BEMPEDOIC ACID (ETC-1002)
1002-041

AN OPEN-LABEL STUDY TO EVALUATE THE PHARMACOKINETICS, PHARMACODYNAMICS, AND SAFETY OF BEMPEDOIC ACID IN PEDIATRIC PATIENTS (6 TO 17 YEARS OF AGE) WITH HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

Study Phase: 2

IND Number: [redacted]

EU CT Number: 2024-515864-30-00

Indication: Treatment of primary hyperlipidemia (primary hypercholesterolemia)

Investigators: Approximately 25 sites worldwide

Sponsor: Esperion Therapeutics, Inc.
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Version	Date
Original Protocol:	23 October 2018
Amendment 1:	22 February 2022
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Amendment 2.1*	29 January 2025

*Amendment 2.1 applies to European Union sites only

[redacted]

[redacted]

1. SYNOPSIS

Name of Sponsor/Company: Esperion Therapeutics, Inc.

Title of Study:
An Open-Label Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Bempedoic Acid in Pediatric Patients (6 to 17 Years of Age) with Heterozygous Familial Hypercholesterolemia.

Study Number: 1002-041

EU CT Number: 2024-515864-30-00

Phase of Development: 2

Clinical Sites: Approximately 25 sites worldwide

Name of Investigational Medicinal Product (IMP):
bempedoic acid 60- and 90-mg tablets
bempedoic acid liquid suspension (20 mg/mL) – Liquid suspension available for use through Protocol Amendment 1 only

Objectives:

Primary Objectives:

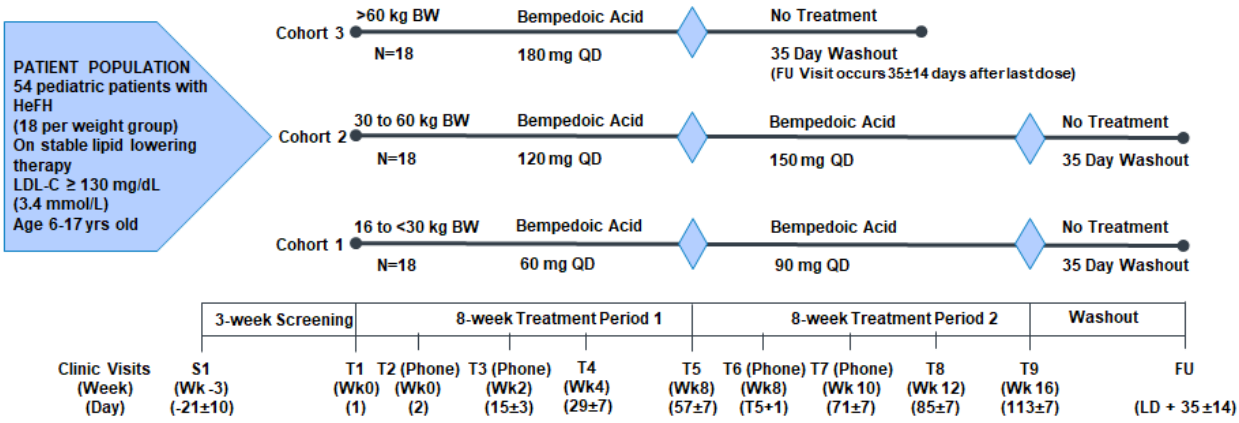
- To assess the pharmacokinetics (PK) of bempedoic acid (ETC-1002) in pediatric patients (6 to 17 years of age) with heterozygous familial hypercholesterolemia (HeFH) treated for 8 weeks.

Secondary Objectives:

- To assess the PK of ESP15228 (active metabolite).
- To assess bempedoic acid exposure/low-density lipoprotein cholesterol (LDL-C)-lowering response relationship.
- To assess the percent and absolute change from baseline to Weeks 8 and 16 in LDL-C, total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C), and high-sensitivity C-reactive protein (hsCRP).
- To monitor the acceptability (taste and ease of swallowing) of the age-appropriate formulations.
- To assess the safety and tolerability of bempedoic acid in pediatric patients with HeFH treated.

Study Design:

This is a Phase 2, open-label, uncontrolled, multicenter study of bempedoic acid administered for 8 and 16 weeks in pediatric patients (6 to 17 years of age) with HeFH and LDL-C ≥ 130 mg/dL (3.4 mmol/L) and who are on an optimal dose of statin. An overview of the study design is presented below.



Patients aged 6 to 17 years old with a history of HeFH and who are on an optimal dose of statin will be screened for eligibility during screening (prior to Visit T1) which will be conducted within 21 ± 10 days before planned enrollment into the study, but the period between Visit S1 and Visit T1 can be extended for an additional 14 days, if needed, to obtain written consent and records from family members for use of documented FH diagnosis described in inclusion criteria 4, or for other reasons. Patients who meet all inclusion/exclusion criteria will be scheduled for their first treatment visit.

Patients will report to the study site for the first treatment visit (Visit T1/Day 1) after a minimum 10-hour fast. Patients who continue to meet the study inclusion/exclusion criteria will be enrolled into different cohorts and will receive once daily bempedoic acid 60 mg (Cohort 1: 16 to <30 kg body weight, n = 18), 120 mg (Cohort 2: 30 to 60 kg body weight, n = 18), or 180 mg (Cohort 3: >60 kg body weight, n = 18). Body weight at Screening Visit S1 will be used to determine weight cohort assignment for the study.

At Day 2 (Visit T2) and Week 2 (Visit T3) sites will conduct a phone or telemedicine visit with patients to collect information on concomitant medications, treatment-emergent adverse events (TEAEs) and ability to swallow IMP. At Week 4 (Visit T4) and Week 8 (Visit T5), patients will return for clinic visits for safety and laboratory assessments. Patients in Cohort 3 will receive the last dose of 180 mg bempedoic acid the day prior to Visit T5. Patients in Cohort 1will dose escalate from 60 to 90 mg and Cohort 2 will dose escalate from 120 to 150 mg following clinical assessments at Visit T5. At Week 8 (Visit T6) and at Week 10 (Visit T7) the site will conduct a phone or telemedicine interview visit with patients in Cohort 1 and Cohort 2 to collect information on concomitant medications, TEAEs and ability to swallow IMP. Patients in Cohort 1 and Cohort 2 will return for clinic visits at Week 12 (Visit T8) and Week 16 (Visit T9) for safety and laboratory assessments. Patients in Cohort 1 and Cohort 2 will receive the last dose of bempedoic acid the day prior to Visit T9. All patients, including those who withdraw from treatment, will return 35 ± 14 days after receiving the final dose of bempedoic acid for the safety follow-up (Visit FU).

Patients will report to each of the study site visits after a minimum 10-hour fast approximately 24-hours after dosing from previous day and without having taken their dose of bempedoic acid and will bring their IMP with them. Alternatively, to accommodate scheduling of site visits later in the day without fasting

requirements; provisions are provided for use of local laboratories to collect fasting lab samples 24-hours after dosing from previous day if permitted and allowed by regional regulatory authorities, site practices and appropriate IRB/IEC. For local laboratory collection of fasting samples; within 7 days prior to site visits at Week 4 (Visit T4), Week 12 (Visit T8), Week 16 (Visit T9) and the Follow-Up visit (FU) laboratory samples may be collected at a local laboratory approved by the research site after a minimum 10-hour fast. Following collection at a local laboratory; samples must be processed and then shipped to the research site according to the instructions in the laboratory manual (provided by the central laboratory). Sample will be subsequently shipped to the central laboratory for protocol-specified analysis and tests.

Bempedoic acid will be administered after fasting blood and urine samples have been drawn. If fasting laboratory samples are collected at the site, then Study site personnel will administer the bempedoic acid to the patient. All other doses of bempedoic acid will be self-administered by the patients (with caregiver support as necessary) including dates with fasting laboratory samples are collected at a local laboratory. The last dose will be taken the day prior to the final clinic visit of the treatment period (Visit T9 for patients in Cohorts 1 and 2, Visit T5 for patients in Cohort 3).

Visits may be conducted by a qualified health care provider (HCP) with appropriate designated study responsibilities at the patient's home or alternative facility provided the site institution has a IRB/IEC approved policy that enables remote/at-home clinic visits that has been reviewed and approved by the Sponsor. Site visits can only occur at a location other than the site if all scheduled procedures can be assessed.

Controls will be established to ensure that approximately 25% of total patients are taking background ezetimibe.

An independent Data Monitoring Committee (DMC) will review accumulating blinded and unblinded safety data from this and other ongoing studies of bempedoic acid approximately 4 times per year. Safety data reviewed by the DMC will include AEs, clinical endpoints, and lipids. The committee has a charter that includes additional details.

Study Population:

54 male and female patients aged 6 to 17 years old (approximately 18 patients in each weight cohort: Cohort 1, 16 to <30 kg, Cohort 2, 30 to 60 kg, and Cohort 3 >60 kg) with a history of HeFH and who are on an optimal dose of statin and who meet the inclusion and exclusion criteria will be enrolled.]

Subject Inclusion Criteria

Patients must satisfy all the following criteria during Screening (Prior to Visit T1 unless otherwise specified) for enrollment in the study:

1. The patient's parent(s)/guardian(s) must be willing to provide written informed consent and the patient must provide informed assent before any study-specific procedures are performed;
2. The patient must be aged 6-17 years old and willing to swallow tablets;
3. The patient must weigh at least 16 kg;
4. The patient must have a diagnosis of HeFH prior to receiving the first dose of study medication at Treatment Visit T1 per MEDPED (Make Early Diagnosis to Prevent Early Deaths project) criteria by meeting at least one of the following clinical criteria*:
   a) Documented diagnosis of HeFH determined by positive genetic testing; or
   b) Documented LDL-C or total cholesterol (TC) meeting one or more of the following criteria:

i. LDL-C >200 mg/dL (5.2 mmol/L) or TC >270 mg/dL (7.0 mmol/L), with no first-second- or third-degree relative with documented FH diagnosis (general population); or

ii. LDL-C >155 mg/dL (4.0 mmol/L) or TC >220 mg/dL (5.7 mmol/L), and also having a first-degree relative with documented familial hypercholesterolemia (FH) diagnosis; or

iii. LDL-C >165 mg/dL (4.3 mmol/L) or TC >230 mg/dL (5.9 mmol/L), and also having a second-degree relative with documented FH diagnosis; or

iv. LDL-C >170 mg/dL (4.4 mmol/L) or TC >240 mg/dL (6.2 mmol/L), and also having a third-degree relative with documented FH diagnosis

*Note: Adapted from MEDPED criteria (Williams 1993). Secondary causes of hypercholesterolemia, such as nephrosis, pregnancy, hypothyroidism, obstructive jaundice/obstructive liver disease, corticosteroid medications, familial combined hyperlipidemia, homozygous FH (HoFH) and Cushing's disease will be assessed by the investigator and must be precluded. The LDL-C value at screening Visit S1 or documented LDL-C value in medical charts may be applied toward criteria; if triglycerides are greater than 400 mg/dL at the time of the applicable LDL-C value, then LDL-C measured by ultracentrifugation must have been used. Positive genetic testing documenting HeFH mutations in LDL receptor (LDLr), apolipoprotein B (ApoB), low-density lipoprotein receptor adaptor protein 1 (LDLRAP1), and proprotein convertase subtilisin/kexin type 9 (PCSK9) genes may be documented in medical records or assessed as part of this trial prior to randomization provided patient/parental/guardian consent or assent to perform optional genetic testing during trial screening prior to randomization and according to country specific regulations. First-degree relatives include parents, offspring, brothers and sisters; second-degree relatives include aunts, uncles, grandparents, nieces, nephews; third-degree relatives include first cousins and siblings of grandparents. First-, second- or third-degree relatives may need written consent in advance authorizing the collection of documented FH diagnosis depending on local law requirements for access and sharing of personal information.

5. Current treatment with approved stable lipid-modifying therapy (LMT), including an optimal dose of statin with or without other LMT(s), at stable dose for at least 4 weeks prior to Treatment Visit T1 (6 weeks for fibrates; however, gemfibrozil is not allowed in patients taking a statin as per co-administration instructions defined in the statin label). Patients must remain on that stable dose throughout the duration of the trial.

   Optimal dose of statin will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of LMT. A patient's optimal dose of statin is defined as meeting one of the following criteria:

   a) the highest approved dose of statin prescribed for the age of the patient based on regional practice or local guidelines; or
   b) less than the highest approved dose of statin, including no statin, prescribed for the age of the patient based on regional practice or local guidelines (including no statin) if:

      i. the patient has previously taken 2 or more statin therapies at any dose and not able to tolerate or unresponsive due to their mutations (null); or

ii. the patient has previously taken 1 or more statin therapies at any dose and is unwilling to attempt another statin at any dose or advised by a physician to not attempt another statin at any dose.

c) Patient/parent and investigator attestation to the patient's unwillingness to attempt and/or physician advice to not attempt additional statin therapy will be recorded.

6. The patient must have a fasting LDL-C level ≥130 mg/dL (3.4 mmol/L) while on stable LMT as defined in inclusion criteria 5;

7. The patient may be male or female. Females must not be pregnant (or planning to become pregnant within 30 days after the last dose of investigational medicinal product (IMP) or breastfeeding and must be sexually inactive or willing to use 1 acceptable method of birth control. The minimal requirement for use of acceptable contraception is from the time the informed consent form (ICF) is signed, during the study period, and for at least 30 days after the last dose of IMP. Acceptable methods of birth control include:

   a) placement of an intrauterine device (IUD) with or without hormones,
   b) established use of oral, implanted, topical, or injectable, or hormonal method of contraception associated with inhibition of ovulation, or
   c) barrier methods, including condom or occlusive cap with spermicidal foam or spermicidal jelly

   There are no protocol-specific birth control requirements for males who have partners that can become pregnant.

