Study Protocol

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

Investigational product	Lomitapide		
Indication	Homozygous Familial Hypercholesterolaemia (HoFH)		
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Study number	APH-19		
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Author(s)	Dr Tracy Cunningham, LRCPI & SI, MB, BCh, BAO, FRCPI, AFPM		
Compliance	The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable federal and local regulations.		
Sponsor	**Amryt Pharmaceuticals DAC** 45 Mespil Road, Dublin 4, Ireland Phone: +35-3-1-518-0200		

SIGNATURE PAGE

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09-Feb-2023
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INVESTIGATOR'S AGREEMENT

I have read and understood the protocol and agree with its content.

I will conduct the study in compliance with the protocol, Good Clinical Practice, national law, and all applicable regulatory requirements. In addition, I will conduct the study in accordance with the ethical principles of the Declaration of Helsinki.

I am familiar with the nonclinical and clinical data of the investigational product and with its known and potential benefits and risks.

I agree to assume responsibility for the proper conduct of the study at this site and I will ensure that all persons assisting in the study under my supervision are adequately informed about the protocol/amendments, the investigational product and their study-related duties and functions as described in the protocol.

I will not implement any deviation from, or changes to the protocol without agreement from Amryt Pharmaceuticals DAC and prior submission to and written approval from the responsible regulatory authorities and Independent Ethics Committee/Institutional Review Board of an amendment, except when necessary to eliminate an immediate hazard to the patients.

I understand that either Amryt Pharmaceuticals DAC or myself may terminate the study or may suspend enrolment at any time, if it becomes necessary to protect the patients' best interest.

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LIST OF TERMS AND ABBREVIATIONS

Term or Abbreviation	Description
AA	Arachidonic acid
ACTH	Adrenocorticotrophic hormone
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse Event of Special Interest
ALA	Alpha-linolenic acid
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AP	Alkaline phosphatase
apo A-I	Apolipoprotein A-I
apo B	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
BG	Blood glucose
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
Ca	Calcium
CAS	Completer analysis set
CBC	Complete blood count
c-het	compound heterozygous
CIMT	Carotid intima-media thickness
CK	Creatinine kinase
Cl	Chloride
C_{max}	Maximum concentration
C-R	Concentration-Response
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CVD	Cardiovascular disease
CYP	Cytochrome P 450
D	Day(s)
DHA	Docosahexaenoic acid
DSMB	Data Safety Monitoring Board
EAP	Expanded Access Programme
EAS	European Atherosclerosis Society
EASL	European Association for the Study of the Liver
EC	European Commission
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EEA	European Economic Area
EFA	Essential fatty acids

Term or Abbreviation	Description
EMA	European Medicines Agency
EoT	End of Treatment
EPA	Eicosapentaenoic acid
EPAR	European Public Assessment Report
FAS	Full analysis set
FDA	Food and Drug Administration
FH	Familial Hypercholesterolaemia
FMD	Flow-mediated dilatation
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HDL-C	High-density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
HoFH	Homozygous familial hypercholesterolaemia
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDL	Intermediate density lipoprotein
IEC	Independent Ethics Committee
INR	International normalised ratio
IRB	Institutional Review Board
ITT	Intent-to-treat (analysis set)
IU	International units
IV	Intravenous
K	Potassium
LA	Lipoprotein apheresis
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol (conventional mg/dL units can be converted to SI [mmol/L] units using the factor 0.0259)
LDLR	LDL receptor
LDLRAP1	LDL-receptor adapter protein 1
LFT	Liver function test
LH	Luteinising hormone
LLT	Lipid-lowering therapy (including LA, where applicable)
LOCF	Last observation carried forward
LOWER	Lomitapide Observational Worldwide Evaluation Registry
Lp(a)	Lipoprotein a
MACE	Major adverse cardiac event(s)
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities

Term or Abbreviation	Description
MTD	Maximum tolerated dose
MTP	Microsomal triglyceride transfer protein
Na	Sodium
NASH	Non-alcoholic steatohepatitis
NMR	Nuclear magnetic resonance
Non-HDL-C	Non-high-density lipoprotein cholesterol
NYHA	New York Heart Association
PBPK	Physiologically based pharmacokinetic modelling
PCSK9	Proprotein convertase subtilisin/kexin type 9
PFT	Pulmonary function test
PK	Pharmacokinetics
PP	Per-protocol (analysis set)
RMP	Risk Management Plan
SADR	Serious adverse drug reaction
SAE	Serious adverse event
SAF	Safety analysis set
SD	Standard deviation
SOC	Standard of care
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TC	Total cholesterol
TG	Triglycerides
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
V	Visit
VLDL-C	Very low-density lipoprotein cholesterol
W	Week(s)
WHO	World Health Organization

1 SUMMARY OF CLINICAL STUDY

1.1 Study Synopsis

Title of study
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
Sponsor
Amryt Pharmaceuticals DAC, 45 Mespil Road, Dublin 4, Ireland
Coordinating investigator
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Study centres
International multi-centre study with approximately 15 study sites
Countries
Germany, Israel, Italy, Saudi Arabia, Spain, and Tunisia with potential for others as needed
Phase of development
Phase III
Number of patients
Approximately 45 patients to achieve 30 evaluable patients at Week 24±3 days
Study objectives
Primary objective
To evaluate the efficacy of lomitapide, as defined by the percent change in low-density lipoprotein cholesterol (LDL-C) at the maximum tolerated dose (MTD) at Week 24±3 days compared to Baseline, when added to stable lipid-lowering therapy (LLT, including lipoprotein apheresis [LA] where applicable) in paediatric patients (5 to ≤17 years of age) with HoFH.
Secondary objectives
To evaluate the efficacy of lomitapide in paediatric HoFH patients as assessed by: • Percent change from Baseline at Week 24±3 days in lipid parameters, including total cholesterol (TC), non high-density lipoprotein cholesterol (Non-HDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides (TG), lipoprotein(a) [Lp(a)], and apolipoprotein B (apo B). • Percent change from Baseline in TC, non-HDL-C, LDL-C, TG, VLDL-C, Lp(a), and apo B at all other time-points through Week 104±1 week. • Change in LLT and LA from Week 24±3 days through Week 104±1 week. • Number (percent) of paediatric HoFH patients achieving the European Atherosclerosis Society (EAS) recommended target LDL-C of <135 mg/dL (3.5 mmol/L) at Week 24±3 days and at any time on study.
Safety objectives
To evaluate the long-term safety and tolerability of lomitapide in paediatric HoFH patients as assessed by: • Incidence in reported adverse events (AEs) and in clinically significant abnormal findings of physical examinations including weight and body mass index (BMI), electrocardiogram (ECG), standard of care echocardiography (if available), vital signs, pulmonary function tests (PFT), and laboratory parameters including hepatic and renal function tests.

Safety objectives (continued)

- Effects on growth, bone health and bone age will be assessed using both measurements of children's height and growth charts to track age-appropriate progress at Screening and from Baseline at every visit through Week 104±1 week and/or at EoT, together with analysis of Vitamin D and K levels at Screening, Baseline, Week 24±3 days, Week 56±3 days, Week 80±1 week, Week 104±1 week and/or at EoT (and at Week 108 for patients who opt not to participate in or are unsuitable for the Expanded Access Programme [EAP; <18 years of age]/opt not to transition to commercial product [≥18 years of age]).
- Potential effects on maturation, reproductive development, gonadotropins, and variables of the pituitary-adrenal axis at Screening, Baseline, Week 56±3 days, Week 104±1 week and/or at EoT will be analysed; potential effects on the levels of sex steroids will be analysed for patients assessed as Tanner Stage ≥2.
- Lipid accumulation in the liver as measured by nuclear magnetic resonance (NMR) imaging or echography (i.e., ultrasound scan) at Baseline and at Week 24±3 days, Week 56±3 days, and at Week 104±1 week (for patients who opt not to participate in or are unsuitable for the EAP [<18 years of age]/opt not to transition to commercial product [≥18 years of age], lipid accumulation in the liver will be measured at Baseline, at Week 24±3 days, Week 56±3 days, and at Week 108). All patients will undergo NMR imaging unless it is contraindicated or not feasible (e.g., due to the need for sedation or general anaesthesia in very young or anxious patients). In this case, ultrasound scans will be used at the discretion of the investigator.

Exploratory objectives

To evaluate the exploratory assessments of:

- Change from Baseline at Week 56±3 days and Week 104±1 week in mean carotid intima-media thickness (CIMT, mandatory) and flow-mediated dilatation (FMD, whenever possible).
- Resolution and/or regression of pre-existing xanthomas at Week 56±3 days and at Week 104±1 week.
- Changes from Baseline through Week 24±3 days in cholesterol and triglyceride content of VLDL, intermediate density lipoprotein (IDL), LDL and HDL, particle number and size of VLDL, LDL, and HDL as well as particle number of their respective lipoprotein subclasses (large, medium, and small) as assessed based on 2D NMR (Liposcale® Test) of pharmacokinetics (PK) samples.

Palatability objective

- 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 will be used to determine whether they find lomitapide "pleasant", "unpleasant" or are "not sure".
- Ease of administration of the study medication and dietary supplements by the parent(s)/legal guardian(s) will be assessed 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)."

Pharmacokinetics objective

- To evaluate the pharmacokinetics (PK) of lomitapide in paediatric HoFH patients through sparse blood sampling.

Study endpoints

Primary endpoint

Percent change from Baseline in LDL-C at Week 24±3 days.

Secondary endpoints

- Percent change from Baseline at Week 24±3 days for the following lipid parameters: TC, Non-HDL-C, VLDL-C, TG, Lp(a), and apo B.
- Percent change from Baseline at all other time points through Week 104±1 week for the following lipid parameters: LDL-C, TC, Non-HDL-C, VLDL-C, TG, Lp(a), and apo B.
- Total number and percent of patients with a change from Baseline in LLT and LA from Week 24±3 days through Week 104±1 week.
- Total number and percent of patients achieving the EAS recommended target LDL-C of <135 mg/dL (3.5 mmol/L) in paediatric HoFH patients at Week 24±3 days and at any time on study.

Safety endpoints

Safety evaluations and endpoints from Baseline through Week 104±1 week include:

- Incidence of AEs overall and by severity and relatedness.
- Physical examinations including regular measurements of height, weight, and BMI.
- Sexual maturation (Tanner staging):
  - In patients with Tanner Stage ≥2: Changes from Baseline in sex hormones (serum testosterone and serum oestradiol).
- 12-Lead safety ECG (read locally), standard of care echocardiography (if available), vital signs and blood pressure.
- PFT.
- Laboratory tests:
  - Standard haematology (complete blood count [CBC]) and clinical chemistry panels.
  - Liver function tests: Alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP), total bilirubin, and serum albumin.
  - High-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (apo A-I).
  - Creatinine kinase (CK).
  - Serum lipase.
  - Serum levels of essential fatty acids (EFA): Linoleic acid, alpha linoleic acid (ALA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), arachidonic acid (AA), and eicosatrienoic acid.
  - Serum concentrations of fat-soluble vitamins: Vitamin A (retinol), vitamin E (alpha tocopherol), ratio of vitamin E to total lipids (total cholesterol plus fasting triglycerides), and vitamin D (25-hydroxy-D). Levels of vitamin K will be assessed indirectly by measuring total and uncarboxylated levels of serum osteocalcin. (Bone health will be assessed indirectly using growth to track age-appropriate progress, and measurement of 25-hydroxy-D as well as total and uncarboxylated osteocalcin levels.).
  - Pituitary-adrenal hormone levels (thyroid stimulating hormone [TSH], follicle stimulating hormone [FSH], luteinising hormone [LH], adrenocorticotrophic hormone [ACTH], and morning serum cortisol).
  - Urinalysis.
- Lipid accumulation in the liver as measured by NMR imaging or echography (i.e., ultrasound scan) at Baseline and at Week 24±3 days, Week 56±3 days, and at Week 104±1 week (Week 108 for patients who opt not to participate in or are unsuitable for the EAP [<18 years of age]/opt not to transition to commercial product [≥18 years of age]). All patients will undergo NMR imaging unless it is contraindicated or not feasible (e.g., due to the need for sedation or general anaesthesia in very young or anxious patients). In this case, ultrasound scans will be used at the discretion of the investigator.

Exploratory endpoints

- Percent change from Baseline at Week 56±3 days and Week 104±1 week in CIMT and FMD.
- Total number and percent of patients with resolution and/or regression of pre-existing xanthomas at Week 56±3 days and at Week 104±1 week.
- Changes from Baseline through Week 24±3 days in cholesterol and triglyceride content of VLDL, IDL, LDL and HDL, particle number and size of VLDL, LDL, and HDL as well as particle number of their respective lipoprotein subclasses (large, medium, and small) as assessed based on 2D NMR (Liposcale® Test) of PK samples at Week 4±3 days, Week 8±3 days, Week 12±3 days, Week 16±3 days, Week 20±3 days and at Week 24±3 days.

Palatability endpoints

- Total number and percent of patients for each response of palatability:
  - Able to swallow capsule (including food media responses if used).
  - Palatability rating (using a 5-point facial hedonic scale).
  - Parent/guardian interpretation of child's reaction/facial expression (using a 3-point scale).
  - Parent/guardian experience problems in giving medication to child because they refuse to take or throw up immediately after taking.
  - Parent/guardian experience problems in giving dietary supplement to child because they refuse to take or throw up immediately after taking.

Pharmacokinetic endpoints

- The PK data from this study will be incorporated into an existing population PK model in adult HoFH patients.

Study design

This is a single-arm, open-label, multi-centre phase III study to evaluate the efficacy and long-term safety of lomitapide in paediatric patients with HoFH receiving stable LLT (including LA, when applicable) comprising the following phases:

- Screening Period (starting at Week -12, i.e., ≤12 weeks prior to Baseline for up to 6 weeks).
- Stratified Enrolment and Start of Run-in Period (starting at minimum at Week -6, i.e., 6 weeks prior to Baseline for a minimum of 6 weeks):
  - Enrolment will be stratified to ensure approximately equal numbers of patients in the following age groups: 5 to 10 years, 11 to 15 years, and 16 to ≤17 years (with ≥8 patients in any individual age group).
  - Patients must be stabilised on current LLT (including LA, when applicable) and established on a diet supplying <20% of energy (calories) from fat or <30 g fat, whichever is the lesser amount.
  - Daily supplementation with vitamin E (200 international units [IU] for patients 5 to 8 years of age, 400 IU for patients 9 to ≤17 years of age) and an EFA supplement containing approximately 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA starting at Week -2.
- Efficacy Phase (starting at Baseline, i.e., Day [D] 0 for 24 weeks±3 days):
  - Approximately 45 paediatric patients with HoFH will be treated with lomitapide given orally, added to their current, stable LLT (including LA, when applicable) established during the Run-in Period.
  - Assuming a withdrawal rate of approximately 33% by Week 24±3 days, this would result in 30 evaluable patients at Week 24±3 days (with ≥8 patients in any individual age group).
  - After stabilisation of the patient on his/her current MTD of LLT (including LA, when applicable) during the 6-week Run-in Period, treatment with lomitapide will be started as an add-on therapy on D0 of the Efficacy Phase.
  - Dosing will be initiated at the recommended starting dose and escalated to the maximum dose as applicable to the age groups based upon safety and tolerability in addition to LDL-C values.
  - The first dose of study medication will be administered at the study site on D0.
  - During the 24-week Efficacy Phase, patients will be required to remain on the stable LLT regimen (including LA, when applicable) established during the 6-week Run-in Period.
- Safety Phase (starting at Week 24±3 days for 80±1 weeks):
  - Patients will enter the 80-week Safety Phase after the Week 24±3 days assessments have been completed. Each patient will continue receiving the MTD of lomitapide he/she achieved during the Efficacy Phase (unless criteria is met for reducing or increasing the dose) for an additional 80±1 weeks in the Safety Phase.
  - If after Week 24±3 days both the investigator and the sponsor consider 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 can 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 patient tolerates this new dose for ≥4 weeks, then this will be considered the new MTD.

Study design (continued)

- If after Week 24±3 days, a patient has crossed over into the next age category, the study drug can be escalated to the maximum dose applicable for the new age category. If the patient tolerates this new dose for ≥4 weeks, then this will be considered the new MTD.
- During the 80-week Safety Phase, the lomitapide dose can be reduced from the MTD due to tolerability or safety issues, and the patient can be re-challenged after a minimum period of 4 weeks following dose reduction with a higher dose of lomitapide once these issues resolve, but the dose during the Safety Phase cannot exceed the MTD established during the Efficacy Phase unless eligibility for exceptional dose escalation described above is met.
- Adjustments to background LLT (including LA, when applicable) will be allowed at the discretion of the investigator.

- Follow-up (starting at Week 104±1 week for 4 weeks):
  - At Week 104±1 week, eligible patients who complete the study per protocol and are <18 years of age may choose to enter the EAP. Patients ≥18 years of age may opt to transition to commercial product under the approved product label for adults. For both these patient groups, a follow-up phone call will be conducted at Week 108±1 week to monitor safety including AE and concomitant medication reporting.
  - Patients who opt not to participate in or are unsuitable for the EAP (<18 years of age), or patients ≥18 years of age who opt not to transition to commercial product will discontinue lomitapide treatment at Week 104±1 week and enter a 4-week Follow-up period during which they will remain on concomitant LLT (including LA, when applicable). These patients will then attend in person for a Week 108±1 week visit.

Study population

Paediatric population of male and female patients aged 5 to ≤17 years with HoFH who are receiving optimal, stable LLT (including LA, when applicable), and who meet the definition of functional HoFH as defined in the Inclusion Criteria below.

Inclusion criteria

A patient will be eligible for study participation only, if all of the following criteria apply:

1. Male and female patients 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, Bruckert et al. 2014):
   a. Genetic confirmation of 2 mutant alleles at the LDL receptor (LDLR), apo B, Proprotein convertase subtilisin/kexin type 9 (PCSK9), or LDL-receptor 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
      - Cutaneous or tendon xanthoma before age 10 years or
      - Untreated LDL-C levels consistent with heterozygous FH in both parents.
2. Baseline LDL-C on LLT (maximum concentration [C_{max}] immediately prior to LA, if applicable) of either:
   a. >160 mg/dL (4.1 mmol/L, no documented cardiovascular disease [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 World Health Organization (WHO) Growth Charts for Boys and Girls 5 to 19 Years of Age.
4. Patient and/or his/her legal representative has/have been informed, has/have read and understood the patient information/informed consent form, and has/have given written informed assent/consent.

Inclusion criteria (continued)

5. Patient and/or his/her legal representative must be able and willing to follow study procedures and instructions, particularly that:
   a. LLT (including LA, when applicable) must be stable for at least 6 weeks prior to Baseline (Run in Period) and remain stable through Week 24±3 days (end of Efficacy Phase).
   b. The patient must be compliant with both the low fat diet supplying <20% of energy (calories) from fat or <30 g fat, whichever is the lesser amount starting at the beginning of the Run in Period and the dietary supplement regimen starting at Week -2 of the Run in Period, both continuing until completion of the study (and during the EAP/administration of commercial product, when applicable).
6. Postmenarchal female adolescents must be willing to use an effective form of birth control with failure rates <1% per year (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). Patients taking oestrogen-based oral contraceptives should be advised about possible loss of effectiveness due to diarrhoea and/or vomiting. Additional contraceptive measures should be used for 7 days after resolution of symptoms.
7. Patient must be in stable physical and mental health at Screening.

Exclusion criteria

A patient will not be eligible to participate in this study, if any of the following criteria apply:

1. Other forms of primary hyperlipoproteinaemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism).
2. Contraindications for the use of lomitapide according to section 4.3 of the Summary of Product Characteristics (SPC; included in the Lojuxta® SPC in lieu of an Investigator's Brochure [IB]), such as hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of the SPC, known significant or chronic inflammatory bowel disease or malabsorption.
3. Moderate (Child-Pugh B) or severe hepatic impairment (Child-Pugh C), active liver disease and/or abnormal liver function tests at Screening (AST or ALT >1.5 x upper limit of normal (ULN) and/or total bilirubin >1.5 x ULN in the absence of Gilbert's syndrome or AP >1.5 x ULN [based on appropriate age and gender normal values]).
4. Serum CK >2 x ULN.
5. Chronic renal insufficiency with glomerular filtration rate (GFR) <70 mL/min/1.73 m^2 calculated using the Schwartz formula.
6. Uncontrolled hypertension (defined as mean systolic and/or diastolic blood pressure ≥95% of normal for age and sex) despite medical therapy.
7. New York Heart Association (NYHA) Class III or IV congestive heart failure.
8. Precocious/delayed puberty or endocrine disorder affecting growth (e.g., hypothyroidism, premature adrenarche).
9. 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).
10. Life expectancy predicted to be <5 years.
11. History of a non-skin malignancy (with the exception of cervical cancer *in situ*) within 3 years prior to enrolment.
12. Treatment with any Investigational Medicinal Product (IMP) within 6 months or 5 times the terminal half-life of the corresponding IMP, whichever is longer, before Screening (Visit 1).
13. Patient is a dependent of the sponsor, of the investigational team or his/her immediate family.
14. Pregnant or nursing women.

Treatment plan

Investigational product

Lomitapide is a first in class oral, selective inhibitor of microsomal transfer protein (MTP), an intracellular lipid-transfer protein that is found in the lumen of the endoplasmic reticulum and is responsible for binding and shuttling individual lipid molecules between membranes. MTP plays a key role in the assembly of apo B containing lipoproteins in the liver and intestines. Inhibition of MTP reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids including cholesterol, LDL-C and triglycerides.

The European Commission (EC) granted authorisation for lomitapide under the trade name 'Lojuxta®' in July 2013. Lomitapide is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without LA in adult patients with HoFH. Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinaemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded.

Dosage and mode of administration

- Run-in Period (starting at minimum at Week -6, i.e., 6 weeks prior to Baseline for a minimum of 6 weeks):
  - Patients must be stabilised on current LLT (including LA, when applicable) and established on a diet supplying <20% of energy (calories) from fat or <30 g fat, whichever is the lesser amount.
  - Week -2: Start of daily supplementation with vitamin E (200 IU for patients 5 to 8 years of age, 400 IU for patients 9 to ≤17 years of age) and an EFA supplement containing approximately 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA.
- Efficacy Phase (Baseline, D0 for 24 weeks±3 days):
  - During the 24-week Efficacy Phase, patients will be required to remain on the stable LLT (including LA, when applicable) regimen established during the 6-week Run-in Period.
  - Lomitapide capsules will be provided in 4 dose strengths: 2, 5, 10 and 20 mg. Each patient will take 1 to 3 capsule(s) once daily with a glass of water, without food, at least 2 hours after their evening meal to achieve the doses specified in the titration scheme.
  - Oral administration: Patients who are unable to swallow intact capsules may open the capsule and sprinkle the capsule content on 1 tablespoon of apple sauce or mashed banana.
  - Titration from 2 mg lomitapide (in 5 to 15 year old patients) or 5 mg lomitapide (in 16 to ≤17 year old patients) at D0 to the maximum recommended dose by age group based upon safety and tolerability in addition to LDL-C values according to the table below:

Dose escalation by age group

Age Group (years)	Lomitapide Dose (mg)					
	D0	Week 4	Week 8	Week 12	Week 16	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)

  - Lomitapide will not be escalated, if LDL-C is less than the target threshold:
    - LDL-C is <100 mg/dL (<2.5 mmol/L, in patients without CVD at Baseline)
    - LDL-C is <70 mg/dL (<1.8 mmol/L, in patients with CVD at Baseline)
  - Dose must be tolerated for ≥4 consecutive weeks before escalation to the next higher dose.
  - If a dose reduction is required, dosage will either be reduced to the previous tolerated dose or to an intermediate dose. Please note that only down-titrations to intermediate doses are allowed, dose escalations need to follow the guidance provided in the table above. After resolution of the cause for dose reduction, patients may be re-challenged after a minimum period of 4 weeks following dose reduction with prior doses in stepwise increments based on dose escalation guidelines, but may not exceed the MTD established during the Efficacy Phase until Week 24±3 days, after which further increase is only possible if patients have crossed into the next age category or if both the investigator and the sponsor consider 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 based on individual safety, efficacy, and concomitant LLT criteria.

Dosage and mode of administration (continued)

- If the investigator determines that a patient is not tolerating any particular dose (per specified criterion), the investigator may request a dose reduction or a hold on the current dose until the next scheduled visit. Once the patient has stabilised on the reduced dose, the dose can be increased back to the next step again, and the patient may progress through subsequent dose increases. If the patient does not tolerate the re-challenge dose, then the MTD is considered the reduced dose and will be the highest dose allowed for the remainder of the study.
- The MTD is defined as the highest dose of lomitapide that does not result in tolerability or safety concerns.

- Efficacy Phase (Baseline, D0 for 24 weeks±3 days):
  - Week 0 through Week 24±3 days establish the MTD; Week 20±3 days is the last visit that the lomitapide dose can be increased, except when there has been a down-titration at/or after Week 16±3 days. Re-challenging will depend on the assessment of safety and tolerability criteria and the LDL-C value relative to the LDL-C goal of <135 mg/dL (3.5 mmol/L), and is at the discretion of the investigator except for Hy's law cases or comparable signs of liver toxicity, irrespective of origin, in which no re-challenge will be allowed. The study drug can be escalated as a re-challenge dose during the next scheduled visit after a minimum period of 4 weeks following dose reduction. In addition, a re-challenge with lomitapide will not be performed, if the LDL-C is below the target threshold while the patient was receiving the reduced dose.
  - The dose of lomitapide will be reduced with the addition of a concomitant Cytochrome P 450 (CYP) 3A4 inhibitor during the Safety Phase; in patients with hepatic or renal impairment; and in patients who experience liver enzyme elevations above prespecified thresholds.
- Safety Phase (Week 24±3 days for 80±1 weeks):
  - Adjustments to background LLT (including LA, when applicable) will be allowed at the discretion of the investigator.
  - If after Week 24±3 days both the investigator and the sponsor consider 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 can 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 patient tolerates this new dose for ≥4 weeks, then this will be considered the new MTD.
- Follow-up (Week 104±1 week for 4 weeks):
  - At Week 104±1 week, eligible patients who complete the study per protocol and are <18 years of age may choose to enter the EAP. Patients ≥18 years of age may opt to transition to commercial product under the approved product label for adults. For both these patient groups, a follow-up phone call will be conducted at Week 108±1 week to monitor safety including AE and concomitant medication reporting.
  - Patients who opt not to participate in or are unsuitable for the EAP (<18 years of age), or patients ≥18 years of age who opt not to transition to commercial product will discontinue lomitapide at Week 104±1 week and enter a 4-week Follow-up period during which they will remain on concomitant LLT (including LA, when applicable). These patients will then attend in person for a Week 108±1 week visit.

Concomitant treatment/medication

Permitted concomitant treatment/medication

The following medication will be permitted during study and follow-up:

- Lipid-lowering medicinal products including statins, fibrates, bile acid sequestrants, and PCSK9 inhibitors

  Please note: Patients who receive atorvastatin, should separate the dose of the medicinal products by 12 hours, e.g., by taking atorvastatin in the morning and lomitapide in the evening. Patients who receive bile acid sequestrants, should separate the dose of the medicinal products by 4 hours. Concomitant administration of >40 mg simvastatin is not permitted.

Concomitant treatment/medication (continued)

- Oestrogen-based oral contraceptives

  Please note: Postmenarchal female adolescent patients taking oestrogen-based oral contraceptives should be advised that diarrhoea and/or vomiting may reduce hormone absorption. In case of protracted or severe diarrhoea and/or vomiting lasting more than 2 days, the investigator should advise according to national practice, which additional contraceptive measures (such as sexual abstinence, barrier methods) should be used for 7 days after resolution of symptoms.
- Supportive therapy upon the investigators' discretion

The following medication will be permitted during the Safety Phase of the study:

- If a weak CYP 3A4 inhibitor, e.g., aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, glucocorticoids, modafinil and phenytoin inhibitor is required during the Safety Phase, the dose of lomitapide should be reduced.

  Please note: Patients who receive weak CYP 3A4 inhibitors, should separate the dose of the medicinal products by 12 hours.

If atorvastatin is given concomitantly, it should be administered in the morning to separate it from lomitapide dosing by 12 hours. In case it is not possible to administer atorvastatin and lomitapide 12 hours apart, the lomitapide dose should be reduced by half.

Non-permitted concomitant treatment/medication

The following medication will not be permitted during the study:

- Contraindications for the use of lomitapide according to Section 4.3 of the SPC (included in the Lojuxta® SPC in lieu of an IB), such as
  - Concomitant administration of >40 mg simvastatin.
  - Concomitant use of strong or moderate CYP 3A4 inhibitors, e.g., antifungal azoles such as itraconazole, fluconazole, ketoconazole, voriconazole, posaconazole; macrolide antibiotics such as erythromycin or clarithromycin; ketolide antibiotics such as telithromycin; HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil, and the anti-arrhythmic dronedarone.

The following medication will not be permitted during the Efficacy Phase of the study:

Weak CYP 3A4 inhibitors, e.g., aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, glucocorticoids, modafinil and phenytoin. If a weak cytochrome CYP 3A4 inhibitor is required during the Safety Phase, the dose of lomitapide should be reduced and the doses of medicinal products should be separated by 12 hours.

The use of the following food or substances should be avoided with lomitapide:

- Alcohol: Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury.
- Grapefruit juice: Grapefruit juice is a moderate inhibitor of CYP 3A4 and is expected to substantially increase exposure to lomitapide.
- Peppermint oil or Seville oranges.
- St. John's Wort (i.e., *Hypericum perforatum*).

Duration of patient participation in the study

Each patient will participate for up to 120 weeks (about 2.5 years) in the study:

- Screening Period: starting at Week -12, i.e., ≤12 weeks prior to Baseline for up to 6 weeks.
- Stratified Enrolment and Start of Run-in Period: ≥6 and ≤12 weeks starting at minimum at Week -6, i.e., 6 weeks prior to Baseline for a minimum of 6 and a maximum of 12 weeks.
- Efficacy Phase: 24 weeks±3 days.
- Safety Phase: 80 weeks±1 week.
- Follow-up Period: 4 weeks.

Timelines of study

- Estimated Date of First Patient Screened: Quarter 4 2020
- Estimated Date of Last Patient Screened: Quarter 1 2022
- Estimated Date of Last Patient Last Visit: Quarter 4 2023

Number of visits (study)

There will be 23 visits from Screening through Follow-up:

- Screening: n = 1.
- Run-in Period: n = 2.
- Efficacy Phase: n = 7, every 4 weeks±3 days.
- Safety Phase including End of Treatment (EoT):
  - After Week 24±3 days through Week 52±3 days: n = 8, every 4 weeks±3 days.
  - After Week 56±3 days through Week 104±1 week: n = 4, every 12 weeks±1 week.
- Follow-up: n = 1.

Patient discontinuation criteria

Patients and/or their parents/legal guardians will have the right to withdraw from the study at any time for any reason without prejudice to their future medical care. A patient may be withdrawn from the study at any time at either the investigator's, sponsor's, or Data Safety Monitoring Boards discretion.

A patient **must** be discontinued from the study for any of the following reasons:

- The patient matches the criteria referred to as "Hy's law case" according to the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines on Drug-induced Liver Injury (EASL 2019) and the FDA Guidance for Industry Drug-Induced Liver Injury Premarketing Clinical Evaluation (FDA 2009). Any Hy's law case or comparable signs of liver toxicity, irrespective of origin, must lead to permanent treatment discontinuation of the individual patient (no re-challenge allowed).
- The patient and/or his/her parent/legal guardian withdraws assent/consent.
- Pregnancy as evidenced by a positive pregnancy test.
- If a patient becomes pregnant during the study, during the follow up, or 30 days within the last application of study medication, the sponsor will have to be informed within 24 hours. The investigator will be asked to complete a pregnancy report provided by the sponsor. He/she will be asked to obtain data on the course of the pregnancy, including perinatal and neonatal outcome.
- Any AE which, in the opinion of the investigator, places the patient at unacceptable risk, including intolerable AE(s) after attempted dose reduction.

