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

AMRYT Pharmaceuticals DAC Study No: APH-19
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Statistical Analysis Plan

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Modification History

Version	Change History	Reason	Date
1.0	First Version	N/A	14APR2022
2.0	Updated to Second Version	• To accommodate protocol version no 6 and PIP modification approved 01 August 2022. • Add additional palatability objectives from the protocol that were omitted in error from the SAP. • Added age group definition for clarity so now 2 groups (age 5 to 10 years; 11 to 17 years) for analyses. • Added profile plots for displaying adverse events. • Added profile plots for liver function tests. • Added scatter plots for lipid accumulation in the liver. • Added waterfall and spaghetti plots for BMI / weight over time. • Added additional subgroup analysis for reach MTD / not reach MTD. • Amend subgroup analysis for LLT to LLT meds (excluding LA) vs LLT meds (including LA).	01SEP2022
3.0	Updated to Third Version	• Update analysis visit windows (section 5.3) to define analysis study weeks and nominal study visit. • Update patient disposition (section 5.6) to include summary of subject study visits. • Update demography and baseline (section 5.8.1) to include summary for country, HDL and Apo A1, • Update prior and concomitant medications (section 5.9) to combine prior and 'run-in' period. • Update study treatment exposure (section 5.10) to define average daily exposure (mg/day). • Update primary analysis (section 5.11.1.1) to clarify methods for analysis study week window and additional sensitivity analysis using nominal study visit.	02DEC2022

4.0	Updated to Fourth Version	• Minor typo and format corrections. • To accommodate protocol version no 7 approved 09 February 2023. • Updated visit windows to add window for the follow-up visit. • Amended definition of completer analysis set (section 5.4). • Addition of TC/HDL-C ratio as secondary endpoint. • Add additional exploratory endpoints for the 2023 EAS and 2018 American College of Cardiology LDL-C recommended target levels. • Clarification of the process of determination of compliance with LLT. • Update demography and baseline lipids (section 5.8.1) to include TC/HDL-C ratio and LDL receptor function classification. • Update exposure (section 5.10) to include summaries of duration on maintenance dose, IMP distribution over time, compliance to IMP and time to first dose interruption and discontinuation analyses. • Addition of a summary of Lipoprotein apheresis regimen and days from LA to LDL-C assessment. • Update primary and secondary endpoint (section 5.11.1 and 5.11.2) to include sensitivity analysis using baseline observation carried forward, responder analysis and an additional subgroup analysis based on sex. • Update adverse events (section 5.13.1) to include additional summaries for most frequent TEAEs and by AESI group. Addition of analysis for time to first gastrointestinal and hepatic TEAE. Addition of subgroups based on sex and compliance with low-fat diet. • Update clinical laboratory evaluation (section 5.14) to add additional summaries for liver function test. • Update vital signs (section 5.15) to include percentage change and plots over time. • Addition of summary of number of subjects with worsening from baseline in echocardiography (section 5.17) assessment. • Update lipid accumulation in the liver (section 5.18) to include additional analyses based on NMR data and analysis of number of subjects with increases in hepatic fat. Addition of scatter plots to assess correlation between liver function tests and hepatic fat. Addition of sensitivity analyses to assess the impact of a different NMR scan on Site 12. • Update physical examination (section 5.19) to include waterfall plots of change in BMI-Z-score by baseline BMI for age Z score, maximum weight loss and maximum z-score and spaghetti plots to assess the evolution of weight and Z-scores over time. • Update diet and dietary supplement compliance (section 5.21) to include a summary of compliance with diet and dietary supplement compliance by study phase.	04MAR2024

		• Update Xanthoma assessment (section 5.24.1) to include a cumulative summary of changes to pre-existing xanthoma by dose group.	
5.0	Updated to Fifth Version	• Addition of HDL-C as secondary endpoint (section 2.3.2 and 5.11.2.2). • Section 5.9, cosmetic updates and addition of a summary for subjects taking >= 2 and >=3 LLT during run-in. • Addition of Wilcoxon-Signed rank test as a sensitivity analysis for primary and secondary efficacy endpoints (section 5.11.1.1). • Addition of a summary of related TEAEs for elevated serum transaminases (section 5.13.1). • Update to present summaries based on nominal (protocol) visits. Addition of percentage change to support safety evaluation of serum clinical chemistry parameters (section 5.14). • Update Lipid accumulation in the liver (section 5.18) to include Spearman's rank correlation coefficient for Ultrasound scans.	28JUN2024

Contents

LIST OF ABBREVIATIONS

AA	Arachidonic acid
ACTH	Adrenocorticotrophic hormone
AE	Adverse event
AESI	Adverse Event of Special Interest
AIC	Akaike Information Criterion
ALA	Alpha-linolenic acid
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AP	Alkaline phosphatase
apo A-I	Apolipoprotein A-I
apo B	Apolipoprotein B
AST	Aspartate transaminase
BMI	Body mass index
BOCF	Baseline observation carried forward
BSA	Body surface area
CAS	Completer analysis set
CBC	Complete blood count
CDF	Cummulative distribution function
CK	Creatinine kinase
CI	Confidence interval
CIMT	Carotid intima-media thickness
CSR	Clinical Study Report
D	Day(s)
DHA	Docosahexaenoic acid
DRM	Data Review Meeting
DSMB	Data Safety Monitoring Board
EAP	Expanded Access Programme
EAS	European Atherosclerosis Society
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EFA	Essential fatty acids
EPA	Eicosapentaenoic acid
EoT	End of Treatment
FAS	Full analysis set
FH	Familial Hypercholesterolaemia
FMD	Flow-mediated dilatation
FSH	Follicle stimulating hormone
FU	Follow-up
GGT	Gamma-glutamyl transferase
HDL-C	High-density lipoprotein cholesterol
HoFH	Homozygous familial hypercholesterolaemia
IDL	Intermediate density lipoprotein
ITT	Intent-to-treat (analysis set)
IU	International units
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)
Lp(a)	Lipoprotein a
LOCF	Last observation carried forward
LSMean	Least squares mean
MACE	Major adverse cardiac events
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MTD	Maximum tolerated dose
N	Non-missing observations
NMR	Nuclear magnetic resonance
Non-HDL-C	Non-high-density lipoprotein cholesterol
NTEAE	Non-treatment emergent adverse event
PCSK9	Proprotein convertase subtilisin/kexin type 9
PDC	Protocol deviation criteria
PFT	Pulmonary function test
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PPS	Per-protocol (analysis set)
PT	Preferred Term
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Standard deviation
SE	Standard error
SOC	System Organ Class
SMQ	Standardized MedDRA Query
TC	Total cholesterol
TC/HDL-C	Total cholesterol: high-density-lipoprotein ratio
TEAE	Treatment emergent adverse event
TFL	Table, figure and listing
TG	Triglycerides
TSH	Thyroid stimulating hormone
VLDL-C	Very low-density lipoprotein cholesterol
WHO	World Health Organization

1 INTRODUCTION

This document details the statistical analysis of the data that will be performed for the Amryt Pharmaceuticals DAC 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.

The proposed analysis is based on the contents of the Final Version 7.0 of the protocol (dated 09 February 2023). The Statistical Analysis Plan (SAP) should be read in conjunction with the study protocol, electronic case report form (eCRF) and the table, figure and listing (TFL) shell. In the event of future amendments to the protocol and/or eCRF this SAP may be modified to account for changes relevant to the statistical analysis.

The table, listing and figure shells are supplied in a separate document.

2 STUDY OBJECTIVES AND DESIGN

This is a prospective, single-arm, open-label study.

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of the study is:

- 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] when applicable) in paediatric patients (5 to ≤17 years of age) with HoFH.

2.1.2 Secondary Objectives

The secondary objectives of the study are 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 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.

- Percent change from baseline in total cholesterol: high-density-lipoprotein cholesterol ratio (TC/HDL-C)* and high-density-lipoprotein cholesterol (HDL-C)* at all timepoints upto Week 104±1 week.

* HDL-C and TC/HDL-C are non-key secondary endpoints.

2.1.3 Exploratory Objectives

- Evaluate exploratory assessments of:
  - The 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 nuclear magnetic resonance (NMR) (Liposcale® Test) of pharmacokinetics (PK) samples.

2.1.4 Safety Objectives

- Evaluate the long-term safety and tolerability of lomitapide in paediatric HoFH patients as assessed by:
  - Incidence in reported (treatment-emergent) adverse events [(TE)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) and 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 end of treatment (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 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.

2.1.5 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)."

2.1.6 PK Objective

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

2.2 Study Estimands

The primary estimand is defined as a 'treatment policy' estimand.