Subject Exclusion Criteria

Patients who meet any of the following criteria during Screening (Prior to Visit T1 unless otherwise specified) will be excluded from the study:

1. The patient has a diagnosis of homozygous familial hypercholesterolemia (HoFH) or compound HeFH;
2. The patient has a fasting triglyceride (TG) level ≥400 mg/dL (4.5 mmol/L);
3. The patient has uncontrolled hypothyroidism, including a value for thyroid-stimulating hormone (TSH) < lower limit of normal (LLN) or >1.5 × the upper limit of normal (ULN);
4. The patient has liver disease or dysfunction, including:
   a. positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C virus antibodies (HCV-AB), or
   b. serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value ≥2 × ULN and/or serum total bilirubin (TB) value ≥2 × ULN. If the serum TB value is ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and, if consistent with Gilbert's disease or if the patient has a history of Gilbert's disease, the patient may be enrolled in the study.
5. The patient has renal dysfunction or glomerulonephritis, including an estimated glomerular filtration rate (eGFR) <75 mL/min/1.73 m^2 (as determined by the central laboratory using the Revised ["Bedside"] Schwartz formula);
6. The patient has Stage 2 hypertension (based on gender, age and height; see Appendix 4);
7. The patient has a gastrointestinal condition that may affect drug absorption;
8. The patient has a history of hematologic or coagulation disorders, anemia, or a hemoglobin (Hgb) level <11.5 g/dL;
9. The patient has type 1 or type 2 diabetes, or newly diagnosed impaired glucose tolerance (within 3 months of Screening);
10. The patient had an active malignancy, including those requiring surgery, chemotherapy, and/or radiation, in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed;
11. The patient has an unexplained (ie, not associated with recent trauma or physically strenuous activity) serum creatine kinase (CK) value >3 × ULN at any time before randomization. Patients with an explained elevation in serum CK must have single repeat serum CK value ≤3 × ULN before enrollment;
12. The patient has a history of drug or alcohol abuse within the last 2 years or is unwilling to refrain from alcohol consumption for the duration of the study, or uses any illicit drugs, or has a history of amphetamine or derivatives abuse or cocaine abuse. Patients who are using amphetamine derivatives prescribed by and who are under the care of a health care practitioner can be enrolled after evaluation by the Investigator;
13. The patient has donated blood, undergone multiple blood draws in a clinical study, experienced major trauma, received a blood transfusion, or undergone surgery, with or without blood loss, within 30 days before enrollment;

14. The patient has used any experimental or investigational drugs within 30 days before screening and throughout the trial;
15. The patient has previously participated in a clinical study of bempedoic acid;
16. The patient is taking any of the following medications or therapies, except as indicated below:
    a. Mipomersen or lomitapide (current or within 6 months of Screening).
    b. PCSK9 inhibitors including evolocumab or alirocumab (current or within 3 months of Screening).
    c. Lipid apheresis (current or within 8 weeks of Screening or intends to have lipid apheresis treatments throughout the trial).
    d. Systemic corticosteroids (current or within 4 weeks prior to enrollment; topical and inhaled corticosteroids are allowed).
    e. Red yeast rice extract (also known as monascus purpureus extract or Cholestin) containing products (current or within 4 weeks of Screening);
    f. Lipid altering nutritional supplements including berberine, psyllium (Metamucil®), green tea extract, sitostanol (found in oral nutritional supplements and some margarines, such as Benecol), beta-sitosterol (found in oral nutritional supplements and some margarines, such as Promise Activ), pantothine and policosanol (current or within 4 weeks of Screening).
    g. Bile acid sequestrants, fibrates, omega 3 fatty acids, or niacin, unless the dose has been stable for ≥6 weeks prior to Screening and will remain stable throughout the trial.
    h. Simvastatin >20 mg or pravastatin >40 mg (current or within 4 weeks of Screening).
17. The patient has a history or evidence of any other clinically significant condition or planned or expected procedure that in the opinion of the Investigator, may compromise the patient's safety or ability to complete the study.
18. The patient has a situational (ie, geographical) finding that, in the Investigator's opinion, may compromise the patient's safety or ability to complete the study;
19. The patient is an employee or contractor of the facility that is conducting the study or is a family member of the Investigator, sub-Investigator, or any Sponsor personnel.

IMP Dosage and Mode of Administration:

Bempedoic acid is supplied as 60- and 90-mg tablets and as a liquid suspension (20 mg/mL). – Liquid suspension available for use through Protocol Amendment 1 only.

Bempedoic acid dosage is individually determined based on weight at Screening Visit S1 and treatment period and includes:

- Cohort 1: 16 to <30 kg body weight at Screening Visit S1
  - 60 mg (one 60-mg tablet),
  - 90 mg (one 90-mg tablet),
- Cohort 2: 30 to 60 kg body weight at Screening Visit S1
  - 120 mg (two 60-mg tablets),
  - 150 mg (one 60-mg and one 90-mg tablet), and
- Cohort 3: >60 kg body weight at Screening Visit S1
  - 180 mg (two 90-mg tablets).

All IMP will be ingested orally once daily at a similar time of day with or without food.

All IMP will be provided by Esperion Therapeutics.

Study Duration:

The expected study duration is cohort-dependent: approximately 169 days for Cohort 1 and 2 (participating in both Treatment Period 1 and 2) and 113 days for Cohort 3 (participating in Treatment Period 1 but not Treatment Period 2), including an approximate 21-day screening period (Visit S1/Day -21), followed by a 57-day Treatment Period 1 beginning at Day 1 and ending at Day 57 (Visit T5). A dose escalation for Cohort 1 and Cohort 2 will begin at Day 57 (Visit T5) through a 57-day Treatment Period 2 and ending at Day 113 (Visit T9); while Cohort 3 will not participate in Treatment Period 2. All patients will complete the trial after a follow-up visit (Visit FU) 35 days after receiving the last dose of bempedoic acid, occurring at approximately Day 148 for patients in Cohort 1 and Cohort 2, and at approximately Day 92 for patients in Cohort 3. Cohort 1 and Cohort 2 are anticipated to attend 7 site visits and participate in 4 phone interview visits during the course of the study. Cohort 3 is anticipated to attend 4 site visits and participate in 2 phone interview visits during the course of the study.

Criteria for evaluation:

Primary Endpoints

- Observed trough plasma concentration of ETC-1002 following 8 weeks of steady-state dosing of bempedoic acid
- Model-based PK parameters including steady-state estimates of:
  - area under the plasma concentration-time curve (AUC^{ss}),
  - average plasma concentration ($C_{avg,ss}$) and
  - maximum plasma concentration ($C_{max,ss}$)

Secondary Endpoints

- Observed trough plasma concentration of ESP15228 (active metabolite) following 8 weeks of steady-state dosing of bempedoic acid
- Plasma concentration at 4 hours (C_{4hr}) of ETC-1002 and ESP15228 following first dose
- ETC-1002 dose and exposure/LDL-C-lowering response relationship.
- Percent and absolute from baseline to Weeks 8 and 16 in LDL-C, TC, non-HDL-C, and hsCRP.
- Evaluation of acceptability (taste and ease of swallowing) of the age-appropriate formulations.

Safety Endpoints

- Adverse events;
- Clinical safety laboratories (hematology, clinical chemistry, and urinalysis);
- Vital signs;
- Electrocardiogram (ECG) readings;
- Physical examinations (PEs).

Clinical Laboratory Assessments:

- Hematology: Hematocrit (Hct), Hgb, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, red blood cell (RBC) count, white blood cell (WBC) count with differential (absolute values only).
- Serum Chemistry (fasting): Albumin (ALB), alkaline phosphatase (ALK-P), ALT (or serum glutamic pyruvic transaminase [SGPT]), AST (or serum glutamic oxaloacetic transaminase [SGOT]), blood urea nitrogen (BUN), calcium (Ca), carbon dioxide (CO_2), chloride (Cl), creatinine, CK, glucose, glycosylated hemoglobin A1c (HbA1c), lactate dehydrogenase (LDH), phosphorus, potassium (K), sodium (Na), total and direct bilirubin, total protein, uric acid.
- Urinalysis (dipstick): clarity, bilirubin, color, glucose, ketones, leukocyte esterase, nitrate, occult blood, pH, protein, specific gravity, urobilinogen. Urinalysis (microscope – only if dipstick result is abnormal): bacteria, casts, crystals, epithelial cells, red blood cells (RBC), white blood cells (WBC).
- Other assessments: HBsAg, hepatitis C virus (HCV), urine pregnancy test (only for females who are of childbearing potential), TSH.
- Specialty laboratories for this pediatric population: cortisol, dehydroepiandroestrone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (in females), testosterone (in males) and urine pregnancy (in female patients of childbearing potential) to be assessed at Visits S1, T1, T5 and T9. Prothrombin Time (PT) and International Normalized Ratio (INR) tests assessed as-needed accompanying repeat liver function test (LFT) elevation per Section 14.6.4.1.

Statistical Methods

Sample Size

The sample size in this PK/PD study (54 patients; approximately 18 patients per weight group) was selected to provide adequate data to support the dose selection, sample-size calculation, and general study design considerations for subsequent Phase 3 studies in this patient population (Julious 2005). The sample size of 54 patients accounts for at least 16 evaluable patients per cohort, accounting for a 10% dropout rate, and is expected to provide approximately 90% power to detect a difference of 25% in clearance of bempedoic acid measured by the primary endpoint of observed trough plasma concentration of ETC-1002 following 8 weeks of steady-state dosing of bempedoic acid. These power calculations are based on simulations to detect a 25% change in CL/F stratified by weight cohort using a smoothed parametric bootstrapping procedure of 1000 sets of parameters generated using the multivariate normal distribution as an approximate asymptotic posterior distribution based on the final estimates from and variance-covariance matrix from the adult base PK model output. Controls will be established to ensure that approximately 25% of total patients are taking background ezetimibe across the study to provide sufficient representation to assess patients taking concurrent bempedoic acid and ezetimibe.

Analysis Populations

The following analysis populations will be defined:

- The PK population will include all patients who receive at least 1 dose of bempedoic acid and have at least 1 evaluable PK data point.
- The full analysis population, used for all PD and safety related analysis, will include all patients enrolled into the study (all patients who receive at least 1 dose of bempedoic acid). .
- The completer population will include all patients who complete all assigned treatment-period doses.

Subgroups by IMP Formulation

Primary, secondary, and safety endpoints will be analyzed by subgroups of IMP formulation. The details will be specified in the Statistical Analysis Plan (SAP).

Disposition, Demographic, and Baseline Characteristics

Disposition, including reason for withdrawal from the study, will be summarized by cohort. Demographic and other baseline characteristics will be summarized by cohort and formulation using descriptive statistics (number, mean, median, standard deviation, minimum, and maximum) for continuous variables and counts and percentages for categorical variables.

Baseline is defined as the last assessment measurements before the first dose of IMP. No missing data of postbaseline will be imputed in this study.

Pharmacokinetic and Exposure-Response Analyses

The primary PK parameters are based on the most appropriate structural and error population model including a full covariate analysis that best describes the concentration-time relationship through iterative model fitting using nonlinear mixed effects modeling (NONMEM). Initial model development will be based on experience gained from population PK modeling in adults.

The typical values for plasma PK parameters of ETC-1002 will be estimated using population PK analyses.

The following individual PK parameters will be determined for each patient, based on the plasma concentrations of ETC-1002:

- AUC_{ss} area under the plasma concentration-time curve over the dosing interval at steady state
- $C_{max,ss}$ maximum plasma concentration at steady state
- $C_{avg\ ss}$ average plasma concentration over the dosing interval at steady state
- C_{trough} plasma concentration observed just prior to dosing

Other parameters may be added as appropriate; the final model-based parameters and post hoc PK parameter estimates reported will be detailed in the statistical analysis plan (SAP).

Pharmacodynamic and Exposure-Response Analyses

Descriptive statistics (number, mean, median, standard deviation, minimum, maximum, Q1, Q3) will be used to summarize LDL-C, TC, HDL-C, non-HDL-C, TGs, and hsCRP at each assessment by cohort and

formulation to summarize the change from baseline and the percent change from baseline by cohort at each postbaseline assessment.

A model for exposure–LDL-C response will be developed that can provide simulations for dosing recommendations in subsequent pediatric trials. Clinically relevant safety observations may be included in determining an optimal dose regimen/therapeutic index for pediatric patients' therapeutic index.

Adverse Events

The summarization of AEs will include TEAEs, defined as AEs with an onset date on or after initiation of study treatment. TEAEs and SAEs will be summarized by system organ class (SOC), severity, and relationship to study drug for each cohort. These AE summaries will include cumulative incidence (percent of patients experiencing the AE) and patient-year adjusted incidence rates. If appropriate, absolute and relative risk differences will be calculated using both cumulative incidence and patient-year adjusted incidence rates. Deaths and withdrawal from study treatment due to AEs will each be summarized by cohort and formulation. Each AE will be coded using the latest version of MedDRA.

Safety narratives will be generated for deaths, AEs leading to discontinuation of bempedoic acid or study, pregnancies, SAEs, and SUSARs. These safety events will also be summarized overall and by cohort and formulation.

All AEs of Special Interest (AESI) will be identified and evaluated by routine safety monitoring of AEs and laboratory values (where appropriate) and will be summarized by severity and relationship to IMP for each cohort and formulation.

The following are considered AESI for this study:

- Hepatic Safety, including liver-associated enzymes, TB, and any Hy's law cases (≥3 × ULN for either ALT or AST, with accompanying TB >2 × ULN in the setting of no known other cause)
- Musculoskeletal Safety, including CK
- Diabetes and Glycemia, including new onset of diabetes and worsening of diabetes
- Hypoglycemia Associated with Metabolic Acidosis
- Renal Impairment, including lab measures of renal function
- Neurocognitive Events
- Atrial Fibrillation
- Tendon rupture

Laboratory Values, Physical Exam, ECG and Vital Signs

Clinical safety laboratories, including hematology and blood chemistry; PE findings, ECG and vital signs will be summarized by the value and by change from baseline in the value (where appropriate) at each post-baseline time point for each cohort and formulation.

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
ACL	adenosine triphosphate-citrate lyase
ACS	acyl-CoA synthetase
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALB	Albumin
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase
ApoB	apolipoprotein B
ASCVD	Atherosclerotic Cardiovascular Disease
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
AUC_{ss}	area under the plasma concentration-time curve over the dosing interval at steady state
BCS	Biopharmaceutical Classification System
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
C_{4hr}	Plasma concentration at 4 hours
$C_{max, ss}$	maximum plasma drug concentration at steady state
Ca	Calcium
$C_{avg\ ss}$	average plasma concentration over the dosing interval at steady state
CCMO	Central Committee on Research Involving Human Subjects
CFR	Code of Federal Regulations
CI	confidence interval
CIMT	carotid intima-media thickness
CK	creatine kinase
Cl	Chloride
CO_2	carbon dioxide

Abbreviation or Specialist Term	Explanation
CrCl	creatinine clearance
C_{trough}	observed plasma concentration observed just prior to dosing
CV	Cardiovascular
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EU	European Union
eCRF	electronic case report form
EENT	eyes, ears, nose, and throat
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
ESP15228	metabolite of bempedoic acid (ETC-1002)
ETC-1002	bempedoic acid
FDA	Food and Drug Administration
FH	familial hypercholesterolemia
FSH	follicle-stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
HbA_{1C}	glycosylated hemoglobin, type A_{1C}
HBsAg	hepatitis B surface antigen
HCT	Hematocrit
HCV	hepatitis c virus
HCV-AB	hepatitis C virus antibody
HDL-C	high-density lipoprotein cholesterol
HeFH	heterozygous familial hypercholesterolemia
Hgb	Hemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
hsCRP	high-sensitivity C-reactive protein
HTN	Hypertension
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee

Abbreviation or Specialist Term	Explanation
IMP	investigational medicinal product(s)
IND	investigational new drug
INR	international normalized ratio
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web response system
K	Potassium
LDH	lactate dehydrogenase
LDL-C	low-density lipoprotein cholesterol
LDLR	low-density lipoprotein receptor
LDLRAP1	low-density lipoprotein receptor adaptor protein 1
LFT	liver function test
LH	luteinizing hormone
LLN	lower limit of normal
LMT	lipid-modifying therapy
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MEDPED	Make Early Diagnosis to Prevent Early Deaths project
N/A	not available
Na	Sodium
N/D	not done
Non-HDL-C	non-high-density lipoprotein cholesterol
NONMEM	nonlinear mixed effects modeling
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic(s)
PE	physical examination
PK	pharmacokinetic(s)
PT	prothrombin time
RBC	red blood cell
RNA	ribonucleic acid

Abbreviation or Specialist Term	Explanation
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
PATIENT ID	patient identification number
SUSARs	suspected unexpected serious adverse reactions
TB	total bilirubin
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	Triglycerides
TSH	thyroid-stimulating hormone
UGT	uridine-5'-glucuronyltransferase
ULN	upper limit of normal
US	United States
WBC	white blood cell

3. INTRODUCTION

3.1. Heterozygous Familial Hypercholesterolemia in Pediatric Patients

Familial hypercholesterolemia (FH) is an autosomal dominant disorder resulting in markedly elevated low-density lipoprotein cholesterol (LDL-C) levels from birth onward to prevent future atherosclerotic cardiovascular disease (ASCVD). Exposure to elevated LDL-C at a young age is an independent ASCVD risk factor (Gidding 2019). The most common indication for statin therapy in children is heterozygous familial hypercholesterolemia (HeFH). Children with HeFH have inherited a genetic mutation from one parent (Daniels 2011; Wiegman 2015). Mutations leading to HeFH impact LDL receptor (LDLR) function including those of the LDL receptor (LDLR), apolipoprotein B (ApoB), low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) and proprotein convertase subtilisin/kexin type 9 (PCSK9) (Goldberg 2011, Tada 2011). HeFH should be suspected in children with repeat LDL-C level ≥160 mg/dL (4.14 mmol/L) (Wiegman 2015). HeFH is estimated to exist globally in approximately 1 in 250 individuals (Wald 2016, Akioyamen 2017).

