Amsterdam, 26 March 2026
EMADOC-1700519818-3190011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lojuxta

International non-proprietary name: Lomitapide

Procedure No. EMA/X/0000258068

Note

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

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List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
apo AI	Apolipoprotein AI
apo B	Apolipoprotein B
ARH	Autosomal recessive hypercholesterolaemia
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CRP	C-reactive protein
CSR	Clinical study report
CV	Cardiovascular
CVD	Cardiovascular disease
DSMB	Data safety monitoring board
EAP	Early access programme
ECG	Electrocardiogram
EFA	Essential fatty acid
ERKNet	European Rare Kidney disease Network
ESPN	European Society of Paediatric Nephrology Dialysis Working Group
EU	European Union
FAS	Full analysis set
FH	Familial hypercholesterolaemia
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HDL-C	High density lipoprotein cholesterol
HoFH	Homozygous familial hypercholesterolaemia
IC_{50}	Half-maximal inhibitory concentration
IQR	Inter Quartile Range
ITT	Intent-to-Treat
LA	Lipoprotein apheresis
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein cholesterol
LDLR	Low density lipoprotein receptor
Lp(a)	Lipoprotein a
LFT	Liver function test
LLT	Lipid lowering therapy
LOCF	Last observation carried forward
MAA	Marketing authorisation application

MOA	Mechanism of action
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MTP	Microsomal triglyceride transfer protein
NA	Not applicable
NMRS	Nuclear magnetic resonance spectroscopy
non-HDL-C	Non-high density lipoprotein cholesterol
PBPK	Physiologically based pharmacokinetic
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamics
PFT	Pulmonary function test
PK	Pharmacokinetics
pop-PK	Population PK
SAE	Serious adverse event
SD	Standard deviation
SOC	System Organ Class
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
US	United States
VLDL	Very low density lipoprotein
VLDL-C	Very low density lipoprotein cholesterol
WHO	World Health Organisation

1. Administrative/regulatory information and recommendations on the procedure

1.1. Submission of the dossier

On 07/03/2025, Chiesi Farmaceutici S.p.A. submitted a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type	Annexes affected
C.I.7.b	Deletion of a strength	IB	I, IIIa, IIIb
C.I.7.b	Deletion of a strength	IB	I, IIIa, IIIb
C.I.7.b	Deletion of a strength	IB	I, IIIa, IIIb
C.I.6.a	Addition of a new therapeutic indication or modification of an approved one	II	I, II, IIIa, IIIb

Extension application to add a new strength of 2 mg hard capsules.

In addition, the MAH proposed:

- 3 x type IB variations (C.I.7.b): to delete the 30 mg, 40 mg and 60 mg strengths from the Lojuxta marketing authorisation (EU/1/13/851/004 - 006).

- 1 x type II variation (C.I.6.a): an Extension of Indication to include treatment of paediatric patients aged 5 years and older with homozygous familial hypercholesterolaemia (HoFH) for LOJUXTA, based on final results from the pivotal paediatric study APH-19; this is a phase 3, single-arm, open-label, international, multi-centre study to evaluate the efficacy and safety of lomitapide in paediatric patients with homozygous familial hypercholesterolaemia (HOFH) on stable lipid-lowering therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Annex II and Package Leaflet are updated accordingly. The RMP version 7.5 has also been approved. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.4.

The MAH applied for the following indication for Lojuxta for the new strength: 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 **for the treatment of** adult **and paediatric patients aged 5 years and older** with homozygous familial hypercholesterolaemia (HoFH).

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.

1.2. Legal basis, and dossier content

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point(s) (c) - Extensions of marketing authorisations.

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Scientific advice and protocol assistance

Not applicable.

1.4. Information on paediatrics

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0374/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0374/2024 was completed.

The PDCO issued an opinion on compliance for the PIP P/0374/2024.

1.5. Information on orphan market exclusivity

Not applicable.

1.5.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH 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.

1.6. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur:	Patrick Vrijlandt

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur:	Bianca Mulder

The application was received by the EMA on	07 March 2025
The procedure started on	27 March 2025
The CHMP Rapporteur's first Assessment Report was received on	16 June 2025
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	24 July 2025
The MAH submitted the responses to the CHMP consolidated List of Questions on	10 October 2025
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	17 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	11 December 2025
The MAH submitted the responses to the CHMP List of Outstanding Issues on	27 January 2026
The CHMP Rapporteur circulated the Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 February 2026

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 to Lojuxta on	26 March 2026

1.7. CHMP outcome

1.7.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.4. of this report.

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0374/2024 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

1.7.2. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of 2 mg hard capsules of Lojuxta is favourable in the following indication(s):

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 for the treatment of adult and paediatric patients aged 5 years and older with homozygous familial hypercholesterolaemia (HoFH).

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.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Lojuxta, subject to the conditions described in the following sections.

In addition, the CHMP does recommend the variations to the terms of the marketing authorisation concerning the following changes:

Variation(s) adopted		Type	Annexes affected
C.I.7.b	Deletion of a strength	IB	I, IIIa, IIIb
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- 3 x type IB variations (C.I.7.b): to delete the 30 mg, 40 mg and 60 mg strengths from the Lojuxta marketing authorisation (EU/1/13/851/004 - 006).

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and Package Leaflet are updated accordingly. The RMP version 7.5 has also been approved. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.4.

1.7.3. Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

1.7.4. Other conditions and requirements of the marketing authorisation

1.7.4.1. Periodic safety update reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

1.7.5. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.7.5.1. Risk management plan (RMP)

The marketing authorisation holder (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.

1.7.5.2. Additional risk minimisation measures

- **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 brochures
- Patient alert cards

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

- 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 and adolescents 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 (or 200 IU vitamin E for children aged 5 to 8 years), approximately 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 medicinal products 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:
  For paediatric patients:
  - Imaging for hepatic fat content by ultrasound or NMR imaging
  - Gamma-GT and serum albumin to detect possible liver injury
  For adult patients:
  - 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:
    - gammaGT, serum albumin (liver injury);-GT,
    - high sensitivity C-reactive protein (hsCRP), 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).

Use in women and adolescents of childbearing potential

- That lomitapide was teratogenic in non-clinical studies and is contraindicated in women and adolescents 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 and adolescents 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.

Drug interactions

- 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 prescriber's 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 (LOWER)

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 lomitapide 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 medicines they are taking as special care should be taken if other medicines 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 lomitapide was teratogenic in non-clinical studies and should not be taken during pregnancy or by patients trying to get pregnant;
- Women and adolescents 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 medicinal product 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**
Non-interventional PAES: in order to evaluate the effect of lomitapide treatment on major adverse cardiovascular events (MACE), the MAH should conduct and submit the results of an observational, multi-centre, long-term, open-label, retrospective and prospective study in EU patients with homozygous familial hypercholesterolemia.	30 June 2027

1.7.6. 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
LOWER registry – long term prospective observational study to systematically collect information on the safety and effectiveness outcomes of patients treated with lomitapide and 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. 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: 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. The outcome of primary interest is major congenital anomalies. • 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.	An annual report will be submitted at time of annual reassessment

2. Introduction

Therapeutic Context

HoFH is a rare, life-threatening, genetic disorder of cholesterol metabolism, which leads to very high levels of low density lipoprotein cholesterol (LDL-C) in the blood (from as early as *in utero*) and markedly reduced life expectancy compared to the general population and patients with the related disorder, heterozygous familial hypercholesterolaemia (HeFH) (Gidding, 2015, *Circulation*; McErlean, 2023, *BMJ*).

The definition, criteria and methods of diagnosis, as well as the management of HoFH are widely discussed and defined by panels with worldwide experts, notably, the European Atherosclerosis Society's (EAS) HoFH panel, led by Dr Marina Cuchel2 from the US. This panel includes other members from the US, which makes their work recognised worldwide. Indeed, following the publication of the EAS 2023 Consensus Statement on HoFH (Cuchel, 2023, Eu*r Heart J*), recommendations of actionable measures have also been made to improve early diagnosis through population-based screening for HoFH in the US (Gidding, 2024, Glob Heart).

The worldwide prevalence of HoFH is estimated at between 1:250,000 to 1:360,000 in the EAS 2023 consensus statement (Cuchel, 2023 *Eur Heart J*), with an estimated 23,000 new cases worldwide (Tromp, 2022, *Lancet*). A recent worldwide meta-analysis of 11 million subjects produced an estimate that was roughly in line with those cited in the EAS 2023 guidance (Beheshti, 2020, *J Am Coll Cardiol*).

Elevated LDL-C is a critical risk factor for developing accelerated premature and progressive atherosclerotic cardiovascular disease (ASCVD), resulting in coronary heart disease (CHD), being reflected in figures from the World Health Organisation which estimate that approximately 60% of CVD events resulting from coronary heart disease (CHD) and approximately 20% of strokes can be attributed to elevated cholesterol. The symptoms of HoFH start early in life: HoFH plasma LDL-C levels are chronically and extremely elevated from birth or even in utero (Gidding, 2015, Circulation; McErlean, 2023 BMJ), premature CVD, atherosclerosis and aortic stenosis developing as early as in childhood, and the high risk of an early cardiac-related death if patients are left untreated (Thompson, 2018, Eur Heart J). Despite their young age, patients with HoFH often initially present with extensive xanthomas on the skin and tendons, prompting further medical investigation and the subsequent HoFH diagnosis.

Data from contemporary registries also reflect the severity of untreated LDL-C levels in children affected by the disease:

• In a cohort of 412 patients aged <18 years at HoFH diagnosis (drawn from the HoFH International Clinical Collaboration [HICC] and the international registry for Children with Homozygous Hypercholesterolaemia on Lipoprotein Apheresis [CHAIN]), median untreated LDL-C was 690 mg/dL, inter-quartile range (IQR) 570-800 mg/dL. (Reijman, 2024, *Lancet Child Adolesc Health*).

• Interrogation of the US Family Heart Database, comprising >81 million individuals, using diagnostic criteria that reflect genetically confirmed HoFH (i.e., LDL-C ≥400 mg/dL or total cholesterol ≥500 mg/dL) and excluding secondary hypercholesterolaemia identified 277 individuals with HoFH, 52 (18.8%) aged <18 years, with a median LDL-C of 444 mg/dL (IQR 423 to 509 mg/dL).

• The only US registry of familial hypercholesterolaemia (FH) (the US CASCADE [Cascade Screening for Awareness and Detection] FH registry) follows phenotypic diagnostic criteria that align with those of the EAS (Cuchel, 2023 *Eur Heart J*). In 16 children diagnosed with HoFH, median untreated LDL-C

levels were comparable in patients with and without an established genetic diagnosis (776 [IQR 704–892] mg/dL vs. 721 mg/dL) (Cuchel, 2023 J Am Heart Assoc; Gidding, 2024, Glob Heart).

Early diagnosis, and initiation of aggressive treatment for HoFH subjects *during childhood* is therefore essential to lower LDL-C levels early on in the disease, thus minimising damage to the cardiovascular system, and reducing the risk of premature cardiac-related death (Gidding, 2024, *Glob Heart*). Indeed, these needs (early diagnosis and initiation of treatment) in paediatric HoFH patients has been recognised in the updated 2023 clinical guidance from EAS on the management of HoFH (Cuchel, 2023 *Eur Heart J*). Strong recommendations were made by the EAS panel for universal paediatric familial hypercholesterolaemia (FH) screening and expanding paediatric guidance to include newborn screening in the presence of diagnosed HeFH in both parents, hypercholesterolaemia or in regions with a strong founder effect. The EAS panel also stressed the importance of education programmes, and multidisciplinary collaborations (between paediatricians, primary healthcare providers, lipid specialists, cardiologists and geneticists) to reduce time to diagnosis. Currently it is estimated that less than 5% of HoFH patients are identified (Tromp, 2022, *Lancet*). Finally, the panel revised down the previously recommended LDL-C goals for children and adolescents with HoFH, lowering these goals (from those in 2014 guidance in Cuchel, 2014 *Eur Heart J*) to <3 mmol/L (<115 mg/dL) if lipid-lowering treatment is initiated before 18 years and imaging assessment does not indicate ASCVD. The EAS guidance suggests an even lower goal (unquantified) in patients with established ASCVD. In all HoFH cases, the EAS 2023 guidance recommends starting lipid-lowering therapy as soon as possible after diagnosis, with an aim (in paediatric patients) to ensure adherence to the LLT regimen from an early age.

Historically, HoFH was thought to be an autosomal co-dominant disorder caused by genetic mutations in both alleles of the *LDLR* gene that encodes the LDL receptor (LDLR), leading to a failure of normal cholesterol metabolism. However, it is now estimated that *LDLR* gene loss-of-function variants account for 85%-90% of HoFH cases, with recent advances highlighting the prevalence and heterogeneity of the genetic defects underlying HoFH and its clinical phenotype. Mutations in at least three other genes alter the function or expression of *LDLR* or adversely affect LDL to LDLR interactions. These genes include the apolipoprotein B gene-receptor binding- impaired variants (*APOB*) (5%-10% of cases), proprotein convertase subtilisin/kexin type 9 (*PCSK-9*) gene gain-of-function variant (1-3% of cases), and the autosomal recessive *LDLRAP1* (hypercholesterolaemia LDLR adapter protein) loss of function variants (<1% of cases) (Cuchel, 2023 *Eur Heart J*; Berberich, 2019, *Nat Rev Cardiol*). Rarely, genetically confirmed compound heterozygous HoFH has been found to have one heterozygous mutation in *LDLR* together with a heterozygous mutation in one of the three other loci (*APOB*, *PCSK9* or *LDLRAP1*) (Cuchel, 2014 *Eur Heart J*). The consequence of these gene defects is altered LDLR activity to varying degrees (depending on the nature of the underlying mutations), and resultant reduced uptake of LDL-C from circulation, leading to chronically and severely elevated plasma LDL-C levels as early as *in utero* (Gidding, 2015, *Circulation*; McErlean, 2023 *BMJ*). The amount of residual LDLR function also has a fundamental impact on the effectiveness of pharmacological intervention (Cuchel, 2023 *Eur Heart J*).

Available therapies

There is only a limited number of effective pharmacological therapies that have been licensed for paediatric HoFH patients, particularly for patients under 10 years of age.

The key clinical guidance prepared by the EAS and followed both inside and outside Europe (Cuchel, 2023 *Eur Heart J*) recommends initiating life-style changes, (i.e. following a low-fat diet) and treatment with high-intensity statins and ezetimibe at diagnosis. Of note, the authors of the 2023 EAS guidance acknowledge that most patients will need additional LLTs to attain sufficient reduction of LDL-C levels, due to the reduction in effectiveness of statins and ezetimibe with decreasing residual-, or missing LDLR function. Within 8 weeks from start of treatment with statins and ezetimibe, PCSK9-

directed therapy (at approved doses for HoFH) should be considered where available (see M2.7.3 Section 1.1.4.1.2). Response to PCSK9-directed therapies is also dependent on the patient's residual LDLR activity - PCSK9 inhibitors are not effective if there is no residual LDLR function. If patients show >15% additional LDL-C reduction, PCSK9-directed therapy may be continued, but if response is poor, clinicians should consider stopping this therapy. Of note, the only PCSK-9 inhibitor licensed in the EU for treatment of HoFH is Repatha (evolocumab), which is indicated for children over 10 years of age.

If LDL-C is still >300 mg/dL (8 mmol/L), the 2023 EAS guidance recommends that mechanical removal of excess lipoproteins by lipoprotein apheresis (LA) should be considered. This is consistent with the recommendation from the European Rare Kidney disease Network (ERKNet) and the European Society of Paediatric Nephrology Dialysis Working Group (ESPN) (Reijman, 2024, *Atherosclerosis*), the consensus across different expert networks being that earlier and more aggressive treatment in paediatric HoFH patients is warranted. Of note, ERKNet and ESPN also recommend starting LA i) in paediatric patients diagnosed with HoFH and (subclinical) ASCVD if LDL-C levels are >130 mg/dL (>3.4 mmol/L) despite optimal LLT, and ii) in paediatric patients diagnosed with HoFH without (subclinical) ASCVD if LDL-C levels are between 3.4 mmol/L (130 mg/dL) and 7.8 mmol/L (300 mg/dL) despite optimal LLT.

The long-term effects of LA regarding ASCVD risk reduction remain under discussion in the literature (see below), alongside the common adverse events including iron deficiency (18.3%), problems with vascular access for lipoprotein apheresis treatment (17.3%), abdominal pain or nausea (17.3%), or less commonly reported ones such as hypotension, anaphylactic or allergic reaction, fatigue, and portrelated sepsis, (Luirink, 2019, *J Clin Lipidol*; Luirink, 2020, *Atherosclerosis*) as well as increased risk of depression, anaemia and fatigue (Kayikcioglu, 2019, *J Clin Lipidol*). Moreover, the practical limitations of the procedure and notably negative impacts on patient quality of life is well documented also (Cuchel, 2023 *Eur Heart J*). While response to statins, ezetimibe, and PCSK9 inhibitors is dependent on the degree of residual LDLR activity, LA is an LDLR-independent therapy. However, the cholesterol rebound phenomenon after LA described by Thompsen and Thompson in 2006 (Thompsen and Thompson, 2006, *Atherosclerosis*) makes it necessary to perform LA sessions weekly, while lipid-lowering drugs induce constantly low LDL-C levels (Julius, 2016, *Med Devices (Auckl)*). Still, even weekly or biweekly LA failed to prevent progression of ASCVD in HoFH patients (Graesdal, 2012, *Lipidol*; Klaus, 2018 *Pediatr Nephrol*; Giammanco, 2020, *Curr Med Chem*) and until recently, the impact of LA on the onset of CVD remained unclear. Notably, only a recent study (using data from two global HoFH registries HICC & CHAIN) has shown that in HoFH patients, LA initiated during childhood and adolescence is associated with reduced long-term risk of ASCVD and death (Reijman, 2024, *Lancet Child Adolesc Health*).

If LDL-C is still >115 mg/dL (3 mmol/L), the 2023 EAS guidance recommends considering novel therapies, if available and affordable. Novel therapies approved in the EU are detailed below. Overall, the aim of treatment is to rapidly lower LDL-C levels by as much as possible, and for most patients this will typically involve combination therapy. If these LDL-C goals remain out of reach, liver transplantation could be considered as a last resort.

Novel therapies licensed for paediatric HoFH patients

In December 2023, a few months after the publication of the 2023 EAS guidance, Evkeeza (evinacumab) became the first novel LDLR-independent therapy to be approved for use in children with HoFH as young as 5 years of age. A Type II Variation (EC Decision issued 13 December 2024) has extended the indication to children with HoFH as young as 6 months old. Evkeeza (evinacumab) is indicated "as an adjunct to diet and other LDL-C lowering therapies for the treatment of adult and paediatric patients aged 6 months and older with HoFH". Evkeeza (evinacumab) is administered via intravenous (IV) infusion once a month (Evkeeza SmPC). Despite the recent approval of evinacumab

for paediatric HoFH patients who are 6 months and older, very few LLTs are approved for the youngest paediatric age groups, and access might be limited in certain regions. Therefore, there remains an unmet need in this patient group for effective, appropriately investigated LDLR-independent pharmaceutical therapies that can be initiated in paediatric patients to rapidly reduce LDL-C levels to EAS-recommended goals as soon as possible following diagnosis. This will be particularly critical for patients whose access to LA is limited or impractical. Moreover, daily oral therapy such as lomitapide, would benefit patients for whom evinacumab is contraindicated, not acceptable/feasible due to the IV mode of administration, or where regular travel for IV infusions is impractical. We note as well, that in severe cases, multiple LDLR independent therapies, e.g. evinacumab, lomitapide and/or LA, might be needed to achieve LDL-C goals. Recent research in a small number of patients treated with both lomitapide and evinacumab suggests the LDL-C-lowering effects of these three therapies are additive (Wiegman, 2024, *Circulation*).

2.1. Aspects of development

Up to 31 July 2024 (data lock point for latest PSUR), a total of 1,252 participants have been enrolled in clinical trials with lomitapide, of which 1,032 received oral lomitapide either as monotherapy or co-administered with another therapy, including 78 (35 adult and 43 paediatric) subjects with HoFH.

The pivotal paediatric study that is presented in this variation is APH-19. The unmet need in the paediatric HoFH population was recognised by the EMA prior to the submission of the marketing authorisation application for lomitapide in adults with HoFH, with PDCO agreeing the design of the pivotal paediatric study (APH-19).

For this line-extension grouped with an extension of indication and several Type II variations, the Applicant is submitting the full clinical study report (CSR) for the complete 104 week-study in paediatric HoFH patients. This includes the primary efficacy endpoint at Week 24 and importantly, the long-term safety and efficacy data for the full 2 years, enabling the evaluation of lomitapide treatment on the growth and development of the paediatric subjects over the full duration of the study.

Please refer also to section 6.1.2.

2.2. Description of the product

Lomitapide is an orally administered, effective, selective small molecule inhibitor of microsomal triglyceride transfer protein (MTP), whose mechanism of action is LDLR-independent. MTP is an intracellular lipid-transfer protein found in the lumen of the endoplasmic reticulum that is responsible for binding and shuttling individual lipid molecules between membranes (Hussain, 2003 *J Lipid Res*; Liao, 2003 *J Lipid Res*). MTP is responsible for transferring triglycerides onto apolipoprotein B (apo B) in the assembly of very low density lipoprotein (VLDL), the precursor to LDL, by transporting individual lipid molecules from the site of lipid synthesis to the emerging apo B molecule (Boren, 1993 *Arterioscler Thromb*). Normal concentrations and function of MTP in the liver and intestine are necessary for the proper assembly and secretion of apo Bcontaining lipoproteins including VLDL (which is converted into LDL) from the liver, and chylomicrons (containing dietary cholesterol and triglycerides) from the intestine (Liao, 2003 *J Lipid Res*).

Currently, lomitapide (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 HoFH.

Based on the results of the Phase 3 study in paediatric patients with HoFH (APH-19), the proposed label revision will extend the currently approved indication to paediatric patients aged 5 years and

older with HoFH as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without LDL apheresis.

3. Quality aspects

Introduction

This application concerns a line-extension for the addition of a new strength of the same pharmaceutical form i.e. 2 mg hard capsules to the already authorised Lojuxta 5, 10 and 20 mg hard capsules, to support an extension of the indication to include treatment of patients 5 years of age and older.

The finished product is presented as hard capsule containing 2 mg lomitapide (as mesylate) as active substance.

Other ingredients of the capsule content are: pregelatinised starch (maize), microcrystalline cellulose, lactose monohydrate, sodium starch glycolate (Type A), colloidal anhydrous silica and magnesium stearate. The capsule shell consists of gelatine, titanium dioxide (E171) and black iron oxide(E172). The printing ink consists of shellac, black iron oxide (E172) and propylene glycol.

The product is available in a high-density polyethylene (HDPE) bottle fitted with a polyester/aluminium foil/cardboard induction seal and polypropylene screw cap.

3.1. Active substance

Except for batch analysis data (section 3.2.S.4.4.) no section 3.2.S has been provided. This is acceptable since the finished product is a line-extension of the already authorised products 5, 10 and 20 mg Lojuxta and the active substance Lomitapide is the same as for the authorised 5, 10 and 20 mg hard capsules.

3.2. Finished medicinal product

3.2.1. Description of the product and pharmaceutical development

Description of the product

The lomitapide finished product is supplied as 2, mg size 1 (19.4 x 6.9 mm) hard-shell gelatine capsules. The milligram strength refers to the amount of lomitapide free base per capsule. The finished product will be packed in 100 cc (mL) high-density polyethylene (HDPE) bottles with a tamper evident induction seal and fitted with a 38 mm twist-off closure. Each bottle will contain 28 capsules.

The introduced 2 mg strength is a hard capsule with grey capsule body imprinted with '2 mg' and grey capsule cap imprinted with 'A733'. The 2 mg strength product is sufficiently distinguishable from the already approved strengths by colour and imprint.

For the colorants used in the capsule shell, compliance with the purity criteria of Regulation 231/2012 is made. For iron oxide black used in the printing ink, reference is made to 2008/128/EC. This is acceptable since only traces of ink will be present in the final finished product.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. The excipients used in the lomitapide finished product are typical excipients found in hard-shell gelatin capsule solid oral dosage forms. The functions of the excipients are well understood and each excipient is characterised to the appropriate industry and pharmacopeia standards. The excipient

functionalities include granulation binders, fillers, disintegrants, glidants, and lubricants. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Pharmaceutical development

A 2 mg strength was developed to facilitate the administration in the paediatric population. The prior development studies for the authorized Lomitapide capsule finished products were leveraged for the development of the 2 mg capsule.

The differences between the commercial presentation and the clinical batches (colour of capsules) are considered minor changes that are not expected to affect quality, safety or efficacy of the finished product. This is supported by comparative dissolution results in the QC medium of two batches with the development capsule orange shell, including clinical batch 3899406 and three commercial batches with the grey shell with imprinting. All dissolution profiles were comparable and achieved more than 85% dissolution in 15 minutes and are considered similar.

Comparative dissolution results in graphical presentation have been provided for one 5 mg batch and three 2 mg batches in five media across the PH range. In the release dissolution testing medium more than 85% dissolution is achieved in 15 minutes for al tested batches so the dissolution profiles are considered similar. For the other dissolution media f2 calculations are performed to demonstrated similarity between the 2 mg and 5 mg product dissolution profiles. However, it could not be checked if the f2 values were correctly calculated since no individual numerical results and % RSD values were provided. Furthermore, comparative dissolution results in pH 6.8 without surfactant are missing. However, in this case no objection was raised since the application is based on final results from the pivotal paediatric study APH-19 and therefore bioequivalence between the proposed 2 mg strength and already authorised strengths is not required.

There are no overages for lomitapide finished product for any of the strengths.

The manufacturing process development has been described in sufficient detail. The prior development studies for the authorised Lomitapide capsule finished products were leveraged for the development of the 2 mg finished product. Batch size, equipment train, and process parameter setpoints for the Lomitapide 2 mg capsules are equivalent to the current Lomitapide 5 mg and 10 mg marketed products. In addition, the unit formula for these products is also equivalent with only an adjustment to the active substance and bulking diluent quantities for the lower 2mg strength.

Four commercial scaled batches were made to investigate impact of wet granulation parameters and 11 day hold time of the bulk blend on the manufacturability and quality attributes. It was demonstrated that the proposed process parameters and in-process controls result in blends with comparable particle size distribution and good flowability. The encapsulated dosage units also demonstrated good weight control and met the in-process specifications for the finished product. The results from blend uniformity and content uniformity testing confirmed good homogeneity and acceptable uniformity of dosage units. Blend uniformity is considered a critical parameter due to the low active substance content (1.14%) in the 2 mg strength. The results showed similar assay values and within the acceptance criteria for potency and dissolution. The established processing setpoints are therefore deemed applicable for defining the process targets, PARs and critical processing parameters (CPPs) for manufacturing Lomitapide 2 mg capsules.

Microbiological attributes have been sufficiently discussed. The risk for microbiological contamination is expected to be low since the finished product is a solid oral dosage form. Furthermore, control of microbial is included in the release and shelf-life specification of the finished product. No additional

risks for microbiological attributes are foreseen for the 2 mg as for the authorised 5, 10 and 20 mg capsules.

Age-appropriateness

The hard capsules are taken once daily on an empty stomach (with a glass of water). Capsules size 1 (19.4 mm) are used for the formulation. If the patient is unable to swallow the intact capsule(s), the capsule(s) can be opened and the contents sprinkled on a small amount (1 tablespoon) of apple sauce or mashed banana, which are essentially fat-free.

The following instruction is added to section 4.2 of the SmPC: 'If the patient is unable to swallow the intact capsule(s), the capsule(s) can be opened and the contents sprinkled on a small amount (1 tablespoon) of apple sauce or banana puree, which are essentially fat-free.'

Compatibility of the 20 mg finished product in applesauce and banana has been demonstrated up to eight hours. This is sufficient to support the proposed administration instructions in the SmPC. No signs for a negative impact on taste and patient acceptability of opening of the capsules and sprinkling of capsule content on soft foods was seen during the adult bioequivalence study.

Suitability of the capsule size 1 has been adequately justified. The provided justification in the PIP procedure to delete the quality measure to develop a suitable formulation for paediatric use including demonstration of bioequivalence between intact lomitapide capsules and the capsule contents sprinkled on soft foods was approved by the PDCO. The suitability of the size 2 capsule was further supported by the results of the APH-19 study. Ease of opening of the capsules in practice has been discussed. No problems are foreseen based on experiences during clinical studies and performed compatibility studies where over 90 capsules were opened by analysts. Furthermore, an adequate safety assessment on excipients of proposed finished product has been provided. No direct safety issues are foreseen with regards to the excipients and their quantities in the formulation for use in children of 5-12 year.

Drug acceptability was evaluated during the clinical studies. Ease of administration of both the investigational product and dietary supplement regimen was assessed by a questionnaire to parents/guardians at each visit. No problems with administration of lomitapide when swallowing the capsule were indicated: of the 40 subjects (5-10 years n=18, 11 – 17 years, n=21) with data available at Baseline, only 3 subjects reported being unable to swallow the capsule at some time points. Palatability was rated as 'good' and there were no issues with refusal to take or vomiting. The majority of parents/guardians (>80% at all time points on study) reported a pleasant reaction from their child on taking the study drug and did not report issues with refusal.

3.2.2. Manufacture of the product and process controls

Manufacture

The manufacturing sites for Lojuxta 2 mg are the same as for the authorised 5, 10 and 20 mg products. Catalent CTS Kansas City, USA is responsible for manufacturing primary packaging, release, microbial and stability testing. Arvato SE Nordrhein-Westfalen, Germany and CIT Srl Burago di Molgora, Italy are both responsible for secondary packaging and labelling. Amryt Pharmaceuticals DAC, Dublin, Ireland performs finished product batch release. These sites have been checked for GMP compliance.

The manufacturing process of the 2 mg product is similar to the manufacturing process of the authorised 5, 10 and 20 mg products. The main steps are dry blending, wet granulation, drying,

milling, blending, encapsulation, empty capsule elimination, weight sorting and packaging. The manufacturing process is described in sufficient detail. Since for the 2 mg strength the active contributes to less than 2% of the composition, the manufacturing process is considered as non-standard.

A bulk hold time of 6 months is justified by bulk hold stability studies presented in section 3.2.P.8. demonstrating that capsules may be stored in bulk containers (tied double polyethylene bags placed in a fiber drum) for up to 6 months with no adverse effect on quality. Compliance with the EMA NfG on start of shelf-life of the finished dosage has been confirmed in section 3.2.P.3.3.

The critical process parameters are discussed and are controlled by parameter settings established during development or controlled by in-process controls. The proposed in process controls and acceptance criteria are in line with the in-process controls of the authorized 5, 10 and 20 mg product. Based on provided blend uniformity results, which are comparable for the 2 mg strength and the approved higher strengths, absence of blend uniformity IPC is justified.

Production scale validation data in the marketing authorisation dossier at the time of regulatory submission is required since the manufacturing process is considered non-standard. The manufacturing process has been adequately validated on three production scale batches of lomitapide capsules. Results support the process parameter settings. Blend uniformity was confirmed. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

3.2.3. Product specification

Specifications

The finished product release and shelf-life consists of Description (visual), Identification (HPLC, MS), Assay (HPLC), Related substances (HPLC), Dissolution (Ph.Eur.2.9.3, Apparatus 2), Uniformity (HPLC, Ph.Eur.2.9.40), Water (KF) and Microbiological control (Ph.Eur.2.6.12/13).

The proposed analytical procedures and corresponding specification limits are adequate for routine control of the finished product at release and shelf life. They are in line with ICH guidelines and Ph. Eur. The 2 mg specifications in general are similar to the specifications of the authorised 5, 10 and 20 mg strengths except for the acceptance criterium for description and dissolution. At Day 120 a Major Objection was raised to the proposed dissolution limit selected by the applicant. The applicant was requested to justify the choice of dissolution limit which should be set based either on the dissolution profiles of the 2 mg batches used in phase 3 clinical study APH-19 (3769565 and 5264987) or to apply the same dissolution limit for the 2 mg as for the authorised 5, 10 and 20 mg capsules provided bioequivalence between the developed 2 mg and authorised products is demonstrated.

At D195 the company submitted the information based on the dissolution profile of batch 3769565 used in the clinical phase 3 study APH-19 and the observed variability in dissolution results (intra batches observed during stability without a clear trend and also inter batches) which could be related to the nature of hard capsules. The dissolution limit for the 2 mg was tightened. In view of the data submitted during the assessment of this line extension, the applicant was requested to review, if need, the dissolution specification limits for the approved presentations (**REC 1**).

The proposed impurity limits for the 2 mg strength are in line with the approved control limits of the authorised 5, 10 and 20 mg strengths. The proposed finished product specifications are acceptable.

No additional risk for nitrosamines is expected for the 2 mg finished product. Therefore, absence of nitrosamine control is justified, in line with the authorized 5, 10 and 20 mg product.

Analytical procedures and reference standards

The analytical procedures for the 2 mg product are identical to those used for the authorised 5, 10 and 20 mg products, with only some slight differences with regards to the sample preparation where needed to accommodate for the difference in strength. The methods have been described in sufficient detail and were adequately validated in accordance with the ICH guidelines.

The standards used are the same as for the authorised 5, 10 and 20 mg products.

Batch analysis

Batch analysis results of three production scaled batches Lomitapide 2 mg capsules have been provided, demonstrating compliance with the specification and batch to batch consistency. This is considered sufficient.

Container closure

For the 2 mg capsules the same packaging is used as for the authorised 5,10 and 20 mg capsules: 100 cc (ml) high-density polyethylene (HDPE) bottle with a tamper evident induction seal and fitted with a 38 mm child twist-off closure. Also, the same bulk packaging is used for the 2 mg as for the authorised higher strengths.

3.2.4. Stability of the product

Stability data have been provided on three production scale batches stored at 25 °C / 60% RH (24 months) and 40 °C / 75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed commercial HDPE bottles. The following parameters were investigated: description, package appearance, assay, impurities, water content, dissolution and microbial quality. At both the long-term (25 °C / 60% RH) and accelerated (40 °C / 75% RH) storage condition no trends were seen in the tested parameters and all reported values were within the specified limits. No changes or trends were seen in related substances. The hydrolysis impurity was not detected in any of the stability batches. The levels of unidentified and total impurities remained within specification limits and no increasing trend was observed. Water content was below the specification acceptance criteria.

The proposed shelf life of 3 years is justified.

The proposed storage condition when packed in high density polyethylene (HDPE) bottle fitted with a polyester/aluminium foil/cardboard induction seal and polypropylene screw cap are "Store below 30 °C." (in accordance with the general Ph. Eur. monograph on capsules) and "Keep the bottle tightly closed in order to protect from moisture." (in view of the type of product and sensitivity of the active substance for moisture) is in line with the storage condition of the authorised 5, 10 and 20 mg products and acceptable. In the original application it was demonstrated that the active substance was not light sensitive.

It is accepted that no in-use shelf life is defined for the 2 mg product in line with the authorised 5, 10 and 20 mg strengths based on the similar formulation and packaging system.

Additionally, it has been sufficiently demonstrated that the 2 mg bulk product can be stored in the bulk packaging up to 6 months at room temperature.