The primary estimand components are as follows:

A. Population: The population is defined by the inclusion/exclusion criteria to reflect the targeted patient population.

B. Variable: The primary variable is the percentage change from baseline in LDL-C at week 24±3 days.

C. Intercurrent Events: The following intercurrent events and strategy have been defined for this study:

   a. Dose adjustment of study drug: All data collected will be used in the analysis, irrespective of any dose adjustments to the investigational study drug.

   b. Use of alternative treatments/change in background LLT: All data collected will be used in the analysis, irrespective of any use of alternative treatments or changes in background LLTs.

   c. Study drug discontinuation: All data collected will be used in the analysis, irrespective of study drug discontinuation. If a subject does not have any data post study drug discontinuation, the data will be considered missing and imputed.

D. Population-level Summary: The population-level summary measure is the mean percentage change from baseline in LDL-C at week 24±3 days.

2.3 Study Endpoints

The study endpoints are as follows. Note that the terms 'endpoint' and 'variable' may be used interchangeably throughout this SAP to refer to the measurement of interest. The following efficacy endpoints: LDL-C, Non-HDL-C, TC, VLDL-C, apo B, TG and Lp(a), will be based on centralized core lab data from the fasting lipid panel, with the exception of Lp(a), which will be based on local labs as Lp(a) was not collected by the central lab at the beginning of the study.

2.3.1 Primary Endpoint

The primary efficacy endpoint of the study is:

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

2.3.2 Secondary Endpoints

The secondary efficacy endpoints of the study are:

- Percent change from baseline at Week 24±3 days for the following lipid parameters: Non-HDL-C, TC, VLDL-C, apo B, TG and Lp(a).
- Percent change from baseline at all other time points through Week 104±1 week for the following lipid parameters: LDL-C, Non-HDL-C, TC, VLDL-C, apo B, TG and Lp(a).
- 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 2014 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.
- Percent change from baseline at all timepoints upto Week 104±1 week for HDL-C* and TC/HDL-C*.

* HDL-C and TC/HDL-C are non-key secondary endpoints.

2.3.3 Exploratory Endpoints

The exploratory efficacy endpoints of the study are:

- 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.
- Total number and percent of patients achieving the 2023 EAS recommended target LDL-C of <115 mg/dL (3.0 mmol/L) in paediatric HoFH patients at Week 24±3 days and at any time on study.
- Total number and percent of patients achieving the 2018 American College of Cardiology/American Heart Association Task Force recommended target LDL-C of <110 mg/dL (i.e. 2.9 mmol/L) in paediatric HoFH patients at week 24+/- 3 days and at any time on the study

The Liposcale® Test exploratory endpoint will be reported separately.

2.3.4 Safety and Tolerability Endpoints

- Incidence of (TE)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.
- Pulmonary function test.
- Laboratory tests:
    - Standard haematology (complete blood count [CBC]) and clinical chemistry panels (including comprehensive metabolic panel).
    - Liver function tests: Alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP), total bilirubin, and serum albumin.
    - 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 expanded access programme (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.

2.3.5 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 giving medication to child because they refuse to take or throw up immediately after taking.
  - Parent/guardian problems in giving dietary supplement to child because they refuse to take or throw up immediately after taking.

2.3.6 PK Endpoints

The PK endpoints will be reported separately.

2.4 Study Design

The APH-19 study 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).

The study will consist of 5 distinct periods:

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 stabilized 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 alpha linolenic acid (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.

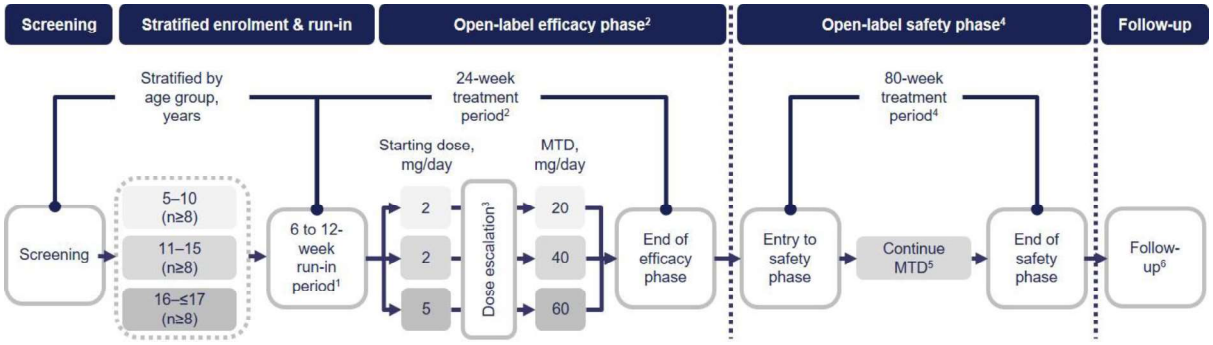
- Assuming a withdrawal rate of approximately 33% by Week 24±3 days, this would result in 30 evaluable patients at Week 24±3 days (with ≥8 patients in any individual age group).
- After the stabilization of the patient on his/her current MTD of LLT (including LA, when applicable) during the 6-week Run-in 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.

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) or participation in the EAP of this study:

- 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.

See Figure 1 below for further information on the study periods.

Figure 1: Design of Study



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

1. Stabilize 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) are 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.

2.5 Visit Structure

The visit structure and scheduled assessments are detailed in Section 1.2 of the study protocol.

3 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; as well, it 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.

On 25 April 2022, Amryt Pharmaceuticals DAC submitted an application for modification of the agreed Paediatric Investigation Plan (PIP) to the European Medicines Agency (EMA). On 01 August 2022, the EMA Paediatric Committee agreed with the proposed change for the number of study participants by paediatric subset from '*at least 30 evaluable patients at Week 24 (with at least 8 patients in the following age groups: 5 to 10 years, 11 to 15 years and 16 to less than 18 years of age)*' to '*at least 30 evaluable patients at Week 24 (with at least 12 patients in each of the following age groups: 5 to 10 years and 11 to less than 18 years of age)*'. In addition, the due date for completion (last patient, last visit) has been extended from April 2023 to August 2024.

As the PIP amendment was approved, age groups for statistical analysis are now based on the 2 age groups (i.e. 5 to 10 years and 11 to 17 years) as detailed below.

4 ANALYSIS TIMINGS, SAFETY REVIEWS AND PUBLICATIONS

The primary efficacy analysis will be conducted when all patients have completed (or withdrawn prior to) Visit 10 at Week 24±3 days (end of efficacy phase), for reporting in a Clinical Study Report (CSR). 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 analyses.

No planned interim analyses for efficacy and/or futility will be performed, as detailed in the protocol.

An independent Data Safety Monitoring Board (DSMB) will be periodically reviewing the safety data, as described in Section 4.3 of the study protocol as described within the DSMB Statistical Analysis Plan.

The final statistical analysis will occur when all patients have completed follow-up Visit 23 at Week 108, and the CSR will be updated to include the final analysis. Efficacy, safety and exploratory data collected during the Safety phase and follow-up phase will be included.

5 ANALYSIS PLAN

5.1 General

Summary statistics for continuous variables will consist of number of non-missing observations (n), mean, SD, minimum, median, maximum, 25th and 75th percentiles unless specified otherwise. The precision of these variables is defined in the table, figure and listing shells document.

For categorical variables the number and percentage of subjects in each category will be presented, based on the number of subjects in the analysis set, unless otherwise specified.

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.

5.2 Data Review Meeting

The Sponsor will convene a data review meeting (DRM) after the data for the Week 24±3 days lock has been cleaned and before the study is locked. The DRM will make decisions that will include, but will not be limited to:

- the determination of whether protocol deviations are 'major' or 'minor', or not a protocol deviation at all;
- the allocation of subjects to the per protocol analysis set (PPS);

If required, after the DRM and prior to database lock, a SAP amendment will be issued and all changes based on the DRM will be documented in the SAP, including the reason for the change.

On November 2022 the DRM was performed and subject allocation to PPS was performed. No changes were made in the SAP based on the DRM.

5.3 General Derivations

This section provides details of general derivations. Derivations specific to the parameter of interest are detailed within the specific SAP section.

- Definition of Baseline

  Baseline is defined as the last non-missing value (including scheduled and unscheduled assessments) prior to the subject receiving study treatment in the efficacy phase (Visit 4). If a baseline value is missing, it is not appropriate for this study, to carry forward screening / run-in period values for the fasting lipid panel prior to stabilisation of the patient on LLT. Thus, if baseline is missing, then it should remain as missing.

- Definition of Study Day

  Throughout this SAP any references to “Visit XX” refer to the pre-specified visits defined in the protocol. Data listings will additionally present study days. Study day will be calculated relative to the first date of administration of study treatment, Day 0 (study day 1). Any calculations referencing study day are calculated as (end date- start date) +1.