In the pediatric population (from birth to age 17 years), FH can be diagnosed either via genetic testing or clinically using one of several validated diagnosis tools and pediatric adaptations where available (Simon Broome Registry, Make Early Diagnosis to Prevent Early Death [MED-PED], Dutch Lipid Network) (World Health Organization. Familial hypercholesterolemia (FH) 1998; Committee Simon Broome Register Group 1991; Williams 1993; Fouchier 2001). Based on current guidelines in the United States (US) and Europe, most children with HeFH are candidates for lipid-lowering medication with statins as the preferred agents (Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents 2011; Youngblom 2014; Grundy 2018).

Lipid-lowering therapy, typically statins, is recommended in children with HeFH whose LDL-C remains significantly elevated following dietary treatment. Studies ranging in length from 12 weeks to 2 years in children with HeFH have consistently shown that statins are safe and well tolerated in children (Knipscheer 1996; Lambert 1996; Stein 1999; De Jongh 2002; De Jongh 2002a; De Jongh 2002b; McCrindle 2003; Avis 2010; Vuorio 2019). Treatment beginning in adolescence dramatically reduces atherosclerotic events and reduces cardiovascular (CV) mortality compared to their parents (Luirink 2019).

Despite the use of available lipid-lowering therapies (including maximally tolerated statin therapy), some children with HeFH fail to achieve their lipid goals (Langslet 2015; Humphries 2018). These pediatric patients may benefit from additional non-statin lipid-lowering therapies.

Bempedoic acid and bempedoic acid and ezetimibe, under the marketed names of Nexletol® and Nexlizet™ respectively, have been approved by the United States (US) Food and Drug Administration (FDA) as an adjunct to diet and maximally tolerated statin therapy for the treatment of heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease in adults who require additional lowering of LDL-C (Nexletol 2020; Nexlizet 2020). In the European Union (EU) bempedoic acid and bempedoic acid and ezetimibe have been approved by the European Commission and are marketed under the names Nilemdo® and Nustendi®, respectively, for the treatment of primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia as an adjunct to diet: in combination with a

statin or statin with other lipid-lowering therapies in adults unable to reach LDL-C goals with the maximum tolerated dose of statin, or alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant or for whom a statin is contraindicated. Additionally, Nustendi® is indicated in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin (Nilemdo 2020; Nustendi 2020).

The availability of new lipid-modifying treatments could be beneficial for children with elevated LDL-C due to FH who are not meeting their LDL-C goals with currently available therapies. This 16-week, open-label, dose-escalation study will be to evaluate the pharmacokinetic (PK)/pharmacodynamic (PD) relationship of bempedoic acid in pediatric patients with HeFH on stable statin therapy ± ezetimibe. The results of this study will be used to select the appropriate dose of bempedoic acid for Phase 3 studies.

3.2. Overview of Bempedoic Acid

Bempedoic acid is an inhibitor of adenosine triphosphate-citrate lyase (ACL) (adenosine triphosphate [ATP] citrate lyase), an enzyme upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase in the cholesterol biosynthesis pathway. It is an oral, first-in-class small molecule designed to lower LDL-C levels in patients with primary hyperlipidemia and high CV risk. Bempedoic acid has been evaluated in a large Phase 3 program as an adjunct to diet alone or in combination with other lipid-lowering therapies, including maximally tolerated statins which may have included no statin, for treatment of adults with primary hyperlipidemia who require additional lowering of LDL-C. The available nonclinical and clinical experience with bempedoic acid is available in the current edition of the Investigator's Brochure.

3.3. Risk-Benefit Assessment

Nonclinical and clinical data indicate that bempedoic acid has a favorable risk-benefit profile in indicated patients. The ability of bempedoic acid to achieve clinically meaningful LDL-C-lowering responses while demonstrating a favorable adverse event (AE) profile has been demonstrated in a variety of patient populations when given alone and as add-on therapy to statins and other lipid-lowering therapies, including ezetimibe. The Phase 3 program for bempedoic acid 180 mg comprised more than 3500 adult patients with elevated LDL-C and included studies with treatment durations up to 52 weeks. A large cardiovascular outcomes trial is underway. No clinically significant safety concerns have been identified that would preclude the continued development of bempedoic acid in children with HeFH. The following warnings, precautions and clinical trial experience for the use of bempedoic acid in adults are summarized in the US package insert (Nexletol 2020).

Hyperuricemia

Bempedoic acid inhibits renal tubular organic anion transporter 2 (OAT2) and may increase blood uric acid levels. In clinical trials, 26% of bempedoic acid-treated patients with normal baseline uric acid values (versus 9.5% placebo) experienced hyperuricemia one or more times, and 3.5% of patients experienced clinically significant hyperuricemia reported as an adverse reaction (versus 1.1% placebo). Increases in uric acid levels usually occurred within the first 4 weeks of treatment initiation and persisted throughout treatment. After 12 weeks of treatment,

the mean placebo-adjusted increase in uric acid compared to baseline was 0.8 mg/dL for patients treated with bempedoic acid. Elevated blood uric acid may lead to the development of gout. Gout was reported in 1.5% of patients treated with bempedoic acid and 0.4% of patients treated with placebo. The risk for gout events was higher in patients with a prior history of gout (11.2% bempedoic acid versus 1.7% placebo), although gout also occurred more frequently than placebo in patients treated with bempedoic acid who had no prior gout history (1.0% bempedoic acid versus 0.3% placebo).

Tendon Rupture

Bempedoic acid is associated with an increased risk of tendon rupture or injury. In clinical trials, tendon rupture occurred in 0.5% of patients treated with bempedoic acid versus 0% of placebo treated patients and involved the rotator cuff (the shoulder), biceps tendon, or Achilles tendon. Tendon rupture occurred within weeks to months of starting bempedoic acid. Tendon rupture may occur more frequently in patients over 60 years of age, in those taking corticosteroid or fluoroquinolone drugs, in patients with renal failure, and in patients with previous tendon disorders.

Most Frequent Adverse Event

Treatment-emergent adverse events (TEAE) occurring in ≥2% of patients and occurring greater than placebo in patients treated with bempedoic acid while on background statins and other lipid-lowering therapies for 52 weeks in Phase 3 trials of adult patients with ASCVD and/or HeFH are presented in Table 1 (Nexletol 2020). Additional information on clinical trial experience with bempedoic acid can be found in the current edition of the Investigator's Brochure.

Table 1: Most Common TEAE in 52-Week Phase 3 Trials in Adult Patients with ASCVD and/or HeFH

Treatment-Emergent Adverse Events	Bempedoic Acid (n = 2009) %	Placebo (n = 999) %
Upper respiratory tract infection	4.5	4.0
Muscle spasms	3.6	2.3
Hyperuricemia[a]	3.5	1.1
Back pain	3.3	2.2
Abdominal pain or discomfort[b]	3.1	2.2
Bronchitis	3.0	2.5
Pain in extremity	3.0	1.7
Anemia	2.8	1.9
Elevated liver enzymes[c]	2.1	0.8

[a] Hyperuricemia includes hyperuricemia and blood uric acid increased preferred terms.
[b] Abdominal pain or discomfort includes abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.
[c] Elevated liver enzymes includes AST increased, ALT increased, hepatic enzyme increased, and liver function test increased.

Currently there is no information regarding efficacy and safety of bempedoic acid in children or adolescents. Nonclinical studies in juvenile rats have been completed and the results support the safety of the selected doses for this study (see Investigator's Brochure).

The population PK model suggests that body weight and estimated creatinine clearance (CrCl) are parameters related to bempedoic acid exposure, and these factors have been taken into account when estimating the starting doses for this initial clinical study in children (see Section 6.2). Pediatric patients with abnormal renal function having an estimated glomerular filtration rate (eGFR) < 75 mL/min/1.73 m^2 (Pottel 2015) will be excluded in this Phase 2 trial to reduce the potential confounding impact of CrCl on PK assessment of the selected doses.

Taken together, these data support further development of bempedoic acid to treat elevated LDL-C in pediatric patients with HeFH. This study will be the first study of bempedoic acid in children and adolescents and will provide important information on safety, PK, and PD that will aid in the design of future Phase 3 studies in this population.

4. TRIAL OBJECTIVES AND PURPOSE

4.1. Primary Objectives

- To assess the pharmacokinetics (PK) of bempedoic acid (ETC-1002) in pediatric patients (6 to 17 years of age) with HeFH treated for 8 weeks.

4.2. Secondary Objectives

- To assess the PK of ESP15228 (active metabolite).
- To assess bempedoic acid exposure/LDL-C-lowering response relationship;
- To assess the absolute and percent change from baseline to Weeks 8 and 16 in LDL-C, total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C) and high-sensitivity C-reactive protein (hsCRP);
- To monitor the acceptability (taste and ease of swallowing) of the age-appropriate formulations;
- To assess the safety and tolerability of bempedoic acid in pediatric patients with HeFH treated with escalating, multiple oral doses of bempedoic acid based on body weight for 8 and 16 weeks.

4.3. Study Endpoints

4.3.1. Primary Endpoints

- Observed trough plasma concentration of ETC-1002 following 8 weeks of steady-state dosing of bempedoic acid;
- Model-based PK parameters including steady-state estimates of:
  - area under the plasma concentration-time curve (AUC_{ss}),
  - average plasma concentration ($C_{avg,ss}$) and
  - maximum plasma concentration ($C_{max,ss}$).

4.3.2. Secondary Endpoints

- Observed trough plasma concentration of ESP15228 (active metabolite) following 8 weeks of steady-state dosing of bempedoic acid;
- Plasma concentration at 4 hours (C_{4hr}) of ETC-1002 and ESP15228 following first dose;
- ETC-1002 dose and exposure/LDL-C-lowering response relationship;
- Percent and absolute from baseline to Weeks 8 and 16 in LDL-C, TC, non-HDL-C, and hsCRP;
- Evaluation of acceptability (taste and ease of swallowing) of the age-appropriate formulations.

4.3.3. Safety Endpoints

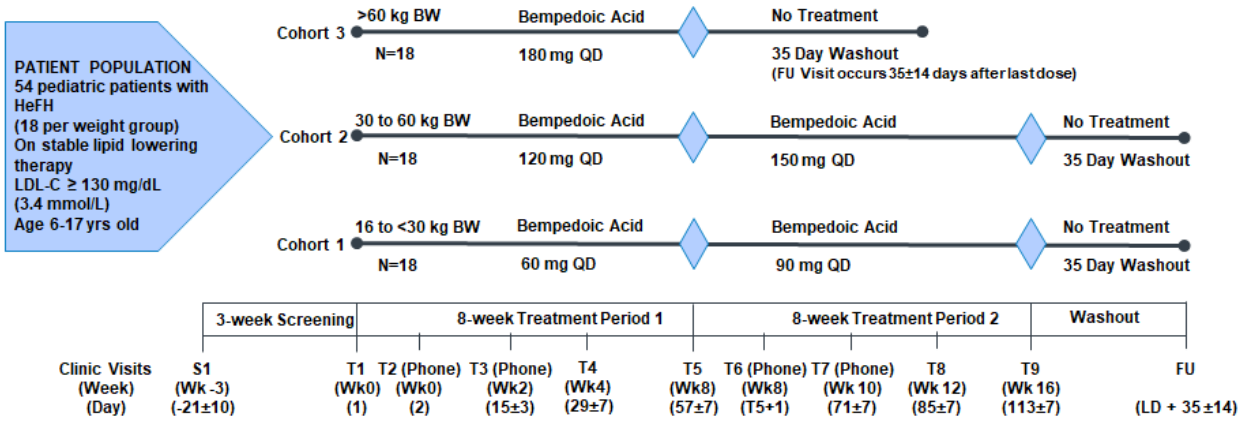
- Adverse events;
- Clinical safety laboratories (hematology, clinical chemistry, and urinalysis);
- Vital signs;
- Electrocardiogram (ECG) readings;
- Physical examinations (PEs).

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design

This is a Phase 2, open-label, uncontrolled, multicenter study of bempedoic acid administered for 8 and 16 weeks in pediatric patients (6 to 17 years of age) with HeFH and LDL-C ≥130 mg/dL (3.4 mmol/L) and who are on an optimal dose of statin. An overview of the study design is presented in Figure 1.

Figure 1: Overview of Study Design



Patients, aged 6 to 17 years old with a history of HeFH and who are on an optimal dose of statin will be screened for eligibility during screening (prior to Visit T1), which will be conducted within 21 ± 10 days before planned enrollment into the study, but the period between Visit S1 and Visit T1can be extended for an additional 14 days, if needed, to obtain written consent and records from family members for use of documented FH diagnosis described in inclusion criteria 4, or for other reasons. Patients who meet all inclusion/exclusion criteria will be scheduled for their first treatment visit.

Patients will report to the study site for the first treatment visit (Visit T1/Day 1) after a minimum 10-hour fast. Patients who continue to meet the study inclusion/exclusion criteria will be enrolled and will receive once daily bempedoic acid 60 mg (Cohort 1: 16 to <30 kg body weight, n = 18), 120 mg (Cohort 2: 30 to 60 kg body weight, n = 18), or 180 mg (Cohort 3:

>60 kg body weight, n = 18). Body weight at Screening Visit S1 will be used to determine weight cohort assignment for the study.
At Day 2 (Visit T2) and Week 2 (Visit T3) sites will conduct a phone or telemedicine visit with patients to collect information on concomitant medications, treatment-emergent adverse events (TEAEs) and ability to swallow IMP. At Week 4 (Visit T4) and Week 8 (Visit T5), patients will return for clinic visits for safety and laboratory assessments. Patients in Cohort 3 will receive the last dose of 180 mg bempedoic acid the day prior to Visit T5. Patients in Cohort 1will dose escalate from 60 to 90 mg and Cohort 2 will dose escalate from 120 to 150 mg following clinical assessments at Visit T5. At Week 8 (Visit T6) and at Week 10 (Visit T7) the site will conduct a phone or telemedicine interview visit with patients in Cohort 1 and Cohort 2 to collect information on concomitant medications, TEAEs and ability to swallow IMP. Patients in Cohort 1 and Cohort 2 will return for clinic visits at Week 12 (Visit T8) and Week 16 (Visit T9) for safety and laboratory assessments. Patients in Cohort 1 and Cohort 2 will receive the last dose of bempedoic acid the day prior to Visit T9. All patients, including those who withdraw from treatment, will return 35 ± 14 days after receiving the final dose of bempedoic acid for the safety follow-up (Visit FU).

Patients will report to each of the study visits after a minimum 10-hour fast approximately 24-hours after dosing from previous day and without having taken their dose of bempedoic acid and will bring their IMP with them. Alternatively, to accommodate scheduling of site visits later in the day without fasting requirements; provisions are provided for use of local laboratories to collect fasting lab samples 24-hours after dosing from previous day if permitted and allowed by regional regulatory authorities, site practices and appropriate IRB/IEC. For local laboratory collection of fasting samples; within 7 days prior to site visits at Week 4 (Visit T4), Week 12 (Visit T8), Week 16 (Visit T9) and the Follow-Up visit (FU) laboratory samples may be collected at a local laboratory approved by the research site after a minimum 10-hour fast approximately 24-hours after dosing from previous day. Following collection at a local laboratory; samples must be processed and then shipped to the research site according to the instructions in the laboratory manual (provided by the central laboratory). Sample will be subsequently shipped to the central laboratory for protocol-specified analysis and tests.