3.2.5. Post-approval change management protocols

Not applicable

3.2.6. Adventitious agents

Lactose monohydrate and the capsule shells (gelatine) are the only materials of animal origin. Magnesium stearate is of vegetable origin.

Lactose monohydrate is manufactured in compliance with the CPMP NfG on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products. Certification from the supplier regarding the control of lactose monohydrate, including a BSE/TSE statement is provided.

The gelatine capsules can be prepared from blends of several pharmaceutical gelatines. When bovine gelatine is used it is alkali processed, pharmaceutical grade, and is in full compliance with all pharmaceutical regulatory statutes. Any bovine gelatine used is derived from healthy animals slaughtered in a slaughterhouse that has been inspected by a veterinarian and deemed fit for animals for human consumption. Certification from the supplier regarding the control of gelatine in the capsule shells, including a BSE/TSE statement is provided.

3.3. Discussion and conclusions on chemical, pharmaceutical and biological aspects

This application concerns a line-extension for the addition of a new strength of the same pharmaceutical form i.e. 2 mg hard capsules to the already authorised Lojuxta 5, 10 and 20 mg hard capsules, to support an extension of the indication to include treatment of patients 5 years of age and older.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure a Major Objection was raised concerning the dissolution specification limit, which was resolved by tightening the release specification.

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.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertain to the dissolution limits of the authorised strengths. This point is put forward and agreed as a recommendation for future quality development.

3.4. 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.

3.5. Recommendation for future quality development

In the context of the obligation of Chiesi Farmaceutici S.p.A. to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. - To consider tightening the dissolution release limit of the authorised 5, 10 and 20 mg strengths by submitting a variation.

4. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. The expansion of the treated patient population to include paediatric patients and use of a 2 mg strength capsule does not increase the environmental risk, as PECsurfacewater calculations for phase 1 risk assessment have been made assuming the total patient population is treated with lomitapide at a maximum dose of 60 mg per day. The refined Fpen is based on a prevalence of 1:323625 patients, which is 0.0000031. When using the refined Fpen, the PECsurfacewater is calculated as 0.00009 µg/L, which is below the trigger value for phase 2.

4.1.1. Conclusions

No new non-clinical data have been submitted to support the extension of indication, nor are they required. The line extension to expand the indication is approvable from a non-clinical perspective.

5. Clinical aspects

Introduction

5.1.1. GCP aspects

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier (see section 3.3.3.).

5.1.2. Tabular overview of clinical trials

Table 1: Tabular overview of main clinical studies

Protocol, Phase	Population, Primary Inclusion	Study Design	Dose Regimen/ Duration	Number of Subjects Treated/Completed‡:				% M/F Mean Age (yrs)	Primary Efficacy Endpoint
				Lomitapide Alone	Lomitapide + LLT *	Control	Total		
Studies in Subjects with Homozygous Familial Hypercholesterolemia									
APH-19 Phase 3	HoFH Aged 5 to ≤17 years	MD, OL, 6-wk run-in, 24-wk dose escalation, 80-wk long-term treatment; low-fat diet, and standard of care LLT including LA (where applicable)	Multiple oral dose dependent on age (see Table 2)	N/A	20/20 LOM+ROSU 10/9 LOM+ATOR Ca 9/9 LOM+ATOR 34/30 LOM+EZE 4/4 LOM+EVOL 33/32 LOM+EZE+ statin 19/19 LOM+LA	0	43/39	19/24 10.7	Percent change in LDL-C after 24 weeks of treatment
AEGR-733-032, Phase 1	Healthy subjects	open-label, randomised, crossover study	Single dose 20 mg	32/30	N/A	0	32/30	17/15 25.9	Analysis of relative bioavailability

Key: ATOR=atorvastatin, ATOR Ca=atorvastatin calcium, DB=double-blind, EVOL=evolocumab, EZET=ezetimibe, F=female, FENO=fenofibrate, HoFH=homozygous familial hypercholesterolemia, LA=lipoprotein apheresis, LDL-C=low density lipoprotein cholesterol, LLT=lipid-lowering therapy, 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; ROSU=rosuvastatin, wk=week, R=randomized, SIMVA=simvastatin, TG=triglycerides.

5.2. Clinical pharmacology

5.2.1. Methods

The bioanalytical method used in the clinical studies providing pharmacokinetic data in support of this submission (the paediatric study APH-19 and bioequivalence study AEGR-733-032) was the same analytical method used previously in clinical studies earlier in development and provided in the initial MAA.

The APH-19 bioanalytical report indicated that three samples required repeat analysis as the original results were observed to be above the upper limit of quantification. The samples were successfully repeated with dilution. There were 38 samples (10.1% of total) reanalysed to test the reproducibility of the method. It was observed that 100% of the ISR results had a relative % difference within ±20%.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

APH-19 was a Phase 3, multinational, multicentre, open-label, single-arm paediatric clinical trial, designed to evaluate both the efficacy and long-term safety of lomitapide in paediatric subjects with HoFH (homozygous familial hypercholesterolaemia) on stable LLT (lipid lowering therapy) and a low-fat diet, at an age-specific maximum dose. In Study APH-19, the commercially approved 5 mg, 10 mg and 20 mg hard capsules and a new lower strength (2 mg hard capsule) were used. The applicant developed a 2 mg formulation of lomitapide capsule to facilitate initial dosing in younger children (aged 5 to 15 years). In order to combine and compare adult and paediatric data an integrated popPK model was developed (LOM-POP-PK-2024, section 6.2.2.2.1.).

To address possible difficulties in swallowing the capsule in paediatric patients, the applicant also conducted a Phase I, open-label, randomised, crossover study in adults to determine the bioavailability of 20 mg lomitapide in which the capsule has been opened and the contents sprinkled onto applesauce or mashed banana, compared to a single oral capsule dose of 20 mg lomitapide (study AEGR-733-032).

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population Pharmacokinetics

Objective

The popPK model was developed to combine previously obtained adult data with the new paediatric data. Therefore previous models were adjusted. In addition, the PK was compared between different age groups and adults.

Data included in the model

The integrated Pop PK model was developed using data from studies APH-19, BMS-CV145-001, BMS-CV145-002, BMS-CV145-003 and UP1002/AEGR-733-005. APH-19 is a paediatric study which includes data from 43 paediatric patients with HoFH stratified into 3 age groups: 5 to 10 years (N=20), 11 to 15 years (N=17) and 16 to ≤ 17 years (N=6). The starting dose and schedule for dose escalation in study APH-19 is shown below (Table 5). Samples for evaluation of (steady-state) PK and PD were

collected from Week 4 (Visit 5) through Week 24 (Visit 10). Single PK samples were collected at Weeks 4, 12, 16, and 24 and 2 PK samples were collected at least 1 hour apart at Weeks 8 and 20.

Table 2. study APH-19 age-dependent starting dose and dose escalation schedule

Age Group (years)	Lomitapide Dose (mg)					
	D0	Week 4 ±3 days	Week 8 ±3 days	Week 12 ±3 days	Week 16 ±3 days	Maximum
5 to 10	2	2	5	10	20	20 (10, in Child-Pugh A)
11 to 15	2	5	10	20	40	40 (20, in Child-Pugh A)
16 to ≤17	5	10	20	40	60	60 (40, in Child-Pugh A)

Studies BMS-CV145-001 (N=6), BMS-CV145-002 (N=24), BMS-CV145-003 (N=24) and UP1002/AEGR-733-005 (N=28) are previously conducted adult studies including in total 82 subjects receiving 1 to 200 mg doses after IV infusion or oral administration. Sparse and intensively sampled PK data were available.

Methods

A non-linear mixed effect modelling approach was applied by the applicant. The first-order conditional estimation method with interactions (FOCE-I) in NONMEM® (version 7.4.4, ICON Development Solutions, Ellicott City, MD, USA) was used.

A three-compartment model was previously identified as structural model in adult and paediatric only models and was used as a basis for exploring the dataset including both adult and paediatric subjects. The non-linear mixed effect modelling approach was applied to the dataset presented in the integrated (combined adult and paediatric) dataset above to estimate PK parameters (including variability terms). Allometric scaling with standard scaling exponents of 1, 0.75 or 0.25 for volumes, clearances and rate constant respectively were used to scale parameters based on body weight of the patients with the exception of Ka (absorption rate constant) and F (drug bioavailability).

Inter-individual variability (IIV) was included for CL, V, K24, K42, F and Ka. IIV was characterized by an exponential error model. The residual unexplained variability (RUV) was included using a proportional error model. Covariate relationships were assessed using the automated stepwise covariate model building method (SCM) in NONMEM®.

The final model was selected based on the evaluation of objective functions values (OFV) and visual inspection of standard goodness-of-fit plots (i.e. plots included Observed Concentrations (DV) vs. Population Predictions (PRED), Observed Concentrations (DV) vs. Individual Predictions (IPRED), Conditional Weighted Residuals (CWRES) vs. Time, and Conditional Weighted Residuals (CWRES) vs. Population Predictions (PRED)), as well as the physiological plausibility of parameter estimates. Prediction-corrected visual predictive checks (pcVPC) and non-parametric bootstraps were used for final model qualification.

After the final model development N=1000 subjects were simulated for each population (i.e. adult and paediatric age groups) of patients. Adult PKs were simulated as a reference assuming body weight to be normally distributed with a mean of 79.84 kg (13.74 SD), as determined from the source dataset. Each group of virtual paediatric patients were generated from uniformly distributed age assuming same proportion of male and female and body weight extracted from distributions obtained from the Center for Disease Control and Prevention (CDC).

Results

The final integrated PopPK model parameters estimates are depicted in Table 6 below. Dose level was found to be correlated with an increase in the bioavailability in paediatric patients. This effect also impacts the CL/F and V/F parameters in the paediatric population.

Table 3. Parameter estimates final popPK model.

Population Parameters Estimates (Theta θ)		
Parameter	Estimate	RSE (%)
CL (L/h)	35.89	4.6
V (L)	57.37	9.6
K23 (1/h)	7.54	10.3
K32 (1/h)	0.90	10.3
K24 (1/h)	1.00	21.8
K42 (1/h)	0.06	19.8
F1	0.073	7.9
Ka (1/h)	0.12	9.7
DOSE_F	1.97	18.2
BW effect on V	1 (fixed)	
BW effect on CL	0.75 (fixed)	
BW effect on K23, K32, K24 and K42	-0.25 (fixed)	
Between-Subject Variability "Variance" "Omega2" ω2		
Omega1_CL	0.022	41.1
Omega2_V	0.073	46.9
Omega5_K24	0.68	31
Omega6_K42	0.073	118.5
Omega7_F	0.403	29
Omega8_Ka	0.214	44.5
Residual Error Model Parameter "Sigma" "Epsilon" (ε)		
Proportional	0.099	12.1

Abbreviations: CLT, Total clearance; Epsilon, residual error model parameter; F1, Fraction of dose absorbed; K23, Transfer rate constant from the central compartment to the shallow peripheral compartment; K24, Transfer rate constant from the central compartment to the deep peripheral compartment; K32, Transfer rate constant from the shallow peripheral compartment to the central compartment; K42, Transfer rate constant from the deep peripheral compartment to the central compartment; Ka, First-order absorption rate constant; Omega2_CLT, Inter-individual variability on total clearance; RSE, Relative standard error; V2, Volume of distribution of the central compartment.

Observed concentrations were compared with population predicted and individual predicted concentrations Figure 2. Among other model diagnostics, Conditional Weighted Residuals (CWRES) vs. time after dose and v.s. population predicted concentrations were provided by the applicant (Figure 3). The robustness of the model as well as its predictive performance were evaluated by pcVPCs for all data, adult data only and for paediatric data (Figure 4 A, 3B and 3C, respectively).

Figure 1. Observed concentrations v.s. popPK model population- and individual-predicted concentrations

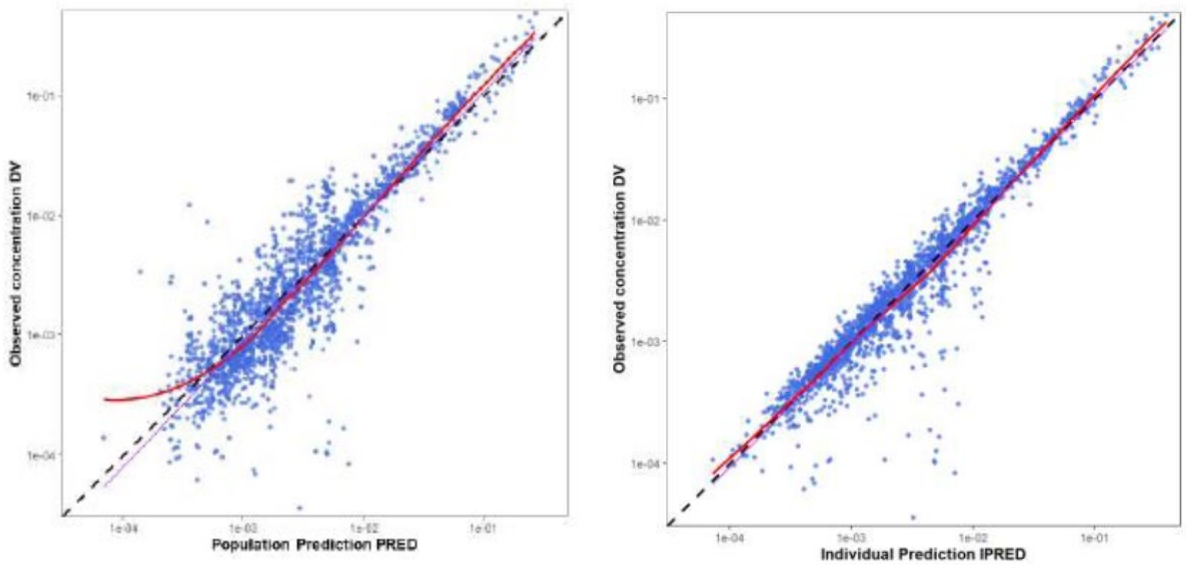


Figure 2. Conditional weighed residuals v.s. time after dose and populations predictions

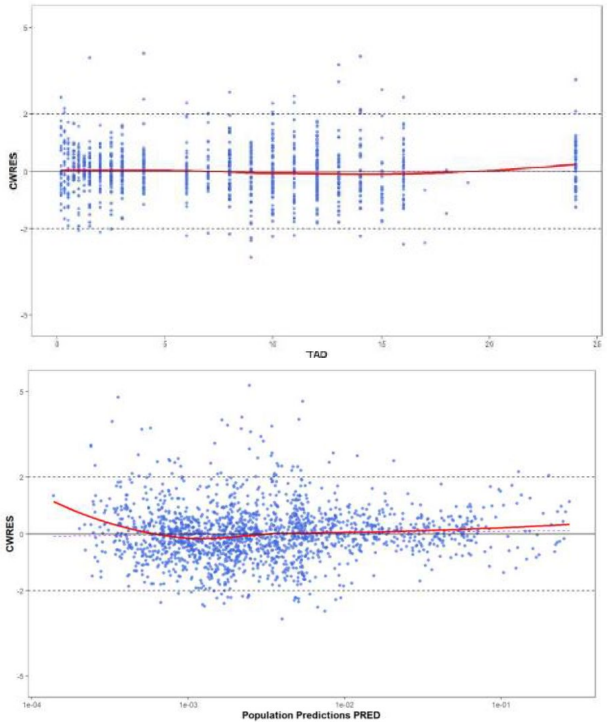
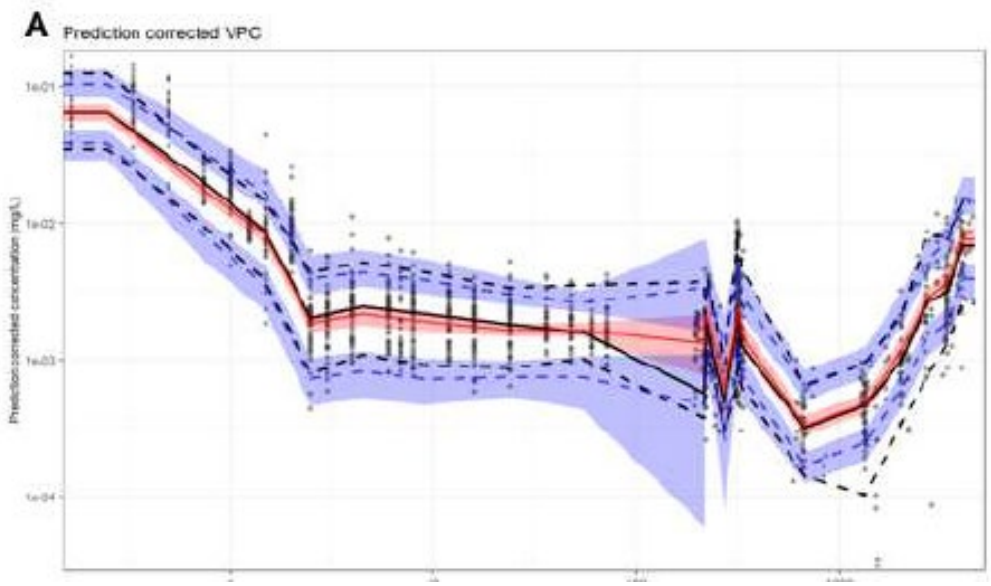
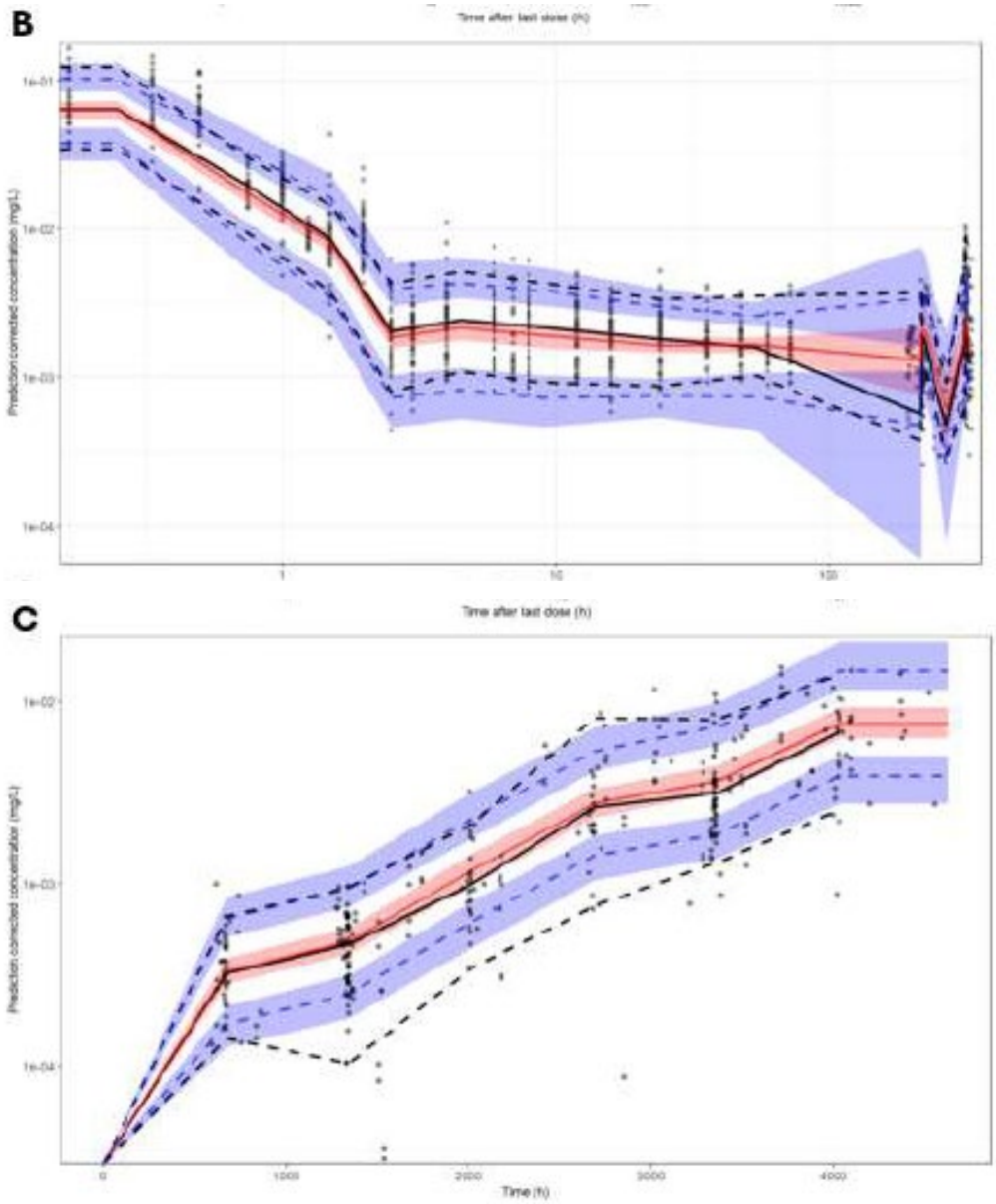


Figure 3. pcVPCs for all data (A), adult-only data (B) and paediatric-only data (C).

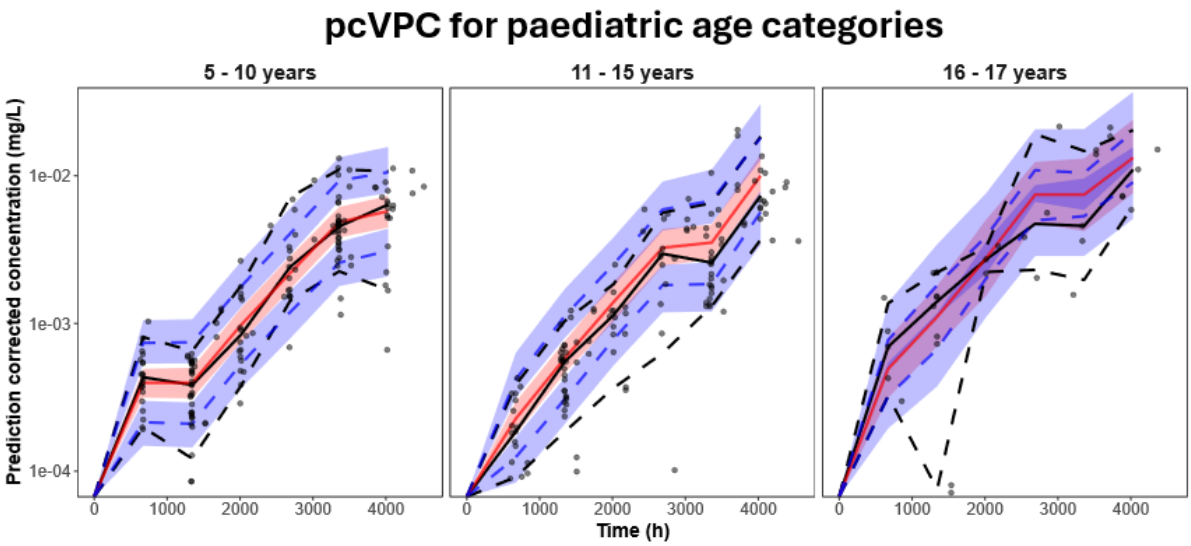




Abbreviations: VPC, visual predictive check. Results are based upon 500 simulated datasets. Red line: model-predicted mean, orange shaded area: 95% confidence interval for the model-predicted mean, blue shaded areas: 95% confidence intervals for the 5th and 95th percentiles.

VPCs per paediatric age group were provided in the second round (Figure 5).

Figure 4. Prediction-corrected Visual Predictive Checks for Paediatric Age Categories



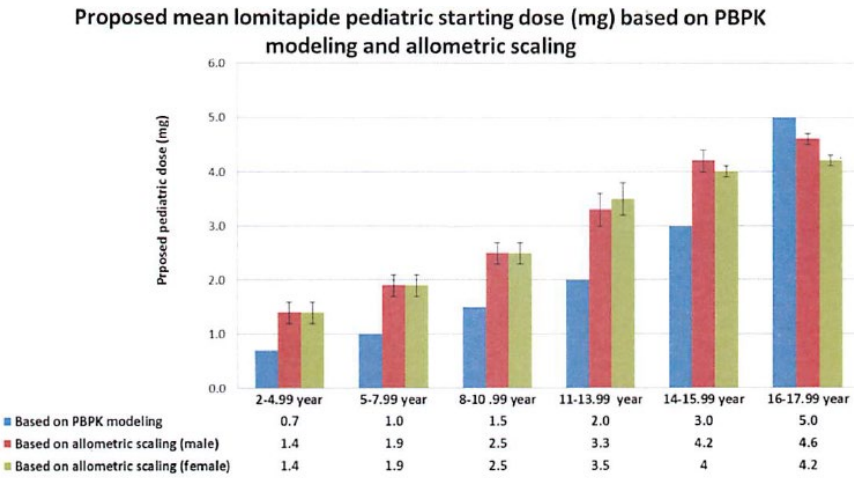
5.2.2.2.2. Physiology based pharmacokinetic model

The starting doses for lomitapide used in study APH-19 were identified by both PBPK modelling and allometric scaling. The applicant has provided a summary of this approach. The PBPK model incorporated age-related maturation in physiological parameters impacting elimination. It was assumed that the fraction absorbed was equal between children and adults. A dose resulting in similar exposure compared to adults was identified. Allometric scaling incorporated a specific function describing enzyme maturation. See equation below:

$$Cl/F = TV_{(Cl/F)} \cdot \frac{PNA^{0.83}}{PNA^{0.83} + 0.31} \cdot \left(\frac{BW}{70}\right)^{0.75}$$

The final selected starting doses for study APH-19 based on both models are depicted below (Figure 5).

Figure 6. Proposed mean lomitapide paediatric starting dose (mg) based on PBPK modelling and allometric scaling.



Subsequent to study APH-19, paediatric exposure data was combined with adult exposure data and analysed using the popPK model described in section 6.2.2.2.1, which was used for confirmation of the selected starting doses.

5.2.2.3. Bioequivalence

A Phase 1, open-label, randomised, crossover study (AEGR-733-032) was performed to determine the bioavailability of a single oral dose 20 mg lomitapide in which the capsule has been opened and the contents sprinkled in applesauce or mashed banana compared to a single oral capsule dose of 20 mg Lomitapide in healthy subjects. The goal of this study was to address possible difficulties in swallowing the capsule in paediatric patients.

Methods

On Day 1 (of each period), following an overnight fast, each subject was administered the contents of a 20 mg capsule of lomitapide sprinkled in applesauce (A) or mashed banana (B), or a single oral intact capsule dose of 20 mg lomitapide (C). Blood samples for PK analyses were collected pre-dose and post-dose at 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 48, 72, 96, 120, 144 and 168 h post-dosing on each dosing day. A washout period of at least 14 days was used. Pharmacokinetic parameters (AUC0-t, AUC0-inf, Cmax, tmax, and t½) were calculated. Analysis of relative bioavailability was performed based on the 'two one-sided test' using the asymptotic 90% confidence intervals (CIs) for the ratios of the geometric means of natural log-transformed PK parameters for the test and reference formulations. The 90% CI for the different comparisons were calculated, using a mixed-effect model with sequence, period and treatment as fixed effects and subject nested within sequence as a random effect.

Results

Thirty-two (32) healthy subjects were planned to enter the study and thirty subjects completed the study. Two subjects were withdrawn due to non-compliance (1x prescription medication taken, 1x non-compliant with contraception restrictions).

The mean (±SD) concentration-time profiles for lomitapide following a single oral dose of 20 mg lomitapide to healthy subjects (PK statistics set) during Treatments A, B, and C are presented in Figure 8. The statistical output including 90% confidence intervals is provided in Table 7.

Figure 6. Mean (±SD) plasma concentration of lomitapide following a single oral dose of 20 mg

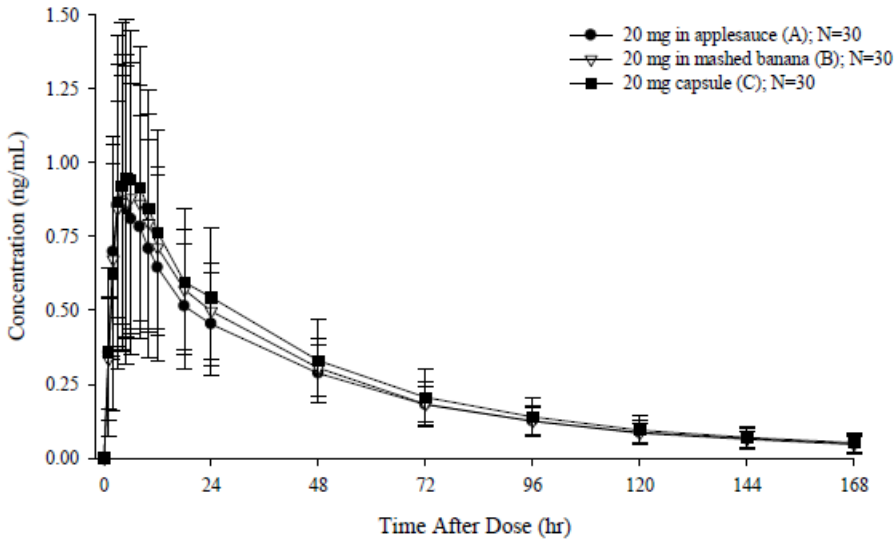


Table 4. Statistical analysis of the lomitapide PK parameters between treatment A and B v.s. treatment C.

Parameter (Unit)	Treatment[a]	N[b]	Geometric LS Means[c]	Ratio of Geometric LS Means to Arm C (%)[d]	90% Confidence Interval for the Ratio(%)[e]	
					Lower	Upper
C_{max} (ng/mL)	A	30	0.880	87.0	77.1	98.2
	B	30	0.947	93.6	83.0	105.6
	C	30	1.01			
AUC_{0-t} (ng·h/mL)	A	30	35.9	88.4	82.4	94.9
	B	30	38.3	94.3	87.9	101.2
	C	30	40.7			
$AUC_{0-\infty}$ (ng·h/mL)	A	30	39.7	89.8	83.9	96.2
	B	30	41.6	94.1	87.9	100.8
	C	30	44.2			

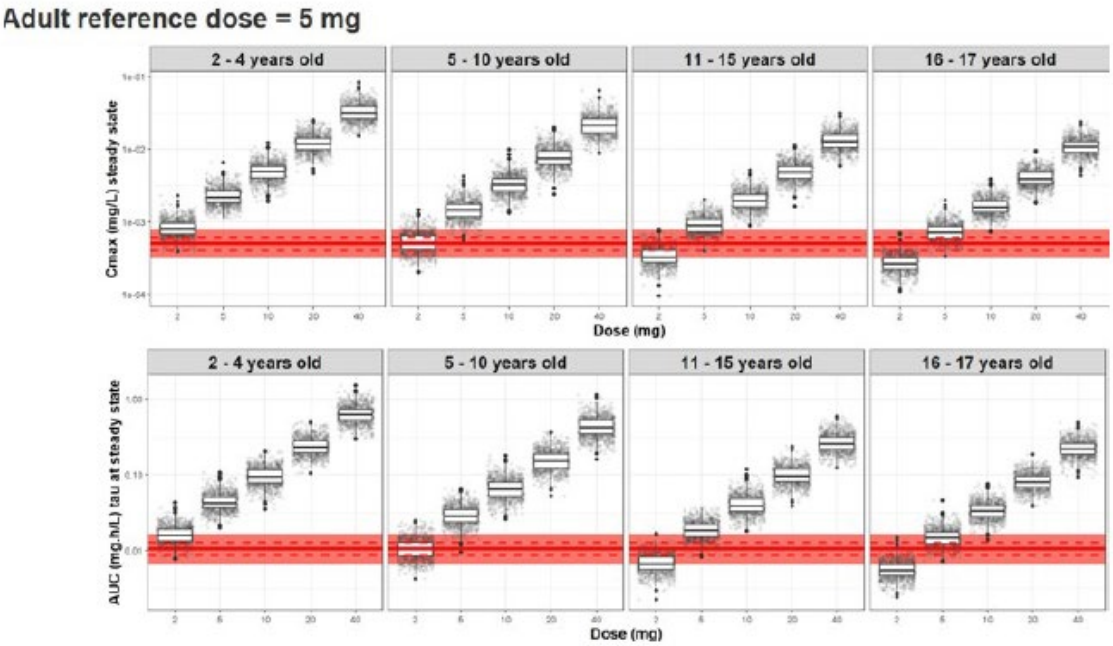
Source: PK report in Appendix 16.2.6.
Mixed Model: ln(PK)= Treat + Period + Sequence + Subject(Sequence) + Error, where Subject(Sequence) was random and other effects were fixed.
Note: Subjects 101 and 114 were excluded from the statistical analysis as they did not complete all three periods.
a A = The contents of a single 20 mg capsule of lomitapide sprinkled in applesauce; B = The contents of a single 20 mg capsule of lomitapide sprinkled in mashed banana; C = One 20 mg intact capsule of lomitapide with 240 mL water.
b Number of Subjects.
c Geometric least squares means from Mixed Model, calculated by transforming the natural log means back to the linear scale.
d Ratio of geometric LS means by back-transforming to the linear scale from the difference calculated on the natural log scale (expressed as a percent).
e 90% confidence interval for ratio of parameter LS means of natural log transformed parameter (expressed as a percent). Natural log transformed confidence limits transformed back to the linear scale.

5.2.2.4. Pharmacokinetics in the target population

Paediatric v.s. adult popPK model simulations

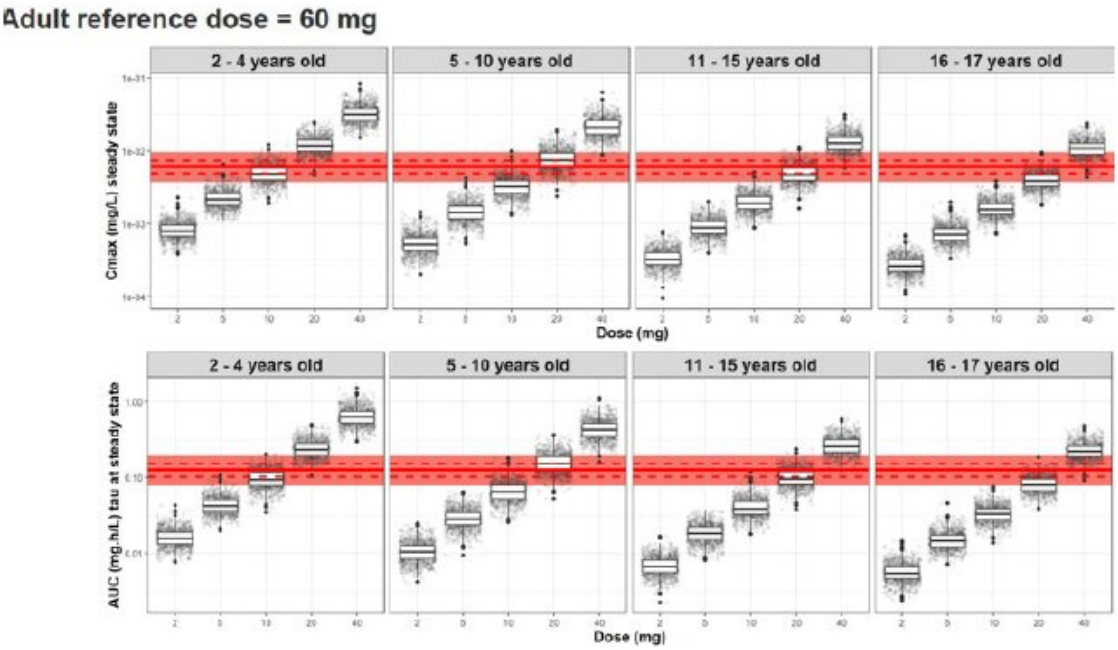
Using the popPK model developed lomitapide exposure in different age groups of patients was simulated and compared with simulations in adults (which was used as a reference). Simulations were provided both to assess exposure between age groups at the starting dose (Figure 8) as well as the maximum dose (Figure 9).