The investigator will be able to withdraw patients from the study for the following reasons:

- Hepatobiliary criteria for discontinuation
- Hepatobiliary AE Common Terminology Criteria for Adverse Events (CTCAE) Grade 4, regardless of relationship to study drug
- Biochemical hepatobiliary guideline Level 4 Hepatotoxicity or Level 3 Hepatotoxicity that persists despite interruption of study drug
- Histopathological diagnosis of Type 3 or Type 4 non-alcoholic steatohepatitis (NASH)
- Patient is noncompliant with the study procedures or medications in the opinion of the investigator
- Progression of a medical condition, which in the opinion of the investigator should preclude further participation of the patient in the study (e.g., excessive weight loss)
- Administration of non-permitted concomitant medication(s), substances, foods, or supplements
- Investigators' decision that a change of therapy is in the patients' best interest
- Occurrence of an AE (including abnormal laboratory findings), which makes discontinuation desirable or necessary in the investigators' and/or the patients' and/or parents/legal guardians opinion

If a patient discontinues the study or the follow-up prematurely due to an AE/serious adverse event (SAE), he/she will be followed up until the resolution or stabilisation of the AE/SAE.

If a patient discontinues the study prematurely, the assessment of the EoT visit should be made.

All data collected before premature discontinuation of the study will be used for analysis. Patients who drop out will not be replaced unless the assumptions for drop-out have been exceeded

Data Safety Monitoring Board

Periodic safety analyses will be performed by an independent Data Safety Monitoring Board (DSMB). The DSMB will have an initial organizational meeting at which time the composition, activities, and responsibilities of the DSMB will be detailed in a Charter as agreed upon by the sponsor and the DSMB members. The DSMB will be comprised of at least 3 members who are not otherwise involved in the conduct of the study; at least 1 of whom will be a statistician. The DSMB will meet at least 3 times during the conduct of the study. The DSMB in consultation with the sponsor will have the authority to stop the study for any reason including, but not limited to, unacceptable safety risks. Interim safety analyses may be performed by the DSMB at their discretion, at any time, on an 'as needed' basis according to ongoing study results. If a patient discontinues treatment permanently due to a Hy's law case or comparable signs of liver toxicity irrespective of origin, the DSMB will initiate an immediate recruitment stop as an urgent safety measure and will assess individual benefits and risks for the patients being treated with study medication regarding further therapy.

Statistical methods

The primary efficacy analysis will be conducted once all patients have completed (or withdrawn prior to) Visit 10 at Week 24±3 days (End of the Efficacy Phase). The primary efficacy analysis will include the key primary/secondary efficacy data, all safety data available up to the data cut-off date of the last patient reaching Week 24±3 days, and PK parameter analysis. The reporting of Week 24±3 days data will allow for an early submission of an application for regulatory approval of Lojuxta® in the paediatric indication. The final statistical analysis will be performed when all patients have completed the Follow-up Visit (Visit 23) at Week 108±7 days. Efficacy, safety, and exploratory data collected during the Safety Phase and follow-up will be included.

Tests of hypotheses and significance levels

The primary and secondary efficacy parameters collected during the Efficacy Phase of the study will be statistically tested using a 2-sided test at the 5% significance level.

To address the efficacy objectives, the efficacy parameters will be tested sequentially in a step-wise fashion, thereby controlling the overall type I error. First, the primary testing for percent change from Baseline in LDL-C at Week 24±3 days will be performed. If this test is statistically significant with a 2-sided $\alpha = 0.05$ and is statistically significant in a positive direction, then the tests of the secondary hypotheses will be performed in the following specified order at Week 24±3 days: (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 is reached, further tests in the sequence will be performed and p-values will be reported as a measure of the strength of effect without declaring statistical significance.

Analysis of other secondary endpoints collected during the Efficacy Phase and of endpoints collected during the Safety Phase will be analysed without adjustment for multiplicity.

Sample size of the study

The study will have 92% power to declare a treatment effect ($\alpha = 0.05$, 2-sided) in the reduction of LDL-C at Week 24±3 days compared to Baseline. The study sample size is based on the assumption that the true percent reduction from Baseline in LDL-C at Week 24±3 days would be 25%, with a standard deviation of 40%. As a conservative assumption, this estimated 25% reduction represents approximately 60% (relatively) of the 41% reduction from Baseline to Week 26 (End of Efficacy Phase) seen in the adult study UP1002/733-005, Intent-to-treat (ITT) population. This is the same assumption used for the sample size in the adult study. Further, the standard deviation (SD) represents an approximate 1/3 increase from the corresponding 31% SD seen in the adult study. This increase in SD was used to account for potentially increased variability across the 3 age groups.

A total of 30 evaluable patients will be required; to allow for up to a 33% drop-out rate during the Efficacy Phase (prior to Week 24±3 days), approximately 45 patients will be enrolled.

1.2 Flow Chart of Study and Follow-up

Examination	Screening	Run-in Period		Efficacy Phase		Safety Phase		EoT[B]	Follow-up[C]
		Enrolment	Compliance	Baseline	Efficacy	Safety/Tolerability			
Visit	**1[A]**	**2[A]**	**3**	**4**	**5 to 10**	**11 to 18**	**19 to 21**	**22**	**23**
Week(s)	**Up to -12**	**Minimum -6**	**-2**	**0 (Day 0)**	**4/8/12/16/ 20/24**	**28/32/36/40/ 44/48/52/56**	**68/80/92**	**104**	**108**
Window Procedure			**-1 week**		**±3 days**	**±3 days**	**±1 week**	**±1 week**	**-**
Window Procedure for LA					**±3 days**	**±3 days**	**±3 days**		
Eligibility & Safety Assessments									
▪ Informed consent & assent	X								
▪ Inclusion/exclusion criteria	X			X					
▪ Medical history	X								
▪ Physical exam (incl. xanthomas, height, weight, BMI, BSA)[D]	X			X	X	X	X	X	X
▪ Tanner staging[D]	X			X	X[D]	Week 56		X	
▪ 12-Lead safety ECG (read locally)				X	Week 24	Week 56	Week 80	X	
▪ Most recent standard of care echocardiography on file[E] (if available)				X	Week 24	Week 56		X	
▪ Vital signs and blood pressure	X			X	X	X	X	X	X
▪ Pulmonary function test[F]				X	Week 24	Week 56		X	
▪ Lipid accumulation in liver (NMR or echography)[G,H]				X	Week 24	Week 56		X[H]	X[H]
▪ Genetic testing[I]	X								
Dietary Counselling[J]		X	X	X	Week 4				
▪ 2-Day Diet record		X[K]	X	X	X	X	X	X	
Efficacy Assessments									
▪ CIMT (mandatory) and FMD (whenever possible)				X		Week 56		X	
Laboratory Tests									
▪ CBC	X			X		Week 56		X	X
▪ Metabolic panel (albumin, BG, BUN, Ca, carbon dioxide, Cl, creatinine, CRP, K, Na, total protein), CK[L]	X			X	X	X	X	X	X
▪ LFTs: ALT, AST, GGT, AP, total bilirubin, (in)direct bilirubin	X			X	X	X	X	X	X
▪ Fasting lipid panel: LDL-C, TC, HDL-C, Non-HDL-C, VLDL-C, TG, Lp(a), apo A-I, apo B[M]	X		X	X[N]	X	X	X	X	X

Examination	Screening	Run-in Period		Efficacy Phase		Safety Phase		EoT[B]	Follow-up[C]
		Enrolment	Compliance	Baseline	Efficacy	Safety/Tolerability			
Visit	**1[A]**	**2[A]**	**3**	**4**	**5 to 10**	**11 to 18**	**19 to 21**	**22**	**23**
Week(s)	**Up to -12**	**Minimum -6**	**-2**	**0 (Day 0)**	**4/8/12/16/ 20/24**	**28/32/36/40/ 44/48/52/56**	**68/80/92**	**104**	**108**
Window Procedure			**-1 week**		**±3 days**	**±3 days**	**±1 week**	**±1 week**	**-**
Window Procedure for LA					**±3 days**	**±3 days**	**±3 days**		
Laboratory Tests (Continued)									
▪ Serum levels of EFA: Linoleic acid, ALA, EPA, DHA, AA, and eicosatrienoic acid	X			X	Week 24	Week 56	Week 80	X	X
▪ Serum lipase				X	Week 24	Week 56		X	
▪ Fat-soluble vitamin levels[O] (retinol, 25-hydroxy-D, alpha tocopherol, ratio alpha tocopherol/total lipids, ratio uncarboxylated osteocalcin/total osteocalcin)	X			X	Week 24	Week 56	Week 80	X	X
▪ TSH, FSH, LH, ACTH, serum cortisol (between 6:00 and 08:00 a.m.)[P]	X			X		Week 56		X	
▪ In patients who are Tanner Stage ≥2: Serum testosterone (males), serum oestradiol (females)	X			X		Week 56		X	
▪ Pharmacokinetics[Q]				X	X				
▪ Urinalysis (bilirubin, blood, colour, glucose, ketones, pH, protein, turbidity, white blood cells)	X			X		Week 56		X	X
▪ Urine pregnancy test[R]	X	X	X	X	X	X	X	X	X
Investigational Medicinal Product									
▪ Administration[S], compliance check[S] & palatability assessment[T]				X	X	X	X		
Dietary Supplements[U]			X	X	X	X	X		
Adverse Events & Concomitant Medication									
▪ Incidence, severity, and relatedness of AEs/SAEs		Continuously throughout the study until resolution or stabilisation of the AE/SAE							
▪ Review of concomitant medication	Continuously throughout the study with date of onset until Follow-up Visit 23								
Withdrawal from Study	End of Treatment Visit 22 Assessments (Week 104±1 week) should be conducted.								

Abbreviations

AA	Arachidonic acid	ACTH	Adrenocorticotrophic hormone	AE	Adverse event	ALA	Alpha linoleic acid
ALT	Alanine aminotransferase	AP	Alkaline phosphatase	apo A-I	apolipoprotein A-I	apo B	apolipoprotein B
AST	Aspartate aminotransferase	BG	Blood glucose	BMI	Body mass index	BSA	Body surface area
BUN	Blood urea nitrogen	Ca	Calcium	CBC	Complete blood count	CIMT	Carotid intima-media thickness
CK	Creatinine kinase	Cl	Chloride	CRP	C-reactive protein	DHA	Docosahexaenoic acid
ECG	Electrocardiogram	EFA	Essential fatty acids	EoT	End of Treatment	EPA	Eicosapentaenoic acid

Abbreviations (continued)

FMD	Flow-mediated dilatation	FSH	Follicle stimulating hormone	GGT	Gamma-glutamyl transferase	HDL-C	High-density lipoprotein cholesterol
K	Potassium	LA	Lipoprotein apheresis	LDL-C	Low-density lipoprotein cholesterol	LFTs	Liver function tests
LH	Luteinising hormone	Lp(a)	Lipoprotein(a)	Na	Sodium	NMR	Nuclear Magnetic Resonance
Non-HDL-C	Non high-density lipoprotein cholesterol	PK	Pharmacokinetic	SAE	Serious adverse event	TC	Total cholesterol
TG	Triglycerides	TSH	Thyroid stimulating hormone	ULN	Upper limit of normal	VLDL-C	Very low-density lipoprotein cholesterol

A. There is no minimum timeframe between Screening, Enrolment and Start of the Run-in Period, as long as all results of diagnostic tests determining eligibility are available.

B. In the event of early termination, EoT assessments should be performed. If a patient discontinues the study or the follow-up prematurely due to an AE/SAE, he/she will be followed up until the resolution or stabilisation of the AE/SAE.

C. Patients entering the Expanded Access Programme (<18 years of age)/transitioning to commercial product (≥18 years of age) will have a follow-up phone call at Week 108±1 week to monitor safety including AE and concomitant medication reporting. Patients who have opted not to participate in or are unsuitable for the Expanded Access Programme (<18 years of age)/opted not to transition to commercial product (≥18 years of age) will return for an in person safety Follow-up Visit.

D. A full physical exam, including growth and sexual maturation assessments, a genitourinary exam per the Principal Investigator's judgment, but not rectal exam, will be performed at Screening, Baseline, Week 12±3 days, Week 24±3 days, Week 56±3 days, Week 104±1 week and/or at EoT. At all other time points shown, an abbreviated physical exam including measurement of height, weight, BMI and BSA may be performed. Please note that weight will be measured using a consistent approach at Screening and at each visit after the Run-in Period (i.e., child/adolescent always weighed in same amount of clothing, either in underwear, hospital gowns or by subtracting the weight of clothes). Xanthomas will be evaluated at every physical exam.

E. It is anticipated that echocardiography will be performed annually as standard of care in this patient population. For this study, echocardiography is not mandated but data/results will be included as part of the study safety data. Information in relation to the most recent echocardiography on file (if available) will be documented in the electronic Case Report Form at the following visits: Baseline, Week 24±3 days; Week 56±3 days, and Week 104±1 week.

F. Spirometry with $D_{L,CO}$ (diffusion capacity of the lung for carbon monoxide) will be performed to include: forced vital capacity (FVC); forced expiratory volume during 1 s (FEV_1); maximal mid-expiratory flow (FEF_{25-75})

G. All patients will undergo NMR imaging unless it is contraindicated or not feasible (e.g., due to the need for sedation or general anaesthesia in very young or anxious patients). In this case, echography (i.e., ultrasound scan) will be used at the discretion of the investigator.

H. Lipid accumulation in the liver will only be determined at Week 104 in patients entering the Expanded Access Programme (<18 years of age)/transitioning to commercial product (≥18 years of age). In patients who have opted not to participate in or are unsuitable for the Expanded Access Programme (<18 years of age)/opted not to transition to commercial product (≥18 years of age), lipid accumulation in the liver will be determined at Week 108.

I. Genetic testing is strongly encouraged, but not mandatory and not required for determining eligibility. Patients who have not previously had genetic testing, will be asked, whether they would consent to genetic testing. A separate informed consent will be obtained for genetic testing. A blood sample will be collected according to central laboratory procedures specified in the '*Laboratory Manual*' for genotyping at Screening (Visit 1). If it is not possible to do this at Screening (Visit 1) it can be done at a later visit.

J. The Principal Investigator can request additional dietary counselling as clinically indicated.

K. The 2-day diet record collected at this visit will be used to make any necessary adjustments to the patient's diet before starting study medication. A dietary compliance check will be performed at Week -2.

L. CK monitoring and evaluation
   1. If CK values are found to be elevated >5 x ULN on routine testing, the patient should be questioned about muscle symptoms.
   2. A study site physician should be alerted to the occurrence of unexplained muscle symptoms and any CK values >5 x ULN, and must take immediate action if CK is >10 x ULN.
   3. If CK values are >5 x ULN with muscle symptoms or >10 x ULN with or without muscle symptoms the following steps should be taken:
      a. Clarify the nature, duration and intensity of any muscle symptoms.
      b. Review possible predisposing factors, such as: unaccustomed exercise, heavy alcohol intake, viral illness (consider performing serology), concomitant medication and consider diagnosis of other conditions which cause myopathy.
      c. Physical examination for muscle tenderness, weakness and rash.
      d. Measure CK again within a few days.

e. Measure serum creatinine.
f. Urine dipstick.
g. Arrange to review the patient again in 4 to 10 days, or earlier if symptoms of myopathy appear or worsen, or if the urine becomes very dark.

4. Discontinue study medication for CK values >10 x ULN with or without muscle symptoms.
5. For CK values 5 to 10 x ULN:
   a. If asymptomatic, or if symptomatic but alternative explanation exists, symptoms should be followed and CK levels tested weekly until it is no longer a medical concern or symptoms worsen and meet criteria for any of the above.
   b. If symptomatic, and no alternative explanation exists, withhold therapy.
6. Throughout the study, patients should be instructed to promptly report any unexplained muscle pain or weakness, particularly if associated with malaise or fever. If this should occur, CK should be measured as soon as possible.

M. Draw 2 blood samples for the fasting lipid panel, of which 1 will be analysed in the local hospital laboratory and 1 will be sent to the central laboratory specified in the '*Laboratory Manual*'.
N. Baseline values of lipid and lipoprotein parameters will be obtained as the maximum concentration (C_{max}) immediately prior to LA, if applicable before start of study treatment.
O. Bone health and bone age will be assessed by measurement of 25-hydroxyvitamin D and total uncarboxylated osteocalcin levels (as a reflection of vitamin K levels).
P. The blood sample for testing of serum cortisol must be obtained in the early morning (6:00 to 8:00 am).
Q. A single PK sample will be collected at Baseline, at Visit 5 (Week 4±3 days), Visit 7 (Week 12±3 days), Visit 8 (Week 16±3 days), and Visit 10 (Week 24±3 days). Two PK samples will be collected at least 1 hour apart at Visit 6 (Week 8±3 days) and Visit 9 (Week 20±3 days); these samples must be collected as separate blood draws (time between separate blood draws might be used for undertaking other procedures scheduled for the respective visit(s)).
R. Urine pregnancy tests will be conducted in postmenarchal female adolescent patients using test strips at every scheduled visit from Visit 1 through Visit 23 and every 4 weeks after Visit 18 at Week 56±3 days through Week 104±1 week.
S. Patients will be instructed to refrain from taking study medication within 8 hours prior to their study visits. They will be asked to bring all unused study medication with them to the clinical site at every visit (including Safety/Tolerability Visits) for a compliance check.
T. At Visit 4, a 5-point facial hedonic scale will be used to record the child's assessment of palatability of study medication on the first occasion that any patient who is unable to swallow the intact capsule(s) opens the capsule(s) and sprinkles the capsule content on a small amount (1 tablespoon) of either apple sauce or mashed banana (i.e., if a patient tries both food media, assessment will be made at the first instance of taking the study medication with apple sauce and the first instance of taking the study medication with mashed banana). The type of food media (apple sauce or mashed banana) will be captured. At Visit 5, the investigator will ask the parent(s)/legal guardian(s) to evaluate the children's reaction to investigational product and dietary supplement administration. A 3-point scale that assesses the parent(s)/legal guardian(s) interpretation of the child's reaction/facial expression will be used to determine whether they find lomitapide "pleasant", "unpleasant" or are "not sure". In addition, an assessment of ease of administration will be incorporated by asking the parent(s)/legal guardian(s) the following question: "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)." The same question will be asked for the administration of dietary supplements. Timing of the reaction relative to dosing will be recorded to help distinguish between palatability of the investigational product and gastrointestinal events that are a result of the investigational products mechanism of action.
U. Dietary supplements will be dispensed at the Week -2 (Run-in Compliance) Visit and will be administered daily throughout the Efficacy and Safety Phases of the study. Dietary supplements should be taken in the morning.

2 INTRODUCTION

2.1 Background

2.1.1 Homozygous Familial Hypercholesterolaemia

Homozygous familial hypercholesterolaemia (HoFH) is a rare and life-threatening inherited disorder of lipid metabolism with an estimated prevalence of 1 per 160,000 to 300,000 in the European population (Cuchel, Bruckert et al. 2014, Sjouke, Kusters et al. 2015).

The Consensus Panel on Familial Hypercholesterolaemia (FH) of the European Atherosclerosis Society (EAS) recommends the following criteria for the diagnosis of HoFH (Cuchel, Bruckert et al. 2014):

- Genetic confirmation of 2 mutant alleles at the LDL receptor (LDLR), apolipoprotein B (apo B), proprotein convertase subtilisin/kexin type 9 (PCSK9), or LDL-receptor adapter protein 1 (LDLRAP1) gene locus or
- An untreated low-density lipoprotein cholesterol (LDL-C) >500 mg/dL (13 mmol/L) and treated LDL-C ≥300 mg/dL (8 mmol/L), respectively together with either
  - Cutaneous or tendon xanthomas before the age of 10 years or
  - Untreated LDL-C levels consistent with heterozygous FH in both parents.

Significantly elevated LDL-C levels lead to premature, severe, and progressive atherosclerosis and development of early cardiovascular disease (CVD). The average age of death is 18 years if untreated and effective lipid-lowering therapy (LLT) greatly improves survival in HoFH (Thompson, Blom et al. 2018).

Based on the evidence that treatment can delay the onset of CVD, primary prevention is suggested to start as early as possible and mainly consists of lowering LDL-C levels to <135 mg/dL (<3.5 mmol/L) in paediatric HoFH patients and to <100 mg/dL (<2.5 mmol/L) in adults. Secondary prevention comprises a decrease of LDL-C levels to <70 mg/dL (<1.8 mmol/L) in adults with CVD as recommended by the EAS (Cuchel, Bruckert et al. 2014).

2.1.2 Treatment Options and Medical Need

Lipid-lowering Medicinal Products

Therapeutic options include 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins, cholesterol absorption inhibitors such as ezetimibe, bile-acid sequestrants, and PCSK9 inhibitors. Statins and ezetimibe reduce LDL-C levels by about 25%. The PCSK9 inhibitor evolocumab decreases LDL-C beyond other lipid-lowering drugs by about 20% with wide variability depending on receptor status, as patients with receptor-negative mutations and less *LDLR* expression and activity respond less or not at all to PCSK9 inhibitors (Santos 2018, Thedrez, Blom et al. 2018).

Lipoprotein Apheresis

A current standard of care in HoFH includes lipoprotein apheresis (LA), a physical method of purging the plasma of LDL-C. The International Consensus Paper on integrating LA and new lipid-lowering drugs considers LA plus high dose statins and ezetimibe as first-line treatment in HoFH, as it reduces LDL-C, CVD, and prolongs life (Stefanutti, Julius et al. 2017).

However, the rebound phenomenon after LA described by Thompsen and Thompson in 2006 (Thompsen and Thompson 2006) makes it necessary to perform LA sessions weekly, since lipid-lowering drugs induce constantly low LDL-C levels (Julius 2016). In fact, time-averaged LDL-lowering ranges between 26% for biweekly LA treatment to 47%, if LA is done twice a

week (Thompson 2015). However, even weekly LA combined with high-dose statins and ezetimibe failed to prevent progression of CVD in HoFH patients (Graesdal, Bogsrud et al. 2012). Despite combination of conventional LLT and weekly or biweekly LA, about 50% of HoFH patients suffer progressive atherosclerosis and major cardiovascular events (Giammanco, Cefalu et al. 2019).

This fact has recently been confirmed by a publication on multimodal LLT in paediatric patients with HoFH, which revealed that 24% of children who started chronic LA before the age of 18 suffered progressive CVD despite weekly LA including 1 death due to coronary and cerebrovascular disease. Of 17 patients with genetically proven HoFH or compound heterozygous (c-het) FH in this study, 12 patients underwent LA weekly and 5 patients twice a week. The authors concluded that early and intensified LLT including LA is needed to improve the outcome (Klaus, Taylan et al. 2018).

Luirink et al. recently published a systematic review on the evidence for the safety and efficacy of LA in paediatric patients with HoFH. They evaluated 76 studies with 209 children starting LA at a mean age of 9.3 years (range 2 to 18 years). Mean pre-apheresis LDL-C levels were 604 mg/dL (15.6 mmol/L) and were reduced by a mean of 67.2% per session using semiselective LA, by 63.3% using nonselective LA, and by 71.6% using selective LA. While xanthomas regressed or disappeared in 83% of patients, surrogate parameters of CVD remained stable in most patients. Of 123 patients, 24 experienced a CVD event of whom 10 had experienced a CVD before LA onset. Six patients died at follow-up. The authors concluded that the impact of LA on the onset of CVD remains unclear and that more robust data was needed, particularly as LA is an invasive therapy with an important impact on daily life for children (Luirink, Determeijer et al. 2019).

Liver Transplantation

Liver transplantation is the only curative treatment for HoFH (Alim, Tokat et al. 2016), as it replaces the missing LDLR and normalises LDL-C. According to data from the European Liver Transplant Registry, 21 liver transplants for HoFH were performed between 1988 and 2009.

Paediatric liver transplantation in HoFH patients has been shown to sustainably normalise LDL-C levels within 1 month following transplantation. However, due to the high transplantation-related morbidity and mortality, the shortage of donors, and the need for life-long immunosuppressive therapy, the EAS does not recommend liver transplantation as first-line therapy for HoFH (Cuchel, Bruckert et al. 2014). HEART UK even considers to balance the early use of lomitapide and evolocumab beyond current licensed age restriction in severely affected children and young adults against the risks of liver transplantation (France, Rees et al. 2016).

In a longitudinal cohort of 31 molecularly defined HoFH patients enrolled in the Spanish HoFH registry, which is a subset of the SAFEHEART (Spanish Familial Hypercholesterolaemia Cohort Study, NCT02693548) registry, at inclusion 4 patients had received a liver transplant at a mean age of 13 years. Of these 4 patients, 2 withdrew LLT after the liver transplant, while 2 still required moderate doses of statins. During follow-up, a further patient underwent liver transplant at the age of 15 years. Overall, 2 patients died, 1 because of septicaemia due to immunosuppression and 1 during the postoperative period (Alonso, Diaz-Diaz et al. 2016). One of the 31 HoFH patients started lomitapide as an adjunct to LLT and achieved an additional LDL-C reduction of 52% without significant AEs.

Beyond the high transplantation-related morbidity and mortality and the need for life-long immunosuppressive therapy, there is some evidence that CVD is the leading cause of long-term morbidity and mortality in liver transplant recipients due to a proatherogenic lipoprotein profile (Chhatrala, Siddiqui et al. 2015) and that LDL-C independently predicts CVD events (Siddiqui, Arshad et al. 2019). This may contribute to the need for LLT treatment after liver transplant.

2.2 Investigational Product

Lomitapide is a first in class oral, selective inhibitor of microsomal transfer protein (MTP), an intracellular lipid-transfer protein that is found in the lumen of the endoplasmic reticulum and is responsible for binding and shuttling individual lipid molecules between membranes. MTP plays a key role in the assembly of apo B containing lipoproteins in the liver and intestines. Inhibition of MTP reduces lipoprotein secretion and circulating concentrations of lipoprotein-borne lipids including cholesterol and triglycerides.

The European Commission (EC) granted authorisation for lomitapide under the trade name 'Lojuxta®' in July 2013. Lomitapide is a "lipid modifying agent" according to the Anatomical Therapeutic Chemical (ATC) Classification System (ATC code C10AX12). It is indicated as an adjunct to a low-fat diet and other lipid-lowering medicinal products with or without LA in adult patients with HoFH. Genetic confirmation of HoFH should be obtained whenever possible. Other forms of primary hyperlipoproteinaemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism) must be excluded.

Please refer to Section 6.1 *Description of the Investigational Product* for details regarding formulation, packaging, and labelling as well as storage of lomitapide.

2.3 Summary of Non-clinical Studies with Lomitapide

Please refer to Section 2.3 of the European Public Assessment Report (EPAR) of the European Medicines Agency for Lojuxta® dated 30 May 2013 for a summary of non-clinical studies with lomitapide.

2.4 Summary of Clinical Studies with Lomitapide

According to the EPAR of the European Medicines Agency for Lojuxta® dated 30 May 2013 the clinical development programme for Lojuxta® included 15 phase I studies, 7 phase II studies and 3 phase III studies. In total, 1,145 healthy subjects and patients were treated, including 943 who received lomitapide, either as monotherapy or co-administered with other LLT. The majority of subjects (959 out of 1,145) were enrolled in placebo and/or active-controlled studies. The clinical studies were performed in accordance with Good Clinical Practice (GCP). Clinical studies conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC. In support of the clinical studies in man, the marketing authorisation application also included 12 *in vitro* studies using human samples or human cell material.

Please refer to Section 2.4 of the EPAR of the European Medicines Agency for Lojuxta® dated 30 May 2013 for further details.

2.4.1 Clinical Pharmacology and Pharmacokinetics

Please refer to Section 2.4 of the EPAR for Lojuxta® dated 30 May 2013 for a summary of clinical aspects of pharmacokinetics and pharmacodynamics of lomitapide.

2.4.2 Clinical Efficacy and Safety

Global Phase III Study and Long-Term Extension Study

The efficacy and safety of lomitapide as an adjunct to a low-fat diet and LLT with or without LA was investigated in a single-arm, multi-national phase III study (UP1002/AEGR-733-005, NCT00730236) in adult patients with HoFH. The study had a 26-week Efficacy Phase during which all background LLT including LA remained fixed and lomitapide was titrated to the maximum tolerated dose (MTD, range 5 to 60 mg, mean dose 40 mg) and a 52-week Safety Phase during which lomitapide dose was continued at the MTD and background LLT could be altered with physician discretion.

Overall, 23 of 29 patients (16 male, 13 female, mean age of 30.7 years) completed the Efficacy Phase of the study. By Week 26, mean LDL-C decreased significantly by 40% in the Intent-to-treat (ITT) and by 50% in the completer population. Reductions in LDL-C were maintained during the Safety Phase with a mean change from Baseline to Week 56 of 44.0% ($p<0.001$) and to Week 78 of 38.4% ($p<0.001$). Concurrent LLT was reduced in 15 of 23 patients (65%); 6 of 13 patients (46%) who were receiving LA either permanently stopped LA (n=3) or permanently increased the interval in between LA treatments (n=3). LDL-C values of <100 mg/dL (<2.5 mmol/L) were observed at least once in 55%, LDL-C values of <70 mg/dL (<1.8 mmol/L) in 31% of patients (Cuchel, Meagher et al. 2013).

Long-term data of the extension study (AEGR-733-012, NCT00943306) that enrolled 19 of the 23 patients who completed the pivotal study with a mean age of 30.4 years (10 male, 9 female) confirmed efficacy and safety of lomitapide. The median treatment duration with lomitapide across both studies was 5.1 years (range, 2.1 to 5.7 years).

From Baseline through Week 246, a total of 14 (74%) patients achieved LDL-C <100 mg/dL (<2.5 mmol/L), and 11 (58%) patients achieved LDL-C <70 mg/dL (<1.8 mmol/L) on at least 1 occasion. One additional patient discontinued LA in the long-term extension study. The most common adverse events (AEs) reported were gastrointestinal, including diarrhoea, nausea, dyspepsia, and vomiting. For most drug-related AEs, the incidence was lower in the extension study compared with the pivotal study (42.1% versus 84.2%) (Blom, Averna et al. 2017)

LOWER Registry

The Lomitapide Observational Worldwide Evaluation Registry (LOWER, NCT02135705, European PAS register number ENCEPP/SDPP/5326) is an international, multi-centre, observational registry to prospectively assess long-term safety and efficacy of lomitapide. The LOWER Registry is an EU Risk Management Plan (RMP) Category 2 study following a specific obligation on the exceptional marketing authorisation of lomitapide dated 31 July 2013.

As of 01 March 2018, a total of 178 patients with a mean age of 52.1 years have been enrolled. The duration of lomitapide exposure ranged from 0.3 to 60.1 months with a median exposure duration of 21.7 months and doses ranging from 2.5 mg to 40 mg daily.

At any time after initiating lomitapide treatment, 104 (59.4%) patients experienced a reduction in LDL-C by at least 50%, 117 (66.9%) patients experienced an LDL-C value <100 mg/dL (<2.5 mmol/L) and 73 (41.7%) patients experienced an LDL-C value of <70 mg/dL (<1.8 mmol/L). Mean percent changes in LDL-C and other serum lipids and lipoproteins were consistent with mean percent changes reported in the phase III pivotal study (Cuchel, Meagher et al. 2013).