Bempedoic acid will be administered after fasting blood and urine samples have been drawn. If fasting laboratory samples are collected at the site, then Study site personnel will administer the bempedoic acid to the patient. All other doses of bempedoic acid will be self-administered by the patients (with caregiver support as necessary) including dates with fasting laboratory samples are collected at a local laboratory. The last dose will be taken the day prior to the final clinic visit of the treatment period (Visit T9 for patients in Cohorts 1 and 2, Visit T5 for patients in Cohort 3).

Visits may be conducted by a qualified health care provider (HCP) with appropriate designated study responsibilities at the patient's home or alternative facility provided the site institution has a IRB/IEC approved policy that enables remote/at-home clinic visits that has been reviewed and approved by the Sponsor. Site visits can only occur at a location other than the site if all scheduled procedures can be assessed.

Controls will be established to ensure that approximately 25% of total patients are taking background ezetimibe.

An independent Data Monitoring Committee (DMC) will review accumulating blinded and unblinded safety data from this and other ongoing studies of bempedoic acid approximately

4 times per year. Safety data reviewed by the DMC will include AEs, clinical endpoints, and lipids. Each of these committees has a charter that includes additional details.

5.2. Rationale for Dose Selection

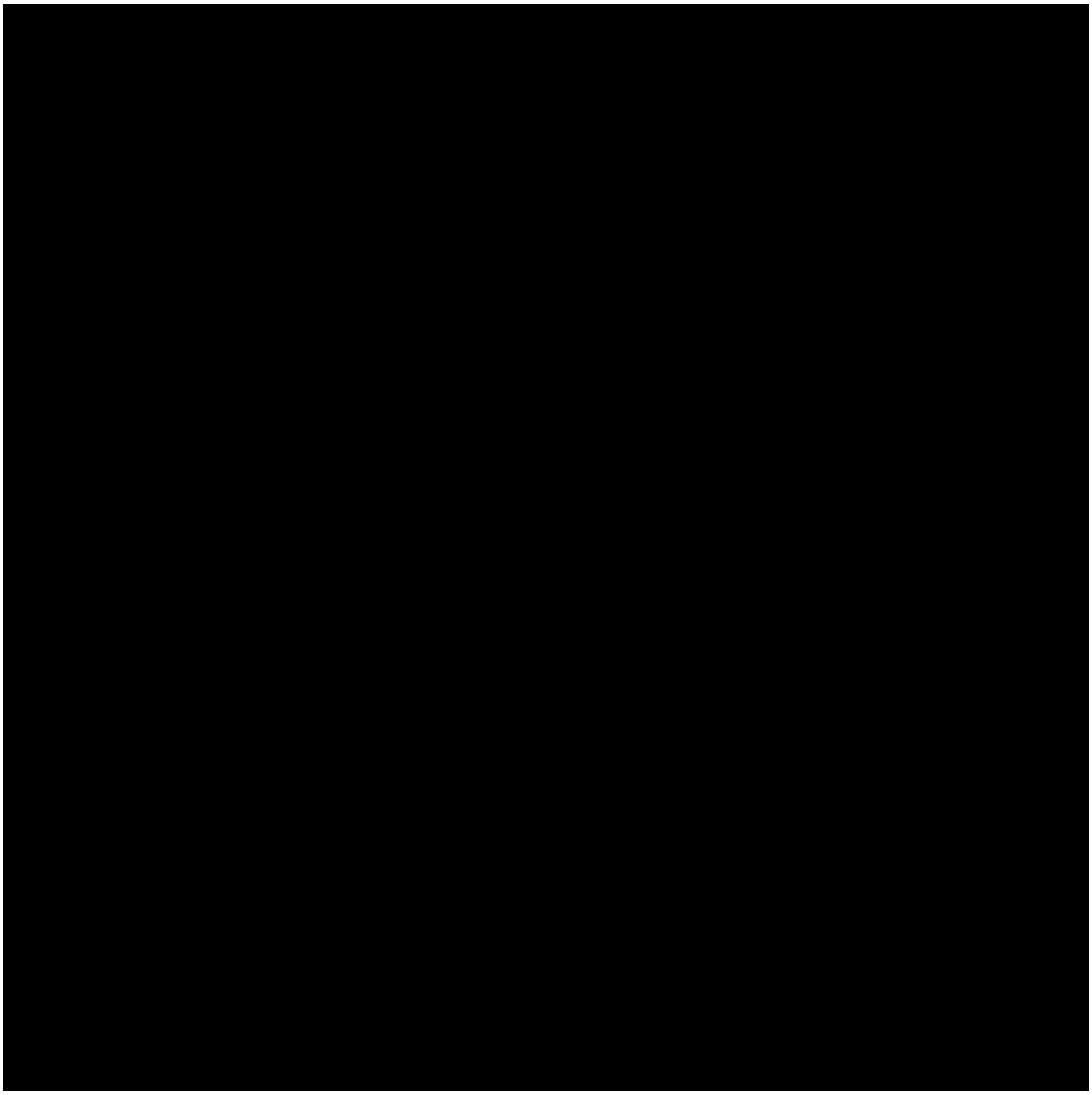
The dose selection and dose escalation for this first study in an HeFH pediatric population is based on matching predicted steady-state exposures (AUC_{ss}) in children to adults using simple allometric scaling of model-based PK parameters derived from the most appropriate subpopulation of adults with hypercholesterolemia from Phase 1,2 and 3 in clinical trials with bempedoic acid (Report 1002-073). This exposure-driven approach to pediatric dosing assumes that the exposure-response relationship for LDL-C lowering and safety are similar between pediatric and adult populations. Safety and LDL-C lowering response was similar in adult patients with and without HeFH in Phase 3 studies of bempedoic acid (Integrated Summary of Safety 2018; Integrated Summary of Efficacy, 2018). The response to treatment is expected to be similar in children and adults, as HeFH is caused by an inherited genetic defect that is the same in children and adults.

Model-Based Exposure Predictions in Pediatric Patients Using Allometric Scaling

Simple allometric scaling approaches were deemed most appropriate based on the Food and Drug Administration (FDA) Guidance and a lack of specific age-related differences in the major bempedoic acid clearance pathway, uridine-5'-glucuronyltransferase (UGT) 2B7 (General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, Guidance for Industry, FDA 2014; Bhatt 2019). In addition, body weight was examined as a covariate on adult model parameters and found to be statistically significant and very similar to model-based estimates of allometric exponents.

To select pediatric doses for the 3 weight categories, the post-hoc steady-state area under the plasma concentration-time curve over the dosing interval at steady state (AUC) estimates obtained from the pediatric simulations of each category were benchmarked against steady-state AUC exposures and their corresponding 90% confidence intervals (CIs) in adults. Mean estimates of AUC are represented by the blue line and the grey shaded area represents the 90% prediction interval exposure in the reference adult population.

Figure 2: Boxplots of AUC Estimates by Body Weight Categories Obtained from Pediatric Simulations from Adult Exposures



Based on the predicted AUC_{ss} exposures in children relative to adults, the following initial dose regimen and escalation scheme was selected: Cohort 1 (16 to <30 kg body weight), 60 mg once daily for 8 weeks then escalating to 90 mg once daily for 8 weeks; Cohort 2 (30 to 60 kg body weight), 120 mg once daily for 8 weeks then escalating to 150 mg once daily for 8 weeks; Cohort 3 (>60 kg body weight), 180 mg once daily for 8 weeks.

The interval between the initial dose and the subsequent dose escalation is based on observed time to steady state for LDL-C and safety laboratory changes in adults (Integrated Summary of Safety, Integrated Summary of Efficacy). Therefore, 56 days (8 weeks) was selected as the interval before escalation to ensure that patients were near steady state for their LDL-C and safety laboratory parameters before escalation to the next dose.

5.3. Formulation

This study will evaluate PK of both a tablet and a liquid formulation (Liquid Suspension available for use through Protocol Amendment 1 only) for use in pediatric populations. Patients will be assigned by interactive web response system (IWRS) to one of three cohorts based on body weight.

5.4. Study Duration

The expected study duration is cohort-dependent: approximately 169 days for Cohort 1 and 2 (participating in both Treatment Period 1 and 2) and 113 days for Cohort 3 (participating in Treatment Period 1 but not Treatment Period 2), including an approximate 21-day screening period (Visit S1/Day -21), followed by a 57-day Treatment Period 1 beginning at Day 1 and ending at Day 57 (Visit T5). A dose escalation for Cohort 1 and Cohort 2 will begin at Day 57 (Visit T5) through a 57-day Treatment Period 2 and ending at Day 113 (Visit T9); while Cohort 3 will not participate in Treatment Period 2. All patients will complete the trial after a Follow-up visit (Visit FU) approximately 35 days after receiving the last dose of bempedoic acid, occurring at approximately Day 148 for patients in Cohort 1 and Cohort 2, and at approximately Day 92 for patients in Cohort 3. Cohort 1 and Cohort 2 are anticipated to attend 7 site visits and participate in 4 phone interview/telemedicine device visits during the course of the study. Cohort 3 is anticipated to attend 4 site visits and participate in 2 phone interview visits during the course of the study.

5.5. Number of Patients

54 male and female patients aged 6 to 17 years old (approximately 18 patients in each weight cohort: Cohort 1, 16 to <30 kg, Cohort 2, 30 to 60 kg, and Cohort 3, >60 kg) with a history of HeFH and who are on an optimal dose of statin and who meet the inclusion and exclusion criteria will be enrolled. The sample size of 54 patients accounts for at least 16 evaluable patients per cohort, accounting for a 10% dropout rate, and is expected to provide approximately 90% power to detect a difference of 25% in clearance of bempedoic acid measured by the primary endpoint of the model-derived estimates of AUC_{ss}, 24 (CL/F) for ETC-1002 following 8 weeks of steady-state dosing. These power calculations are based on simulations to detect a 25% change in CL/F stratified by weight cohort using a smoothed parametric bootstrapping procedure of 1000 sets of parameters generated using the multivariate normal distribution as an approximate asymptotic posterior distribution based on the final estimates from and variance-

covariance matrix from the adult base PK model output. Controls will be established to ensure that approximately 25% of total patients are taking background ezetimibe across the study to provide sufficient representation to assess patients taking concurrent bempedoic acid and ezetimibe.

5.6. Replacement of Patients

Patients who are withdrawn from the study for any reason may be replaced at the discretion of the sponsor.

5.7. Number of Clinical Sites

Approximately 25 clinical sites worldwide will participate in this study. Additional sites may be invited to participate to ensure study timelines are met.

6. SELECTION AND WITHDRAWAL OF PATIENTS

6.1. Subject Inclusion Criteria

Patients must satisfy all the following criteria during Screening (prior to Visit T1 unless otherwise specified) for enrollment in the study:

1. The patient's parent(s)/guardian(s) must be willing to provide written informed consent and the patient must provide informed assent before any study-specific procedures are performed.
2. The patient must be aged 6-17 years old and willing to swallow tablets.
3. The patient must weigh at least 16 kg.
4. The patient must have a diagnosis of HeFH prior to receiving the first dose of study medication at Treatment Visit T1 per MEDPED criteria by meeting at least one of the following clinical criteria*:
    a. Documented diagnosis of HeFH determined by positive genetic testing; or
    b. Documented LDL-C or TC meeting one or more of the following criteria:
        i. LDL-C >200 mg/dL (5.2 mmol/L) or total cholesterol (TC) >270 mg/dL (7.0 mmol/L), with no first- second- or third-degree relative with documented FH diagnosis (general population); or
        ii. LDL-C >155 mg/dL (4.0 mmol/L) or TC >220 mg/dL (5.7 mmol/L), and also having a first-degree relative with documented familial hypercholesterolemia (FH) diagnosis; or
        iii. LDL-C >165 mg/dL (4.3 mmol/L) or TC >230 mg/dL (5.9 mmol/L), and also having a second-degree relative with documented FH diagnosis; or
        iv. LDL-C >170 mg/dL (4.4 mmol/L) or TC >240 mg/dL (6.2 mmol/L), and also having a third-degree relative with documented FH diagnosis.

*Note: Adapted from MEDPED criteria (Williams 1993). Secondary causes of hypercholesterolemia, such as nephrosis, pregnancy, hypothyroidism, obstructive jaundice/obstructive liver disease, corticosteroid medications, familial combined hyperlipidemia, HoFH and Cushing's disease will be assessed by the investigator and must be precluded. The LDL-C value at screening Visit S1 or documented LDL-C value in medical charts may be applied toward criteria; if triglycerides are greater than 400 mg/dL at the time of the applicable LDL-C value, then LDL-C measured by ultracentrifugation must have been used. Positive genetic testing documenting HeFH mutations in LDL receptor (LDLr), apolipoprotein B (ApoB), low-density lipoprotein receptor adaptor protein 1 (LDLRAP1), and proprotein convertase subtilisin/kexin type 9 (PCSK9) genes may be documented in medical records or assessed as part of this trial prior to randomization provided patient/parental/guardian consent or assent to perform optional genetic testing during trial screening prior to randomization and according to country specific regulations. First-degree relatives include parents, offspring, brothers and sisters; second-degree relatives include aunts, uncles, grandparents, nieces, nephews; third-degree relatives include first cousins and siblings of grandparents. First-, second- or third-degree relatives may need written consent in advance authorizing the collection of documented FH diagnosis depending on local law requirements for access and sharing of personal information.

5. Current treatment with approved stable lipid-modifying therapy (LMT), including an optimal dose of statin with or without other LMT(s), at stable dose for at least 4 weeks prior to Treatment Visit T1 (6 weeks for fibrates; however, gemfibrozil is not allowed in patients taking a statin as per co-administration instructions defined in the statin label). Patients must remain on that stable dose throughout the duration of the trial.

   Optimal dose of statin will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of LMT. A patient's optimal dose of statin is defined as meeting one of the following criteria:

   a. the highest approved dose of statin prescribed for the age of the patient based on regional practice or local guidelines; or

   b. less than the highest approved dose of statin, including no statin, prescribed for the age of the patient based on regional practice or local guidelines (including no statin) if:

      i. the patient has previously taken 2 or more statin therapies at any dose and not able to tolerate or unresponsive due to their mutations (null); or

      ii. the patient has previously taken 1 or more statin therapies at any dose and is unwilling to attempt another statin at any dose or advised by a physician to not attempt another statin at any dose.

   Patient/parent and investigator attestation to the patient's unwillingness to attempt and/or physician advice to not attempt additional statin therapy will be recorded.

6. The patient must have a fasting LDL-C level ≥130 mg/dL (3.4 mmol/L) while on stable LMT as defined in inclusion criteria 5

7. The patient may be male or female. Females must not be pregnant (or planning to become pregnant within 30 days after the last dose of investigational medicinal product [IMP]) breastfeeding and must be sexually inactive or willing to use 1 acceptable method of birth control. The minimal requirement for use of acceptable contraception is from the time the informed consent form (ICF) is signed, during the study period, and for at least 30 days after the last dose of IMP. Acceptable methods of birth control include:
    a. placement of an intrauterine device (IUD) with or without hormones,
    b. established use of oral, implanted, topical, or injectable, or hormonal method of contraception associated with inhibition of ovulation, or
    c. barrier methods, including condom or occlusive cap with spermicidal foam or spermicidal jelly,

    There are no protocol-specific birth control requirements for males who have partners that can become pregnant.