- Definition of Study Duration

  Study duration will be derived as the number of days between first day of the 'run-in' period and date of study completion or the date of early study withdrawal (i.e. (date of study completion or date of early study withdrawal - date of starting the 'run-in' period) +1).

- Definition of Treatment Duration

  Treatment duration will be derived as the number of days between the first administration of study drug and the date of the last administration of study drug (i.e. date of last administration of study drug – date of first administration of study drug) +1).

- Definition of 'Run-in'

  The 'Run-in' period is defined as Visit 2 to Visit 4. If a subject drops out during the 'Run in' period they are considered a 'Run-in failure'.

- Age at Screening

  Age at screening is recorded in years and months, but will be calculated for summary measures as age in years, defined as [years + (months) / 12] (e.g. 12 years 6 months = 12.5 years)].

- Age groups

  Children will be divided into two age groups, based on their age at screening. The two age groups will be defined as:

  - Age 5 to 10 years (i.e. >=5 years to <=10 years);
  - Age 11 to 17 years (i.e. >=11 years to <=17 years).

- Body Mass Index

  BMI is calculated as (weight (kg) / height (m)²).

- z-scores and percentile

  The z-scores and percentiles for BMI and height will be calculated using the World Health Organization (WHO) growth reference data for 5-19 years in the following indicators: BMI-for-age (5-19 years), Height-for-age (5-19 years), Weight-for-age (5-10 years).

  Note: According to the WHO, weight-for-age reference data are not available beyond age 10 because this indicator does not distinguish between height and body mass in an age period where many children are experiencing the pubertal growth spurt and may appear as having excess weight (by weight-for-age) when in fact they are just tall.

- Body Surface Area

  Body Surface Area (BSA) is calculated using the Mosteller formula:

$$\text{BSA(m2)} = \sqrt{\left(\frac{\text{Height (cm)x Weight (kg)}}{3600}\right)}$$

  (Mosteller RD. Simplified calculation of body surface area. N Engl J Med. 1987;317:1098).

- Ratios

  The following ratios will be calculated (if possible) at each timepoint:

  - Vitamin E to total lipids ratio

    Vitamin E : total lipid ratio = [Vitamin E (µmol/L) / total lipid (mmol/L)

    (where total lipids is the defined as total cholesterol (mmol/L) plus fasting triglycerides (mmol/L))

  - Vitamin E to total cholesterol

    Vitamin E : total cholesterol ratio = [Vitamin E (µmol/L) / total cholesterol (mmol/L)

  - Vitamin E to triglycerides

    Vitamin E : triglycerides ratio = [Vitamin E (µmol/L) / triglycerides (mmol/L)

    TC : HDL-C ratio = [TC (mmol/L) / HDL-C (mmol/L)]

- Incomplete dates

  For calculation purposes, incomplete dates will be completed using worst case, the most conservative value possible. Further details are detailed in the relevant sections as required.

- Non-numeric values

  In the case where a variable is recorded as “>x”, “≥x”, “<x” or “≤x”, then for analysis purposes a value of x will be taken. Where a range of values is quoted the midpoint of the range will be taken. For example, if a laboratory safety parameter is reported as being below the limit of quantification or <x, the value of the limit will be used in the calculation of summary statistics. The recorded value will be reported in listings.

- Methods for handling withdrawals and missing data

  As this is a single-arm study, for patients who have missing data at the timepoint of interest, the last observation carried forward (LOCF) approach will be used in the efficacy phase analyses of primary and key secondary endpoints. If a baseline value is missing, it is not appropriate to carry forward screening / run-in period values for the fasting lipid panel prior to stabilisation of the patient on LLT. Thus, if efficacy phase baseline is missing, then it should remain as missing.

- Analysis Study Week Windows and Analysis Study Visit

  Analysis study week windows will be applied to the Fasting Lipid panel data for the analysis of the primary endpoint and secondary endpoints. The study protocol (Final Version 7.0, dated 09 February 2023) stated Fasting Lipid panel data should be collected within +/- 3 days of the target assessment date for Week 4 to Week 56 inclusive and +/- 7 days of the target assessment date for Week 68 to Week 104 inclusive).

  However, it was not always possible to adhere to the tight study window of ±3 days of the target assessment date for the following reasons: In 5 subjects, visits were either missed or out of window due to infections including COVID-19 (n=4), in 2 subjects, visits had to be postponed due to malfunction of lipoprotein apheresis machines, 1 subject had to travel abroad for a case of death in the family and 1

subject could not visit the site in time due to bad weather conditions and a distance of 317 km to the site. The majority of visits out of window occurred in the Middle East, where subjects had to travel a median distance of 296 km to the sites (minimum of 30 km, maximum of 985 km) and could not attend the sites in time, because their father could not accompany them, the visit did not match the lipoprotein apheresis schedule, or the visit fell into a period of cultural holidays, such as Ramadan. To allow for these various reasons the Analysis Visit Window for the Lipid Panel data has been adapted to accommodate.

The Analysis study week window will be defined so study visits are mapped onto the relevant study week, as defined by the corresponding study day the study assessment occurred for scheduled and unscheduled visits. If more than one scheduled / unscheduled visit falls within a study week window, then the study assessment visit closest to the intended target day of assessment should be used for that study week window. If more than one scheduled / unscheduled visit falls within a study week window and are equal distance from the target day of assessment then the average of the two study assessment visits should be used for that study week window.

In addition to the Analysis study week windows, the Nominal Analysis Study Visit will be defined as the nominal study visit attached to the corresponding study assessment. The nominal study visit will only be applied to the Lipid panel data for statistical analyses.

Study Week	**Target day of assessment (according to protocol)**	**Analysis study day window (Lipid panel data)**	**Analysis study day window (All Non-Lipid data for secondary objectives)**
Baseline	1	-1 to 1	-1 to 14
Week 4	28±3	15 to 42	15 to 42
Week 8	56±3	43 to 70	43 to 70
Week 12	84±3	71 to 98	71 to 98
Week 16	112±3	99 to 126	99 to 126
Week 20	140±3	127 to 154	127 to 154
Week 24	168±3	155 to 182	155 to 182
Week 28	196±3	183 to 210	183 to 210
Week 32	224±3	211 to 238	211 to 238
Week 36	252±3	239 to 266	239 to 266
Week 40	280±3	267 to 294	267 to 294
Week 44	308±3	295 to 322	295 to 322
Week 48	336±3	323 to 350	323 to 350
Week 52	364±3	351 to 378	351 to 378
Week 56	392±3	379 to 434	379 to 434

Study Week	Target day of assessment (according to protocol)	Analysis study day window (Lipid panel data)	Analysis study day window (All Non-Lipid data for secondary objectives)
Week 68	476±7	435 to 518	435 to 518
Week 80	560±7	519 to 602	519 to 602
Week 92	644±7	603 to 686	603 to 686
Week 104	728±7	687 to 748	687 to 748
Week 108	756±7	749 to LPLV	749 to LPLV

Study Visit / Week (according to protocol)	Nominal analysis study visit (Lipid panel data)
Visit 4, Baseline, Day 0	Visit 4
Visit 5, Week 4	Visit 5
Visit 6, Week 8	Visit 6
Visit 7, Week 12	Visit 7
Visit 8, Week 16	Visit 8
Visit 9, Week 20	Visit 9
Visit 10, Week 24	Visit 10
Visit 11, Week 28	Visit 11
Visit 12, Week 32	Visit 12
Visit 13, Week 36	Visit 13
Visit 14, Week 40	Visit 14
Visit 15, Week 44	Visit 15
Visit 16, Week 48	Visit 16
Visit 17, Week 52	Visit 17
Visit 18, Week 56	Visit 18
Visit 19, Week 68	Visit 19
Visit 20, Week 80	Visit 20
Visit 21, Week 92	Visit 21
Visit 22, EOT / Week 104	Visit 22
Visit 23, Follow-Up Week 108	Visit 23

5.4 Analysis Sets

The following analysis set definitions will be used in the data presentations:

The **Enrolled Set** is defined as all participants who pass screening and enter onto the Run-in period, irrespective of whether they receive the study treatment.

The **Safety Analysis Set (SAF)** is defined as all participants who are treated with at least one dose of the IMP. The SAF will be used for all safety analyses.

The **Full Analysis Set (FAS)** is defined as all participants who receive at least one dose of the IMP and who have a baseline and at least one post-baseline measurement of LDL-C. The FAS will be used for all efficacy analyses.

