on pulmonary function.

Weight loss was not uncommon in the HoFH patients, with 6 patients experiencing such effect. Weight loss was considered drug-related in 4 of these 6 patients and was in order of 2.5-3.5 kg. It is thought to be only of limited clinical importance, as there was no substantial change in BMI and no patient reached a BMI < 18.5 kg/m2.

Infections were seen in a large proportion of the HoFH patients (59%), e.g. nasopharyngitis (17%), gastroenteritis (14%), and influenza (14%). The adverse effects in this system organ class seem to be dose-related, as most infections were observed with the 60 mg dose. A large proportion of the infections showed an expected seasonal pattern. Data are limited and it is unlikely that the infections would be directly linked to lomitapide treatment. Of note, non-infectious gastro-enteritis could be linked to lomitapide treatment. Serious adverse events occurred between 10-17% in HoFH patients and 1-3% in the hypercholesterolemic patients and can be considered infrequent. These were mostly cardiovascular events probably associated with

the underlying disease state of the patients and not likely to be associated with study drug. One patient died, but this death was not considered to be related to study drug.

Levels of fat soluble vitamins were evaluated during studies with HoFH and some studies with the hypercholesterolemic patients. Patients treated with lomitapide took vitamin supplements and due to this intake, no significant shifts in vitamin levels could be observed in the HoFH studies. In the hypercholesterolemic studies some shifts in vitamin E were seen despite extra intake. With vitamin supplements, vitamin deficiencies may be prevented during the lomitapide treatment. The need for monitoring of vitamin levels is adequately addressed in the SmPC. A large reduction of up to 51% in several fatty acids was observed. The drop in these levels occurs during the initial titration phase, reaches the minimum at week 26 and thereafter levels off. However the data do not indicate that the levels drop to unacceptable levels. The recommendation for additional intake of vitamin E and essential fatty acids in section 4.2 of the SmPC is therefore supported. Subgroup analyses did not reveal noticeable differences in safety profiles. However, the safety database was limited to observe any but very large differences, and therefore caution with use of lomitapide in certain sub-groups is warranted. The CHMP agreed with the adequate contraindications and warnings in the SmPC.

In view of the above discussed safety issues identified for lomitapide, the limited safety database, especially for the HoFH patients, while also considering the high unmet medical need in this subgroup of patients, the CHMP agreed a specific obligation to observe patients treated with lomitapide *via* a registry with a special focus on: hepatic events, gastrointestinal events, MACE, occurrence and outcomes of pregnancy, long term maintenance of serum lipid levels. Treating physicians and patients will also be issued with educational material advising how to manage the safety risks associated with the use of lomitapide.

In addition, the CHMP was of the opinion that the originally proposed indication is to be amended to ensure that only HoFH patients will receive lomitapide. Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded.

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC.

Additional expert consultations

Due to CHMP's concerns mainly with respect to the safety profile of lomitapide and the expected cardiovascular benefit based on the surrogate endpoint of lowering the LDL-C level, the opinion of additional clinical experts with experience in treatment of cardiovascular, lipid and hepatic diseases was requested. Thus, an ad-hoc expert group convened in order to address the following questions:

1. *What are the clinical implications of hepatotoxicity, due to fat accumulation in the liver associated with the decrease in ApoB? Only limited evidence is available and long term safety remains to be established, in particular:*

    a. *whether there might be a risk to develop progressive and non-reversible liver damage as a consequence of persistent liver steatosis and whether its consequences would still outweigh the benefits of lomitapide if liver damage would occur.*

b. *appropriate measures to minimise this risk, including e.g. close monitoring of liver parameters, serial scanning, biopsies, among others, and whether patients at risk could be identified by these methods at a stage where reversibility might still be expected.*

The experts agreed that fat accumulation is a natural consequence of the mechanism of action of lomitapide, and is of concern since the product is to be used long-term. The clinical data show increase of fat liver content and several fold increase in the AST and ALT levels in many patients shortly after initiation of lomitapide therapy. Moreover, there is no guarantee that apart from its mechanism of action (inhibition of MTP) there are no other effects of lomitapide on liver resulting in toxicity. Furthermore, a strong concern was expressed with respect to the link between fat accumulation in liver and the progression of the inflammatory disease, and whether the fat accumulation in liver seen with lomitapide can lead to inflammation which can result in fibrosis and eventually cirrhosis. Some experts believed that the treatment with lomitapide would need to be stopped after fat accumulation is detected and restarted post liver recovery.

The usefulness of monitoring markers of inflammation in addition to liver function biomarkers was also discussed. The experts noted that the applicant monitored some inflammatory markers as part of a standard set, e.g. hsCRP, but the direct link between the changes in their levels and liver toxicity is still unclear. All experts agreed that the only suitable and reliable method for detection of inflammatory steatosis and fibrosis (and differentiation from plain steatosis) is a biopsy, but currently, data from only one patient is available. Thus, the experts advocate a lower threshold for performing biopsies, and that these are to be conducted in all patients suspected of liver inflammation.

Conclusion: Considering the high unmet medical need in the HoFH population, the experts agreed by consensus that even if there might be a probability that liver steatosis would develop into fibrosis and long-term liver damage cannot be completely ruled out based on the data available to date, there could be a benefit for use of lomitapide. In order to achieve this assumed clinical benefit, the applicant must implement the following risk minimisation measures to monitor the hepatic effects of lomitapide, in order to minimise the risk of progression of liver steatosis into fibrosis:

- Patient monitoring shall be conducted in specialised centres and all patients shall be included in a registry.
- The applicant should identify the most sensitive liver biomarkers suggestive of inflammatory liver disease (e.g. γGT, albumin, and validated marker combinations such as the Enhanced Liver Fibrosis test, ELF), in addition to non-specific inflammatory markers (e.g. CRP, TNFα, IL-6), and their regular monitoring is mandatory.
- In addition, monitoring using at least one imaging technique (e.g., elastography with validated software such as CAP) is essential.
- The threshold for referring patients to a hepatologist and the conduct of biopsy must be lowered in order to ensure earlier identification of potential signs of liver inflammation.

These measures can be revisited at a later stage when more data become available.
Furthermore, the current SmPC wording on alcohol consumption shall be strengthened in order to limit this even further.

2. *Is there scope to use specific genetic and/or clinical diagnostic criteria (such as documented functional mutation in LDL receptor alleles and alleles known to affect LDL receptor functionality, levels of untreated or treated total or LDL cholesterol, presence of xanthomas, or family history of familial hypercholesterolaemia for both parents) to better define the HoFH population in order to ensure that only these patients will receive lomitapide?*

In general, the experts believed that a combination of genetic confirmation of the HoFH and a clinical proof of the increased LDL-C level should be recommended for identification of the most appropriate patient population for the treatment with lomitapide.

Based on the above, the criteria as proposed by the applicant should be strengthened to avoid that broader population (e.g. patients with HeFH) would be incorrectly treated with lomitapide. The following changes are recommended:

- the quantification as proposed by the applicant based on untreated total cholesterol $\geqslant$ 13 mmol/L (500 mg/dL) should be deleted, since blood cholesterol levels can be higher in type 1, 3, 4 or5 hyperlipoproteinemia patients not suffering from FH, and therefore, this parameter is not reflective of the adequate medical need.
- the criterion of untreated total cholesterol should be replaced by untreated LDL-C $\geqslant$ 10.4 mmol/L (400 mg/dL).
- the proposed limit of treated LDL-C $\geqslant$ 7.8 mmol/L (300 mg/dL) should be maintained.
- DNA confirmation of 2 mutant alleles in FH genes is obligatory, if untreated or treated LDL-C fall below10.4 mmol/L (400 mg/dL) or 7.8 mmol/L (300 mg/dL), respectively.
- Where diagnosis is based on xanthoma in childhood, this must be confirmed by positive family history, i.e. at least heterozygous FH and/or genetic testing.