Overall, 133 (76.0%) patients experienced at least 1 AE, with diarrhoea (n=57, 32.6%) and nausea (n=20, 11.4%) being the most commonly reported, consistent with the prescribing information and the phase III clinical study (Cuchel, Meagher et al. 2013). Events that were considered treatment-related by the investigator were reported in approximately half of the patients (n=97, 55.4%), the majority of which were mild (n=48, 27.4%) or moderate (n=38, 21.7%) with the remaining considered severe (n=10, 5.7%). The most common treatment-related AEs were diarrhoea (n=49, 28.0%) and nausea (n=15, 8.6%) as expected. Serious AEs were reported in 34 (19.4%) patients, and the SAEs experienced by >2% of patients were acute myocardial infarction (n=4, 2.3%), angina pectoris (n=5, 2.9%), cardiac failure congestive (n=3, 1.7%), coronary artery disease (n=7, 4.0%), and pneumonia (n=4, 2.3%). Overall, no new safety signals have been identified.

In about a quarter of enrolled patients (n=41, 23.4%), permanent discontinuation of lomitapide was due to AEs, mostly due to GI events (n=25, 14.3%), specifically diarrhoea (n=15, 8.6%), which was slightly higher than the 10% (n=3/29) of patients discontinuing due to GI AEs in the phase III study and increases in hepatic enzymes/liver function tests (LFTs) (n=12, 6.9%).

Given the high risk associated with the extreme LDL-C levels experienced by patients with HoFH, the results of this analysis of data collected in the LOWER registry support the favourable benefit-risk profile of lomitapide when used as directed.

Cohort Analyses and Case Studies

There are several publications that report data in case studies and cohort analyses following treatment with lomitapide in the real world that show superior efficacy and similar or improved tolerability compared with the phase III study data that led to the exceptional approval by the European Medicines Agency (EMA).

Van Lennep et al. reports data on 4 HoFH cases: Each patient was commenced on lomitapide according to the prescribed protocol and subjected to routine follow-up. All 4 patients experienced clinically meaningful reductions in LDL-C levels of 35 to 73% (Roeters van Lennep, Averna et al. 2015).

Stefanutti et al. reports data on 7 patients with genetically determined HoFH who were treated with lomitapide in the normal course of their therapy. All patients received LA either weekly or biweekly. Lomitapide was administered according to the approved EU prescribing information. The LDL-C reductions ranged from 5% (early in treatment) to 83% with a mean reduction of 40% (Stefanutti, Morozzi et al. 2016).

The publication by deGoma reports in detail the case history of a patient receiving treatment with lomitapide in the US. The patient had a pre-apheresis LDL-C ranging from 146 to 188 mg/dL prior to treatment with lomitapide. After 12 weeks and on a dose of 5 mg, his LDL-C reduced to 64 mg/dL and he stopped apheresis. The LDL-C increased slightly to 107 mg/dL and the lomitapide dose was increased to 10 mg. He was also able to stop treatment with colesevelam, ezetimibe and fenofibric acid (deGoma 2014).

Comparably, 1 of 2 HoFH patients reported by Real et al. experienced a dramatic reduction of LDL-C values at lomitapide doses of 5 to 10 mg/day. The first patient maintained LDL-C levels <70 mg/dL (<1.8 mmol/L) and stopped LA. His brother received a dose of 20 mg/day and showed interapheresis LDL-C levels of <100 mg/dL(<2.5 mmol/L) (Real, Arbona et al. 2018).

Kolovou et al. reviewed their experience in treating 4 HoFH patients with lomitapide as an adjunct to LLT including LA for 14 months. Two patients showed LDL-C reductions of 54% and 65%, respectively (called hyper-responders), while LDL-C levels in 2 patients decreased by 35% and 11% (called hypo-responders). Dr Kolovou reported the variability in response may be due to MTP gene expression (Kolovou, Kolovou et al. 2016).

The biggest dataset in real world use comes from Italy and includes 15 HoFH patients treated for up to 3 years with mean Baseline LDL-C levels of 426.0±204.0 mg/dL despite receiving treatment with statins, ezetimibe and LA (in 10 of the 15 patients). With a rather low mean dose of 19±13.3 mg lomitapide/day as an adjunct to LLT, LDL-C was lowered by a mean of 76.2%±16.7%. Overall, 8 of 10 patients on LA were able to discontinue LA completely, while the 2 remaining patients decreased the frequency of LA. After stopping LA and adjusting other LLT, the mean LDL-C reduction at the last timepoint was 68.2±24.8% versus Baseline. At their last visit, 60% of patients achieved LDL-C <100 mg/dL (<2.5 mmol/L), and 46.6% of patients achieved LDL-C <70 mg/dL (<1.8 mmol/L) (D'Erasmo, Cefalu et al. 2017).

Evidence on Efficacy and Safety in Paediatric Patients

Chacra et al. have published a case report describing a 49-month compassionate use of lomitapide in a 7.6-year old female child with HoFH. The patient presented with LDL-C values of 1,009 mg/dL at the age of 29 months. After 10 months of low-saturated fat/cholesterol diet, atorvastatin 5 mg/day and ezetimibe 10 mg/day were introduced. Atorvastatin was titrated to 40 mg/day and the mean LDL-C reduction under this regimen was 44%. Due to the *LDLR* null mutations in this patient, the administration of PCSK9 inhibitors was not considered. Lomitapide was started at 5 mg/day at the age of 92 months when LDL-C was 428 mg/dL, as

the left ventricle-aortic peak gradient of the patient had increased and valve regurgitation was progressive. Lomitapide was gradually titrated up to the MTD of 20 mg/day and achieved a 37% reduction in LDL-C on top of atorvastatin and ezetimibe. Lomitapide was safe and well tolerated and the patient presented with adequate growth and sexual maturation. However, despite the efficiency of lomitapide in reducing LDL-C levels, CVD was progressive, possibly due to the already established damage of the aortic valve at start of treatment. The authors concluded that further studies with lomitapide in this very high-risk population are urgently warranted to establish long-term safety and efficiency and to investigate whether lomitapide can retard the onset and progression of CVD (Chacra, Ferrari et al. 2019).

Ben-Omran et al. have recently reported a case series of 11 paediatric HoFH patients at a mean age of 11.6±1.1 years who have received treatment with lomitapide on a named-patient basis, as their cases have been deemed ‘urgent to treat’ due to early CVD, lack of sufficient response to standard of care (SOC) treatment and inability to wait for study APH-19 to start. These patients have received lomitapide at a mean dose of 24.5±4.3 mg/day for 20.0±2.9 months as an adjunct to their LLT (including LA in 5 patients). Mean Baseline LDL-C of 419±74.6 mg/dL was reduced by 58.4±6.8% to a nadir of 176.7±46.3 mg/dL. Six patients achieved EAS target levels of <135 mg/dL (3.5 mmol/L), 3 of whom reduced their LA frequency, and 2 stopped LA completely. Adverse events were consistent with those seen in the phase III study in adults and in real world use. The majority of AEs consisted of gastrointestinal (GI) complaints, presented early in the treatment course, and resolved with minimal active management. Transient increases in LFTs resolved either with brief dose reductions or without intervention. Overall, efficacy and safety were comparable to the results reported in adult HoFH patients. Consistent with real-world data from adult patients, efficacy was higher at a lower mean dose. The authors compared their approach of dose titration based on LDL-C levels as opposed to MTD with the results of D’Erasmo et al. who reported a mean LDL-C decrease of 76.2%±16.7% at a rather low mean dose of 19±13.3 mg lomitapide/day (D'Erasmo, Cefalu et al. 2017). According to Ben-Omran et al. an important and positive outcome for 5 children in this case series was the ability to reduce or stop LA, which was a benefit given increasing time commitments as age advanced (Ben-Omran, Masana et al. 2019).

In summary, global pivotal phase III study data and real world evidence for lomitapide as an adjunct to a low-fat diet and LLT with or without LA in both adult and paediatric patients confirm the feasibility to reach EAS targets of LDL-C levels <135 mg/dL (3.5 mmol/L) in children and <100 mg/dL (<2.5 mmol/L) in primary or <70 mg/dL (<1.8 mmol/L) in secondary prevention in adults (see Figure 1).

Figure 1 Percentage of Patients Achieving EAS Treatment Goals with Lomitapide across Pivotal Studies and in Real-world Evidence

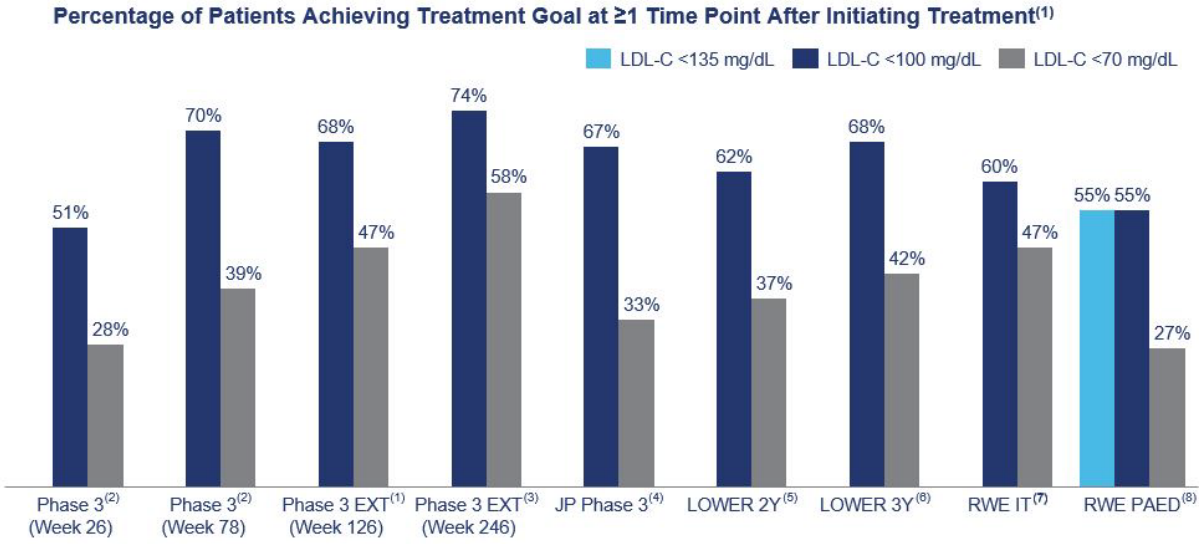


Figure based on Underberg J, J Clin Lipidol 2018;12(2):561-562 (Underberg, Harada-Shiba et al. 2018) showing percentage of patients achieving EAS treatment goals (LDL-C <135 mg/dL [3.5 mmol/L] in paediatric patients and LDL-C <100 mg/dL [<2.5 mmol/L] in primary and <70 mg/dL [<1.8 mmol/L] in secondary prevention in adults) at ≥1 time point after initiating treatment with lomitapide

IT = Italy; JP = Japan; LOWER = Lomitapide Observational Worldwide Evaluation Registry; LDL-C = Low-density lipoprotein C; PAED = Paediatrics; RWE = Real world evidence

1. Underberg J, J Clin Lipidol 2018;12(2):561-562 (Underberg, Harada-Shiba et al. 2018)
2. Cuchel M, Atherosclerosis Suppl 2014;15(2):33-45 (Cuchel, Bruckert et al. 2014)
3. Blom DJ, Circulation 2017;136(3):332-335 (Blom, Averna et al. 2017)
4. Harada-Shiba M, J Atheroscler Thromb 2017;24(4):402-411 (Harada-Shiba, Ikewaki et al. 2017)
5. Underberg J, Circulation 2016;134(suppl1): A12117-A12117 (Underberg, Cannon et al. 2016)
6. Underberg J, J Clin Lipidol 2018;12(2):561-562 (Underberg, Cannon et al. 2018)
7. D'Erasmo L, Adv Ther 2017;34(5):1200-1210 (D'Erasmo, Cefalu et al. 2017)
8. Ben-Omran T, Adv Ther 2019; https://doi.org/10.1007/s12325-019-00985-8 (Ben-Omran, Masana et al. 2019)

2.5 Rationale for Dose Selection

Paediatric starting doses, dose escalation regimens, and appropriate maximum doses for different age ranges were determined using allometric scaling and physiologically-based pharmacokinetic modeling (PBPK) as well as simulation approaches (see Section 18.1 *Source Documents, Lomitapide Pediatric Trial Dose Selections Using Two Approaches: Allometric Scaling and Physiologically-based Pharmacokinetic (PBPK) Modeling; Final Report, 26 June 2013*).

The calculation is based on the approved dosing regimen for adults. It takes into account the assumptions that disease progression, response to intervention and concentration-response (C-R) are similar in children and adults. These assumptions are considered reasonable due to the genetic cause of HoFH and the mechanism of action of lomitapide.

Figure 2 displays the proposed paediatric dose (mg) by age group and method: The age-dependent doses calculated by allometric scaling were combined to calculate a mean dose for each age group specified in the PBPK modelling. The error bars represent the standard deviation of the calculated mean dose. As can be seen, the proposed mean paediatric doses were overall 0.5 to 1 mg higher using the allometric scaling approach compared to the PBPK approach except in the oldest age group (see Figure 2).

Figure 2 Proposed Mean Lomitapide Paediatric Starting Dose Based on Physiologically-based Pharmacokinetic Modelling and Allometric Scaling

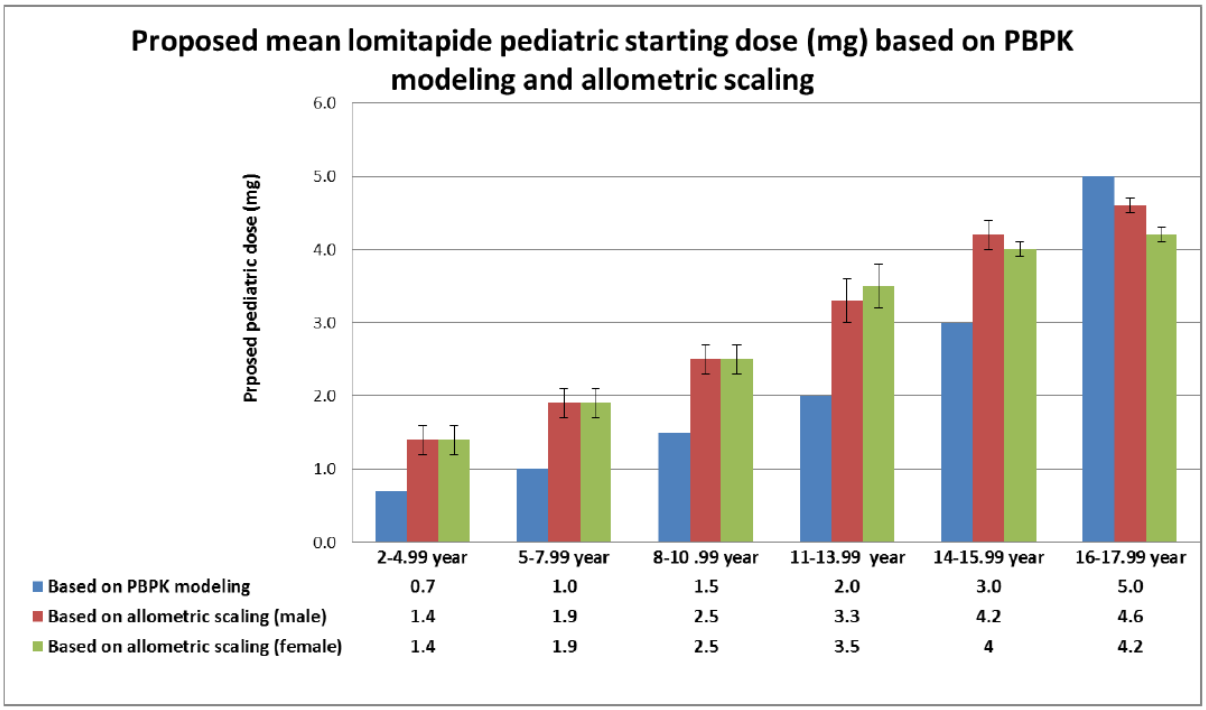


Table 1 shows the recommended first-in-paediatric doses by age group, for which both the calculated doses based on PBPK modelling and allometric scaling and the availability of minimum dosage form strength (2 mg) and next higher dosage strength (5 mg) have been taken into consideration.

Table 1 Suggested Lomitapide Starting Doses by Age Group Based on Physiologically-based Pharmacokinetic Modelling and Allometric Scaling

Age Group (years)	Suggested Starting Dose (mg)		
	PBPK Modelling	Allometric Scaling	Recommendation
5 to 10	1.0 to 1.5	1.9 to 2.5	2.0
11 to 15	2.0 to 3.0	3.3 to 4.2	2.0
16 to ≤17	5.0	4.0 to 4.5	5.0

PBPK = Physiologically-based Pharmacokinetic

Please refer to Section 7.2 *Treatment Schedule* for corresponding starting doses, dose escalation regimens, and maximum doses of lomitapide by age group.

2.6 Known and Potential Benefits and Risks

2.6.1 Unmet Medical Need

Due to their cumulative LDL-C burden, paediatric HoFH patients suffer early-onset atherosclerotic cardiovascular disease (ASCVD) at the age of 12.5 years and die at the age of 18 years, if the disease is undetected or untreated (Nordestgaard, Chapman et al. 2013).

Lipid-lowering medicinal products reduce LDL-C levels by up to 45% with wide variability depending on receptor status (Santos 2018, Thedrez, Blom et al. 2018). Time-averaged LDL-C-lowering of LA ranges between 26% for biweekly LA treatment to 47%, if LA is done twice a week (Thompson 2015). However, despite standard of care LLT including LA,

paediatric patients with HoFH rarely achieve EAS LDL-C target levels and suffer early progressive CVD (Klaus, Taylan et al. 2018, Luirink, Determeijer et al. 2019).

Since the EAS does not recommend liver transplantation as first-line therapy for HoFH (Cuchel, Bruckert et al. 2014) and HEART UK considers to balance the early use of lomitapide in severely affected children against the risks of liver transplantation (France, Rees et al. 2016), lomitapide is a “last-resort” treatment for paediatric patients, who respond less or not at all to PCSK9 inhibitors due to receptor-negative mutations with less *LDLR* expression and activity (Thedrez, Blom et al. 2018) and for those who either do not have access to LA or suffer progressive CVD despite receiving LLT including LA (Ben-Omran, Masana et al. 2019).

Please refer to Section 2.1.2 *Treatment Options and Medical Need* for further details.

2.6.2 Known and Potential Benefits

Lomitapide is a first in class oral, selective MTP inhibitor that functions independently of the LDLR. It is administered orally and is subject to a high first-pass effect following ingestion resulting in a low systemic bioavailability of approximately 7% (see Section 2.3.3 of the EPAR for Lojuxta® dated 30 May 2013). The pharmacodynamic activity of lomitapide is not dependent on systemic exposure but is directly related to local concentrations achieved in the small intestine and liver.

The high first-pass effect observed to limit systemic availability of lomitapide is likely to be dominated by significant metabolism by CYP 3A4 inhibitors. The parent molecule is cleaved into 2 primary metabolites (M1 and M3) that lack activity against MTP. Systemic concentrations of lomitapide are low following oral administration and there is a large apparent volume of distribution despite a high level of protein binding. This suggests loose binding to low-affinity sites, mitigating the likelihood of interactions by displacement of other protein-bound drugs. Excretion of unchanged lomitapide is minimal by any route, and the majority of the drug appears as water soluble (polar) metabolites in the bile.

Therefore, strong or moderate CYP 3A4 inhibitors are not permitted during the study as described in Section 7.6.3 *Non-Permitted Concomitant Medication, Food or Substances*. Weak CYP 3A4 inhibitors are only permitted during the Safety Phase of the study and doses of lomitapide or concomitant medication should either be administered 12 hours apart or modified (see Section 7.3.3 *Dose Modification for Concomitant Medication*).

The central role of LDL-C in the pathophysiology of ASCVD is well established. Every 1 mmol/L (38.6 mg/dL) reduction in LDL-C levels is associated with a corresponding 22% decrease in cardiovascular mortality and 12% reduction in total mortality over 5 years (Baigent, Blackwell et al. 2010).

Published evidence shows lomitapide to reduce LDL-C consistently and significantly by a mean 40% to 50% across the whole spectrum of molecularly-defined adult HoFH patients irrespective of LA and independent of LDLR function. There was no loss of efficacy in patients with genotypes predicting the most severely compromised LDLR function, who tend to be non-responsive to other therapies like statins and PCSK9 inhibitors (Hegele, Shah et al. 2018).

Global pivotal phase III study data and real world evidence for lomitapide as an adjunct to a low-fat diet and LLT with or without LA confirmed the feasibility to reach EAS targets of LDL-C levels <135 mg/dL (3.5 mmol/L) in 55% of paediatric and <100 mg/dL (<2.5 mmol/L) in 51 to 74% or <70 mg/dL (<1.8 mmol/L) in 28 to 58% of adult HoFH patients (see Figure 1).

This magnitude of LDL-C reduction is unprecedented in clinical experience within the HoFH patient population, in whom LDL-C levels have largely proven refractory to oral therapy, necessitating use of regular LA to effect further reductions. For the first time, it is now feasible to reach target LDL-C goals and maintain these levels during chronic treatment.

According to a modelling analysis in 149 HoFH patients LDL-C lowering of lomitapide could increase median life expectancy by 11.6 years and delay time to the first major cardiovascular

event (MACE) by 5.7 years (Leipold, Raal et al. 2017). Correspondingly, Blom et al. have shown that the annualised MACE rates in HoFH patients treated with mipomersen, lomitapide and evolocumab were 11.4%, 2.0%, and 2.1% versus 26.1% in the pre-mipomersen exposure cohort of the mipomersen study (Blom, Cuchel et al. 2018). Of note, HoFH in patients in the lomitapide cohort was more severe as evidenced by a higher mean Baseline LDL-C value of 336 mg/dL and a Baseline CVD rate of 93%.

2.6.3 Known and Potential Risks

Inhibition of MTP is expected to cause accumulation of triglycerides in intestinal mucosa and hepatocytes, and malabsorption of fat and fat-soluble vitamins from the diet. Major histological findings from non-clinical toxicological experiments showed increased incidences of lipid vacuolation in small intestinal mucosal epithelium and hepatocytes.

However, increased incidences of liver and small intestine tumours in mice were not noted in clinical studies and may not be expected to occur in clinical use due to the lack of genotoxicity, immunotoxicity, or other cellular injury associated with high levels of lomitapide exposure. In addition, unphysiological factors in the non-clinical experiments such as vitamin E depletion and severe hypocholesterolaemia will be prevented by administering dietary supplements (see Section 6.3 *Dietary Supplements*) and by closely monitoring LDL-C levels (see Section 1.2 *Flow Chart of Study and Follow-up*).

In the pivotal phase III study, 10 of 29 patients experienced elevations of ALT and/or AST >3 x ULN once or more during the study. Four of these patients exhibited ALT increases >5 x ULN. No patient discontinued treatment permanently due to LFT elevations and all elevations were managed either by dose reduction or temporary interruption of lomitapide as per protocol. Of note, 3 of 4 patients with LFT elevations >5 x ULN reported consuming quantities of alcohol higher than those allowed per protocol. No patient experienced elevations in bilirubin or AP levels (Cuchel, Meagher et al. 2013).

During the extension study, 4 of 19 (21.1%) patients experienced a ≥5 x ULN increase in ALT or AST. Increases ≥5 x ULN were typically associated with concomitant use of CYP 3A4 inhibitors or excess alcohol use. These events were successfully managed by discontinuing offending medication, lomitapide dose reductions or suspension, and reintroduction of lomitapide after normalisation of transaminases (Blom, Averna et al. 2017).

Management of elevated hepatic aminotransferases in this study is carefully specified by an algorithm in Section 7.3.2 *Dose Modification, Interruption or Discontinuation for Adverse Events*. In addition, an independent DSMB will provide oversight of patient safety (see Section 4.3 *Data Safety Monitoring Board*).

Due to the potential for lomitapide to cause elevations in ALT/AST levels, it should be used in caution in patients who consume alcohol. Further, caution should be exercised when lomitapide is co-administered with agents known to be hepatotoxic (see Section 7.6.3 *Non-Permitted Concomitant Medication, Food or Substances*) and is contraindicated in patients with moderate to severe hepatic impairment and those with active liver disease, including patients with unexplained persistent abnormal liver function tests (see Section 5.2 *Exclusion Criteria*).

In the pivotal phase III study, hepatic fat was measured non-invasively using NMR. Mean hepatic fat content of 20 evaluable patients was 1.0% at Baseline, 8.6% at Week 26, 5.8% at Week 56 and 8.3% at Week 78 (Cuchel, Meagher et al. 2013). In the extension study, 18 patients had ≥1 assessment of hepatic fat by NMR after Baseline. Median hepatic fat increased from 0.7% at Baseline to 6.5% at Week 78 and was 7.7%, 10.3%, and 10.2% at Weeks 126, 174, and 246, respectively (Blom, Averna et al. 2017).

Clinical data suggest that hepatic fat accumulation is reversible after stopping treatment with lomitapide. For this reason, hepatic fat content will be measured 4 weeks after EoT in patients who opt not to participate in or are unsuitable for the Expanded Access Programme (EAP;

<18 years of age)/opt not to transition to commercial product (≥18 years of age; see Section 8.1.2 *Safety Assessments*).

The most common AEs in the phase III study included abdominal pain or discomfort, nausea, vomiting, dyspepsia, diarrhoea, and constipation. Diarrhoea was the most common symptom. This finding is expected since MTP inhibition is known to cause fat malabsorption and steatorrhea. As the occurrence and severity of GI AEs associated with the use of lomitapide decreases in the presence of a low-fat diet, patients will start to follow a diet supplying <20% of energy from fat or <30 g fat, whichever is the lesser amount at the Start of the Run-in Period, and will continue this diet until the EoT or through the administration of lomitapide in the EAP (<18 years of age) or during administration of commercial lomitapide (≥18 years of age; see Section 8.6.1 *Diet Instructions and Diet Records*).

In the pivotal phase III study, decreased body weight was reported as an AE in 6 of 29 patients. All cases were assessed as mild to moderate in severity, non-serious and none led to study drug discontinuation. The combination of gastrointestinal (GI) symptoms (e.g., diarrhoea, nausea), fat malabsorption, and adherence to a strict fat-restricted diet, may result in a calorie deficit relative to daily requirements. Appropriate dietary supervision and monitoring is an important component to improve GI tolerability and the maintenance of an adequate diet to avoid unintended weight loss. In this study, weight will be measured at each visit after the Run-in Period and patients of normal or below normal body weight based on gender and age-specific World Health Organization (WHO) growth charts with weight loss >3% since the last visit will be instructed by the dietitian on how to increase caloric intake based on individual needs (see Section 8.6.1 *Diet Instructions and Diet Records*). Patients with below normal body weight any time during the study who continue to lose weight while on study medication despite all appropriate measures taken to correct for the weight loss and who are deemed to be at clinical risk in the judgment of the treating investigator should discontinue study medication and should be followed until an acceptable stable weight is reached as judged by the investigator (see Section 7.3.2 *Dose Modification, Interruption or Discontinuation for Adverse Events*).

MTP inhibition with lomitapide is likely to cause a deficiency in fat-soluble vitamins, particularly vitamin E. Therefore, all patients in this study will receive daily oral supplementation with vitamin E (200 IU for patients 5 to 8 years of age, 400 IU for patients 9 to ≤17 years of age) and an EFA supplement containing approximately 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA (see Section 6.3 *Dietary Supplements*).

The SPC (included in the Lojuxta® SPC in lieu of an Investigator's Brochure [IB]; see Section 18.1 *Source Documents*) provides guidance in key areas to minimise risk to patients during treatment with lomitapide, which is reflected in the design of this study. Use of lomitapide in patients with moderate or severe hepatic impairment, active liver disease, or pregnancy is contraindicated (see Section 5.2 *Exclusion Criteria*). Contraindications also include co-administration with strong or moderate inhibitors of CYP 3A4 and co-administration with doses of simvastatin >40 mg (see Section 7.6.3 *Non-Permitted Concomitant Medication, Food or Substances*). In the presence of atorvastatin (a weak CYP 3A4 inhibitor), lomitapide should be taken 12 hours apart. Since patients will be required to remain on their concomitant LLT (including LA when applicable) established during the 6-week Run-in Period during the Efficacy Phase of the study through Week 24±3 days, a potential concomitant treatment with atorvastatin will remain unchanged during the Efficacy Phase, when lomitapide dosing will start. If atorvastatin is given concomitantly, it should be administered in the morning to separate it from lomitapide dosing by 12 hours. If during the 80-week Safety Phase it is not possible to administer atorvastatin and lomitapide 12 hours apart, the lomitapide dose should be reduced by half. After a minimum period of 4 weeks following dose reduction the patient can be re-challenged with a higher dose of lomitapide once these issues resolve (i.e., if atorvastatin can be administered 12 hours apart or if atorvastatin is discontinued), but the dose during the Safety Phase cannot exceed the MTD established during the Efficacy Phase unless eligibility for exceptional dose escalation is met (described in Section 7.3.1 *Dose Escalation, Dose*

Reduction and Re-challenge). For patients on a stable maintenance dose of lomitapide who receive any other weak CYP 3A4 inhibitor, the dose of the medications should be separated by 12 hours (see Section 7.3.3 *Dose Modification for Concomitant Medication*). Use in patients with known significant or chronic bowel disease is also contraindicated since MTP inhibition is known to cause fat malabsorption and steatorrhea. Use in patients with rare hereditary problems of galactose intolerance, the Lapp-lactase deficiency or glucose-galactose malabsorption, are contraindicated in accordance with EU guidance (EC Volume 3B Guidelines, *Medicinal Products for Human Use, Safety, Environment and Information: Excipients in the Label and Package Leaflet of Medicinal Products for Human Use*, July 2003) since the drug product contains lactose (see Section 5.2 *Exclusion Criteria*). Hepatic aminotransferase levels must be determined prior to initiating therapy, and then monitored prior to each dose escalation, and regularly during treatment (see Section 1.2 *Flow Chart of Study and Follow-up*). In the event that hepatic aminotransferases become elevated, a detailed algorithm for dose adjustment or treatment discontinuation is provided (see Section 7.3.2 *Dose Modification, Interruption or Discontinuation for Adverse Events*). This algorithm is based on the approach agreed with the DSMB hepatologist that was used successfully in the pivotal phase III study and is consistent with the FDA's draft guidance *Drug-Induced Liver Injury: Premarketing Clinical Evaluation*, October 2007. Dietary advice, including fat content (see Section 8.6.1 *Diet Instructions and Diet Records*) and supplementation with vitamin E and essential fatty acids (see Section 6.3 *Dietary Supplements*), is also specified, and dosing is escalated gradually to minimise GI side effects and allow for regular hepatic aminotransferase determination (see Section 7.2 *Treatment Schedule*). These elements of safety monitoring are designed to allow the optimum individualised dose to be selected for each patient in order to maximise the benefit of LDL-C reduction, ensure compliance with treatment, and avoid AEs.

2.6.4 Benefits and Risks Conclusions

Patients with HoFH deal with a life-threatening disease every day in the absence of effective treatment to reduce their LDL-C to target levels. For the first time, it is now feasible to reach target LDL-C goals and maintain these levels during chronic treatment. LDL-C lowering of lomitapide was modelled to increase median life expectancy of HoFH patients by 11.6 years and delay time to the first MACE by 5.7 years (Leipold, Raal et al. 2017).

Lomitapide treatment is a major advance in the treatment of a devastating disease through modification of a risk factor that is currently uncontrolled by available treatment interventions, supporting a favourable benefit-risk assessment for its use in this high-risk patient population.