The **Completer Analysis Set (CAS)** is defined as a subset of the FAS and will include all participants who have not discontinued the efficacy phase (up to Week 24) of the study early irrespective of the reason for discontinuation. The CAS will be used for supplementary efficacy analyses during the efficacy phase.

The **Per-Protocol Set (PPS)** will be a subset of the Full Analysis Set consisting of those participants who reasonably adhere 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 within the efficacy phase of the trial. The PPS will be used for supplementary efficacy analyses during the efficacy phase.

The Analysis Set Planning form will indicate which analysis data sets (e.g. PPS) require individual subject assignments to be listed for review and agreement at the final DRM prior to final analysis. The Analysis Set Planning form will document the timing of the data reviews. Where analysis sets do not require data review of individual subject assignments, the definitions are considered sufficient to determine the subjects included within these analysis sets without listing and data review.

5.5 Data presentations

All data are unblinded due to the nature of the study (i.e., open-label).

If a participant is a 'run-in failure' (i.e., has entered the study but not received study treatment), the treatment variable will be labelled as 'Not Treated'.

The data will be summarised in tabular form for all treated subjects.

All post-baseline laboratory, vital signs, ECG, echocardiography and NMR scan values will be tabulated and listed; in particular all clinically significant values will be noted.

Eligibility and analysis set listings will be based on the enrolled set and all other listings will be based on the SAF set.

Listings will be sorted by subject number and date/time of assessment. Graphical presentations of the data will also be provided where appropriate.

Analysis sets will be summarised using the enrolled set. Study disposition will be summarised using the enrolled set and SAF. Protocol deviations will be listed using the SAF. Background and demographic characteristics will be summarised using the SAF set. The primary efficacy endpoint will be summarised using the FAS, CAS and PPS sets. The secondary efficacy endpoints (i.e. fasting lipid panel at week 24±3 days) that are adjusted for multiplicity (as defined in section 5.12) will be summarised using the FAS, CAS and PPS sets. All other secondary efficacy endpoints will be

summarised using the FAS. Prior/concomitant medications, administration of study treatment exposure and safety will be summarised using the SAF.

5.6 Disposition of participants

The number and percentages of all participants will be presented for the following:

- Screen failures.
- Run-in failures.
- Completed the 'Run-in Period'.
- Analysis sets (i.e. Enrolled, FAS, CAS, PPS, SAF).
- Completed the efficacy phase of the study.
- Completed the safety phase of the study.
- Prematurely discontinued from the study.
- Reason for study withdrawal.

The percentages for 'run-in' failures and completed the 'run-in' period will be based off the Enrolled set. All other percentages for the analysis sets (FAS, CAS, PPS, SAF), completed study, prematurely discontinued study will be based off the SAF.

The following parameters will be presented as summary statistics, with weeks as the unit of measure:

- Study duration.
- Treatment duration.

The number and percentage of participants will be summarised by their reason for withdrawal from study / treatment.

'Run-in failures' are defined as subjects who enter the 'Run-in Period' and discontinue the study before receiving a first dose of study treatment.

Subjects who prematurely discontinue from the study due to a reason relating to COVID-19 are identified as either of the following:

- Reason for withdrawal of 'Other' with a corresponding free text reason containing a text version of 'COVID-19'.
- Reason for withdrawal of 'Adverse Event' with a corresponding COVID-19 related AE reported on the AE eCRF page.

Patients who prematurely discontinue from study due to a reason relating to COVID-19 will be classified during the DRM. The number and percentage of subjects who prematurely discontinue due to either of these definitions will be presented as a reason for withdrawal of 'COVID-19'.

Eligibility for each of the analysis sets and reasons for exclusion will be listed. Eligibility criteria, informed consent and assent, study completion/withdrawal and Visit dates data will be listed. The number of subjects attending each study visit will also be summarised.

5.7 Protocol Deviations

All protocol deviations will be assessed and documented on a case-by-case basis prior to the database lock. Major protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Major protocol deviations and their impact on the analysis sets for this study are decided by the study team.

Prior to database lock, Amryt may review the individual deviations to confirm that major protocol deviations have been captured correctly and to agree impact to analysis sets as indicated in the Protocol Deviation Criteria (PDC) form.

Details of all major protocol deviations (date, deviation type, deviation category and specific details) and participant eligibility will be listed. Details of all minor protocol deviations will also be listed.

Missing data and protocol deviations are expected as a result of COVID-19. All protocol deviations regarding visits and assessments due to the COVID-19 pandemic will be presented in a separate listing.

Compliance with lipid lowering therapy will be determined through manual review of protocol deviations.

5.8 Background and Demographic Characteristics

5.8.1 Demography and Baseline Characteristics

Demographic characteristics (age, sex, race and ethnicity), body measurements (height, weight, BMI, and BSA), height percentile, height z-score, BMI percentile, and BMI z-score collected at Baseline will be summarised overall and by age group.

Baseline lipids (i.e. LDL-C, TC, Non-HDL-C, VLDL-C, Lp(a), TG, apo B, HDL-C, TC/HDL-C ratio, and apo A1) will be summarised overall and by age group.

Age at screening (in years) will be presented as a summary measure (as defined in section 5.3) and will be summarised overall and by age group.

All subject demographic and baseline characteristic data, including informed consent, will be listed.

5.8.2 Diagnosis of HoFH

Details regarding the diagnosis of HoFH will be summarised overall and by age group:

- Duration of HoFH diagnosis.
- Genetic confirmation of 2 mutant alleles (including mutant alleles).
    - LDL receptor (LDLR) gene locus
    - apo B gene locus
    - Proprotein convertase subtilisin/kexin type 9 (PCSK9) gene locus
    - LDL receptor adapter protein 1 (LDLRAP1) gene locus
    - Unknown
    - Other (please specify)
- Classification of mutations in LDL receptor.
- An untreated LDL-C value >500 mg/dL (13 mmol/L) or treated LDL-C value ≥300 mg/dL (8 mmol/L) AND cutaneous or tendon xanthoma before age of 10 years.
- An untreated LDL-C value >500 mg/dL (13 mmol/L) or treated LDL-C value ≥300 mg/dL (8 mmol/L) AND untreated LDL-C levels consistent with heterozygous FH in both parents.

Duration of HoFH diagnosis (months) will be calculated as:

*12 * [date of baseline – date of HoFH diagnosis + 1] / 365.25*

Mutations in LDLR can impair LDLR activity at different levels and therefore are classified according to their phenotypic behaviour (Galicia-Garcia 2020; Gidding 2015) as:

- Class 1: Synthesis of receptor or precursor protein is absent,
- Class 2: Absent or impaired formation of receptor protein, partial or complete retention of LDLR in the endoplasmic reticulum,
- Class 3: Normal synthesis of receptor protein, but abnormal or defective binding to apo B,
- Class 4: Defective endocytosis, clustering in coated pits, and internalization of the receptor complex does not take place,
- Class 5: Diminished LDLR recycling capacity, receptors are not recycled and are rapidly degraded.

According to Gidding et al. the functional defects in the LDLR are complex, and a mutation can belong to more than one class. Therefore, LDLR mutations will be classified upon medical review into 4 groups: subjects with the LDLR variant category 'defective/defective', subjects with the LDLR variant category 'defective/negative', subjects with the LDLR variant category 'negative/negative' and subjects with unknown LDLR variant category.

All diagnosis of HoFH data will be listed.

5.8.3 Medical and Cardiovascular History

Medical history events and cardiovascular disease history events will be coded using the latest MedDRA dictionary version. The version used will be indicated in the data summaries and listings. The number and percentage of participants will be presented for ongoing conditions and previous conditions separately by system organ class (SOC), and preferred term (PT), where SOC and PT will be presented in decreasing frequency of the total number of participants with medical history / cardiovascular disease history events.

Medical history will be summarised overall and by age group.

Cardiovascular disease history collected at Screening will be summarised overall and by age group. Established cardiovascular disease history will be defined as aortic valve disease and/or coronary atherosclerosis.

All medical history / cardiovascular disease history events will be listed.

5.9 Prior and Concomitant Medications and Procedures

Medications will be coded using the latest World Health Organization Drug dictionary (WHO Drug) version. The version used will be indicated in the data summaries and listings.

Procedures will be coded using the latest MedDRA version. The version used will be indicated in the data summaries and listings.

Prior medications and procedures are defined as those that started and ended prior to the enrolment date visit (Visit 2) (i.e. start of the 'Run-in Period').

'Run-in' medications and procedures are defined as those that are ongoing at the time of starting the 'Run-in Period' (i.e. Visit 2) or started after the start of the 'Run-in Period', but before the time of first administration of study treatment.