Figure 7. Comparison of adult steady state exposure following administration of the 5 mg starting dose to corresponding paediatric exposures following different doses per age group



Note: the red solid line represents the median value for adults at the reference doses, the dashed line are 25th and 75th percentiles (quartiles) and the ribbon is the 90% prediction interval (95th to 5th percentiles).

Figure 8. Comparison of adult steady state exposure following administration of the 60 mg QD dose to corresponding paediatric exposures following different doses per age group.



Note: the red solid line represents the median value for adults at the reference doses, the dashed line are 25th and 75th percentiles (quartiles) and the ribbon is the 90% prediction interval (95th to 5th percentiles).

5.2.2.5. Special populations

Except for the paediatric population (section 6.2.2.4) no other populations have been studied and assessed in this procedure.

5.2.3. Pharmacodynamics

5.2.3.1. 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.

5.2.3.2. Primary and secondary pharmacology

Not applicable

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

Not applicable

5.2.3.4. Genetic differences in PD response

Not applicable

5.2.3.5. Immunological events

Not applicable

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Objective

The popPK model developed was linked with safety and pharmacodynamic markers (LDL-C, ALT, AST) to evaluate the proposed dosing strategy in the different age groups of paediatric patients.

Data included in the model

Paediatric LDL-C, ALT and AST data from study APH-19 was used. See section 6.2.1.

Methods

Efficacy of lomitapide was explored by linking the plasma concentrations with the LDL-C data. The PK/PD model was described by the following equation:

$$Effect = R0 * (1 - Imax * Cp / (IC50 + Cp))$$

where R0 is the baseline value for LDL-C, Cp is the lomitapide concentration in the central compartment, Imax is the maximum effect of LDL-C inhibition, and IC50 is the concentration needed to achieve 50% of the maximum effect.

Furthermore, lomitapide exposures, expressed as $AUC_{0\text{-}24h}$ at steady state, were simulated for each patient and each visit completed by the subjects to evaluate the link between lomitapide exposure and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values, expressed as upper limit of normal (ULN), using a loglinear regression model:

$$log(ST) = log(BASELINE) + SLOPE * PK$$

where ST is the endpoint of interest, BASELINE is its baseline value, and SLOPE defines the trend of the safety endpoints with $AUC_{0\text{-}24h}$.

Results

Final model parameter estimates for the PK/PD Imax model were reported in Table 8. The baseline LDL-C and IC50 values were estimated and IIV parameters were included for both baseline LDL-C and IC50 parameters. Age was found to be related to LDL-C baseline values. A proportional error model was used to describe the residual error in the PK/PD model.

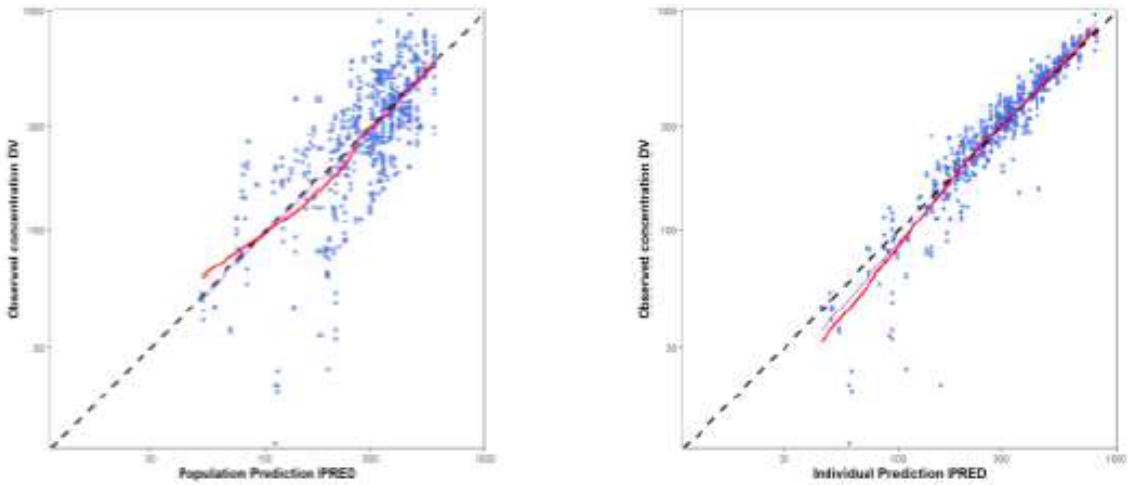
Table 5. lomitapide population PK/PD model parameter estimates

Population Parameters Estimates (Theta θ)		
Parameter	Estimate	RSE (%)
Imax	1.0 (FIX)	-
Baseline (mg/dL)	386.116	1.0
IC_{50} (mg/L)	0.0042	2.1
AGE_Baseline	-0.5192	24.6
Between-Subject Variability "Variance" "Omega2" ω2		
Omega1_Imax	0.0 (FIX)	-
Omega2_ IC_{50} (mg/L)	0.442	19.3
Omega3_Baseline (mg/dL)	0.127	16.8
Residual Error Model Parameter "Sigma" "Epsilon" (ε)		
Proportional_PD	0.0394	17.2
Proportional_PK	0.118	11.8

Abbreviations: PD, pharmacodynamics; DV, dependent variable; RSE, relative standard error. The data are shown as log values for all parameters.

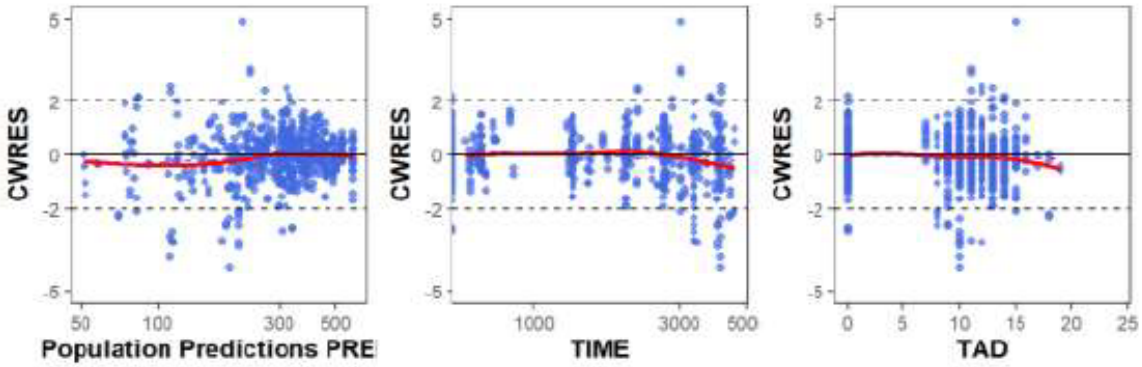
Observed concentrations were compared with predicted concentrations on both a population and individual level (Figure 10). Conditional Weighted Residuals (CWRES) v.s. population predictions, v.s. time and v.s. time after dose is shown in Figure 10.

Figure 9. Observed effect v.s. population- and individua-predictions



Abbreviations: PRED, Population predictions; IPRED, Individual predictions. The dashed line represents the line of unity, the red line represents the smoothening line, the purple line represents the linear regression line and blue dots represent observations.

Figure 10. Conditional weighed residuals v.s. population predictions, time and time after dose



Abbreviations: CWRES, Conditional weighed residuals; PRED, predictions; TAD, time after dose. The black horizontal line represents the zero line, the red line represents the smoothening line, the purple line represents the linear regression line and blue dots represent observations.

The following mathematical relationships were derived from the observed data linking lomitapide plasma concentration (conc) expressed in Ug/mL and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) hepatic markers (normalized by the upper limit of normal [ULN] values):

log(AST) = log(BaselineAST) + SlopeAST * conc

where BaselineAST is the AST baseline value and SlopeAST defines the trend of the safety endpoint with the lomitapide concentration;

log(ALT) = log(BaselineALT) + SlopeALT * conc

where BaselineALT is the ALT baseline value and SlopeALT defines the trend of the ALT endpoint with the lomitapide concentration.

Table 9 collects the estimated regression parameters for the AST log linear regression model.

Table 6 Final PK/PD Log Linear Model Parameter Estimates for AST Elevations

Parameter	Units	Estimate	RSE	95% Confidence Intervale
$Baseline_{AST}$	ULN	0.66	2.8%	[0.62; 0.69]
$Slope_{AST}$	$(\mu g/mL)^{-1}$	27.1	21.5%	[15.6; 38.6]

Abbreviations: AST=Aspartate aminotransferase; RSE=Relative Standard Error=100*Standard Error/Estimate; ULN=Upper limit of normal

Table 10 collects the estimated regression parameters for the ALT log linear regression model.

Table 7 Final PK/PD Log Linear Model Parameter Estimates for ALT Elevations

Parameter	Units	Estimate	RSE	95% Confidence Intervale
$Baseline_{ALT}$	ULN	0.51	3.7%	[0.47; 0.55]
$Slope_{ALT}$	$(\mu g/mL)^{-1}$	36.8	21.0%	[21.6; 52.1]

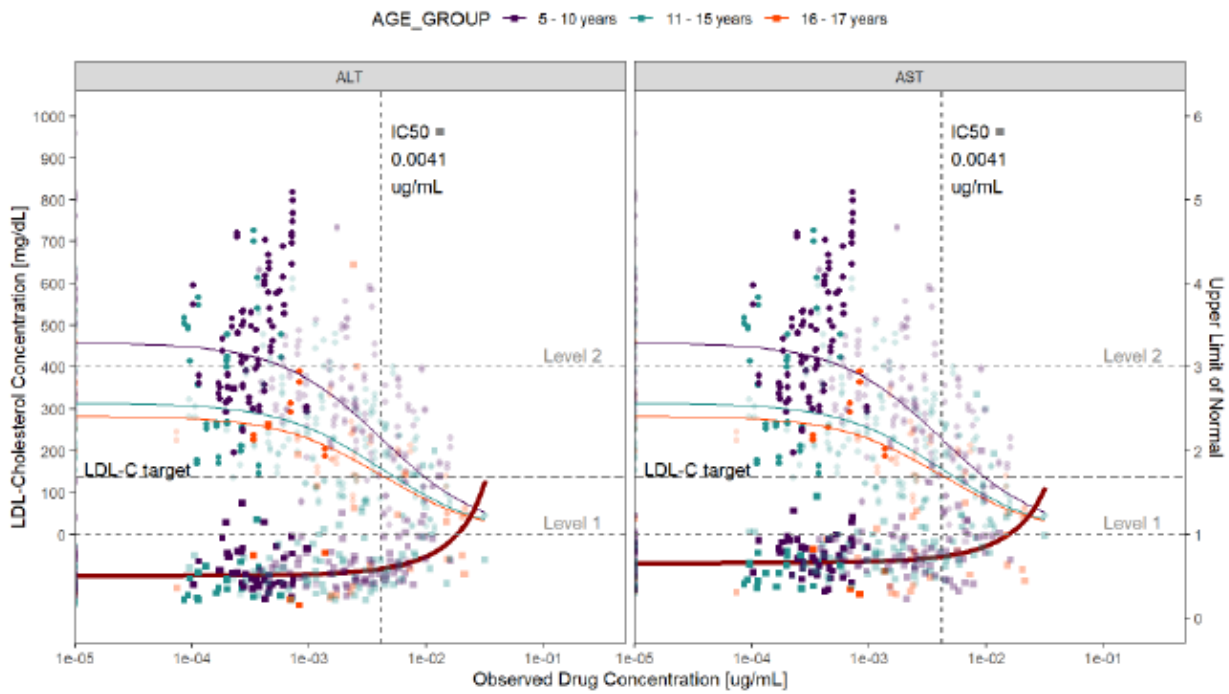
Abbreviations: ALT=Alanine aminotransferase; RSE=Relative Standard Error=100*Standard Error/Estimate; ULN=Upper limit of normal

5.2.5. Dose selection and therapeutic window

PopPK/PD model simulations

Results of the exposure-response model simulations on lomitapide concentration v.s. LDL-C and lomitapide concentration v.s. ALT/AST for the different age groups are combined in Figure 12. In addition, PK/PD plots describing the relationship between lomitapide concentration and LDL-C are also depicted in Figure 13 for three different age groups (i.e. 5-10, 11-15 and 16-17 years). In the bottom part of the figure the percentage of subjects exceeding the model based IC50 value for LDL-C reduction has been described per dosing group.

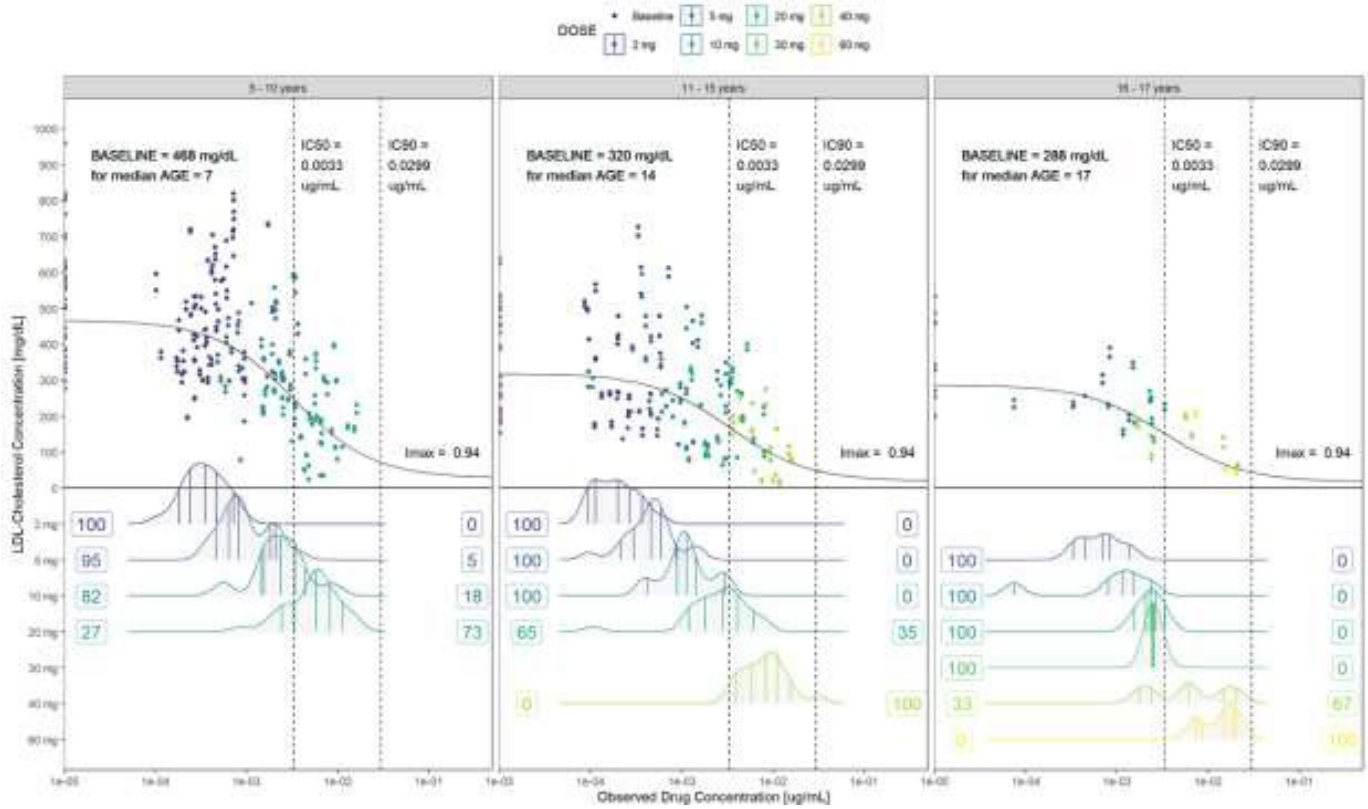
Figure 11. PK/PD plot including lomitapide concentration v.s. LDL-C and lomitapide concentration v.s. ALT/AST data



Key:
Age group stratification by colour;
Rounded spots: PK/PD (LDL-C) relationships;
Squared spots: PK/safety relationship respectively;

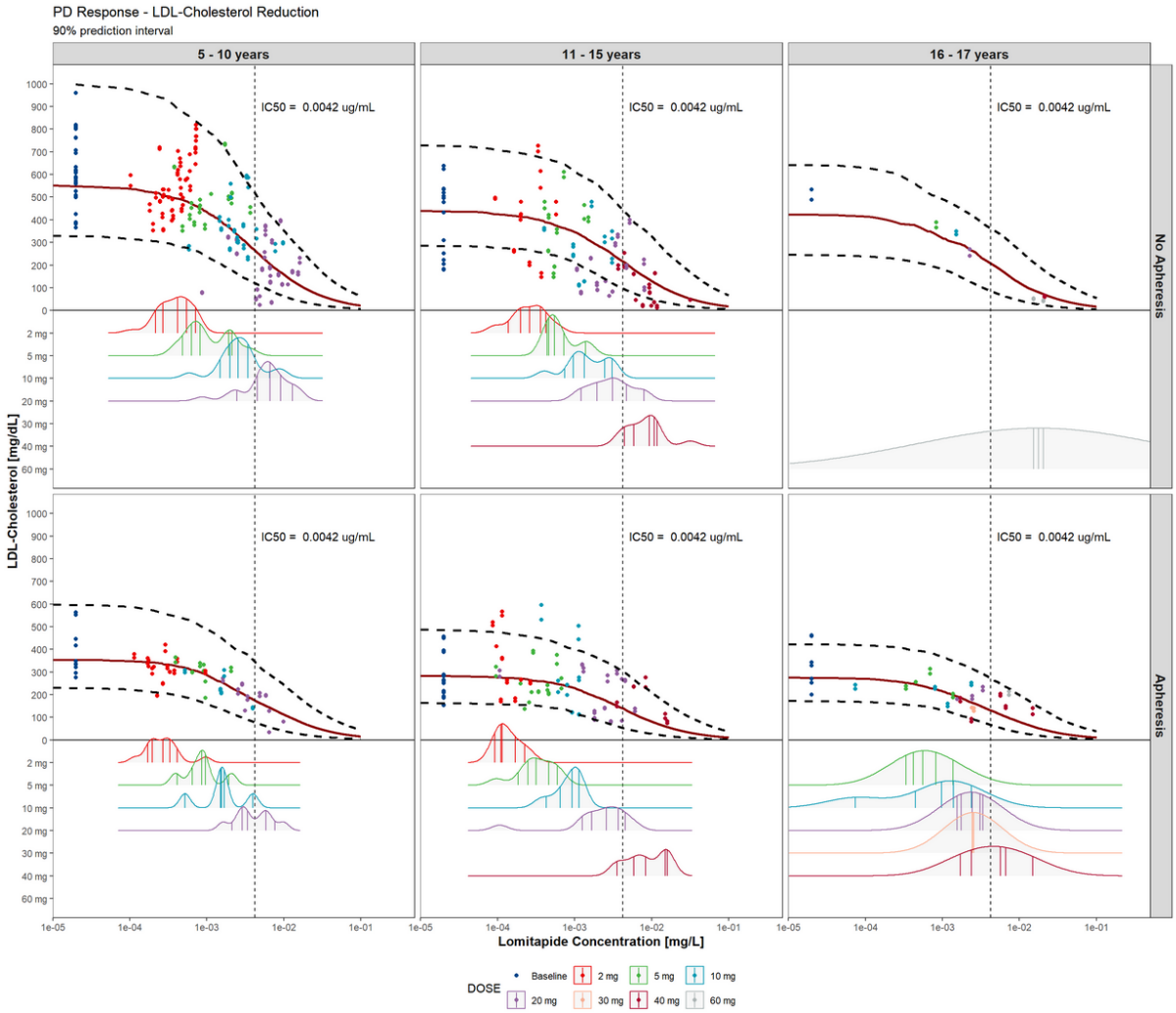
Concentrations following starting doses are highlighted using darker colours;
Dotted vertical line as references for IC_{50}=0.0041 ug/mL
Horizontal lines are a reference for AST and ALT normal range (≤1 x ULN) vs Hepatotoxicity Level 1 (>1 and <3 x ULN) vs Hepatotoxicity Level 2 or higher (≥3 x ULN) and LDL-C target value of <135 mg/dL

Figure 12. LDL-C values vs exposure as separated by paediatric age group and dose



Figures for the popPK/PD model including the covariate apheresis and inter-individual variability were provided in the second round (Figure 14).

Figure 13. Observed and predicted Exposure-response profiles stratified by age group and apheresis (typical profiles were represented, continuous red lines, with 90% prediction interval comprised between the dotted profiles).



5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Bioequivalence

The study design of the single dose bioavailability study in healthy volunteers is considered adequate to study exposure for opened capsules with content sprinkled on mashed banana or apple sauce versus an intact capsule. The reason for withdrawal of subjects was sufficiently described and the sampling scheme was sufficient for description of Cmax, and AUC parameters. Although formally the Cmax ratio 90% confidence interval for capsule content sprinkled in apple sauce v.s. the intact capsule was not maintained within the standard bioequivalence limits 80-125% (i.e. 77.1-98.2%), this is not expected to be an issue due to the fact that the lower limit only falls marginally short of the 80% limit, and the product will be titrated to an effective dose in clinical practice. Comparisons for all other parameters were within the 80-125% BE margin. It is therefore agreed that the capsule formulation with the option of sprinkling the contents onto apple sauce or mashed banana is appropriate for paediatric use and SmPC adjustments are accepted. The bioanalytical report of study AEGR-733-032 was provided.

Although no evaluation of QCs and ISR have been conducted in the context of study 8294376, this issue is not further pursued due to the use of a validated bioanalytical method. Of note, 3 subjects in study APH-19 reported being unable to swallow the capsule at some timepoints. In such cases the capsule was opened and sprinkled on mashed banana.

Defining starting dose (APH-19) in children

Allometric scaling and PBPK modelling was used in order to obtain a starting dose in children for study APH-19 based on exposure matching. It is considered reassuring that both independent methods resulted in reasonably similar predicted starting doses. This approach is therefore considered acceptable. Further confirmation of these doses will be based on popPK modelling (see below).

PopPK(PD) model development

The available paediatric PK data available was sparse (1/2 samples per study visit per individual), however approximately equally divided over the age groups for which dosing recommendations will be made. In addition, samples were available at different doses. The popPK model (LOM-POP-PK-2024) development is generally considered acceptable. The applicant indicated that the model structure was based on the three-compartment structure which was previously identified in adult only and paediatric only models. In the current adult and paediatric integrated model parameters were reassessed, and the covariates analysis was re-run based on the pooled dataset. Age turned out to be an significant covariate on bioavailability. Fixed scaling exponents of 1, 0.75 or 0.25 for volumes, clearances and rate constant are used, which are accepted based on allometric theory in children above 5 years of age. Population parameters were estimated with sufficient precision (RSD<21.8%). In addition, goodness-of-fit plots indicated acceptable model performance. PcVPCs also generally indicated acceptable model performance, although the 5th percentile of the 95% CI for paediatric subjects appears slightly overpredicted. For additional model evaluation, shrinkage values were provided for the adult model and after inclusion of paediatric data in the second round of assessment. These were considered acceptable. In addition, the applicant provided pcVPCs stratified by the different paediatric and adult age-categories (5-10 years, 10-15 years, 16-17 years, adults) to confirm acceptable model performance in the different age groups.

The PD LDL-C model was sufficiently described. The applicant indicated what covariates were tested in the PD part of the model and included apheresis as a covariate, which affected baseline LDL-C concentrations. PD model population parameters were estimated with sufficient precision (RSD<24.6%) and goodness-of-fit plots indicated acceptable model performance. The model indicated that age was (negatively) related to baseline LDL-C. The explanation by the applicant that older patients tend to have more aggressive concomitant lipid-lowering therapy and thus this age to baseline LDL-C relationship was expected is considered plausible. An alternative hypothesis/contributing factor could be that more severe cases would be diagnosed earlier.

Evaluation of the loglinear regression model was provided in the second round of assessment. The applicant provided model estimates and model evaluation for the link between lomitapide exposure and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values, using the loglinear regression model. This was considered acceptable.

Exposure analysis and exposure-response analysis

When comparing the exposures associated with paediatric specific starting doses (different between age categories, see table 10) with exposure in adults (i.e. following the adult starting dose of 5 mg), it is agreed that exposure is largely similar for all age groups for the formulations currently available. In addition, it is acknowledged that exposure was below the IC50 for all children included in study APH-19

and therefore pronounced PD effects are not expected at this dose. AST and ALT levels were largely below ULN 2 at the proposed starting doses.

Exposures associated with the proposed maximum doses (SmPC) in children are slightly higher when compared to exposure in adults (associated with adult maximum dose of 60 mg). At the age-dependent maximum dose more than 2/3 of the paediatric subjects exceeded the estimated IC50 (and therefore had >50% LDL-C reduction) in each age group. Lomitapide appears to show an exposure-dependent increase in ALT and AST. However, only one patient was reported experiencing hepatotoxicity Level >1 on the recommended maximum dose during the efficacy phase of study APH-19, which was used in PK/PD model development. More hepatotoxicity level > 1 findings are observed during the safety phase which were not studied in the model (see clinical safety section below) and might be time-dependent. In order to further evaluate variability in efficacy and safety responses, the applicant provided exposure-response simulations including the between-subject variability in PK and PD parameters. It is agreed with the applicant that the therapeutic window could be dependent on baseline LDL-C value, concomitant therapy, and target LDL-C concentration. Therefore, in this case, titration of the dose seems to be a sensible approach in order to achieve an optimum between efficacy and safety.

5.2.6.2. Conclusions

Although only sparse PK/PD data have been obtained in children, the pharmacokinetics and pharmacodynamics of lomitapide are considered sufficiently estimated using a popPK/PD model.

5.3. Clinical efficacy

5.3.1. Dose response study(ies)

Starting doses of lomitapide for paediatrics aged 5-17 years in study APH-19 were previously extrapolated from the approved 5 mg starting dose in adults using two commonly employed model-based scaling approaches (PBPK modelling and allometric scaling). Please refer to section 6.2.5.

5.3.2. Main study(ies)

5.3.2.1. APH-19

5.3.2.1.1. APH-19

Phase III, Single-arm, Open-label, International, Multi-centre Study to Evaluate the Efficacy and Safety of Lomitapide in Paediatric Patients with Homozygous Familial Hypercholesterolaemia (HoFH) on Stable Lipid-lowering Therapy.

Study design

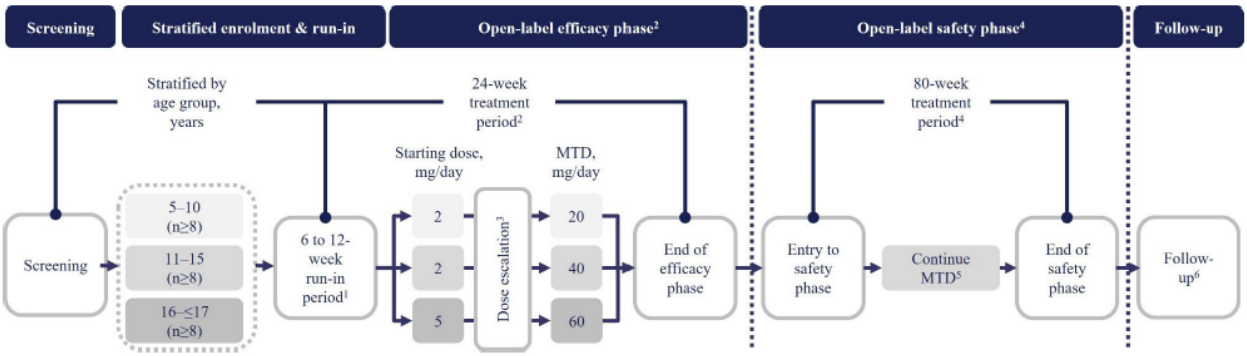
APH-19 was a Phase 3, single-arm, open-label clinical study designed to evaluate the efficacy and long-term safety of lomitapide in paediatric subjects with homozygous familial hypercholesterolaemia (HoFH) at an maximum tolerated dose (MTD) as applicable to the age groups based on safety and

tolerability in addition to LDL-C goals. Subjects were receiving stable lipid-lowering therapy (LLT) (with or without lipoprotein apheresis (LA)).

The single-arm, non-comparator design of APH-19 was approved by the PDCO (PIP Decision P/0374/2024).

The study consisted of 5 periods as summarised in the Figure below.

Figure 14: Design of Study



AE = adverse event; ALA = alpha-linoleic acid; DHA = docosahexaenoic acid; EFA = essential fatty acid; EPA = eicosapentaenoic acid; LA = lipoprotein apheresis; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; MTD = maximum tolerated dose

1. Stabilised current LLT (including LA, when applicable), established diet <20% energy from fat or <30 g fat, whichever was the lesser amount, dietary supplementation from Week -2 (daily 200 IU [5 to 8 years of age] 400 IU [≥9 years of age] vitamin E and EFA supplement [approx. 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA]).
2. During the 24-week Efficacy Phase, subjects were required to remain on the stable LLT regimen (including LA, when applicable) established during the 6-week Run-in Period.
3. Based on safety, tolerability, and efficacy parameters.
4. Adjustments to background LLT (including LA, when applicable) were allowed at the discretion of the Investigator.
5. Dose adjustment rules applied.
6. Eligible subjects who completed the study per protocol at Week 104 and were <18 years of age could choose to enter the Early Access Programme. Subjects ≥18 years of age could opt to transition to commercial product under the approved product label for adults. For both these subject groups, a follow-up phone call was conducted at Week 108±1 week to monitor safety including AE and concomitant medication reporting. Subjects who opted not to participate in or were unsuitable for the Early Access Programme, or subjects ≥18 years of age who opted not to transition to commercial product discontinued lomitapide treatment at Week 104±1 week and entered a 4-week Follow-up Period during which they remained on concomitant LLT (including LA, when applicable). These subjects were to attend in person for a Week 108±1 week visit.

Liver function tests (ALT, AST, GGT, AP, total bilirubin, (in)direct bilirubin) and metabolic panel were to be performed each 4 weeks up to Week 56, followed by each 12 weeks up to week 104.

5.3.2.1.1.1. Treatment

Lomitapide capsules were administered orally once daily to all subjects who met study entry criteria. Lomitapide capsules were provided in 4 dose strengths of 2 mg, 5 mg, 10 mg, and 20 mg in high-density polyethylene bottles.

After stabilization of each subject on his/her current MTD of LLT (including LA, if applicable) during the 6-week Run-in Period, treatment with lomitapide was started as add-on therapy on Day 0 of the Efficacy Phase.

The dose was initiated at the recommended starting dose for the subject's age and escalated to the maximum dose applicable to their age as shown in the Table below based upon safety and tolerability in addition to LDL-C values.

Table 8: Lomitapide Starting Dose and Dose Escalation by Age Group

	Lomitapide Dose (mg)					
Age Group	**Day 0 [a]**	**Week 4 ±3 days**	**Week 8 ±3 days**	**Week 12 ±3 days**	**Week 16 ±3 days**	**Maximum**
5 to 10 years	2	2	5	10	20	20 (10 in Child Pugh A)
11 to 15 years	2	5	10	20	40	40 (20 in Child Pugh A)
16 to ≤17 years	5	10	20	40	60	60 (40 in Child Pugh A)

[a] Start of treatment (Day 1 of dosing/Study Day 1) was designated as Day 0 in the study protocol.

Dose escalation

Subjects were categorised according to disease severity as determined by the presence or absence of clinically evident CVD, which was defined by documented aortic valve disease or coronary atherosclerosis at Baseline.

Lomitapide was not to be escalated, if LDL-C was less than the target threshold:

- LDL-C was <100 mg/dL (<2.5 mmol/L) in subjects without CVD at Baseline
- LDL-C was <70 mg/dL (<1.8 mmol/L) in subjects with CVD at Baseline

Each subject was to continue to receive their MTD of lomitapide achieved during the Efficacy Phase (unless criteria were met for reducing or increasing the dose) for an additional 80±1 weeks in the Safety Phase (for a total treatment period of 2 years).

If after Week 24±3 days both the Investigator and the Sponsor considered a subject 5 to 15 years of age to be eligible for further escalation of the lomitapide dose beyond the maximum recommended dose by the respective age group, the lomitapide dose could be increased to an extent defined by the Investigator after consultation with the Sponsor based on individual safety, efficacy, and concomitant LLT criteria. If the subject tolerated this new dose for ≥4 weeks, then this was to be considered their new MTD.

If after Week 24±3 days, a subject crossed over into the next age category, the dose of lomitapide could have been escalated to the maximum dose applicable for the new age category. If the subject tolerated this new dose for ≥4 weeks, then this was to be considered their new MTD.

Dose Modification, Interruption or Discontinuation for Adverse Events

The Investigator and/or DSMB could reduce study medication dosage or discontinue study medication in a subject if situations developed that, in the opinion of the Investigator or DSMB, compromised the subject's safety or successful participation in the study. In particular, modifications in dosage or discontinuation of treatment were to be instituted if any of the following situations applied:

Dose Modification Based on Hepatobiliary Adverse Events

If a subject matched the criteria referred to as "Hy's law case" or showed comparable signs of liver toxicity, irrespective of origin, treatment had to be permanently discontinued and no re-challenge was allowed.

Upon the Investigator's discretion study medication was to be discontinued permanently if a subject experienced any CTCAE Grade 3 or Grade 4 hepatobiliary AE, regardless of relationship to study drug.

Biochemical Hepatobiliary Guidelines

If aminotransferase elevations were accompanied by clinical symptoms of liver injury (such as nausea, vomiting, abdominal pain, fever, jaundice, lethargy, flu-like symptoms), increases in bilirubin ≥2 × ULN, study drug was to be discontinued, the event was to be reported to the DSMB by the sponsor (or its designee) immediately upon notification and the subject referred to a hepatologist for further work up.

Dose modifications were required based on hepatotoxicity levels: .