Causes of secondary LDL-C elevations (e.g. nephrotic syndrome, hypothyreodism) should be excluded by appropriate clinical tests.
Primary forms of hyperlipoproteinemias which may concomitantly increase total cholesterol or LDL-C (e.g. lipoprotein lipase deficiency, familial type 3 hyperlipoproteinemia) should be excluded by appropriate clinical tests.

In addition, the experts agreed by consensus that the SmPC of lomitapide should state that the treatment must be stopped if no effect on LDL-C is shown (i.e. at least a 15% reduction of LDL-C level).

3. *Does the available evidence of efficacy and safety provide sufficient confidence for the medicine to be used in clinical practice? If so, what additional data on efficacy and safety do the experts suggest that would need to be collected post-authorisation, taking into account the limitations associated with the very small target population?*

The experts were aware that there are no large randomised controlled clinical outcome trials in patients with HoFH, and data for HoFH are extrapolated from studies in different (combined) populations. Despite the limited data, the experts stated their confidence that currently, the

expectance of a clinical effect in terms of possible cardiovascular benefit is reasonable with the observed LDL-C lowering effect of lomitapide, and the benefit/risk profile of lomitapide could be positive, provided adequate risk minimization measures for hepatotoxicity and drug-drug interactions are agreed. Nevertheless, further clinical evidence on cardiovascular surrogate endpoints should be collected post-authorisation during long-term use.

In the HoFH population, there is a high burden of atherosclerosis and cardiovascular complications in patients already before even starting treatment with lomitapide, and thus, the clinical benefit of lomitapide on the longer-term must be proven. While the experts acknowledged that performance of a controlled, randomized study with hard clinical endpoints in order to confirm cardiovascular benefit of lomitapide in HoFH patients would be difficult or even unethical, collection of long term cardiovascular outcome data can be achieved indirectly by long-term monitoring (~ 5 years) of the vascular outcomes using appropriate and scientifically validated imaging techniques or other acknowledged vascular surrogate endpoints such as endothelial function.

The experts concluded that the post-approval registry suggested for all patients treated with lomitapide should be accompanied by a clinical study with active long-term monitoring of cardiovascular benefits. The experts strongly advise that the applicant should design a study with adequate surrogate endpoints on vascular outcomes using imaging techniques of atherosclerosis burden (such as MRI, intravascular ultrasound, etc.) or vascular function. The study should be adequately powered and standardized collection of cardiovascular events is to be ensured. The applicant could also consider investigations of disease stabilization or demonstration of regression. The protocol of the study should be agreed with the CHMP.

4. *Do the experts have any comments on the potential clinical impact of the 'drug-drug interaction' with CYP3A4 inhibitors, including weak inhibitors, and any suggestions as to how the risks of increased exposure should be handled in clinical practice?*

Given the HoFH condition and the likelihood of the patients being treated with several medicinal products concomitantly, the potential impact of interactions with lomitapide (metabolised primarily via CYP3A4) are not negligible. The experts noted that use of lomitapide is contraindicated with strong and moderate CYP3A4 inhibitors, however, reliable data on weak CYP3A4 inhibitors are lacking (only simulations from an insufficiently validated PK model were submitted.)

It should also be considered that treatment with lomitapide foresees gradual dose titration and the effect of adding a CYP3A4 inhibitor can be different at each stage of titrating. The interaction is expected to lead to a two-fold increase in exposure of lomitapide (estimated from a cross-study comparison to be the maximum increase following co-administration with a single weak CYP3A4 inhibitor and consequent increases of AST and ALT levels as well as increased gastrointestinal toxicity. It is of note that the applicant proposed to half the lomitapide (~30 mg) during the concomitant use of lomitapide and such inhibitors, but no supportive clinical data exist. Some experts suggested interrupting the treatment of lomitapide during administration of a weak CYP3A4 inhibitor(s).

In conclusion:

- It is agreed to contraindicate the concomitant use of moderate and strong CYP3A4 inhibitors and lomitapide.
- An adequately designed PK study in an appropriate patient population must be committed to conduct with a concomitant administration of two weak CYP3A4 inhibitors on top of lomitapide. The two weak CYP3A4 inhibitors should be selected among those most likely to be co-administered with lomitapide (e.g. atorvastatin, oral contraception, and platelet inhibitors like clopidogrel, prasugrel, ticagrelor).
- The wording in the SmPC of lomitapide should be strengthened: all patients with concomitant use of weak CYP3A4 inhibitor(s) should be closely monitored. Special attention should be given to patients optimally titrated on lomitapide, but who are subsequently administered a weak CYP3A4 inhibitor.
- The applicant's proposals for educational material for physicians and patients (Wallet card) to warn on risks of interactions are strongly supported.

Additional safety data needed in the context of an MA under exceptional circumstances

The applicant did not provide results from a full clinical development with lomitapide and the CHMP agreed with the applicant's argument that the patient population of lomitapide is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive clinical data on the safety and efficacy of this medicinal product. The true long-term impact of the above discussed effects is not known yet and thus, warrant collection of such information during the post-authorisation phase. Therefore, the CHMP considers the following measures necessary to address the missing safety data in the context of an MA under exceptional circumstances:

The applicant shall set up a long term prospective observational study to systematically collect information on the safety and effectiveness outcomes of patients treated with lomitapide.

The objectives of the study are:

- To evaluate the occurrence of the following in patients treated with lomitapide:
  - Hepatic events
  - Gastrointestinal events
  - Small bowel, hepatic, colorectal and pancreatic tumours
  - Events associated with coagulopathy
  - Major Adverse Cardiovascular Events (MACE) events
  - Death, including cause of death
- To evaluate the occurrence and outcomes of pregnancy in females of reproductive potential treated with lomitapide who decide to continue the pregnancy following advice from a teratologist.
- To evaluate the long-term effectiveness of lomitapide in maintaining control of serum lipid levels in clinical practice.
- To evaluate whether prescribers of lomitapide are following the screening and monitoring recommendations as specified in the product information and the educational materials.

These specific obligations shall be annually reassessed.

2.6.2. Conclusions on the clinical safety

Although the safety data from clinical studies conducted with lomitapide are limited, the observed safety profile does to some extent limit the continued and long term use of lomitapide. In terms of tolerability, the GI symptoms often result in periods of dose interruption and dose reduction and in some cases to treatment discontinuation. However, it is noted that a serious impact on the observed efficacy should not be evident as most patients can be successfully re-challenged and the overall effect on the LDL-C levels appears to be minor. The GI symptoms were also an important reason why not all patients were treated with the maximum dose.

Liver safety remains undetermined because data on long term effects of the observed considerable impact on transaminase levels and durable increase in hepatic fat content are unknown. The CHMP recommended a close collaboration between the treating physician monitoring the patient's liver enzymes levels (as per the SmPC) and the specialised hepatologist to whom the patient might be referred, as stated in the SmPC. New, exploring ways to detect any progression of liver disease, such as non-invasive elastography, are also foreseen and can further aid the hepatologist in hepatic risk assessment. The SmPC details the need for monitoring of hepatic biomarkers suggestive of inflammatory liver disease (γGT, albumin, and validated marker combinations such as Enhanced Liver Fibrosis test, ELF) in addition to the non-specific markers such as CRP and TNFα. Although these and other safety issues, such as potential vitamin and essential fatty acids depletion or weight loss, seem to be manageable, the true long term impact of these effects warrant intense monitoring and will be reviewed by the CHMP during annual reassessments.

Furthermore, the dose escalation approach for patients starting lomitapide treatment appears to be an additional reasonable method for managing the above described adverse reactions. All physicians and patients will also receive educational material explaining the risk minimisation activities needed for ensuring safe treatment with lomitapide.