6.2. Subject Exclusion Criteria

Patients who meet any of the following criteria during Screening (prior to Visit T1 unless otherwise specified) will be excluded from the study:

1. The patient has a diagnosis of HoFH or compound HeFH;
2. The patient has a fasting triglyceride (TG) level ≥400 mg/dL (4.5 mmol/L);
3. The patient has uncontrolled hypothyroidism, including a value for thyroid-stimulating hormone (TSH) < lower limit of normal (LLN) or >1.5 × the upper limit of normal (ULN);
4. The patient has liver disease or dysfunction, including:
    a. positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C virus antibodies (HCV-AB), or
    b. serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) value ≥2 × ULN and/or serum total bilirubin (TB) value ≥2 × ULN. If the serum TB value is ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained and, if consistent with Gilbert's disease or if the patient has a history of Gilbert's disease, the patient may be enrolled in the study.
5. The patient has renal dysfunction or glomerulonephritis, including an estimated glomerular filtration rate (eGFR) <75 mL/min/1.73 m^2 (as determined by the central laboratory using the Revised ["Bedside"] Schwartz formula).
6. The patient has Stage 2 hypertension (based on gender, age and height; see Appendix 4).
7. The patient has a gastrointestinal condition that may affect drug absorption.
8. The patient has a history of hematologic or coagulation disorders, anemia, or a hemoglobin (Hgb) level <11.5 g/dL;
9. The patient has type 1 or type 2 diabetes, or newly diagnosed impaired glucose tolerance (within 3 months of Screening);

10. The patient had an active malignancy, including those requiring surgery, chemotherapy, and/or radiation, in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed;
11. The patient has an unexplained (ie, not associated with recent trauma or physically strenuous activity) serum creatine kinase (CK) value >3 × ULN at any time before randomization. Patients with an explained elevation in serum CK must have single repeat serum CK value ≤3 × ULN before enrollment.
12. The patient has a history of drug or alcohol abuse within the last 2 years or is unwilling to refrain from alcohol consumption for the duration of the study, or uses any illicit drugs, or has a history of amphetamine or derivatives abuse or cocaine abuse. Patients who are using amphetamine derivatives prescribed by and who are under the care of a health care practitioner can be enrolled after evaluation by the Investigator.
13. The patient has donated blood, undergone multiple blood draws in a clinical study, experienced major trauma, received a blood transfusion, or undergone surgery, with or without blood loss, within 30 days before enrollment.
14. The patient has used any experimental or investigational drugs within 30 days before screening and throughout the trial
15. The patient has previously participated in a clinical study of bempedoic acid.
16. The patient is taking any of the following medications or therapies, except as indicated below:
    a. Mipomersen or lomitapide (current or within 6 months of Screening).
    b. PCKS9 inhibitors including evolocumab or alirocumab (current or within 3 months of Screening).
    c. Lipid apheresis (current or within 8 weeks of Screening or intends to have lipid apheresis treatments throughout the trial).
    d. Systemic corticosteroids (current or within 4 weeks prior to enrollment; topical and inhaled corticosteroids are allowed).
    e. Red yeast rice extract (also known as monascus purpureus extract or Cholestin) containing products (current or within 4 weeks of Screening);
    f. Lipid altering nutritional supplements including berberine, psyllium (Metamucil®), green tea extract, sitostanol (found in oral nutritional supplements and some margarines, such as Benecol), beta-sitosterol (found in oral nutritional supplements and some margarines, such as Promise Activ), pantothine and policosanol (current or within 4 weeks of Screening).
    g. Bile acid sequestrants, fibrates, omega 3 fatty acids, or niacin, unless the dose has been stable for ≥6 weeks and will remain stable throughout the trial.
    h. Simvastatin >20 mg or pravastatin >40 mg (current or within 4 weeks of Screening).
17. The patient has a history or evidence of any other clinically significant condition, or planned or expected procedure that in the opinion of the Investigator, may compromise the patient's safety or ability to complete the study;

18. The patient has a situational (ie, geographical) finding that, in the Investigator's opinion, may compromise the patient's safety or ability to complete the study;
19. The patient is an employee or contractor of the facility that is conducting the study or is a family member of the Investigator, sub-Investigator, or any Sponsor personnel.

6.3. Lifestyle and Dietary Guidelines

Patients will fast for a minimum of 10 hours prior to collection of all laboratory samples (water and concomitant medications, but not IMP are permitted).

Beginning at Screening, patients will be counseled to follow a healthy diet as per local or regional guidelines and should be encouraged (as able) to participate in a stable, regular exercise program throughout the study.

Alcohol consumption and illicit drug use is prohibited throughout the study.

6.4. Investigator/Sponsor Suspension or Termination of Patient Enrollment

If, in the opinion of the Investigator, the clinical observations in the study suggest that it may be unwise to continue, the Investigator may suspend or terminate patient's participation in the study after consultation with the Sponsor. A written statement fully documenting the reasons for such a termination will be provided to the Sponsor (or designee) and to the institutional review board (IRB) or independent ethics committee (IEC).

The Sponsor has the right to terminate the study and remove all study materials from the investigational site. A written statement will be provided to the Investigator, the IRB/IEC, and regulatory authorities, if required.

Possible reasons for termination of the study include, but are not limited to:

- unsatisfactory enrollment with respect to quantity or quality,
- inaccurate or incomplete data collection on a chronic basis,
- falsification of records,
- failure to adhere to the protocol, and
- lack of study oversight by the Principal Investigator and/or designee.

In the event any serious or nonserious Adverse Events (AEs) occur, all documentation relating to the event(s) must be obtained.

7. TREATMENT OF PATIENTS

7.1. Investigational Medicinal Product Dosage and Mode of Administration

Bempedoic acid is supplied as 60- and 90-mg tablets and as a liquid suspension (20 mg/mL) - Liquid Suspension available for use through Protocol Amendment 1 only.

Bempedoic acid dosage is individually determined based on weight at the Screening Visit. All IMP will be ingested orally once daily at a similar time of day with or without food.

Patients will be enrolled and receive bempedoic acid in accordance with their body weight measured at the Screening Visit:

- **Cohort 1: 60 mg:** One (1) bempedoic acid 60-mg tablet once daily for 56 ± 2 days, (Period 1) followed by **90 mg;** one (1) bempedoic acid 90-mg tablet once daily for 56 ± 2 days (Period 2) or
- **Cohort 2: 120 mg:** Two (2) bempedoic acid 60-mg tablets once daily for 56 ± 2 days (Period 1), followed by **150 mg;** one (1) bempedoic acid 60-mg tablet and one (1) bempedoic acid 90-mg tablet once daily for 56 ± 2 days (Period 2); or
- **Cohort 3: 180 mg:** Two (2) bempedoic acid 90-mg tablets once daily for 56 ± 2 days (Period 1).

On Day 1 (Visit T1), patients will receive tablets to assess a minimum of 24-hour PK at daily doses of 60, 120, and 180 mg.

At Week 8 (Visit T5), following clinical assessments, Cohort 1 will dose escalate from 60 to 90 mg and Cohort 2 will dose escalate from 120 to 150 mg. Patients in Cohort 3 will receive the last dose of 180 mg bempedoic acid the day prior to Visit T5. Patients in Cohort 1 and Cohort 2 will receive the last dose of bempedoic acid the day prior to Visit T9.

7.2. Treatment Assignment

During the Treatment Period, patients will receive open-label IMP. On Day 1 (Visit T1), patients will be enrolled and will receive bempedoic acid in accordance with their body weight at Screening Visit S1 (Cohort 1: 60 mg for patients <30 kg; Cohort 2: 120 mg for patients ≥30 to ≤60 kg; Cohort 3: 180 mg for patients >60 kg). Assigned study drug will be dispensed to patients according to the interactive web response system (IWRS).

7.3. Investigational Medicinal Product Adherence

Patients will be instructed to bring their patient dosing log to each study visit beginning at Visit T3 and completing at Visit T9. If the patient has not taken multiple doses as instructed, the patient will be queried for a reason, findings will be documented, and the patient (and caregiver) will be counseled on the importance of carefully following all dosing instructions. Factors contributing to poor adherence will be determined and, if possible, remedied. Patients demonstrating poor adherence during the Treatment Period will continue to be counseled on the importance of carefully following all dosing instructions but will not be removed from the study. In addition, at all treatment visits T1 through T9, patients and caregivers will be asked to

complete a dosing acceptability questionnaire to collect information on the taste and ease of swallowing of the age-appropriate formulation that the patient had taken for the period between the last and current visits.

7.4. Overdose

There is no specific antidote for an overdose of bempedoic acid. Management of an overdose should be focused on the treatment of symptoms. These symptoms should be managed according to current standards of care with appropriate supportive measures. Discontinuation of study drug should also be considered, as per medical judgement.

7.5. Concomitant Medications

Patients (with caregiver support as needed) will be instructed to report the use of any concomitant medication to the Investigator and will be reminded about the importance of not taking any prohibited medications without consulting the Investigator. Patients will be questioned about concomitant medication use at each study visit during the screening and treatment periods. All prior medications, herbal remedies, dietary supplements, or vitamins that were taken within 3 months before screening (Visit S1) will be recorded. Any concomitant medication that is taken from the time the first dose of IMP is taken (Visit T1) through the study completion for the specific patient (defined as either the last scheduled visit attended or the last dose of bempedoic acid, whichever is later) or early termination from the study must be recorded, with indication, daily dose, and start and stop dates of administration.

7.5.1. Prohibited Medications

Modification of background lipid-modifying therapies (LMT) use during the study is prohibited. In addition, use of any of the following drugs within 4 weeks prior to Screening (unless otherwise stated) or a plan to use any of these drugs during the study is **prohibited**:

The following Lipid-Modifying Therapies (LMT)

- Lipid altering nutritional supplements including berberine, psyllium (Metamucil®), green tea extract, sitostanol (found in oral nutritional supplements and some margarines, such as Benecol), beta-sitosterol (found in oral nutritional supplements and some margarines, such as Promise Activ), pantothine and policosanol;
- Lipid apheresis (current or within 8 weeks of Screening or intends to have lipid apheresis treatments at any time during the trial)
- Mipomersen (Kynamro®) or lomitapide (Juxtapid®) (current or within 6 months of Screening);
- PCSK9 inhibitors including evolocumab (Repatha®) and alirocumab (Praluent®) (current or within 3 months prior to Screening);
- Red yeast rice extract (also known as monascus purpureus extract or Cholestin)-containing products;
- Gemfibrozil (prohibited only in patients taking concomitant statins);

- Simvastatin >20 mg;
- Pravastatin >40 mg.

Other Prohibited Medications

- Systemic corticosteroids (current or within 4 weeks prior to enrollment); topical and inhaled corticosteroids are allowed;
- Any experimental or investigational drugs within 30 days before Screening.

7.5.2. Allowed Medications

Permitted medication doses including optimal dose of statin +/- other LMT(s), or non-statin LMT(s) must be stable for at least 4 weeks prior to Visit T1 (6 weeks for fibrates); and must remain on that stable dose throughout the duration of the trial.

A patient's optimal dose of statin or other LMT(s) will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of LMT, and should be an approved dose for the patient in accordance with regional and local approved therapies for the age of the patient described in greater detail in Inclusion Criteria #5 (Section 6.1). Optimal dose of statin includes statin regimens other than daily dosing, including no to very low doses. Medications for other indications are allowed so long as stable and not listed as a prohibited medication (Section 7.5.1). Stable is defined as no addition or cessation of a drug or change in the dose of a drug.

7.5.3. Contraception

Females of childbearing potential must be sexually inactive or use 1 acceptable method of birth control, minimally, from the time the ICF is signed through at least 30 days after the last dose of IMP. Acceptable methods of birth control include:

a. placement of an IUD with or without hormones;
b. established use of oral, implanted, topical, or injectable, or hormonal method of contraception associated with inhibition of ovulation; or
c. barrier methods, including condom or occlusive cap with spermicidal foam or spermicidal jelly

If a patient who is sexually inactive at the time the ICF is signed becomes sexually active, she must agree to use 1 acceptable method of contraception, as described above. There are no protocol-specific birth control requirements for male participants who have partners that can become pregnant. Contraceptive requirements do not apply to individuals who are exclusively in same-sex relationships.

8. INVESTIGATIONAL MEDICINAL PRODUCT

8.1. Description of Investigational Medicinal Product

8.1.1. Bempedoic Acid 60- and 90-mg Tablets

Bempedoic acid 60- and 90-mg tablets will be provided by Esperion Therapeutics. A description of the tablets is provided in Table 2. The tablets used in this study are in the size range that young children (≥6 years old) can swallow (Tuleu 2011). The acceptability (taste and ease of swallowing) of these formulations will be assessed in the study.

8.1.2. Bempedoic Acid Liquid Suspension

Bempedoic acid liquid suspension (20 mg/mL) will be provided by Esperion Therapeutics. A description of the liquid formulation is provided in Table 2. Liquid Suspension available for use through Protocol Amendment 1 only.

Table 2: Description of Bempedoic Acid Tablets and Liquid Suspension

Parameter	Bempedoic Acid 60-mg Tablet	Bempedoic Acid 90-mg Tablet	Bempedoic Acid 20 mg/mL Liquid Suspension
Dosage form:	Film-coated tablet	Film-coated tablet	Liquid suspension
Unit dose:	60 mg bempedoic acid	90 mg bempedoic acid	20 mg/mL bempedoic acid
Container:	High-density polyethylene bottles with a child-resistant closure	High-density polyethylene bottles with a child-resistant closure	High-density polyethylene bottles with a child-resistant closure
Route of administration:	Oral with water with or without food	Oral with water with or without food	Oral with or without food
Physical description:	[redacted]	[redacted]	[redacted]

8.2. Investigational Medicinal Product Supply and Control

Bempedoic acid tablets and bempedoic acid liquid suspension (liquid suspension available for use through Protocol Amendment 1 only) will be supplied to the sites by the Sponsor. The IMP will be distributed and released in accordance with regional and local requirements during the conduct of the study. Study medication will be stored under lock and key, with access limited to those authorized by the Investigator in accordance with applicable regulatory requirements for investigational drugs.

Additional information regarding packaging, labeling, storage, and distribution is provided in the pharmacy manual.

8.3. Administration of Investigational Medicinal Product

The dose of IMP will be administered to the patients at the study site at each of the study visits. The first dose of IMP will be taken at Visit T1/Day 1. The actual time of IMP administration

during study visits will be recorded and will determine the target time of IMP administration for the patient during the treatment period. Patients will self-administer the IMP on all other days (with caregiver support as needed), once daily at a similar time each day with or without food. The last dose of IMP will be taken on the morning of the day prior to Visit T5 for patients in Cohort 3, and the morning of the day prior to Visit T9 for patients in Cohort 1 and Cohort 2.

Bempedoic acid dosage is individually determined based on weight at Screening Visit S1 and treatment period and includes:

- Cohort 1: 16 to <30 kg body weight at Screening Visit S1
  - 60 mg (one 60-mg tablet),
  - 90 mg (one 90-mg tablet),
- Cohort 2: 30 to 60 kg body weight at Screening Visit S1
  - 120 mg (two 60-mg tablets),
  - 150 mg (one 60-mg and one 90-mg tablet), and
- Cohort 3: >60 kg body weight at Screening Visit S1
  - 180 mg (two 90-mg tablets).

Patients and caregivers will be instructed on the importance of maintaining 24-hour intervals between doses. If the daily dose of IMP is not taken at the usual time due to unforeseen circumstances, the patient may take the dose as soon as possible after the target time but no later than noon. If the daily dose is not taken by noon, the patient will be instructed to skip the dose on that day and to resume dosing on schedule the next day. Patients will maintain a daily dosing log to monitor IMP dosing adherence.