In this study, lomitapide will be carefully titrated to the MTD based upon safety, tolerability and LDL-C levels and safety will be monitored by an independent DSMB (see Section 4.3 *Data Safety Monitoring Board*). Therefore, the benefits will outweigh the risks.

2.7 Rationale of the Study and of the Study Design

Lomitapide has been approved for use in adult patients with HoFH in the European Union (EU) and European Economic Area (EEA), United States of America (USA), Israel, Argentina, Canada, Colombia, and Japan. This study is designed to determine if lomitapide is effective and can be safely administered to paediatric patients with HoFH. If the efficacy and safety so far observed in adults is confirmed in paediatric patients, the potential exists to significantly lower LDL-C levels in paediatric patients with HoFH. Furthermore, the lower LDL-C levels may reduce atherosclerosis progression and would be expected to benefit these paediatric patients with HoFH.

A single-arm, non-comparator design has been selected due to the rarity of the disease and because the evaluation of safety variables such as growth and sexual maturation requires longer term observation than would not be feasible in the context of a placebo-controlled study.

In addition, similar efficacy cannot reasonably be assumed in a 2-arm design with standard of care LLT including LA as comparator, and, as a result, randomisation of these very high risk patients to placebo for longer than 6 months would not be acceptable.

Finally, the high incidence of GI AEs expected in lomitapide-treated patients and the corresponding inability to keep patients and physicians blinded to treatment would introduce an assessment bias.

To mitigate the disadvantages of a single-arm design, the study includes a Run-in Period of at least 6 weeks during which current LLT (including LA, when applicable) will be stabilised to establish Baseline levels allowing each patient to serve as his/her own control. Patients will also remain on stable LLT (including LA, when applicable) during the Efficacy Phase of the study through Week 24±3 days.

3 STUDY OBJECTIVES

3.1 Primary Objective

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

3.2 Secondary Objectives

- Evaluate the efficacy of lomitapide in paediatric HoFH patients as assessed by:
  - Percent change from Baseline at Week 24±3 days in lipid parameters, including total cholesterol (TC), non high-density lipoprotein cholesterol (Non-HDL-C), very low-density lipoprotein cholesterol (VLDL-C), triglycerides (TG), lipoprotein(a) [Lp(a)], and apolipoprotein B (apo B).
  - Percent change from Baseline in TC, non-HDL-C, LDL-C, TG, VLDL-C, Lp(a), and apo B at all other time-points through Week 104±1 week.
  - Change in LLT and LA from Week 24±3 days through Week 104±1 week.
  - Number (percent) of patients achieving the EAS recommended target LDL-C of <135 mg/dL (3.5 mmol/L) at Week 24±3 days and at any time on study.

3.3 Safety Objectives

- Evaluate the long-term safety and tolerability of lomitapide in paediatric HoFH patients as assessed by:
  - Incidence in reported AEs and in clinically significant abnormal findings of physical examinations including weight and BMI, electrocardiogram (ECG), standard of care echocardiography (if available), vital signs, pulmonary function tests (PFT), and laboratory parameters including hepatic and renal function tests.
  - Effects on growth, bone health and bone age will be assessed using both measurements of children's height and growth charts to track age-appropriate progress at Screening and from Baseline at every visit through Week 104±1 week and/or at EoT, together with analysis of Vitamin D and K levels at Screening, Baseline, Week 24±3 days, Week 56±3 days, Week 80±1 week, Week 104±1 week and/or at EoT (and at Week 108 for patients who opt not to participate in or are unsuitable for the EAP [<18 years of age]/opt not to transition to commercial product [≥18 years of age]).
  - Potential effects on maturation, reproductive development, gonadotropins, and variables of the pituitary-adrenal axis at Screening, Baseline, Week 56±3 days, Week 104±1 week

and/or at EoT will be analysed; potential effects on the levels of sex steroids will be analysed for patients assessed as Tanner Stage ≥2.

- Lipid accumulation in the liver as measured by nuclear magnetic resonance (NMR) imaging or echography (i.e., ultrasound scan) at Baseline and at Week 24±3 days, Week 56±3 days, and at Week 104±1 week (for patients who opt not to participate in or are unsuitable for the EAP [<18 years of age)/opt not to transition to commercial product [≥18 years of age], lipid accumulation in the liver will be measured at Baseline, at Week 24±3 days, Week 56±3 days, and at Week 108). All patients will undergo NMR imaging unless it is contraindicated or not feasible (e.g., due to the need for sedation or general anaesthesia in very young or anxious patients). In this case, ultrasound scans will be used at the discretion of the investigator.

3.4 Exploratory Objectives

- Evaluate exploratory assessments of:
  - Change from Baseline at Week 56±3 days and Week 104±1 week in mean carotid intima-media thickness (CIMT, mandatory) and flow-mediated dilatation (FMD, whenever possible).
  - The resolution and/or regression of pre-existing xanthomas at Week 56±3 days and at Week 104±1 week.
  - Changes from Baseline through Week 24±3 days in cholesterol and triglyceride content of VLDL, intermediate density lipoprotein (IDL), LDL and HDL, particle number and size of VLDL, LDL, and HDL as well as particle number of their respective lipoprotein subclasses (large, medium, and small) as assessed based on 2D NMR (Liposcale® Test) of pharmacokinetics (PK) samples.

3.5 Palatability Objective

- 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 will be used to determine whether they find lomitapide "pleasant", "unpleasant" or are "not sure".
- Ease of administration of the study medication and dietary supplements by the parent(s)/legal guardian(s) will be assessed 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)."

3.6 Pharmacokinetic Objective

- Evaluate the PK of lomitapide in paediatric HoFH patients through sparse blood sampling.

4 INVESTIGATIONAL PLAN

All references to “the investigator” throughout this document refer to “the investigator or a delegated sub-investigator”.

4.1 Study Endpoints

4.1.1 Primary Endpoint

- Percent change from Baseline in LDL-C at Week 24±3 days.

4.1.2 Secondary Endpoints

- Percent change from Baseline at Week 24±3 days for the following lipid parameters: TC, Non-HDL-C, VLDL-C, TG, Lp(a), and apo B.
- Percent change from Baseline at all other time points through Week 104±1 week for the following lipid parameters: LDL-C, TC, Non-HDL-C, VLDL-C, TG, Lp(a), and apo B.
- Total number and percent of patients with a change from Baseline in LLT and LA from Week 24±3 days through Week 104±1 week.
- Total number and percent of patients achieving the EAS recommended target LDL-C of <135 mg/dL (3.5 mmol/L) in paediatric HoFH patients at Week 24±3 days and at any time on study.

4.1.3 Safety Endpoints

- Incidence of AEs overall and by severity, and relatedness.
- Physical examinations including regular measurements of height, weight, and BMI.
- Sexual maturation (Tanner staging).
  - In patients with Tanner Stage ≥2: Change from Baseline in sex hormones (serum testosterone and serum oestradiol).
- 12-Lead safety ECG (read locally), standard of care echocardiography (if available), vital signs and blood pressure.
- PFT.
- Laboratory tests:
  - Standard haematology (complete blood count [CBC]) and clinical chemistry panels).
  - Liver function tests: ALT, AST, gamma-glutamyl transferase (GGT), alkaline phosphatase (AP), total bilirubin, and serum albumin.
  - High-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (apo A-I).
  - Creatinine kinase (CK).
  - Serum lipase.
  - Serum levels of essential fatty acids (EFA): Linoleic acid, alpha linoleic acid (ALA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), arachidonic acid (AA), and eicosatrienoic acid.
  - Serum concentrations of fat-soluble vitamins: Vitamin A (retinol), vitamin E (alpha tocopherol), ratio of vitamin E to total lipids (total cholesterol plus fasting triglycerides), and vitamin D (25-hydroxy-D). Levels of vitamin K will be assessed indirectly by measuring total and uncarboxylated levels of serum osteocalcin. (Bone health will be

assessed indirectly using growth to track age-appropriate progress, and measurement of 25-hydroxy-D as well as total and uncarboxylated osteocalcin levels.)

- Pituitary-adrenal hormone levels (thyroid stimulating hormone [TSH], follicle stimulating hormone [FSH], luteinising hormone [LH], adrenocorticotrophic hormone [ACTH], and morning serum cortisol).
- Urinalysis.

- Lipid accumulation in the liver as measured by NMR imaging or echography (i.e., ultrasound scan) at Baseline and at Week 24±3 days, Week 56±3 days, and at Week 104±1 week (for patients who opt not to participate in or are unsuitable for the EAP (<18 years of age)/opt not to transition to commercial product (≥18 years of age), lipid accumulation in the liver will be measured at Baseline and at Week 24±3 days, Week 56±3 days, and at Week 108). All patients will undergo NMR imaging unless it is contraindicated or not feasible (e.g., due to the need for sedation or general anaesthesia in very young or anxious patients). In this case, ultrasound scans will be used at the discretion of the investigator.

4.1.4 Exploratory Endpoints

- Percent change from Baseline at Week 56±3 days and Week 104±1 week in CIMT and FMD.
- Total number and percent of patients with resolution and/or regression of pre-existing xanthomas at Week 56±3 days and at Week 104±1 week.
- Changes from Baseline through Week 24±3 days in cholesterol and triglyceride content of VLDL, IDL, LDL and HDL, particle number and size of VLDL, LDL, and HDL as well as particle number of their respective lipoprotein subclasses (large, medium, and small) as assessed based on 2D NMR (Liposcale® Test) of PK samples at Week 4±3 days, Week 8±3 days, Week 12±3 days, Week 16±3 days, Week 20±3 days and at Week 24±3 days.

4.1.5 Palatability Endpoints

- Total number and percent of patients for each response of palatability:
  - Able to swallow capsule (including food media responses if used).
  - Palatability rating (using a 5-point facial hedonic scale).
  - Parent/guardian interpretation of child's reaction/facial expression (using a 3-point scale).
  - Parent/guardian experience problems in giving medication to child because they refuse to take or throw up immediately after taking.
  - Parent/guardian experience problems in giving dietary supplement to child because they refuse to take or throw up immediately after taking.

4.1.6 Pharmacokinetic Endpoint

- The PK data from this study will be incorporated into an existing population PK model in adult HoFH patients.

4.2 Overall Study Design

This is a single-arm, open-label, multi-centre phase III study to evaluate the efficacy and long-term safety of lomitapide in paediatric patients with HoFH receiving stable LLT (including LA, when applicable). Each patient will participate for up to 120 weeks (about 2.5 years) in the study (see Figure 3).

4.2.1 Study

The study will consist of 5 periods (see Figure 3):

1. Screening Period (starting at Week -12, i.e., ≤12 weeks prior to Baseline for up to 6 weeks).
2. Stratified Enrolment and Start of Run-in Period (starting at minimum at Week -6, i.e., 6 weeks prior to Baseline for a minimum of 6 weeks):
    - Enrolment will be stratified to ensure approximately equal numbers of patients in the following age groups: 5 to 10 years, 11 to 15 years, and 16 to ≤17 years (with ≥8 patients in any individual age group).
    - Patients must be stabilised on current LLT (including LA, when applicable) and established on a diet supplying <20% of energy (calories) from fat or <30 g fat, whichever is the lesser amount.
    - Daily supplementation with vitamin E (200 international units [IU] for patients 5 to 8 years of age, 400 IU for patients 9 to ≤17 years of age) and an EFA supplement containing approximately 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA starting at Week -2.
3. Efficacy Phase (starting at Baseline, i.e., Day [D] 0 for 24 weeks±3 days):
    - Approximately 45 paediatric patients with HoFH will be treated with lomitapide given orally, added to their current, stable LLT (including LA, when applicable) established during the Run-in Period.
    - Assuming a withdrawal rate of approximately 33% by Week 24±3 days, this would result in 30 evaluable patients at Week 24±3 days (with ≥8 patients in any individual age group).
    - After stabilisation of the patient on his/her current MTD of LLT (including LA, when applicable) during the 6-week Run-in Period, treatment with lomitapide will be started as an add-on therapy on D0 of the Efficacy Phase.
    - Dosing will be initiated at the recommended starting dose and escalated to the maximum dose as applicable to the age groups based upon safety and tolerability in addition to LDL-C values (see Section 7.2 *Treatment Schedule* and Table 2).
    - The first dose of study medication will be administered at the study site on D0.
    - During the 24-week Efficacy Phase, patients will be required to remain on the stable LLT regimen (including LA, when applicable) established during the 6-week Run-in Period
4. Safety Phase (starting at Week 24±3 days for 80±1 weeks)
    - Patients will enter the 80-week Safety Phase after the Week 24±3 days assessments have been completed. Each patient will continue receiving the MTD of lomitapide he/she achieved during the Efficacy Phase (unless criteria is met for reducing or increasing the dose) for an additional 80±1 weeks in the Safety Phase.
    - If after Week 24±3 days both the investigator and the sponsor consider 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 can 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 patient tolerates this new dose for ≥4 weeks, then this will be considered the new MTD.
    - If after Week 24±3 days, a patient has crossed over into the next age category, the study medication can be escalated to the maximum dose applicable for the new age

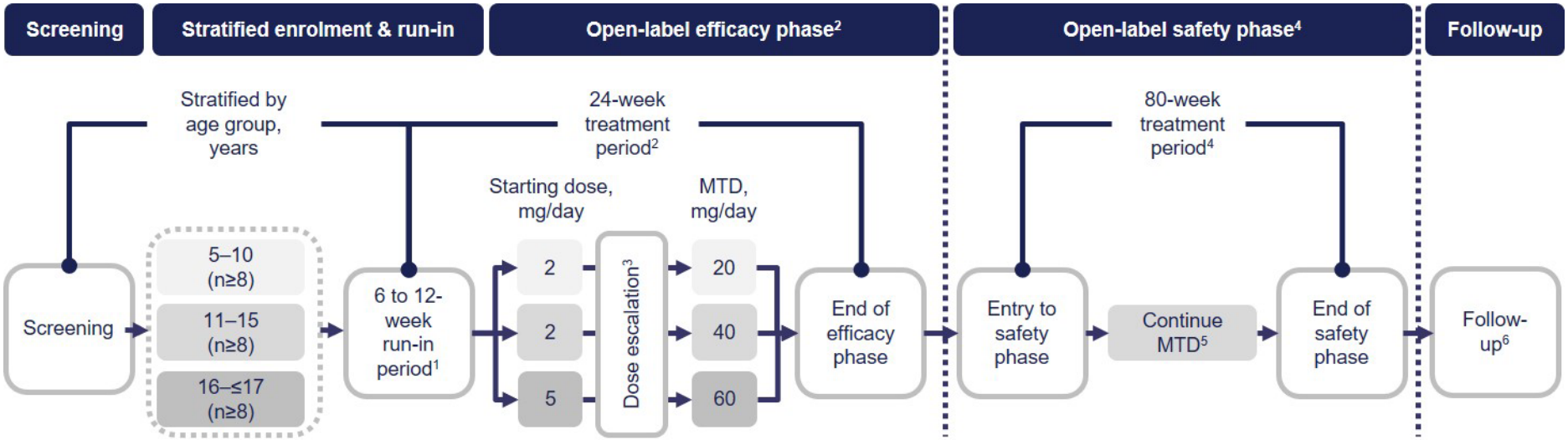
category. If the patient tolerates this new dose for ≥4 weeks, then this will be considered the new MTD.

- During the 80-week Safety Phase, the lomitapide dose can be reduced from the MTD due to tolerability or safety issues, and the patient can be re-challenged after a minimum period of 4 weeks following dose reduction with a higher dose of lomitapide once these issues resolve, but the dose during the Safety Phase cannot exceed the MTD established during the Efficacy Phase unless eligibility for exceptional dose escalation described above is met.
- Adjustments to background LLT (including LA, when applicable) will be allowed at the discretion of the investigator.

5. Follow-up (starting at Week 104±1 week for 4 weeks):

   - At Week 104±1 week, eligible patients who complete the study per protocol and are <18 years of age may choose to enter the EAP. Patients ≥18 years of age may opt to transition to commercial product under the approved product label for adults. For both the patient groups, a follow-up phone call will be conducted at Week 108±1 week to monitor safety including AE and concomitant medication reporting.
   - For patients who opt not to participate in or are unsuitable for the EAP, or patients ≥18 years of age who opt not to transition to commercial product will discontinue lomitapide treatment at Week 104±1 week and enter a 4-week Follow-up period during which they will remain on concomitant LLT (including LA, when applicable). These patients will then attend in person for a Week 108±1 week visit.

Figure 3 Design of Study



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

1. Stabilise current LLT (including LA, when applicable), establish diet <20% energy from fat or <30 g fat, whichever is 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, patients will be 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) will be allowed at the discretion of the investigator.
5. Dose adjustment rules apply.
6. Eligible patients who complete the study per protocol at Week 104 and are <18 years of age may choose to enter the Expanded Access Programme. Patients ≥18 years of age may opt to transition to commercial product under the approved product label for adults. For both these patient groups, a follow-up phone call will be conducted at Week 108±1 week to monitor safety including AE and concomitant medication reporting. Patients who opt not to participate in or are unsuitable for the Expanded Access Programme, or patients ≥18 years of age who opt not to transition to commercial product will discontinue lomitapide treatment at Week 104±1 week and enter a 4-week Follow-up period during which they will remain on concomitant LLT (including LA, when applicable). These patients will attend in person for a Week 108±1 week visit.

4.2.2 End of Study

The End of Study is defined as completion of the last visit or assessment for the last patient.

4.3 Data Safety Monitoring Board

An independent DSMB will be assigned to periodically review and evaluate study data for participant safety and to advise for continuation, modification or discontinuation in individual patients and of the study. Interim safety data reviews may be performed by the DSMB at their discretion, at any time, on an 'as needed' basis according to ongoing study results.

The DSMB will have an initial organisational meeting at which time the composition, activities, and responsibilities of the DSMB will be detailed in a Charter as agreed upon by the sponsor and the DSMB members. The DSMB will be comprised of at least 3 members who are not otherwise involved in the conduct of the study, at least 1 of whom will be a statistician. The DSMB will meet at least 3 times during the conduct of the study.

The DSMB in consultation with the sponsor will have the authority to stop the study for any reason including, but not limited to, unacceptable safety risks. If a patient discontinues treatment permanently due to a Hy's law case or comparable signs of liver toxicity irrespective of origin, the DSMB will initiate an immediate recruitment stop as an urgent safety measure and will assess individual benefits and risks for the patients being treated with study medication regarding further therapy.

5 STUDY POPULATION

5.1 Inclusion Criteria

A patient will be eligible for study participation only if all of the following criteria apply:

1. Male and female patients 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, Bruckert et al. 2014):
    a. Genetic confirmation of 2 mutant alleles at the LDLR, apo B, PCSK9, or 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
        - Cutaneous or tendon xanthoma before age 10 years or
        - Untreated LDL-C levels consistent with heterozygous FH in both parents
2. Baseline LDL-C on LLT (C_{max} 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 (see Appendix 4 *WHO Growth Charts*).
4. Patient and/or his/her legal representative has/have been informed, has/have read and understood the patient information/informed consent form, and has/have given written informed assent/consent.
5. Patient and/or his/her legal representative must be able and willing to follow study procedures and instructions, particularly that:

a. LLT (including LA when applicable) must be stable for at least 6 weeks prior to Baseline (Run-in Period) and remain stable through Week 24±3 days (end of Efficacy Phase).

b. The patient must be compliant with both the low-fat diet supplying <20% of energy (calories) from fat or <30 g fat, whichever is the lesser amount starting at the beginning of the Run-in Period and the dietary supplement regimen starting at Week -2 of the Run-in Period, both continuing until completion of the study (and during the EAP/administration of commercial product, when applicable).

6. Postmenarchal female adolescents must be willing to use highly effective methods of birth control that, alone or in combination, result 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). Postmenarchal female adolescent patients taking oestrogen-based oral contraceptives should be advised that diarrhoea and/or vomiting may reduce hormone absorption. In case of protracted or severe diarrhoea and/or vomiting lasting more than 2 days, the investigator should advise according to national practice, which additional contraceptive measures (such as sexual abstinence, barrier methods) should be used for 7 days after resolution of symptoms.
7. Patient must be in stable physical and mental health at Screening.

5.2 Exclusion Criteria

A patient will not be eligible to participate in this study, if any of the following criteria apply:

1. Other forms of primary hyperlipoproteinaemia and secondary causes of hypercholesterolaemia (e.g., nephrotic syndrome, hypothyroidism).
2. Contraindications for the use of lomitapide according to section 4.3 of the Summary of Product Characteristics (SPC included in the Lojuxta® SPC in lieu of an IB; see Section 18.1 *Source Documents*), such as hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of the SPC, known significant or chronic inflammatory bowel disease or malabsorption.
3. Moderate (Child-Pugh B, see Appendix 1 *Child-Pugh Score*) or severe hepatic impairment (Child-Pugh C), active liver disease and/or abnormal liver function tests at Screening (AST or ALT >1.5 x ULN and/or total bilirubin >1.5 x ULN in the absence of Gilbert's syndrome or AP >1.5 x ULN [based on appropriate age and gender normal values]).
4. Serum CK >2 x ULN.
5. Chronic renal insufficiency with glomerular filtration rate (GFR) <70 mL/min/1.73 m^2 calculated using the Schwartz formula (see Appendix 2 *Schwartz Formula*).
6. Uncontrolled hypertension (defined as mean systolic and/or diastolic blood pressure ≥95% of normal for age and sex) despite medical therapy.
7. New York Heart Association (NYHA) Class III or IV congestive heart failure.
8. Precocious/delayed puberty or endocrine disorder affecting growth (e.g., hypothyroidism, premature adrenarche).
9. 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).
10. Life expectancy predicted to be <5 years.
11. History of a non-skin malignancy (with the exception of cervical cancer *in situ*) within 3 years prior to enrolment.

12. Treatment with any Investigational Medicinal Product (IMP) within 6 months or 5 times the terminal half-life of the corresponding IMP, whichever is longer, before Screening (Visit 1).
13. Patient is a dependent of the sponsor, of the investigational team or his/her immediate family.
14. Pregnant or nursing women.

6 STUDY MEDICATION

6.1 Description of the Investigational Product

6.1.1 Formulation, Packaging and Labelling

The investigational product will be supplied in high-density polyethylene bottles with polyester, aluminium foil, and cardboard induction seals and child-resistant polypropylene screw caps. It will be packed and labelled according to applicable regulatory requirements.

Lomitapide is prepared as a crystalline methanesulfonate salt. The investigational product will be administered orally in opaque, hard gelatin capsules. Four bottle types will contain 28 capsules each by 2 mg, 5 mg, 10 mg, and 20 mg strength. Each hard capsule contains lomitapide mesylate equivalent to its strength and the following inactive excipients: pregelatinised starch (maize), sodium starch glycolate (Type A), microcrystalline cellulose, lactose monohydrate, colloidal, anhydrous silica, and magnesium stearate.

Please refer to the Lojuxta® SPC in lieu of an IB and to the Investigational Medicinal Product Dossier for the 2 mg lomitapide hard capsules regarding the excipients and colours of the capsule shells, which differ by strength (see Section 18.1 *Source Documents*). Further details regarding physical, chemical, and pharmaceutical properties and concerning the formulation, respectively are described in the EPAR Lojuxta® dated 30 May 2013, Section 2.2.

Please refer to Section 2.2 *Investigational Product* for further details regarding the mechanism of action and therapeutic indication of lomitapide.

6.1.2 Storage and Stability

Keep the bottle tightly closed in order to protect from moisture. Store below 30°C.

6.1.3 Drug and Dietary Supplements Accountability

A sufficient number of lomitapide bottles will be provided to sites in bulk at appropriate intervals depending on the phase of the study and accrual of patients. Dietary supplements will be sourced locally, where possible (see Section 6.3 *Dietary Supplements*). The investigator, or the person designated by the investigator, will be responsible for dispensing the appropriate bottle or combination of bottles to a patient at each study visit. At each site, the investigator, or the person designated by the investigator, will be responsible for keeping accurate records of study medication accountability comprising the receipt, the dispensing, and the return of all used and partially unused study medication throughout the study. The drug accountability form should be kept up to date and will be reviewed periodically by the study monitor. Patients will be asked to keep all used and partially unused bottles of study medication and return them to the site during the scheduled visits. For drug accountability, the number of used and partially unused bottles and unused capsules will be counted. Compliance with dietary supplements is discussed with the patients at each visit and is documented in the electronic Case Report Form (eCRF). It is also verified by reviewing the patient Diet Records (see Section 8.6.1 *Diet Instructions and Diet Records*). After drug accountability is completed, all unused or partially used study medication may be returned to the sponsor or disposed of by the study site. The study monitor will instruct the site on the return of all study medication. A final inventory of the total amount of study medication and dietary supplements at each study site against the

amount used and returned must be recorded. Inventory records must be readily available for inspection by the study monitor and/or auditor, and open to government inspection at any time.

6.2 Investigational Product Compliance

Patients and their parents/legal guardians will be instructed to return all unused study medication and dietary supplements to the clinical site at the visits indicated in Section 1.2 *Flow Chart of Study and Follow-up*. Site study team members will count and record the number of capsules remaining in each of the bottles and record this information on the eCRF. Study drug compliance checks will be performed at all visits during the Efficacy and Safety Phases of the study.

6.3 Dietary Supplements

Patients will be administered daily oral supplementation with vitamin E (200 IU for patients 5 to 8 years of age, 400 IU for patients 9 to ≤17 years of age) and an EFA supplement containing approximately 200 mg linoleic acid, 210 mg ALA, 110 mg EPA, and 80 mg DHA. Dietary supplements will be dispensed during Visit 3 at Week -3 to Week -2 (Run-in Compliance), during Visit 4 at D0 (Baseline, Efficacy Phase), and at every visit thereafter until Visit 21 at Week 92±1 week. Please refer to Section 6.1.3 *Drug and Dietary Supplements Accountability* for dietary supplements accountability.

7 STUDY TREATMENT

7.1 Treatment Assignment, Blinding Procedure

This is an open-label study, blinding of treatment is not applicable.

7.2 Treatment Schedule

After stabilisation of the patient on his/her current MTD of LLT (including LA when applicable) during the 6-week Run-in Period, treatment with lomitapide will be started as add-on therapy on D0 of the Efficacy Phase.

Lomitapide capsules will be provided in 4 dose strengths of 2 mg, 5 mg, 10 mg, and 20 mg. Dosing will be initiated at the recommended starting dose and escalated to the maximum dose as applicable to the age groups (see Table 2 and Figure 3) based upon safety and tolerability in addition to LDL-C values.

Table 2 Lomitapide Starting Dose and Dose Escalation by Age Group

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)

Each patient will take 1 to 3 capsule(s) once daily to achieve the doses specified in the titration scheme. The first dose of study medication will be administered at the study site on D0.

As of D1, patients will self-administer (or the patient's parent/legal guardian will administer to the patient) lomitapide orally, once daily, at approximately the same time each day. It is recommended to administer lomitapide at least 2 hours after the evening meal (e.g., at bedtime) with a glass of water on an empty stomach because the fat content of a recent meal may adversely impact GI tolerability. Patients who are unable to swallow the intact capsule(s)

may open the capsule(s) and sprinkle the capsule content on 1 tablespoon of apple sauce or mashed banana, which are fat-free.

In case of a missed dose, patients should be instructed to take missed doses of lomitapide only if they can be taken at least 12 hours prior to the next scheduled dose. Dietary supplements are suggested to be taken in the morning. Patients taking bile acid sequestrants should be reminded that they should take lomitapide 4 hours before or 4 hours after this class of medications. If atorvastatin is given concomitantly, lomitapide should be administered 12 hours apart.

7.3 Dose Modifications and Interruptions

7.3.1 Dose Escalation, Dose Reduction and Re-challenge

Dose Escalation

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

Lomitapide will not be escalated, if LDL-C is less than the target threshold:

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

For each of the 3 age groups, lomitapide dosing will escalate following the applicable dose titration scheme in Table 2 at Week 4±3 days, Week 8±3 days, and Week 12±3 days to the maximum allowable dose by Week 16±3 days or the MTD by Week 20±3 days based upon acceptable safety and tolerability criteria in addition to LDL-C values.

Each dose must be tolerated for ≥4 consecutive weeks before being escalated to the next higher dose in stepwise increments. The MTD is defined as the highest dose of lomitapide through Week 24±3 days that does not result in tolerability or safety concerns. This is the highest dose that does not result in dose reduction, dosing interruption, or discontinuation, but may include a re-challenged dose level.

Each patient will continue receiving the MTD of lomitapide he/she achieved during the Efficacy Phase (unless criteria is 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 consider 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 can 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 patient tolerates this new dose for ≥4 weeks, then this will be considered the new MTD.

If after Week 24±3 days, a patient has crossed over into the next age category, the study medication can be escalated to the maximum dose applicable for the new age category. If the patient tolerates this new dose for a minimum of 4 weeks, then this will be considered the new MTD.

Dose Reduction and Re-challenge

If a dose reduction is required, dosage will either be reduced to the previous tolerated dose or to an intermediate dose. Please note that only down-titrations to intermediate doses are allowed, dose escalations need to follow the guidance provided in Table 2. After resolution of the cause for dose reduction, patients may be re-challenged after a minimum period of 4 weeks following dose reduction with prior doses in stepwise increments based on dose escalation guidelines, but may not exceed the MTD established during the Efficacy Phase until

Week 24±3 days, after which further increase is only possible if patients have crossed into the next age category or eligibility for exceptional dose escalation as described above is met.

If the investigator determines that a patient is not tolerating any particular dose (per specified criterion), the investigator may request a dose reduction or a hold on the current dose until the next scheduled visit. Once the patient has stabilised on the reduced dose, the dose can be increased back to the next step again, and the patient may progress through subsequent dose increases at a minimum of 4-week intervals. If the patient does not tolerate the re-challenge dose, then the MTD is considered the reduced dose and will be the highest dose allowed for the remainder of the study.

Weeks 0 through 24±3 days establish the MTD, Week 20±3 days is the last visit that the lomitapide dose can be increased, except when there has been a down-titration at/or after Week 16±3 days. Re-challenging will depend on the assessment of safety and tolerability criteria and the LDL-C value relative to the LDL-C goal of <135 mg/dL (3.5 mmol/L) and is at the discretion of the investigator except for Hy's law cases or comparable signs of liver toxicity, irrespective of origin, in which no re-challenge will be allowed (see Section 7.4 *Patient Discontinuation Criteria*).

The study medication can be escalated as a re-challenge dose during an unscheduled visit after the investigator consults with the study medical monitor, but any additional dose escalations, i.e., dose titration, must be made during a completed scheduled visit. In addition, a re-challenge with lomitapide will not be performed if the LDL-C is below the target threshold while the patient was receiving the reduced dose.

During the 80-week Safety Phase, the lomitapide dose can be reduced from the MTD due to tolerability or safety issues, and the patient can be re-challenged with a higher dose of lomitapide once these issues resolve (after a minimum period of 4 weeks following dose reduction), but the dose during the Safety Phase cannot exceed the MTD established during the Efficacy Phase unless eligibility for exceptional dose escalation described above is met.

Please refer to Section 7.3.2 *Dose Modification and Interruption for Adverse Events* for further details regarding dose reductions due to AEs and to Section 7.3.3 *Dose Modification for Concomitant Medication* for detailed information about dose reductions depending on concomitant medication.

7.3.2 Dose Modification, Interruption or Discontinuation for Adverse Events

The investigator and/or DSMB have the authority to reduce study medication dosage or discontinue study medication in a patient if situations develop that, in the opinion of the investigator or DSMB, would compromise the patient's safety or successful participation in the study (see Section 4.3 *Data Safety Monitoring Board* and Section 7.4 *Patient Discontinuation Criteria*). In particular, modifications in dosage or discontinuation of treatment will be instituted if any of the situations below apply.