- Subjects who experienced confirmed Level 4 Hepatotoxicity were to immediately interrupt study medication. Subjects were to return to the study site weekly or sooner if clinically indicated until resolution. Following evaluation by a hepatologist, a subject was allowed to resume lomitapide treatment if the Level 4 Hepatotoxicity was resolved, and in the opinion of the Investigator, DSMB and sponsor, the benefit of treatment justified any risk of recurrent toxicity.
- Subjects who experienced confirmed Level 3 Hepatotoxicity were to immediately interrupt study medication. Subjects were to return to the clinic for repeat blood tests including alkaline phosphatase, bilirubin and International Normalised Ratio every 7 days until the aminotransferase levels had fallen <3 × ULN. Once this occurred, study drug dosing could have been resumed at the dose level below that associated with Level 3 Hepatotoxicity. If this dose level was tolerated without elevation of ALT or AST >3 × ULN, then this dose was defined as the MTD. If aminotransferases increased to ≥3 × ULN, further dose reduction or interruption may have been necessary consistent with the guidance provided in the protocol. Elevations in ALT or AST >3 × ULN that persisted despite dose reduction or interruption for ≥4 weeks were to be reported to the DSMB by the sponsor (or its designee) immediately upon notification. Subjects were to be referred to a hepatologist for further work up.
- Subjects who experienced confirmed Level 2 Hepatotoxicity were to have the dose of study medication reduced to the previous tolerated dose. Subjects were to return to the clinic for repeat blood tests including alkaline phosphatase, bilirubin and International Normalised Ratio every 7 days until the aminotransferase levels had fallen to <3 × ULN. Once this occurred, lomitapide dosing could have been resumed at the dose level below that associated with Level 2 Hepatotoxicity. If this dose level was tolerated without elevation of ALT or AST >3 × ULN, then this dose was defined as the MTD. If aminotransferases increased to >3 × ULN, further dose reduction or interruption may have been necessary consistent with the guidance provided in the protocol. Elevations in ALT or AST >3 × ULN that persisted despite dose interruption for ≥4 weeks were to be reported to the DSMB by the sponsor (or its designee) immediately upon notification. Subjects were to be referred to a hepatologist for further work up.
- No dose modification was required for subjects who experienced Level 1 Hepatotoxicity (ALT or AST 1.1 to 2.9 × ULN).

Considerations for Liver Biopsy and Histopathological Guidelines

A percutaneous liver biopsy was to be considered for persistent Level 2 Hepatotoxicity defined as AST or ALT ≥3 × ULN for ≥6 months but could also be performed at the discretion of the Investigator.

If a subject underwent a liver biopsy and the specimen showed the following features, the subject was to be discontinued from the study and followed by a hepatologist:

- Type 3 non-alcoholic steatohepatitis (NASH) characterised by fat accumulation and ballooning degeneration, or

- Type 4 NASH characterised by fat accumulation, ballooning degeneration, and either Mallory's hyaline or fibrosis.

Subjects with fatty liver alone (Type 1 NASH) or fat accumulation and lobular inflammation but without ballooning degeneration and/or Mallory's hyaline or fibrosis (Type 2 NASH) could continue on study medication, and discontinuation was to be dictated by biochemical criteria.

5.3.2.1.1.2. Randomisation

Not applicable. This was an open-label study; all subjects received lomitapide.

5.3.2.1.1.3. Blinding

Not applicable. This was an open-label study; all subjects received lomitapide.

5.3.2.1.1.4. Patient population

Inclusion Criteria

A subject was eligible for study participation only if all of the following criteria applied:

1. Male and female subjects aged 5 to ≤17 years with HoFH as defined by any of the following criteria recommended by the Consensus Panel on Familial Hypercholesterolaemia of the EAS (Cuchel, 2014, Eur Heart J):
    a. Genetic confirmation of 2 mutant alleles at the LDLR, apo B, PCSK9, or LDLR adapter protein 1 (LDLRAP1) gene locus or
    b. An untreated LDL-C >500 mg/dL (13 mmol/L) or treated LDL-C ≥300 mg/dL (8 mmol/L) together with either
        i. Cutaneous or tendon xanthoma before age 10 years or
        ii. Untreated LDL-C levels consistent with heterozygous familial hypercholesterolaemia in both parents
2. Baseline LDL-C on LLT (Cmax of LDL-C immediately prior to LA, if applicable) of either:
    a. >160 mg/dL (4.1 mmol/L, no documented CVD) or
    b. >130 mg/dL (3.4 mmol/L, established CVD defined as aortic valve disease and/or coronary atherosclerosis)
3. Body weight ≥15 kg or BMI and height both >10th percentile according to WHO Growth Charts for Boys and Girls 5 to 19 Years of Age.
4. Postmenarchal female adolescents had to be willing to use highly effective methods of birth control that, alone or in combination, resulted in a low failure rate (i.e., <1% per year) when used consistently and correctly (e.g., implant, injectable, combined oral contraceptive, intrauterine contraceptive device, sexual abstinence, vasectomy or vasectomised partner) during participation in the study (and at least 4 weeks thereafter).

Exclusion Criteria

A subject was not eligible to participate in this study, if any of the following criteria applied:

1. Other forms of primary hyperlipoproteinaemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism).
2. Contraindications for the use of lomitapide Moderate (Child-Pugh B) or severe hepatic impairment (Child-Pugh C), active liver disease and/or abnormal liver function tests (LFTs) at Screening (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] >1.5 × upper limit of normal [ULN] and/or total bilirubin >1.5 × ULN in the absence of Gilbert's syndrome or alkaline phosphatase >1.5 × ULN [based on appropriate age and sex normal values]).
3. Serum creatine kinase (CK) >2 × ULN.
4. Chronic renal insufficiency with glomerular filtration rate <70 mL/min/1.73 m2 calculated using the Schwartz formula .
5. Uncontrolled hypertension despite medical therapy.
6. New York Heart Association Class III or IV congestive heart failure.
7. Precocious/delayed puberty or endocrine disorder affecting growth (e.g., hypothyroidism, premature adrenarche).
8. History of drug abuse within the last 3 years or habitual alcohol consumption (defined as >1 ounce [28 g] of liquor or 4-ounce glass [113 g] of wine, or the equivalent, ≥3 times per week).
9. Life expectancy predicted to be <5 years.
10. History of a non-skin malignancy (with the exception of cervical cancer in situ) within 3 years prior to enrolment.
11. Pregnant or nursing women.

5.3.2.1.2. Objectives and estimands

5.3.2.1.2.1. Primary objective

To evaluate the efficacy of lomitapide as defined by the percent change in LDL-C at the maximum tolerated dose (MTD) at Week 24±3 days compared to Baseline when added to stable LLT (including LA when applicable) in paediatric subjects (5 to ≤17 years of age1) with HoFH.

5.3.2.1.2.2. Estimands for the primary objective

Table 9: Estimands for primary objective

Population	Paediatric patients (5 to ≤17 years of age) with homozygous familial hypercholesterolaemia (HoFH)
Treatment condition	Initiation of oral lomitapide escalated to the maximum tolerated dose (MTD) for the age group (5-10, 11-15 and 16-≤17) added to stable lipid-lowering therapy (LLT) and including lipoprotein apheresis (LA) when applicable, regardless of dose adjustments, drug discontinuations, use of alternative treatments and changes in background LLT.
Endpoint (variable)	Percentage change from baseline in LDL-C at week 24±3 days
Population-level summary	Mean percentage change from baseline in LDL-C at week 24±3 days

Intercurrent events and strategy to handle them	
Dose adjustments	Treatment policy
Drug discontinuations	Treatment policy
Use of alternative treatments/change in background LLT	Treatment policy

The primary objective was to evaluate the mean percentage change from baseline in LDL-C at week 24 (±3 days) in paediatric patients (5 to ≤17 years of age) with HoFH treated with lomitapide at the maximum tolerated dose (MTD) for their age group and added to stable lipid-lowering therapy (LLT) including lipoprotein apheresis (LA) when applicable, regardless of dose adjustments, drug discontinuations, use of alternative treatments and changes in background LLT.

Statistical methods for estimation and sensitivity analysis on primary estimands

The percentage change in LDL-C at Week 24 was analysed using the one-sample t-test to test the null hypothesis that the percentage change from baseline is equal to zero. Two-sided significance level of 5% will be used. The percentage change at Week 24, together with the corresponding two-sided 95% confidence interval (CI) and p-value will be presented. Primary analysis was performed in full analysis set defined as all participants who received at least one dose of the IMP and have a baseline and at least one post-baseline measurement of LDL-C. Missing data was be imputed using Last Observation Carried Forward (LOCF). Percent change from baseline data in primary endpoint was presented by age-group using a waterfall plot.

Sensitivity analyses included analyses using the nominal study visit number, a Baseline Observation Carried Forward (BOCF) method for handling missing data, analyses using a Wilcoxon Signed-Rank test and an MMRM under a missingness at random assumption. Supplementary analyses for primary endpoint with one-sample t-test and Wilcoxon Signed Rank test were be performed in in a completer and per protocol analysis set.

Supplementary descriptive responder analyses will also be provided using the following cut-offs for a responder defined by >15% reduction in LDL-C at Week 24, >25% reduction in LDL-C at Week 24, >50% reduction in LDL-C at Week 24.

To control the overall type I error at the 5% level, a hierarchical testing procedure is used. Key secondary endpoints are only tested when primary endpoint is significant.

Subgroup analyses were prespecified for age group, sex, documented cardiovascular disease history at screening, established cardiovascular disease history at screening, subjects taking concomitant LLT medications (excluding LA), subjects having dose reductions or dose interruptions, subjects who reached MTD within age group and LDLR variant category. Subgroup analyses will be done using ANCOVA with fixed effect for subgroup.

5.3.2.1.2.3. Secondary objectives

The *key secondary endpoints* were percent change in lipid parameters (non-HDL-C, TC, VLDL-C, apo B, triglycerides, and Lp(a)) from Baseline to Week 24.

The *non-key secondary efficacy endpoints* were:

- Percent change from Baseline at all other time points through Week 104±1 week for the following lipid parameters: LDL-C, non-HDL-C, TC, VLDL-C, apo B, triglycerides, and Lp(a).

- Total number and percent of subjects with a change from Baseline in LLT and LA from Week 24±3 days through Week 104±1 week.
- Total number and percent of subjects achieving the 2014 EAS recommended target LDL-C of <135 mg/dL (3.5 mmol/L) in paediatric HoFH subjects at Week 24±3 days and at any time on study.
- Percent change from Baseline in TC/HDL-C ratio and HDL-C at all time points up to Week 104±1 week.

5.3.2.1.2.4. Estimand for the secondary objectives

No formal estimand seems to be defined for the key secondary endpoints, but since the exact same analysis strategy was used, an estimand similar to that for the primary endpoint is likely to be targeted, i.e. treatment policy handling of dose adjustments, study drug discontinuations and use of alternative treatments/change in background LLT.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

Analyses for key-secondary efficacy endpoints, *i.e.,* percentage change from baseline for Non-HDL-C, TC, VLDL-C, apo B, TG, and Lp(a) at Week 24, used the same analysis methods as outlined for the primary efficacy endpoint in the full analysis set. Missing data was imputed using Last Observation Carried Forward (LOCF). The same sensitivity, supplementary analyses and subgroup analysis were planned for the key secondary endpoints, but analysis with MMRM was not performed for key secondary endpoints.

Percent change from baseline for LDL-C, Non-HDL-C, TC, VLDL-C, apo-B, TG and Lp(a) at all time points through to EOT / Week 104 (other than at Week 24) was analysed using MMRM models where the mean change at each timepoint for each lipid parameter will be estimated. The number and percentage of patients treated with standard LLT (including LA when applicable) at any post-baseline assessment will be summarised overall and by age group, using the number of patients attending the post-baseline visit as a denominator. The number and percentage of patients with LDL-C falling below the recommended target level of 135 mg/dL (i.e. 3.5 mmol/L) will be summarised by study visit (based on analysis visit), at any time up to Week 24 and at any time up to Week 104 by age group and overall.

Percent change from baseline up to Week 104 ± 1 week for non-key secondary endpoints HDL-C and TC/HDL-C was analysed using an MMRM model. LS mean, SE, 95% confidence interval and two-sided p-value will be reported for each timepoint.

In case primary endpoint of LCL-C at Week 24 is significantly different from 0 in a positive direction, then the key secondary endpoints (all at Week 24) are tested in the following order: 1. Non-HDL-C, 2. TC, 3. VLDL-C, 4. Apo B, 5. TG, 6. Lp(a). If at any step of the testing procedure a non-significant p-value was reached, further tests in the sequence were be performed, but reported p-values were to be considered nominal.

5.3.2.1.2.5. Tertiary (exploratory) objectives

Exploratory objectives

The *exploratory endpoints* were:

- Percent change from Baseline at Week 56±3 days and Week 104±1 week in CIMT and FMD.
- Total number and percent of subjects with resolution and/or regression of pre-existing xanthomas at Week 56±3 days and at Week 104±1 week.
- Total number and percent of subjects achieving the 2023 EAS recommended target LDL-C of <115 mg/dL (3.0 mmol/L) in paediatric HoFH patients at Week 24±3 days and at any time on study.
- Total number and percent of subjects achieving the 2018 American College of Cardiology/American Heart Association Task Force recommended target LDL-C of <110 mg/dL (i.e. 2.9 mmol/L) in paediatric HoFH patients at Week 24±3 days and at any time on the study

Palatability Objectives

- To assess the palatability of the study medication using a 5-point facial hedonic scale anchored with descriptors, to record the children's assessment of palatability in terms of overall liking. The parent(s)/legal guardian(s) interpretation of the child's reaction/facial expression was used to determine whether they find lomitapide "pleasant", "unpleasant" or were "not sure".
- To assess the ease of administration of the study medication and dietary supplements by the parent(s)/legal guardian(s) using the following question at each visit during the treatment phase: "Do you sometimes have problems in giving the medication to your child because he/she refuses to take it or throws it up immediately after taking it? (Yes/No)."

5.3.2.1.2.6. Estimands for the tertiary objectives

No estimands were defined for exploratory objectives.

5.3.2.1.3. Results

5.3.2.1.3.1. Participant flow and numbers analysed

A total of 46 subjects were enrolled in this study. Of these, 3 (6.5%) subjects were 'Run-in' failures and did not complete the Run-in Period. Therefore, a total of 43 (93.5%) subjects entered the Efficacy Phase at Visit 4.

Fourty-one of these 43 (95.3%) subjects completed lomitapide treatment through the primary efficacy endpoint at Week 24 (end of Efficacy Phase) and entered the 80-week Safety Phase.

A total of 39 (90.7%) subjects completed the Safety Phase of the study. Four (9.3%) subjects prematurely discontinued the study, all in the 11 to 17 years age group:

- During Efficacy Phase, 2 [4.7%) subjects prematurely discontinued due to adverse events of special interest (AESIs);
- During Safety Phase, 2 [4.7%) subjects prematurely discontinued, 1 due to voluntary withdrawal and 1 due to "frequent AEs and non-compliance".

Table 10: Subject Disposition

	5 to 10 years	11 to 17 years	Overall
Enrolled Set	**N=21 n (%)[a]**	**N=25 n (%)[a]**	**N=46 n (%)[a]**
Run-in Failures	1 (4.8)	2 (8.0)	3 (6.5)
Completed Run-in Period	20 (95.2)	23 (92.0)	43 (93.5)
Study duration (weeks)			
Mean (SD)	109.38 (24.832)	97.10 (38.059)	102.70 (32.937)
Minimum	1.1	8.9	1.1
Median	114.57	115.14	114.71
Maximum	117.7	124.6	124.6
Safety Analysis Set	**N=20 n (%)[b]**	**N=23 n (%)[b]**	**N=43 n (%)[b]**
Completed Efficacy Phase (Attended Week 24 Visit)	20 (100.0)	21 (91.3)	41 (95.3)
Completed Safety Phase (Attended Week 104 Visit)	20 (100.0)	19 (82.6)	39 (90.7)
Prematurely discontinued study	0	4 (17.4)	4 (9.3)
During the Efficacy Phase			
Adverse event	0	2 (8.7)	2 (4.7)
During the Safety Phase			
Voluntary withdrawal	0	1 (4.3)	1 (2.3)
Other [c]	0	1 (4.3)	1 (2.3)
Treatment duration (weeks)			
Mean (SD)	104.26 (0.748)	92.89 (28.809)	98.18 (21.632)
Minimum	103.1	10.9	10.9
Median	104.14	104.14	104.14
Maximum	106.0	110.0	110.0

Abbreviations: N=number of subjects in the analysis set; n=number of subjects meeting the criterion. (%)=n/N×100

[a] N=number of subjects in the Enrolled Set. The calculation of study duration is based on the Enrolled Set.

[b] N=number of subjects in the Safety Analysis Set.

[c] Other: the Investigator specified that "frequent AEs and non-compliance" were the reasons for withdrawal.

5.3.2.1.3.2. Deviations from study plan

Protocol deviations

Major deviations were reported by a total of 33 (76.7%) subjects including 12 (60.0%) subjects aged 5 to 10 years and 21 (91.3%) subjects aged 11 to 17 years as summarised in the Table below. Most of the major protocol deviations were due to non-compliance with the IMP administration regimen; any deviation in lomitapide dosing was to be reported as a major protocol deviation. Compliance with IMP dosing during the study was defined as 80% to 100% of IMP doses taken.

Table 11: Major Protocol Deviations (Safety Analysis Set)

Deviation Category	5 to 10 years N=20 n (%)	11 to 17 years N=23 n (%)
Any major deviation[a]	12 (60.0)	21 (91.3)
Informed Consent	0	1 (4.3)
Consent not correctly signed	0	1 (4.3)
Investigational product	9 (45.0)	17 (73.9)
Non-compliance with IMP administration regimen	9 (45.0)	17 (73.9)
Non-compliance with IMP storage/accountability	1 (5.0)	0
Non permitted concomitant medication	2 (10.0)	7 (30.4)
Change of LLT during Efficacy Phase/LA sessions missed	2 (10.0)	6 (26.1)
Prohibited concomitant medication/moderate CYP3A4 inhibitor	0	1 (4.3)
SAE/AESI reporting (delay in reporting)	2 (10.0)	0
Study procedures	1 (5.0)	11 (47.8)
Incorrect procedure, non-fasting lipid panels	1 (5.0)	4 (17.4)
Missed procedure, pregnancy test	0	7 (30.4)

Abbreviations: AESI=adverse event of special interest; IMP=Investigational Medicinal Product; LA=lipoprotein apheresis; LLT=lipid lowering therapy; N=number of subjects in the analysis set; n=number of subjects meeting the criterion; SAE=serious adverse event.

[a] Subjects could report a deviation in more than 1 category.

Treatment compliance

During the Efficacy Phase, the majority of subjects (86.0%) were assessed as compliant with study drug dosing. Overall compliance was higher in the 5 to 10 years age group (100.0%) compared with the 11 to 17 years age group (73.9%). Compliance reported at each visit during the Efficacy Phase ranged from 95.0% to 100.0% in the 5 to 10 years age group and 76.2% to 95.2% in the 11 to 17 years age group. Notably, while compliance dropped in the 11 to 17 years age group starting at the Week 20 visit, initially it was higher, ranging from 95.5% to 85.7% at the Week 4 to 16 visits. During the Safety Phase, overall compliance was lower than during the Efficacy Phase in both age groups. Compliance at each visit during the Safety Phase ranged from 90.0% to 100.0% in the 5 to 10 years age group and 70.0% to 90.5% in the 11 to 17 years age group.

Table 12: Treatment Compliance (Safety Analysis Set)

Subject compliant with study drug dosing[a]	5 to 10 years n (%)	11 to 17 years n (%)	Overall n (%)
Overall	**N=20**	**N=23**	**N=43**
Yes	19 (95.0)	16 (69.6)	35 (81.4)
No	1 (5.0)	7 (30.4)	8 (18.6)
During Efficacy Phase	**N=20**	**N=23**	**N=43**
Yes	20 (100.0)	17 (73.9)	37 (86.0)
No	0	6 (26.1)	6 (14.0)
During Safety Phase	**N=20**	**N=21**	**N=41**
Yes	18 (90.0)	14 (66.7)	32 (78.0)
No	2 (10.0)	7 (33.3)	9 (22.0)

Abbreviations: N=number of subjects in the analysis set; n=number of subjects taking a concomitant medication. (%)=n/N×100.

[a] Subject compliance was medically reviewed on a subject-level basis by assessing the number of missed doses by visit. Subjects were considered compliant at the respective visit, if they had taken >80% and <120% of doses. Subjects were assessed as being compliant during the Efficacy or Safety Phase, respectively, if they were compliant for >80% of corresponding visits.

Compliance with Lipid-lowering Therapy

Subjects were to remain on their stable LLT/LA regimen (as established during the Run-in Phase) during the Efficacy Phase, and changes to LLT were to be reported as protocol deviations. Compliance

with lipid lowering therapy was determined through manual review of protocol deviations. The majority of subjects were compliant with their LLT (including LA) during the Efficacy Phase. Major protocol deviations related to use of LLT were reported for 8 (18.6%) subjects (2 [10.0%] subjects 5 to 10 years of age and 6 [26.1%] subjects 11 to 17 years of age):

• and had a change of LLT, as they missed several LA sessions.

• stopped concomitant LLT at Baseline.

• and had concomitant LLT interrupted for 14 days due to COVID-19.

• discontinued evolocumab at Visit 6.

• missed several LA sessions.

• requested a change of LLT regimen by decreasing the frequency of LA from every 2 weeks to once a month.

5.3.2.1.3.3. Baseline data

Demographics and baseline BMI data for participants in Study APH-19 are shown in the Table below.

Table 13: Demographic characteristics, Study APH-19 (Safety Analysis Set)

	5 TO 10 YEARS N=20	11 TO 17 YEARS N=23	OVERALL N=43
Sex, n (%)			
Male	10 (50.0)	9 (39.1)	19 (44.2)
Female	10 (50.0)	14 (60.9)	24 (55.8)
Age, years			
Mean (SD)	7.0 (1.54)	14.0 (1.97)	10.7 (3.99)
Range	5 to 10	11 to 17	5 to 17
Race, n (%)			
White	19 (95.0)	23 (100.0)	42 (97.7)
Black or African American	1 (5.0)	0	1 (2.3)
BMI at Baseline, kg/m^2			
Mean (SD)	15.78 (3.338)	21.52 (4.840)	18.85 (5.071)
Median	14.90	20.70	18.90
Range	12.5 to 27.4	11.2 to 32.6	11.2 to 32.6
BMI percentile[a]			
Mean (SD)	38.867 (34.3409)	62.191 (32.6468)	51.343 (35.0762)
Median	28.500	64.340	50.000
Range	1.00 to 99.0	0.10 to 99.00	0.10 to 99.00
BMI z score[b]			
Mean (SD)	-0.311 (1.3881)	0.263 (1.7024)	-0.004 (1.5728)
Median	-0.445	0.390	-0.070
Range	-2.39 to 3.01	-4.71 to 2.51	-4.71 to 3.01

Abbreviations: BMI=body mass index; N=number of subjects; SD=standard deviation.
[a]Percentiles calculated using either WHO growth reference indicators for children 5 to 19 years or CDC website (https://www.cdc.gov/healthyweight/bmi/calculator.html).
[b] z-scores calculated using the WHO growth reference indicators for children 5 to 19 years.
(%)=n/N×100. BMI=weight (kg)/height (m)2.

HoFH diagnosis

Time since HoFH diagnosis was a median of 58.6 months (range: 3 to 172 months) overall, with a median of 44.8 months in the 5 to 10 years age group (range: 14 to 85 months), and 60.6 months in the 11 to 17 years age group (range 3 to 172 months).

The majority of subjects (39 (90.7%) had genetic confirmation of 2 mutant alleles at the LDLR gene locus. 1 subject had "unknown" genetic testing results at Screening but later during the APH-19 study was confirmed as having homozygous mutation of the LDLRAP1 gene locus (i.e. ARH, which is phenotypically consistent with HoFH). Therefore, overall, genetic diagnosis was confirmed in 40 (93.0%) of subjects in study APH-19.

As the functional defects in the LDLR are complex, a mutation can belong to more than one class (Gidding, 2015, Circulation). Therefore, for the purpose of sub-group analysis based on LDLR variant, mutations were classified upon medical review into 4 groups: subjects with the LDLR variant category 'defective/defective', subjects with the LDLR variant category 'defective/negative', subjects with the LDLR variant category 'negative/negative', and subjects with an 'unknown' category.

In addition to the genetic confirmations (which were not mandatory for inclusion into the APH-19 study), in 3 subjects HoFH diagnosis was based on clinical criteria (per inclusion criterion #1b . Most of the subjects with genetic confirmation of their HoFH diagnosis also reported clinical criteria, but not all. Reported clinical criteria are summarized below:

- 34 (79.1%) subjects had an untreated LDL-C >500 mg/dL (13 mmol/L) or treated LDL-C ≥300 mg/dL (8 mmol/L) AND cutaneous or tendon xanthoma before the age of 10 years.
- 6 (14.0%) subjects had an untreated LDL-C >500 mg/dL (13 mmol/L) or treated LDL-C ≥300 mg/dL (8 mmol/L) AND untreated LDL-C levels consistent with HeFH in both parents.

Medical conditions, prior and concomitant treatments, and baseline lipids

Overall, 41 (95.3%) subjects reported medical history conditions, with 25 (58.1%) subjects reporting past medical history conditions. Ongoing medical conditions (excluding CVD) were reported in 33 (76.7%) of subjects, the most frequently reported of which, in both age groups, was xanthoma (25 [58.1%] subjects overall; 18 (90.0%) subjects aged 5 to 10 years and 7 (30.4%) subjects aged 11 to 17 years).

Twenty-eight (65.1%) subjects had an ongoing cardiovascular condition at Baseline:

- 11 (55%) were in the 5 to 10 years age group (despite their younger age and being on SoC LLT, including LA where applicable), and
- 17 (73.9%) of 11 to 17-year-old subjects (despite their more intense SoC LLT regimen including evolocumab, and LA).

Aortic valve disease was more frequent (in 34.9% of subjects overall) compared with data from the HoFH International Clinical Collaborators registry (29%) (Tromp, 2022 Lancet).

Ten (23.3%) subjects reported a past cardiovascular history condition. Twenty-one (48.8%) of the 43 subjects had "established cardiovascular disease" (defined as previous and/or ongoing CVD of aortic valve disease and/or coronary atherosclerosis) at Screening; for these subjects a lower threshold of LDL-C at Screening applied – see inclusion criterion #2.

Prior and concomitant LLT medication

All subjects reported at least 1 prior and/or "Run-in" LLT medication at study entry. The most frequently reported were HMG CoA reductase inhibitors (statins, including rosuvastatin, atorvastatin)

(39 [90.7%] subjects), and other lipid modifying agents (32 [74.4%] subjects, including ezetimibe and evolocumab).

All subjects were receiving concomitant LLT during the Efficacy Phase as required by the protocol. While all subjects in both age groups were receiving HMG CoA reductase inhibitors, other lipid modifying agents such as ezetimibe and evolocumab were more frequently administered to subjects 11 to 17 years of age (87.0% and 17.4% during the Efficacy Phase, respectively) as opposed to subjects 5 to 10 years of age (60.0% received ezetimibe, none received evolocumab).

A total of 19 (44.2%) subjects were receiving LA during the Run-in Period and during the Efficacy Phase (through to Week 24), including 6 (30.0%) subjects 5 to 10 years and 13 (56.5%) subjects 11 to 17 years.

5.3.2.1.3.4. Outcomes and estimation

Maximum tolerable dose

The MTD was defined as the highest dose of lomitapide through Week 24 that had not resulted in tolerability or safety concerns. In the 5 to 10 years age group, the maximum allowable dose of 20 mg was the MTD for 19 (95.0%) subjects, while 1 (5.0%) subject had an MTD of 5 mg. During the Safety Phase, 6 (30.0%) subjects achieved a maximum dose of 30 mg (beyond the original maximum dose for the age group, as per protocol amendment 5.0).

In the 11 to 17 years age group, the majority of subjects achieved an MTD of 40 mg (13 [56.5%] subjects), while 3 (13.0%) subjects had an MTD of 60 mg. Maximum allowed dose was higher for subjects aged 16 to 17 years at Screening; of the 6 subjects in this age range, 3 subjects reached an MTD of 60 mg. For subjects aged 11 to 15 years, the maximum dose was 40 mg, and 13 of the 17 subjects in this age range achieved this dose. All 3 subjects who reached an MTD of 60 mg during the Efficacy Phase had to down-titrate soon after reaching this dose.

Treatment compliance

During the Efficacy Phase, the majority of subjects (86.0%) were assessed as compliant with study drug dosing. Overall compliance was higher in the 5 to 10 years age group (100.0%) compared with the 11 to 17 years age group (73.9%). Compliance reported at each visit during the Efficacy Phase ranged from 95.0% to 100.0% in the 5 to 10 years age group and 76.2% to 95.2% in the 11 to 17 years age group. Notably, while compliance dropped in the 11 to 17 years age group starting at the Week 20 visit, initially it was higher, ranging from 95.5% to 85.7% at the Week 4 to 16 visits.

During the Safety Phase, overall compliance was lower than during the Efficacy Phase in both age groups. Compliance at each visit during the Safety Phase ranged from 90.0% to 100.0% in the 5 to 10 years age group and 70.0% to 90.5% in the 11 to 17 years age group.

Primary efficacy endpoint

Study APH-19 met its primary efficacy endpoint. Treatment with lomitapide escalated to each subject's MTD (up to the maximum allowable dose for age group), administered concurrently with other LLTs and a low-fat diet for 24 weeks reduced LDL-C levels in subjects with HoFH. The mean percent reduction of LDL-C levels from Baseline to Week 24/LOCF was 53.9% and statistically significant.

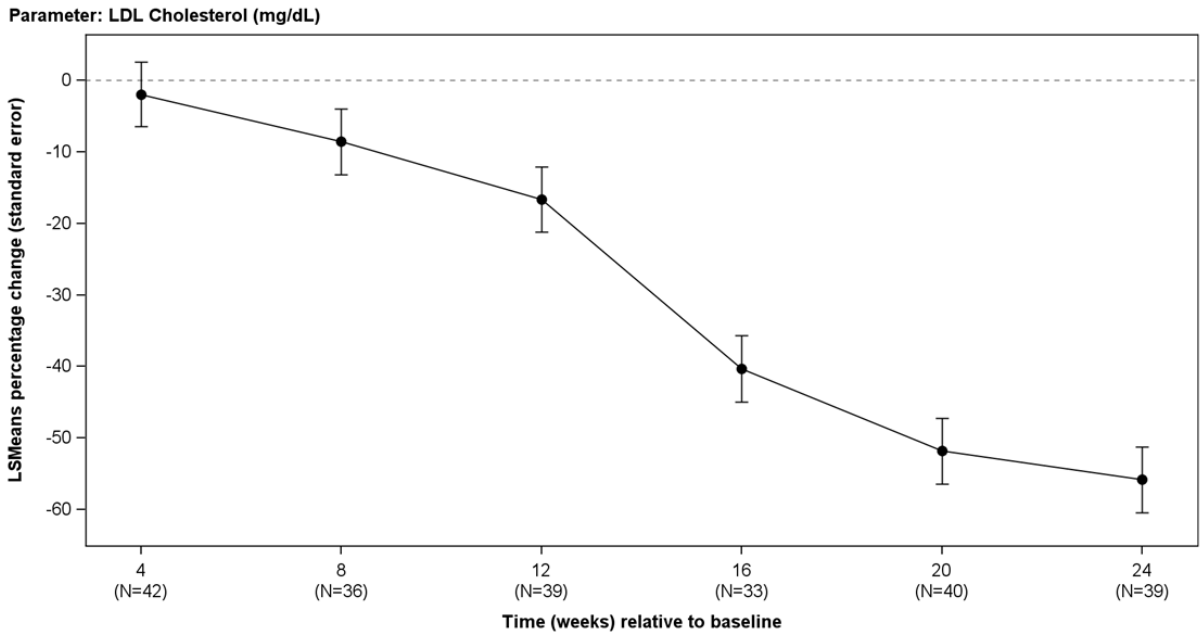
A summary of percent changes (LSM) from Baseline through Week 24 in LDL-C is shown in the Table and Figure below.

Table 14: Primary Efficacy Endpoint in APH-19: LDL-C (mg/dL) at Baseline and Week 24/LOCF (FAS)

	OVERALL N=43			
	Observed Value (mg/dL)	**Change from Baseline (mg/dL)**	**Percent Change from Baseline**	**p-value**
Baseline				
N	43			
Mean (SD)	435.791 (189.4620)			
Median	390.517			
Range	152.34 to 902.44			
IQR	279.548 to 571.855			
Week 24/LOCF				
N	43	43	43	<0.0001
Mean (SD)	175.404 (89.8979)	-260.386 (192.1284)	-53.910 (25.8287)	
Median	162.393	-200.285	-56.512	
Range	20.11 to 392.45	-794.18 to 5.80	-95.61 to 2.52	
IQR	114.062 to 236.243	-437.688 to -110.969	-75.052 to -37.117	
(95% CI)a			(-61.8590, -45.9612)	

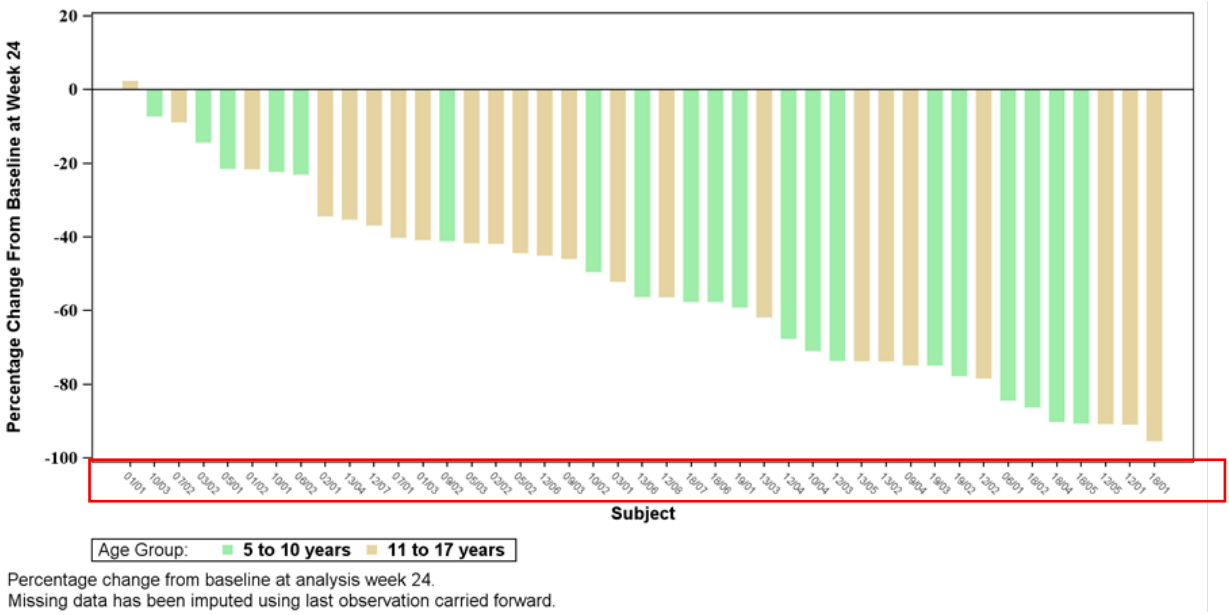
[a] 95% CI for mean percentage change
CI=confidence interval; IQR=interquartile range; LDL-C=low-density lipoprotein cholesterol; LOCF=last observation carried forward; N=number of subjects in the analysis set; n=number of subjects with a measurement; SD=standard deviation.

Figure 15: Least squares mean percent changes from baseline in LDL-C in paediatric Study APH-19 through Week 24 (the Primary Endpoint) (N = 43)



With the exception of 1 subject (in the 11 to 17 years age group, and for whom a significant number of major protocol deviations were reported [subject stopped taking LLT medication during the Efficacy Phase, did not observe fasting before blood sampling, and may have been non-compliant with dietary restrictions and study drug intake at several time points], a decrease from Baseline in LDL-C was observed in all subjects, as shown in the figure below.