Concomitant medications / procedures are defined as those that are:

- Ongoing at the time of first administration of study treatment or
- Started or ended on or after the time of first administration of study treatment or
- Started prior to the end/last dose of study treatment.

Prior LLT medications and procedures (including LA) are defined as those that started and ended prior to the enrolment date visit (Visit 2) (i.e. start of the 'Run-in Period').

'Run-in' LLT medications and procedures (including LA) are defined as any LLT or procedure that are ongoing at the enrolment visit (visit 2) date (i.e. start of the 'Run-in Period') and or started after the start of the 'Run-in Period', but before the time of first administration of study treatment.

'Concomitant' LLT medications and procedures (including LA) (efficacy phase) are defined as any LLT or procedure that are ongoing at the time of first administration of study treatment or started on or after the time of first administration of study treatment or started prior to the end/last dose of study treatment within the efficacy phase.

'Concomitant' LLT medications and procedures (including LA) (safety phase) are defined as any LLT or procedure that are ongoing at the start of the safety phase or started on or after the start of the safety phase or started prior to the end/last dose of study treatment within the safety phase.

If medication / procedure dates are incomplete and it is not clear whether the medication / procedure was concomitant, it will be assumed to be concomitant.

All medications / procedures will be medically reviewed for accurate classification of LLT medications / procedures.

The number and percentage of participants (overall and by age group) taking the following will be summarised by medication class and standardised medication name:

- Prior and 'Run-in' medications and procedures (except for LLT),
- Concomitant medications and procedures (except for LLT),
- Prior and 'Run-in' LLT medications and procedures,
- Concomitant LLT medications and procedure (efficacy phase and safety phase).

In the summary tables, the medication class and standardised medication name will be presented in decreasing frequency of the total number of participants with medications. Participants taking multiple medications in the same medication class or having the same standardised medication recorded multiple times in the study will be counted only once for that specific medication class and standardised medication name. For LLT medications, the number of subjects taking at least 2 and at least 3 medications during Run-in will be presented.

Medication and procedure data will be listed.

5.10 Administration of Study Treatment and Exposure

After the stabilization of the participant on their current LLT (including LA when applicable) during the 6-week 'Run-in Period', treatment with lomitapide will be started as add-on therapy on baseline (Day 0, D0) of the efficacy phase.

The age of the child at baseline (D0) will be used to determine their age group for the starting dosing of lomitapide.

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 1) based upon safety and tolerability in addition to LDL-C values.

Table 1 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.

Full details of permitted dose escalation, dose reduction and re-challenge are provided in the protocol (section 7.3.1). Full details of permitted dose modification, interruption or drug discontinuation for adverse events are provided in the protocol (section 7.3.2) and details for permitted dose modification for concomitant medication are provided in the protocol (section 7.3.3).

If a participant changes dose, they will be analysed according to the dose cohort assigned at D0 (start of efficacy phase).

The total number of weeks of exposure to the study treatment will be calculated as:

[(last date of dosing – first date of dosing) + 1] / 7

The average daily exposure (mg/day) to the study treatment will be calculated as:

*(Number of doses received * treatment dose (mg)) / (number of days exposed)*

Study drug exposure to the maintenance dose (i.e., not including the time the subject was titrating the dose to reach the maintenance dose) (mean, median, and range of exposure) will also be summarised. The total number of weeks of exposure to the maintenance dose will be calculated as:

[(last date of dosing – date when maintenance dose is reached) + 1]/7

Study treatment, exposure (weeks and mg/day), maximum tolerated dose (mg), number of doses received, number of dose increases, number of dose reductions, number of dose interruptions, number of dose reductions due to concomitant medication, number of dose reductions due to adverse events, number of dose interruptions due to concomitant medication, number of dose interruptions due to adverse events, number of drug discontinuations due to adverse events and dose at drug discontinuation due to adverse events will be summarised by study phase and listed using the Safety population. In the listings, the reason for dose change will also be given.

In addition, a summary of the time to first dose interruption and first dose reduction will be presented for the efficacy phase, the safety phase and overall, using the Safety population. The summary will use the Kaplan-Meier method to estimate the time to each event, with results displayed using a Kaplan-Meier plot and in tabular form. For the safety phase summary, time 0 will be set as the start of the safety phase (i.e., the date of the week 24 visit). Additionally, patients who do not enter the safety phase will be censored at time 0. If a patient discontinues study drug they will be counted as an event for both dose interruption and dose reduction at the time of study drug discontinuation. If a patient has not had a dose interruption or reduction and is still on study drug, they will be censored at their last visit assessment date.

Compliance with IMP dosing during the study will be reviewed medically on a patient level basis. The proportion of patients compliant with IMP dosing during the efficacy phase will be reported as yes/no (n(%)). The proportion of patients compliant with IMP dosing during the safety phase will also be reported as yes/no (n(%)), with patients who do not enter the safety phase, excluded from the summary.

The number and percentage of subjects with the achieved doses at Week 24, Week 56 and Week 104 will be provided by age group.

5.11 EFFICACY EVALUATION

Unless specified otherwise, all listings will be based on the FAS set.

All hypothesis tests will be two-sided and conducted at the 5% significance level, unless otherwise specified.

Analysis of all lipid panel data will be based on data from the Central Lab, with the exception of Lp(a), which will be based on Local Labs as Lp(a) was not collected by the central lab at the beginning of the study.

5.11.1 Primary Endpoint

5.11.1.1 Percent change in LDL-C at Week 24±3 days

Primary Analysis

The primary endpoint is percent change in LDL-C at Week 24±3 days compared to baseline.

Analysis Study Weeks will be used as specified in the visit window table (see Section 5.3).

The observed values at baseline and Week 24 and observed change and percentage change from baseline at Week 24 will be summarised overall and by age group.

*Percentage change = [(Week 24 – baseline) / baseline] * 100%*

The primary efficacy endpoint (i.e. percentage change at Week 24) 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, together with the corresponding two-sided 95% confidence interval (CI) and p-value will be presented.

Percent change from baseline data will be presented by age-group using a waterfall plot.

Missing data will be imputed using LOCF as described in Section 5.3.

The primary efficacy analysis will be based on the FAS.

Sensitivity Analysis – using Nominal study visit number

Nominal Study Visit will be used as specified in Section 5.4 above.

The percentage change at Visit 10 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 Visit 10, together with the corresponding two-sided 95% confidence interval and p-value will be presented.

Missing data will be imputed using LOCF as described in Section 5.3.

The analysis will be based on the FAS only.

Sensitivity Analysis – using MMRM model

Analysis Study Weeks will be used as specified in the visit window table (see Section 5.3).

A sensitivity analysis using a Mixed Model Repeated Measures (MMRM) model with the missing at random (MAR) assumption (i.e. missing data will not be imputed using LOCF or any other method) will be conducted. The MMRM model will estimate the mean percentage change and 95% CI at Week 24 and will include the percentage change as the dependent variable and visit as a categorical fixed effect. An unstructured covariance structure will be used. If the model does not converge, alternative covariance structures for repeated visits within a subject will be evaluated, including compound symmetry, 1st order autoregressive, and Toeplitz. The Akaike Information Criterion (AIC) will be used to assess model fit for the alternative covariance structures. The covariance structure resulting in the smallest AIC indicating the best model will be selected.

The primary efficacy sensitivity analysis will be based on the FAS only.

Sensitivity Analysis – using baseline observation carried forward (BOCF)

Analysis Study Weeks will be used as specified in the visit window table (see Section 5.3). Missing data at week 24 will be imputed using BOCF. If a baseline value is missing, it is not appropriate to carry forward screening / run-in period values for the fasting lipid panel prior to stabilisation of the patient on LLT. Thus, if efficacy phase baseline is missing, then it should remain as missing.

Sensitivity Analysis – using Wilcoxon Signed-Rank test

Analysis Study Weeks will be used as specified in the visit window table (see Section 5.3). A sensitivity analysis using a non-parametric approach, Wilcoxon Signed-Rank test, will be conducted.

Missing data will be imputed using LOCF as described in Section 5.3.

The analysis will be based on the FAS.

Supplementary Analysis

Supplementary analysis for the primary efficacy endpoint will include the one-sample t-test, Wilcoxon Signed-Rank test and summaries based on the PPS and the CAS. Analysis Study Weeks will be used as specified in the visit window table (see Section 5.3).

Responder Analysis

Supplementary responder analyses for the primary efficacy endpoint (overall and by age-group) will also be provided using the following cut-offs for a responder:

- >15% reduction in LDL-C at Week 24
- >25% reduction in LDL-C at Week 24
- >50% reduction in LDL-C at Week 24

Number and percentage of subjects achieving the above cut-offs will be presented. If a patient discontinued study medication early, they will be considered a non-responder. A cumulative distribution function (CDF)plot for the percent reduction will also be provided by age group and overall (early discontinuations will be assigned a percent change of 0). These analyses will also be repeated based on achieving the above targets anytime on or after Week 8 (if a patient discontinued study medication prior to Week 8 they will be considered a non-responder and assigned a percent change of 0 for the CDF plot.)