The revised, restricted indication of lomitapide directing the use of this medicinal product to the most appropriate patient population, along with the thorough liver function monitoring are considered by the CHMP fully appropriate in terms of managing the identified risks. In addition, the CHMP considers the following measures necessary to address the missing safety data in the context of an MA under exceptional circumstances:

The applicant shall set up a long term prospective observational study to systematically collect information on the safety and effectiveness outcomes of patients treated with lomitapide.

The objectives of the study are:

- To evaluate the occurrence of the following in patients treated with lomitapide:
  - Hepatic events
  - Gastrointestinal events
  - Small bowel, hepatic, colorectal and pancreatic tumours
  - Events associated with coagulopathy
  - Major Adverse Cardiovascular Events (MACE) events
  - Death, including cause of death
- To evaluate the occurrence and outcomes of pregnancy in females of reproductive potential treated with lomitapide who decide to continue the pregnancy following advice from a teratologist.
- To evaluate the long-term effectiveness of lomitapide in maintaining control of serum lipid levels in clinical practice.
- To evaluate whether prescribers of lomitapide are following the screening and monitoring

recommendations as specified in the product information and the educational materials.

These specific obligations shall be annually reassessed.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

PRAC Advice

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (version 3.4):

1. Based on the outcome of the CHMP discussion regarding the SmPC wording on hepatic safety monitoring, the study protocol of the registry and the key elements of the educational material should be updated.
2. The summary of the RMP in section 5.1 should be updated with the DDI program as additional pharmacovigilance activity for the safety concern “interaction with weak CYP3A4 inhibitors”.
3. The term “wallet card” should be changed into “patient alert card” throughout the entire RMP.
4. The Applicant should include the following safety concerns in the educational material for prescribers (and patients): hepatic fibrosis, pre-existing hepatic disease, concomitant use with potential hepatotoxic agents.
5. The key elements to be included in the educational material for the patients should be complemented with two additional recommendations
    - Following a low-fat diet (i.e. patients should follow a diet supplying less than 20% of energy from fat),
    - Timing of medicine intake (Lojuxta should be taken at bedtime with a glass of water without food)

Furthermore, a key element that addresses the existence and importance of the lomitapide registry should be added to the key elements to be included in the material for the patients.

The CHMP endorsed this advice with changes and emphasized the need to align the hepatic information to be collected in the long term prospective observational study with the hepatic safety monitoring recommendations that are included in the updated SmPC. Furthermore, the CHMP requested the inclusion of the non-clinical studies investigating drug-drug interaction and

pharmacokinetics of lomitapide in the RMP. In addition, the agreed long term prospective observational study will remain open and interim reports will be provided annually.

The Applicant submitted an updated version (3.7) of the RMP based on the following content:

- **Safety concerns**

Important identified risks	Hepatic effects (elevated aminotransferases, hepatic steatosis)
	Gastrointestinal effects (nausea, diarrhoea, weight loss, malabsorption of fat soluble vitamins, decline in essential fatty acids)
	Interaction with statins
Important potential risks	Hepatic fibrosis
	Primary hepatic tumours
	Small intestinal tumours
	Pancreatic tumours
	Off label use
	Unintended pregnancy
Important missing information	Use during pregnancy
	Use in the paediatric population
	Use with alcohol
	Use in non-Caucasian patients
	Pre-existing hepatic disease
	Concomitant use with potential hepatotoxic agents
	Interaction with weak CYP3A4 inhibitors

- **Pharmacovigilance plans**

Safety Concern	Planned action(s)
Important identified risks	
Hepatic effects (elevated aminotransferases, hepatic steatosis)	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Expedited reporting of specific hepatic abnormalities (see Section 2.2 of RMP) 3. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Gastrointestinal effects (nausea, diarrhoea, weight loss, malabsorption of fat soluble vitamins, decline in essential fatty acids)	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Expedited reporting of specific gastrointestinal effects (see Section 2.2 of RMP) 3. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Interaction with statins	Routine pharmacovigilance activities, including review as AESI in PSURs.
Important potential risks	
Hepatic fibrosis	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Expedited reporting of specific hepatic abnormalities (see Section 2.2 of RMP) 3. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Primary hepatic tumours	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Expedited reporting of hepatic tumours. 3. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Small intestinal tumours	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Expedited reporting of small bowel/ intestinal tumours. 3. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Pancreatic tumours	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Expedited reporting of pancreatic tumours. 3. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.

Safety Concern	Planned action(s)
Off label use	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Unintended pregnancy	1. Routine pharmacovigilance activities, including review as AESI in PSURs. 2. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide. 3. Pregnancy exposure registry.
Important missing information	
Use during pregnancy	1. Routine pharmacovigilance activities, including review of pregnancy cases in PSURs. 2. Pregnancy exposure registry. 3. Expedited reporting of major congenital anomalies
Use in the paediatric population	Routine pharmacovigilance activities, including review of paediatric cases in PSURs
Use with alcohol	1. Routine pharmacovigilance activities, including review of cases in PSURs. 2. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Use in non-Caucasian patients	1. Routine pharmacovigilance activities, including review of cases in PSURs. 2. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide.
Pre-existing hepatic disease	1. Routine pharmacovigilance activities, including review of cases in PSURs 2. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide
Concomitant use with potential hepatotoxic agents	1. Routine pharmacovigilance activities, including review of cases in PSURs 2. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide
Interaction with weak CYP3A4 inhibitors	1. Routine pharmacovigilance activities, including review of cases in PSURs 2. Lomitapide Observational Worldwide Evaluation Registry (LOWER): Observational registry of patients treated with lomitapide 3. DDI programme and PBPK modeling

- **Risk minimisation measures**

Safety Concern	Routine risk minimisation activities sufficient?	Description and Justification
Important identified risks		
Hepatic effects (elevated aminotransferases, hepatic steatosis)	No	Although this risk is thoroughly addressed in the proposed SPC, lomitapide effects following long-term treatment are unknown. Therefore, the Applicant will distribute educational material to prescribers and patients to foster understanding of the hepatic risks associated with lomitapide. Proposed SPC This risk is thoroughly addressed in Section 4.3 and Section 4.4 of the proposed SPC. • Section 4.3 Patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests. • Section 4.4 Liver enzyme abnormalities and liver monitoring Lomitapide can cause elevations in alanine aminotransferase [ALT] and aspartate aminotransferase [AST] and hepatic steatosis. The extent to which lomitapide-associated hepatic steatosis promotes the elevations in aminotransferase is unknown. Although cases of hepatic dysfunction (elevated aminotransferase with increase in bilirubin or International Normalized Ratio [INR]) or hepatic failure have not been reported, there is concern that lomitapide could induce steatohepatitis, which can progress to cirrhosis over several years. The clinical studies supporting the safety and efficacy of lomitapide in HoFH would have been unlikely to detect this adverse outcome given their size and duration. Elevations in aminotransferases (ALT and/or AST) are associated with lomitapide (see Section 5.1). There were no concomitant or subsequent clinically meaningful elevations in serum bilirubin, INR, or alkaline phosphatase. Liver enzyme changes occur most often during dose escalation, but may occur at any time during therapy. Monitoring of liver function tests Measure ALT, AST, alkaline phosphatase, total bilirubin, gamma-glutamyl transferase (gamma-GT) and serum albumin before initiation of treatment with Lojuxta. The

<table>
<tr><th>Safety Concern</th><th>Routine risk minimisation activities sufficient?</th><th>Description and Justification</th></tr>
<tr><td></td><td></td><td>medicinal product is contraindicated in patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests. If the baseline liver-related tests are abnormal, consider initiating the medicinal product after appropriate investigation by a hepatologist and the baseline abnormalities are explained or resolved.