HEPATOBILIARY GUIDELINES

Dose Modification Based on Hepatobiliary Adverse Events

If a patient matches the criteria referred to as "Hy's law case" according to the European Association for the Study of the Liver (EASL) Clinical Practice Guidelines on Drug-induced Liver Injury (EASL 2019) and the FDA Guidance for Industry Drug-Induced Liver Injury Premarketing Clinical Evaluation (FDA 2009) or shows comparable signs of liver toxicity, irrespective of origin, treatment must be permanently discontinued and no re-challenge will be allowed.

Upon the investigator's discretion study medication will be discontinued permanently if a patient experiences any CTCAE Grade 3 or Grade 4 hepatobiliary AE (see Appendix 3

Common Terminology Criteria for Adverse Events, Hepatobiliary Disorders), regardless of relationship to study drug.

Biochemical Hepatobiliary Guidelines

Note: The toxicity "levels" described below are different and separate from CTCAE "grades". The toxicity levels do NOT correlate to CTCAE grades nor should they be used for grading AEs.

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

Level 4 Hepatotoxicity

Level 4 Hepatotoxicity is defined as follows:

- ALT or AST levels reach ≥10 x ULN at 1 single time point. Patients should be referred to a hepatologist or gastroenterologist for further work up.
- In symptomatic patients, ALT >5 x ULN AND total bilirubin >2 x ULN on 2 separate occasions and at least 7 days apart.
- AP is >5 x ULN on 2 separate occasions and at least 7 days apart.
- Total bilirubin is >2 x ULN on 2 separate occasions and at least 7 days apart in the absence of Gilbert's syndrome or haemolysis.

Patients who experience confirmed Level 4 Hepatotoxicity will immediately interrupt study medication. Patients will return to the study site weekly or sooner if clinically indicated until resolution. Any Level 4 Hepatotoxicity will be reported to the DSMB by the sponsor (or its designee) immediately upon notification.

Following evaluation by a hepatologist, a patient may resume lomitapide treatment if the Level 4 Hepatotoxicity is resolved, and in the opinion of the investigator, DSMB and sponsor, the benefit of treatment justifies any risk of recurrent toxicity.

Level 3 Hepatotoxicity

Level 3 Hepatotoxicity is defined as follows:

- Patients who experience ALT or AST ≥5 x ULN on 2 separate occasions and at least 7 days apart.

Patients who experience confirmed Level 3 Hepatotoxicity will immediately interrupt study medication. The patient will return to the clinic for repeat blood tests including AP, bilirubin and International normalised ratio (INR) every 7 days until the aminotransferase levels have fallen <3 x ULN. Once this occurs, study drug dosing may be resumed at the dose level below that associated with Level 3 Hepatotoxicity.

If this dose level is tolerated without elevation of ALT or AST >3 x ULN, then this dose will be defined as the MTD. If aminotransferases increase ≥3 x ULN further dose reduction or interruption may be necessary consistent with the guidance provided in this protocol.

Elevations in ALT or AST >3 x ULN that persist despite dose reduction or interruption for ≥4 weeks will be reported to the DSMB by the sponsor (or its designee) immediately upon notification. Patients will be referred to a hepatologist for further work up.

Level 2 Hepatotoxicity

Level 2 Hepatotoxicity is defined as follows:

- Patients who experience ALT or AST 3.0 to 4.9 x ULN on 2 separate occasions and at least 7 days apart.

Patients who experience confirmed Level 2 Hepatotoxicity will have the dose of study medication reduced to the previous tolerated dose. The patient will return to the clinic for repeat blood tests including AP, bilirubin and INR every 7 days until the aminotransferase levels have fallen to <3 x ULN. Once this occurs, lomitapide dosing may be resumed at the dose level below that associated with Level 2 Hepatotoxicity.

If this dose level is tolerated without elevation of ALT or AST >3 x ULN, then this dose will be defined as the MTD. If aminotransferases increase >3 x ULN further dose reduction or interruption may be necessary consistent with the guidance provided in this protocol.

Elevations in ALT or AST >3 x ULN that persist despite dose interruption for ≥4 weeks will be reported to the DSMB by the sponsor (or its designee) immediately upon notification. Patients will be referred to a hepatologist for further work up.

Level 1 Hepatotoxicity

Level 1 Hepatotoxicity is defined as follows:

- Patients who experience ALT or AST 1.1 to 2.9 x ULN.

No dose modification will be required.

Considerations for Liver Biopsy and Histopathological Guidelines

Considerations for Liver Biopsy

A percutaneous liver biopsy should be considered for persistent Level 2 Hepatotoxicity defined as AST or ALT ≥3 x ULN for ≥6 months but can also be performed at the discretion of the investigator.

Histopathological Hepatobiliary Guidelines

If a patient undergoes a liver biopsy and the specimen shows the following features, the patient will 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.

Patients 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) will continue on study medication, and discontinuation will be dictated by biochemical criteria.

Creatinine Kinase Monitoring and Evaluation

If CK values are found to be elevated >5 x ULN on routine testing, the patient should be questioned about muscle symptoms.

A study site physician should be alerted to the occurrence of unexplained muscle symptoms and any CK values >5 x ULN, and must take immediate action if CK is >10 x ULN.

If CK values are >5 x ULN with muscle symptoms or >10 x ULN with or without muscle symptoms the following steps should be taken:

- Clarify the nature, duration and intensity of any muscle symptoms.

- Review possible predisposing factors, such as: unaccustomed exercise, heavy alcohol intake, viral illness (consider performing serology), concomitant medication and consider diagnosis of other conditions which cause myopathy.
- Physical examination for muscle tenderness, weakness and rash.
- Measure CK again within a few days.
- Measure serum creatinine.
- Urine dipstick.
- Arrange to review the patient again in 4 to 10 days, or earlier if symptoms of myopathy appear or worsen, or if the urine becomes very dark.

Discontinue study medication for CK values >10 x ULN with or without muscle symptoms.

For CK values 5 to 10 x ULN:

If asymptomatic, or if symptomatic but alternative explanation exists, symptoms should be followed and CK levels tested weekly until it is no longer a medical concern or symptoms worsen and meet criteria for any of the above.

If symptomatic, and no alternative explanation exists, withhold therapy.

Throughout the study, patients should be instructed to promptly report any unexplained muscle pain or weakness, particularly if associated with malaise or fever. If this should occur, CK should be measured as soon as possible.

Dose Modification Based on Weight Loss

Weight will be measured using a consistent approach at Screening and at each visit after the Run-in Period (i.e., child/adolescent always weighed in same amount of clothing, either in underwear, hospital gowns or by subtracting the weight of clothes). Patients of normal or below normal body weight based on gender and age-specific WHO growth charts (see Appendix 4 *WHO Growth Charts*) with weight loss >3% since the previous visit will meet with the dietitian for further instruction. Patients with below normal body weight any time during the study who continue to lose weight while on study medication despite all appropriate measures taken to correct for the weight loss and who are deemed to be at clinical risk in the judgment of the treating investigator should discontinue study drug and be followed until an acceptable stable weight is reached as judged by the investigator.

7.3.3 Dose Modification for Concomitant Medication

Weak Cytochrome P450 (CYP) 3A4 Inhibitors

Medicinal products that induce CYP 3A4 would be expected to increase the rate and extent of metabolism of lomitapide. CYP 3A4 inducers exert their effect in a time-dependent manner, and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP 3A4 induction may take at least 2 weeks to decline.

Co-administration of a CYP 3A4 inducer is expected to reduce the effect of lomitapide. Any impact on efficacy is likely to be variable. When co-administering CYP 3A4 inducers (i.e., aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, glucocorticoids, modafinil and phenytoin) with lomitapide, the possibility of a drug-drug interaction affecting efficacy should be considered.

Strong or moderate cytochrome CYP 3A4 inhibitors are not permitted during the study as described in Section 7.6.3 *Non-Permitted Concomitant Medication, Food or Substances*.

Weak cytochrome CYP 3A4 inhibitors are only permitted during the Safety Phase of the study, but lomitapide should be administered 12 hours apart. If atorvastatin is given concomitantly, it should be administered in the morning to separate it from lomitapide dosing by 12 hours. In case it is not possible to administer atorvastatin and lomitapide 12 hours apart, the lomitapide

dose should be reduced by half, as the lomitapide dose can be reduced from the MTD due to tolerability or safety issues during the 80-week Safety Phase. After a minimum period of 4 weeks following dose reduction the patient can be re-challenged with a higher dose of lomitapide once these issues resolve (i.e., if atorvastatin can be administered 12 hours apart or if atorvastatin is discontinued), but the dose during the Safety Phase cannot exceed the MTD established during the Efficacy Phase unless eligibility for exceptional dose escalation is met (described in Section 7.3.1 *Dose Escalation, Dose Reduction and Re-challenge*).

HMG-CoA Reductase Inhibitors ('Statins')

Lomitapide increases plasma concentrations of statins. Patients receiving lomitapide as adjunctive therapy to a statin should be monitored for AEs that are associated with the use of high doses of statins. Statins occasionally cause myopathy. In rare cases, myopathy may take the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and can lead to fatality. All patients receiving lomitapide in addition to a statin should be advised of the potential increased risk of myopathy and told to report promptly any unexplained muscle pain, tenderness, or weakness (see Section 7.3.2 *Dose Modification, Interruption or Discontinuation for Adverse Events, Creatinine Kinase Monitoring and Evaluation*).

Concomitant administration of >40 mg simvastatin will not be permitted during the study as described in Section 7.6.3 *Non-permitted Concomitant Medication, Food or Substances*.

Since patients will be required to remain on their concomitant LLT (including LA, when applicable) established during the 6-week Run-in Period during the Efficacy Phase of the study through Week 24±3 days, a potential concomitant treatment with atorvastatin will remain unchanged during the Efficacy Phase, when lomitapide dosing will start. If atorvastatin is given concomitantly, it should be administered in the morning to separate it from lomitapide dosing by 12 hours. If during the 80-week Safety Phase it is not possible to administer atorvastatin and lomitapide 12 hours apart, the lomitapide dose should be reduced by half. After a minimum period of 4 weeks following dose reduction the patient can be re-challenged with a higher dose of lomitapide once these issues resolve (i.e., if atorvastatin can be administered 12 hours apart or if atorvastatin is discontinued), but the dose during the Safety Phase cannot exceed the MTD established during the Efficacy Phase unless eligibility for exceptional dose escalation is met (described in Section 7.3.1 *Dose Escalation, Dose Reduction and Re-challenge*).

Coumarin-based Anticoagulants

Lomitapide increases the plasma concentrations of warfarin and increases INR. Increases in the dose of lomitapide may lead to supratherapeutic anticoagulation, and decreases in the dose may lead to subtherapeutic anticoagulation. Patients taking warfarin should undergo regular monitoring of the INR, especially after any changes in the dose of lomitapide. The dose of warfarin should be adjusted as clinically indicated.

Hepatotoxic Agents

Caution should be exercised when lomitapide is used with other medicinal products known to have potential for hepatotoxicity, such as isotretinoin, amiodarone, acetaminophen (>4 g/day for ≥3 days/week), methotrexate, tetracyclines, and tamoxifen. The effect of concomitant administration of lomitapide with other hepatotoxic medicine is unknown. More frequent monitoring of liver function tests may be warranted.

7.4 Patient Discontinuation Criteria

Patients and/or their parents/legal guardians will have the right to withdraw from the study at any time for any reason without prejudice to their future medical care. A patient may be withdrawn from the study at any time at either the investigator's, sponsor's, or DSMB's discretion.

A patient **must** be discontinued from the study for any of the following reasons:

- The patient matches the criteria referred to as “Hy’s law case” according to the EASL Clinical Practice Guidelines on Drug-induced Liver Injury (EASL 2019) and the FDA Guidance for Industry Drug-Induced Liver Injury Premarketing Clinical Evaluation (FDA 2009). Any Hy's law case or comparable signs of liver toxicity, irrespective of origin, must lead to permanent treatment discontinuation of the individual patient (no re-challenge allowed).
- The patient and/or his/her parent/legal guardian withdraws assent/consent.
- Pregnancy as evidenced by a positive pregnancy test.

  If a patient becomes pregnant during the study, during the follow-up, or 30 days within the last application of study medication, the sponsor will have to be informed within 24 hours. The investigator will be asked to complete a pregnancy report provided by the sponsor. He/she will be asked to obtain data on the course of the pregnancy, including perinatal and neonatal outcome (see Section 11.5.4 *Other Reportable Information*).
- Any AE which, in the opinion of the investigator, places the patient at unacceptable risk, including intolerable AE(s) after attempted dose reduction (see Section 7.3.2 *Dose Modification, Interruption, or Discontinuation for Adverse Events*).

The investigator will be able to withdraw patients from the study for the following reasons:

- Hepatobiliary criteria for discontinuation
- Hepatobiliary AE CTCAE Grade 4 (see Appendix 3 *Common Terminology Criteria for Adverse Events, Hepatobiliary Disorders*), regardless of relationship to study drug
- Biochemical hepatobiliary guideline Level 4 Hepatotoxicity or Level 3 Hepatotoxicity that persists despite interruption of study drug
- Histopathological diagnosis of Type 3 or Type 4 NASH
- Patient is noncompliant with the study procedures or medications in the opinion of the investigator
- Progression of a medical condition, which in the opinion of the investigator should preclude further participation of the patient in the study (e.g., excessive weight loss)
- Administration of non-permitted concomitant medication(s), substances, or foods
- Investigators’ decision that a change of therapy is in the patients’ best interest
- Occurrence of an AE (including abnormal laboratory findings), which makes discontinuation desirable or necessary in the investigators’ and/or the patients’ opinion

If a patient discontinues the study or the follow-up prematurely due to an AE/SAE, he/she will be followed up until the resolution or stabilisation of the AE/SAE.

If a patient discontinues the study prematurely, the EoT visit assessments should be made (see Section 9.7 *End of Treatment Visit*).

All data collected before premature discontinuation of the study will be used for analysis. Patients who drop out will not be replaced unless the assumptions for drop-out have been exceeded.

7.5 Overdose

There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Liver function tests should be monitored. Haemodialysis is unlikely to be beneficial given that

lomitapide is highly protein-bound. Please refer to the SPC, Section 4.9 (included in the Lojuxta® SPC in lieu of an IB; see Section 18.1 *Source Documents*) for further details.

7.6 Concomitant Medication

All medications that the patient is taking will be recorded in the eCRF. For each concomitant medication, the name of the medication, start and stop date, dose, indication, frequency of dosing and route of administration will be recorded. During the study, only changes of information from the previous visit at the time points indicated in Section 1.2 *Flow Chart of Study and Follow-up* will be recorded.

7.6.1 Concomitant Lipid-lowering Treatment

Patients will be required to remain on their concomitant LLT (including LA, when applicable) established during the 6-week Run-in Period during the Efficacy Phase of the study through Week 24±3 days. Patients with HoFH are expected to be following different treatment regimens that usually include a statin together with additional LLT such as fibrates, bile acid sequestrant, and ezetimibe, as well as LA.

Each patient's individual therapeutic regimen should not be changed during the first 24 weeks±3 days of lomitapide treatment (Efficacy Phase). After Week 24±3 days, adjustments to background LLT (including LA, when applicable) may be made as necessary for optimal standard of care.

LA treatment causes a sharp drop in LDL-C, followed by a rebound phase. Therefore, in patients undergoing LA, it is important that lipid parameters are evaluated at a time that is as close as possible to and before the scheduled LA treatment. Once established, this time point for lipid profile blood draws should always be maintained, relative to the previous LA visit, so that lipid profiles are always performed at the same point on the LDL-C rebound curve.

During the Run-in Period a stable frequency regimen (i.e., LA every X number of days) will be established. This frequency of LA needs to be maintained during the Efficacy Phase (through Week 24±3 days). The frequency of LA is usually personalised to meet the patient's needs and the centre's capacity. Therefore, windows are provided in Section 1.2 *Flow Chart of Study and Follow-up* for each visit to allow flexibility when patients can be seen. If a patient is unable to come for an LA per his/her usual regimen, LA should be rescheduled as soon as possible. If LA was missed at a time a study visit was scheduled, then blood for lipid profile should be drawn before the LA treatment and as close as possible to the LA regimen established during the Run-in Period or as revised if during the Safety Phase.

However, for Visits 4 through 21 (i.e., during the Efficacy and Safety Phase) fasting lipids must be drawn just prior to the LA and LA must occur ±3 days from the regimen established during the Run-in Period.

7.6.2 Permitted Concomitant Medication

<u>The following medication will be permitted during study and follow-up:</u>

- Lipid-lowering medicinal products including statins, fibrates, bile acid sequestrants, and PCSK9 inhibitors

  <u>Please note</u>: Patients who receive atorvastatin, should separate the dose of the medicinal products by 12 hours, e.g., by taking atorvastatin in the morning and lomitapide in the evening (see Section 7.3.3. *Dose Modification for Concomitant Medication*). Patients who receive bile acid sequestrants, should separate the dose of the medicinal products by 4 hours. Concomitant administration of >40 mg simvastatin is <u>not permitted</u> (see Section 7.6.3 *Non-permitted Concomitant Medication, Food or Substances*).

- Oestrogen-based oral contraceptives

  Please note: Postmenarchal female adolescent patients taking oestrogen-based oral contraceptives should be advised that diarrhoea and/or vomiting may reduce hormone absorption. In case of protracted or severe diarrhoea and/or vomiting lasting more than 2 days, the investigator should advise according to national practice, which additional contraceptive measures (such as sexual abstinence, barrier methods) should be used for 7 days after resolution of symptoms.

- Supportive therapy upon the investigators' discretion.

The following medication will be permitted during the Safety Phase of the study:

- If a weak CYP 3A4 inhibitor, e.g., aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, glucocorticoids, modafinil and phenytoin inhibitor is required during the Safety Phase, the dose of lomitapide should be reduced as described in Section 7.3.3 *Dose Modification for Concomitant Medication*.

  Please note: Patients who receive weak CYP 3A4 inhibitors, should separate the dose of the medicinal products by 12 hours.

  If atorvastatin is given concomitantly, it should be administered in the morning to separate it from lomitapide dosing by 12 hours. In case it is not possible to administer atorvastatin and lomitapide 12 hours apart, the lomitapide dose should be reduced by half (see Section 7.3.3 *Dose Modification for Concomitant Medication*).

7.6.3 Non-permitted Concomitant Medication, Food or Substances

Non-permitted Concomitant Medication

The following medication will not be permitted during the study:

- Contraindications for the use of lomitapide according to section 4.3 of the SPC (included in the Lojuxta® SPC in lieu of an IB; see Section 18.1 *Source Documents*), such as
  - Concomitant administration of >40 mg simvastatin.
  - Concomitant use of strong or moderate CYP 3A4 inhibitors, e.g., antifungal azoles such as itraconazole, fluconazole, ketoconazole, voriconazole, posaconazole; macrolide antibiotics such as erythromycin or clarithromycin; ketolide antibiotics such as telithromycin; HIV protease inhibitors; the calcium channel blockers diltiazem and verapamil, and the anti-arrhythmic dronedarone.

The following medication will not be permitted during the Efficacy Phase of the study:

- Weak CYP 3A4 inhibitors, e.g., aminoglutethimide, nafcillin, non-nucleoside reverse transcriptase inhibitors, phenobarbital, rifampicin, carbamazepine, pioglitazone, glucocorticoids, modafinil and phenytoin. If a weak CYP 3A4 inhibitor is required during the Safety Phase, the dose of lomitapide should be reduced as described in Section 7.3.3 *Dose Modification for Concomitant Medication*.

Non-permitted Concomitant Food or Substances

The use of the following food or substances should be avoided with lomitapide:

- Alcohol: Alcohol may increase levels of hepatic fat and induce or exacerbate liver injury.
- Grapefruit juice: Grapefruit juice is a moderate inhibitor of CYP 3A4 and is expected to substantially increase exposure to lomitapide.
- Peppermint oil or Seville oranges.
- St. John's Wort (i.e., *Hypericum perforatum*).

8 ASSESSMENTS

Please refer to Section 1.2 *Flow-Chart of Study and Follow-up* for a tabular overview of assessments by visit.

8.1 Eligibility and Safety Assessments

8.1.1 Eligibility Assessments

Informed Consent

The investigator will obtain written informed assent (according to applicable local regulations) and/or consent from the patient and his/her parent/legal guardian before he/she will initiate any study-specific procedure.

The following criteria will be assessed for eligibility prior to enrolment:

Inclusion/Exclusion

The investigator will assess the patient's eligibility as outlined in Section 5.1 *Inclusion Criteria* and Section 5.2 *Exclusion Criteria* including confirmation of a negative urine pregnancy test in postmenarchal female adolescents.

Demographics

Age, gender, and ethnic origin will be recorded at Screening (Visit 1).

Medical History/Current Medical Conditions

The investigator will ask the patient and/or his/her parent/legal guardian for the patient's general and disease-specific medical history and current medical conditions. Changes in current medical conditions, particularly cardiovascular procedures and events, will be recorded at each visit thereafter.

For those patients who have had genetic testing in the past, information should be collected regarding the details of the alleles for the genes involved.

Genetic Testing

Genetic testing is strongly encouraged, but not mandatory and not required for determining eligibility. Patients who have not previously had genetic testing, will be asked, whether they would consent to genetic testing. A separate informed consent will be obtained for genetic testing. For those patients who have signed a separate informed consent form (ICF) for this procedure, a blood sample will be collected according to central laboratory procedures for genotyping specified in the *'Laboratory Manual'* at Screening (Visit 1). If it is not possible to do this at Screening (Visit 1) it can be done at a later visit.

Physical Examination

The investigator will do a complete physical examination including growth and sexual maturation assessments of the patient (and a genitourinary, but not rectal exam at the investigator's discretion) and will document height, weight, body mass index (BMI), body surface area (BSA) and all clinically relevant findings at Screening (Visit 1), at Visit 7 (Week 12±3 days), Visit 10 (Week 24±3 days), Visit 18 (Week 56±3 days), at Visit 22 (Week 104±1 week), and in case of premature discontinuation.

At all other 4-week study visits, an abbreviated physical examination, to include a focused evaluation of general appearance, skin, thorax/lungs, CV, and abdomen, will be conducted. Xanthomas will be evaluated at every physical exam.

Weight will be measured using a consistent approach at Screening and at each visit after the Run-in Period (i.e., child/adolescent always weighed in same amount of clothing, either in underwear, hospital gowns or by subtracting the weight of clothes):

- Patients of normal or below normal body weight (based on BMI with weight loss >1.5 kg since the previous visit) and their parent/legal guardian will meet with the dietitian for further instruction.
- Patients with below normal body weight at any time during the study who continue to lose weight while on study medication despite all appropriate measures taken to correct for the weight loss and who are deemed to be at clinical risk in the judgment of the treating investigator should discontinue study medication and be followed until an acceptable stable weight is reached as judged by the investigator (see Section 7.3.2 *Dose Modification, Interruption or Discontinuation for Adverse Events*).

Tanner Staging

Tanner Staging is required for this study, and every attempt should be made to collect this information. Tanner Staging must be completed together with the physical exam by the same study-affiliated clinician (e.g., paediatrician) in the most inconspicuous manner for the patient as possible. When Tanner Staging is not completed at a required visit, it should be performed at the next study visit.

Tanner Staging assessment consists of 2 domains (pubic hair and breast development) for girls and 3 domains (pubic hair, penis development, and testes development) for boys. The Tanner Staging assessment as a reference for the completing clinician is included in Appendix 5 *Tanner Staging*. A patient who reaches Stage 5 (both in pubic hair and genitalia) does not need to continue with Tanner staging.

Sites should make attempts to have examiners of both gender types available and to have the examination performed by the same gender as the patient, where possible. Otherwise, patient's parent/guardian or a study-affiliated person (e.g., nurse) who is the same gender as the patient should be in the same examination room with the patient while the examination is performed.

8.1.2 Safety Assessments

Concomitant Medication

During the Screening and Run-in Period, at Baseline, during the Efficacy and Safety Phases as well as during the follow-up period, all concomitant medications and treatments (including LA, when applicable) will be recorded. The name, start and stop date, dosage, indication, frequency and route of administration of all medications as well as the name, start and stop date, indication, and frequency of all treatments will be recorded on the eCRF at first report and again only if anything has changed since the last visit.

Adverse Events

Adverse events occurring before the first administration of study medication will be recorded in the Medical History/Current Medical Conditions section of the eCRF. AEs occurring during the Efficacy and Safety Phases, and during the follow-up period until 30 days after the last administration of study medication will be recorded in the AE section of the eCRF. During the Screening and Run-in Period (<D0) and at Baseline (D0 of the Efficacy Phase) before study medication administration, AEs related to study procedures should also be reported. For reporting of AEs, please refer to Section 11.2 *Recording of Adverse Events and Serious Adverse Events*.

Serious Adverse Events

Serious AEs will be recorded in the SAE section of the eCRF during the Screening and Run-in Period, at Baseline, during the Efficacy and Safety Phases as well as during the follow-up period. For reporting of SAEs, please refer to Section 11.5 *Immediately Reportable Information*.

Vital Signs

Vital signs, including systolic and diastolic blood pressure, heart rate, body temperature, and respiratory rate, will be measured at Screening (Visit 1), at Baseline (Visit 4), and at every visit thereafter (see Section 1.2 *Flow Chart of Study and Follow-up*). Blood pressure and heart rate will be measured after 5 minutes of rest in a sitting position.

Electrocardiogram

A 12-lead ECG will be recorded and read locally at Baseline (Visit 4), at Visit 10 (Week 24±3 days), Visit 18 (Week 56±3 days), Visit 20 (Week 80±1 week), and at EoT (Week 104±1 week) (see Section 1.2 *Flow Chart of Study and Follow-up*).

Electrocardiograms will be obtained after the patient has been supine for 5 minutes. The ECG recordings are to be reviewed by the investigator and classified as 'normal' or 'abnormal'. Abnormal ECGs must in addition be classified as 'abnormal, clinically significant' or 'abnormal, not clinically significant'. The reason(s) for 'abnormal' findings should be documented. Abnormal, clinically significant findings occurring after first administration of study medication should be reported as an AE (unless already pre-existing at Baseline with the same severity).

Standard of Care Echocardiography

It is anticipated that echocardiography will be performed annually as standard of care in this patient population. For this study, echocardiography is not mandated but data/results will be included as part of the study safety data. Information in relation to the most recent echocardiography on file (if available) will be documented in the eCRF at the following visits: Baseline (Visit 4), Visit 10 (Week 24±3 days), Visit 18 (Week 56±3 days), and at EoT (Week 104±1 week) (see Section 1.2 *Flow Chart of Study and Follow-up*).

Pulmonary Function Test

Pulmonary function tests, i.e., spirometry with $D_{L,CO}$ (diffusion capacity of the lung for carbon monoxide) will be performed to include: forced vital capacity (FVC); forced expiratory volume during 1 s (FEV_1) and maximal mid-expiratory flow (FEF_{25-75}) at Baseline (D0), Visit 10 (Week 24±3 days), Visit 18 (Week 56±1 week), and at EoT (Week 104±1 week) (see Section 1.2 *Flow Chart of Study and Follow-up*).

Nuclear Magnetic Resonance Imaging

The terms Magnetic Resonance Imaging (MRI) and Nuclear Magnetic Resonance (NMR) are synonymous as are echography and ultrasound scan.

Lipid accumulation in the liver (i.e., hepatic fat content) will be assessed at Baseline (D0), Visit 10 (Week 24±3 days), Visit 18 (Week 56±1 week), and at EoT (Week 104±1 week) in patients entering the EAP (<18 years of age)/transitioning to commercial product (≥18 years of age) or at Follow-up (Week 108) in patients who opt not to participate in or are unsuitable for the EAP (<18 years of age)/opt not to transition to commercial product (≥18 years of age; see Section 1.2 *Flow Chart of Study and Follow-up*). All patients will undergo NMR imaging unless it is contraindicated or not feasible (e.g., due to the need for sedation or general anaesthesia in very young or anxious patients). In this case, ultrasound scans will be used at the discretion of the investigator. The NMR images will be processed by a central reader, the ultrasound scans will be interpreted locally.

Safety Laboratory Assessments

The following safety laboratory tests are to be conducted as outlined in Section 1.2 *Flow Chart of Study and Follow-up*. See Appendix 6 *Laboratory Tests* for a comprehensive list of all laboratory tests to be performed. The total blood volume collected from each patient for the entire study is within the guidelines set forth by the WHO (Howie 2011).

Comprehensive Metabolic Panel and Liver Function Tests

The comprehensive metabolic panel includes sodium (Na), potassium (K), calcium (Ca), carbon dioxide, chloride (Cl), blood glucose (BG), C-reactive protein (CRP), renal parameters (blood urea nitrogen [BUN], creatinine), creatinine kinase (CK), total protein, and albumin.

Liver function tests include alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP) and total bilirubin including direct and indirect bilirubin.

Fasting Lipid Panel

The patient should be fasting for at least 8 hours, except for water and medications, prior to drawing the fasting lipid panel. The fasting lipid panel includes the efficacy parameters TC, LDL-C, VLDL-C, calculated Non-HDL-C, TG, apo B, and Lp(a) (see Section 8.3.1 *Fasting Lipid Panel*) and the safety parameters high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (apo A-I).

As the fasting lipid panel will be analysed at both the local hospital laboratory and the central laboratory, 2 separate samples must be drawn (see Section 10 *Collection, Storage, and Shipment of Laboratory Samples*).

Complete Blood Count

The complete blood count (CBC) includes white blood cell count, haemoglobin, haematocrit, platelet count, red blood cell count, red cell distribution width, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC).

Fat-Soluble Vitamin Levels

Vitamin A (retinol), vitamin E (alpha tocopherol), and vitamin D (25-hydroxy-D) will be assessed by measuring serum concentrations of the individual vitamins. In addition, vitamin E will also be reported as the ratio of alpha tocopherol/total lipids (TC + fasting TG). Levels of vitamin K will be assessed indirectly by measuring carboxylation of serum osteocalcin (ratio uncarboxylated osteocalcin/total osteocalcin).

Fat-soluble vitamin levels will be analysed at the central laboratory specified in the *'Laboratory Manual'* (see Section 10 *Collection, Storage, and Shipment of Laboratory Samples*).

Serum Levels of Essential Fatty Acids (EFA)

The Essential Fatty Acid (EFA) profile comprises serum levels of linoleic acid, alpha linoleic acid (ALA), arachidonic acid (AA), docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and eicosatrienoic acid.

Serum levels of EFA will be analysed at the central laboratory specified in the *'Laboratory Manual'* (see Section 10 *Collection, Storage, and Shipment of Laboratory Samples*).

Hormones

Thyroid stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), serum cortisol, and sex hormones (serum follicle stimulating hormone [FSH] and luteinising hormone [LH]) will be assessed. The blood sample for testing of serum cortisol must be obtained in the early morning (6:00 to 8:00 a.m.). For patients who are Tanner Stage ≥2, serum oestradiol will be assessed for female patients and serum testosterone will be assessed for male patients.

Urinalysis

Urinalysis includes the assessment of urine colour, turbidity, pH, glucose, bilirubin, ketones, blood, protein, and white blood cells.

Pregnancy Tests

Urine pregnancy tests will be conducted in postmenarchal female adolescent patients using test strips at every scheduled visit from Visit 1 through Visit 23 and every 4 weeks after Visit 18 at Week 56±3 days through Week 104±1 week.

If a patient becomes pregnant during the study, during the follow-up, or 30 days within the last application of study medication, the study medication must be discontinued immediately (see Section 7.4 *Patient Discontinuation Criteria*) and the sponsor will have to be informed within 24 hours.