Sub-group Analysis

Analysis Study Weeks will be used as specified in the visit window table (see Section 5.3).

Additional supplementary analysis will be conducted using sub-group analysis. For each sub-group analysis, an analysis of covariance (ANCOVA) model will be conducted using the sub-group as a fixed effect and estimating the mean percentage change and two-sided 95% CI within each sub-group at Week 24±3 days. The following sub-group analyses will be performed:

- Age groups (i.e. 5 to 10 years; 11 to 17 years);
- Sex (male; female);
- Subjects with documented cardiovascular disease history vs no documented cardiovascular disease history at screening (pooled across age groups);
- Subjects with established cardiovascular disease history (defined as aortic valve disease and/or coronary atherosclerosis) vs no established

cardiovascular disease history (as defined previously) at screening (pooled across age groups);

- Subjects who have taken concomitant LLT medications (excluding LA) vs those who have taken concomitant LLT medications (including LA) (pooled across age groups);
- Subjects who have no dose reductions / no dose interruptions vs at least one dose reduction / dose interruption (pooled across age groups);
- Subjects who reach MTD within age group vs subjects who do not reach MTD within age group (pooled across age groups;
- Subjects with the LDLR variant category ‘defective/defective’ vs subjects with the LDLR variant category ‘defective/negative’ vs subjects with the ≥ variant category ‘negative/negative’, if there are at least 3 subjects, in each sub-group.
-

Results for the sub-group analysis will be presented in tables and displayed using a forest plot.

Subgroup analysis will only be based on the FAS.

The subgroup analysis will be repeated using the Nominal Study Visit as specified in Section 5.3 above. Results for the additional sub-group analysis will be presented in tables only.

Results for the sub-group analysis (based on Nominal Study Visit) will also be displayed using a forest plot.

Fasting Lipid Panel data will be listed fully by age group using the SAF population set, as detailed in section 5.14.

Sensitivity analyses will be conducted to determine the impact (if any) of COVID-19 on the primary endpoint and will be described in the CSR.

5.11.2 Secondary Endpoints

The primary analysis of all secondary endpoints will be based on the FAS. Supplementary analyses on the key-secondary efficacy endpoints will be conducted using the PPS and CAS. Adjustment for multiplicity among key-secondary efficacy endpoints are outlined in Section 5.12

5.11.2.1 Percent change at Week 24 ± 3 days

The key-secondary efficacy endpoint analyses will use the same methods as outlined for the primary efficacy endpoint. The same sensitivity analysis, supplementary analyses and sub-group analyses as the primary endpoint will also be conducted.

Key-secondary efficacy endpoints are the percent change from baseline at Week 24±3 days for the following lipid parameters:

Non-HDL-C, TC, VLDL-C, apo B, TG, and Lp(a).

Fasting Lipid Panel data will be listed fully by age group using the SAF population set, as detailed in section 5.14. Lp(a) data will be listed for the local labs only.

5.11.2.2 Percent change at all other time points to Week 104 ± 1 week

Additional secondary efficacy endpoints are the percent change from baseline at all other time points through to EOT / Week 104 for the following lipid parameters:

LDL-C, Non-HDL-C, TC, VLDL-C, apo-B, TG and Lp(a).

Scheduled study visits (based on analysis study visit) conducted between specific study days will be included in the secondary efficacy analysis, as detailed in the table of study visits in Section 5.3.

A summary of the observed change and percentage change from baseline at each timepoint, will be presented overall and by age group. In addition, the mean and median dose at each timepoint will be presented alongside these results.

A MMRM model will be used to estimate the mean change at each timepoint. The model will include visit as a categorical fixed effect. An unstructured covariance structure will be used. If the model does not converge alternative covariance structures for repeated visits within a subject, will be evaluated including compound symmetry, spatial spherical, spatial power, spatial Gaussian. The AIC will be used to assess model fit for the alternative covariance structures. The covariance structure resulting in the smallest AIC indicating the best model will be selected. Missing data will be maintained as missing. Least Squares means (LSMeans), standard error (SE), two-sided 95% CI and associated p-value will be presented at each timepoint.

Figures showing the raw percent change from baseline and SD and estimated LSMeans percent change from baseline and SE, over time, for each endpoint will also be provided. In addition, the number of subjects, mean and median dose at each timepoint will be presented in the figures.

Fasting Lipid Panel data will be listed fully by age group using the SAF population set, as detailed in section 5.14.

5.11.2.3 Change in LLT (and LA) from Week 24 ± 3 days through Week 56 and week 104 ± 1 week

The number and percentage of patients treated with standard LLT (including LA when applicable) at any post-baseline assessment will be summarised overall and by age group (based on analysis study visit). For this summary the percentages will be calculated using the number of patients attending the post-baseline visit as a denominator.

Changes to the standard LLT from week 24 through Week 56 and 104 will be summarised, cumulatively, including the number and percentage of patients treated with LA, when applicable.

The following changes to standard LLT are of notable interest and will be summarised, including the reason of change:

- Dose reduction of standard LLT
- Reduced frequency of / extended interval between LA
- Discontinuation of LLT
- Discontinuation of LA

Any dose increases of standard LLT / increased frequency of LA will also be summarised.

The percentage of changes to standard LLT and LA (i.e., dose reduction of standard LLT; reduced need for LA; discontinuation of LLT / LA; dose increase of LLT; increased need for LA) will use the number of patients treated with standard LLT (including LA) at Week 24 (end of efficacy phase).

For subjects who were on apheresis at baseline, the apheresis regimen established during run-in and the weighted average of the days since previous LA will be presented. The weighted average will be derived as:

$$\frac{\sum(\text{Days since previous LA x Number of days})}{\sum \text{Number of days}}$$

Additionally, the duration in days between the most recent apheresis and the LDL-C assessment at Baseline (Week 0) and Week 24 will be presented. For subjects discontinuing the study before Week 24, the duration between the most recent apheresis and the last LDL-C assessment will be presented.

Lipoprotein Apheresis history and treatment data will be fully listed by age group using the Safety set.

5.11.2.4 Recommended target of LDL-C at Week 24 ± 3 days and at any time on study

The 2014 EAS recommends a target LDL-C of <135 mg/dL (i.e. 3.5 mmol/L) in paediatric HoFH patients (secondary endpoint).

The number and percentage of patients with LDL-C falling below the target level of 135 mg/dL (i.e. 3.5 mmol/L) will be summarised by study visit (based on analysis visit), at any time up to Week 24 and at any time up to Week 104 by age group and overall.

Within each age group, the lomitapide dose at the time when LDL-C fell below the target level of 135 mg/dL (i.e. 3.5 mmol/L) will be summarised by study visit.

The above analyses will also be repeated using the 2023 EAS recommended target LDL-C of <115 mg/dL (i.e. 3.0 mmol/L) in paediatric HoFH patients.

Finally, the above analyses will be repeated using the 2018 American College of Cardiology/American Heart Association Task Force recommended target LDL-C of <110 mg/dL (i.e. 2.9 mmol/L) in paediatric HoFH patients.

A CDF plot showing the cumulative distribution function of the LDL-C data for all patients will be plotted. A reference line at 135 mg/dL will be added indicting the EAS recommended target LDL-C of <135 mg/dL. A CDF plot will be plotted (using the analysis visit data) for Week 24 and for at any time on study.

5.11.2.5 Percent change from baseline upto Week 104 ± 1 week for HDL-C and TC/HDL-C (non-key secondary)

Scheduled study visits (based on analysis study visit) conducted between specific study days will be included in the non-key secondary efficacy analysis, as detailed in the table of study visits in Section 5.3.

A summary of the observed change and percentage change from baseline at each timepoint, will be presented overall and by age group. In addition, the mean and median dose at each timepoint will be presented alongside these results.

A MMRM model will be used to estimate the mean change at each timepoint. The model will include visit as a categorical fixed effect. An unstructured covariance structure will be used. If the model does not converge alternative covariance structures for repeated visits within a subject, will be evaluated including compound symmetry, spatial spherical, spatial power, spatial Gaussian. The AIC will be used to assess model fit for the alternative covariance structures. The covariance structure resulting in the smallest AIC indicating the best model will be selected. Missing data will be maintained as missing. LSMeans, SE, two-sided 95% CI and associated p-value will be presented at each timepoint.