8.4. Investigational Medicinal Product Accountability, Handling and Disposal

The Principal Investigator must maintain accurate records of the receipt of all study medication shipped by the Sponsor/Sponsor representative and the disposition of that study medication. The Principal Investigator will ensure that all IMP is stored in a secured area, under recommended storage conditions (at room temperature [15°C/59°F to 30°C/86°F] protected from any extreme conditions of temperature, light, or humidity) in accordance with applicable regulatory requirements for investigational drugs. Access to IMP will be limited to those clinical site personnel authorized by the Investigator.

Upon completion or termination of the study, all used and unused IMP will be returned to the Sponsor (or designee) for destruction or disposed of by the study site, per Sponsor written instruction. All IMP returns must be accompanied by the appropriate documentation.

Investigational medicinal product records or logs must comply with applicable regulations, local law, and guidelines, and should include:

- amount received/placed in storage area;
- amount currently in storage area;
- label identification or batch number;
- dates and initials of person responsible for product inventory (including entry/movement/disposition);
- date and amount dispensed to each patient, including unique patient identifier;
- data returned by patient, review of dosing log, and relevant documentation of discrepancies;
- nonstudy disposition (ie, lost, broken, wasted); and
- amount returned to Sponsor/Sponsor designee.

The Sponsor will provide forms to facilitate inventory control if the staff at the investigational site does not have an established quality system that meets the needs of this requirement.

9. STUDY PROCEDURES AND SCHEDULE OF ASSESSMENTS

9.1. Informed Assent/Consent

Written informed assent/consent is required from each patient and the patient's parent/legal guardian, respectively, prior to any testing under this protocol, including screening assessments and evaluations.

The background of the proposed study and the benefits and risks of the assessments and study must be explained to the patient and their parent(s)/legal guardian(s). Parent(s)/legal guardian(s) of patients must provide written informed consent prior to the patient participating in the study and informed assent will be obtained from the patient prior to any procedures.

It is the responsibility of the Investigator to obtain assent/consent and to provide the patient and parent/guardian with a copy of the signed and dated ICF. Confirmation of a patient's informed assent/consent must also be documented in the patient's medical record prior to any testing under this protocol, including screening assessments and evaluations.

All ICFs used in this study must be approved by the appropriate Institutional Review Board/Ethics Committee (IRB/IEC) and by the Sponsor or designee. The ICF must not be altered without the prior agreement of the relevant IRB/IEC and the Sponsor.

For patients requiring documented FH diagnosis of first-, second- or third-degree relatives to meet the HeFH inclusion criteria 4; the first-, second- or third-degree relative may need to provide written consent in advance authorizing the collection of documented FH diagnosis depending on local law requirements for access and sharing of personal information.

9.2. Patient Identification Numbers

A unique patient identification number (patient ID) will be assigned to identify each patient throughout the study and will be entered on all documentation. If a patient is not eligible to receive treatment or discontinues from the study, that patient's identification number cannot be assigned to another patient. Patient identification numbers will be assigned sequentially.

9.3. Rescreening

Patients who are screening failures due to stability requirements for a condition or concurrent medication or other reason may be considered for rescreening after consultation with the Sponsor (or designee). If rescreened, these patients must also be re-consented and screening procedures must be repeated. If a patient is a screen failure, or if a patient discontinues from the study, their patient ID number will not be assigned to another patient. Rescreened patients will be assigned a new patient ID number.

9.4. Procedures and Schedule of Assessments

The schedule of study events is provided in Appendix 1. However, a patient can be seen at any time for reasons of safety.

All relevant data will be captured on electronic case report forms (eCRFs) according to the eCRF completion guidelines.

9.5. General Visit Guidelines

Patients will report to each of the study visits after a minimum 10-hour fast approximately 24-hours after dosing from previous day and without having taken their dose of bempedoic acid and will bring their IMP with them. Alternatively, to accommodate scheduling of site visits later in the day without fasting requirements; provisions are provided for use of local laboratories to collect fasting lab samples if permitted and allowed by regional regulatory authorities, the site institution and appropriate IRB/IEC. For local laboratory collection of fasting samples; within 7 days prior to site visits at Week 4 (Visit T4), Week 12 (Visit T8), Week 16 (Visit T9) and the Follow-Up visit (FU) laboratory samples may be collected at a local laboratory approved by the research site after a minimum 10-hour fast approximately 24-hours after dosing from previous day. Following collection at a local laboratory; samples must be processed and then shipped to the research site according to the instructions in the laboratory manual (provided by the central laboratory). Sample will be subsequently shipped to the central laboratory from the site for protocol-specified analysis and tests.

Bempedoic acid will be administered after fasting blood and urine samples have been drawn. If fasting laboratory samples are collected at the site, then study site personnel will administer the bempedoic acid to the patient. All other doses of bempedoic acid will be self-administered by the patients (with caregiver support as necessary) including days on which fasting laboratory samples are collected at a local laboratory. The last dose will be taken the day prior to the final clinic visit of the treatment period (Visit T9 for patients in Cohorts 1 and 2, Visit T5 for patients in Cohort 3).

Visits may be conducted by a qualified health care provider (HCP) with appropriate designated study responsibilities at the patient's home or alternative facility provided the site institution has an IRB/IEC approved policy or procedure for remote/at-home clinic visits that has been reviewed and approved by the Sponsor. Site visits can only occur at a location other than the site if all scheduled procedures can be assessed.

The following assessments will be conducted at each visit unless otherwise specified and per the schedule of study events provided in Appendix 1. All blood samples other than PK samples should be collected in a fasted state and prior to taking the study medication on the date of collection:

- Review of medical history, prior and concomitant medications;
- Assess AEs and SAEs;
- PE;
- Vital signs;
- ECG reading;
- Urine sampling for safety laboratories or exploratory biomarkers;
- Blood sampling for basic fasting lipid assessments (LDL-C, non-HDL-C, TC, TG, HDL-C) and hsCRP;
- Blood sampling for clinical safety laboratories;
- Blood sampling for exploratory biomarkers or genetic sampling;
- Predose blood sampling for PK;

9.6. Screening Period

9.6.1. Screening Period Visit 1 (Visit S1/ Day -21 ± 10)

Patients will be screened for study eligibility at Visit S1 (Day =21 ± 10), but period between Visit S1 and Visit T1 can be extended for an additional 14 days, if needed, to obtain written consent and records from family members for use of documented FH diagnosis described in inclusion criteria 4, or for other reasons. The following evaluations will be performed at this visit:

- Written informed consent/assent will be obtained before any study-related procedures are conducted;
- Determine eligibility for participation based upon inclusion/exclusion criteria.
- Demographic data will be recorded;
- Recent clinically relevant medical history and AEs will be recorded;
- Prior, concomitant, and prohibited medications will be reviewed and recorded;
- Weight (in kilograms) and height (in centimeters) will be measured;
- ECG reading;

- PE;
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be recorded;
- Blood and urine specimens will be obtained for the following:
  - urine pregnancy test (for females of childbearing potential);
  - basic fasting lipid panel and hsCRP;
  - serum TSH;
  - glycosylated hemoglobin, type A_{1C} (HbA_{1C});
  - clinical safety laboratories (hematology, clinical chemistry and urinalysis);
  - urine drug screen;
  - blood and urine exploratory biomarkers;
  - optional genetic blood sample for testing of HeFH gene mutations;
- Conduct diet and exercise counseling;
- Contact IWRS to register patient.

Patients aged 6 to 17 years old with a diagnosis of HeFH and LDL-C ≥ 130 mg/dl (3.4 mmol/L) and who are on an optimal dose of statin and who meet the other protocol inclusion/exclusion criteria during the Screening period prior to Visit T1 will be contacted by phone to schedule the Baseline Visit (Visit T1) to occur within 11 to 31 days after Visit S1. A repeat assessment of LDL-C for qualification may be scheduled between Visit S1 and Visit T1 if needed to allow 4-weeks of optimal dosing of statin during screening or for other reasons. The screening period prior to Visit T1 may be extended 2 weeks if necessary. The repeat LDL-C value following 4-weeks of stable LMT dosing will be used to determine eligibility.

Patients who fail to meet any entry criterion are considered to be screen failures and are not required to return for additional visits (although a patient can be seen at any time for safety reasons).

Under rare circumstances, patients who are considered to be screen failures or were otherwise withdrawn from the study prior to taking any dose of study medication that is considered to warrant rescreening after consultation with the Sponsor (or designee) may be rescreened. These patients must be re-consented, re-registered in the IWRS, and will have a new patient ID assigned.

9.7. Treatment Period

9.7.1. Treatment Period 1 Visit 1 (Visit T1/Day 1): All Cohorts

Patients will arrive at the study site in the morning after a minimum 10-hour fast.

Procedures and evaluations will be performed during this visit:

- Determine eligibility for participation based upon inclusion/exclusion criteria;

- Concomitant and prohibited medications will be reviewed and recorded as needed;
- Adverse events will be assessed;
- Weight (in kilograms) and height (in centimeters) will be measured;
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be recorded;
- PE;
- Tanner staging score (sexual maturation) will be assessed;
- Blood and urine specimens will be obtained prior to dosing for the following:
  - basic fasting lipid panel and hsCRP;
  - clinical safety laboratories (hematology, clinical chemistry and urinalysis);
  - urine pregnancy test (for females of childbearing potential);
- PK sampling prior to dosing of bempedoic acid (pre-dose).
- Patients will be assigned to cohort based on their weight at Screening Visit S1 (Cohort 1: 60 mg bempedoic acid for patients weighing 16 to <30 kg, Cohort 2: 120 mg bempedoic acid for patients weighing 30 to <60 kg, or Cohort 3: 180 mg bempedoic acid for patients weighing >60 kg);
- Patients will take their first dose of bempedoic acid based on cohort assignment
- Patient will be queried as to ability to swallow the tablets
- Site will review with patient the daily dosing instructions, storage instructions, daily dosing log and IMP adherence;
- Conduct diet and exercise counseling;
- PK sampling at 1hour ± 15 minutes, and 4 hours ± 15 minutes post dosing of bempedoic acid (post-dose);
- Patients will leave the clinic following all assessments and will be reminded that the site will contact them by phone the next day for Visit T2.

9.7.2. Treatment Period 1 Phone Visit 2 (Visit T2/Day 2): All Cohorts

The site will contact the patient/guardian by telephone or telemedicine device to collect the following information:

- Concomitant and prohibited medications will be reviewed and recorded as needed;
- Adverse events will be assessed;
- Assess taste and ability to swallow tablets;
- Site will review with patient the daily dosing instructions, storage instructions, daily dosing log and IMP adherence;
- Conduct diet and exercise counseling;

- Visit T3 (Phone Visit) will be scheduled.

The site PI should accompany designated site staff for phone or telemedicine interviews to discuss patient concomitant medications and adverse events.

9.7.3. Treatment Period 1 Phone Visit (Visit T3/Day 15 ± 3): All Cohorts

The site will contact the patient/guardian by telephone or telemedicine device to collect the following information:

- Concomitant and prohibited medications will be reviewed and recorded as needed;
- Adverse events will be assessed;
- Assess taste and ability to swallow the tablets;
- Site will review with patient the daily dosing instructions, storage instructions, daily dosing log and IMP adherence;
- Conduct diet and exercise counseling;
- Visit T4 will be scheduled.

9.7.4. Treatment Period 1 Visit 4 (Visit T4/Day 29 ± 7): All Cohorts

Patients will arrive at the study site after a minimum 10-hour fast approximately 24-hours after dosing from previous day, having not yet taken the daily dose of bempedoic acid unless fasted samples were collected by a local laboratory as described in Section 9.5. Patients will bring their IMP to the visit. Procedures and evaluations will be performed during this visit:

- Concomitant and prohibited medications will be reviewed and recorded as needed;
- Adverse events will be assessed;
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) and body weight will be recorded;
- ECG reading;
- Blood and urine will be obtained for the following prior to dosing:
  - PK sample;
  - basic fasting lipid panel;
  - clinical safety laboratories (hematology, clinical chemistry and urinalysis);
  - blood and urine exploratory biomarker samples;
- Patients will take their daily dose of bempedoic acid after collection of blood specimens;
- Review patient dosing log and assess taste and ability to swallow the tablets;
- Site will review with patient the daily dosing instructions, storage instructions, and IMP adherence;

- Conduct diet and exercise counseling;
- Patient/caregiver will be provided with daily dosing and storage instruction reminder;
- Visit T5 will be scheduled.

9.7.5. Treatment Period 1 Visit 5 (Visit T5/Day 57 ± 7): Cohort 3

Patients in Cohort 3 will arrive at the study site after a minimum 10-hour fast approximately 24-hours after dosing from previous day, having not yet taken the daily dose of bempedoic acid. Patients will bring their IMP to the visit.

Procedures and evaluations will be performed during this visit:

- Concomitant and prohibited medications will be reviewed and recorded as needed;
- Adverse events will be assessed;
- Weight (in kilograms) and height (in centimeters) will be measured, and body mass index (BMI) and body surface area (BSA) will be calculated;
- PE;
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be recorded;
- Tanner staging score (sexual maturation) will be assessed;
- Blood and urine will be obtained for the following prior to dosing:
  - PK sample;
  - basic fasting lipid panel and hsCRP;
  - clinical safety laboratories (hematology, clinical chemistry and urinalysis);
  - $HbA_{1C;}$
- Urine pregnancy test (for females of childbearing potential);
- Patients will take no more bempedoic acid; last dose is day prior to this visit;
- Review patient dosing log and assess taste and ability to swallow the tablets;
- Site will review with patient the daily dosing instructions, storage instructions, and IMP adherence;
- Return of bempedoic acid;
- FU visit will be scheduled 35 ± 5 days after this visit.

9.7.6. Treatment Period 1/2 Visit 5 (Visit T5/Day 57 ± 7): Cohort 1 and Cohort 2

Patients in Cohort 1 and Cohort 2 will arrive at the study site after a minimum 10-hour fast approximately 24-hours after dosing from previous day, having not yet taken the daily dose of bempedoic acid. Patients will bring their IMP to the visit.

Procedures and evaluations will be performed during this visit:

- Concomitant and prohibited medications will be reviewed and recorded as needed;
- Adverse events will be assessed;
- Weight (in kilograms) and height (in centimeters) will be measured;
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be recorded;
- PE;
- Tanner staging score (sexual maturation) will be assessed;
- Blood and urine will be obtained for the following prior to dosing:
  - PK sample;
  - basic fasting lipid panel and hsCRP;
  - clinical safety laboratories (hematology, clinical chemistry and urinalysis);
  - urine pregnancy (for females of childbearing potential);
  - $HbA_{1C;}$
- Patient's bempedoic acid regimen will be escalated to the next treatment dose based on their weight cohort at Screening (Cohort 1: 90 mg bempedoic acid for patients weighing 16 to <30 kg, Cohort 2: 150 mg bempedoic acid for patients weighing 30 to <60 kg);
- Patients will take their first escalated dose of bempedoic acid after collection of blood and urine specimens;
- Review patient dosing log and assess taste and ability to swallow the tablets;
- Site will review with patient the daily dosing instructions, storage instructions, daily dosing log and IMP adherence;
- Patient will be queried as to taste and ability to swallow the given formulation
- Conduct diet and exercise counseling;
- PK sampling at 1 hour ± 10 minutes and 4 hours ± 15 minutes post dosing of bempedoic acid;
- Patients will leave the clinic following all assessments and will be reminded that the site will contact them by phone the next day for Visit T6.