During the first year, measure liver-related tests (ALT and AST, at a minimum) prior to each increase in dose or monthly, whichever occurs first. After the first year, do these tests at least every 3 months and before any increase in dose. Decrease the dose of Lojuxta if elevations of aminotransferase are observed and discontinue treatment for persistent or clinically significant elevations (see Table 1 below for specific recommendations).

<u>Dose modification based on elevated hepatic aminotransferases</u>

Table 1 below summarizes recommendations for dose adjustment and monitoring for patients who develop elevated aminotransferase during therapy with Lojuxta.

Table 1: Dose Adjustment and Monitoring for Patients with Elevated Aminotransferases
<table>
<tr><th>ALT or AST</th><th>Treatment and monitoring recommendations*</th></tr>
<tr><td>≥3x and <5x Upper Limit of Normal (ULN)</td><td>• Confirm elevation with a repeat measurement within one week.
• If confirmed, reduce the dose and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR).
• Repeat tests weekly and withhold dosing if there are signs of abnormal liver function (increase in bilirubin or INR), if aminotransferase levels rise above 5x ULN, or if aminotransferase levels do not fall below 3x ULN within approximately 4 weeks. Refer patients with persistent elevations in aminotransferase >3x</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Safety Concern</th><th>Routine risk minimisation activities sufficient?</th><th>Description and Justification</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td>ULN to a hepatologist for further investigation.
• If resuming Lojuxta after aminotransferase levels resolve to <3x ULN, consider reducing the dose and monitor liver-related tests more frequently.</td></tr>
<tr><td>≥5x ULN</td><td>• Withhold dosing and obtain additional liver-related tests if not already measured (such as alkaline phosphatase, total bilirubin, and INR). If aminotransferase levels do not fall below 3x ULN within approximately 4 weeks refer the patient to a hepatologist for further investigation.
• If resuming Lojuxta after aminotransferase levels resolve to <3x ULN, reduce the dose and monitor liver-related tests more frequently.</td></tr>
</table>
*Recommendations based on an ULN of approximately 30-40 international units/L.

If aminotransferase elevations are accompanied by clinical symptoms of liver injury (such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin ≥2x ULN, or active liver disease, discontinue treatment with Lojuxta and refer the patient to a hepatologist for further investigation.

Reintroduction of treatment may be considered if the benefits are considered to outweigh the risks associated with potential liver disease.

<u>Hepatic steatosis and risk of progressive liver disease</u>

Consistent with the mechanism of action of lomitapide, most treated patients exhibited increases in hepatic fat content. In an open-label Phase 3 study, 18 of 23 patients with HoFH developed hepatic steatosis (hepatic fat >5.56%) as measured by nuclear magnetic resonance spectroscopy (MRS) (see Section 5.1). The median absolute increase in hepatic fat was 6% after both 26 weeks and 78 weeks of treatment, from 1% at baseline, measured by MRS. Hepatic steatosis is a risk factor for progressive liver disease including steatohepatitis and cirrhosis. The long term consequences of hepatic</td></tr>
</table>

Safety Concern	Routine risk minimisation activities sufficient?	Description and Justification
		steatosis associated with Lojuxta treatment are unknown. Clinical data suggest that hepatic fat accumulation is reversible after stopping treatment with Lojuxta, but whether histological sequelae remain is unknown, especially after long-term use. See "Hepatic Fibrosis" in this section for screening recommendations for steatohepatitis and fibrosis. <u>Hepatotoxic agents</u> Caution should be exercised when Lojuxta is used with other medicinal products known to have potential for hepatotoxicity, such as isotretinoin, amiodarone, acetaminophen (>4 g/day for ≥3 days/week), methotrexate, tetracyclines, and tamoxifen. The effect of concomitant administration of Lojuxta with other hepatotoxic medicine is unknown. More frequent monitoring of liver-related tests may be warranted. Educational materials will also be provided to prescribers and to patients to provide advice on this risk.
Gastrointestinal effects (nausea, diarrhoea, weight loss, malabsorption of fat soluble vitamins, decline in essential fatty acids)	No	The proposed educational material for prescribers and patients will result in clear understanding of the GI effects associated with lomitapide use. <u>Proposed SPC</u> • Section 4.2: The recommended starting dose is 5 mg once daily. After 2 weeks the dose may be increased, based on acceptable safety and tolerability, to 10 mg and then at a minimum of 4-week intervals, to 20 mg, 40 mg, and the maximum recommended dose of 60 mg. The dose of lomitapide should be escalated gradually to minimise the incidence and severity of gastrointestinal side effects and aminotransferase elevations. Administration with food may increase exposure to Lojuxta. Lojuxta should be taken on an empty stomach, at least 2 hours after the evening meal because the fat contect of a recent meal may adversely impact gastrointestinal tolerability. The occurrence and severity of gastrointestinal adverse reactions associated with the use of Lojuxta decreases in the presence of a low fat diet. Patients should follow a diet supplying less than 20% of energy from fat prior to initiating Lojuxta treatment, and should continue this diet during treatment. Dietary counselling should be provided.

Safety Concern	Routine risk minimisation activities sufficient?	Description and Justification
		Based on observations of decreased essential fatty acid and vitamin E levels in clinical trials, patients should take daily dietary supplements that provide 400 IU vitamin E, and at least 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), 210 mg alpha linolenic acid (ALA) and 80 mg docosahexaenoic acid (DHA) per day, throughout treatment with Lojuxta. • Section 4.3: The use of Lojuxta is contraindicated in patients with a known significant or chronic bowel disease such as inflammatory bowel disease or malabsorption. • Section 4.4: Given its mechanism of action in the small intestine, lomitapide may reduce the absorption of fat-soluble nutrients. In the Phase 3 trial, patients were provided daily dietary supplements of vitamin E, linoleic acid, ALA, EPA and DHA. In this trial, the median levels of serum vitamin E, ALA, linoleic acid, EPA, DHA, and arachidonic acid decreased from baseline to Week 26 but remained above the lower limit of the reference range. Adverse clinical consequences of these reductions were not observed with lomitapide treatment of up to 78 weeks. Patients treated with Lojuxta should take daily supplements that contain 400 international units vitamin E and at least 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA. • Section 4.8: The most common adverse reactions were gastrointestinal effects. The tabulated list of adverse reactions in HoFH patients mentions diarrhoea, nausea, vomiting, abdominal discomfort, dyspepsia, abdominal pain, abdominal pain upper, flatulence, abdominal distension and constipation as very common and gastritis, rectal tenesmus, aerophagia, defaecation urgency, eructation, frequent bowel movements, gastric dilation, gastric disorder, gastrooesophageal reflux disease, haemorrhoidal haemorrhage, and regurgitation as common gastrointestinal disorders, respectively.
Interaction with statins	Yes	<u>Proposed SPC</u> • Section 4.3: The concomitant administration of >40 mg simvastatin is contraindicated. • Section 4.5 Use with statins: Lomitapide increases plasma concentrations of statins. When lomitapide 60 mg was

Safety Concern	Routine risk minimisation activities sufficient?	Description and Justification
		administered to steady state prior to simvastatin 40 mg, simvastatin acid AUC and Cmax increased 68% and 57%, respectively. When lomitapide 60 mg was administered to steady state prior to atorvastatin 20 mg, atorvastatin acid AUC and Cmax increased 52% and 63%, respectively. When lomitapide 60 mg was administered to steady state prior to rosuvastatin 20 mg, rosuvastatin Tmax increased from 1 to 4 hours, AUC was increased 32%, and its Cmax was unchanged. The risk of myopathy with simvastatin is dose related. Use of Lojuxta is contraindicated in patients treated with high doses of simvastatin (> 40 mg) (see Section 4.3 and Section 4.4). Educational materials will also be provided to prescribers and patients to advise of this risk.
Hepatic fibrosis	No	The hepatic effects of long-term treatment with lomitapide are unknown. Therefore, the Applicant will distribute educational material to prescribers and patients to foster understanding of the hepatic risks associated with lomitapide. <u>Proposed SPC</u> • Section 4.4: <u>Monitoring for evidence of progressive liver disease.</u> Regular screening for steatohepatitis/fibrosis should be performed at baseline and on an annual basis using the following imaging and biomarker evaluations: • Imaging for tissue elasticity, e.g. Fibroscan, acoustic radiation force impulse (ARFI), or magnetic resonance (MR) elastography • Gamma-GT and serum albumin to detect possible liver injury • At least one marker from each of the following categories: • High sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), CK-18 Fragment, NashTest (liver inflammation) • Enhanced Liver Fibrosis (ELF) panel, Fibrometer, AST/ALT ratio, Fib-4 score, Fibrotest (liver fibrosis) The performance of these tests and their interpretation should involve collaboration between the treating physician and the hepatologist. Patients with results suggesting the presence of steatohepatitis or fibrosis should be considered for liver biopsy.