The investigator will be asked to complete a pregnancy report provided by the sponsor. He/she will be asked to obtain data on the course of the pregnancy, including perinatal and neonatal outcome (see Section 11.5.4 *Other Reportable Information*).

Bone Health

Bone health will be assessed indirectly using growth to track age-appropriate progress, and measurement of 25-hydroxy-D and total and uncarboxylated osteocalcin levels (as reflection of vitamin K levels). Effects on growth, bone health and bone age will be assessed using both measurements of children's height and growth charts to track age-appropriate progress at Screening and from Baseline at every visit through Week 104±1 week and/or at EoT, together with analysis of Vitamin D and K levels at Screening, Baseline, Week 24±3 days, Week 56±3 days, Week 80±1 week, Week 104±1 week and/or at EoT (and at Week 108 for patients who opt not to participate in or are unsuitable for the EAP [<18 years of age]/opt not to transition to commercial product [≥18 years of age]).

8.2 Pharmacokinetics

Plasma levels of lomitapide will be measured. Baseline PK will be taken at D0. Steady-state PK from Visit 5 (Week 4±3 days) through Visit 10 (Week 24±3 days) will be evaluated. Single PK samples will be collected at Visit 5 (Week 4±3 days), Visit 7 (Week 12±3 days), Visit 8 (Week 16±3 days), and at Visit 10 (Week 24±3 days). Two PK samples will be collected at least 1 hour apart at Visit 6 (Week 8±3 days) and at Visit 9 (Week 20±3 days); these samples must be collected as separate blood draws (time between separate blood draws might be used for undertaking other procedures scheduled for the respective visit(s)).

All samples taken are trough samples of about 3.5 mL each (the volume of blood taken might be adjusted based on the body weight of the patient and central laboratory procedures). Samples will not be taken in duplicate. The date and time of the patient's last lomitapide dose and the date and time of the sample(s) should be recorded in the eCRF.

8.3 Assessment of Efficacy

8.3.1 Fasting Lipid Panel

The patient should be fasting for at least 8 hours, except for water and medications, prior to drawing the fasting lipid panel. The fasting lipid panel includes TC, LDL-C, VLDL-C, calculated Non-HDL-C, TG, apo B, and Lp(a) and the safety parameters HDL-C and apo A-I (see Section 8.1.2 *Safety Assessments*).

At Screening (Visit 1), LDL-C may be estimated from the Friedewald formula if TG are <400 mg/dL; however, if TG are ≥400 mg/dL, LDL-C will be measured directly.

Friedewald formula: $LDL\text{-}C = TC - (HDL\text{-}C + \frac{TG}{5})$

At all other visits, LDL-C is measured directly.

For patients on LA, fasting lipid panels must be drawn at all assessments required by the protocol and (as applicable) are to be obtained immediately before the scheduled LA treatment (see Section 7.6.1 *Concomitant Lipid-Lowering Treatment*).

As the fasting lipid panel will be analysed at both the local hospital laboratory and the central laboratory, 2 separate samples must be drawn (see Section 10 *Collection, Storage, and Shipment of Laboratory Samples*).

8.3.2 LDL-C Treatment Criteria

The LDL-C values for Screening (Visit 1) and Week -3 to Week -2 (Visit 2) must be as follows for a patient to be eligible to begin treatment on D0.

Baseline LDL-C on LLT (C_{max} 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)

8.4 Exploratory Assessments

8.4.1 Regression or Resolution of Xanthomas

The patient's xanthomas (tendon and cutaneous, size and location) will be evaluated during physical examination at Screening (Visit 1), at Baseline (Visit 4, D0) and at every visit thereafter.

8.4.2 Assessment of Carotid Intima-Media Thickness and Flow-mediated Dilation

Carotid intima-media thickness (CIMT, mandatory) and flow-mediated dilation (FMD, whenever possible) will be assessed using ultrasound scan to evaluate carotid atherosclerotic vascular disease and brachial artery dilation after a transient period of forearm ischaemia at Baseline (Visit 4, D0), at Visit 18 (Week 56±3 days), and at EoT (Week 104±1 week).

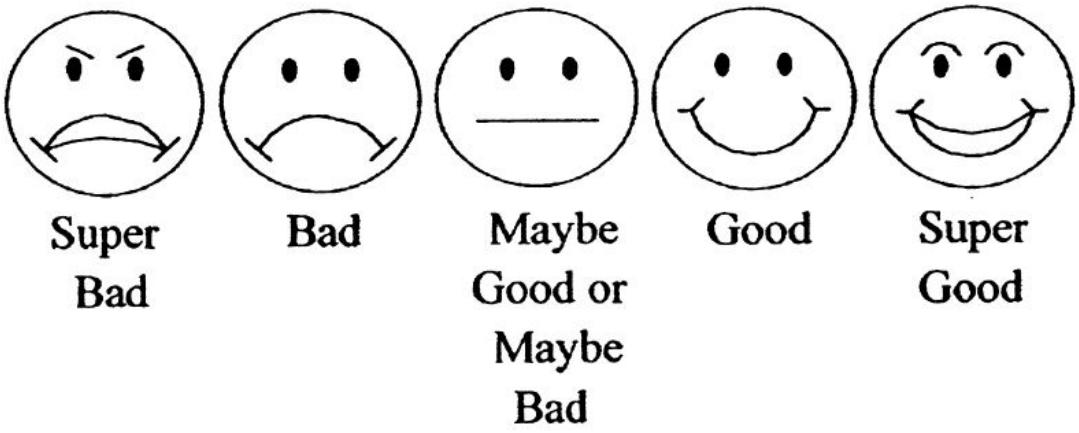
8.4.3 Liposcale® Test

The Liposcale® Test will be used to assess changes from Baseline through Week 24±3 days in cholesterol and triglyceride content of VLDL, IDL, LDL and HDL, particle number and size of VLDL, LDL, and HDL as well as particle number of their respective lipoprotein subclasses (large, medium, and small), from PK samples at Week 4±3 days, Week 8±3 days, Week 12±3 days, Week 16±3 days, Week 20±3 days and Week 24±3 days. For this 2D NMR analysis, 200 µL aliquots will only be taken from each PK sample at the central laboratory specified in the *'Laboratory Manual'*, if sufficient sample material has been provided and would otherwise be discarded. No additional blood sampling from the patient at the site will be required (see Section 10 *Collection, Storage and Shipment of Laboratory Samples*).

8.5 Palatability

Palatability will be assessed using a 5-point facial hedonic scale, anchored with descriptors, to record the children's assessment of palatability in terms of overall liking (see Figure 4).

Figure 4 Example of a 5-Point Facial Hedonic Scale Used for Hedonic Ratings by Children (Guinard 2000)



Palatability will be assessed on the first occasion that any patient who is not able to swallow the intact capsule(s) takes lomitapide by opening and sprinkling the capsule onto either food media (i.e., if a patient tries both food media, assessment will be made at the first instance of taking the study medication with apple sauce and the first instance of taking the study medication with mashed banana).

The investigator or a study team member will also ask the parent(s)/legal guardian(s) to evaluate the children's reaction to investigational product and dietary supplement administration. A 3-point scale that assesses the parent(s)/legal guardian(s) interpretation of the child's reaction/facial expression will be used to determine whether they find lomitapide "pleasant", "unpleasant" or are "not sure".

In addition, an assessment of ease of administration will be incorporated by asking the parent(s)/legal guardian(s) 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)." The same question will be asked for the administration of dietary supplements.

Timing of the reaction relative to dosing will be recorded to help distinguish between palatability of the investigational product and GI events that are a result of the investigational products mechanism of action.

8.6 Other Assessments

8.6.1 Diet Instructions and Diet Records

The occurrence and severity of GI AEs associated with the use of lomitapide decreases in the presence of a low-fat diet. Patients will start to follow a diet supplying <20% of energy from fat or <30 g fat, whichever is the lesser amount at Visit 2 (Start of the Run-in Period) and will continue this diet until the EoT (and throughout the EAP [<18 years of age]/administration of commercial product [≥18 years of age], when applicable).

A dietitian will provide dietary counselling to the patients and their parents/legal guardians from Visit 2 (Start of the Run-in Period) through Visit 5 (Week 4±3 days). Patients and parents/legal guardians will be instructed on how to consume <20% energy from fat or <30 g fat, whichever is the lesser amount. Instructions will include detailed information concerning the role of dietary

fat and GI-related symptoms and patients will be encouraged to pay special attention to foods they eat when/if they experience these symptoms. The dietitian will review current eating habits in order to point out needed changes and address potential adherence problems. The dietitian will provide diet instructions that are tailored to each patient's caloric needs to promote healthy weight maintenance.

The dietitian will also review compliance with the diet and discuss any issues or concerns the patient and his/her parents/legal guardians may have with the diet at Visit 3 (Week -3 to Week -2). The dietitian will inform patients and their parents/legal guardians to call him/her to discuss over the phone or schedule a meeting to address any diet-related questions or concerns at any time during the study. Additional resources pertaining to the diet will be available to the dietitian and the patient and his/her parent/legal guardian.

Weight will be measured using a consistent approach at Screening and at each visit after the Run-in Period (i.e., child/adolescent always weighed in same amount of clothing, either in underwear, hospital gowns or by subtracting the weight of clothes). Patients of normal or below normal body weight with weight loss >3% since the last visit will be instructed by the dietitian on how to increase caloric intake based on individual needs. The standard recommended fat intake for children >2 years old is to follow a diet with <30% energy from fat, hence, decreasing dietary fat intake to <20% or <30 g fat, whichever is the lesser amount should not pose any risk to patients of any age that may be enrolled in this study.

The investigator can request additional dietary counselling as clinically indicated. At the same visits, 2-Day Diet Records will be given to the patients and their parents/legal guardians.

In order to assess dietary compliance and to provide information for interpreting possible GI AEs, patients will be instructed to document all food and beverages consumed periodically throughout the study, using Diet Records. A 2-Day Diet Record will be dispensed and returned from Visit 2 (Start of the Run-in Period) through Visit 21 (Week 92±1 week).

If diet-related problems are noted during the study, e.g., weight loss or GI-related complaints such as diarrhoea, the patients may be requested to fill out additional Diet Records. Note that Diet Records collected during the Run-in Period do not get analysed, but are used by the dietitian on site to assess compliance before beginning lomitapide treatment.

Patients treated with lomitapide and their parents/legal guardians should be advised of the potential risk of dehydration in relation to GI AEs and take precautions to avoid fluid depletion.

Please refer to Section 6.3 *Dietary Supplements* for details regarding oral supplementation with vitamin E and essential fatty acids.

9 VISIT SCHEDULE

The visit schedule is summarised in Section 1.2 *Flow Chart of Study and Follow-up.* The calculation of all study days is based on D0, which is defined as the day of the first application of study medication.

9.1 Screening Period (Starting at Week -12, i.e., ≤12 Weeks Prior to Baseline for a Minimum of 6 Weeks), Visit 1

Study sites might contact patients who are registered in centre-specific databases to inform them about the study and to invite them for screening.

The investigator will have to obtain written informed assent/consent (according to applicable local regulations) from the patient and written informed consent from his/her parent/legal guardian before any study-related procedure will be initiated (see Section 14.3 *Patient and Parent/Legal Guardian Information and Informed Consent*). If the patient and his/her parent/legal guardian consent to the optional genetic testing, written informed consent for genetic testing will also be obtained.

9.1.1 Visit 1 (Up to Week -12)

During Visit 1 up to Week -12, the following will be completed:

- Confirmation of patient eligibility using the inclusion criteria (see Section 5.1 *Inclusion Criteria*) and exclusion criteria (see Section 5.2 *Exclusion Criteria*)
- Record of general and disease-specific medical history and current medical conditions including cardiovascular procedures and events
- Record of demographic data (age, gender, and ethnic origin)
- Complete physical examination of the patient (and a genitourinary, but not rectal exam at the investigator's discretion) including the documentation of height, weight, BMI, BSA and all clinically relevant findings, such as xanthomas (see Section 8.1.1 *Eligibility Assessments*)
- Determination of sexual maturation based on Tanner staging (see Section 8.1.1 *Eligibility Assessments* and Appendix 5 *Tanner Staging*)
- Measurement of vital signs and blood pressure (see Section 8.1.1 *Eligibility Assessments*)
- Record of concomitant medication including LLT and/or LA when applicable (see Section 7.6.1 *Concomitant Lipid-lowering Treatment* and Section 8.1.2 *Safety Assessments*)
- Collection of blood samples for the following tests (see Section 8.1.2 *Safety Assessments*):
  - Complete blood count
  - Comprehensive metabolic panel
  - Liver function tests
  - Fasting lipid panel (see Section 8.3.1 *Fasting Lipid Panel*)
  - Serum level of essential fatty acids
  - Fat-soluble vitamin levels
  - Hormones (TSH, ACTH, serum cortisol [to be measured between 06:00 and 08:00 a.m.], FSH, LH)
  - In patients who are Tanner Stage ≥2, serum oestradiol will be assessed for female patients and serum testosterone will be assessed for male patients
- Urinalysis (urine colour, turbidity, pH, glucose, bilirubin, ketones, blood, protein, and white blood cells)
- A urine pregnancy test in all postmenarchal female adolescents (see Section 8.1.2 *Safety Assessments*)
- Genetic testing in patients who have not previously had genotyping and who have consented to this procedure (collection of a blood sample according to central laboratory procedures specified in the *'Laboratory Manual'*, see Section 8.1.1 *Eligibility Assessments*). If it is not possible to do genetic testing at Screening (Visit 1) it can be done at a later visit.

9.2 Re-screening

If the patient is a screen failure, he/she can be re-screened on 2 separate occasions within 2 weeks of the previous (re-)screening. The patient can only be re-screened for the purpose of repeating LDL-C (inclusion criterion 2), serum CK (exclusion criterion 4) or blood pressure (exclusion criterion 6) measurement(s), as deemed appropriate by the investigator, since these parameters might change within a short timeframe. A new screening for eligibility based on all other inclusion and exclusion criteria is not possible, because they are not expected to change

within a short timeframe. The patient must be reconsented for the re-screening procedure(s); however, to reduce study burden and blood draws in this paediatric patient population, other screening procedures must not be repeated. The patient will be assigned a new patient number.

9.3 Stratified Enrolment and Start of Run-in Period (Starting at Minimum at Week -6, i.e., 6 Weeks Prior to Baseline for a Minimum of 6 Weeks, Visits 2 to 3

9.3.1 Visit 2 (Stratified Enrolment and Start of Run-in Period, at Minimum Week -6)

Upon confirmation of eligibility, patients will come back to the study site for Visit 2 (at minimum Week -6) for stratified enrolment and to start the Run-in Period. At Visit 2, the following procedures will be conducted:

- Dietary counselling (see Section 8.6.1 *Diet Instructions and Diet Records*)
- Dispensing of 2-Day Diet record (used to enable adjustments to the patient's diet before starting study drug; see Section 8.6.1 *Diet Instructions and Diet Records*)
- A urine pregnancy test in all postmenarchal female adolescents (see Section 8.1.2 *Safety Assessments*)
- Record of concomitant medication including LLT and/or LA when applicable (see Section 7.6.1 *Concomitant Lipid-lowering Treatment* and Section 8.1.2 *Safety Assessments*)
- Enquiry about any AEs/SAEs and record in the AE section of the eCRF.

9.3.2 Visit 3 (Compliance, Week -3 to Week -2)

The patient will visit the study site for Visit 3 (Week -3 to Week -2) and must present in fasting state. The following procedures will be conducted:

- Dietary counselling (see Section 8.6.1 *Diet Instructions and Diet Records*)
- Dispensing of new and collection of old 2-Day Diet records (see Section 8.6.1 *Diet Instructions and Diet Records*)
- Collection of blood samples for fasting lipid panel (see Section 8.3.1 *Fasting Lipid Panel*)
- Dispensing of dietary supplements (see Section 6.3 *Dietary Supplements*)
- A urine pregnancy test in all postmenarchal female adolescents (see Section 8.1.2 *Safety Assessments*)
- Record of concomitant medication including LLT and/or LA when applicable (see Section 7.6.1 *Concomitant Lipid-lowering Treatment* and Section 8.1.2 *Safety Assessments*)
- Enquiry about any AEs/SAEs and record in the AE section of the eCRF.

9.4 Efficacy Phase (Baseline, D0 to Week 24±3 days), Visits 4 to 10

9.4.1 Visit 4 (Baseline, D0)

The patient will visit the study site for the Baseline assessment of the Efficacy Phase at Visit 4 (D0) and must present in fasting state. The following procedures will be conducted:

- Confirmation of patient eligibility using the inclusion criteria (see Section 5.1 *Inclusion Criteria*) and exclusion criteria (see Section 5.2 *Exclusion Criteria*)

- Abbreviated physical examination (including a focused evaluation of general appearance, skin, thorax/lungs, CV, abdomen, and xanthomas) and record of height, weight, BMI, and BSA (see Section 8.1.1 *Eligibility Assessments*)
- Determination of sexual maturation based on Tanner staging (see Section 8.1.1 *Eligibility Assessments* and Appendix 5 *Tanner Staging*)
- Record of 12-lead ECG (read locally, see Section 8.1.2 *Safety Assessments*)
- Collection of information in relation to the most recent standard of care echocardiography on file (if available, see Section 8.1.2 *Safety Assessments*)
- Measurement of vital signs and blood pressure (see Section 8.1.1 *Eligibility Assessments*)
- Pulmonary Function Test (see Section 8.1.2 *Safety Assessments*)
- NMR imaging of liver for hepatic fat assessment; if NMR imaging is contraindicated or not feasible (e.g., due to the need for sedation or general anaesthesia in very young or anxious patients), ultrasound scans will be used at the discretion of the investigator (see Section 8.1.2 *Safety Assessments*)
- Dietary counselling (see Section 8.6.1 *Diet Instructions and Diet Records*)
- Dispensing of new and collection of old 2-Day Diet records (see Section 8.6.1 *Diet Instructions and Diet Records*)
- Carotid intima-media thickness (CIMT, mandatory) and flow-mediated dilation (FMD, whenever possible) using ultrasound scan (see Section 8.4.2 *Assessment of Carotid Intima-Media Thickness and Flow-mediated Dilation*)
- Collection of blood samples for the following tests (see Section 8.1.2 *Safety Assessments*):
  - Complete blood count
  - Comprehensive metabolic panel
  - Liver function tests
  - Fasting lipid panel (see Section 8.3.1 *Fasting Lipid Panel*)
  - Serum level of essential fatty acids
  - Serum lipase
  - Fat-soluble vitamin levels
  - Hormones (TSH, ACTH, serum cortisol [to be measured between 06:00 and 08:00 a.m.], FSH, LH)
  - In patients who are Tanner Stage ≥2, serum oestradiol will be assessed for female patients and serum testosterone will be assessed for male patients
  - Pharmacokinetics (single trough sample, date and time of the patient's last lomitapide dose and time of the sample should be recorded in the eCRF)
- Urinalysis (urine colour, turbidity, pH, glucose, bilirubin, ketones, blood, protein, and white blood cells)
- A urine pregnancy test in all postmenarchal female adolescents (see Section 8.1.2 *Safety Assessments*)
- Dispensing of dietary supplements and collection of used dietary supplement bottles as needed (see Section 6.3 *Dietary Supplements*)
- Dispensing of study medication (see Section 7.2 *Treatment Schedule*): The first dose of study medication will be administered at the study site.

- Palatability assessment: A 5-point facial hedonic scale will be used to record the child's assessment of palatability of study medication on the first occasion that any patient who is unable to swallow the intact capsule(s) and opens the capsule(s) and sprinkles the capsule content on a small amount (1 tablespoon) of either apple sauce or mashed banana (i.e., if a patient tries both food media, assessment will be made at the first instance of taking the study medication with apple sauce and the first instance of taking the study medication with mashed banana). The type of food media (apple sauce or mashed banana) will be captured (see Section 8.5 *Palatability*)
- Record of concomitant medication including LLT and/or LA when applicable (see Section 7.6.1 *Concomitant Lipid-lowering Treatment* and Section 8.1.2 *Safety Assessments*)
- Enquiry about any AEs/SAEs and record in the AE section of the eCRF.

9.4.2 Visits 5, 6, 8, and 9 (Week 4±3 days, Week 8±3 days, Week 16±3 days, and Week 20±3 days)

The patient will visit the study site for Visits 5, 6, 8 and 9 of the Efficacy Phase and must present in fasting state. The following procedures will be conducted:

- Abbreviated physical examination (including a focused evaluation of general appearance, skin, thorax/lungs, CV, abdomen, and xanthomas) and record of height, weight, BMI, and BSA (see Section 8.1.1 *Eligibility Assessments*)
- Measurement of vital signs and blood pressure (see Section 8.1.1 *Eligibility Assessments*)
- Dietary counselling (see Section 8.6.1 *Diet Instructions and Diet Records*) at Visit 5 (Week 4±3 days) only and as clinically indicated thereafter
- Dispensing of new and collection of old 2-Day Diet records (see Section 8.6.1 *Diet Instructions and Diet Records*)
- Collection of blood samples for the following tests (see Section 8.1.2 *Safety Assessments*):
  - Comprehensive metabolic panel
  - Liver function tests
  - Fasting lipid panel (see Section 8.3.1 *Fasting Lipid Panel*)
  - Pharmacokinetics (single trough samples at Visit 5 [Week 4±3 days] and Visit 8 [Week 16±3 days]; date and time of the patient's last lomitapide dose and time of the sample should be recorded in the eCRF)
  - Two PK samples will be collected at least 1 hour apart at Visit 6 (Week 8±3 days) and Visit 9 (Week 20±3 days); date and time of the patient's last lomitapide dose and time of the samples should be recorded in the eCRF; these samples must be collected as separate blood draws (time between separate blood draws might be used for undertaking other procedures scheduled for the respective visit(s)).
- A urine pregnancy test in all postmenarchal female adolescents (see Section 8.1.2 *Safety Assessments*)
- Dispensing of dietary supplements and collection of used dietary supplement bottles as needed (see Section 6.3 *Dietary Supplements*)
- Dispensing of study medication and collection of used study medication bottles as needed (see Section 7.2 *Treatment Schedule*).
- Study medication compliance check (see Section 6.2 *Investigational Product Compliance*)
- Palatability assessment (see Section 8.5 *Palatability*):

  - The investigator will ask the parent(s)/legal guardian(s) to evaluate the children's reaction to investigational product and dietary supplement administration. A 3-point scale that assesses the parent(s)/legal guardian(s) interpretation of the child's reaction/facial expression will be used to determine whether they find lomitapide "pleasant", "unpleasant" or are "not sure".
  - In addition, an assessment of ease of administration will be incorporated by asking the parent(s)/legal guardian(s) 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)." The same question will be asked for the administration of the dietary supplements.
  - Timing of the reaction relative to dosing will be recorded to help distinguish between palatability of the investigational product and GI events that are a result of the investigational products mechanism of action.
- Record of concomitant medication including LLT and/or LA when applicable (see Section 7.6.1 *Concomitant Lipid-lowering Treatment* and Section 8.1.2 *Safety Assessments*)
- Enquiry about any AEs/SAEs and record in the AE section of the eCRF.

9.4.3 Visit 7 (Week 12±3 days)

The patient will visit the study site for Visit 7 of the Efficacy Phase and must present in fasting state. The following procedures will be conducted:

- Complete physical examination of the patient (and a genitourinary, but not rectal exam at the investigator's discretion) including the documentation of height, weight, BMI, BSA and all clinically relevant findings, such as xanthomas (see Section 8.1.1 *Eligibility Assessments*)
- Determination of sexual maturation based on Tanner staging (see Section 8.1.1 *Eligibility Assessments* and Appendix 5*Tanner Staging*)
- Measurement of vital signs and blood pressure (see Section 8.1.1 *Eligibility Assessments*)
- Dietary counselling (see Section 8.6.1 *Diet Instructions and Diet Records*) as clinically indicated
- Dispensing of new and collection of old 2-Day Diet records (see Section 8.6.1 *Diet Instructions and Diet Records*)
- Collection of blood samples for the following tests (see Section 8.1.2 *Safety Assessments*):
  - Comprehensive metabolic panel
  - Liver function tests
  - Fasting lipid panel (see Section 8.3.1 *Fasting Lipid Panel*)
  - Pharmacokinetics (single trough sample, date and time of the patient's last lomitapide dose and time of the sample should be recorded in the eCRF)
- A urine pregnancy test in all postmenarchal female adolescents (see Section 8.1.2 *Safety Assessments*)
- Dispensing of dietary supplements and collection of used dietary supplement bottles as needed (see Section 6.3 *Dietary Supplements*)
- Dispensing of study medication and collection of used study medication bottles as needed (see Section 7.2 *Treatment Schedule*).
- Study medication compliance check (see Section 6.2 *Investigational Product Compliance*)

- Record of concomitant medication including LLT and/or LA when applicable (see Section 7.6.1 *Concomitant Lipid-lowering Treatment* and Section 8.1.2 *Safety Assessments*)
- Enquiry about any AEs/SAEs and record in the AE section of the eCRF.

9.4.4 Visit 10 (Week 24±3 days)

The patient will visit the study site for Visit 10 of the Efficacy Phase and must present in fasting state. The following procedures will be conducted:

- Complete physical examination of the patient (and a genitourinary, but not rectal exam at the investigator's discretion) including the documentation of height, weight, BMI, BSA and all clinically relevant findings, such as xanthomas (see Section 8.1.1 *Eligibility Assessments*)
- Determination of sexual maturation based on Tanner staging (see Section 8.1.1 *Eligibility Assessments* and Appendix 5*Tanner Staging*)
- Record of 12-lead ECG (read locally, see Section 8.1.2 *Safety Assessments*)
- Collection of information in relation to the most recent standard of care echocardiography on file (if available, see Section 8.1.2 *Safety Assessments*)
- Measurement of vital signs and blood pressure (see Section 8.1.1 *Eligibility Assessments*)
- Pulmonary Function Test (see Section 8.1.2 *Safety Assessments*)
- NMR imaging of liver for hepatic fat assessment; if NMR imaging is contraindicated or not feasible (e.g., due to the need for sedation or general anaesthesia in very young or anxious patients), ultrasound scans will be used at the discretion of the investigator (see Section 8.1.2 *Safety Assessments*)
- Dietary counselling (see Section 8.6.1 *Diet Instructions and Diet Records*) as clinically indicated
- Dispensing of new and collection of old 2-Day Diet records (see Section 8.6.1 *Diet Instructions and Diet Records*)
- Collection of blood samples for the following tests (see Section 8.1.2 *Safety Assessments*):
  - Comprehensive metabolic panel
  - Liver function tests
  - Fasting lipid panel (see Section 8.3.1 *Fasting Lipid Panel*)
  - Serum levels of essential fatty acids
  - Serum lipase
  - Fat-soluble vitamin levels
  - Pharmacokinetics (single trough sample, date and time of the patient's last lomitapide dose and time of the sample should be recorded in the eCRF)
- A urine pregnancy test in all postmenarchal female adolescents (see Section 8.1.2 *Safety Assessments*)
- Dispensing of dietary supplements and collection of used dietary supplement bottles as needed (see Section 6.3 *Dietary Supplements*)
- Dispensing of study medication and collection of used study medication bottles as needed (see Section 7.2 *Treatment Schedule*).
- Study medication compliance check (see Section 6.2 *Investigational Product Compliance*)

- Record of concomitant medication including LLT and/or LA when applicable (see Section 7.6.1 *Concomitant Lipid-lowering Treatment* and Section 8.1.2 *Safety Assessments*)
- Enquiry about any AEs/SAEs and record in the AE section of the eCRF.

9.5 Safety Phase (Week 28±3 Days to Week 92±1 Week), Visits 11 to 21

9.5.1 Visits 11 to 17 (Week 28±3 days, Week 32±3 days, Week 36±3 days, Week 40±3 days, Week 44±3 days, Week 48±3 days, and Week 52±3 days)

The patient will visit the study site for Visits 11 through 17 of the Safety Phase and must present in fasting state. The following procedures will be conducted:

- Abbreviated physical examination (including a focused evaluation of general appearance, skin, thorax/lungs, CV, abdomen, and xanthomas) and record of height, weight, BMI, and BSA (see Section 8.1.1 *Eligibility Assessments*)
- Measurement of vital signs and blood pressure (see Section 8.1.1 *Eligibility Assessments*)
- Dietary counselling (see Section 8.6.1 *Diet Instructions and Diet Records*) as clinically indicated
- Dispensing of new and collection of old 2-Day Diet records (see Section 8.6.1 *Diet Instructions and Diet Records*)
- Collection of blood samples for the following tests (see Section 8.1.2 *Safety Assessments*):
  - Comprehensive metabolic panel
  - Liver function tests
  - Fasting lipid panel (see Section 8.3.1 *Fasting Lipid Panel*)
- A urine pregnancy test in all postmenarchal female adolescents (see Section 8.1.2 *Safety Assessments*)
- Dispensing of dietary supplements and collection of used dietary supplement bottles as needed (see Section 6.3 *Dietary Supplements*)
- Dispensing of study medication and collection of used study medication bottles as needed (see Section 7.2 *Treatment Schedule*).
- Study medication compliance check (see Section 6.2 *Investigational Product Compliance*)
- Record of concomitant medication including LLT and/or LA when applicable (see Section 7.6.1 *Concomitant Lipid-lowering Treatment* and Section 8.1.2 *Safety Assessments*)
- Enquiry about any AEs/SAEs and record in the AE section of the eCRF.

9.5.2 Visit 18 (Week 56±3 days)

The patient will visit the study site for Visit 18 of the Safety Phase and must present in fasting state. The following procedures will be conducted:

- Complete physical examination of the patient (and a genitourinary, but not rectal exam at the investigator's discretion) including the documentation of height, weight, BMI, BSA and all clinically relevant findings, such as xanthomas (see Section 8.1.1 *Eligibility Assessments*)

- Determination of sexual maturation based on Tanner staging (see Section 8.1.1 *Eligibility Assessments* and Appendix 5 *Tanner Staging*)
- Record of 12-lead ECG (read locally, see Section 8.1.2 *Safety Assessments*)
- Collection of information in relation to the most recent standard of care echocardiography on file (if available, see Section 8.1.2 *Safety Assessments*)
- Measurement of vital signs and blood pressure (see Section 8.1.1 *Eligibility Assessments*)
- Pulmonary Function Test (see Section 8.1.2 *Safety Assessments*)
- NMR imaging of liver for hepatic fat assessment; if NMR imaging is contraindicated or not feasible (e.g., due to the need for sedation or general anaesthesia in very young or anxious patients), ultrasound scans will be used at the discretion of the investigator (see Section 8.1.2 *Safety Assessments*)
- Dietary counselling (see Section 8.6.1 *Diet Instructions and Diet Records*) as clinically indicated
- Dispensing of new and collection of old 2-Day Diet records (see Section 8.6.1 *Diet Instructions and Diet Records*)
- Carotid intima-media thickness (CIMT, mandatory) and flow-mediated dilation (FMD, whenever possible) using ultrasound scan (see Section 8.4.2 *Assessment of Carotid Intima-Media Thickness and Flow-mediated Dilation*)
- Collection of blood samples for the following tests (see Section 8.1.2 *Safety Assessments*):
  - Complete blood count
  - Comprehensive metabolic panel
  - Liver function tests
  - Fasting lipid panel (see Section 8.3.1 *Fasting Lipid Panel*)
  - Serum levels of essential fatty acids
  - Serum lipase
  - Fat-soluble vitamin levels
  - Hormones (TSH, ACTH, serum cortisol [to be measured between 06:00 and 08:00 a.m.], FSH, LH)
  - In patients who are Tanner Stage ≥2, serum oestradiol will be assessed for female patients and serum testosterone will be assessed for male patients
- Urinalysis (urine colour, turbidity, pH, glucose, bilirubin, ketones, blood, protein, and white blood cells)
- A urine pregnancy test in all postmenarchal female adolescents (see Section 8.1.2 *Safety Assessments*)
- Dispensing of dietary supplements and collection of used dietary supplement bottles as needed (see Section 6.3 *Dietary Supplements*)
- Dispensing of study medication and collection of used study medication bottles as needed (see Section 7.2 *Treatment Schedule*).
- Study medication compliance check (see Section 6.2 *Investigational Product Compliance*)
- Record of concomitant medication including LLT and/or LA when applicable (see Section 7.6.1 *Concomitant Lipid-lowering Treatment* and Section 8.1.2 *Safety Assessments*)

- Enquiry about any AEs/SAEs and record in the AE section of the eCRF.