Figure 16: Waterfall Plot of Percentage Change from Baseline in LDL-C at Week 24 by Age Group, Study APH-19 (Full Analysis Set, Analysis Visit



Secondary efficacy endpoint

Key secondary endpoints

Non-HDL-C, Total Cholesterol, VLDL-C, apo B, Triglycerides and Lp(a) to Week 24/LOCF, FAS

Results for the key secondary efficacy endpoints of non-HDL-C, total cholesterol, VLDL-C, apo B and triglycerides were consistent in direction and magnitude of change with the primary endpoint of LDL-C. A statistically significant mean percent decreases from Baseline to the end of the Efficacy Phase (Week 24/LOCF) were observed for all 5 parameters ($p<0.0001$). Mean absolute and mean percent changes from Baseline for all secondary endpoint lipid parameters are shown in the Table below.

Analysis of Lp(a) based on units reported by the local laboratories is presented in the Table below. Fewer subjects had values reported in mg/dL than in nmol/l. Of note, the overall sample size was limited and splitting by laboratory units diminished the power of the statistical analysis. A mean reduction of Lp(a) at Week 24 was observed only for values reported in nmol/L (26.8% change from Baseline). Nonetheless, the combined p-value was significant (using Fisher's method), and so the data supported the effect of lomitapide on Lp(a) reduction.

Table 15: Secondary Efficacy Endpoint: Mean Absolute Values and Percent Changes from Baseline to Week 24/LOCF in Lipid Parameters, Study APH-19 (Full Analysis Set)

PARAMETER (UNITS)	BASELINE	WEEK 24/LOCF (N = 43)		
	MEAN (SD)	MEAN (SD)	% CHANGE (SD) [95% CI^]	P-VALUE
Total Cholesterol (TC) (mg/dL)	485.53 (188.18)	216.87 (94.15)	-50.18 (24.54) [-57.7281, -42.6237]	<0.0001

PARAMETER (UNITS)	BASELINE	WEEK 24/LOCF (N = 43)		
	MEAN (SD)	MEAN (SD)	% CHANGE (SD) [95% CI[A]]	P-VALUE
Apolipoprotein B (apo B) (mg/dL)	316.60 (133.05)	131.30 (62.59)	-53.1 (24.76) [-60.7167, -45.4777]	<0.0001
Triglycerides (TG) (mg/dL)	91.90 (39.08)	42.07 (23.12)	-49.29 (31.73) [-59.0515, -39.5221]	<0.0001
Non-high-density lipoprotein cholesterol (non-HDL-C) (mg/dL)	454.13 (191.87)	183.63 (92.06)	-54.19 (25.03) [-61.8872, -46.4837]	<0.0001
Very-low-density lipoprotein cholesterol (VLDL-C) (mg/dL)	18.33 (8.00)	8.34 (4.72)	-49.68 (31.61) [-59.4066, -39.9487]	<0.0001
Lipoprotein (a) (Lp(a)) (mg/dL)[b]	n = 14 42.22 (54.36)	n = 15 32.96 (31.29)	n = 14 0.88 (46.99) [-26.2535, 28.0075]	0.0021[c]
Lipoprotein (a) (Lp(a)) (nmol/L)[b]	n = 27 132.15 (107.26)	n = 28 82.49 (75.51)	n = 27 -26.76 (32.57) [-39.6398, - 13.8733]	

LOCF = last observation carried forward; SD = standard deviation; N=number of subjects in the analysis set; n=number of subjects meeting the criterion.
A 95% CI for mean percentage change; b reported by local laboratories using different devices and assays (see Section 2.2.3.2.1.2 for a link to further detail on the different n-s). Given the limitations on conversion from mass to molar units, data were analyzed separately and then results combined using Fisher's combination test; c Fisher combined p-value (Individual p-values were 0.9454 and 0.0002 for data reported in mg/dL and nmol/L, respectively).

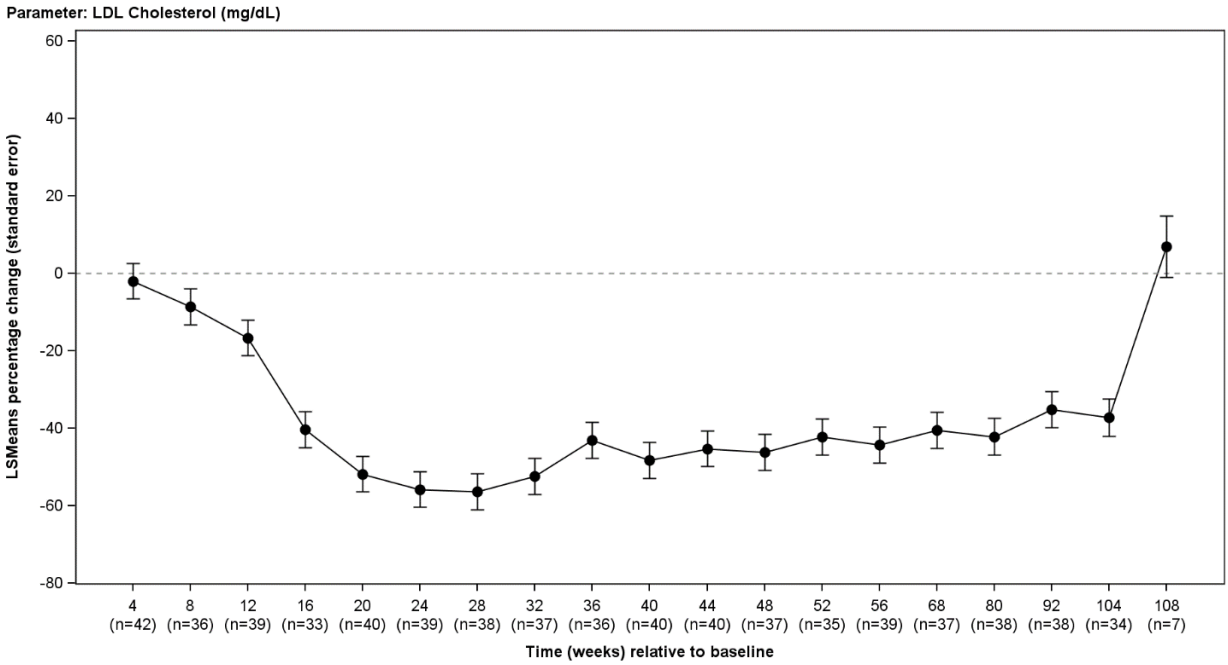
Secondary endpoints

Percent change in lipid parameters from Baseline at all other timepoints through Week 104

Mean decreases in LDL-C and other lipid parameters occurred as early as Week 8, with the maximum decrease occurring after the end of the Efficacy Phase at Week 24 and 28. Mean decreases from Baseline in LDL-C were statistically significant from Week 12 through Week 104. LS mean percentage change from Baseline for LDL-C is presented in the Figure below. Notably, maximum change from Baseline coincided with the highest mean dose of lomitapide.

Overall, efficacy was maintained throughout the Safety Phase. At the start of the Safety Phase, lipid parameter levels increased slightly and were then maintained until Week 104. However, it should be noted that changes to background LLT/LA were allowed in the Safety Phase. For the 7 subjects who discontinued lomitapide treatment at Week 104, most lipid parameters returned to Baseline levels by Week 108.

Figure 17: Profile Plot of LS Means Percentage Change from Baseline Over Time in LDL-C, Study APH-19 (Full Analysis Set)



Exceptions to this pattern were the parameters Lp(a) reported in mg/dL and HDL-C:

- While Lp(a) reported in nmol/L showed a similar pattern of decrease to other lipid parameters, the same pattern was not clear for the Lp(a) data reported in mg/dL. Assays measuring Lp(a) in mass units (mg/dL) are unreliable because they measure the Apo(a) protein (a component of Lp(a) which varies in length between individuals) rather than the lipid content of the Lp(a) particles (Boot, 2022, *Br J Cardiol*).
- Mean HDL-C levels showed a modest improvement from Baseline during the Efficacy Phase, which was maintained in the Safety Phase.

Change in LLT and LA from Week 24 through Week 104

After the Efficacy Phase, adjustments to background LLT (including LA, if applicable) were allowed at the discretion of the Investigator, to ensure an optimal standard of care. Changes to LLT medications and LA anytime during Safety Phase are summarized separately in the Table below, along with the reasons for the changes.

Briefly, the percentage of subjects receiving LLT medications changed little during the Safety Phase (ranging from 95.1% to 100.0% across visits).

However, there was a change in LA regimens, for those subjects receiving LA during the Run-in Period and Efficacy Phase as compared to the Safety phase.

Overall subjects adhered to the LA regimen established during the Run-in Period throughout the Efficacy Phase.

The percentage of subjects reporting LA treatment decreased in the Safety Phase (25.6% to 36.6% overall across visits) compared with the Efficacy Phase (41.5% to 44.2% overall across visits). Overall, LA frequency was reduced and/or discontinued in 8 of the 17 subjects (47.1%) receiving LA at Week

24; 6 subjects had a reduction in LA frequency and 2 subjects completely discontinued LA in the Safety Phase. Briefly:

- in the 5 to 11 years age group, 6 subjects received LA at the Week 24 visit, but the number of subjects reporting LA decreased to 3 by Week 32, before increasing again to 5 subjects by Week 48.
- in the 11 to 17 years age group, the number of subjects receiving LA decreased more consistently from 11 subjects at Week 24 to 9 subjects by Week 48 and was maintained at that level until the end of study (with some fluctuations).

Table 16: Therapeutic changes to LLT and LA Anytime During the Safety Phase of Study APH-19 (Week 28 to Week 104; Full Analysis Set)

	LLT			**LA**		
	5 to 10 yrs (N=20) n (%)	**11 to 17 yrs (N=23) n (%)**	**Overall (N=43) n (%)**	**5 to 10 yrs (N=20) n (%)**	**11 to 17 yrs (N=23) n (%)**	**Overall (N=43) n (%)**
N of subjects treated at Week 24 (m)	20	21	41	6	11	17
Reduction due to						
Adverse event	0	0	0	1 (16.7)	0	1 (5.9)
Low LDL-C	1 (5.0)	1 (4.8)	2 (4.9)	1 (16.7)	2 (18.2)	3 (17.6)
Other	0	0	0	3 (50.0)	1 (9.1)	4 (23.5)
Discontinuation due to						
Lomitapide increase	1 (5.0)	0	1 (2.4)	0	0	0
Low LDL-C	0	0	0	1 (16.7)	0	1 (5.9)
Other	1 (5.0)	1 (4.8)	2 (4.9)	1 (16.7)	0	1 (5.9)
Increase due to						
High LDL-C	3 (15.0)	0	3 (7.3)	0	0	0
Other	1 (5.0)	0	1 (2.4)	0	0	0

Abbreviations: LA=lipoprotein apheresis; LDL-C=low-density lipoprotein cholesterol; LLT=lipid-lowering therapy; N=number of subjects in the analysis set; n=number of subjects meeting the criterion; yrs=years. m = number of subjects treated with LLT (including LA) at Week 24. (%) = number of subjects meeting the criterion/m×100.

Subjects achieving recommended target of LDL-C at Week 24 and at any time during the study

A further secondary endpoint was the total number and percent of subjects achieving the EAS recommended target LDL-C level (Cuchel, 2014, Eur Heart J), at the time the APH-19 study was designed and the primary efficacy analysis was conducted) of <135 mg/dL (3.5 mmol/L) at Week 24±3 days and at any time on study. Of note: While Study APH-19 was running, the EAS updated its recommended target LDL-C levels (Cuchel, 2023, Eur Heart J), and therefore an additional exploratory endpoint was added to the APH-19 SAP (to analyze the total number and percent of subjects achieving this new 2023 EAS LDL-C target of <115 mg/dL [3.0 mmol/L]).

At any time up to Week 24, a total of 18 (41.9%) subjects had achieved the 2014 EAS recommended target LDL-C level of <135 mg/dL including 7 (35.0%) subjects 5 to 10 years and 11 (47.8%) subjects 11 to 17 years. At any time up to Week 104, a total of 23 (53.5%) subjects had achieved the

recommended target LDL-C level of <135 mg/dL. A greater percentage of subjects aged 11 to 17 years reached recommended target levels compared with subjects aged 5 to 10 years.

A considerable proportion of APH-19 subjects achieved the revised lowered LDL-C goals recommended by 2023 EAS <115 mg/dL and the 2018 ACC/AHA <110 mg/dL, respectively. Nearly half (46.5%) of subjects achieved the further lowered, 2023 EAS LDL-C goal at any time up to Week 104. The results for all LDL-C target levels are summarized in the Table below.

Table 17: APH-19 subjects reaching recommended targets of LDL-C (Full Analysis Set)

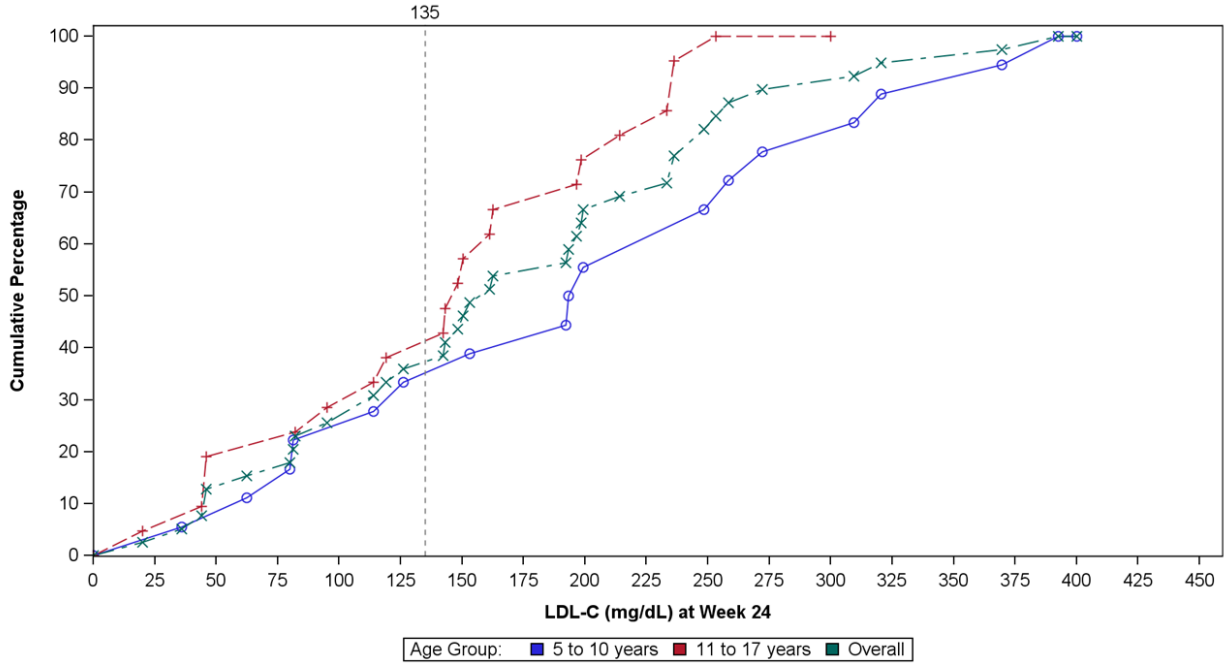
RECOMMENDED TARGET	VISIT	5 TO 10 YEARS (N=20) N (%)	11 TO 17 YEARS (N=23) N (%)	OVERALL (N=43) N (%)
<135 mg/dL [a]	Anytime up to Week 24	7 (35.0)	11 (47.8)	18 (41.9)
	Anytime up to Week 104	10 (50.0)	13 (56.5)	23 (53.5)
<115 mg/dL [b]	Anytime up to Week 24	5 (25.0)	11 (47.8)	16 (37.2)
	Anytime up to Week 104	7 (35.0)	13 (56.5)	20 (46.5)
<110 mg/dL [c]	Anytime up to Week 24	4 (20.0)	10 (43.5)	14 (32.6)
	Anytime up to Week 104	6 (30.0)	13 (56.5)	19 (44.2)

Abbreviations: EAS= European Atherosclerosis Society; LDL-C=low-density lipoprotein cholesterol; N=number of subjects in the analysis set; n=number of subjects meeting the criterion.
[a] 3.5 mmol/L; EAS Consensus Statement 2013 (Cuchel, 2014, Eur Heart J), secondary endpoint
b 3.0 mmol/L; EAS Consensus Statement 2023 (Cuchel, 2023 Eur Heart J); exploratory endpoint
[c] 2.9 mmol/L; 2018 American College of Cardiology/American Heart Association Task Force; exploratory endpoint

The dose of lomitapide at the time when LDL-C was <135 mg/dL was 20 mg for all subjects aged 5 to 10 years who achieved this target level. For subjects 11 to 17 years, the dose of lomitapide at the time when LDL-C was <135 mg/dL ranged from 10 mg to 60 mg. A similar pattern was seen for the lower LDL-C targets of <115 mg/dL and <110 mg/dL.

A Cumulative Distribution Function (CDF) plot of LDL-C at Week 24 for all subjects and by age group is provided in the Figure below, with a reference line at 135 mg/dL indicating the 2014 EAS recommended target (the secondary endpoint). Overall, approximately 35% of subjects achieved an LDL-C value of <135 mg/dl at Week 24.

Figure 18: Cumulative Distribution Function (CDF) Plot of LDL-C at Week 24, Study APH-19 (Full Analysis Set)



The CDF plot shows the cumulative percentage of APH-19 subjects on the y-axis that achieved the LDL-C threshold on the x axis
LDL-C=low-density lipoprotein cholesterol.

Exploratory endpoints

Carotid Intima-Media Thickness and Flow-mediated Dilation

Carotid Intima-Media Thickness (CIMT) and Flow-mediated Dilation (FMD) were assessed at Baseline, Week 56, and Week 104.

Changes from Baseline in CIMT were relatively small, with mean percentage change from Baseline ranging from -5.0% to 8.2% for right carotid CIMT in both age groups and left carotid CIMT in the 5 to 10 years old age group. For left carotid CIMT, an outlier in the 11 to 17 years age group skewed mean change values (Subject 12/01 with 450% and 600% change from Baseline at Week 56 and Week 104, respectively). Overall median change from Baseline was 0 for both time points and left and right carotid measurements.

Results for change from Baseline in FMD were only available for 3 subjects overall, and only 1 subject at any one time point.

Resolution or Regression of Xanthomas

Of the 27 (62.8%) subjects presenting with pre-existing xanthomas at Baseline:

- 24 subjects (88.9% of subjects with pre-existing xanthomas) reported a size reduction,
- 13 subjects (48.1% of subjects with pre-existing xanthomas) reported resolution of a xanthoma during the study.
- Increases in size of pre-existing xanthomas were reported for 3 subjects overall.

No new xanthomas were reported during the Efficacy Phase. During the Safety Phase, no new tendon xanthomas were reported for any subject. New cutaneous xanthomas were reported for 4 subjects overall, 2 subjects 5 to 10 years of age, and 2 subjects 11 to 17 years of age.

Palatability Variables

Palatability data collected indicate no problems with administration of lomitapide when swallowing the capsule. Only 3 subjects reported being unable to swallow the capsule at some time points; in such cases the capsule was opened, and the subject took study drug sprinkled on mashed banana (as allowed per protocol). The majority of parents/guardians (>80% at all time points on study) reported a pleasant reaction from their child on taking the study drug and did not report issues with refusal to take.

The majority of parents/guardians (>80% at all time points on study) did not report problems in giving the dietary supplement to their child.

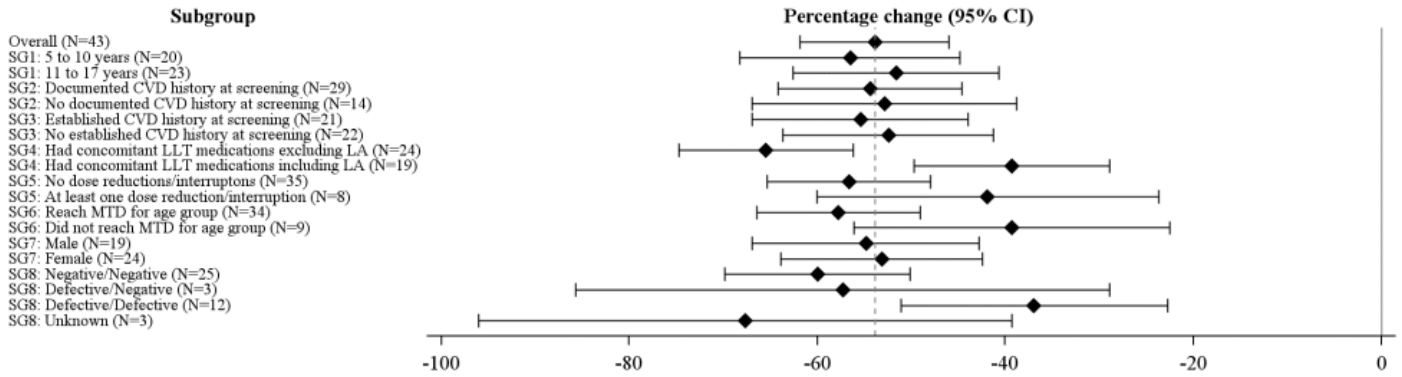
5.3.2.1.3.5. Pre-defined and post-hoc subgroup analyses

Sub-group analysis primary efficacy endpoint

Results of all subgroup analyses are summarised in the Figure below.

Overall, the results from the subgroup analyses showed consistent results across most subgroups. Percent changes in LDL-C from Baseline to Week 24 were similar for both age groups, sexes, as well as groups based on documented and established CVD history, reaching MTD for age group, and having dose reduction during the Efficacy Phase. Two subgroup analyses showed differential effect with subjects who received concomitant LLT medications including LA and subjects with LDLR function defective/defective showing smaller decreases in LDL-C.

Figure 19: Forest Plot of Subgroup Analysis for Primary Endpoint (Percentage Change at Week 24) (Full Analysis Set)



Sub-group analysis secondary endpoints

Overall, the results from the sub-group analyses of the secondary endpoints were similar to that of the primary endpoint. Percent changes in all lipid parameters from Baseline to Week 24 were similar for both age groups, sexes, as well as groups based on documented and established CVD history, reaching MTD for age group, and having dose reduction during the Efficacy Phase. The other subgroup analyses showed differential effect with subjects who received concomitant LLT medications including LA and subjects with LDLR function defective/defective showing smaller decreases in lipid parameters.

5.3.2.1.3.6. Results

Primary efficacy endpoint

Using Nominal Study Visit Number

A sensitivity analysis was performed using Nominal Study Visit 10 instead of Analysis Week 24. Results were comparable to the primary analysis results and indicated a mean change from Baseline in LDL-C of -55.3% at Week 24 (95% CI: -63.4% to -47.2%; p<0.0001).

Using Mixed Model Repeated Measures (MMRM) Model

A sensitivity analysis was performed using an MMRM model with the MAR assumption (i.e., missing data was not imputed using LOCF or any other method). Results were also comparable to the primary analysis results and indicated a mean change from Baseline in LDL-C of -55.9% at Week 24 (95% CI: -64.8% to -47.0%; p<0.0001).

Using Baseline Observation Carried Forward (BOCF)

A sensitivity analysis using BOCF to impute missing data was performed. Results were again comparable to the primary analysis results. Using Analysis Study Week 24, mean change from Baseline in LDL-C was -49.5% at Week 24 (95% CI: -58.7% to -40.3%; p<0.0001) as summarised in Table 14.2.1.1. Using Nominal Study Visit 10 instead of Week 24, mean change from Baseline in LDL-C was -53.8% at Week 24 (95% CI: -62.5% to -45.1%; p<0.0001).

Using Wilcoxon Signed-Rank Test

A sensitivity analysis using a non-parametric approach, Wilcoxon Signed-Rank test, was performed with missing data imputed using LOCF. This analysis also showed a statistically significant (p<0.0001) percent mean change from Baseline in LDL-C.

Supplementary analyses in the CAS and PPS population

Supplementary analysis in the completer analysis set showed a mean change from Baseline in LDL-C of -55.0% at Week 24 (95% CI: -63.2% to -46.8%; p < 0.0001). Supplementary analysis in the per protocol set showed a mean change from Baseline in LDL-C of -58.2% at Week 24 (95% CI: -68.0% to -48.5%; p < 0.0001).

5.3.2.1.3.7. Ancillary analyses

Responder Analysis

Supplementary responder analyses for the primary efficacy endpoint were performed, presenting the number and percentage of subjects achieving a range of cut-offs at Week 24 as well as anytime on or after Week 8. At Week 24, approximately half of all subjects (48.8% overall) achieved a >50% reduction in LDL-C, and 86.0% of subjects achieved this cut-off at least one time point between Week 8 and end of study.

Table 18: Primary Efficacy Endpoint Supplementary Analysis: LDL-C Responder Analysis (Full Analysis Set)

	Subjects achieving a reduction in LDL-C of:	5 to 10 years N=20 n (%)	11 to 17 years N=23 n (%)	Overall N=43 n (%)
At Week 24	>15%	16 (80.0)	19 (82.6)	35 (81.4)
	>25%	13 (65.0)	19 (82.6)	32 (74.4)
	>33%	13 (65.0)	19 (82.6)	32 (74.4)
	>40%	13 (65.0)	16 (69.6)	29 (67.4)
	>50%	11 (55.0)	10 (43.5)	21 (48.8)
At any time from Week 8 [a]	>15%	20 (100.0)	23 (100.0)	43 (100.0)
	>25%	20 (100.0)	22 (95.7)	42 (97.7)
	>33%	19 (95.0)	22 (95.7)	41 (95.3)
	>40%	18 (90.0)	21 (91.3)	39 (90.7)
	>50%	18 (90.0)	19 (82.6)	37 (86.0)

Abbreviations: LDL-C=low-density lipoprotein cholesterol; N=number of subjects in the analysis set; n=number of subjects with a measurement; SD=standard deviation.

[a] Anytime on or after Week 8 up to end of study

Post-hoc analysis on 30 mg in children aged 5-10 years instead of an MTD of 20 mg

Exposure:

Initially, the comparison of adult steady state exposure to paediatric groups' exposures has shown that the maximum recommended dose of 20 mg/day compared with the reference maximum dose of 60 mg/day in adults was higher than the median value for adults at the reference doses, i.e., between the 50th and 95th percentile (please refer to Figure 8 in the PK section). Hence, based on the results of the integrated population pharmacokinetic (PK), PK/Pharmacodynamic (PD) (safety and efficacy) model, a maximum dose of 30 mg was not recommended for patients aged 5 to 10 years, as Cmax and AUC0-24h compared with the adult reference dose were considered too high in individual cases. However, individual PK parameters in the 6 subjects who increased their maximum tolerated dose (MTD) beyond the maximum recommended dose by the respective age group confirmed that the median average concentration (Cavg) and the median maximum concentration (Cmax) in these 6 subjects both were below the median average and maximum concentration for the age group, respectively (-57.8% versus -60.1%). . It was noted that the patients who increased were not close to crossing the age range, did not have a high BMI and had standard background LLT, including LA in three of them.

Efficacy:

Protocol amendment 5.0 dated 05 May 2022 allowed a dose increase beyond the original maximum dose for the age group specifying that, if after Week 24±3 days both the Investigator and the Applicant considered a patient 5 to 15 years of age to be eligible for further escalation of the lomitapide dose beyond the maximum recommended dose by the respective age group, the lomitapide dose could be increased to an extent defined by the Investigator after consultation with the Applicant based on individual safety, efficacy, and concomitant lipid-lowering treatment (LLT) criteria.

The analysis of individual and aggregated efficacy data in subjects aged 5 to 10 years with an MTD of 20 mg/day compared with those who received an MTD of 30 mg/day has shown that subjects who achieved an MTD of 30 mg/day had lower mean Baseline LDL-C levels (451.48 mg/dL, standard deviation [SD] 151.05 mg/dL versus 596.84 mg/dL, SD 204.10 mg/dL), below average change from Baseline in LDL-C at Week 24 (40.54%, SD 24.51% versus -68.65%, SD 22.56%), but achieved a comparable change in LDL C from Baseline at Week 104, when all subjects had increased their MTD

from 20 mg/day to 30 mg/day (-40.97%, SD 24.66% versus 46.23%, SD 27.02%), see also Table below. This reduction in LDL-C values is particularly noteworthy since 3 of the 6 subjects only increased to 30 mg/day late in the study (Week 92) and for all 3 subjects on lipoprotein apheresis (LA) in this subgroup, the purpose of the dose increase was to allow a reduction in frequency (n=3) or discontinuation of LA (n=3).

Table 19 LDL-C (mg/dL) and Change from Baseline at Visit after Dose Increase and Week 104 in Subjects 5 to 10 Years of Age with a Maximum Tolerated Dose of 30 mg/day

Subject	MTD 30 mg	LDL-C	Change from Baseline					
		BL	W 24		Visit after MTD		W 104	
		(mg/dL)	(mg/dL)	(%)	(mg/dL)	(%)	(mg/dL)	(%)
05/01	W 36	409.46	-88.93	-21.7	-257.12	-62.8	-270.27	-66.0
06/01	W 76 (unscheduled)	741.98	-627.92	-84.6	-595.83	-80.3	N/A	N/A
06/02	W 52	481.77	-112.13	-23.3	-250.55	-52.0	-239.34	-49.7
09/02	W 92	339.48	-140.35	-41.3	-195.26	-57.5	-195.26	-57.5
10/01	W 92	351.46	-79.26	-22.6	-90.09	-25.6	-90.09	-25.6
10/02	W 92	384.72	-191.39	-49.7	-23.20	-6.0	-23.20	-6.0

Safety and Tolerability:

Post-hoc analyses on the incidence and event rates of treatment-emergent adverse events (TEAEs) starting while the subjects were on a dose of 20 mg/day versus 30 mg/day have shown that the total incidence of TEAEs was lower (66.7% versus 89.5%), the incidence of gastrointestinal TEAEs was comparable (50.0% versus 47.4%) and the incidence of TEAEs belonging to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) of Investigations (including Preferred Terms [PTs], such as Alanine aminotransferase increased or Aspartate aminotransferase increased) was lower (16.7% versus 57.9%) in subjects who received a dose of 30 mg/day. The observation that some TEAE incidences in the subgroup on the lower maximum dose were even higher supports the hypothesis that the Investigators of the APH-19 study correctly identified those subjects who derived benefit of an increased LDL-C response due to an increase of the lomitapide dose to 30 mg/day, but did not experience tolerability or safety issues.

Table 20 Summary of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term by Dose Received at Start of Adverse Event in Subjects 5 to 10 Years of Age: Unadjusted Incidence and Event Count (Safety Analysis Set)

MedDRA SOC	2 mg		5 mg		10 mg		20 mg		30 mg	
MedDRA PT	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Total number of patients (N)	20		20		19		19		6	
Total number of TEAEs	12 (60.0)	41	7 (35.0)	27	8 (42.1)	16	17 (89.5)	117	4 (66.7)	15
Gastrointestinal disorders	5 (25.0)	17	5 (25.0)	13	4 (21.1)	4	9 (47.4)	31	3 (50.0)	5
Diarrhoea	2 (10.0)	2	1 (5.0)	1	0		5 (26.3)	9	1 (16.7)	1
Abdominal pain	5 (25.0)	9	3 (15.0)	6	0		5 (26.3)	8	0	
Vomiting	2 (10.0)	4	3 (15.0)	3	3 (15.8)	3	6 (31.6)	11	1 (16.7)	1
Investigations	8 (40.0)	10	3 (15.0)	4	2 (10.5)	2	11 (57.9)	33	1 (16.7)	1
ALT increased	1 (5.0)	2	2 (10.0)	2	0		7 (36.8)	7	0	
AST increased	2 (10.0)	2	1 (5.0)	1	1 (5.3)	1	5 (26.3)	5	0	

5.3.3. Clinical studies in special populations

Except for the paediatric population no other populations have been assessed in this procedure.

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

There is only a single study in paediatric HoFH patients (APH-19), and this population is biologically different from the adult population. Therefore data from the APH-19 paediatric study will not be pooled with the adult studies UP1002/733-005 and AEGR-733-012, and there is no plan for an integrated summary of safety.

5.3.5. Overall discussion and conclusions on clinical efficacy

5.3.5.1. Discussion

Study design. In terms of dose finding, no dose-response study was performed in paediatric patients. Instead, the starting doses, dose escalation regimens, and appropriate maximum doses for the different paediatric age ranges were determined using allometric scaling and physiologically-based PK (PBPK) modelling based on the adult starting dose of 5 mg. Both methods resulted in a similar predicted starting dose of 2 mg for the age group 5-10 and 11-15 years and of 5 mg for the age group 16-17 years. Similar as for adults, dose escalation is aimed for attenuation of GI adverse events and minimize hepatic events.

The clinical programme consisted of one pivotal study (APH-19) in paediatric patients. Study APH-19 was a Phase 3, single-arm open-label study, consisting of a 24-week dose escalation phase, followed by a 80-week long-term treatment phase to evaluate the efficacy and safety of lomitapide on top of standard of care, i.e. lipid lowering therapy (LLT) with, if applicable, lipoprotein apheresis (LA) in homozygous familial hypercholesterolemia (HoFH). The design of the pivotal study was discussed and approved by the PDCO. The design of the paediatric study is in line with the pivotal study in adults, i.e. open-label and on top of lipid lowering therapy. The study consisted of 5 periods. The screening period is followed by a run-in period of at least 6 weeks, in which patients were stabilised on current LLT (including LA, if applicable), and, following counselling by a qualified nutritionist/dietitian, were established on a diet supplying <20% of energy (calories) from fat or <30 g fat. This is considered appropriate. The efficacy phase was 24 weeks in which all patients received oral lomitapide as an add-on therapy. During the efficacy phase, subjects were to continue on the same dose of their current LLT and lomitapide was initiated at the recommended starting dose for the subject's age and escalated to the maximum dose applicable to their age. If tolerated, each four weeks, except for the first dose increase in the 5-10 years group which was eight weeks, the dose was escalated until the maximum tolerated dose (MTD) applicable to the age group (20 mg in 5-10 years, 40 mg in 11-15 years and 60 mg in 16-17 years). The efficacy phase was followed by the 80-week safety phase in which patients received the MTD of lomitapide achieved during the efficacy phase. Of note, during the safety phase, adjustments to background LLT were allowed. Since the study is a single arm study, both patients and investigators are not blinded. This was discussed and approved by the PDCO and is in line with the pivotal study in adults. Furthermore, a Data Safety Monitoring Board (DSMB) was allocated to assess the validity and integrity of the safety data. In case of tolerability issues, the dose could be reduced to a previous tolerated dose or an intermediate dose and after resolution of the cause for reduction, patients could be re-challenged. The criteria for discontinuation and dose reduction during the trial are in line with the current text in section 4.4 of the SmPC and therefore considered acceptable.