Safety Concern	Routine risk minimisation activities sufficient?	Description and Justification
		If a patient has biopsy-proven steatohepatitis or fibrosis, the benefit-risk should be reassessed and treatment stopped if necessary.
Primary hepatic tumours	Yes	Proposed SPC Preclinical safety data are summarised in Section 5.3.
Small intestinal tumours	Yes	Proposed SPC Preclinical safety data are summarised in Section 5.3.
Pancreatic tumours	Yes	Proposed SPC Preclinical safety data are summarised in Section 5.3.
Off label use	No	The proposed educational material will make sure that prescribers understand the appropriate use of Lojuxta within the approved indication, patients with HoFH. Proposed SPC • Section 4.1 Lojuxta is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without LDL apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH). Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded. • Section 4.2 Treatment with lomitapide should be initiated and monitored by a physician experienced in the treatment of lipid disorders.
Unintended pregnancy	No	Educational material for prescribers and patients is proposed to raise awareness about the possible loss of effectiveness of oral contraceptives due to diarrhoea or vomiting and the need for additional contraception for 7 days after symptoms have resolved. Proposed SPC • Section 4.4 Contraception measures in women of child-bearing potential Before initiating treatment in women of child-bearing potential, appropriate advice on effective methods of contraception should be provided, and effective contraception initiated. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting. Oestrogen-containing oral contraceptives are weak CYP3A4 inhibitors (see Section 4.2). • Section 4.5 When lomitapide 50 mg was administered to steady state

Safety Concern	Routine risk minimisation activities sufficient?	Description and Justification
		along with an oestrogen-based oral contraceptive, no clinically meaningful nor statistically significant impact on the pharmacokinetics of the components of the oral contraceptive (ethinyl estradiol and 17-deacetyl norgestimate, the metabolite of norgestimate) were observed. Lomitapide is not expected to directly influence the efficacy of oestrogen-based oral contraceptives; however diarrhoea and/or vomiting may reduce hormone absorption. In cases of protracted or severe diarrhoea and/or vomiting lasting more than 2 days, additional contraceptive measures should be used for 7 days after until resolution of symptoms. • Section 4.6 <u>Use in women of child-bearing potential</u> Before initiating treatment in women of child-bearing potential, the absence of pregnancy should be confirmed, appropriate advice on effective methods of contraception provided, and effective contraception initiated. Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting. Additional contraceptive measures should be used until resolution of symptoms (see Section 4.5).
Important missing information		
Use during pregnancy	No	Educational material for prescribers and patients is proposed to promote understanding that lomitapide use may be associated with a risk of teratogenesis and thus is contraindicated during pregnancy. <u>Proposed SPC</u> Lomitapide is contraindicated during pregnancy. • Section 4.6 Lojuxta should not be used during pregnancy as there are no reliable data on its use in pregnant women. Animal studies have shown developmental toxicity (teratogenicity, embryotoxicity, see Section 5.3). The potential risk for humans is unknown.
Use in the paediatric population	Yes	<u>Proposed SPC</u> • Section 4.2: The safety and efficacy of Lojuxta in children <18 years have not been established and the use of this medicinal product in children is therefore not recommended. No data are available.

Safety Concern	Routine risk minimisation activities sufficient?	Description and Justification
Use with alcohol	No	Alcohol has the potential to induce or exacerbate liver injury and should not be used by patients taking lomitapide. The Applicant will distribute educational material to prescribers and patients to foster understanding of the hepatic risks associated with lomitapide. Proposed SPC • Section 4.4: Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury. In the phase 3 trial, 3 of 4 patients with ALT elevations >5 xULN reported alcohol consumption beyond the limits recommended in the protocol. The use of alcohol during lomitapide treatment is not recommended.
Use in non-Caucasian patients	Yes	The limited data available do not provide any indication that the safety profile of lomitapide varies depending on ethnic background. Proposed SPC • Section 5.2: No dose adjustment is required for Caucasian or Latino patients. There is insufficient information to determine if lomitapide requires dose adjustment in other races. However, since the medicinal product is dosed in an escalating fashion according to individual patient safety and tolerability, no adjustment to the dosing regimen is recommended based on race.
Pre-existing hepatic disease	No	The Applicant will distribute educational material to prescribers and patients to: a) foster understanding of the hepatic risks associated with Lojuxta; b) emphasize that Lojuxta is contraindicated in patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests. Proposed SPC • Section 4.3: Lojuxta is contraindicated in patients with moderate or severe hepatic impairment and those with unexplained persistent abnormal liver function tests.

Safety Concern	Routine risk minimisation activities sufficient?	Description and Justification
Concomitant use with potential hepatotoxic agents	No	The Applicant will distribute educational material to prescribers and patients to emphasize that caution should be exercised when Lojuxta is co-administered with potential hepatotoxic agents. <u>Proposed SPC</u> • Section 4.4: Caution should be exercised when Lojuxta is used with other medicinal products known to have potential for hepatotoxicity, such as isotretinoin, amiodarone, acetaminophen (>4 g/day for ≥3 days/week), methotrexate, tetracyclines, and tamoxifen. The effect of concomitant administration of Lojuxta with other hepatotoxic medicine is unknown. More frequent monitoring of liver-related tests may be warranted.

Safety Concern	Routine risk minimisation activities sufficient?	Description and Justification
Interaction with weak CYP3A4 inhibitors	Yes	<u>Proposed SPC</u> Weak CYP3A4 inhibitors may substantially increase the exposure of lomitapide. The dose of Lojuxta should be reduced when administered with a weak CYP 3A4 inhibitor and patients monitored carefully (see Section 4.2) • Section 4.2 Patients on a stable maintenance dose of Lojuxta who receive a weak CYP3A4 inhibitor should reduce the dose of Lojuxta as follows: • Patients on 40 mg or 60 mg should reduce to 10 mg • Patients on doses < 40 mg should reduce to 5 mg Careful up-titration may be considered according to LDL-C response and safety/tolerability. Consider limiting the maximum dose of Lojuxta according to desired LDL-C response. Upon discontinuation of the weak CYP3A4 inhibitor, the dose of Lojuxta should be up-titrated according to LDL-C response and safety/tolerability. Exercise additional caution if administering more than 1 weak CYP3A4 inhibitor with Lojuxta • Section 4.5 Interaction between weak CYP3A4 inhibitors and Lojuxta has not been studied. Weak CYP3A4 inhibitors are predicted to have a substantial impact on lomitapide's pharmacokinetics. A 4-10 fold increase of lomitapide exposure can be expected based on the results of the study with the strong CYP3A4 inhibitor ketoconazole and on historical data for the model CYP 3A4 probe midazolam.