9.5.3 Visits 19 to 21 (Week 68±1 week, Week 80±1 week, and Week 92±1 week)

The patient will visit the study site for Visits 19 through 21 of the Safety Phase and must present in fasting state. The following procedures will be conducted:

- Abbreviated physical examination (including a focused evaluation of general appearance, skin, thorax/lungs, CV, abdomen, and xanthomas) and record of height, weight, BMI, and BSA (see Section 8.1.1 *Eligibility Assessments*)
- Record of 12-lead ECG (read locally, Visit 20 only, see Section 8.1.2 *Safety Assessments*)
- Measurement of vital signs and blood pressure (see Section 8.1.1 *Eligibility Assessments*)
- Dietary counselling (see Section 8.6.1 *Diet Instructions and Diet Records*) as clinically indicated
- Dispensing of new and collection of old 2-Day Diet records (see Section 8.6.1 *Diet Instructions and Diet Records*)
- Collection of blood samples for the following tests (see Section 8.1.2 *Safety Assessments*):
  - Comprehensive metabolic panel
  - Liver function tests
  - Fasting lipid panel (see Section 8.3.1 *Fasting Lipid Panel*)
  - Serum levels of essential fatty acids (Visit 20 only)
  - Fat-soluble vitamin levels (Visit 20 only)
- A urine pregnancy test in all postmenarchal female adolescents (see Section 8.1.2 *Safety Assessments*)
- Dispensing of dietary supplements and collection of used dietary supplement bottles as needed (see Section 6.3 *Dietary Supplements*)
- Dispensing of study medication and collection of used study medication bottles as needed (see Section 7.2 *Treatment Schedule*).
- Study medication compliance check (see Section 6.2 *Investigational Product Compliance*)
- Record of concomitant medication including LLT and/or LA when applicable (see Section 7.6.1 *Concomitant Lipid-lowering Treatment* and Section 8.1.2 *Safety Assessments*)
- Enquiry about any AEs/SAEs and record in the AE section of the eCRF.

9.6 Unscheduled Visits

Unscheduled visits should be performed whenever necessary, e.g., in case of AEs or SAEs.

Evaluations and/or assessments should be performed, as deemed appropriate by the investigator based on the nature of the event prompting an unscheduled visit.

The results of all examinations during an unscheduled visit should be documented in the patient's file and should be recorded in the eCRF. If a patient is withdrawn from the study, all examinations scheduled for the EoT visit should be performed.

9.7 End of Treatment (Week 104±1 week), Visit 22

The EoT visit should be performed for all patients at Week 104 and should also be performed at any time if the patient is prematurely discontinued from the study. The patient must present in fasting state. The following procedures will be conducted:

- Complete physical examination of the patient (and a genitourinary, but not rectal exam at the investigator's discretion) including the documentation of height, weight, BMI, BSA and all clinically relevant findings, such as xanthomas (see Section 8.1.1 *Eligibility Assessments*)
- Determination of sexual maturation based on Tanner staging (see Section 8.1.1 *Eligibility Assessments* and Appendix 5 *Tanner Staging*)
- Record of 12-lead ECG (read locally, see Section 8.1.2 *Safety Assessments*)
- Collection of information in relation to the most recent standard of care echocardiography on file (if available, see Section 8.1.2 *Safety Assessments*)
- Measurement of vital signs and blood pressure (see Section 8.1.1 *Eligibility Assessments*)
- Pulmonary Function Test (see Section 8.1.2 *Safety Assessments*)
- NMR imaging of liver for hepatic fat assessment; if NMR imaging is contraindicated or not feasible (e.g., due to the need for sedation or general anaesthesia in very young or anxious patients), ultrasound scans will be used at the discretion of the investigator (see Section 8.1.2 *Safety Assessments*)
- Dietary counselling (see Section 8.6.1 *Diet Instructions and Diet Records*) as clinically indicated
- Collection of old 2-Day Diet records (see Section 8.6.1 *Diet Instructions and Diet Records*)
- Carotid intima-media thickness (CIMT, mandatory) and flow-mediated dilation (FMD, whenever possible) using ultrasound scan (see Section 8.4.2 *Assessment of Carotid Intima-Media Thickness and Flow-mediated Dilation*)
- Collection of blood samples for the following tests (see Section 8.1.2 *Safety Assessments*):
  - Complete blood count
  - Comprehensive metabolic panel
  - Liver function tests
  - Fasting lipid panel (see Section 8.3.1 *Fasting Lipid Panel*)
  - Serum levels of essential fatty acids
  - Serum lipase
  - Fat-soluble vitamin levels
  - Hormones (TSH, ACTH, serum cortisol [to be measured between 06:00 and 08:00 a.m.], FSH, LH)
  - In patients who are Tanner Stage ≥2, serum oestradiol will be assessed for female patients and serum testosterone will be assessed for male patients
- Urinalysis (urine colour, turbidity, pH, glucose, bilirubin, ketones, blood, protein, and white blood cells)
- A urine pregnancy test in all postmenarchal female adolescents (see Section 8.1.2 *Safety Assessments*)

- Collection of used dietary supplement bottles as needed (see Section 6.3 *Dietary Supplements*)
- Collection of used study medication bottles as needed (see Section 7.2 *Treatment Schedule*).
- Record of concomitant medication including LLT and/or LA when applicable (see Section 7.6.1 *Concomitant Lipid-lowering Treatment* and Section 8.1.2 *Safety Assessments*)
- Enquiry about any AEs/SAEs and record in the AE section of the eCRF.

9.8 Follow-up (Week 108), Visit 23

9.8.1 Visit 23 (Week 108)

Patients entering the EAP (<18 years of age)/transitioning to commercial product (≥18 years of age) will have a follow-up phone call at Week 108±1 week to monitor safety including AE and concomitant medication reporting. Patients who have opted not to participate in or are unsuitable for the EAP (<18 years of age)/opted not to transition to commercial product (≥18 years of age) will return for an in person safety Follow-up Visit at Week 108. The patient must present in fasting state. The following procedures will be conducted:

- Abbreviated physical examination (including a focused evaluation of general appearance, skin, thorax/lungs, CV, abdomen, and xanthomas) and record of height, weight, BMI, and BSA (see Section 8.1.1 *Eligibility Assessments*)
- Measurement of vital signs and blood pressure (see Section 8.1.1 *Eligibility Assessments*)
- NMR imaging of liver for hepatic fat assessment; if NMR imaging is contraindicated or not feasible (e.g., due to the need for sedation or general anaesthesia in very young or anxious patients), ultrasound scans will be used at the discretion of the investigator (see Section 8.1.2 *Safety Assessments*)
- Collection of blood samples for the following tests (see Section 8.1.2 *Safety Assessments*):
  - Complete blood count
  - Comprehensive metabolic panel
  - Liver function tests
  - Fasting lipid panel (see Section 8.3.1 *Fasting Lipid Panel*)
  - Serum levels of essential fatty acids
  - Fat-soluble vitamin levels
- Urinalysis (urine colour, turbidity, pH, glucose, bilirubin, ketones, blood, protein, and white blood cells)
- A urine pregnancy test in all postmenarchal female adolescents (see Section 8.1.2 *Safety Assessments*)
- Record of concomitant medication including LLT and/or LA when applicable (see Section 7.6.1 *Concomitant Lipid-lowering Treatment* and Section 8.1.2 *Safety Assessments*)
- Enquiry about any AEs/SAEs and record in the AE section of the eCRF.

10 COLLECTION, STORAGE AND SHIPMENT OF LABORATORY SAMPLES

The following laboratory tests will be performed at the local hospital laboratories to allow for taking therapeutic decisions upon availability of results:

1. Comprehensive Metabolic Panel: Na, K, Ca, carbon dioxide, Cl, BG, CRP, BUN, creatinine, CK, total protein, and albumin
2. Serum Lipase
3. Liver Function Tests: ALT, AST, GGT, AP, and total bilirubin including direct and indirect bilirubin
4. Fasting Lipid Panel: TC, LDL-C, VLDL-C, calculated Non-HDL-C, TG, apo B, Lp(a), HDL-C, and apo A-I

   Please note: Fasting lipid panels will also be analysed in the central laboratory specified in the '*Laboratory Manual*'. As the fasting lipid panel will be analysed at both the local hospital laboratory and the central laboratory, 2 separate samples must be drawn.
5. Complete Blood Count: White blood cell count, haemoglobin, haematocrit, platelet count, red blood cell count, red cell distribution width, MCV, MCH, and MCHC
6. Hormones: TSH, ACTH, serum cortisol, FSH and LH; the blood sample for testing of serum cortisol must be obtained in the early morning (6:00 to 8:00 a.m.)
7. Sex hormones (in patients who are Tanner Stage ≥2): serum oestradiol for female patients and serum testosterone for male patients
8. Urinalysis: urine colour, turbidity, pH, glucose, bilirubin, ketones, blood, protein, and white blood cells
9. Pregnancy Test: Urine pregnancy test strips will be provided to the sites for conducting urine pregnancy tests in female postmenarchal adolescent patients.

The following laboratory tests will be performed at the central laboratories specified in the '*Laboratory Manual*':

1. Genetic Testing: For those patients who have signed a separate ICF for genetic testing, a blood sample will be collected according to central laboratory procedures for genotyping specified in the *'Laboratory Manual'* at Screening (Visit 1) or at a later visit.
2. Fasting Lipid Panel: TC, LDL-C, VLDL-C, calculated Non-HDL-C, TG, apo B, Lp(a), HDL-C, and apo A-I

   Please note: As the fasting lipid panel will be analysed at both the local hospital laboratory and the central laboratory, 2 separate samples must be drawn. All samples will be kept for up to 2 years after the study is completed.
3. Fat-Soluble Vitamin Levels: Retinol, alpha tocopherol, 25-hydroxy-D, ratio of alpha tocopherol/total lipids (TC + fasting TG), ratio uncarboxylated osteocalcin/total osteocalcin
4. Serum Levels of EFA: Linoleic acid, ALA, AA, DHA, EPA, and eicosatrienoic acid
5. Pharmacokinetics: Lomitapide; pharmacokinetics will be sampled, processed and shipped to the central pharmacokinetics laboratory as described in the '*Laboratory Manual*'.
6. Liposcale® Test: The central laboratory specified in the *'Laboratory Manual'* will take aliquots from each PK sample for the exploratory Liposcale® Test, if sufficient sample material has been provided and would otherwise be discarded (see *'Laboratory Manual'* for further details). Neither additional blood sampling nor processing or shipping of separate samples for the Liposcale® Test will be required at the site.

11 DRUG SAFETY

The investigator is responsible for the detection and documentation of events meeting the definition of an AE or an SAE as provided in Section 11.1 *Definitions*. This includes the evaluation of its seriousness, its severity, and the causal relationship to the investigational product and/or concomitant therapy (see Section 11.2 *Recording of Adverse Events and Serious Adverse Events*).

At each visit, the patient and parent/legal guardian will be asked whether any AEs have occurred. A diagnosis of the event based on signs, symptoms and/or other clinical information should be established if possible. The diagnosis should be recorded as an AE and/or SAE in the corresponding section of the eCRF rather than the individual symptoms. If no diagnosis is known and neither clinical signs nor symptoms are present, the abnormal finding should be recorded.

The patient should be observed and monitored carefully until the AE has resolved, the condition has stabilised or its cause has been identified. The investigator will be responsible to ensure that follow-up will include any supplemental investigations that may be indicated to elucidate the nature and/or the cause of the event.

11.1 Definitions

The definitions in this section follow the tripartite harmonised International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines E6 '*Good Clinical Practice (GCP)'* and E2A '*Clinical Safety Data Management: Definitions and Standards for Expedited Reporting'*.

11.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal product, whether or not considered related to the medicinal product.

11.1.2 Adverse Drug Reaction

Adverse Drug Reactions (ADRs) are all noxious and unintended responses to a medicinal product related to any dose. The phrase 'responses to a medicinal product' means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All AEs judged by the reporting investigator or the sponsor as having a reasonable causal relationship to the study medication qualify as ADRs.

11.1.3 Unexpected Adverse Drug Reaction

If the nature or severity of the ADR is not consistent with the Lojuxta® SPC in lieu of an IB (Serious Adverse Reactions Expected in the Paediatric Population Table Page 1; see Section 18.1 *Source Documents*), it is an unexpected ADR.

11.1.4 Serious Adverse Event or Adverse Drug Reaction

Special medical or administrative criteria are needed to define reactions that, either due to their nature ('serious') or due to the significant, unexpected information they provide, justify expedited reporting.

Please refer to Section 11.2.2 *Assessment of Severity* for the difference between the terms 'serious' and 'severe'.

An SAE or serious ADR (SADR) is any untoward medical occurrence or effect that at any dose:

- Results in death (death is an outcome, the condition leading to death is the SAE)
- Is life-threatening

  The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical and scientific judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs may not be immediately life-threatening, result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above. These should also be considered serious.

11.1.5 Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a suspected adverse reaction related to the study medication that is both unexpected and serious.

The nature or severity of the unexpected ADR is not consistent with the Lojuxta® SPC in lieu of an IB (Serious Adverse Reactions Expected in the Paediatric Population Table Page 1; see Section 18.1 *Source Documents*).

If the investigator or the Medical Monitor judges an SAE not previously documented in the Lojuxta® SPC in lieu of an IB (Serious Adverse Reactions Expected in the Paediatric Population Table Page 1; see Section 18.1 *Source Documents*) to be related to study medication, the event will qualify as SUSAR and will be subject to expedited regulatory reporting.

11.1.6 Adverse Events of Special Interest

Adverse events of special interest (AESI) include the following:

- Hepatic, small bowel/intestinal, pancreatic and colorectal tumours
- Hepatic abnormalities
  - Elevations of hepatic transaminases resulting in discontinuation of lomitapide
  - Elevations of hepatic transaminases >3 x ULN that persist despite dose reduction or interruption
  - Elevations of hepatic transaminases ≥5 x ULN
  - Symptomatic liver injury
  - Other hepatic evaluation and testing or any histology obtained from liver biopsy and imaging evaluations
- Gastrointestinal effects
  - Events leading to permanent treatment discontinuations
  - Hospitalisation due to gastrointestinal events
  - Events triggering additional investigations such as endoscopy

- Major congenital anomalies

Enhanced Pharmacovigilance will include systematically collecting and reviewing AESIs. In addition to reporting AESIs within 15 calendar days (see Section 11.5.2 *Reporting of Adverse Events of Special Interest*), they will be discussed in relevant safety aggregate reports.

The AESIs will also be diligently followed-up with the investigators using specialised query follow-up forms and they will also be identified as potential signals that will be reviewed during routine monthly signal detection activities (see Section 11.5.2 *Reporting of Adverse Events of Special Interest*).

11.2 Recording of Adverse Events and Serious Adverse Events

The definitions in this section follow the '*Detailed Guidance on the Collection, Verification and Presentation of Adverse Event/Reactions Reports Arising from Clinical Trials on Medicinal Products for Human Use (CT-3)*' of the EC and the EMA '*Note for Guidance – EudraVigilance Human – Processing of Safety Messages and Individual Case Safety Reports (ICSRs)*.

11.2.1 Assessment of Seriousness

See Section 11.1.4 *Serious Adverse Event or Adverse Drug Reaction* for the definition of SAEs and SADRs.

11.2.2 Assessment of Severity

The severity of AEs will be evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (Section 18.1 *Source Documents*).

The terms 'severe' and 'serious' are not synonymous:

- **Severity:** The term 'severe' is often used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).
- **Seriousness:** The term 'serious' is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

If an AE term is not listed in the CTCAE classification, the severity of the event should be assessed as follows:

- **Grade 1 (mild):** The AE is noticeable to the patient but does not interfere with routine activity.
- **Grade 2 (moderate):** The AE interferes with routine activity but responds to symptomatic therapy or rest.
- **Grade 3 (severe):** The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy.
- **Grade 4 (life-threatening):** The patient is at immediate risk of death.
- **Grade 5 (death):** Death related to the AE.

11.2.3 Assessment of Causality

Careful medical judgment of the investigator is necessary to determine if there is a causal relationship between an AE and the investigational product.

If there are facts (evidence) or arguments to suggest a reasonable relationship between the AE and the investigational product, the investigator will make a determination of a **'reasonable causal relationship'**. In all other cases, there is a **'non-reasonable causal relationship'** between the AE and the investigational product.

To provide sufficient guidance for the investigator, which previously known assessments of causality now fall under the categories of 'reasonable causal relationship' and 'non-reasonable causal relationship', the former assessments of causality are listed below for information only. Please note that both the SAE forms and the eCRF will only offer the choice between 'reasonable causal relationship' and 'non-reasonable causal relationship'.

Former assessments of causality qualifying for 'reasonable causal relationship' (for guidance and information only):

- **Certain:** A clinical event, including laboratory test abnormality occurring in a plausible time relationship to drug administration, which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, using a satisfactory re-challenge procedure if necessary.
- **Probable:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfil this definition.
- **Possible:** A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Former assessment of causality qualifying for 'non-reasonable causal relationship' (for guidance and information only):

- **Unlikely:** A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration, which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

11.3 Monitoring Laboratory Assessments

Please refer to Section 10 *Collection, Storage and Shipment of Laboratory Samples* for laboratory tests that will be performed at the local hospital laboratories to allow for taking therapeutic decisions upon availability of results. The clinical laboratory values are to be reviewed by the investigator and classified as 'normal' or 'abnormal'. Abnormal laboratory values must in addition be classified as 'abnormal, clinically significant' or 'abnormal, not clinically significant'. The reason(s) for 'abnormal' findings should be documented. Abnormal, clinically significant findings occurring after first administration of study medication should be reported as an AE (unless already pre-existing at Baseline with the same severity).

Please note that fasting lipid panels will also be analysed in the central laboratory specified in the '*Laboratory Manual*' (see Section 10 *Collection, Storage and Shipment of Laboratory Samples*).

11.4 Documenting of Adverse Events and Serious Adverse Events

All information regarding AEs and SAEs, whether reported by the patient/parent/legal guardian or observed by the investigator, must be documented in the patient's medical record and recorded in the AE/SAE section of the eCRF. For SAEs, the paper SAE form in the investigator site file must also be completed (see Section 11.5.1 *Reporting of Serious Adverse Events*).

The investigator is responsible for recording and reporting AEs observed from the first dose of study medication (D0) until follow-up at Week 108.

All AEs occurring during Screening (i.e., after obtaining the patient's written consent, but before starting study medication) should be recorded in the Medical History/Current Medical

Conditions section of the eCRF, except those resulting from a protocol-mandated procedure, which should be reported in the AE/SAE section of the eCRF.

All patients will be followed-up for AEs/SAEs until the resolution or stabilisation of the AEs/SAEs. At the end of the study, the Medical Monitor will review all ongoing AEs/SAEs. For patients who enter the EAP, all ongoing AEs/SAEs will be followed up during the EAP. For all other patients, the Medical Monitor will determine appropriate follow-up required for any ongoing AEs/SAEs with the corresponding investigator for the respective patient.

If an investigator learns of an SAE to be reasonably related to study medication any time after study medication dosing has stopped, he/she should promptly notify the sponsor.

11.5 Immediately Reportable Information

11.5.1 Reporting of Serious Adverse Events

All SAEs should be reported immediately, i.e., within 24 hours of learning that the event meets the definition of an SAE. The investigator should complete the SAE report form in the investigator site file and send the initial SAE report within 24 hours to the Pharmacovigilance Department at **APH-19-Safety@emmes.com**.

If the SAE is fatal or life-threatening and is considered at least possibly related to the study medication, the completed SAE form should be sent to the Safety and Pharmacovigilance Department immediately.

The minimum information required for the initial SAE report is:

- Identifiable patient
- Identifiable reporter
- Investigational product
- Description of the event

If relevant information is missing at the time of the initial SAE report, the reporter should provide it in follow-up SAE report(s) upon availability. The follow-up report should contain new, updated or corrected information. It should further describe whether the event has resolved or continues, and if and how it was treated including documentation of all supportive actions taken.

11.5.2 Reporting of Adverse Events of Special Interest

All AESIs (see Section 11.1.6 *Adverse Events of Special Interest*) should be reported within 15 calendar days. The investigator should complete the AESI report form in the investigator site file and send the initial AESI report to the Pharmacovigilance Department at **APH-19-Safety@emmes.com.**

The minimum information required for the initial AESI report is:

- Identifiable patient
- Identifiable reporter
- Investigational product
- Description of the event

If relevant information is missing at the time of the initial AESI report, the reporter should provide it in follow-up AESI report(s) upon availability. The follow-up report should contain new, updated or corrected information. It should further describe whether the event has resolved or

continues, and if and how it was treated including documentation of all supportive actions taken.

All AESIs will be diligently followed-up using specialised query follow-up forms. They will be systematically collected, reviewed, and discussed in relevant safety aggregate reports. AESIs will be identified as potential signals that will be reviewed during routine monthly signal detection activities.

Specific hepatic and gastro-intestinal abnormalities, hepatic fibrosis, primary hepatic tumours, small bowel/intestinal or pancreatic tumours and major congenital abnormalities will be reported expeditedly.

11.5.3 Reporting Safety Observations by the Investigator to the IEC/IRB

At each clinical site, the Principal Investigator is responsible for promptly notifying the relevant IEC/IRB of the following information, as applicable:

- All SAEs and subsequent follow-up information.
- Any SAE reports and follow-up reports received from the sponsor or the sponsor's designee.

11.5.4 Other Reportable Information: Pregnancy

In the event that a patient is confirmed to be pregnant during the study or during follow-up, the investigational product must be discontinued immediately and permanently.

Any pregnancy or fathering of a child, which occurs up to 30 days within the last application of study medication should immediately be reported. The investigator will be asked to complete a pregnancy report provided by the sponsor. In addition, the investigator should provide follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome.

12 STATISTICAL ANALYSIS

12.1 Statistical Methods

The primary efficacy analysis will be conducted once all patients have completed (or withdrawn prior to Visit 10) at Week 24±3 days (End of the Efficacy Phase). The primary efficacy analysis will include the key primary/secondary efficacy data, all safety data available up to the data cut-off date of the last patient reaching Week 24±3 days, and PK parameter analysis. The reporting of Week 24±3 days data will allow for an early submission of an application for regulatory approval of Lojuxta® in the paediatric indication. The final statistical analysis will be performed when all patients have completed the Follow-up Visit (Visit 23) at Week 108±7 days. Efficacy, safety, and exploratory data collected during both the Safety Phase and follow-up will be included.

No interim efficacy analyses for efficacy and/or futility will be performed as outlined in Section 12.3.3 *Interim Analysis*.

12.1.1 Tests of Hypotheses and Significance Levels

The primary and secondary efficacy parameters collected during the Efficacy Phase of the study will be statistically tested using a 2-sided test at the 5% significance level.

To address the efficacy objectives, the efficacy parameters will be tested sequentially in a step-wise fashion, thereby controlling the overall type I error. First, the primary testing for percent change from Baseline in LDL-C at Week 24±3 days will be performed. If this test is statistically significant with a 2-sided $\alpha = 0.05$ and is statistically significant in a positive

direction, then the tests of the secondary hypotheses will be performed in the following specified order at Week 24±3 days:

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 is reached, further tests in the sequence will be performed and p-values will be reported as a measure of the strength of effect without declaring statistical significance.

Analysis of other secondary endpoints collected during the Efficacy Phase and of endpoints collected during the Safety Phase will be analysed without adjustment for multiplicity.

12.1.2 Determination of Sample Size

At least 30 evaluable patients (≥8 patients in each of the following age groups, determined by age at Baseline: 5 to 10 years, 11 to 15 years, and 16 to ≤17 years) are required at Week 24±3 days to provide 92% power, assuming a 25% reduction from Baseline in LDL-C with a standard deviation (SD) of 40% and a 2-sided α of 0.05. To allow for up to 33% dropout during the Efficacy Phase (prior to Week 24±3 days), an additional 15 patients will be enrolled, resulting in a total sample size of approximately 45 patients. Enrolment will be stratified to ensure approximately equal numbers of patients in the following age groups: 5 to 10 years, 11 to 15 years, and 16 to ≤17 years.

As a conservative assumption, the estimated 25% mean reduction represents approximately 60% of the 41% mean reduction from Baseline to Week 26/End of Efficacy Phase seen in the adult study UP1002/733-005, Intent-to-Treat (ITT) Population. This is the same assumption that was used for the sample size in the adult study. The SD represents an approximate 1/3 increase from the 31% SD observed in the adult study. This increase in SD was used to account for potentially increased variability across the 3 age groups.

12.2 Definition of Study Populations

The statistical analysis will be based on the following study populations:

- The safety analysis set (SAF) will include all patients treated with at least 1 dose of study medication. The SAF will be used for all safety analyses.
- The full analysis set (FAS) will include all patients in the SAF who receive at least 1 dose of study medication and who have a Baseline and at least 1 post-Baseline measurement of LDL-C. The FAS will be used for all efficacy analyses.
- All patients from the FAS will be assigned to a completer analysis set (CAS), if they have not discontinued the study during the Efficacy Phase (up to Week 24) irrespective of the reason for discontinuation. The CAS will be used for all efficacy analyses during the Efficacy Phase.
- Patients who reasonably adhered to all protocol conditions i.e., who have met the eligibility criteria and will have received planned study medication without important protocol deviations considered to have a serious impact on the efficacy results with the Efficacy Phase of the study, will constitute the per-protocol analysis set (PP). The PP will be used for supplementary efficacy analyses during the Efficacy Phase.

The data obtained will be used to check whether the study protocol was adhered to (e.g., inclusion and exclusion criteria, time windows, concomitant medication). Case-by-case decisions regarding exclusions of patients from the PP analysis will be made in a data review meeting.

Patients who are not treated will not be assigned to any of these analysis sets. All participants who pass Screening and enter the run-in period, irrespective of whether they received study medication, will be included in the Enrolled Set.

The FAS will serve as the primary population for the analysis of efficacy data in this study. Specifically, the primary, confirmatory endpoint analysis will be done using the FAS. In addition, efficacy analyses will be done using the PP and the CAS, serving as sensitivity analyses. Safety analyses will be conducted using the SAF.

12.3 Planned Analysis

Full details of the planned analyses will be documented in a Statistical Analysis Plan prior to database lock. The primary estimand will be a 'treatment policy' estimand which will be defined in the Statistical Analysis Plan.

12.3.1 Disposition and Exposure

Patient disposition, medical history, prior and concomitant medication use including current LLT and LA, and study medication exposure will be summarised.

12.3.2 Demographic Data and other Baseline Characteristics

Demographics and other Baseline characteristics will be summarised in total and by age group by means of summary statistics (number of patients, mean, standard deviation, minimum, median, maximum) for continuous variables and by absolute and relative frequencies for categorical variables. Baseline characteristics are defined as all results of the examinations performed prior to the first administration of study medication.

Relevant demographic and Baseline characteristics will be summarised using descriptive statistics. These variables include:

- Demographic variables: Age, gender, race, and ethnicity
- Baseline:
  - Height, weight, BMI, and BSA
  - LDL-C, TC, Non-HDL-C, VLDL-C, Lp(a), TG, and apo B
  - Disease characteristics

12.3.3 Interim Analysis

No interim efficacy analyses for efficacy and/or futility will be performed.

The primary efficacy analysis and final statistical analysis will be performed as described in Section 12.1 *Statistical Methods*.

An independent DSMB will periodically review the safety data as described in Section 4.3 *Data Safety Monitoring Board*.

12.3.4 Planned Analysis for Primary Endpoint

The primary efficacy endpoint, percent change from Baseline in directly measured LDL-C at Week 24±3 days, will be analysed using the one-sample t-test to test the null hypothesis that the percentage change from Baseline is equal to zero against the alternative hypothesis the percentage change from Baseline is not equal to zero. The percentage change at

Week 24±3 days, together with the corresponding 2-sided 95% confidence interval and p-value will be presented. Missing data will be imputed using last observation carried forward (LOCF). The analysis will be based on the FAS Population.

A sensitivity analysis will be performed using a Mixed Model Repeated Measures (MMRM) model with the missing at random assumption (i.e., missing data will not be imputed using LOCF or any other method). The analysis will be based on the FAS Population.

Supplementary analyses will include the one-sample t-test and summaries based on the PP and CAS.

Sub-group analyses will be conducted using an Analysis of Covariance (ANCOVA) model to estimate the mean percentage change and 2-sided 95% confidence intervals within each sub-group at Week 24±3 days. Sub-group analyses will be performed for the 3 age groups and also based on documented CVD history, established CVD history, concomitant LLT medication, and dose reduction of study medication. These analyses will be based on the FAS Population.

12.3.5 Planned Analysis for Secondary Endpoints

The secondary lipid parameter endpoints will be analysed as described for the primary endpoint in Section 12.3.4 *Planned Analysis for Primary Endpoint*.

As secondary analyses of the pattern of LDL-C and lipid parameter change over time, a MMRM model will be used, including all available data (all visits from Baseline through Week 104±1 week). Observed changes and percent changes from Baseline at each timepoint will be summarised.

Number and percentage of patients treated with standard LLT (including LA when applicable) will be summarised overall and by age group. Any dose increases of standard LLT/increased frequency of LA will be summarised.

Number and percentage of patients with LDL-C falling below the target level will be summarised by study visit at any time up to Week 24±3 days and at any time up to Week 104 by age group and overall.

12.3.6 Planned Analysis for Safety Endpoints

Safety will be assessed using the SAF Population, including all patients who receive any amount of study medication, and will be based on evaluation of AEs, laboratory data, vital signs and physical examination findings, height, weight, BSA and BMI, ECG, echocardiography (if available) and hepatic fat. Safety data summary statistics will be presented overall and by age group.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarisation. All AEs occurring during the study will be included in by-patient data listings and will be summarised overall and by age group. Events leading to death, SAEs, and events resulting in study discontinuation will be summarised. Adverse events of special interest, such as hepatobiliary AEs and hepatotoxicity of different levels, will be summarised (see Section 11.1.6 *Adverse Events of Special Interest*).

Reported clinical laboratory results and changes from Baseline will be summarised using descriptive statistics overall and by age group. Shift tables and summaries of potentially clinically significant findings will be presented. Reported values and changes from Baseline for vital signs, ECG findings, and echocardiography (if available) will be summarised by time point overall and by age group. For lipid accumulation in the liver, the number and percentage of patients with liver fat content ≤10%, >10% and ≤20%, and >20% will be summarised overall and by age group. Changes from Baseline over time will be presented in shift tables for ECG results, echocardiography (if available) and lipid accumulation in the liver.

To assess sexual maturation, changes from Baseline in Tanner staging results will be presented in shift tables and graphically.

12.3.7 Planned Analysis for Exploratory Endpoints

The percentage change from Baseline in mean CIMT and mean FMD at Week 56±3 days and at Week 104±1 week will be assessed overall and by age group.

The number and percentage of patients with (tendon/cutaneous) xanthomas present, and locations, will be summarised overall and by age group at Baseline, Week 56±3 days and Week 104±1 week. The number and percentage of patients with resolution and regression of pre-existing xanthoma (Baseline) to Week 56±3 days and Week 104±1 week will be summarised overall and by age group.