The main **inclusion criteria** were male and females, aged 5 to ≤17 years with HoFH on current LLT, including LA. HoFH was defined as genetic confirmation of 2 mutant alleles at the LDLR, apo B, PCSK9, or LDLR adapter protein 1 (LDLRAP1) gene locus or an untreated LDL-C >500 mg/dL (13 mmol/L) or treated LDL-C ≥300 mg/dL (8 mmol/L) together with either i) Cutaneous or tendon xanthoma before age 10 years or ii) Untreated LDL-C levels consistent with heterozygous familial hypercholesterolaemia in both parents. Main **exclusion criteria** were contraindications for the use of lomitapide according to section 4.3 of the EMA Summary of Product Characteristics (SmPC), including known significant or chronic inflammatory bowel disease or malabsorption, other forms of primary hyperlipoproteinaemia and secondary causes of hypercholesterolaemia, hepatic impairment (including AST or ALT at screening of >1.5 x ULN), renal insufficiency (GFR <70 mL/min/1.73 m2), uncontrolled hypertension or a life expectancy of <5 years. These are considered acceptable. Of note, the adult pivotal study included also chronic pancreatitis as exclusion criteria but the subsequent marketing authorisation and SmPC adopted broader terminology and the applicant decided to be consistent with the SmPC of authorised SmPC, i.e. to exclude chronic pancreatitis from the exclusion criteria. The dietary requirements are in general in line with those presented in the proposed SmPC. In addition to fasting lipid panel measures at several occasions during both the efficacy and safety phase (i.e. each four weeks during the first 56 weeks, then each 12 weeks up to week 104), also liver function tests were performed. This is in line with the accepted text in the current SmPC, "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".

The **primary objective and endpoint** of percent change in LDL-C from baseline to Week 24 is considered acceptable, as LDL-C is an established surrogate endpoint, although the exact impact on cardiovascular disease has not been formally tested. For patients on LA, pre-aphaeresis LDL-C levels were used. The primary endpoint and timing are clearly defined. A treatment policy strategy was used for all intercurrent events, including drug discontinuations, use of alternative treatments and changes in background LLT. This estimand may reflect the effect of initiating lomitapide therapy in clinical practice, but as it allows additional therapies to be changed based on the participants overall condition, in turn affecting outcomes. Several sensitivity analyses were defined. Five subjects (11.6%) had at least one dose reduction, 6 (14.0%) had at least one dose interruption and 2 (4.6%) discontinued study drug. Five (11.6%) subjects had a change in LLT background therapy, but a sensitivity analysis in which these subjects were excluded showed an effect very similar to the primary analysis. The **(key) secondary objectives and endpoints** are considered appropriate, in particular the change in other lipids at week 24 and the percent patients achieving the EAS recommended LDL-C target levels are relevant. No targeted estimand seems to be defined for endpoints other than the primary endpoint. But as the same estimation methods will be used, the targeted estimated is likely the same as for the primary endpoint. Therefore comments as those provided for the estimand for the primary endpoint also apply here. The analysis population and statistical methods seem appropriate for the study. In the primary analysis, a one sample t-test was used to test whether mean percentage change in LDL-C at Week 24 was different from zero. The study was powered to detect a mean percentage change in LDL-C at Week 24 of 25% which is approximately 60% of that found in the adult study. Primary and secondary analyses were all restricted to participants with at least one post-baseline follow-up measurement, which could have introduced selection bias. However, it seems that all 43 (out of 46) patients who completed the run-in phase, have been included in the FAS and primary analysis. Last observation carried forward used for imputation of missing outcomes may lead to overoptimistic estimates when the LDL-C in those that discontinue treatment increases, the sensitivity analyses that uses baseline observation carried forward may give more realistic estimates under that scenario. A hierarchical testing procedure was used to control two-sided type I error at the 5% level across the primary and key secondary endpoints. The statistical analysis plan was amended twice after first

database lock, but before final database lock (SAP version 4 and 5). Additions and changes included the responder analysis (to align with adult study), analysis for key secondary endpoint Lp(a) (because of being provided in two different units by local labs) and sensitivity analyses using BCOF (requested by FDA) and Wilcoxon signed-rank test (to align with adult study). No changes were made to primary and key secondary endpoints.

Results. A relatively high percentage of major protocol deviations was reported, mainly in the age group 11-17 years (91.3%). The majority was related to non-compliance with the IMP, this is explained by the fact that there was a conservative approach for categorisation of IMP issues (i.e. major PD for any single missed lomitapide dose). Furthermore, in 10% (5-10 years) and 26.2% (11-17 years) of the cases this involved change of LLT during the efficacy phase or LA sessions missed. Three subjects missed several LA sessions, one subjects stopped concomitant LLT at baseline, one stopped evolocumab at visit 6 (week 8), two interrupted LLT for 14 days due to covid-19, and one requested LA frequency decrease from every two weeks to once a month. Although changes in LLT, including LA, should not have happened, the reasons have been described well and are understandable. Furthermore, a planned subgroup analysis on patients with and without major protocol deviations (PP population) was performed, showing consistent results (see below). A total of 43 paediatric patients entered the efficacy phase. Although this is a relatively low number of participants, in view of the rarity of the disease and compared to the number of participant in the adults study, it is considered acceptable. Of these, a high percentage of 41 (95.3%) completed the efficacy phase of 24 weeks. The two discontinuations were due to an adverse event and both in the 11-17 years group (please refer to safety section). All 41 patients entered the safety phase of which almost all (n=39 (91%)) completed the study, which is reassuring. The 2 patients (both in the 11-17 years group) discontinued the study during the safety phase, due to a voluntary withdrawal and one due to frequent AE and non-compliance. Compliance is considered acceptable, with 100% in the group of 5-10 years and 73.9% in the 11-17 years group during the efficacy phase. A lower compliance in adolescents can be expected due to puberty and a switch from responsibility from parent to child. During the safety phase, compliance reduced to 90% and 66.7% for the age group 5-10 and 11-17 years, respectively. The decrease of compliance in the safety phase is not expected to be related to tolerability issues, but more a known phenomenon, which has previous been observed during clinical trials in paediatric and adolescent patients with other chronic diseases. Compliance to low-fat diet and dietary supplements is also considered acceptable, about 90% in the efficacy phase and 63.4-73.2% up to week 104. The MTD of 20 mg during the efficacy phase was reached in 95% of the subjects aged 5-10 years, during the safety phase 65% remained at 20 mg while 30% achieved a maximum dose of 30 mg (i.e. above the original MTD). Based on the post-hoc analysis provided, in the patients who were up titrated to 30 mg this resulted in improved efficacy with a similar safety profile. However, the dose was increased on investigator discreet and only in 6 patients. Therefore, an increase to 30 mg can be considered if sufficient clinical response is not seen after 6 months of treatment, if safety and tolerability permit (please see SmPC assessment). In the 11-17 years group the maximum dose of 40 mg was reached in 56.5% and remained relatively stable in the safety phase (61.9%). For patient ≥16 years at baseline the maximum dose was defined as 60 mg, which was reached in 3/6 patients, but they had to decrease in the safety phase. Furthermore, since it was subsequently determined that a 40 mg dose in this age group more closely matches the exposure of adults receiving 60 mg based on pharmacokinetic data the 40 mg dose is the maximum recommendation for patients aged 16 to 17 years in the product information, which is considered acceptable. Concerning the **demographics**, slightly more females were included, mainly due to the 11-17 years age group (39.1% males and 60.9% females). The main age was 10.7 years and all but one patients were white. Initially three age groups were defined, 5-10, 11-15 and 16-17 years, each with an intended number of patients of 8 (total of 24). After discussion with the PDCO that inclusion of 8 patients aged 16-17 was difficult, two age groups were defined (5-10 and 11-17, still with a total of 24 patients). Nevertheless, 6 patients aged ≥16 at baseline were

included. The median time since HoFH diagnosis was 44.8 months for the age group 5-10 and 60.6 months for the age group 11-17 years. The majority (90.7%) had genetic confirmation of 2 mutant alleles at the *LDLR* gene locus. Of the 43 subjects, 21 (48.8%) had established CVD (defined as aortic valve disease and/or atherosclerosis) at Screening. All patients reported at least 1 LLT medication, 67.4% reporting ≥2 medications and 11.6% reporting ≥3 medications, most frequently HMG CoA reductase inhibitors (including rosuvastatin, atorvastatin, and atorvastatin calcium) and other lipid modifying agents (74.4%; including ezetimibe and evolocumab). A total of 6 (30.0%) subjects 5 to 10 years and 13 (56.5%) subjects 11 to 17 years received LA during the efficacy phase, most of them on a weekly basis.

Concerning the **primary efficacy endpoint**, treatment with lomitapide resulted in a substantial reduction in LDL-C of 53.9%, corresponding to a decrease in median baseline LDL-C of 11.3 mmol/L (435.8 mg/dL) to 4.5 mmol/L (175.4 mg/dL)($p<0.0001$), which is considered a clinically relevant effect. The different sensitivity and supplementary analyses showed robustness of conclusion for the primary endpoint, including the per-protocol analysis in the 27 patients without major protocol deviations such as change in LLT (mean difference -58.2%). The **key secondary endpoint**, change in non-HDL-C, TC, VLDL-C, apo-B, triglycerides are in line with the primary endpoint on LDL-C. Concerning Lp(a), the number of subjects is limited, but the results point in a similar direction, although slightly less clear. The effect on improvement on HDL-C is moderate. Both the primary and key secondary efficacy results are in line with those observed in adults. For all lipids, the efficacy shown during the efficacy phase continues during het safety phase, although slightly less. This observation might be explained by a change in LLT or the slightly increase in non-compliance. During the efficacy phase change of LLT and LA was not permitted, but in the safety phase it was. LLT was discontinued in 3 patients, reduced in 2, and increased in 4 subjects, all except for one in the 5-10 years group. In total, in 8 out of 17 subjects receiving LA at baseline, LA was reduced in frequence and/or discontinued. Nevertheless, also the effect sizes observed in the safety phase are considered clinically relevant and therefore this issue is not further pursued. Another **secondary endpoint** was achievement of the recommended target of LDL-C. The LDL-C target goal recommended by the European Atherosclerosis Society (EAS) changed during the study period from <135 mg/dL (3.5 mmol/L) (included as secondary endpoint) to 115 mg/dL (3.0 mmol/L) (included as exploratory endpoint). The cumulative percentage of subjects achieving LDL-C threshold of 135 mg/dL *at* 24 weeks was 41.9% (35.0% in the 5-10 years age group and 47.8 in the 11-17 years age group). The more recent target goal of 3.0 mmol/L at 24 weeks was reached in 37.2% of the patients, including 25.0% in the 5-10 years group and 47.8% in the 11-17 years group. No improvements in the exploratory endpoint of carotid intima-media thickness have been observed, which can be expected considering the limited treatment duration for this endpoint. Xanthomas reduced in 88.9% of the patients with pre-existing xanthomas and in 48.1% resolution was reported. In a total of 3 subjects the size increased. During the 104 weeks, a total of 4 new (cutaneous) xanthomas were reported. Overall, the results on xanthomas supports the clinical relevance of LDL-C reduction. Palatability was good, since >80% of the parents/guardians at all time points on study reported a pleasant reaction from their child on taking the study drug and did not report issues with refusal to take. It is noted that the responder analysis have been added to the statistical analysis plan after database closure, which may result in choice of thresholds based on the data. In the adult study the thresholds 15%, 25% and 50% at 24 weeks were used, and will therefore be also discussed for the paediatric patients. A reduction of respectively 15%, 25% and 50% at 24 weeks of treatment was achieved in 80.0%, 65.0% and 55.0% of the patients in the 5-10 years group and 82.6%, 82.6% and 43.5% in the 11-17 years group. This is considered of clinical relevance.

Concerning the **subgroup analyses** of the primary and key secondary endpoints. Overall there is consistency among the subgroups age groups, sexes, documented and established CVD history,

reaching MTD for age group, and having dose reduction during the Efficacy Phase. However, patients with the LDLR function defective/defective (partial or complete reduction in LDLR activity) show a considerable lower effect as compared to the other subgroups (negative/negative, complete absence of functional LDLR). However, it is noted that the baseline value in defective/defective was about 2/5 lower as for negative/negative, and the absolute LDL-C value after 24 weeks was similar. The same holds for patients on LLT with LA, which show a lower effect as compared to patients without LA. However, also in these subgroups a considerable difference in baseline value LDL-C was observed, with patients on LA having lower LDL-C levels (315 mg/dL, 8.1 mmol/L) as compared to those not on LA (532 mg/dL, 13.8 mmol/L) and the absolute LDL-C after 24 weeks was in the same range for both subgroups. Therefore, all effects were considered of clinical relevance.

5.3.5.2. Conclusions on the clinical efficacy

Treatment with lomitapide resulted in a substantial decrease in LDL-C in the paediatric population of 5-17 years of age. The primary endpoint is further supported by beneficial effects in other lipid parameters.

5.4. Clinical safety

Please refer to the table of studies in section 5.1.2.

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The primary data to support the safety and efficacy of lomitapide in paediatric patients with HoFH are derived from the paediatric HoFH study APH-19 that evaluated 43 paediatric subjects from ages 5 to 17 years, in addition to experience in the adult population.

All analyses were performed on the Safety Population, defined as all subjects who received any amount of study medication. Subjects were analysed as treated.

5.4.2. Patient exposure

Overall, 43 paediatric subjects received at least 1 dose of lomitapide in study APH-19. Treatment exposure data for study APH-19 is summarised in the table below.

A total of 19 (95.0%) subjects aged 5 to 10 years achieved the maximum dose for that age group during the Efficacy Phase (20 mg). In the Safety Phase, 6 of these 19 subjects went on to reach an MTD of 30 mg. Per protocol, the maximum dose for subjects 11 to 15 years was 40 mg; of the 17 subjects in this age group, 13 (76.5%) achieved that dose.

The maximum dose for subjects 16 or 17 years was 60 mg; of the 6 subjects in this age group, 3 (50.0%) achieved this dose although they all had to down-titrate soon after reaching this dose due to AEs. Since it was subsequently determined that a 40 mg dose in this age group more closely matches the exposure of adults receiving 60 mg based on pharmacokinetic data the 40 mg dose is the maximum recommendation for patients aged 16 to 17 years in the product information.

Table 21: Summary of Exposure to Lomitapide, Paediatric HoFH Indication (Safety Population)

	Efficacy Phase			Safety Phase		
	5 to 10 years N=20	11 to 17 years N=23	Overall N=43	5 to 10 years N=20	11 to 17 years N=21	Overall N=41
Treatment duration (weeks)						
Mean (SD)	24.38 (0.887)	23.55 (4.136)	23.94 (3.080)	79.81 (1.246)	75.94 (13.706)	77.83 (9.925)
Median	24.00	24.29	24.00	80.07	80.00	80.00
Range	23.6 to 27.0	10.9 to 27.1	10.9 to 27.1	76.6 to 82.1	25.1 to 85.9	25.1 to 85.9
Exposure to maintenance dose (weeks)						
Mean (SD)	9.09 (1.683)	8.62 (2.443)	8.84 (2.112)	69.46 (14.187)	69.51 (19.199)	69.49 (16.730)
Median	8	8	8	77.36	79.57	78.14
Range	7.7 to 13	6 to 16	6 to 16	31 to 81	17 to 85.9	17 to 85.9
Average daily dose (mg/day)						
Mean (SD)	8.77 (1.993)	17.87 (7.452)	13.64 (7.208)	19.48 (4.866)	33.27 (10.332)	26.54 (10.645)
Median	9.73	16.74	9.88	20.00	40.00	21.62
Range	1.9 to 11.0	4.5 to 33.1	1.9 to 33.1	4.7 to 26.5	9.7 to 51.7	4.7 to 51.7
Number of doses received						
Mean (SD)	168.2 (13.13)	164.9 (28.95)	166.4 (22.80)	553.6 (17.46)	531.6 (95.94)	542.3 (69.8)
Median	168.0	170.0	168.0	559.0	560.0	560.0
Range	119 to 189	76 to 190	76 to 190	488 to 568	176 to 601	176 to 601
Maximum tolerated dose, n (%)						
5 mg	1 (5.0)	1 (4.3)	2 (4.7)	1 (5.0)	0	1 (2.4)
10 mg	0	2 (8.7)	2 (4.7)	0	1 (4.8)	1 (2.4)
20 mg [a]	19 (95.0)	3 (13.0)	22 (51.2)	13 (65.0)	3 (14.3)	16 (39.0)
30 mg	0	1 (4.3)	1 (2.3)	6 (30.0)[b]	1 (4.8)	7 (17.1)
40 mg [c]	0	13 (56.5)	13 (30.2)	0	13 (61.9)	13 (31.7)
60 mg [d]	0	3 (13.0)	3 (7.0)	0	3 (14.3)	3 (7.3)

[a] Maximum allowed dose for subjects aged 5 to 10 years at Screening. Overall, 19 of the 20 subjects in this age range reached the maximum dose during the Efficacy Phase.
[b] Subjects were allowed to increase beyond 20 mg following a protocol amendment at the request of the investigator and sponsor approval.
[c] Maximum allowed dose for subjects aged 11 to 15 years at Screening. Overall, 13 of the 17 subjects in this age range reached the maximum dose during the Efficacy Phase.

[d] Maximum allowed dose for subjects aged 16 to 17 years at Screening. Overall, 3 of the 6 subjects in this age range reached the maximum dose during the Efficacy Phase.

5.4.3. Adverse events

Overall adverse events profile

A large number of paediatric subjects (97.7% [95.0% and 100.0% for 5-10 years, and 11-17 years age groups, respectively]) reported at least one AE. Overall, 11 subjects (25.6%) reported serious AEs (20.0% and 30.4% for 5-10 years, and 11-17 years age groups, respectively). Two subjects (in the 11-17 years age group) experienced a AE (4.7%) of moderate diarrhoea resulting in treatment discontinuation.

Table 22: Summary of Treatment-Emergent Adverse Events: Number and Percentage of Subjects with TEAEs and Number of TEAEs (Safety Analysis Set)

	5 to 10 years N=20 n (%) [E]	11 to 17 years N=23 n (%) [E]	Overall N=43 n (%) [E]
Total number of TEAEs	19 (95.0) [217]	23 (100.0) [267]	42 (97.7) [484]
Total number of non-TEAEs	9 (45.0) [15]	12 (52.2) [16]	21 (48.8) [31]
Serious TEAEs	4 (20.0) [4]	7 (30.4) [12]	11 (25.6) [16]
Serious related TEAEs	1 (5.0) [1]	0	1 (2.3) [1]
TEAEs leading to study discontinuation[a]	0	2 (8.7) [2]	2 (4.7) [2]
TEAEs leading to death	0	0	0
Adverse events of special interest[b]	3 (15.0) [5]	2 (8.7) [2]	5 (11.6) [7]
Major Adverse Cardiac Events[c]	0	1 (4.3) [1]	1 (2.3) [1]
Severity[d]			
Mild	11 (55.0) [194]	6 (26.1) [171]	17 (39.5) [365]
Moderate	5 (25.0) [20]	10 (43.5) [78]	15 (34.9) [98]
Severe	3 (15.0) [3]	5 (21.7) [15]	8 (18.6) [18]
Life-threatening	0	2 (8.7) [3]	2 (4.7) [3]
Death	0	0	0
Relationship to study treatment[d]			
Related[e]	13 (65.0) [68]	19 (82.6) [96]	32 (74.4) [164]
Unrelated	6 (30.0) [149]	4 (17.4) [171]	10 (23.3) [320]
Action taken with study treatment[f,g]			
Drug withdrawn	0	2 (8.7) [2]	2 (4.7) [2]
Dose interrupted	4 (20.0) [14]	7 (30.4) [12]	11 (25.6) [26]
Dose decreased	0 [1]	4 (17.4) [19]	4 (9.3) [20]
Dose missed	1 (5.0) [4]	3 (13.0) [5]	4 (9.3) [9]
Re-challenged	0 [1]	0	0 [1]
Dose not changed	14 (70.0) [194]	7 (30.4) [227]	21 (48.8) [421]
Not applicable	0 [3]	0 [2]	0 [5]
Unknown	0	0	0

Abbreviations: AE=adverse event; AESI=adverse event of special interest; eCRF=electronic case report form; N=number of subjects in the analysis set; n=number of subjects meeting the criterion; TEAE=treatment-emergent adverse event (AE that started after the first administration of study drug).

[E]=number of TEAEs; (%)=n/N×100.

[a] TEAEs leading to study discontinuation were non-serious AESIs and considered related to study treatment in both subjects.

[b] All AESIs were considered related to study treatment.

[c] Defined by the clinical team.

[d] If a subject experienced more than 1 TEAE, the subject is counted once at the most severe or most related event.

[e] Related adverse events were those classified as having a reasonable causal relationship to the study treatment.

[f] Action taken with study treatment is presented as documented on the adverse event eCRF pages and

Most commonly reported adverse events

The most frequently reported adverse events are displayed below.

Table 23: Treatment-Emergent Adverse Events Reported in >5% of Subjects Overall (Safety Analysis Set)

	5 to 10 years N=20 n (%)	11 to 17 years N=23 n (%)	Overall N=43 n (%)
Subjects with any TEAEs	19 (95.0)	23 (100.0)	42 (97.7)
Diarrhoea	9 (45.0)	13 (56.5)	22 (51.2)
Abdominal pain	8 (40.0)	11 (47.8)	19 (44.2)
Alanine aminotransferase increased	9 (45.0)	8 (34.8)	17 (39.5)
Aspartate aminotransferase increased	7 (35.0)	8 (34.8)	15 (34.9)
Pyrexia	10 (50.0)	4 (17.4)	14 (32.6)
Vomiting	10 (50.0)	2 (8.7)	12 (27.9)
COVID-19	4 (20.0)	5 (21.7)	9 (20.9)
Anaemia	3 (15.0)	5 (21.7)	8 (18.6)
Cough	6 (30.0)	1 (4.3)	7 (16.3)
Blood creatine phosphokinase increased	4 (20.0)	2 (8.7)	6 (14.0)
C-reactive protein increased	3 (15.0)	3 (13.0)	6 (14.0)
Decreased appetite	2 (10.0)	4 (17.4)	6 (14.0)
Nasopharyngitis	3 (15.0)	3 (13.0)	6 (14.0)
Abdominal pain upper	2 (10.0)	3 (13.0)	5 (11.6)
ECG signs of ventricular hypertrophy [a]	2 (10.0)	3 (13.0)	5 (11.6)
Nausea	2 (10.0)	3 (13.0)	5 (11.6)
Transaminases increased	4 (20.0)	1 (4.3)	5 (11.6)
Headache	2 (10.0)	2 (8.7)	4 (9.3)
Oropharyngeal pain	1 (5.0)	3 (13.0)	4 (9.3)
Upper respiratory tract infection	2 (10.0)	2 (8.7)	4 (9.3)
Vitamin D deficiency	3 (15.0)	1 (4.3)	4 (9.3)
Abnormal loss of weight	0	3 (13.0)	3 (7.0)
Dry skin	1 (5.0)	2 (8.7)	3 (7.0)
Flatulence	2 (10.0)	1 (4.3)	3 (7.0)
Gastroenteritis	2 (10.0)	1 (4.3)	3 (7.0)
Pharyngitis	2 (10.0)	1 (4.3)	3 (7.0)
Xanthoma	2 (10.0)	1 (4.3)	3 (7.0)

Abbreviations: ECG=electrocardiogram; MedDRA= Medical Dictionary for Regulatory Activities; N=number of subjects in the analysis set; n=number of subjects meeting the criterion; TEAE=treatment-emergent adverse event.
(%)=n/N×100.
Adverse events were coded using the MedDRA Dictionary, version 27.0. If a subject experienced more than 1 TEAE, the subject is counted once for each preferred term.
[a] Several of these events were present at Screening but reported as AEs rather than as medical history because they had been identified based on the protocol-mandated ECG assessments.

Adverse drug reactions

Overall, 32 (74.4%) subjects had at least 1 AE considered related to study treatment by the Investigator including 13 (65.0%) subjects 5 to 10 years and 19 (82.6%) subjects 11 to 17 years. One serious related AE of transaminases increased was reported.

The most frequently reported treatment-related AEs in both age groups were in the SOCs of Gastrointestinal disorders and Investigations. AEs of ALT increased and AST increased were each reported for a total of 13 (30.2%) subjects.

Table 24: Treatment-Emergent Adverse Events Related to Study Treatment (Safety Analysis Set)

System organ class Preferred term	5 to 10 years N=20 n (%)	11 to 17 years N=23 n (%)	Overall N=43 n (%)
Subjects with any related TEAEs	13 (65.0)	19 (82.6)	32 (74.4)
Gastrointestinal disorders	9 (45.0)	15 (65.2)	24 (55.8)
Diarrhoea	6 (30.0)	11 (47.8)	17 (39.5)
Abdominal pain	7 (35.0)	10 (43.5)	17 (39.5)
Vomiting	5 (25.0)	2 (8.7)	7 (16.3)
Abdominal pain upper	2 (10.0)	1 (4.3)	3 (7.0)
Nausea	0	3 (13.0)	3 (7.0)
Flatulence	1 (5.0)	0	1 (2.3)
Frequent bowel movements	0	1 (4.3)	1 (2.3)
Investigations	10 (50.0)	11 (47.8)	21 (48.8)
Alanine aminotransferase increased	6 (30.0)	7 (30.4)	13 (30.2)
Aspartate aminotransferase increased	5 (25.0)	8 (34.8)	13 (30.2)
Transaminases increased	4 (20.0)	1 (4.3)	5 (11.6)
Blood creatine phosphokinase increased	2 (10.0)	0	2 (4.7)
Weight decreased	1 (5.0)	0	1 (2.3)
Alanine aminotransferase abnormal	0	1 (4.3)	1 (2.3)
Ultrasound liver abnormal	1 (5.0)	0	1 (2.3)
Metabolism and nutrition disorders	1 (5.0)	5 (21.7)	6 (14.0)
Decreased appetite	1 (5.0)	4 (17.4)	5 (11.6)
Hypophagia	0	1 (4.3)	1 (2.3)
Hepatobiliary disorders	2 (10.0)	0	2 (4.7)
Hepatic steatosis	2 (10.0)	0	2 (4.7)
Hepatomegaly	1 (5.0)	0	1 (2.3)

Abbreviations: MedDRA= Medical Dictionary for Regulatory Activities; N=number of subjects in the analysis set; n=number of subjects meeting the criterion; TEAE=treatment emergent adverse event (defined as an adverse event that started after administration of study drug).
(%)=n/N×100.
If a subject experienced more than 1 TEAE, the subject is counted once for each system organ class and once for each preferred term using the most related event.
Related events are those classified as having a reasonable causal relationship to the study treatment.
Adverse events were coded using the MedDRA Dictionary, version 27.0.

The MAH has identified hypophagia (common), blood creatinine phosphokinase increased (common), ultrasound liver abnormal (common), and alanine aminotransferase abnormal (common) as additional ADRs.

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

Adverse events of special interest

Gastrointestinal adverse effects

Two subjects had AESIs of 'gastrointestinal effects' (moderate diarrhoea) with both subjects () discontinuing from the study.

Table 25: Gastrointestinal Adverse Events (Safety Analysis Set)

System organ class Preferred term	5 to 10 years N=20 n (%)	11 to 17 years N=23 n (%)	Overall N=43 n (%)
All causality			
Gastrointestinal disorders	13 (65.0)	18 (78.3)	31 (72.1)
Diarrhoea	9 (45.0)	13 (56.5)	22 (51.2)
Abdominal pain	8 (40.0)	11 (47.8)	19 (44.2)
Vomiting	10 (50.0)	2 (8.7)	12 (27.9)
Abdominal pain upper	2 (10.0)	3 (13.0)	5 (11.6)
Nausea	2 (10.0)	3 (13.0)	5 (11.6)
Flatulence	2 (10.0)	1 (4.3)	3 (7.0)
Constipation	0	2 (8.7)	2 (4.7)
Odynophagia	2 (10.0)	0	2 (4.7)
Abdominal distension	1 (5.0)	0	1 (2.3)
Dry mouth	0	1 (4.3)	1 (2.3)
Frequent bowel movements	0	1 (4.3)	1 (2.3)
Gastrooesophageal reflux disease	0	1 (4.3)	1 (2.3)
Toothache	1 (5.0)	0	1 (2.3)
Treatment related			
Gastrointestinal disorders	9 (45.0)	15 (65.2)	24 (55.8)
Diarrhoea	6 (30.0)	11 (47.8)	17 (39.5)
Abdominal pain	7 (35.0)	10 (43.5)	17 (39.5)
Vomiting	5 (25.0)	2 (8.7)	7 (16.3)
Abdominal pain upper	2 (10.0)	1 (4.3)	3 (7.0)
Nausea	0	3 (13.0)	3 (7.0)
Flatulence	1 (5.0)	0	1 (2.3)
Constipation	0	0	0
Odynophagia	0	0	0
Abdominal distension	0	0	0
Dry mouth	0	0	0
Frequent bowel movements	0	1 (4.3)	1 (2.3)
Gastrooesophageal reflux disease	0	0	0
Toothache	0	0	0

Abbreviations: MedDRA= Medical Dictionary for Regulatory Activities; N=number of subjects in the analysis set; n=number of subjects meeting the criterion; TEAE=treatment-emergent adverse event.
(%)=n/N×100.
If a subject experienced more than 1 TEAE, the subject is counted once for the system organ class and once for each preferred term.
Related events are those classified as having a reasonable causal relationship to the study treatment.
Adverse events were coded using the MedDRA Dictionary, version 27.0.

Treatment emergent adverse events in the SOC of Gastrointestinal disorders were reported by 72.1%. All events were mild or moderate in severity and none were SAEs. 55.8% of paediatric subjects experienced at least 1 treatment-related GI event. The estimated median time to first gastrointestinal TEAE in paediatric subjects was 130 days.

Hepatic related adverse events

Hepatic related adverse events included elevations of hepatic transaminases resulting in discontinuation of lomitapide; Elevations of hepatic transaminases >3 × ULN that persist despite dose reduction or interruption; Elevations of hepatic transaminases ≥5 × ULN; Symptomatic liver injury; Other hepatic evaluation and testing or any histology obtained from liver biopsy and imaging evaluations.

Hepatic related adverse events are displayed in the table below.

Table 26: Hepatic treatment emergent related adverse events

PREFERRED TERM	ADULT HOFH (≥18 YEARS)	PAEDIATRIC HOFH (5 TO 17 YEARS)
	STUDY UP1002/AEGR-733-005 & AEGR-733-012 (N = 29) N (%)	STUDY APH-19 (N=43) N (%)
Subjects with any hepatic related TEAE	10 (34.5)	21 (48.8)
Alanine aminotransferase increased	6 (20.7)	13 (30.2)
Aspartate aminotransferase increased	3 (10.3)	13 (30.2)
Transaminases increased	1 (3.4)	5 (11.6)
Hepatic steatosis	2 (6.9)	2 (4.7)
Alanine aminotransferase abnormal	0	1 (2.3)
Hepatomegaly	1 (3.4)	1 (2.3)
Ultrasound liver abnormal	0	1 (2.3)
Hepatotoxicity	2 (6.9)	0
International normalised ratio increased[1]	1 (3.4)	0
International normalised ratio abnormal[1]	1 (3.4)	0
Liver function test abnormal	1 (3.4)	0
Blood alkaline phosphatase increased	1 (3.4)	0

[1] Subjects receiving concomitant warfarin

In study APH-19 21 (48.8%) of 43 paediatric subjects with HoFH had at least 1 event of hepatic related AE with similar frequency in the two age groups. All hepatic treatment-related AEs were mild to moderate in intensity, except for the 1 paediatric subject with a SAE.

In the paediatric population, the estimated median time to first hepatic AE was 411 days overall, and longer in the 11 to 17 years age group (644 days) than in the 5 to 10 years age group (350 days).

- Hepatic abnormalities

Three patients all in the 5 to 10 years age group, had AESIs of 'hepatic abnormalities'.

One patient was diagnosed with mild hepatomegaly and mild hepatosteatosis with non-clinically significant elevated ALT and AST, after 197 days of lomitapide treatment. The lomitapide dose remained unchanged and after 1 year the hepatomegaly and steatosis were, based on the ultrasound, resolved and both ALT and AST values had normalized.

Another patient was diagnosed with hepatic steatosis and elevated ALT and AST after 336 days of lomitapide treatment. Lomitapide treatment remained unchanged, but treatment with ezetimibe was discontinued, as it might have increased transaminases according to the Investigator. After 1 month steatosis was considered resolved and AST and ALT values normalised.

The third patient had a severe AESI of transaminases increased, (ALT 8.6 × ULN and AST 4.6 × ULN) which met the criteria for level 4 hepatotoxicity per APH-19 study protocol, from Day 225 which resolved on Day 244. The Investigator considered there was a reasonable causal relationship to study treatment and study treatment was interrupted temporarily until liver function was normalised. This subject experienced a second AESI of transaminases increased starting on Day 580 (ALT 5.4 × ULN and AST 4.0 × ULN, based on external laboratory tests) and treatment was interrupted. On Day 601

AST and ALT were normalised and on Day 605 lomitapide was restarted in decreased dose (10 mg/day). Twenty-two days later ALT (4.5 x ULN) and AST (4.0 x ULN) were elevated, requiring dose interruption. After ALT and AST normalised, lomitapide was restarted at 5 mg/day.

- Liver function tests

A total of 7 subjects had transaminase values exceeding thresholds for Hepatotoxicity Level 2 or higher (AST or ALT >3.0 × ULN or higher).

ALT values >3 × ULN were reported in 3 subjects (15.0%) in the 5 to 10 years age group (one of these subjects also had values >5× ULN) and 3 subjects (13.0%) in the 11 to 17 years age group. ALT values >5 × ULN were reported for 1 subject (5.0%) in the 5 to 10 years age group and 1 subject (4.3%) in the 11 to 17 years age group.

AST values >3 × ULN were reported in 2 subjects (10.0%) in the 5 to 10 years age group and 1 subject (4.3%) in the 11 to 17 years age group.

Concurrent ALT and AST values exceeding hepatotoxicity thresholds were reported for 2 subjects. In addition, one subject had an AST value >3 × ULN and a clinically significant ALT value <3 × ULN at the same time. For all 3 subjects, transaminase values returned to normal levels with either a drug decrease, drug interruption, or no change to dosing levels.

Dose reduction (1 patient) or interruption (2 patients) was reported for 8 hepatic liver adverse events in 3 patients. In both age group this was one patient each due multiple liver enzyme elevations with total of 5 dose alteration events needed.