Safety Concern	Routine risk minimisation activities sufficient?	Description and Justification
		The dose of Lojuxta should be reduced during concomitant administration with a weak CYP 3A4 inhibitor (see Section 4.2). Examples of weak CYP 3A4 inhibitors include: alprazolam, amiodarone, amlodipine, atorvastatin, azithromycin, bicalutamide, cilostazol, cimetidine, ciclosporin, clotrimazole, fluoxetine, fluvoxamine, fosaprepitant, ginkgo, goldenseal, isoniazid, ivacaftor, lacidipine, lapatinib, linagliptin, nilotinib, oestrogen-containing oral contraceptives, pazopanib, peppermint oil, propiverine, ranitidine, ranolazine, ritonavir, roxithromycin, Seville oranges, tacrolimus, ticagrelor, tipranavir and tolvaptan. This list is not intended to be comprehensive and prescribers should check the prescribing information of drugs to be co-administered with Lojuxta for potential CYP 3A4 mediated interactions. The effect of administration of more than one weak CYP3A4 inhibitor has not been tested, but the effect on the exposure of lomitapide is expected to be greater than for co-administration of the individual inhibitors with lomitapide. The list of CYP 3A4 inhibitors will be reviewed annually.

The CHMP endorsed the updated RMP without changes.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Lomitapide is an inhibitor of microsomal triglyceride transfer protein (MTP), inhibiting transfer of triglycerides and cholesterol into apoB in both intestine and liver. One main, pivotal open-label single arm study was conducted to demonstrate efficacy of lomitapide on top of existing optimal lipid lowering treatment in the target HoFH population.

Consistent lipid lowering efficacy was demonstrated in both, the pivotal study and in the short-term supportive studies. Reduction of 40% of LDL-C levels was seen in HoFH patients after 26

weeks of treatment with lomitapide on top of lipid lowering therapy in both, ITT and PP population, with a sustained effect through 56 weeks of treatment. This corresponds to a mean LDL-C decrease from 336 mg/dL (8.7 mmol/L) to 190 mg/dL (4.9 mmol/L), a mean change of -146.9 mg/dL (3.8 mmol/L).

The primary data of LDL-C reduction are supported by significant beneficial changes for secondary endpoints of TC, TG, non-HDL-C, apoB but not for HDL-C and ApoA1. A dose dependent reduction in LDL-C has also seen in other patients with elevated cholesterol levels in short-term statin and ezetimibe controlled studies.

Beneficial effects were observed across several subgroups of age, gender, race, BMI, and apheresis.

Uncertainty in the knowledge about the beneficial effects

It is acknowledged that only twenty-three (of 29) HoFH patients have been treated for up to 78 weeks in a single arm open label fashion. Data on long-term efficacy of lomitapide are limited and long-term effect of lipid reduction of lomitapide on cardiovascular events has not been demonstrated to date. However, clear signs of higher incidence of cardiovascular events in the lomitapide patient group were not observed. At the present time, any conclusion on this would be pre-mature, given the uncontrolled and limited data available. A small proportion of patients (n=19) was included in the PP population analysis due to changes in apheresis schedule and treatment non-compliance.

In addition to the pronounced dose-dependent GI adverse events of lomitapide, the rarity of the HoFH condition and subsequent difficulty to recruit these patients, the suboptimal design of an unblended, single arm trial was necessary, and this could be subject to a potential bias. A poor compliance to diet was observed in the clinical trial; however, this did not seem to have an effect on the efficacy results. Subgroup analyses were underpowered but did not show any substantial differences.

Risks

Unfavourable effects

Based on the submitted data, 845 patients were treated with lomitapide of whom 29 HoFH patients were enrolled in the pivotal study.

Lomitapide treatment was associated with a high frequency of gastrointestinal adverse events (93% patients in the pivotal study). These were severe in 17% of the HoFH population and 9-28% in the other hypercholesterolemic populations. Five patients in the HoFH study population and 4% in the other hypercholesterolemic population discontinued treatment during a dose escalation scheme because of GI events, in contrast to 14-21% discontinuing due to diarrhoea during fixed dose supportive studies. Dose reductions for GI events occurred for seven HoFH patients (24%) and equally, dose interruptions related to GI events were needed in seven patients (24%). However, these were short-term, with a mean duration of 5 days, and most patients were successfully rechallenged.

Liver adverse events were likely to occur (9-34%) with lomitapide treatment, with 13% of the patients discontinuing in the other hypercholesterolemic population. Elevations in liver enzymes were frequent and seem to be reversible and inversely associated with the effect on LDL-C

reduction, and positively associated with the hepatic fat accumulation. Liver enzymes and biomarkers monitoring is recommended in the SmPC. Six patients experienced weight loss in the HoFH patient population, which was considered drug-related for 4 patients, but without long term impact on BMI and no patient's BMI dropping below of 18.

Serious adverse events occurred in 10% in the HoFH population and 1-3% in the other hypercholesterolemic population, and were almost all probably related to the CV underlying disease of the patients and not to study treatment. A notable proportion of the HoFH patients (59%) had infections, but it is unlikely that they are linked to lomitapide treatment.

An association of lomitapide with musculoskeletal events is unlikely. The patients in the pivotal study were already on maximum background statin therapy. Thus, the CHMP agreed that the SmPC statement recommending that all patients receiving lomitapide in addition to a statin should be advised of the potential increased risk of myopathy and report promptly any unexplained muscle pain, tenderness, or weakness, is adequate. Doses of simvastatin >40 mg should not be used, as per the SmPC.

The long-term effects of possible signs of malabsorption do not appear to have clinical consequences. Considerable reductions in fatty acid levels (51%), mainly at start of treatment, were observed. However, these stayed within the normal range with vitamin supplementation. The BMI remained within the normal range without the patient's BMI dropping below 18.

Uncertainty in the knowledge about the unfavourable effects

A limited size safety database is available with uncontrolled data of 29 HoFH patients treated for a maximum of 78 weeks in the pivotal study. Data from 446 patients with other types of hypercholesterolemia treated in controlled studies up to 12 weeks provide additional information. Adverse events on liver in the small HoFH population, and/or a limited follow-up time, lead to an uncertainty in a reliable assessment on the development and occurrence of hepatosteatitis with possible further development of hepatic fibrosis. Although liver toxicity is related to the mechanism of action of lomitapide, generally shows reversible characteristics after drug discontinuation, and its pattern resembles that of benign steatosis, it cannot be ruled out that an individual patient might still develop a non-alcoholic steatohepatitis (NASH), which could in the long-term result in fibrosis and cirrhosis. One patient had a biopsy 2 months after drug discontinuation, was presented with hepatosteatosis and elevated ALT/AST levels, but no NASH. Liver biopsy of another patient with hypertriglyceridemia treated with lomitapide for 13 years showed signs of NASH, but the treatment continues. Thus, identifying patients at risk of developing hepatotoxicity based only on elevations in liver enzyme levels is uncertain. Association of lomitapide treatment with liver fat accumulation was observed, however, data are limited. Only few biopsies were taken. Although clinical laboratory measurements may aid in identifying the patients that need to be referred to a hepatologist, imaging techniques should also be part of routine monitoring. Close collaboration of the treating physician with a hepatologist is warranted. New ways to monitor possible progression of liver disease such as non-invasive elastography are needed to aid in hepatic risk assessment. Other hepatic biomarkers suggestive of inflammatory liver disease (γGT, albumin, and validated marker combinations such as Enhanced Liver Fibrosis test, ELF) in addition to non-specific markers such as CRP and TNFα will be monitored.

A limited number of the other hypercholesterolemic population experienced a CV event (n=3) that was possibly related to the background risk of the patients.

No malignancies have been observed in clinical setting, however, in non-clinical studies, long-term fat accumulation as well as an increased number of tumours was observed in liver, small intestine and pancreas. Fatty liver in itself might be a risk factor for hepatocellular carcinoma.