Figures showing the raw percent change from baseline and SD and estimated LSMeans percent change from baseline and SE, over time, for each endpoint will also be provided. In addition, the number of subjects, mean and median dose at each timepoint will be presented in the figures.

Fasting Lipid Panel data will be listed fully by age group using the SAF population set, as detailed in section 5.14.

5.12 Multiplicity

To address the efficacy objectives, the primary and key-secondary 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 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:

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 and thus should be interpreted with this in mind.

5.13 SAFETY EVALUATION

The safety and tolerability of lomitapide will be based on adverse events, and safety evaluations including clinical laboratory evaluations, vital signs and ECGs.

5.13.1 Adverse Events

AEs will be coded using the latest MedDRA dictionary version. The version used will be indicated in the data summaries and listings.

A TEAE is defined as an AE that started on or after the start of the administration of study treatment up to 30 days post last dose. If adverse event dates are incomplete and it is not clear whether the adverse event was treatment-emergent, it will be assumed to be treatment-emergent.

A non-treatment emergent adverse event (NTEAE) is defined as an AE that started on or after the start of the Run-in Period but before the administration of study treatment.

A treatment-related TEAE is defined as a TEAE with a reasonable causal relationship to the study treatment. If the TEAE has a missing relationship it is assumed to be related to the study treatment for analysis purposes.

Adverse events of special interest (AESI) are defined as follows and will be identified by medical review:

- 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
- Musculoskeletal adverse events and muscle-related biochemical abnormalities (e.g., creatinine kinase)

A summary table will present the following:

- TEAEs.
- Serious TEAEs (SAEs).
- Serious Related TEAEs.
- TEAEs leading to study discontinuation.
- Serious TEAEs leading to study discontinuation.
- Serious Related TEAEs leading to study discontinuation.
- Study treatment-related TEAEs leading to discontinuation of study.
- TEAEs leading to death.
- TEAEs by severity (mild/moderate/severe/life-threatening/death).
- TEAEs by relationship to study treatment category (unrelated/related).
- NTEAEs leading to death
- Treatment emergent AESI’s

- Treatment emergent AESI's leading to study discontinuation.
- Related Treatment emergent AESI's
- Major Adverse Cardiac Events (MACE) as defined by the medical team.
- Action taken with study treatment.

The following tables will be presented:

- TEAEs by SOC and PT
- TEAEs by SOC, PT and severity grade.
- TEAEs by SOC, PT and relationship to study treatment and the pooled related categories (related/unrelated).
- Most frequent TEAEs by SOC and PT defined as ≥2 patients reporting an AE
- Treatment emergent AESI's by AESI grouping, SOC and PT
- Elevated serum transaminases related TEAEs, by country, SOC and PT

Summaries will be presented by study phase (including follow-up) and overall. TEAEs will be presented in the study phase corresponding to their start date. For all of the above, SOC and PT will be presented in decreasing frequency of the total number of subjects with TEAEs, SAEs, and AESIs separately. If a subject experienced more than one TEAE, the subject will be counted once for each SOC and once for each PT. If a subject experienced more than one TEAE, the subject will be counted once using the most related event for the "by relationship to study treatment", "related to study treatment" summaries and the worst severity for the "by severity" summary.

For gastrointestinal and hepatic AEs the time to the first hastrointestinal and first hepatic TEAE will be summarized using the Kaplan-Meier method. Gastrointestinal TEAEs will be defined as the SOC 'Gastrointestinal disorders'. Hepatic TEAEs will be based on the Standardized MedDRA Query (SMQ) 'Drug related hepatic disorders – comprehensive search. In addition, for all gastrointestinal and hepatic AEs a histogram showing the time of onset from the first dose will be provided and a tabular summary of the duration of the events will be provided.

Adverse event data will be listed in full using the Enrolled population set and this will also include a treatment-emergent flag, a run-in flag, a flag to identify gastrointestinal and hepatic TEAEs, the time of onset and cessation of event relative to first dosing of study treatment and duration of AE.

All tables and listings will be presented separately for each age group. Subject profile plot for the distribution of TEAEs and dose at time of TEAE will be plotted.

Age profile for the distribution of TEAEs and MTD will be plotted. Two age profile plots will be displayed for (i) overall; (ii) related TEAEs.

Both subject profile and age profile graphics will be displayed for: (i) all subjects; (ii) each age group.

The following sub-group analyses for TEAEs and AESIs will be provided (presentations for SAEs, TEAEs leading to discontinuation and Grade 3 or higher TEAEs may also be provided):

- Age group (5-10 and 11-17)
- Sex (male, female)

5.14 Clinical Laboratory Evaluation

Clinical laboratory evaluation testing will include the following:

- Standard Haematology (CBC)
- Serum Clinical Chemistry
    - Metabolic panel
    - Liver Function Tests
    - Essential Fatty Acids
    - Fat-Soluble Vitamin levels
    - Hormones
    - Sex hormones
    - Serum Lipase
- Urinalysis

The observed change from baseline, and additionally, for serum clinical chemistry parameters, percentage change from baseline, will be summarised overall and by age group over time (using the nominal visit data).

Clinically significant observed values and clinically significant changes from baseline in haematology, biochemistry, and urinalysis assessments will be marked. If the test results are reported in categorical format, the results will be summarised by subject counts and percentage for each category.

Each haematology, biochemistry, and urinalysis parameter will be classed as low, normal, high, missing based on the reference ranges. Shift tables in relation to the normal range from baseline over time will be presented.

A descriptive summary of the maximum observed values for ALT, AST, total bilirubin, and alkaline phosphatase during the Efficacy Phase (Weeks 0-24), Safety Phase (After Week 24), and overall will also be provided. In addition, a figure of the maximum AST and ALT values vs the corresponding Total Bilirubin value will be provided during the Efficacy Phase (Weeks 0-24), Safety Phase (After Week 24), and overall.

A summary table will be produced for the number and percentage of subjects who have values of AST (>3, >5, >10, >20 x ULN), ALT (>3, >5, >10, >20 x ULN), AP (>1.5 x ULN), or TBL (>1.5, >2 x ULN) at each post baseline timepoint.

Time to Onset and Duration of Liver Function Test (LFT) Abnormalities (for AST and ALT) will also be summarized. The time to first LFT abnormality will be calculated as the date of the first LFT assessment that is ≥3 x ULN subtracted from the first dose date, plus 1. Duration will be calculated as the date of resolution of the first LFT abnormality (resolution defined as <3 x ULN) minus the date of the first LFT assessment that is ≥3 x ULN. Subjects with an ongoing elevation will be censored at their last laboratory assessment date containing both AST and ALT results.

A subject profile plot for the duration of LFT abnormalities and dose at time of LFT abnormality will be plotted, identifying hepatic TEAEs.

Haematology, biochemistry, and urinalysis will be listed separately including change from baseline, reference ranges flagging all out-of-range values and their clinical significance (using analysis visit data).

Listings of clinically significant haematology, biochemistry, and urinalysis laboratory measurements recorded throughout the study will be provided.

All tables and listings will be presented separately for each age group using the SAF population.

The following LFT profiles will be displayed:

- Individual subject profiles of liver function data will be displayed with all liver function data for a given subject on one graphic.
- AST and ALT profiles over time, by subject age, will be displayed.
- AST and ALT profiles over time, by subject MTD, will be displayed.

The following lipid profile plots will be displayed:

- Individual subject profiles of LDL-C over time.
- LDL-C profiles over time, by subject age.
- LDL-C profiles over time, by subject MTD.
- Spaghetti plots with individual lipid profiles, overall and by age group.

The AST, ALT and LDL-C profile plots will be displayed for: (i) all subjects; (ii) each age group. The individual subject profiles of LDL-C will present different symbols identifying dose adjustments and/or lipoprotein apheresis.

5.15 Vital Signs

Vital sign observed values, change and percentage change from baseline by parameter (unit) will be summarised over time (using analysis visit data).

The vital signs parameters to be presented are: weight, height, BMI, BSA, heart rate, respiration rate, systolic blood pressure, diastolic blood pressure and body temperature. Height and weight collected at baseline will be reported with the demography data.

The change from baseline in height / BMI percentile will be reported. Maximum, minimum and last post-baseline values will also be presented.

The change from baseline in height / BMI z-score will be reported. Maximum, minimum and last post-baseline values will also be presented.

Parameters will be presented in the same order as the CRF.

All vital sign data (observed values and change from baseline values) will also be plotted over time using boxplots to display the distribution over time. A waterfall plot of the percent change in BMI, by age group and sex, at Week 24, Week 56 and Week 104 will be presented. All vital sign data will be listed including change and percentage change from baseline (using analysis visit data). Subjects who just met inclusion criterion #3 of having a body weight ≥15 kg, while being below the 10^{th} percentile for Height and BMI, will be flagged.