Changes from Baseline in parameters assessed by the Liposcale® Test will be summarised at Week 4±3 days, Week 8±3 days, Week 12±3 days, Week 16±3 days, Week 20±3 days and at Week 24±3 days.

12.3.8 Planned Analysis for Palatability Endpoints

The number and percentage of patients responding to each question regarding palatability will be presented over time overall and by age group.

12.3.9 Planned Analysis for Pharmacokinetic Endpoint

PK data will be used in population PK/PD modelling for the lomitapide program. This will be described in a separate document.

12.4 Statistical Criteria for Study Termination

No interim analysis for futility will be performed. Therefore, no criteria for early termination of the study from a statistical perspective are considered.

12.5 Handling of Missing Data

Care will be taken during the conduct of this study to minimise the amount of missing data. The FAS will be used for the primary analysis of all efficacy endpoints. Each patient in the FAS will have a Baseline value and at least one post-Baseline value. Because this is a single-arm study, for patients who have missing data at the time point of interest, the LOCF approach will be used in all Efficacy Phase analyses. However, for the fasting lipid panel, it is not appropriate to carry forward Screening/run-in period values if a Baseline value is missing as this value would be obtained prior to stabilisation of the patient on LLT so LOCF will not be used for these analyses.

12.6 Time Windows

Data as evaluated during regular visits will be analysed in accordance to the respective visit. Time window violations will only be considered for lipid data analyses and for analyses using the PP. Visit windows will be defined in the Statistical Analysis Plan. A data review meeting will be performed prior to data base lock and it may be decided to exclude single visits from the PP analyses due to time window violation. For time to event analyses, the exact visit dates and D0 will be taken for calculating the time to event.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Pre-study Documentation

Prior to enrolment of patients at a study site, specific regulatory documents must be available, such as Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval and curricula vitae of investigators and study staff. Amryt Pharmaceuticals DAC will inform the investigator which documents need to be provided according to the applicable regulatory requirements.

13.2 Monitoring

Amryt Pharmaceuticals DAC will appoint qualified and appropriately trained persons to monitor the study and the FU. Monitors will periodically contact the site and perform site visits in accordance with applicable regulations, GCP and Amryt Pharmaceuticals DAC approved procedures. Study objectives, study design, and enrolment rate will determine the extent, nature and frequency of site visits.

The monitor will contact the site before the start of the study to discuss the protocol and data collection procedures with the site study team members.

During site visits, the monitor will:

- Check and assess the progress of the study
- Review study data collected
- Perform source data verification
- Identify any issues and address their resolution

Aim of the site visits is to verify that:

- The data are authentic, accurate and complete
- The safety and rights of patients are being protected
- The study is conducted in accordance with the approved protocol (and any subsequent amendment), GCP and all applicable regulatory requirements

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

The study monitor will record any protocol deviations identified, including, but not limited to, patients that were enrolled even though they did not meet all eligibility criteria, patients who took concomitant medications specifically prohibited by the protocol, patients who received an incorrect dose of study medication, and patients who failed to comply with the protocol-defined dietary restrictions. The Investigator and study team members will collaborate with the study monitor to identify the reason for each protocol deviation.

At study closure, the monitor will conduct all activities as indicated in Section 13.4 *Study and Site Closure*.

13.3 Data Management and Processing

Amryt Pharmaceuticals DAC is responsible for data quality control. Each study site is responsible for the data documentation and for the maintenance of patient files.

13.3.1 Data Collection

The investigator or an authorised delegate from the study staff will have to complete an eCRF for each patient enrolled including patients who discontinue prematurely. If a patient withdraws from the study, the reason should be noted in the eCRF if possible. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

13.3.2 Data Management Procedures

A separate '*Data Management Plan*' will detail data management vendors, systems and processes.

13.3.3 Data Verification Procedures

Data will be checked systematically according to a pre-specified '*Data Validation Plan*' after they have been entered into the study database. Queries will be created for errors or missing data and clarified by the study monitor at the investigational site.

13.3.4 Coding

All AEs and concomitant diseases will be coded according to MedDRA and all concomitant or previous medication based on the World Health Organization (WHO) Drug Dictionary.

13.3.5 Procedures for Analysis of Consistency and Medical Plausibility

A data review meeting will be conducted as soon as all data of the study and the follow-up period has been entered into the eCRF and the database has been confirmed as 'clean'. After resolution of all remaining queries, the Statistical Analysis Plan will be finalised and the database will be locked. All changes to the data will be kept in an audit trail.

13.3.6 Data to be Recorded Directly into the Electronic Case Report Form

The eCRF will serve as source document for the ethnic origin, which will only be recorded for the study.

13.4 Study and Site Closure

Upon completion of the study or premature study (site) closure, the monitor and the investigator will be responsible for

- Return of all study data to Amryt Pharmaceuticals DAC
- Data clarification and/or resolution
- Accounting, reconciliation and return of used and unused study medication
- Review of study site records for completeness
- Return of all study specific equipment to Amryt Pharmaceuticals DAC

Amryt Pharmaceuticals DAC reserves the right to suspend or prematurely discontinue this study at either a single site or at all sites at any time for any reason. Amryt Pharmaceuticals DAC will inform the investigator(s), the IECs/IRBs, and the regulatory authorities if the study will be suspended or stopped prematurely.

13.5 Audits and Inspections

Amryt Pharmaceuticals DAC or its designee may conduct a quality assurance audit of this study to evaluate compliance with the protocol and the principles of GCP. The investigator agrees to allow the auditor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor to discuss findings and any relevant issues.

Regulatory agencies may conduct a regulatory inspection of this study. If a regulatory authority requests an inspection, the investigator must inform Amryt Pharmaceuticals DAC immediately about this request. The investigator agrees to allow the inspector(s) direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the inspector(s) to discuss findings and any relevant issues.

14 LEGAL AND ETHICAL REQUIREMENTS

This study will be conducted in accordance with the harmonised tripartite ICH Guidelines for GCP and all applicable laws and regulations, including the Declaration of Helsinki, June 1964, as modified by the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013 (see Appendix 7 *Declaration of Helsinki*).

14.1 Regulatory Authority Approval

Documents required for the application of this study will be submitted to the responsible competent authority according to the applicable country-specific laws and regulations. The study will not start until the competent authority authorises the study.

14.2 Independent Ethics Committee/Institutional Review Board

This protocol, any amendments if applicable, any material provided to the patient (such as patient information, informed consent form and patient questionnaires) as well as additional documents, which may be required by national regulations and the IEC/IRB, will be submitted to the competent IEC/IRB for review and approval.

Written approval from the IEC/IRB must be obtained before starting the study, and must be documented in a letter specifying the date on which the IEC/IRB met and granted the approval. The IEC/IRB approval letter must identify all documents approved by listing the study number, study title, study sites/investigators, date and version of study protocol, date and version of patient information/informed consent form. A list of IEC/IRB members should be attached to the approval letter.

Any subsequent modifications made to the protocol or to any other documents that must be reviewed by the IEC/IRB must also be submitted to the IEC/IRB in accordance with local procedures and regulatory requirements.

14.3 Patient and Parent/Legal Guardian Information and Informed Consent

In addition to information sheets and consent/assent forms for patients (according to applicable local regulations), parent/legal guardian information sheets and consent forms will be prepared.

The investigator will explain the aims, methods, objectives and potential risks and benefits of the study to the patient and the parent/legal guardian and will obtain written informed consent/assent from the patient (according to applicable local regulations) and written informed consent from the parent/legal guardian before he/she will initiate any study-specific procedure.

The patient and the parent/legal guardian will have sufficient time to ask and resolve any questions pertaining to participation in the study, and to consider study participation. In the

event that a patient is unable to read or will only be able to provide verbal informed consent, the parent/legal guardian may act on the patients' behalf.

The investigator will also explain to the patient and the parent/legal guardian that the patient will be free to refuse entering the study or to withdraw from it at any time for any reason. Neither the refusal to give consent nor the withdrawal of consent will result in discrimination of the patient, in particular regarding his/her subsequent medical treatment.

The patient (according to applicable local regulations) and the parent/legal guardian will be asked to review, sign, and date the informed consent form. He/she will receive a copy of the signed informed consent form, including the investigator's signature. The investigator will retain the original document.

The eCRF for this study will contain a section for documenting informed patient consent, which needs to be completed appropriately. The consent form will be reviewed and updated if the risk/benefit assessment changes or if amendments to the protocol affect the patients' participation in the study. All patients (including those already being treated) and their parents/legal guardians will be informed about the new information. Patients are only allowed to further participate in the study if they and their parents/legal guardians agree to sign the amended form, indicating that they reconsent to participate in the study.

14.4 Data Protection

Medical information about individual patients obtained in the course of this study is confidential and may not be disclosed to third parties, except authorised monitors, auditors or inspectors. Confidentiality will be ensured by the use of patient numbers for the identification of each patient; these patient numbers will also be used for patient data in the patient files and eCRFs. The investigator should keep a patient enrolment log showing codes, names and addresses and should maintain documents, e.g., patients' written consent forms, in strict confidence.

14.5 Notification of Primary Care Physician

The investigator should notify the patients' primary care physician of the patients' participation in the study, if applicable and agreed by the patient and his/her parent/legal guardian.

14.6 Investigator Reporting Requirements

The investigator will ensure that site study team members will promptly bring AEs/SAEs to his/her attention. He/she will report all AEs/SAEs as described in Section 11.4 *Documenting of Adverse Events and Serious Adverse Events* and Section 11.5 *Immediately Reportable Information*. The investigator will inform his/her IEC/IRB of any SAE in accordance with the local reporting requirements.

14.7 Record Retention

Upon closure of the study, the investigator/study site will maintain a copy of all study records in a safe and designated location at the study site in accordance with applicable regulatory requirements. Amryt Pharmaceuticals DAC will inform the investigator/study site of the time for retaining these records to comply with applicable regulatory requirements.

Essential documents as defined in the ICH E6 Guideline of GCP must be retained until

- 2 years after the last approval of a marketing application in an ICH region
- There are no pending or contemplated marketing applications in an ICH region
- 2 years will have elapsed since the formal discontinuation of clinical development of the investigational product
- Longer if required by the applicable regulatory requirement(s)/the sponsor

Unless other Union law (outside of the EU) requires archiving for a longer period, the sponsor and the investigator will archive the content of the clinical trial master file for at least 25 years after the completion or discontinuation of the study. The medical files of patients will be archived in accordance with local regulations.

15 PROTOCOL AMENDMENTS

All protocol amendments must be submitted to the competent IECs/IRBs and Regulatory Agencies for information and/or approval in accordance with local requirements. If applicable, approval must be awaited before changes can be implemented, except for changes necessary to eliminate an immediate hazard to patients.

16 DISCLOSURE OF INFORMATION

All data and records generated during the study except for patient medical records and all inventions discovered in the course of conducting the study, whether patentable or not, are the sole and exclusive property of Amryt Pharmaceuticals DAC.

The investigator and site study team members will keep strictly confidential any information provided by Amryt Pharmaceuticals DAC related to this study and all data and records generated in the course of conducting the study. They will not use the information, data or records for any other purpose than conducting the study without prior written approval of Amryt Pharmaceuticals DAC.

Amryt Pharmaceuticals DAC will prepare an integrated clinical study report in accordance with the harmonised tripartite ICH E3 Guideline '*Structure and Content of Clinical Study Reports'* after completion of the study.

16.1 Publication of Study Findings

Negative and positive results of this study will be presented at scientific meetings and/or will be published in a peer reviewed scientific or medical journal. By signing the clinical study agreement, the investigator agrees that the results of the clinical study may be used for publication. The first publication or disclosure shall be a complete, joint multi-centre publication or disclosure. Authorship will be discussed with all parties involved, depending on such considerations as recruitment. A premature publication or disclosure of partial results is not possible.

The investigator(s) may use the scientific data generated during the study for non-commercial purposes, e.g., for scientific publications of any kind only after prior written consent of Amryt Pharmaceuticals DAC. The investigator(s) will allow Amryt Pharmaceuticals DAC to review the proposed publication or disclosure prior to submission for publication, presenting, using for instructional purposes or otherwise disclosing the results of the study.

If Amryt Pharmaceuticals DAC supposes the proposed publication or disclosure to risk Amryt's ability to patent any invention related to the study, the publication or disclosure will be modified or delayed to allow Amryt Pharmaceuticals DAC to file a patent application.

17 COMPENSATION FOR INJURIES

Insurance coverage for damages emerging from the study and involving study patients treated with the study medication will be provided according to applicable legal requirements. The investigator must inform the patient and parent/legal guardian accordingly and must point out that the patient should seek the investigators' consent before undergoing other medical treatment, whenever possible. The investigator will advise patients and parents/legal guardians that they must inform the investigator immediately of any injury that might have been caused by study participation.

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19 APPENDICES

Appendix 1 Child-Pugh Score

Parameter	Points		
	1	**2**	**3**
Encephalopathy	None	Mild to moderate (CTCAE Grade 1/2)	Severe (CTCAE Grade 3/4)
Ascites	None	Mild to moderate (Diuretics responsive)	Severe (Diuretics refractory)
Bilirubin (mg/dL)	<2	2 to 3	>3
Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Prothrombin time			
• Seconds prolonged	<4	4 to 6	>6
• International normalised ratio	<1.7	1.7 to 2.3	>2.3
Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A	5 to 6 points	(least severe liver disease)	
Class B	7 to 9 points	(moderately severe liver disease)	
Class C	10 to 15 points	(most severe liver disease)	

Sources:

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Appendix 2 Schwartz Formula

$$GFR\ (mL/\min per\ 1.73\ m^2) = 39.1 \left[\frac{height\ (m)}{Scr\ (\frac{mg}{dL})}\right]^{0.516} x \left[\frac{1.8}{cystatin\ C\ (\frac{mg}{L})}\right]^{0.294} [1.099]^{male} \left[\frac{height\ (m)}{1.4}\right]^{0.188}$$

Bedside calculation of 0.413*(height/serum creatinine) provides a good approximation to the estimated GFR formula.

Source: G. J. Schwartz, A. Munoz, M. F. Schneider, R. H. Mak, F. Kaskel, B. A. Warady, S. L. Furth: New Equations to Estimate GFR in Children with CKD. Journal of the American Society of Nephrology 2009, Volume 20, Issue 3, P. 629-637.

Appendix 3 Common Terminology Criteria for Adverse Events (CTCAE), Hepatobiliary Disorders

Hepatobiliary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Bile duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Severely altered GI function; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the bile duct. **Navigational Note:** -					
Biliary fistula	-	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the bile ducts and another organ or anatomic site. **Navigational Note:** -					
Budd-Chiari syndrome	-	Medical management indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; asterixis; mild encephalopathy	Life-threatening consequences; moderate to severe encephalopathy; coma	Death
Definition: A disorder characterized by occlusion of the hepatic veins and typically presents with abdominal pain, ascites and hepatomegaly. **Navigational Note:** -					
Cholecystitis	-	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation involving the gallbladder. It may be associated with the presence of gallstones. **Navigational Note:** -					
Gallbladder fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the gallbladder and another organ or anatomic site. **Navigational Note:** -					
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gallbladder. **Navigational Note:** -					

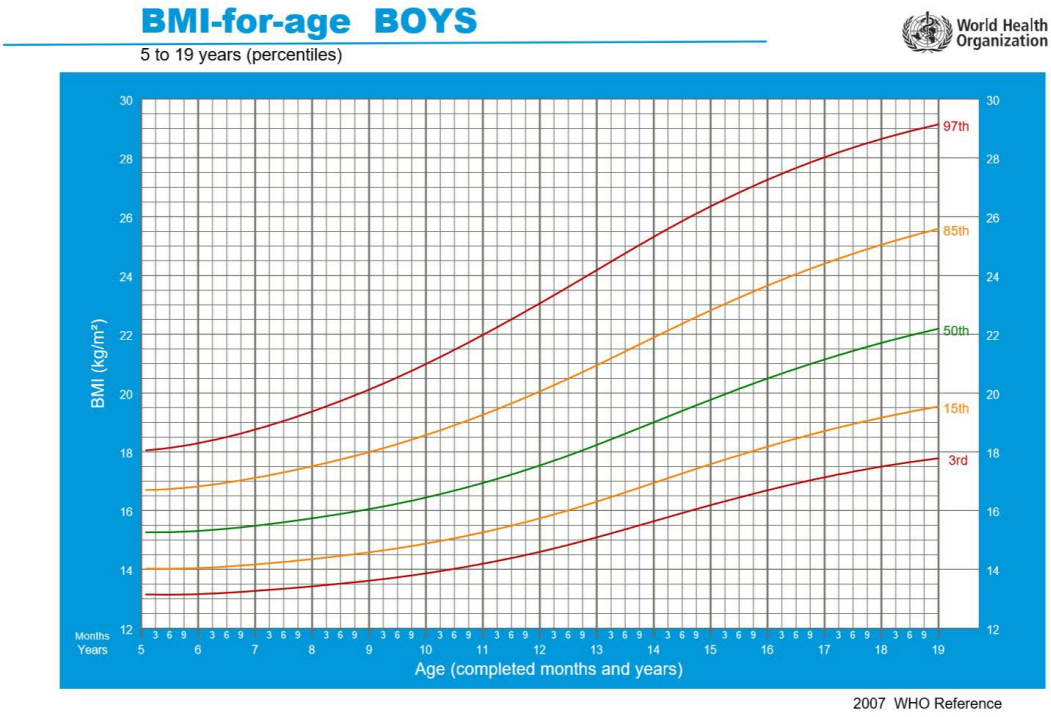
Hepatobiliary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Gallbladder obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents of the gallbladder. **Navigational Note:** -					
Gallbladder pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gallbladder region. **Navigational Note:** -					
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the gallbladder wall. **Navigational Note:** -					
Hepatic failure	-	-	Asterixis; mild encephalopathy; drug-induced liver injury (DILI); limiting self care ADL	Life-threatening consequences; moderate to severe encephalopathy; coma	Death
Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, alkaline phosphatase, aminotransferase, and/or prolongation of prothrombin time (INR.) Drug-induced liever injury (DILI) as defined by Hy's Law. **Navigational Note:** -					
Hepatic hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the liver. **Navigational Note:** -					
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma. **Navigational Note:** -					

Hepatobiliary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hepatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the liver region. **Navigational Note:** -					
Perforation bile duct	-	-	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the extrahepatic or intrahepatic bile duct. **Navigational Note:** -					
Portal hypertension	-	Decreased portal vein flow	Reversal/retrograde portal vein flow; associated with varices and/or ascites	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in blood pressure in the portal venous system. **Navigational Note:** -					
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the formation of a thrombus (blood clot) in the portal vein. **Navigational Note:** -					
Sinusoidal obstruction syndrome	-	Blood bilirubin 2-5 mg/dL; minor interventions required (i.e., blood product, diuretic, oxygen)	Blood bilirubin >5 mg/dL; coagulation modifier indicated (e.g., defibrotide); reversal of flow on ultrasound	Life-threatening consequences (e.g., ventilatory support, dialysis, plasmapheresis, peritoneal drainage)	Death
Definition: A disorder characterized by severe hepatic injury as a result of the blood vessels of the liver becoming inflamed and/or blocked. **Navigational Note:** -					
Hepatobiliary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Source: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 dated 27 November 2017, U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf, accessed 01 September 2020

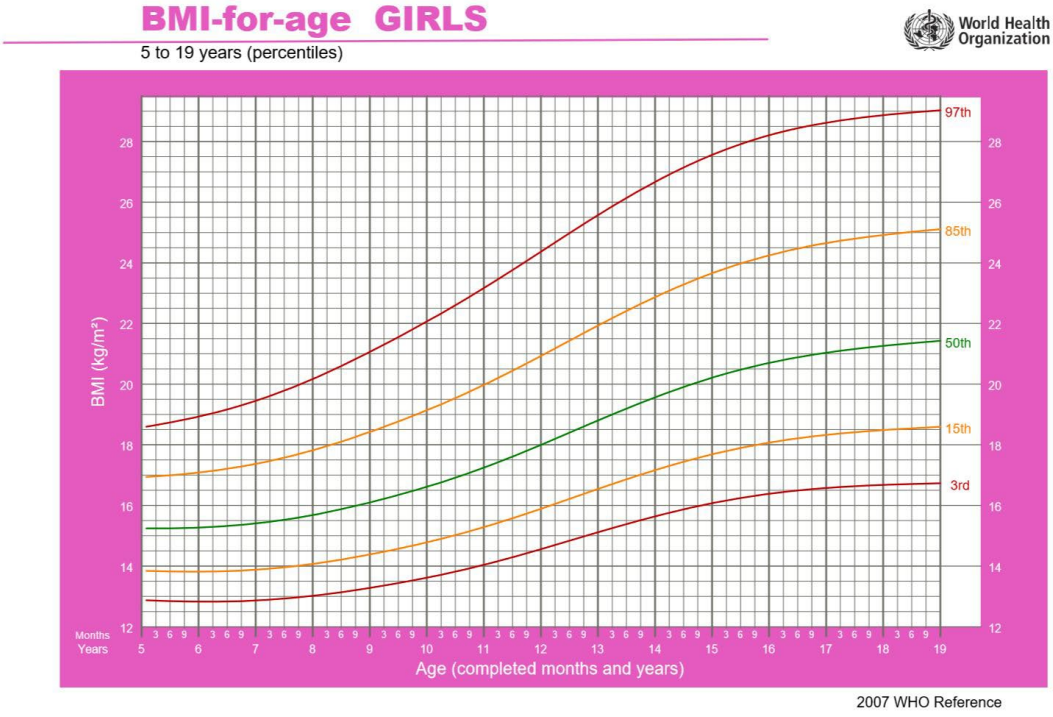
Appendix 4 WHO Growth Charts for Boys and Girls 5 to 19 Years of Age

Appendix-Figure 1 BMI-For-Age, Boys, 5 to 19 Years of Age



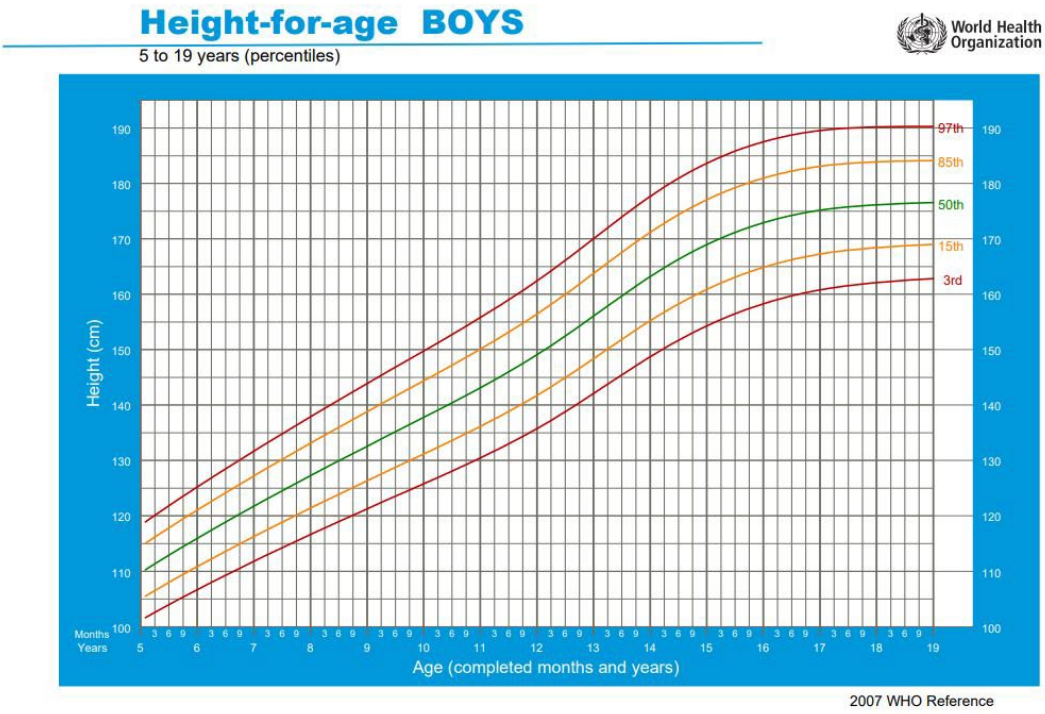
Source: https://www.who.int/growthref/cht_bmifa_boys_perc_5_19years.pdf, accessed 01 September 2020

Appendix-Figure 2 BMI-For-Age, Girls, 5 to 19 Years of Age



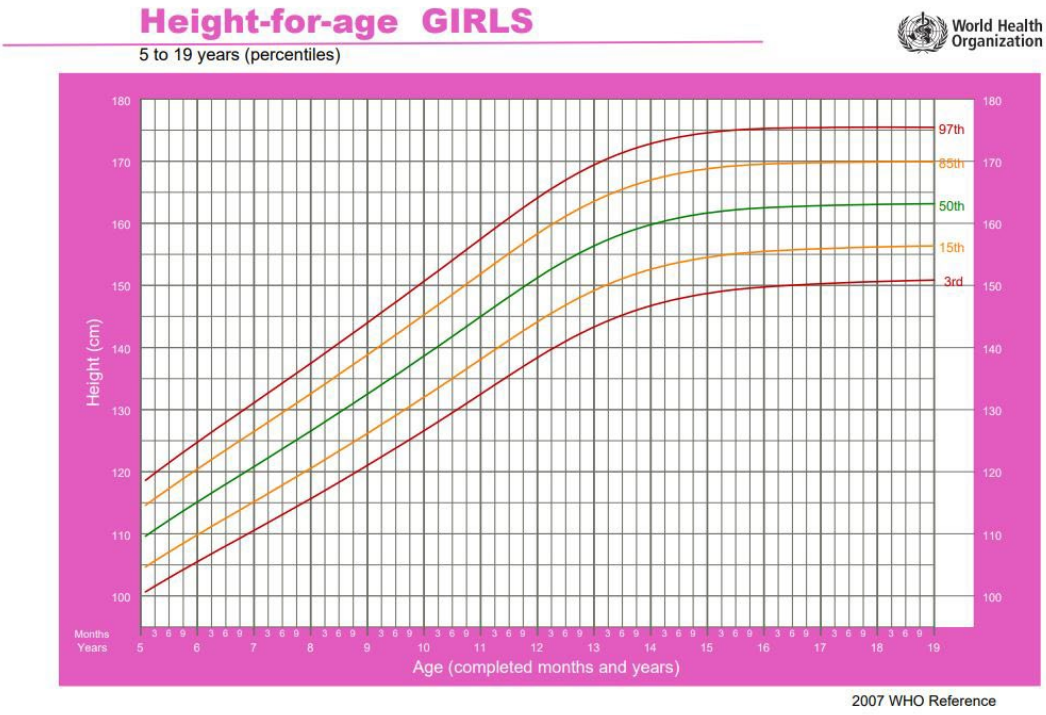
Source: https://www.who.int/growthref/cht_bmifa_girls_perc_5_19years.pdf, accessed 01 September 2020

Appendix-Figure 3 Height-For-Age, Boys, 5 to 19 Years of Age



Source: https://www.who.int/growthref/cht_hfa_boys_perc_5_19years.pdf, accessed 01 September 2020

Appendix-Figure 4 Height-For-Age, Girls, 5 to 19 Years of Age



Source: https://www.who.int/growthref/cht_hfa_girls_perc_5_19years.pdf, accessed 01 September 2020

Appendix 5 Tanner Staging

Appendix-Table 1 Classification of Sex Maturity Stages in Girls

Stage	Pubic Hair	Breasts
1	Preadolescent	Preadolescent
2	Sparse, lightly pigmented, straight, medial border of labia	Breast and papilla elevated as small mound, areolar diameter increased
3	Darker, beginning to curl, increased amount	Breast and areola enlarged, no contour separation
4	Coarse, curly, abundant but amount less than adult	Areola and papilla form secondary mound
5	Adult feminine triangle, spread to medial surface of thighs	Mature, nipple projects, areola part of the general breast contour

Appendix-Table 2 Classification of Sex Maturity Stages in Boys

Stage	Pubic Hair	Penis	Testes
1	None	Preadolescent	Preadolescent
2	Scanty, long, slightly pigmented	Slight enlargement	Enlarged scrotum, pink texture altered
3	Darker, starts to curl, small amount	Longer	Larger
4	Resembles adult type but less in quantity; coarse, curly	Larger, glans and breadth increase in size	Larger, scrotum dark
5	Adult distribution, spread to medial surface of thighs	Adult size	Adult size

Sources:

W. A. Marshall, J. M. Tanner: Variations in pattern of pubertal changes in girls. In: Archives of Disease in Childhood 1969, Volume 44, P. 291–303.

W. A. Marshall, J. M. Tanner: Variations in pattern of pubertal changes in boys. In: Archives of Disease in Childhood 1970, Volume 45, P. 13–23.

Appendix 6 Laboratory Tests

Category, Panel	Parameters
Haematology	
• Complete Blood Count (CBC)	Haematocrit
	Haemoglobin
	Mean corpuscular haemoglobin (MCH)
	Mean corpuscular haemoglobin concentration (MCHC)
	Mean corpuscular volume (MCV)
	Platelet count
	Red blood cell count
	Red cell distribution width
	White blood cell count
Serum chemistry	
• Metabolic panel	Albumin
	Blood glucose (BG)
	Blood urea nitrogen (BUN)
	Calcium (Ca)
	Carbon dioxide
	Chloride (Cl)
	Creatinine
	Creatinine kinase (CK)
	C-reactive protein (CRP)
	Potassium (K)
	Sodium (Na)
	Total protein
	Serum lipase
• Fasting lipid panel	apolipoprotein A-I (apo A-I)
	apolipoprotein B (apo B)
	High-density lipoprotein cholesterol (HDL-C)
	Lipoprotein(a) [Lp(a)]
	Low-density lipoprotein cholesterol (LDL-C)
	Non high-density lipoprotein cholesterol (Non-HDL-C)
	Total cholesterol (TC)
	Triglycerides (TG)
	Very low-density lipoprotein cholesterol (VLDL-C)
• Liver function tests (LFTs)	Alanine aminotransferase (ALT)
	Aspartate aminotransferase (AST)
	Alkaline phosphatase (AP)
	Gamma-glutamyl transferase (GGT)
	Total bilirubin
	Direct bilirubin
	Indirect bilirubin
• Essential fatty acids (EFA)	Arachidonic acid (AA)

Category, Panel	Parameters
• Essential fatty acids (EFA)	Alpha linoleic acid (ALA)
	Docosahexaenoic acid (DHA)
	Eicosapentaenoic acid (EPA)
	Eicosatrienoic acid
	Linoleic acid
• Fat-soluble vitamin levels	Retinol (Vitamin A)
	25-hydroxy-D (Vitamin D)
	Alpha tocopherol (Vitamin E)
	Ratio alpha tocopherol/total lipids
	Ratio uncarboxylated osteocalcin/total osteocalcin
• Hormones	Thyroid stimulating hormone (TSH)
	Adrenocorticotrophic hormone (ACTH)
	Serum cortisol[L]
	Follicle stimulating hormone (FSH)
	Luteinising hormone (LH)
• Sex hormones (Tanner Stage ≥2)	Serum testosterone
	Serum oestradiol
• Pharmacokinetics	Lomitapide
Urine	
• Urinalysis	Bilirubin
	Blood
	Colour
	Glucose
	Ketones
	pH
	Protein
	Turbidity
	White blood cells
• Urine pregnancy test	

Appendix 7 Declaration of Helsinki

World Medical Association Declaration of Helsinki
Ethical Principles for Medical Research
Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician

or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.
20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be

performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

    and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.