9.7.7. Treatment Period 2 Phone Visit 2 (Visit T6/Day T5+1): Cohort 1 and Cohort 2

The site will contact the patient/guardian by telephone or telemedicine device to collect the following information:

- Concomitant and prohibited medications will be reviewed and recorded as needed;
- Adverse events will be assessed;
- Assess taste and ability to swallow the tablets;
- Site will review with patient the daily dosing instructions, storage instructions, daily dosing log and IMP adherence;
- Conduct diet and exercise counseling;
- Visit T7 (Phone Visit) will be scheduled.

The site PI should accompany designated site staff for phone or telemedicine interviews to discuss patient concomitant medications and adverse events.

9.7.8. Treatment Period 2 Phone Visit (Visit T7/Day 71 ± 7): Cohort 1 and Cohort 2

The site will contact the patient/guardian by telephone or telemedicine device to collect the following information:

- Concomitant and prohibited medications will be reviewed and recorded as needed;
- Adverse events will be assessed;
- Assess taste and ability to swallow the tablets;
- Site will review with patient the daily dosing instructions, storage instructions, daily dosing log and IMP adherence;
- Conduct diet and exercise counseling;
- Patient/caregiver will be provided with daily dosing and storage instruction reminder;
- Visit T8 will be scheduled.
- The site PI should accompany designated site staff for phone or telemedicine interviews to discuss patient concomitant medications and adverse events.

9.7.9. Treatment Period 2 Visit 4 (Visit T8/Day 85 ± 7): Cohort 1 and Cohort 2

Patients will arrive at the study site after a minimum 10-hour fast approximately 24-hours after dosing from previous day, having not yet taken the daily dose of bempedoic acid unless fasted samples were collected by a local laboratory as described in Section 9.5. Patients will bring their IMP to the visit. Procedures and evaluations will be performed during this visit:

- Concomitant and prohibited medications will be reviewed and recorded as needed;
- Adverse events will be assessed;
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be recorded;

- ECG reading;
- Blood and urine will be obtained for the following prior to dosing:
  - PK sample;
  - basic fasting lipid panel;
  - clinical safety laboratories (hematology, clinical chemistry and urinalysis);
  - blood and urine exploratory biomarker samples;
- Patients will take their daily dose of bempedoic acid after collection of blood specimens;
- Review patient dosing log and assess taste and ability to swallow the tablets;
- Site will review with patient the daily dosing instructions, storage instructions and IMP adherence;
- Conduct diet and exercise counseling;
- Patient/caregiver will be provided with daily dosing and storage instruction reminder and beginning the following day will begin self-administering bempedoic acid once daily until the next visit;
- Visit T9 will be scheduled.

9.7.10. Treatment Period 2 Visit 5 (Visit T9/Day 113 ± 7): Cohort 1 and Cohort 2

Patients in Cohort 3 will arrive at the study site after a minimum 10-hour fast approximately 24-hours after dosing from previous day, having not taken the daily dose of bempedoic acid. Patients will bring their remaining supply of IMP to the visit. The last dose of IMP administered will occur the day prior to this visit. Procedures and evaluations will be performed during this visit:

- Concomitant and prohibited medications will be reviewed and recorded as needed;
- Adverse events will be assessed;
- Weight (in kilograms) and height (in centimeters) will be measured, and body mass index (BMI) and body surface area (BSA) will be calculated;
- PE;
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be recorded;
- Tanner staging score (sexual maturation) will be assessed;
- Blood and urine will be obtained for the following prior to dosing:
  - PK sample;
  - basic fasting lipid panel and hsCRP;
  - clinical safety laboratories (hematology, clinical chemistry and urinalysis);

- HbA_{1C};
- Urine pregnancy test (for females of childbearing potential);
- Patients will take no more bempedoic acid; Last dose is day prior to this visit;
- Return of bempedoic acid; review of patient dosing log; assessment and recording of bempedoic acid taste and ability to swallow the tablets;
- FU visit will be scheduled 35 ± 5 days after this visit.

9.7.11. Follow-Up Visit (Visit FU/Day 35 ± 5 after last dose): Cohort 1, Cohort 2 and Cohort 3

Patients will be scheduled for their final Follow-up visit 35 ± 14days after their last dose of bempedoic acid; including patients who discontinue taking bempedoic acid prior to the scheduled last dose. Patients will arrive at the study site after a minimum 10-hour fast unless fasted samples were collected by a local laboratory as described in Section 9.5. Patients will bring their IMP to the visit.

Procedures and evaluations will be performed during this visit:

Concomitant and prohibited medications will be reviewed and recorded as needed.

- Concomitant medications will be reviewed and recorded as needed;
- Adverse events will be assessed;
- Weight (in kilograms) will be measured, and BMI and BSA will be calculated;
- Vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) will be recorded;
- PE;
- Blood and urine will be obtained for the following:
  - basic fasting lipid panel and hsCRP;
  - clinical safety laboratories (hematology, clinical chemistry and urinalysis); blood and urine exploratory biomarker samples;
- Complete study status in IWRS (ie, early withdrawal or completed study).

9.8. Patient Withdrawal Criteria

9.8.1. Early Withdrawal from Study

Patients must remain in the study through 35 ± 14 days after Week 16 (Visit T9) for Cohorts 1 and 2, or Week 8 (Visit T5) for Cohort 3 to be considered as having completed the study Patients who prematurely withdraw from study drug will be asked to continue scheduled visits to be followed for safety, as outlined in Appendix 1, and will be asked to attend the Follow-up visit (Visit FU) 35 ± 14 days after receiving the last dose of bempedoic acid.

Participation in the study is voluntary. Patients may refuse or withdraw from participation in this study at any time and for any reason, specified or unspecified, and without penalty or loss of benefits to which the patient is otherwise entitled.

The Investigator has the right and duty to interrupt the treatment of any patient whose health or well-being may be threatened by continued participation in this study. Such patients should be withdrawn from the study and should not be continued under a modified regimen.

Patients who are withdrawn from the study may not re-enter the study unless reviewed and approved by the Sponsor. The reasons for study withdrawal may include:

- Adverse event;
- Patient withdrawal of consent;
- Failure to comply with the protocol;
- Refusal to take IMP as indicated by the protocol;
- Illness, condition, or procedural complication that affects the patient's ability to participate in the study or that requires prohibited medication;
- Sponsor terminates the study;
- Investigator closes the site without an option for another Sponsor-approved site;
- In the Investigator's judgment, it is in the patient's best interest to discontinue participation in the study;
- Death;
- Other (specify).

If a patient is lost to follow-up, study site personnel must make reasonable efforts to contact the patient/caregiver to determine the reason for discontinuation/withdrawal. The measures that are taken to follow-up must be documented.

9.8.2. Procedures for Early Withdrawal

If a patient withdraws or is removed from the study for any reason, the patient should complete the final Treatment Period visit assessments (Visit T9 for cohorts 1 and 2 Visit T5 for cohort 3). Reason for withdrawal, date of the discontinuation, and date of the last dose of study drug should be recorded in the appropriate section of the eCRF. Study drug assigned to the withdrawn patient may not be assigned to another patient.

All effort should be made to have each patient complete all study visits on schedule according to the protocol. Accommodations for early or late visits in special circumstances will be considered by the Sponsor to prevent early withdrawal. Written notice (regardless of cause) is to be provided within 48 hours of the withdrawal to the Sponsor personnel or the Medical Monitor. At the time of discontinuation, every effort should be made to ensure all relevant procedures and evaluations scheduled for the final study visit are performed. Except in the case of a medical emergency, the procedures and assessments detailed in Appendix 1 for Visit T5/T9 will be performed upon early withdrawal from the study.

10. ASSESSMENT OF PHARMACOKINETICS

10.1. Pharmacokinetics Assessments

10.1.1. Sample Collection, Storage, and Shipping

Each venous whole blood sample (2 mL) will be withdrawn by direct venipuncture or indwelling catheter with saline flush into a lavender top K_2 EDTA vacuum blood collection tube. Samples will be mixed by gentle inversion and placed immediately into an ice/water bath. Plasma will be separated from the whole blood within 30 minutes of collection. Samples will be spun in a refrigerated centrifuge at 1000-1500× g relative centrifugal force for approximately 10 to 15 minutes. Plasma (approximately 1 mL) will be separated from other blood constituents using a disposable pipette. If red blood cells (RBCs) are inadvertently drawn into the plasma, the sample should be recentrifuged immediately. The plasma samples will be split equally into 2 aliquots (approximately 0.5 mL) and stored in appropriately labeled screw capped polypropylene tubes at or below -70°C within 1 hour of collection.

Plasma PK samples will be labeled with preprinted information, including study number, patient identification number, study day, nominal time of sample collection, matrix, and a text identification (ie, "Plasma PK").

Blood samples will be collected at the time points specified from the patient in the seated position according to the schedule of events described in Appendix 1.

10.1.2. Shipment of Pharmacokinetic Samples

Plasma PK samples will be shipped frozen on dry ice to the central laboratory according to the instructions in the laboratory manual (provided by the central laboratory). Shipping instructions will be provided to the Investigator and clinical staff prior to initiation of the study.

Samples should be stored at -70^{0}C or lower until shipped on dry ice. If -70^{0}C or lower storage is not available at the site, then samples may be shipped to the central laboratory on dry ice the same day. Sufficient shipping materials including dry ice should be used to ensure the sample arrive frozen at the central laboratory.

Split PK samples from each time point will be sent from the central laboratory to the analytical lab in 2 consecutive shipments. One set of time point aliquots will be sent and received (confirmation by the analytical lab) before the second set of time point aliquots is sent.

Samples should be packaged in ascending order by study day and time point such that all samples collected from the same patient are located in the same box (samples for multiple patients may be stored in the same box).

Samples should be shipped from the central laboratory to the analytical laboratory on a schedule to ensure that samples arrive at the bioanalytical laboratory [redacted] on a weekday. [redacted]. Prior to sample shipment, a notification e-mail that includes the tracking number and sample manifest will be sent to the following:

[redacted]

10.1.3. Analytical Methodology

Plasma concentrations of ETC-1002 and ESP15228 will be determined using a validated analytical procedure and reported in a bioanalytical study report.

11. EXPLORATORY BIOMARKER AND GENETIC TESTING

11.1. Exploratory Biomarker Measurement

Additional exploratory safety, efficacy, or PK related or potential biomarkers may be assayed from stored 5 mL serum samples and/or 10 mL urine samples, and/or plasma PK samples (Section 11.1). Participation in this portion of the study is optional and where is approved by the IRB/IEC and by local law. Those who choose not to provide samples for exploratory biomarker assessments may still participate in the main portion of the study. Samples will be coded before testing to safeguard the confidentiality and privacy of the subject's identity in accordance with local law requirements. Signing additional informed consent is required to obtain these samples.

11.2. Genetic Testing

As part of this study, at the Screening Visit, all patients will be invited to provide a blood sample to be analyzed for genetic markers of HeFH which may include but may not be limited to mutations in genes for LDLr, ApoB, LDLRAP1 and PCSK9. Participation in this portion of the study is optional and available where approved by the IRB/IEC and by local law. Those who choose not to provide a sample for genetic analysis may still participate in the main portion of the study provided they meet the inclusion/exclusion criteria. Samples will be coded before testing to safeguard the confidentiality and privacy of the subject's identity in accordance with local law requirements. Signing additional informed consent is required to obtain this sample and analysis.

12. ASSESSMENT OF PHARMACODYNAMICS

12.1. Pharmacodynamic Assessments

12.1.1. Sample Collection, Storage, and Shipping

Blood samples for basic fasting lipids (LDL-C, non-HDL-C, TC, TG, and HDL-C) and hsCRP will be drawn with the patient in the seated position according to the schedule of events described in Appendix 1. All samples will be collected following a 10-hour fast approximately 24-hours after dosing from previous day. Laboratory samples will be collected by appropriate clinical site personnel and then shipped according to the instructions in the laboratory manual (provided by the central laboratory).

12.1.2. Clinical Laboratory Parameters (Basic Fasting Lipids and hsCRP)

Blood specimens for basic fasting lipids assessments and hsCRP will be collected as shown in Table 3.

Table 3: Clinical Laboratory Parameters (Basic Fasting Lipids and hsCRP)

Clinical Laboratory Test
Basic Fasting Lipid Parameters and hsCRP • Direct low-density lipoprotein cholesterol (LDL-C) • Calculated non-high-density lipoprotein cholesterol (non-HDL-C) • Total cholesterol (TC) • Triglycerides (TG) • High-density lipoprotein cholesterol (HDL-C) • High-sensitivity C-reactive protein (hsCRP)

13. ASSESSMENT OF SAFETY

13.1. Demographics and Medical History

Demographic data and a medical history will be obtained from the patient at Visit S1/Day -14. Conditions that are relevant and/or clinically significant should be captured with at least a start date and an indication of whether the condition is ongoing or resolved. All surgeries, regardless of date, should be reported.

13.2. Vital Signs

Systolic blood pressure, diastolic blood pressure, and pulse rate will be recorded according to the schedule of events (Appendix 1). Measurements should be taken after the patient has been seated quietly for at least 5 minutes in a chair with the back supported, the feet flat on the ground, and the arms bared and supported at heart level.

Blood pressure will be obtained using a calibrated, fully automated machine with a cuff that is appropriate to the size of the upper arm. If a fully automated machine is not available, blood

pressure may be measured manually. The same method (either automated or manual) and the same arm (right or left) must be used throughout the study.

13.3. Weight, Height, Body Mass Index, and Body Surface Area

Height will be measured in centimeters (cm) and weight will be measured in kilograms (kg) on a calibrated scale in the morning while fasting and in street clothing according to the visit schedule in Appendix 1.

Body mass index will be programmed to be calculated as the weight in kilograms divided by the square of body height in meters (kg/m^2). Body surface area will also be calculated using the following equation: body surface area (m^2) = square root of ([weight(kg) x height(cm)]/3600).

13.4. Physical Examination

A complete PE will be performed according to the schedule of events (Appendix 1) or at early termination from the study. A complete PE includes an assessment of the following:

- general appearance;
- skin;
- eyes, ears, nose, and throat (EENT);
- head/neck;
- extremities;
- musculoskeletal examination;
- respiratory examination;
- CV assessment, including rhythm and presence of cardiac abnormalities;
- abdominal examination;
- neurologic examination to record the presence of abnormalities in mental status, motor, and sensory function; and
- any additional assessments necessary to establish baseline status or evaluate symptoms or adverse experiences.

Documentation of the PE will be included in the source documentation at the study site. Changes from baseline (Visit T1/Day 1) in PE findings that meet the definition of an AE will be recorded on the appropriate eCRF. Tanner staging score (sexual maturation) will be assessed at Visit T1/Day 1.

13.5. Electrocardiogram

ECG measurement will be collected in the supine position. ECGs will be assessed using machine readings and physician review.

13.6. Clinical Laboratory Tests

13.6.1. Clinical Safety Laboratory Parameters

Blood and urine specimens for safety laboratory assessments will be collected as shown in Table 4.