Table 27: Transaminase Values Exceeding Level 1 Hepatotoxicity Thresholds and Corresponding Adverse Events (Safety Analysis Set)

Subject ID	Parameter	Week	Value	Reference Range	Lomitapide Dose	Action Taken	AE (LLT)	Severity	Causality
5 to 10 years									
	ALT	32	81.9 U/L	>3 × ULN	20 mg/day	Dose unchanged	ALT increased	Mild	Related
	ALT	52	116 U/L	>3 × ULN	20 mg/day	Dose unchanged	ALT increased	Mild	Related
	AST		140 U/L			Dose unchanged	AST increased	Mild	Related
	ALT	32	388 U/L	>5 × ULN	20 mg/day	Dose interrupted	Transaminases increased	Severe	Related
			286 U/L*	>5 × ULN*					
			346 U/L*	>10 × ULN*					
			283 U/L*	>5 × ULN*					
			141 U/L	>3 × ULN					
	AST		275 U/L	>3 × ULN					
			140 U/L*	>3 × ULN*					
			189 U/L*	>5 × ULN*					
			130 U/L*	>3 × ULN*					
	ALT	80	184 U/L*	>5 × ULN*		Dose interrupted	Transaminases increased	Moderate	Related
			152 U/L*	>3 × ULN*					
	AST		124 U/L*	>3 × ULN*					
			123 U/L*	>3 × ULN*					

* Values marked by an asterisk were obtained at an external laboratory with lower reference ranges

Subject ID	Parameter	Week	Value	Reference Range	Lomitapide Dose	Action Taken	AE (LLT)	Severity	Causality
11 to 17 years									
	ALT	16	93 U/L	>3 × ULN	40 mg/day	Dose reduced	ALT increased	Mild	Related
		28	162 U/L	>5 × ULN	40 mg/day	Dose reduced	ALT increased	Moderate	Related
		36	100 U/L	>3 × ULN	30 mg/day	Dose unchanged	ALT increased	Mild	Related
		40	132 U/L			Dose unchanged	ALT increased	Moderate	Related
		44	93 U/L		30 mg/day	Dose reduced	ALT increased	Mild	Related
		52	112 U/L		20 mg/day	Dose unchanged	ALT increased	Mild	Related
	ALT	48	151.3 U/L	>3 × ULN	20 mg/day	Dose unchanged	ALT abnormal	Moderate	Related
	AST	52	148 U/L	>3 × ULN	40 mg/day	Dose unchanged	AST increased	Mild	Related
	ALT	52	162 U/L	CS <3 × ULN	-	-	-	-	-
	ALT	92	110 U/L	>3 × ULN	40 mg/day	Dose unchanged	ALT increased	Moderate	Related

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CS=clinically significant (abnormal); LLT=lipid-lowering therapy; ULN=upper limit of normal.

Hepatotoxicity levels were defined in Section 7.3.2 of the protocol (Appendix 16.1.1) as follows:

Level 1: ALT or AST 1.1 to 2.9 × ULN

Level 2: ALT or AST 3.0 to 4.9 × ULN on 2 separate occasions and at least 7 days apart

Level 3: ALT or AST ≥5 × ULN on 2 separate occasions and at least 7 days apart

Level 4: ALT or AST levels ≥10 × ULN at 1 single time point

In symptomatic patients, ALT >5 × ULN AND total bilirubin >2 × ULN on 2 separate occasions and at least 7 days apart.

ALP >5 × ULN on 2 separate occasions and at least 7 days apart.

Total bilirubin is >2 × ULN on 2 separate occasions and at least 7 days apart in the absence of Gilbert's syndrome or haemolysis.

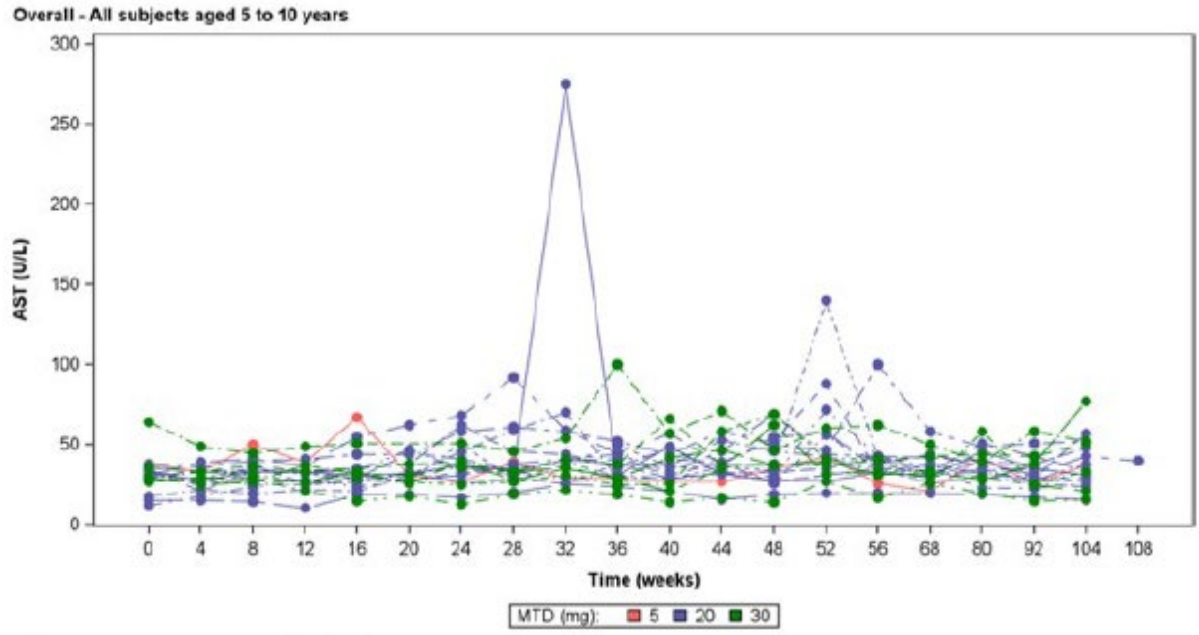
One subject experienced a serious treatment-related event of transaminases increased (up to >10 x ULN by an external local laboratory [closer to the residential area of the subject's family] with lower reference values; equivalent to >5 x ULN according to the internal local laboratory reference range of the investigational site and a subsequent moderate AESI of transaminases increased. However, by dose interruption, reduction and re-escalation, the subject remained within the study to allow continuation of therapy.

Table 28: Hepatic Treatment-Emergent Adverse Events (Safety Analysis Set)

Preferred term	5 to 10 years N=20 n (%)	11 to 17 years N=23 n (%)	Overall N=43 n (%)
Number of subjects with hepatic TEAE	12 (60.0)	11 (47.8)	23 (53.5)
All causality			
Alanine aminotransferase increased	9 (45.0)	8 (34.8)	17 (39.5)
Aspartate aminotransferase increased	7 (35.0)	8 (34.8)	15 (34.9)
Transaminases increased	4 (20.0)	1 (4.3)	5 (11.6)
Blood alkaline phosphatase increased	2 (10.0)	0	2 (4.7)
Hepatic steatosis	2 (10.0)	0	2 (4.7)
Alanine aminotransferase abnormal	0	1 (4.3)	1 (2.3)
Bilirubin conjugated increased	1 (5.0)	0	1 (2.3)
Hepatomegaly	1 (5.0)	0	1 (2.3)
Ultrasound liver abnormal	1 (5.0)	0	1 (2.3)

Liver enzyme elevations over time are displayed in the figures below.

Figure 20: AST Profiles Over Time, by Subject MTD: Paediatric HoFH Study APH-19 (Safety Analysis Set)



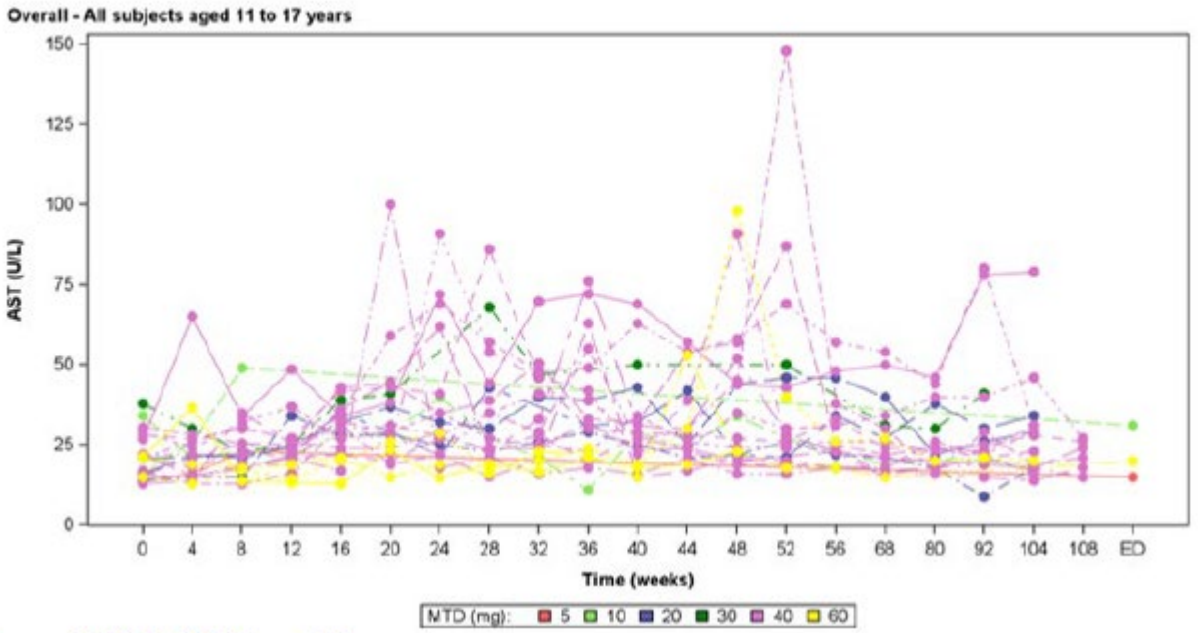


Figure 21: ALT Profiles Over Time, by Subject MTD: Paediatric HoFH Study APH-19 (Safety Analysis Set)

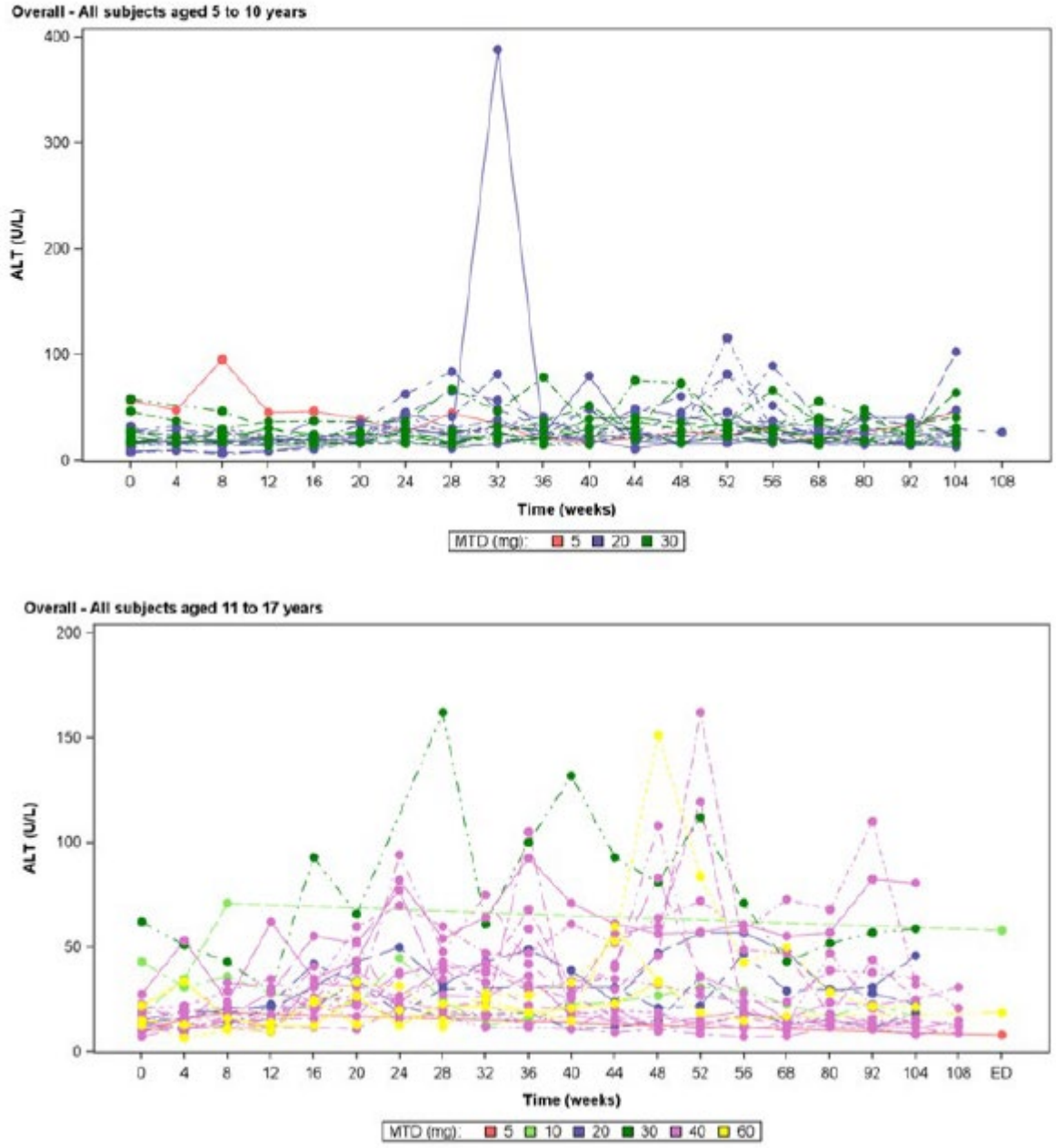


Table 29: Observed Values and Changes from Baseline to Week 24, Week 56 and Week 104 for Liver Function Tests in Paediatric HoFH study APH-19 (Safety Analysis Set)

Age Group	5 to 10 Years (N=20)				11 to 15 Years (N=23)			
Variable / Time Point	Observed Value at Time Point		Observed Change		Observed Value at Time Point		Observed Change	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Alanine aminotransferase (U/L)								
Baseline	20	25.12 (14.081)			23	18.70 (11.993)		
Efficacy Phase, Week 24	20	31.02 (11.950)	20	5.90 (20.533)	20	37.55 (24.495)	20	20.55 (24.651)
Safety Phase, Week 56	20	33.26 (17.755)	20	8.14 (20.388)	20	31.33 (19.305)	20	12.34 (16.469)
EOT, Week 104	20	32.09 (21.031)	20	6.97 (24.023)	19	25.32 (18.727)	19	6.12 (16.325)
Aspartate aminotransferase (U/L)								
Baseline	20	31.01 (10.522)			23	21.17 (6.912)		
Efficacy Phase, Week 24	20	38.59 (14.276)	20	7.58 (15.030)	20	36.60 (20.720)	20	15.65 (20.363)
Safety Phase, Week 56	20	39.10 (17.171)	20	8.10 (16.048)	19	29.00 (11.205)	19	8.07 (12.047)
EOT, Week 104	20	37.20 (15.344)	20	6.20 (14.295)	18	27.17 (15.302)	18	6.24 (14.043)
Total bilirubin (µmol/L)								
Baseline	20	5.944 (2.1174)			23	8.282 (3.7661)		
Efficacy Phase, Week 24	20	6.040 (2.3476)	20	0.095 (2.6882)	20	9.428 (4.3872)	20	1.050 (3.1308)
Safety Phase, Week 56	20	5.881 (2.2248)	20	-0.064 (2.3456)	19	8.70 (3.8163)	19	0.879 (3.6808)
EOT, Week 104	20	6.377 (2.7976)	20	0.432 (2.6485)	19	8.774 (2.9428)	19	0.517 (3.9844)
Alkaline phosphatase (U/L)								
Baseline	20	230.20 (43.906)			23	135.13 (66.415)		
Efficacy Phase, Week 24	20	209.20 (52.289)	20	-21.00 (52.128)	20	118.50 (62.863)	20	-26.80 (36.618)
Safety Phase, Week 56	20	226.65 (50.568)	20	-3.55 (52.561)	20	120.30 (80.243)	20	-25.30 (46.930)
EOT, Week 104	20	270.90 (62.317)	20	40.70 (59.927)	17	117.06 (65.699)	17	-36.18 (48.011)
Lipid accumulation (%), NMR								
Baseline	2	3.435 (0.7283)			17	3.718 (2.1896)		
Efficacy Phase, Week 24	2	11.055 (11.5329)	1	-0.020 (NA)	15	8.765 (5.4235)	15	5.515 (4.8214)
Safety Phase, Week 56	1	16.260 (NA)	0	-	13	8.095 (5.0872)	15	4.092 (4.5038)
EOT, Week 104	4	9.218 (6.4554)	2	1.855 (2.5244)	13	8.172 (4.9446)	13	5.255 (4.4383)

Abbreviations: EoT=end of treatment; N=number of subjects in the analysis set.
Baseline is defined as the last non-missing value prior to the subject receiving study treatment in the Efficacy Phase (Visit 4).
At each time point, only subjects with a value at both Baseline and that time point are included in the change from Baseline column.
Note: The reference ranges differ by age, sex, and site and are therefore not provided.

- Lipid Accumulation in the Liver

Although all subjects in study APH-19 were to undergo NMR imaging unless it was contraindicated or not feasible, NMR imaging was used for hepatic fat assessment predominantly in subjects 11 to 17 years of age (17/23 subjects compared to 2/20 subjects in the 5 to 10 years age group). Vice versa, ultrasound scans were performed in 17/20 subjects 5 to 10 years of age compared to 2/23 in subjects 11 to 17 years of age. Results are provided below.

Table 30: Summary of Lipid Accumulation in the Liver Over Time (Safety Analysis Set)

		NMR Scan		Ultrasound Scan	
Visit	Result	5 to 10 Years	11 to 17 Years	5 to 10 Years	11 to 17 Years
Baseline	Total	2 (100.0)	17 (100.0)	17 (100.0)	2 (100.0)
	≤10% liver fat	2 (100.0)	16 (94.1)	17 (100.0)	2 (100.0)
	>10% and ≤20% liver fat	0	1 (5.9)	0	0
	>20% liver fat	0	0	0	0
Efficacy Phase, Week 24	Total	4 (100.0)	19 (100.0)	15 (100.0)	2 (100.0)
	≤10% liver fat	1 (25.0)	12 (63.2)	15 (100.0)	2 (100.0)
	>10% and ≤20% liver fat	1 (25.0)	2 (10.5)	0	0
	>20% liver fat	0	1 (5.3)	0	0
	No result [a]	2 (50.0)	4 (21.1)	0	0
Safety Phase, Week 56	Total	3 (100.0)	18 (100.0)	16 (100.0)	2 (100.0)
	≤10% liver fat	0	9 (50.0)	15 (93.8)	2 (100.0)
	>10% and ≤20% liver fat	1 (33.3)	4 (22.2)	1 (6.3)	0
	>20% liver fat	0	0	0	0
	No result [a]	2 (66.7)	5 (27.8)	0	0
EoT, Week 104	Total	4 (100.0)	15 (100.0)	15 (100.0)	1 (100.0)
	≤10% liver fat	3 (75.0)	11 (73.3)	15 (100.0)	0
	>10% and ≤20% liver fat	1 (25.0)	4 (26.7)	0	1 (100.0)
	>20% liver fat	0	0	0	0

Baseline Total = number of subjects within each scan type and age group with a scan date on or within 21 days from start of treatment date.
Post-baseline Total = number of subjects with scan date within each scan type and age group.
n = the number of subjects meeting the criterion. (%) = [(n/Total)*100].
[*] One subject (13/06) switched modality of scan type between Baseline and Week 24 (Baseline = ultrasound; Week 24 = NMR).
[a] Most scans with no valid result were done at Site 12, where a large number of scans could not be evaluated due to 'Global Swapping' from Baseline up to and including Week 56; thereafter the NMR scanner at the site was replaced.

- Relation between hepatic fat and liver enzymes

NMR imaging (generally the older age group of 11-17 years) yielded Pearson's correlation coefficients of 0.30 (95% CI: 0.05, 0.52) and 0.18 (95% CI: -0.09, 0.42) for ALT and AST. For ultrasound scans the Spearman ranked correlation coefficient was 0.19 (95% CI: -0.06, 0.42) for both ALT and AST. This weak correlation is consistent with the findings from the pivotal adult HoFH study.

Hepatic, small bowel/intestinal, pancreatic and colorectal tumours

No AESIs in the categories of 'hepatic, small bowel/intestinal, pancreatic, and colorectal tumours' or 'major congenital anomalies' were reported.

Musculoskeletal TEAEs

Five subjects (11.6%) had an AE in the SOC musculoskeletal and connective tissue disorders, all aged 11 to 17 years, including 2 subjects with arthralgia, and 1 subject each with exostosis, myalgia, and

tendon disorder. All events were mild to moderate, assessed as not being related, and resolved without any action taken except for an SAE of tendon disorder that was severe, unrelated, and resulted in a dose interruption because of poor oral intake due to the severe pain resulting from right hip tendinopathy and tear of the left gluteus medius tendon.

The myalgia AE (Day 251) was mild, unrelated to study drug, and resolved without treatment or dose change after 6 days. The subject was taking ezetimibe (10 mg QD) and atorvastatin (80 mg QD). This subject did not experience an increase of CK during the study.

- Creatine Kinase

A total of 6 events of blood creatinine phosphokinase increased were reported in 6 subjects (4 subjects in the 5 to 10 years age group and 2 subjects in the 11 to 17 years age group). Of these, 2 events in 2 subjects (4.7% overall; both in the 5 to 10 years age group) were considered related to treatment (see table below). One subject had study drug interrupted due to one of the related events.

At Week 56, the 5 to 10 years age group showed an increase from Baseline in mean CK levels from 89.85 U/L to 118.45 U/L and the 11 to 17 years age group showed an increase from 88.26 U/L to 103.50 U/L. At Week 104, the 5 to 10 years age group increased to 138.62 U/L in mean CK levels and the 11 to 17 years age group mean CK was 118.37 U/L.

Table 31: Overview of Subjects with Clinically Significant Creatine Kinase Elevations

Subject	Age group	CS CK value(s) post-Baseline	Corresponding AE	Relatedness	Action taken	Last dose before occurence[1]	Concomitant LLT medication
	5 to 10 years	Max on Day 307: 992 U/L (CS) Values at least NCS high Day 255–482, with further CS value on Day 363 (395 U/L)	Blood creatine phosphokinase increased (Day 255–532 [277 days])	Not related	Dose not changed	On 20 mg	Ezetimibe (10 mg QD oral) Rosuvastatin (20 mg QD oral)
	5 to 10 years	Max on Day 222: 276 U/L (CS)	Blood creatine phosphokinase increased (Day 222–253 [31 days])	Not related	Dose not changed	On 20 mg	Atorvastatin (20 mg QD oral)
	5 to 10 years	Max on Day 309: 397 U/L (CS)	Blood creatine phosphokinase increased (Day 309–327 [18 days])	Related	Dose not changed	On 20 mg	Rosuvastatin (10 mg QD oral)
	5 to 10 years	Max on Day 172: 614 U/L (CS)	Blood creatine phosphokinase increased (Day 172–225 [53 days])	Related	Drug interrupted Day 173– Day 174 (1 day)	On 20 mg	Atorvastatin calcium (10 mg QD oral until Day 207, when LLT was interrupted)
	11 to 17 years	Max on Day 279: 253 U/L (NCS) CS values on Day 335 (250 U/L) and Day 362 (164 U/L)	Blood creatine phosphokinase increased (Day 335–393 [58 days])	Not related	Dose not changed	On 20 mg	Atorvastatin (30 mg QD oral) Ezetimibe (10 mg QD oral)
	11 to 17 years	Max on Day 645 (352 U/L) (CS)	Blood creatine phosphokinase increased (Day 645–729 [84 days])	Not related	Dose not changed	On 40 mg	-

Abbreviations: AE=adverse event; CK=creatine kinase; CS=clinically significant; LLT=lipid-lowering therapy; Max=maximum; NCS=not clinically significant; QD=once daily.
[1] Lomitapide capsules were to be administered orally once daily to all subjects. The last dose before occurrence refers to the dose of lomitapide being taken by the subject at the time of the CS CK value(s).

Serious adverse events

Overall, 11 (25.6%) subjects had SAEs during the study, including 4 (20.0%) subjects 5 to 10 years and 7 (30.4%) subjects 11 to 17 years (Table 29). All SAEs occurred in the Safety Phase. Three SAEs were graded as life-threatening: aortic arteriosclerosis (assessed as a MACE by the Sponsor), aortic valve disease mixed, and subdural haematoma. The SAEs of chest pain and cataract were graded as moderate. All other SAEs were graded as severe. The SAE of transaminases increased was considered

related to study treatment by the Applicant. No subject discontinued study treatment permanently due to an SAE.

Table 32: Summary of Serious Adverse Events (Safety Analysis Set)

System organ class Preferred term	5 to 10 years N=20 n (%) [E]	11 to 17 years N=23 n (%) [E]	Overall N=43 n (%) [E]
Subjects with any serious adverse event	4 (20.0) [4]	7 (30.4) [12]	11 (25.6) [16]
Infections and infestations	1 (5.0) [1]	2 (8.7) [3]	3 (7.0) [4]
Vascular device infection	0	2 (8.7) [2]	2 (4.7) [2]
Appendicitis	1 (5.0) [1]	0	1 (2.3) [1]
Septic shock	0	1 (4.3) [1]	1 (2.3) [1]
Injury, poisoning and procedural complications	0	3 (13.0) [3]	3 (7.0) [3]
Arteriovenous fistula thrombosis	0	1 (4.3) [1]	1 (2.3) [1]
Shunt occlusion	0	1 (4.3) [1]	1 (2.3) [1]
Subdural haematoma	0	1 (4.3) [1]	1 (2.3) [1]
Cardiac disorders	0	2 (8.7) [2]	2 (4.7) [2]
Aortic valve disease mixed	0	1 (4.3) [1]	1 (2.3) [1]
Chest pain	0	1 (4.3) [1]	1 (2.3) [1]
Eye disorders	1 (5.0) [1]	0	1 (2.3) [1]
Cataract	1 (5.0) [1]	0	1 (2.3) [1]
General disorders and administration site conditions	1 (5.0) [1]	0	1 (2.3) [1]
Vascular device occlusion	1 (5.0) [1]	0	1 (2.3) [1]
Investigations	1 (5.0) [1]	0	1 (2.3) [1]
Transaminases increased	1 (5.0) [1]	0	1 (2.3) [1]
Musculoskeletal and connective tissue disorders	0	1 (4.3) [1]	1 (2.3) [1]
Tendon disorder	0	1 (4.3) [1]	1 (2.3) [1]
Renal and urinary disorders	0	1 (4.3) [1]	1 (2.3) [1]
Nephrolithiasis	0	1 (4.3) [1]	1 (2.3) [1]
Respiratory, thoracic and mediastinal disorders	0	1 (4.3) [1]	1 (2.3) [1]
Pulmonary embolism	0	1 (4.3) [1]	1 (2.3) [1]
Vascular disorders	0	1 (4.3) [1]	1 (2.3) [1]
Aortic arteriosclerosis	0	1 (4.3) [1]	1 (2.3) [1]

Deaths

No subjects died during study treatment.

One subject died during the Run-in Period, 7 days after having been enrolled in the study and prior to initiation of lomitapide treatment. The subject had only received treatment with atorvastatin for approximately 1 year prior to enrolment into the study. Severe and probably insufficiently treated disease resulted in ischemic heart disease and death of this subject.

Another subject died 103 days after last lomitapide administration and completion of the study of pulseless electrical activity. The subject received 729 days of lomitapide treatment. The subject had experienced 2 SAEs during the study, of which one was a major adverse cardiac event (MACE), i.e., atherosclerosis of aorta when the subject underwent major coronary artery bypass graft (CABG) surgery. The second SAE was subdural haematoma, which prolonged the initial hospitalization for the SAE of atherosclerosis of aorta.

5.4.5. Discontinuation due to adverse events

Two (5%) subjects discontinued within the first three months of the study due to a moderate diarrhoea, who declined to continue the study on a lower dose, and using 10 mg and 20 mg lomitapide, respectively.

Adverse events resulting in a reduction in dose included GI symptoms in 13 patients (abdominal pain (n=5), decreased appetite (n=1), diarrhoea (n=5), nausea (n=1), and vomiting (n=1)), liver related AE (ALT increased (n=1)), and chest pain (n=1).

5.4.6. Safety related to drug-drug interactions and other interactions

Vitamins and essential fatty acids (EFA) supplementation

During the paediatric study, commercially available dietary oral (capsule) supplements were provided which were taken daily including vitamin E (200 IU for patients 5 to 8 years of age (in Italy only this was provided as a liquid formulation), 400 IU for patients 9 to ≤17 years of age) and EFAs (approximately 200 mg linoleic acid, 210 mg alpha linoleic acid (ALA), 110 mg eicosapentaenoic acid (EPA), and 80 mg docosahexaenoic acid (DHA)).

In the paediatric study, there were no abnormal clinically significant values reported for vitamin A, osteocalcin, uncarboxylated osteocalcin, or the ratio of uncarboxylated:total osteocalcin (as a measure of vitamin K). While there were some shifts in 25-OH vitamin D levels during the study, all subjects except one with a medical history of vitamin D deficiency, returned within normal ranges during the study. No post-Baseline clinically significant vitamin E values were reported and no subjects had a vitamin E:total lipids ratio <1.0 at any time point.

Paediatric reference ranges were not available for the central laboratory that assessed EFAs therefore the clinical significance of EFA values could not be assessed. Mean levels of EFAs remained stable or increased (compared to baseline) during the study with the exception of ALA, linoleic acid, EPA and eicosatrienoic acid. ALA, linoleic acid, EPA levels dropped by Week 24 but then increased from Week 56, however remained below baseline mean levels by the end of the study. Mean levels of eicosatrienoic acid decreased during the study for the 5 to 10 years age group, however they increased for the 11 to 17 years age group to within normal adult ranges by the end of the study.

5.4.7. Vital signs and laboratory findings

Growth and maturation

While there were a few clinically significant high thyroid stimulating hormone levels in the study, these were reported as mild, not related to treatment and treatment with lomitapide continued unchanged.

Sexual maturation was assessed using Tanner Staging and sex hormone values were assessed in subjects with Tanner Stage ≥2. No clinically significant values for oestradiol or testosterone were reported during the study; increases in oestradiol and testosterone were within expected developmental ranges. These clinical data override the potential signal observed in the juvenile rat toxicity studies submitted to EMA in a Type II procedure in 2014 (EMEA/H/C/002578/II/012) of delayed sexual maturation.

In the 5 to 10 years age group, all subjects had a Tanner Stage of 1 up-to Week 56; at Week 104, a total of 18 (90%) subjects had a Tanner Stage of 1 and 2 (10%) subjects had Tanner Stage of 2.

In the 11 to 17 years age group, the majority of subjects were Tanner Stage 4 or 5 at Baseline. At Week 104, 14 (73.7%) subjects were Tanner Stage of 5, 4 (21.1%) subjects were Tanner Stage of 4, and 1 (5.3%) subject was Tanner Stage of 3.

Table 33: Tanner Staging at Baseline and Week 24, Week 56, and Week 104 (Safety Analysis Set)

	5 to 10 years N=20 n (%)	11 to 17 years N=23 n (%)	Overall N=43 n (%)
Baseline			
Stage 1	20 (100.0)	2 (8.7)	22 (51.2)
Stage 2	0	0	0
Stage 3	0	3 (13.0)	3 (7.0)
Stage 4	0	6 (26.1)	6 (14.0)
Stage 5	0	12 (52.2)	12 (27.9)
Total	20 (100.0)	23 (100.0)	43 (100.0)
Week 24			
Stage 1	20 (100.0)	2 (10.0)	22 (55.0)
Stage 2	0	0	0
Stage 3	0	2 (10.0)	2 (5.0)
Stage 4	0	5 (25.0)	5 (12.5)
Stage 5	0	11 (55.0)	11 (27.5)
Total	20 (100.0)	20 (100.0)	40 (100.0)
Week 56			
Stage 1	20 (100.0)	1 (5.0)	21 (52.5)
Stage 2	0	1 (5.0)	1 (2.5)
Stage 3	0	0	0
Stage 4	0	4 (20.0)	4 (10.0)
Stage 5	0	14 (70.0)	14 (35.0)
Total	20 (100.0)	20 (100.0)	40 (100.0)
Week 104			
Stage 1	18 (90.0)	0	18 (46.2)
Stage 2	2 (10.0)	0	2 (5.1)
Stage 3	0	1 (5.3)	1 (2.6)
Stage 4	0	4 (21.1)	4 (10.3)
Stage 5	0	14 (73.7)	14 (35.9)
Total	20 (100.0)	19 (100.0)	39 (100.0)

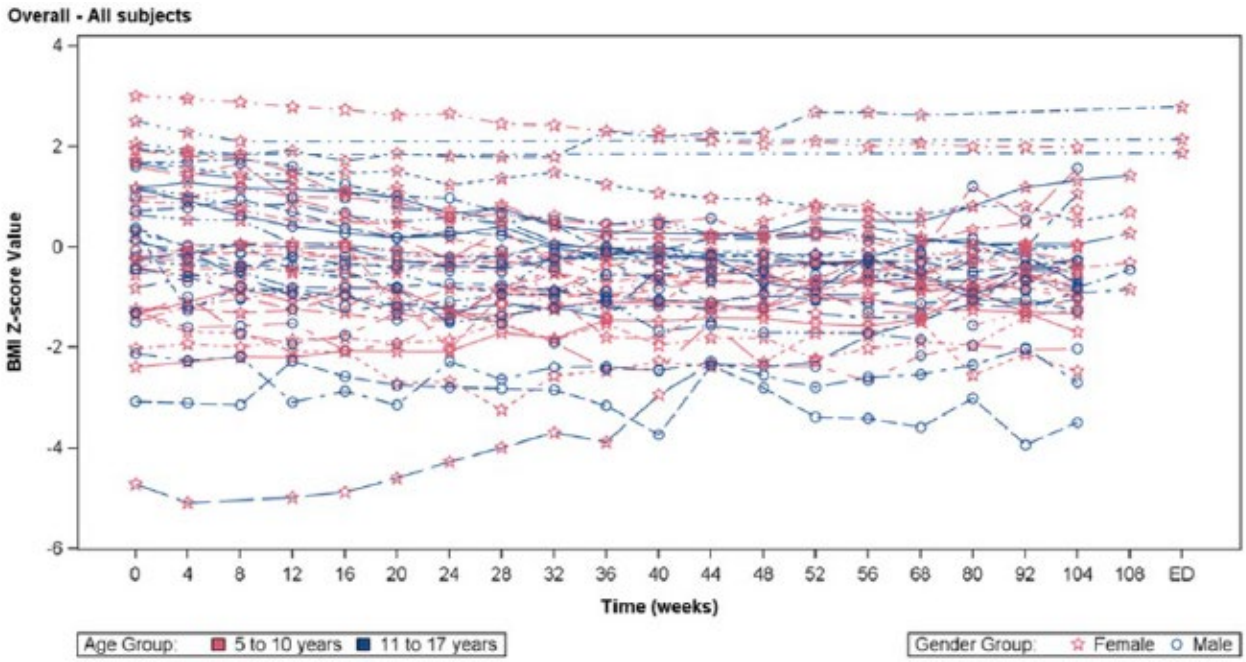
Abbreviations: N=number of subjects in the analysis set; n=number of subjects meeting the criterion.
(%)=[(n/number of subjects with a value at that visit)×100].

In each age category (5 to 10 years; 11 to 17 years) and overall, the mean change in weight, BMI and height from Baseline to each post-Baseline time point was not clinically significant, although the range was wide.

A spaghetti plot displaying BMI-for-age *z* score over time by subject showing that the majority of subjects maintained age-appropriate BMI during the study or shifted towards the normal range (from a high BMI at baseline).