Lomitapide exposure is highly sensitive to co-administration with CYP3A inhibitors. While the effect of the strong CYP3A inhibitor on lomitapide exposure (27-fold increase) is quantified, no appropriately controlled studies of moderate or weak inhibitors were undertaken. Based on the magnitude of the interaction with the strong CYP3A4 inhibitor ketoconazole, other strong and moderate CYP3A4 inhibitors are expected to have a substantial impact on lomitapide's PK and the use of moderate and strong Cyp 3A4 inhibitors is therefore contraindicated.

Weak CYP3A4 inhibitors are predicted to have a substantial impact on lomitapide's PK. A 4-10 fold increase of lomitapide exposure can be expected based on the results of the study with the strong CYP3A4 inhibitor ketoconazole and on historical data for the model CYP 3A4 probe midazolam. As lomitapide is likely to be co-administered with weak CYP3A inhibitors, such as simvastatin, atorvastatin and oral contraceptives, a 5 mg starting dose and careful up-titration of lomitapide is recommended when lomitapide is added to a weak CYP 3A4 inhibitor. When a weak CYP 3A4 inhibitor is added to lomitapide, dose reduction of lomitapide is recommended, followed by careful uptitration. In addition, post-approval two drug-drug interaction studies with the weak CYP3A4 inhibitors will be conducted in post-authorisation phase to further investigate this issue.

In animal studies, lomitapide was shown to be highly concentrated (200-fold) in the liver and since this is the main site of action, the CHMP considered it important to understand if the drug is also concentrated in the liver of humans. Thus, evaluations whether lomitapide is actively or passively transported into the liver at clinically relevant concentrations will be conducted in post-authorisation phase.

Furthermore, defining the target population based on genetic and/or clinical diagnostic criteria is needed to ensure that only the relevant HoFH patients receive lomitapide.

Benefit-risk balance

Importance of favourable and unfavourable effects

Lomitapide demonstrated clinically significant reductions in LDL-C levels in HoFH patients (n=29), a population at high risk for CV events. Efficacy was shown in other types of hypercholesterolemic patients as well. Although the long-term effect of lipid reduction of lomitapide on CV events was not investigated, reduction in LDL-cholesterol is considered an important surrogate endpoint with potential benefits in terms of CV outcome. However, this remains to be investigated in the post-authorisation setting since at present, the uncontrolled studies and the small number of patients studied do not allow to conclude on the long term effect.

The long-term beneficial CV effects were thus not fully demonstrated, although in terms of safety, the rate of events seen with lomitapide is generally within the expected range for this population. However, at present, only uncontrolled and limited data available. The applicant will thus conduct a post-approval observational cohort study (as the specific obligation) with

independent adjudication of CV (MACE) events, amongst others, and compare this to historical data. In addition, a clinical study using imaging techniques to visualize atherosclerosis will also be performed, and is expected to provide early data of potential CV benefit of lomitapide.

Occurrence of GI side effects is a drawback of lomitapide treatment, but this may be partly ameliorated by using a dose escalation scheme as recommended in the SmPC. Severe GI adverse events that occur mostly at start of treatment, are considered manageable for most patients by temporary treatment discontinuation or temporary down titration of the dose.

A further important safety issue is the adverse effect of lomitapide on the liver and although this is related to the pharmacodynamic effect of lomitapide, the potential long-term development of hepatotoxic effects, such as fibrosis cannot be currently assessed, due to limited data. Liver enzyme levels, fat fraction or other imaging markers are not a reliable predictor of such hepatotoxic effects either. As stated in the SmPC, other hepatic biomarkers suggestive of inflammatory liver disease (γGT, albumin, and validated marker combinations such as ELF) in addition to non-specific markers such as CRP and TNFα, and the use of at least one imaging technique, e.g. elastography, is considered essential. The observed hepatosteatosis resembles that of benign steatosis as seen in familial hypobetalipoproteinemia (FHBL), a genetic condition with alterations in apoB coding that results in low apo B/LDL-C associated with moderate to severe steatosis, but not cirrhosis or altered morbidity/mortality. However, it cannot be ruled out that the long-term treatment with lomitapide could lead to NASH and ultimately fibrosis. Thus, the CHMP considered necessary to monitor the hepatic markers during lomitapide treatment as described above, in order to detect early signs and symptoms of serious hepatotoxicity. Referral to a hepatologist is recommended, and a liver biopsy should be considered at an early stage of liver damage suspicion. If the first biopsy shows inflammatory liver disease, the benefit/risk should be re-assessed and treatment be stopped if necessary.

Further safety information (gastrointestinal, liver cardiovascular effects) will continuously become available through the planned registry, as described under the specific obligation.

Benefit-risk balance

The CHMP considered the beneficial effect of lomitapide on LDL-cholesterol clinically relevant, but a benefit in terms of CV outcome remains to be confirmed and may be partly offset by safety issues, in particular hepatic effects. Tolerability issues, specifically the gastrointestinal complaints associated with lomitapide-treatment can lead in some cases to suboptimal dose titration and drop-outs during the long-term treatment. As the drug is a sensitive CYP3A4 substrate, interactions with weak inhibitors of CYP3A4 may result in clinically important increases in lomitapide exposure, with a potential impact on tolerability and safety. Therefore, routine risk minimisation measures were implemented.

Given these important safety issues with lomitapide, the definition of the target population was considered essential to ensure that only HoFH patients that are most likely to benefit from the treatment will receive the drug.

Given the unmet medical need in this rare condition (HoFH) and the fact that the applicant cannot be reasonably expected to provide a full set of safety and efficacy data, the benefit/risk balance of lomitapide in the restricted indication is positive, providing the appropriate monitoring for and management of hepatotoxicity and gastrointestinal adverse events is followed. In

addition, further reassurance of the beneficial effects or at least absence of harm in terms of CV outcome will be examined post-approval, *via* observational registry and an agreed clinical trial measuring vascular outcomes.

Discussion on the benefit-risk balance

HoFH patients are from an early age at a greatly increased cardiovascular risk due to highly elevated LDL-C levels, which usually remain elevated throughout their lifetime, even if treated with aggressive lipid lowering therapy. Treatment of these patients is complicated and current treatment options are limited. Apheresis is available in some specialised clinics only, is time consuming and burdensome to the patient. Therefore, there is an unmet medical need in the HoFH population and additional long-term therapeutic options are needed.

Gastrointestinal adverse effects observed with lomitapide can decrease its tolerability, but with a dose escalation approach and temporary dose interruptions, could be considered acceptable and under these conditions would not significantly affect the B/R balance of lomitapide. However, a potential hepatotoxic effect does affect the B/R balance. Long-term liver effects are unknown and monitoring of standard liver enzymes (ALT, AST) alone cannot be considered a reliable indication of liver disease. Thorough and regular monitoring of appropriate liver biomarkers, employment of imaging techniques, possible liver biopsy, and management of long-term hepatotoxicity is essential since lifelong treatment is foreseen.

An approval under exceptional circumstances is recommended by the CHMP, who took into account that a full, comprehensive clinical data package cannot be expected in order to assess the effects on cardiovascular outcome. This is due to the rarity of the target HoFH population and the fact that data from adequately controlled and designed clinical studies are not feasible. An observational cohort study with independent adjudication of CV (MACE) events and additional data on liver toxicity will be conducted, together with a study using vascular imaging to assess effect on progression of atherosclerosis. In addition, patients and treating physicians will be presented with educational material aimed to minimise and manage the risks associated with lomitapide's treatment.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Lojuxta in the following indication:

"Lojuxta is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without low density lipoprotein (LDL) apheresis in adult patients with homozygous familial hypercholesterolaemia (HoFH).
Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinemia and secondary causes of hypercholesterolemia (e.g. nephrotic syndrome, hypothyroidism) must be excluded"

is favourable and therefore recommends the granting of the marketing authorisation under exceptional circumstances subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products on "restricted" medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within six months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall provide an educational pack prior to launch targeting all physicians who are expected to prescribe/use lomitapide.