All tables and listings will be presented separately for each age group using the SAF population.

5.16 Electrocardiogram

A 12-lead ECG will be recorded and read locally. The ECG recordings will be reviewed by the investigator and classified as 'normal' or 'abnormal'. Abnormal ECGs will be further classified as 'clinically significant' and 'not clinically significant'. Reasons for abnormal findings will be documented.

Findings from the 12-lead ECG examinations will be summarised overall and by age group over time (using analysis visit data). Shift tables from baseline over time will also be presented.

All tables and listings will be presented separately for each age group using the SAF population.

5.17 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. Findings from the standard of care echocardiography examination will be summarised overall and by age group (using analysis visit data). The number and percentage of subjects with a worsening from baseline (defined as a new condition or a progression of a current condition) will be summarised cumulatively over time overall and by age group.

Parameters will be presented in the same order as the CRF.

All tables and listings will be presented separately for each age group using the SAF population.

5.18 Lipid Accumulation in the Liver

Lipid accumulation in the liver will be assessed using NMR or ultrasound. 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.

The observed values and percent change from baseline values for hepatic fat will be summarised over time overall and by age group.

The number and percentage of patients with (i) ≤ 10% liver fat; (ii) >10% and ≤20% liver fat; (iii) >20% liver fat will be summarised overall and by age group over time (using analysis visit data), separately for ultrasound and NMR scan results. Shift tables from baseline over time will also be presented.

In addition, the number and percentage of patients with an increase of hepatic fat ≤5%, >5 to ≤10%, >10 to ≤15%, >15 to ≤20%, >20 to ≤25%, and >25%. 5 from baseline and the maximum post-baseline increase in hepatic fat will be summarized by timepoint

overall and by age group for NMR scan results. CDF plots of the change from baseline will also be provided by timepoint overall and by age group.

NMR scan at Site 12 failed and the assessments performed on Week 56 for 7 Site 12 subjects failed. The scans were repeated, approximately on Week 80, with a different scan. To explore the impact of the new scan used on Site 12 for the unscheduled Week 80 assessment and the Week 104 assessment, sensitivity analyses of the summaries outlined above, excluding Site 12 will be provided. Site 12 results will also be presented.

Tables and listings will be presented using the SAF population.

Scatter plot of the change in hepatic fat up to Week 56 and Week 104 with change in BMI Z-score up to Week 56, by subject age will be plotted.

Scatter plot of the change in hepatic fat up to Week 56 and Week 104 with changes in BMI Z-score up to Week 56, by subject MTD will be plotted.

Scatter plot of change in hepatic fat up to Week 56 and Week 104 and time from lomitapide administration, by subject age will be plotted.

Scatter plot of change in hepatic fat up to Week 56 and Week 104 and time from lomitapide administration, by subject MTD will be plotted.

All scatter plots will be displayed for: (i) all subjects; (ii) each age group.

To examine the relationship between liver steatosis and AST/ALT, scatter plots of ALT (and AST) versus hepatic fat at baseline, Week 24, Week 56 and Week 104 will be produced overall, grouped by age group, separately by imaging technology. Pearson's (for NMR) and Spearman's rank (for Ultrasound) correlation coefficient (and 95% confidence limit) will be included on the scatter plots.

5.19 Physical Examination and Tanner Staging

Individual subject physical examination and Tanner staging data will be listed (using analysis visit data).

To assess sexual maturation (Tanner staging) in patients with a Tanner stage ≥2, the observed values and change from baseline in sex hormones (i.e. serum testosterone and serum oestradiol) will be summarised overall and by age group over time.

Shift tables in Tanner staging results (1 to 5 and missing) from baseline over time will be summarised.

Spaghetti plots will be plotted to assess:

- sexual maturation development (i.e. Tanner staging) of each subject.
- growth development (i.e. BMI percentile) of each subject

Separate spaghetti plots for each age group and sex will be presented.

The following waterfall plots will be displayed:

- Change in BMI Z-score (baseline to Week 24, Week 56 and Week 104), by patient age;
- Change in BMI Z-score (baseline to Week 24, Week 56 and Week 104), by sex;

- Change in BMI Z-score (baseline to Week 24, Week 56 and Week 104), by baseline BMI for Age Z-score.
- Change from baseline to maximum weight loss (minimum post-baseline change from baseline) observed up to and including week 104, by age and gender
- Change from baseline to the minimum BMI z-score observed up to and including week 104, by age and gender

The following spaghetti plots will be displayed:

- Spaghetti plots of BMI Z-score over time by age, sex and baseline BMI-for-Age Z-score;
- Spaghetti plots of BMI absolute value over time by age and sex;
- Spaghetti plots of weight absolute value over time by age and sex.

Individual spaghetti plots of weight and BMI Z-scores over time, by subject. All plots will be displayed for: (i) all subjects; (ii) each age group.

All tables and listings will be presented separately for each age group using the SAF population.

5.20 Pulmonary Function Tests

Pulmonary function test observed values and change from baseline by parameter (unit) will be summarised over time (using analysis visit data). Parameters will be presented in the same order as the CRF. Shift tables from baseline over time will also be presented.

All pulmonary function test data will be listed including change from baseline. All tables and listings will be presented separately for each age group using the SAF population.

5.21 Diet and Dietary Supplement Compliance

Diet and dietary supplement compliance data will be listed.

A summary of the number and percentage of patients compliant with their low-fat diet and dietary supplement regimen overtime will be provided and compliance for the efficacy phase, the safety phase up to Week 56, and the safety phase up to Week 104 will be presented.

A patient will be considered compliant if during the respective phase, they indicated they were compliant with a low fat diet or dietary supplement regimen at least 80% of the time.

5.22 Pregnancy test

Pregnancy test details will be listed.

5.23 Visit Dates

Visit dates will be listed.

5.24 Exploratory Assessments

5.24.1 Xanthoma Assessment

The patient's xanthomas (tendon and cutaneous, size and location) will be evaluated during the physical examination.

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 and EOT / week 104 (using nominal visit data).

The number and percentage of patients with resolution and regression of pre-existing xanthoma (baseline) to Week 56 and EOT / Week 104 will be summarised overall and by age group.

The number and percentage of subjects with changes on pre-existing xanthoma from baseline (apparition of new xanthomas, increases in size, decreases in size or resolution) will be summarised cumulatively over time up to Week 104.

Tables and listings will be presented using the SAF population.

5.24.2 Carotid Intima-Media Thickness and Flow-mediated Dilation

CIMT (mandatory) and FMD (whenever possible) will be assessed using ultrasound scan and brachial artery dilation after a transient period of forearm ischaemia to evaluate carotid atherosclerotic vascular disease.

The percentage change from baseline in mean CIMT and mean FMD at Week 56 and EOT / Week 104 will be assessed overall and by age group (using nominal visit data).

*Percentage change = [(Week X – baseline) / baseline] * 100%*

Tables and listings will be presented using the SAF population.

5.24.3 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. In addition, a 3-point scale will be used to assess the parent(s)/legal guardian(s) interpretation of the child's reaction/facial expression. An assessment of ease of administration of medication and dietary supplements will also be asked of the parents(s)/legal guardian(s).

Palatability will be assessed on the first occasion that the patient is not able to swallow the intact capsule(s) and takes lomitapide by opening and sprinkling the capsule onto food media.

The number and percentage of patients will be presented over time for each question overall and by age group (using nominal visit data).

Tables and listings will be presented using the SAF population.

5.25 Changes from the Protocol Planned Analysis

The following is a list of changes and additional analyses after database lock for the Efficacy phase (Week 24) analysis and prior to the final analysis:

Changes:

1) Lp(a) data was missing from central lipid panels for all subjects (except Site 12) who had their baseline visits before January 2022. Lp(a) data was analysed based on local lab data in two different units (mass and molar). Given the limitations on conversion from mass to molar units, data were analysed separately by unit (either mg/dL or nmol/L; g/dL was converted to mg/dL). Statistical testing (t-test) as for the other endpoints was performed by unit and the p-values were combined using Fisher's method.

Additions:

2) Addition of HDL-C and TC/HDL-C ratio as non-keysecondary efficacy endpoints.
3) New recommended target LDL-C levels added as exploratory endpoints.
4) Addition of additional sensitivity analyses based on BOCF, Wilcoxon Signed-Rank test, subgroup analysis based on sex and responder analyses for primary and key secondary endpoints.

6 REFERENCES

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2. Gidding, S.S. et al. (2015) 'The agenda for familial hypercholesterolemia', Circulation, 132(22), pp. 2167–2192. doi:10.1161/cir.0000000000000297.