Subjects that started the study just meeting the inclusion criterion of body weight $\geq$ 15 kg, while being below the 10th percentile for height and BMI according to WHO Growth Charts for Boys and Girls 5 to 19 Years of Age, all increased their weight at the end of the study. Conversely, those who lost $\geq$10% of weight by the end of the study were those who were considered at risk of being overweight (BMI for age z score >1) at Baseline.

Figure 22: Spaghetti Plot of BMI-for-Age *Z* Score over Time (Safety Analysis Set)



Laboratory values

- C-Reactive Protein

At Week 56, the 5 to 10 years age group showed decrease from Baseline in mean CRP levels from 0.645 mg/dL to 0.095 mg/dL and the 11 to 17 years age group showed a decrease from 0.460 mg/dL to 0.166 mg/dL. At Week 104, the mean CRP for the 5 to 10 years age group was 0.523 mg/dL and the 11 to 17 years age group mean CRP was 0.372 mg/dL.

One subject in the 5 to 10 years age group had an abnormal clinically significant CRP value at Baseline. A total of 11 elevated post-Baseline CRP values were flagged as clinically significant in 7 subjects (3 subjects in the 5 to 10 years age group and 4 subjects in the 11 to 17 years age group). No more than 2 clinically significant CRP values were reported post-Baseline by any single subject. Of the 11 clinically significant CRP values, 6 cases were contemporaneous (±21 days between onsets) with at least 1 TEAE indicating infection or inflammation (e.g., COVID-19, gastroenteritis, myalgia, pyrexia, upper respiratory tract infection, vascular device infection).

A total of 8 events of CRP increased were reported in 6 subjects (3 subjects in each age group) during the study. None were considered related to treatment. For 2 of the subjects with clinically significant high CRP values, both subjects had AEs of infection/inflammation reported at the same time which were the likely reason for CRP elevations.

- Blood panel

There was no indication of a clinically meaningful change in mean haematology parameters (haematocrit, haemoglobin, leukocytes, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, mean corpuscular volume, platelets, red blood cells, red cell distribution width) from Baseline to Week 56 and Baseline to Week 104 for either age group or overall.

5.4.8. Overall discussion and conclusions on clinical safety

5.4.8.1. Discussion

The clinical safety is based on the available data from a pivotal study of HoFH children from 5 to 18 years of age including 20 patients from 5 to 10 and 21 from 11 to 17 years of age, which is **limited but relatively a significant number as compared to the available data for adults**. Although, safety data have not been compared to placebo, some longer-term safety information is available up to 104 weeks with a mean of 80 weeks for the 5 to 10 age group and 76 weeks for the 11 to 17 age group of treatment with lomitapide.

A high number of **adverse events** (95% and 94%) was reported in both age groups. Nevertheless, only 2 patients (8.7%) discontinued treatment due to adverse (diarrhoea) events (both in the 11-17 age group), 4 (20%) and 7 (30%) had their dose interrupted and 0 (0%) and 4 (17%) had their dose decreased. The most frequently reported adverse events were as expected largely related to GI symptoms and liver related effects including diarrhoea (45% and 57%), abdominal pain (40% and 48%), ALT increase (45% and 35%), and AST increase (35% and 35%). A relative high number of **serious adverse events** (20% and 30%) was reported, which all occurred at the later safety phase, of which a transaminase increase was considered related to treatment. Two **cardiovascular events** occurred (aortic valve disease, chest pain) in the 11-17 age group.

A slower (more conservative) **gradual dose escalation** approach was performed of 16 weeks with 4 weeks interval as compared to current approved adult dose escalation recommendation with 2 weeks intervals for the initial dose escalation phase. While, lomitapide treatment was associated with a high frequency of **gastrointestinal adverse events** (72%) of which 56% were considered treatment-related, apparently, this was an appropriate strategy to avoid discontinuation due to **GI symptoms** as 19 (95.0%) subjects aged 5 to 10 years was able to reach the maximum tolerated dose of 20 mg, with 13 (65%) in the longer term (safety) phase, and 6 (30%) even increasing to 30 mg. For the 11 to 17 years age group, 13 (56.5%) reached the maximum dose of 40 mg, with all remaining on this dose during the safety phase (62%). The 60 mg was considered too high as 3 out of 6 patients had to be down titrated instantly based on tolerability issues, while the other 3 remained on this dose. Therefore, it is acceptable to consider 40 mg as the maximum dose. GI adverse events start at initiation of therapy, and may increase with dose escalation, particularly on the higher doses. This is in line with the known safety profile of adults, although the mean time of first GI symptom is slightly earlier in adults. Further, 16 and 17 years patients initiated on a higher dose of 5 mg. Based on PK modelling a comparable exposure appears to be reached as for adults, which would justify it as a starting dose. Further, based on GI tolerability data, a comparable tolerability has been observed as for adults, which is likely higher than for the other paediatric age groups. Although such data need to be taken with caution due to the small subgroup of 6 patients in the 16-17 years of age subgroup. **Dose interruptions/reductions** were required in a substantial proportion of 37/156 (23.7%) of events. 15 subjects with either interrupted or reduced dosing due to 46 TEAEs were reported of whom 11 were were due to GI AEs (29 AEs). In the 5-10 age group (n=20), at Week 24, a dose of 20 mg was achieved for 19 patients (95%), with one patients escalating at Week 36 and one down-titrated and another escalated at Week 52 and 80. Limited numbers were down-titrated, one at Week 36 and at Week 56.

For the 11-17 age group, the achieved dose was more variable with 1 patient on 10 mg, 3 on 20 mg, 14 on 40 mg and 3 on 60 at Week 24. Although the number of patients on 40 mg remained fairly stable (55-63%), and limited number of patients were down-titrated. GI symptoms in 13 patients (abdominal pain (n=5), decreased appetite (n=1), diarrhoea (n=5), nausea (n=1), and vomiting (n=1)), liver related AE (ALT increased (n=1)), and chest pain (n=1)) appeared to be responsible for

dose reduction. And 1 dose reduction and 2 dose interruptions based on liver enzyme elevations, which does not provide sufficient insight. Two patients **discontinued due to an adverse event** of diarrhoea within the first 3 months (both in the older group) who refused to continue on a lower dose. The number of permanent discontinuations is relatively low, which suggest that the intensive dose alteration strategy measures keeps patients on treatment.

Intensive monitoring of **liver enzymes** was performed during the study with every 4 weeks up to week 56 and every 12 weeks thereafter up to 92 weeks monitoring of ALT and AST and other liver enzymes, in line with current (adult) recommendations in the labelling. For a considerable proportion, abnormalities in liver enzymes were reported. ALT increase was reported in 9 (45%) and 8 (35%) and AST in 7 (35%) and 8 (35%) across both age groups, but this was 3 (15%) and 3 (13%) with >3 × ULN (with 1 subject each >5 × ULN), and AST increase >3 × ULN for 2 (10%) and 1 (4%), and two patients with both >3 × ULN for both ALT and AST. As with the adult population, the clinical implications of such liver enzyme elevations for the long-term are unclear. In both age group one patient each with a total of 5 **dose alterations** were needed due to multiple liver enzyme elevations.

Further, consistent with the mechanism of action of lomitapide, **increase in hepatic fat** content may occur. Increase in fat accumulation from ≤10% to 10-20% occurred in 2 patients in the 5-11 years age as based on NMR scanning. This cannot be predicted based on liver enzyme elevations due to its weak association. Further, 3 patients (all > 5 years of age) had a hepatic adverse event (hepatic steatosis and hepatomegaly, hepatic steatosis, ALT and AST increase, respectively). Hepatic steatosis is a risk factor for progressive liver disease including steatohepatitis and cirrhosis. The long term consequences of hepatic steatosis associated with lomitapide treatment are unknown. Clinical data suggest that hepatic fat accumulation is reversible after stopping treatment with lomitapide, but whether histological sequelae remain is still unknown, especially after long-term use. As the liver enzyme elevations and development of liver fat accumulation are unpredictable, **long-term continuous monitoring** is needed, which may put substantial burden on the patients, besides the need for dose interruptions and/or dose reduction (or permanent discontinuation). Current labeling already request for annually monitor based on imaging e.g. (Fibroscan, magnetic resonance (MR) elastography) and biomarker evaluation (Gamma-GT, serum albumin, hs-CRP, CK-18 Fragment, Enhanced Liver Fibrosis (ELF) panel, Fibrometer, Fib-4 score, etc), to screen for steatohpatitis/fibrosis, and evaluate every 3 months the liver enzyme elevations (e.g. ALT/AST). Whether patients will be able to adhere to such measures and still motivated to be treated with lomitapide in the long-term outside of a study setting may be questionable. Data from post-approval LOWER registry in adults suggest that there is considerable non-adherence to the SmPC recommendations of frequent liver monitoring with only 39% being >75% compliant to every 3 months monitoring despite additional education material. Non-adherence to risk minimization measures may thus be an issue. Paediatric patients are already allowed to be included in the LOWER registry, although separate reporting is considered essential (see RMP for further comments).

Although **serious adverse events** were reported in a considerable number of patients including 4 (20.0%) subjects 5 to 10 years and 7 (30.4%) subjects 11 to 17 years, these were found across several different SOCs with no clear pattern. Only the increased transaminase (in the older age group) could reasonably be related to treatment, while others may be related to the underlying disease condition.

No **deaths** occurred during treatment, which seems reassuring. One death occurred during the screening phase and one 103 days after lomitapide treatment which make any association unlikely.

Musculoskeletal events have been reported in 5 subjects (12%; 11-17 years). One serious event of tendon disorder (unrelated) occurred and needed a dose interruption. Further, CK level increase events

occurred in 6 patients (4 and 2), with 2 identified as treatment related and one needing dose interruption.

Infections were seen in a considerable proportion of the patients (nasopharyngitis 6(14%), upper respiratory tract infection 4(9%), gastroenteritis 3 (7%), and pharyngitis 3 (7%)), however, none were considered treatment related, although these are mentioned as ADRs in the labelling.

Vitamin E and fatty acid supplementation (ALA, EPA, DHA) was needed due to known effects of decrease in these levels while treated with lomitapide. There were no abnormal levels in fat soluble vitamins for vitamin A, osteocalcin, uncarboxylated osteocalcin, or the ratio of uncarboxylated:total osteocalcin (as a measure of vitamin K), which appears reassuring. Some variation in ALA, linoleic acid, EPA and eicosatrienoic acid was observed during the study, however, no clinical significant decreases were observed, also due to the supplementation.

There were no clinically significant abnormalities in **other laboratory findings** than liver enzymes and CK levels, including the hsCRP inflammation marker and blood panel markers, which appears reassuring.

While previously delayed **sexual maturation** was observed in juvenile rat toxicity studies, this has not been confirmed in current study with no clinically significant alteration in sex hormone values (oestradiol or testosterone) for children with Tanner Stage ≥2. No abnormal development of Tanner staging was observed in both age groups, although follow-up and number of patients may be limited to robustly evaluate **growth and maturation** based on Tanner staging. Further, while mean change in weight, BMI and height was not significant, these data appear difficult to interpret due to high variability range. Nevertheless, the BMI was generally within the age-appropriate range.

Post-marketing experience exists from the ongoing LOWER registry in adults. Currently the duration of exposure ranges from 9 days to ≥10 years with a median exposure duration of 28.45 months and mean duration of 42.06 months for all doses. Most patients have been treated with lomitapide for 2 to <5 years (n=73), with 58 being treated for 5 to <10 years and 50 for 1 to < 2 years. Doses ranged from 2.5 mg (5 mg every other day [QOD]) to 50 mg daily.

5.4.8.1.1. Overall assessment of available safety data

The safety database in children with HoFH from 5 to 17 years of age is limited but generally in line with the safety profile as known from the treatment with lomitapide in the adult HoFH population. Similar as with the adult population, most prominent safety issues are GI symptoms, for which a conservative dose escalation at initiation of therapy is proposed to mitigate these symptoms. Further, liver associated adverse effects are partly associated with the mechanism of action and unpredictable in the long term which requires regular monitoring. Whether patients are able to adhere to this in the long term may be questioned, also based on experience in adults. Also, long-term consequences of these liver adverse effects are still unknown.

5.4.8.1.2. Adverse drug reactions in the SmPC

The ADRs initially proposed to be included as additional ADRs as part of this procedure included the following: hypophagia (common), blood creatinine phosphokinase increased (common), ultrasound liver abnormal (common), and alanine aminotransferase abnormal (common).

The MAH was requested to elaborate on how the relationship to the proposed ADRs was assessed. The MAH concluded that current data do not support including hypophagia, blood creatinine phosphokinase increased, ultrasound liver abnormal, and alanine aminotransferase abnormal as ADRs in the SmPC,

which was agreed. Little events and evidence exists to identify hypophagia, ultrasound liver abnormal as ADRs. Further, alanine aminotransferase abnormal has already been covered as ADR. Several events of blood creatinine phosphokinase increased have been reported, also post-marketing. However, any clear causal relationship appears difficult to identify due to several possible confounders including statin therapy, and underlying disease or predisposing factors. During post-marketing review this has not been identified as a true signal in predominantly adults.

5.4.8.2. Conclusions on clinical safety

Treatment with lomitapide is associated with some significant safety issues including GI symptoms, for which a conservative dose escalation at initiation of therapy is proposed to mitigate these symptoms. Further, liver associated adverse effects are partly associated with the mechanism of action and unpredictable in the long term which requires regular monitoring. Whether patients are able to adhere to this in the long term may be questioned, also based on experience in adults. Also, long-term consequences of these liver adverse effects are still unknown. Risk minimisation measures including SmPC recommendations are in place and will annually be assessed.

6. Risk management plan

6.1. Safety specification

6.1.1. Proposed safety specification

The MAH proposed the following update to the summary of safety concerns in the RMP:

Table 34: Summary of safety concerns in the proposed RMP

Summary of 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) Rhabdomyolysis with or without acute renal failure due to interaction with statins
Important potential risks	Hepatic fibrosis Primary hepatic tumours Small intestinal tumours Pancreatic tumours Unintended pregnancy
Missing information	Use during pregnancy Long-term safety in children Use with alcohol Use in non-Caucasian patients Pre-existing hepatic disease Concomitant use with potential hepatotoxic agents

6.1.2. Discussion on proposed safety specification

The MAH did not propose new safety concerns based on the new data (clinical trial APH-19). This is supported, as the clinical trial APH-19 did not identify new safety signals. Gastrointestinal events were most frequently reported in the paediatric population, but less frequent and less severe compared to the adult population. Since the concerns of the CHMP regarding the long-term safety in children were initially not reflected in the list of safety concerns, the MAH included, as requested, the missing information "Long-term safety in children" in the RMP.

6.2. Pharmacovigilance plan

6.2.1. Proposed pharmacovigilance plan.

Table 7.2.1 On-going and planned additional pharmacovigilance activities

Description	Due dates
Category 2– Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances	

Description	Due dates
LOWER registry – long term prospective observational study to systematically collect information on the safety and effectiveness outcomes of patients treated with lomitapide and 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. 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: 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. The outcome of primary interest is major congenital anomalies. • 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.	An annual report will be submitted at time of annual reassessment

6.2.2. Discussion on the Pharmacovigilance Plan

6.2.2.1. Routine pharmacovigilance activities

Current routine pharmacovigilance activities include FUQ's related to 'hepatic effects, fibrosis and tumours', 'gastrointestinal effects', 'tumours', and 'use during pregnancy/paediatric outcome'. The existing FUQs as included in the RMP are considered generally compatible to the new paediatric indication. No changes are proposed to the routine pharmacovigilance activities, which is acceptable.

6.2.2.2. Additional pharmacovigilance activities

Additional pharmacovigilance activities included the Lomitapide Observational Worldwide Evaluation Registry (LOWER).

As part of the annual reassessment procedure (EMA/S/0000290089), the MAH has proposed to terminate the LOWER study for adult patients, which the CHMP has agreed to. CHMP requested that the LOWER study should be replaced with a new SOB. Of note, with regards to the new SOB, the annual reassessment procedure only applies to the currently approved indication and does not cover the indication proposed in the current paediatric line extension procedure. The newly proposed SOB has therefore been adapted to ensure that the revised SOB encompasses the entire indication for

lomitapide and has been included as a category 2 study in the pharmacovigilance plan of the RMP as part of the annual reassessment procedure.

6.3. Plans for post-authorisation efficacy studies

Table 7.3.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Evaluation of the effect of lomitapide treatment on major adverse cardiovascular event (MACE) in patients with homozygous familial hypercholesterolemia (HoFH). (LILITH study) Planned	*Primary objective:* The primary objective of the study is to evaluate the occurrence of MACE after three years of treatment with lomitapide as compared to the occurrence of MACE during three years before the initiation of lomitapide. *Secondary objectives:* • To evaluate the changes of LDL-C and other lipoproteins at one, two and three years of lomitapide treatment and the correlation of these laboratory evaluations with changes in MACE occurrence • To evaluate changes in the levels of AST, ALT, GGT at one, two and three years of lomitapide treatment, as measures of safety • To evaluate the discontinuation of LDL apheresis during follow-up and the adherence to lipid-lowering medications (including lomitapide).	Assess changes in the occurrence of MACE from pre to post lomitapide initiation	Protocol Final report	22 Jun 2023 30 Jun 2027

One obligation in regards to a post-authorisation measure is in place. This concerns a non-interventional PAES (LILITH) in order to evaluate the effect of lomitapide treatment on major adverse cardiovascular events (MACE) in patients with homozygous familial hypercholesterolemia (HoFH). No changes are proposed to the PAES, which is acceptable. Children (<18 years of age) are excluded from this study and there is no need to include them in this study. Data collection on adults from the LILITH study is sufficient at this point.

6.4. Risk minimisation measures

6.4.1. Proposed risk minimisation measures

Table 35: Planned routine risk minimisation measures

Safety Concern	**Routine risk minimisation activities**
Hepatic effects (elevated aminotransferases, hepatic steatosis)	Routine risk communication • SmPC section 4.3. Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Gastrointestinal effects (nausea, diarrhoea, weight loss, malabsorption of fat soluble vitamins, decline in essential fatty acids)	Routine risk communication • SmPC section 4.2. • SmPC section 4.3. Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Rhabdomyolysis with or without acute renal failure due to interaction with statins	Routine risk communication • SmPC section 4.3. Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.5. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Hepatic fibrosis	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Primary hepatic tumours	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 5.3. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Small bowel / intestinal tumours	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 5.3. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.

Pancreatic tumours	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 5.3. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Unintended pregnancy	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4. • SmPC section 4.5. • SmPC section 4.6. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Use during pregnancy	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.6. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Long-term safety in children	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.2. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Use with alcohol	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Use in non-Caucasian patients	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 5.2. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Pre-existing hepatic disease	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 5.2. Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.
Concomitant use with potential hepatotoxic agents	Routine risk minimisation activities recommending specific clinical measures to address the risk: • SmPC section 4.4 Other routine risk minimisation measures beyond the Product Information: Legal Status: Prescription only medicine. Ensure appropriate use of Lojuxta by restricting prescription to physicians with experience in treating severe lipid disorders.

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

Current routine risk minimisation measures are not changed with the extension of indication and the addition of the 2 mg strength. This is acceptable.

6.4.2.2. Additional risk minimisation measures

Educational materials for the prescribers and patients are in place, in the form of a prescriber guide, patient brochure and a patient card (patient alert card, PAC). No new educational materials are proposed. This is acceptable, also because no new safety concerns are identified for this new indication. Some of the existing key-messages of the educational materials currently in place are extended, to also include safety information relevant to the new paediatric indication.

6.5. RMP Summary and RMP Annexes overall conclusion

In line with the proposed changes, the summary of the RMP (part VI) is updated to reflect the new paediatric indication.

Annex 6 Details of proposed additional risk minimisation activities

Annex 6 is updated in line with the proposed changes and is considered acceptable.

6.6. Overall conclusion on the Risk Management Plan

The PRAC consider that the updated risk management plan version 7.5 is acceptable.

The MAH is reminded that in case of a Positive Opinion, the body of the RMP and Annexes 4 and 6 (as applicable) will be published on the EMA website at the time of the EPAR publication, so considerations should be given on the retention/removal of Protected Personal Data (PPD) and identification of Commercially Confidential Information (CCI) in any updated RMP submitted throughout this procedure.

7. Pharmacovigilance

Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.1. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

8. Product information

8.1. Summary of Product Characteristics (SmPC)

8.1.1. SmPC section 4.1 justification

The indication is proposed to be extended the following: 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 for the treatment of adult and paediatric patients aged 5 years and older with homozygous familial hypercholesterolaemia (HoFH).

The indication is supported by the PIP required clinical study in paediatric patients from 5 years of age with HoFH, which supports the proposed extension of the indication. Also, an age appropriate formulation of 2 mg tablets has been developed.

8.1.2. SmPC section 5.1 justification

Section 5.1 has included the pivotal study APH-19. The primary endpoint and key secondary endpoints have been described in line with the presentation of data in adults. Further, description of safety aspects of liver enzyme elevations and fat fraction was considered of relevance comparable to adult data.

8.2. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH 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

8.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lojuxta (lomitapide) is included in the additional monitoring list since it is approved under exceptional circumstances [REG Art 14(8), DIR Art (22)].

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Benefit-risk assessment

Therapeutic context

9.1.1. Disease or condition, therapeutic indication

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic life-threatening condition resulting in severely elevated LDL-C (> 13mmol/L) leading to premature cardiovascular disease (CVD) and, in untreated patients, premature death. The prevalence of HoFH is estimated 1/160,000 to 1/320,000 patients worldwide.

If left untreated, HoFH patients rarely live past the first or second decade of life, with one study indicating the mean age of the first ASCVD event at 12.8 years and an average age of ASCVD death of 17.7 years (Raal 2011). Further, a recent retrospective study in Italian and Chinese patients with HoFH showed that despite starting lipid-lowering treatments early (mean age of 5.6 year, Italian cohort, and 10.7 year, Chinese cohort), 22% (Italian cohort) and 45% (Chinese cohort) of the patients had a CVD event before age 20 and 16.7% (Italian cohort) and 31.8% (Chinese cohort) had died before age 21 (Stefanutti 2019). A very recent study further confirmed on the risk for early CV death at a median age of 36 years (Q1-Q3 17-48 years) despite current available therapies (Mulder, JACC, 2025).

The goal of therapy in patients with HoFH is to reduce LDL-C, thereby reducing atherogenesis and subsequently reducing CVD events and mortality. Currently, patients with HoFH tend to be treated with multiple lipid-lowering therapies (LLT) but are not able to achieve guideline-recommended LDL-C targets.

9.1.2. Available therapies and unmet medical need

For a detailed description, please see Section 2. of this document.

Attempts to lower cholesterol levels often require multiple lipid-lowering drugs and LDL apheresis. Despite these therapies, a majority of patients with this disorder does not reach guideline-recommended LDL-C levels. Patients with HoFH are often treated with multiple lipid-lowering treatments (LLTs) including statins, evolocumab, ezetimibe, and lipid apheresis; however, these treatments are largely ineffective for patients either due to LDLR mutations, problems with tolerability, and/or they are not available for the paediatric population. Statin therapy is the cornerstone treatment for LDL-C lowering in the paediatric population aged 6 years and older and causes a 50% reduction in patients with Heterozygous Familial Hypercholesterolemia (HeFH), however only a 15-30% reduction in LDL-C is reached in patients with HoFH. The safety and efficacy of ezetimibe in children with HoFH aged less than 18 years have not been established. Evolocumab, a PCSK9 inhibitor, is indicated for paediatric HoFH patients aged 10 years and older. Anti-PCSK9 therapy on top of maximally tolerated lipid-lowering therapy resulted in a mean reduction in LDL-C of approximately 30% compared to placebo. Of note, only evolocumab is currently approved for patients with HoFH; use of alirocumab in patients with HoFH is considered off label. Recently, evinacumab has been approved already from the age of 6 months, and provides a valuable option due to substantial lipid reduction (24-48%). Although, despite this, a considerable proportion is still not able to reach target goals of normal LDL-levels.

Apheresis is an important adjunctive treatment for HoFH; a single treatment reduces LDL-C by 55%-70% relative to pre-treatment levels. However, apheresis may be burdensome, and its availability is limited. Also, only a temporal reduction in LDL-C is achieved. Liver transplantation can be used to treat HoFH, although it is rarely used and considered as a last resort treatment option due to the many

disadvantages, including a high risk of post-transplantation surgical complications and mortality, the paucity of donors, and the need for life-long treatment with immunosuppressive therapy. Due to the limitations of currently available treatments, there exists a high unmet medical need for new therapeutic options that reduce LDL-C and the inevitable risk for premature ASCVD in paediatric patients with HoFH. The unmet medical need is particularly severe for paediatric HoFH patients with null/null or negative/negative mutations where currently available LLTs provide little benefit in lowering LDL-C and for paediatric HoFH patients who lack treatment options, except for evinacumab.

9.2. Main clinical studies

For a detailed description of the main clinical studies supporting this application, please refer to section 5.3.2. of this document.

The pivotal phase 3 study APH-19 was an open-label, single arm, 24 weeks efficacy study, followed by a 80 weeks safety extension in patients aged 5-≤17 years with HoFH on stable lipid lowering therapy with our without apheresis. A total of 43 patients (n=20 5-10 years, n=23 11-17 years (including n=6 16-17 years)) entered the efficacy phase. The majority (90.7%) had genetic confirmation of 2 mutant alleles at the *LDLR* gene locus. The primary efficacy endpoint was percent change from baseline in LDL-C at 24 weeks. A conservative 16 week dose escalation period was applied to minimize GI tolerability issues. A 2 mg tablet was specifically developed to accommodate a starting dose of 2 mg for the age group 5-10 and 11-15 years, while age group 16-17 years could start on the existing 5 mg capsule. Further, intensive liver monitoring was applied.

9.3. Favourable effects

Lipid lowering efficacy was demonstrated, as the mean LDL-C reduction was -53.9% after 24 weeks of treatment with lomitapide on top of lipid lowering therapy in the ITT population, showing robustness of the results in the PP population (without major protocol deviation, including change in LLT (and LA) treatment, n=27, mean change -58.2%), with a sustained effect through 104 weeks of treatment. The reduction in the ITT population corresponds to a mean LDL-C decrease from 436 mg/dL (11.3 mmol/L) to 175 mg/dL (4.5 mmol/L), a mean change of -260 mg/dL (6.7 mmol/L).

The primary data of LDL-C reduction are supported by significant beneficial changes for secondary endpoints of TC, TG, non-HDL-C, CLDL-C, apoB and triglycerides. The improvements in Lp(a) and HDL-C were less prominent.

Beneficial effects were observed across several subgroups of age, gender, history or established CVD at baseline, with or without dose reduction/interruption and patients who did/did not reach maximum tolerated dose. However, a lower effect was observed for patients on apheresis and patients with LDLR function defective/defective vs LDLR negative/ negative.

9.3.1. Uncertainties and limitations about favourable effects

Clinical outcome. Lomitapide has demonstrated to clinically significantly reduce LDL-C level, an established surrogate marker for CV disease, but its impact on clinical outcomes has not been formally tested.

Sample size. The number of patients (n=43) included in the pivotal paediatric study is limited.

9.4. Unfavourable effects

Longer-term safety information is available up to 104 weeks with a mean of 80 weeks for the 5 to 10 age group and 76 weeks for the 11 to 17 age group of treatment with lomitapide.

Lomitapide treatment was associated with a high frequency of **gastrointestinal adverse events** (72%) of which 56% were considered treatment-related. Diarrhoea (45% and 57%) and abdominal pain (40% and 48%) were most frequently reported. A more conservative dose escalation was applied over a 16 weeks period in comparison to adults to avoid treatment discontinuations resulting in almost every patient reaching the maximum tolerated 20 mg and 40 mg dose for respectively the 5 to 10 years and 11 -17 years age groups. GI adverse events start at initiation of therapy, and may increase with dose escalation, particularly on the higher doses. This is in line with the known safety profile of adults, although the mean time of first GI symptom is slightly earlier in adults.

Liver adverse events were frequent (49%) mainly due to **elevations in liver enzymes** (ALT increase 30%, AST increase 30%), although for 7 patients (17%) this was AST or ALT >3.0 × ULN or higher. Further, hepatobiliary disorders were infrequent (2 patients, 5% in the 5-10 age group; hepatic steatosis, hepatomegaly).

The number of permanent treatment **discontinuation due to adverse events** is low with 2 patients discontinuing due to diarrhoea within the first 3 months (both in the older group) who refused to continue on a lower dose. **Dose interruptions/reductions** were required in a substantial proportion of 37/156 (23.7%) of events, although a large proportion could maintain on the target dose.

A relative high number of **serious adverse events** (20% and 30%) was reported, which all occurred at the later longer term phase. Only transaminase increase was considered related to treatment, while no clear pattern indicated for treatment related serious adverse events. Two cardiovascular events occurred (aortic valve disease, chest pain) in the 11-17 age group. No **deaths** occurred during treatment; one death occurred during the screening phase and one 103 days after lomitapide treatment.

Musculoskeletal events have been reported in 5 subject (12%; 11-17 years). One serious event of tendon disorder (unrelated) occurred and needed a dose interruption. Further, CK level increase events occurred in 6 patients (4 and 2), with 2 identified as treatment related and one needing dose interruption. However, patients use extensive other lipid lowering therapy with a risk of musculoskeletal events.

There was no suggestion of **weight loss**, which occurred only in 3 (7%) patients. BMI was generally within the age appropriate range.

The long-term effects of possible signs of malabsorption do not appear to have clinical consequences. Due to **vitamin E and fatty acid supplementation** there were no signs of reductions in fat soluble vitamins and fatty acid levels.

While previously delayed **sexual maturation** was observed in juvenile rat toxicity studies, this has not been confirmed in current study with no clinically significant alteration in sex hormone values (oestradiol or testosterone) in children with Tanner Stage ≥2. No abnormal development of Tanner staging was observed in both age groups, although follow-up and number of patients may be limited to robustly evaluate **growth and maturation** based on Tanner staging.

9.4.1. Uncertainties and limitations about unfavourable effects

A **limited sized safety database** is available with 20 patients with HoFH from 5 to 10 and 21 from 11 to 17 years of age, but relatively a significant number as compared to the available data for adults with HoFH. Safety data have not been compared to placebo complicating interpretation of the relative contribution of lomitapide treatment to the found adverse events during the study. And although safety follow-up has been reported up to 140 weeks, there are safety issues that may need longer follow-up to better establish its association with lomitapide treatment and its consequences.

Consistent with the mechanism of action of lomitapide, **increase in hepatic fat** content may occur and has been seen in 2 patients, while this cannot be predicted based on liver enzyme elevations due to its weak association. Further, 3 patients (all 5-11 years of age) had a **hepatic adverse event** (hepatic steatosis and hepatomegaly, hepatic steatosis, ALT and AST increase, respectively), although this has not led to dose alterations for these patients. For other patients with ALT > 3 ULN and/or AST > 3 ULN dose interruption and/or dose decrease were needed (5 dose alterations were needed due to multiple liver enzyme elevations). Hepatic steatosis is a risk factor for progressive liver disease including steatohepatitis and cirrhosis. The long term consequences of hepatic steatosis associated with lomitapide treatment are unknown. As the liver enzyme elevations and development of liver fat accumulation are unpredictable, long term continuous monitoring is needed, which may put substantial burden on the patients. Whether patients will be able to adhere to such measures and still motivated to be treated with lomitapide in the long-term outside of a study setting may be questionable, especially since non-adherence has been observed in the current post-approval LOWER registry. Paediatric patients are also allowed to be included in the LOWER registry, and specific reporting on this subpopulation will be mandated in the new SOB being introduced in the annual reassessment procedure EMA/S/0000290089.

9.5. Effects Table for Lojuxta for the paediatric indication

Table 36: Effects Table for lomitapide in children 5 to 17 years of age (data cut-off: 25 Febr 2025).

Effect (short description)	Treatment **Lomitapide**		Uncertainties/ Strength of evidence	Ref
LDL-C change from baseline to Week 24	-53.9%	<Text>	**SoE:** consistent in PP population; responder analysis LDL-C <3.0 mmol/L at 24 weeks of 37.2%; post-hoc responder analysis 50% reduction LDL-C at 24 weeks of 48.8%. **Unc:** slightly lower effect in subgroups defective/defective and patients on LA at baseline	APH-19
Gastrointestinal adverse events	72%>	<Text>	**SoE:** Known effect from adults, mitigation possible with conservative dose escalation. 2 patients discontinued due to diarrhoea **Unc:** first GI event over time not clear	APH-19

Effect (short description)	Treatment **Lomitapide**		Uncertainties/ Strength of evidence	Ref
Liver adverse events	49%	<Text>	**SoE:** ALT/AST increase are frequent (30% ALT and 30% AST; 7 patients with AST or ALT >3.0 × ULN or higher. Liver fat accumulation associated with MoA. 2 patients with hepatobiliary AEs **Unc:** Long term consequences of liver effects unknown	

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence;.

9.6. Benefit-risk assessment and discussion

9.6.1. Importance of favourable and unfavourable effects

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, although evinacumab has recently been approved in children even from the age of 6 months. Further, apheresis is a treatment option, however, 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.

Pivotal evidence concerning this line extension for paediatrics aged 5-≤17 years has been provided by one single arm, open-label efficacy and safety study (APH-19). The design of the study has been discussed and approved by the PDCO and is in general in line with the pivotal study for adults. With regard to the primary efficacy endpoint, a statistically significant effect on the surrogate efficacy parameter LDL-C has been observed at 24 weeks, which is considered clinically relevant. Translation to and benefit in terms of CV outcome is unclear, however, due to the rarity of the disease, unlikely to be sufficiently established.

Due to very frequent gastro-intestinal adverse effects, a conservative dose escalation approach has been applied in the study to be able to avoid treatment discontinuations and try to reach sufficient target doses. Eventually, only 2 patients discontinued treatment permanently. Nevertheless, dose reduction and dose interruptions were frequently needed to maintain patients on treatment, which expressed the poor tolerability of lomitapide as already known from experience in adults.

Another 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, liver 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. However, it cannot be ruled out that the long-term treatment with lomitapide could lead to fibrosis and cirrhosis. Although, current data from the annual review of safety as part of the annual reassessment have not provided clear adverse safety signals on this subject based on adult data. Further, while during a study period children may likely be motivated to adhere to periodic liver

safety monitoring, this may be less for the longer-term outside of a study setting. Risk minimisation measures including SmPC recommendations are in place and will annually be assessed.

Any other safety issues were not significant, including those for growth and maturation, while sufficient measures have been taken to avoid vitamin E and fatty acid reductions by supplementation. Any muscle related adverse effects are difficult to establish and could very likely be associated with the overall lipid lowering treatment paradigm.

9.6.2. Balance of benefits and risks

The beneficial effect of lomitapide on LDL-cholesterol is considered clinically relevant, though a benefit in terms of CV outcome cannot be evaluated. Tolerability issues, specifically the gastrointestinal complaints associated with lomitapide-treatment can lead in some cases to suboptimal treatment during the long-term. Further, regular monitoring for possible liver adverse effects may give a substantial burden to patients, especially for younger patients and in the long-term, possibly jeopardising motivation for long-term treatment, in addition to the still unknown consequences of the liver adverse effects.

Considering the unmet medical need in this rare condition (HoFH) with serious negative health consequences, the benefit/risk balance of lomitapide in the extension to the HoFH paediatric population aged 5 years and older is positive.