The physician educational pack should contain:

- The Summary of Product Characteristics
- The Prescriber Guide
- Patient Alert Cards

- Patient Brochures

The MAH must agree the content and format of the educational materials together with a communication plan with the national competent authority in each Member State prior to distribution in their territory.

The Prescriber Guide shall include the following key elements:

Appropriate patient selection

- Lojuxta is only indicated for use in adult patients with HoFH;
- The safety and effectiveness of Lojuxta in children below the age of 18 have not been established;
- Treatment with Lojuxta should be initiated and monitored by a physician experienced in the treatment of lipid disorders;
- That Lojuxta was teratogenic in non-clinical studies and that women of child-bearing potential must be non-pregnant and using effective contraception prior to initiating treatment.

Gastrointestinal (GI) Effects

- Information on undesirable effects, including diarrhoea, nausea, flatulence, abdominal pain or discomfort, abdominal distension, vomiting, dyspepsia, eructation and decreased appetite;
- Contraindication for use in patients with a known significant or chronic bowel disease such as inflammatory bowel disease or malabsorption;
- Advice on escalating Lojuxta dose gradually to improve tolerability of the medicine;
- Advice to patients about:
  - The need to follow a low-fat diet (i.e. patients should follow a diet supplying less than 20% of energy from fat);
  - The timing of medicine intake (Lojuxta should be taken on an empty stomach, at least 2 hours after the evening meal);
  - The need to take daily dietary supplements (i.e. 400 IU vitamin E, at least 200 mg linoleic acid, 110 mg eicosapentaenoic acid (EPA), 210 mg alpha linolenic acid (ALA) and 80 mg docosahexaenoic acid (DHA) per day);

Hepatic events related to elevated aminotransferases and progressive liver disease

- Information about contraindication in patients with moderate or severe pre-existing hepatic impairment/disease, including those with unexplained persistent abnormal liver function tests;
- Information about clinical findings (i.e., hepatic enzyme increases and steatosis) in subjects treated with Lojuxta during the developmental phase;

• Advice to exercise caution if Lojuxta is used with other hepatotoxic drugs and to consider more frequent monitoring of liver-related tests;

• Advice to patients about the risk of concomitant alcohol intake;

• Advice on monitoring liver function (measuring hepatic enzymes and total bilirubin) before and during treatment with Lojuxta and routine screening to detect presence of steatohepatitis and hepatic fibrosis including specific details of the screening tests at baseline and annually as follows:

- Imaging for tissue elasticity, e.g. Fibroscan, acoustic radiation force impulse (ARFI), or magnetic resonance (MR) elastography;

- Measurement of biomarkers and/or scoring methods. This should include at least one marker in each of the following categories:

  - gamma-GT, serum albumin (liver injury);
  - high sensitivity C-reactive protein (hs-CRP), erythrocyte sedimentation rate (ESR), CK-18 Fragment, NashTest (liver inflammation);
  - Enhanced Liver Fibrosis (ELF) panel, Fibrometer, AST/ALT ratio, Fib-4 score, Fibrotest (liver fibrosis).

<u>Use in Women of Childbearing Potential</u>

• That Lomitapide was teratogenic in non-clinical studies and is contraindicated in women who are or may become pregnant. Women who become pregnant should be counselled and referred to an expert in teratology;

• Before initiating treatment in women of child-bearing potential:

– The absence of pregnancy should be confirmed;

– Appropriate advice on effective methods of contraception should be provided, and effective contraception initiated;

• Warning about possible loss of effectiveness of oral contraceptives due to diarrhoea or vomiting and need for additional contraception until 7 days after resolution of symptoms.

• Women should tell their doctor immediately if they suspect that they might be pregnant

<u>Drug interactions</u>

• Information about interactions with CYP3A4 inhibitors and inducers, coumarin anticoagulants, statins, P-gp substrates, oral contraceptives, bile acid sequestrants and grapefruit juice;

• Importance of fatty acid and soluble vitamins supplementation;

• Compliance with the supplementation regimen should be verified at regular scheduled appointments and the importance emphasised.

Educational materials for patients

Information that the educational materials for patients included in the prescribers pack can be used for patient counselling.

A copy of the patient brochure and patient alert card shall be provided to all patients at the time Lojuxta treatment is initiated.

Patients shall be informed of the necessity to carry the patient alert card with them and show it to all doctors that treat them.

Lomitapide Observational Worldwide Evaluation Registry

Information about the existence and importance of the registry aiming to systematically collect information on the safety and effectiveness outcomes of patients treated with lomitapide.

Prescribers are encouraged to enrol all patients treated with Lojuxta into a global registry.

Patient brochure

The patient brochure shall include the following key elements:

• Not to take Lojuxta if patient has liver problems, or unexplained abnormal liver tests;

• Information that Lojuxta may cause liver problems;

• The need to inform their doctor if they have had any liver problems in the past;

• The need to inform their doctor of all other medications they are taking as special care should be taken if other drugs which can cause liver problems are taken at the same time;

• Symptoms of liver disease for which the patient should consult a doctor;

• An explanation of the types of tests required (imaging and blood) to check liver function and the importance of them being performed regularly;

• Information that Lojuxta was teratogenic in non-clinical studies and should not be taken during pregnancy or by patients trying to get pregnant;

• Women of childbearing potential should have adequate birth control and should tell their doctors immediately if they suspect they may be pregnant;

• Lojuxta may cause diarrhoea and vomiting and if it does, patients using oral contraception should use additional contraceptive methods for 7 days after symptoms have resolved;

• Information about interactions with CYP3A4 inhibitors and inducers, coumarin anticoagulants, statins, P-gp substrates, oral contraceptives, bile acid sequestrants ;

• The need to avoid alcohol;

• The need to avoid grapefruit juice;

• Importance of fatty acid and fat soluble vitamin (Vitamin E) supplementation;

• Information on the importance of following a low-fat diet (a diet supplying less than 20% of energy from fat);

• Information about taking Lojuxta at bedtime with water at least 2 hours after the evening meal and without food;

• Information about the existence and importance of the Lomitapide Observational Worldwide Evaluation Registry aiming to systematically collect information on the safety and effectiveness outcomes of patients treated with lomitapide.

Patient Alert card

The purpose of the patient alert card is to inform health care professionals of potential drug-drug interactions before any additional drug is prescribed. Patients will be instructed to carry this card and show it to all doctors who treat them.

This card will give information about interactions with:

- CYP 3A4 inhibitors
- CYP 3A4 inducers
- coumarin anticoagulants
- statins
- P-gp substrates
- Oestrogen-containing oral contraceptives

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measure:

Description	Due date
Based on CHMP approved protocol, the applicant shall conduct a clinical study with adequate surrogate endpoints on vascular outcomes using imaging techniques to monitor vascular function, disease stabilisation and/or regression.	The final study report shall be submitted by 31 December 2019.

SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
The applicant shall set up a long term prospective observational study to systematically collect information on the safety and effectiveness outcomes of patients treated with lomitapide. The objectives of the study are:	Annual reports will be submitted at time of annual reassessment

Description	Due date
• To evaluate the occurrence of the following in patients treated with lomitapide: o Hepatic events o Gastrointestinal events o Small bowel, hepatic, colorectal and pancreatic tumours o Events associated with coagulopathy o Major Adverse Cardiovascular Events (MACE) events o Death, including cause of death • To evaluate the occurrence and outcomes of pregnancy in females of reproductive potential treated with lomitapide who decide to continue the pregnancy following advice from a teratologist. • To evaluate the long-term effectiveness of lomitapide in maintaining control of serum lipid levels in clinical practice. • To evaluate whether prescribers of lomitapide are following the screening and monitoring recommendations as specified in the product information and the educational materials.	

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considered that the active substance lomitapide contained in the medicinal product Lojuxta is to be qualified as a new active substance in itself.