Table 4: Clinical Safety Laboratory Evaluations

Clinical Laboratory Test	**Clinical Laboratory Test**
Hematology • Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood (RBC) cell count • White blood (WBC) cell count with differential (absolute and %)	Blood Chemistry (serum, fasting) • Albumin (ALB) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT; serum glutamic pyruvic transaminase [SGPT]) • Aspartate aminotransferase (AST; serum glutamic oxaloacetic transaminase [SGOT]) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO_2) • Chloride (Cl) • Creatinine[a] • Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total bilirubin (TB)[b] • Total protein • Uric acid
Urinalysis (Dipstick) • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrate • Occult Blood • pH • Protein • Specific Gravity • Urobilinogen	Urinalysis (Microscope) – only if urine dipstick abnormal • Bacteria • Casts • Crystals • Epithelial cells • RBC • WBC

Table 4: Clinical Safety Laboratory Evaluations

Clinical Laboratory Test	Clinical Laboratory Test
Other Screening Labs	Specialty Laboratories[d]
• Hepatitis B surface antigen (HBsAg) • Hepatitis C virus (HCV)[c] • Thyroid-stimulating hormone (TSH) • Urine drug screen for illicit drug use	• Cortisol • Dihydroepiandroestrone • Follicle-stimulating hormone (FSH) • Glycosylated hemoglobin, type A_{1C} (HbA_{1C}) • Luteinizing hormone (LH) • Estradiol (females) • Testosterone (males) • Urine pregnancy test at Visits S1, T1, T5 and T9 (for female of childbearing potential) • Protrombin time (PT), (if repeat liver function test [LFT] elevation, see Section 13.6.4.1) • International normalized ratio (INR), (if repeat LFT elevation, see Section 13.6.4.1)

[a] eGFR will be calculated (by central laboratory) using the Revised ("Bedside") Schwartz formula.

[n] If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained.

[c] If hepatitis C antibody (HCV-AB) is positive, a reflex HCV RNA will be performed to rule out active disease.

[d] Specialty Laboratories of Cortisol, Dihydroepiandroestrone, FSH, HbA1c, LH, Estradiol (females), Testrosterone (Males), and Urine pregnancy (for female patients of childbearing potential) to be assessed at Visits S1, T1, T5 and T9. PT and INR assessed as-needed accompanying repeat LFT elevation assessment per Section 14.6.4.1.

Patients will be instructed to fast for a minimum of 10 hours before each blood draw; only water will be permitted during the fasting period. If the patient has not fasted for a minimum of 10 hours before the study visit, the blood sample will not be drawn at that visit. The reason for any missing blood samples will be documented.

When ECG, vital signs and blood samples for safety laboratories are to be collected at the same time, measurement of vital signs should precede collection of blood samples.

13.6.2. Sample Collection, Storage, and Shipping

Blood samples will be drawn with the patient in the seated position. Laboratory samples will be collected by appropriate clinical site personnel and then shipped according to the instructions in the laboratory manual (provided by the central laboratory).

13.6.3. General Monitoring and Management of Abnormal Clinical Laboratory Values

The Investigator will review the results of all laboratory tests as they become available and will sign and date the report to document their review. The Investigator will ascertain if any laboratory value is abnormal or represents a clinically significant change from baseline for the individual patient, with baseline defined as the last value or observation before the first dose of

IMP. The investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory test.

If a laboratory value is determined to be an abnormal and clinically significant change from baseline for the patient, the Investigator will determine if it qualifies as an AE (as described below), and if yes, an appropriate eCRF will be completed. All clinically significant laboratory abnormalities that occur during the study that were not present at baseline should be followed and evaluated with additional tests, if necessary, until diagnosis of the underlying cause or resolution. Specific monitoring and management guidelines for laboratories of special interest are outlined in the sections below.

An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- an action is taken with the IMP because of the abnormality;
- intervention for management of the abnormality is required; or
- the abnormality be deemed clinically significant by the Investigator.

13.6.4. Monitoring and Management of Hyperuricemia

Bempedoic acid has been associated with hyperuricemia in prior Phase 3 trials in adults where 26% of patients treated with bempedoic acid and with normal baseline uric acid values (versus 9.5% placebo) experienced hyperuricemia one or more times, and 3.5% of patients experienced clinically significant hyperuricemia reported as an adverse reaction (versus 1.1% placebo). Increases in uric acid levels usually occurred within the first 4 weeks of treatment initiation and persisted throughout treatment. Monitor patients for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate.

13.6.4.1. Monitoring and Management of Elevated Liver Function Tests

If a patient has a new value >3 × ULN for serum ALT and/or AST at any time after randomization, the patient will undergo a repeat confirmatory liver function test (LFT) assessment as soon as is reasonably possible but preferably within 3 to 7 days after the laboratory result is available.

Repeat LFT assessment will include the following: (1) measurement of serum ALT, AST, alkaline phosphatase, TB, direct bilirubin, and CK; prothrombin time (PT)/international normalized ratio (INR); eosinophil count; and antihepatitis A virus (total), HBsAg (confirmation of screening measurement), HCV (confirmation of screening measurement), and anticytomegalovirus/immunoglobulin M; (2) history of concomitant medication use; (3) history of exposure to environmental chemical agents, including ethanol; and (4) questioning for related symptoms. Additionally, further testing may be warranted to rule out additional pathology depending on clinical presentation and should be discussed with the Sponsor personnel or the authorized Medical Monitor.

- If the repeat LFT assessment confirms that the value for serum ALT and/or AST is >3 × ULN, consideration should be given to withdrawing the patient and administering no further doses of IMP. At the Investigator's discretion, IMP may be

interrupted, and the patient may be rechallenged with the IMP after values for the LFTs have returned to baseline levels.

- If repeat LFT assessment confirms a value for serum ALT and/or AST >5 × ULN, the patient will be withdrawn from IMP treatment but will be asked to continue to be followed for safety (as outlined in the protocol-specified visit schedule in Appendix 1 or more frequently as determined by the Investigator).
- If repeat LFT assessment confirms that the value for serum ALT and/or AST level is >3 × ULN and the patient has any of the following findings, the patient will be withdrawn from IMP treatment but will be asked to continue to be followed for safety (as outlined in the protocol-specified visit schedule in Appendix 1 or more frequently as determined by the Investigator):
  - TB value >2 × ULN;

    Note: In the case of patients with Gilbert's disease, TB will be fractionated and the determination of 2 × ULN will be based upon direct (conjugated) bilirubin.
  - INR value >1.5 × ULN (unless the patient is on a stable dose of anticoagulation medication);
  - appearance or worsening of right upper abdominal discomfort, anorexia, fatigue, nausea, vomiting, fever, rash, or eosinophilia.

13.6.4.2. Monitoring and Management of Elevated Serum Creatinine Levels

If at any time after randomization a patient experiences a marked creatinine elevation >1.0 mg/dL (44 µmol/L) above ULN, the site will be notified and the patient will undergo repeat confirmatory assessment as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available.

If repeat creatinine assessment confirms serum creatinine >1.0 mg/dL (44 µmol/L) above ULN or a decrease in eGFR to the level of 30 mL/min/1.73 m^2 or experiences acute renal failure, the patient will be withdrawn from IMP treatment but will be asked to continue to be followed for safety (as outlined in the protocol-specified visit schedule in Appendix 1).

13.6.4.3. Monitoring and Management of Changes in Hemoglobin Levels

If a patient experiences a decrease of >2.0 g/dL (20 g/L) from baseline in hemoglobin (Hgb) or an Hgb reading of 11.0 g/dL (110 g/L) or less at any time after enrollment, the patient will undergo a repeat confirmatory hematology testing as soon as is reasonably possible but preferably within 3 to 7 days after the laboratory test result becomes available.

Repeat hematology assessment will include the following: (1) measurement of Hgb, hematocrit (Hct), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet count, reticulocyte count (percent and absolute), RBC count, and white blood cell (WBC) count with differential (absolute values only); (2) history of concomitant medication use; and (3) questioning for related symptoms and (4) questioning for potential cause (such as recent bleeding, trauma, etc.). Additionally, further

testing may be warranted to rule out additional pathology, depending on clinical presentation, and should be discussed with Sponsor personnel or the authorized Medical Monitor.

- If a repeat assessment confirms a decrease >2.0 g/dL (20 g/L) from baseline in Hgb concentration, the patient should be monitored carefully during the study and return at 2-week intervals after study completion for additional Hgb measurements until the Hgb concentration returns to baseline or reaches a stable level.
- If a repeat assessment confirms a value <11 g/dL (110 g/L) for Hgb, the patient will be withdrawn from IMP treatment. The patient will return at 1-week intervals after withdrawal of IMP treatment for additional Hgb measurements until Hgb concentration returns to baseline or reaches a satisfactory conclusion.
- If a diagnosis of a treatment emergent adverse event of anemia is made the patient will be withdrawn from bempedoic acid treatment. The patient will return at 1-week intervals after withdrawal of bempedoic acid treatment for additional Hgb measurements until Hgb concentration returns to baseline or reaches a satisfactory conclusion.
- Patients who are withdrawn from IMP treatment due to decreases in Hgb concentration will be asked to continue to be followed for safety (as outlined in the protocol-specified visit schedule in Appendix 1).

The Investigator may choose to consult with a specialist at any time to further evaluate the cause of the alteration in hemoglobin.

13.6.4.4. Monitoring and Management of Elevated Creatine Kinase Levels

If a patient has a value >5 × ULN for serum CK at any time after enrollment, the patient will undergo a repeat confirmatory assessment as soon as is reasonably possible but preferably within 3 to 7 days after the laboratory result is available. This assessment will include questioning for related symptoms and inquiry for potential cause (such as recent trauma or physically strenuous activity).

- If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality (value >5 × ULN), the patient should, if asymptomatic, receive further assessment and investigation into the cause. The presence of renal injury should be assessed, and serum CK levels should be measured approximately weekly or more frequently, if clinically indicated, until resolution. If serum CK levels continue to rise, treatment with the IMP should be discontinued.
- If symptomatic, the following steps should be completed:
  - Hold dosing with the IMP;
  - Clarify the nature, duration, and intensity of muscle symptoms;
  - Review possible predisposing factors, such as unaccustomed exercise, heavy alcohol intake, viral illness (consider performing serology);

- Evaluate for additional diagnoses or other conditions, which can cause myopathy, including muscle tenderness (by PE), weakness, rash, measurement of serum creatinine level, and dipstick urinalysis with microscopy, if indicated;
- Obtain clinical chemistries to assess the possibility of lactic acidosis; and
- Follow symptoms and serum CK levels until the abnormality has resolved.

  If, based on the above evaluation, an alternative explanation is suspected, consider resuming IMP once the serum CK level returns to baseline levels. If no alternative explanation exists, consider withdrawing the patient from IMP treatment.

- If the repeat assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality (serum CK value >10 × ULN) even in the absence of symptoms, the patient should be withdrawn from the study and given no further doses of IMP. In all cases, signs/symptoms and laboratory evaluations, as outlined in the bulleted point above, should be evaluated.
- If the patient is withdrawn from IMP treatment, the patient should be asked to continue to be followed for safety (as outlined in the protocol-specified visit schedule in Appendix 1).

13.6.5. Total Blood Volume

The total number of venipunctures and total volume of blood collected during the study will be limited to that needed for PK, PD, and safety assessments and within safe limits in child health research (Howie 2011). The total whole blood volume collected during the study is expected to be approximately 193 mL for each patient (approximately 7% of total body volume per 8 weeks for a 16-kg patient). During any 24-hour period the volume of whole blood collected is expected to be 38 mL for each patient (approximately 3% of total body volume per 24 hours for a 16-kg patient).

13.7. Adverse and Serious Adverse Events

13.7.1. Adverse Events

13.7.1.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, including control, and which does not necessarily have a causal relationship with treatment.

An AE can be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product;
- Any new disease or exacerbation of an existing disease;

- Any deterioration in nonprotocol-required measurements of laboratory value or other clinical test (ie, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from IMP; or
- An adverse drug reaction (ADR; see Section 13.7.1.2).

Treatment-emergent AEs are defined as AEs that begin or worsen after the first dose of IMP.

13.7.1.2. Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an ADR. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (eg, the relationship cannot be ruled out).

An unexpected ADR is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

13.7.1.3. Reporting of Adverse Events

Patients should be instructed to report to the Investigator all AE that they experience from the time the ICF is signed through the study completion for the specific patient (defined as either the last scheduled visit attended or the last dose of bempedoic acid, whichever is later). Investigators should make an assessment for AEs at each visit and record the event on the appropriate eCRF. Any SAE that occurs from the time the ICF is signed through study completion for the specific patient (defined as either the last scheduled visit attended or the last dose of bempedoic acid, whichever is later), should be reported to the Sponsor per Section 13.7.2.4.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, transfusion) should be recorded as an AE, not the procedure.

Any medical condition already present at screening or baseline should not be reported as an AE unless the medical condition or signs or symptoms present at baseline change in severity or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at baseline and significantly worsen during the study should be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. For each AE, the following information will be recorded:

- Description of the event (eg, headache);
- Date of onset;
- Date of resolution (or that the event is continuing);
- Action taken because of the event;
- Seriousness of the event;
- Severity of the event;
- Outcome of the event; and
- Investigator's assessment of relationship to IMP.

A cluster of signs and symptoms that results from a single cause should be reported as a single AE (eg, fever, elevated WBCs, cough, abnormal chest x-ray, etc., can all be reported as "pneumonia").

The Investigator will carefully evaluate the comments of the patient and the response to treatment in order that he/she may judge the true nature and severity of the AE. The question of the relationship of AEs to IMP administration should be determined by the investigator or study physician after thorough consideration of all facts that are available.

Additional information will be collected regarding muscle-related AEs that may include, but may not necessarily be limited to, a muscle-related questionnaire, with questions regarding type of muscle-related symptoms, location of the muscle-related AE, and potential cause of the muscle-related AE.

13.7.1.4. Severity

It is the Investigator's responsibility to assess the intensity (severity) of an AE. The severity of the AE will be characterized as mild, moderate, or severe according to the following definitions:

- Mild: Events are usually transient and do not interfere with the patient's daily activities.
- Moderate: Events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities.
- Severe: Events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up.

Note: A severe AE need not be serious and an SAE need not, by definition, be severe.

13.7.1.5. Relationship

It is the Investigator's responsibility to assess the relationship of the AE to the IMP. The degree of "relatedness" of the AE to the IMP should be described using the following scale:

- Not Related: No temporal association and other etiologies are likely the cause.
- Unlikely: While cannot be definitively ruled as not related to IMP, a causal association is remote, and other etiologies are more likely to be the cause. For reporting and summarization, events assessed as "Unlikely" to be related to IMP will be considered as "Not Related" to IMP for regulatory reporting purposes.
- Possible: Temporal association, but other etiologies are likely the cause. However, involvement of the IMP cannot be excluded.
- Probable: Temporal association, other etiologies are possible but unlikely. The event may respond if the IMP is discontinued.
- Definite: Established temporal association with administration of the IMP with no other more probable cause. Typically, the event should resolve when the IMP is discontinued and recur on re-challenge.

13.7.1.6. Monitoring and Follow-up of Adverse Events

Patients having AEs will be monitored with relevant clinical assessments and laboratory tests, as determined by the Investigator. All follow-up results are to be reported to the Sponsor personnel or the authorized Medical Monitor. Any actions taken and follow-up results must be recorded either on the appropriate page of the eCRF or in appropriate follow-up written correspondence, as well as in the patient's source documentation. Follow-up laboratory results should be filed with the patient's source documentation.

For all AEs that require the patient to be discontinued from the study, relevant clinical assessments and laboratory tests must be repeated at appropriate intervals until final resolution, stabilization of the event(s), or until the patient is lost to follow-up or dies.

Patients with AEs that are ongoing must be followed through study completion for the specific patient (defined as either the last scheduled visit attended or the last dose of bempedoic acid, whichever is later).

13.7.1.7. Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as AEs that begin or worsen after the first dose of IMP through study completion for the specific patient (defined as either the last scheduled visit attended or the last dose of bempedoic acid, whichever is later).

13.7.2. Serious Adverse Events

13.7.2.1. Definition of Serious Adverse Event

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- Results in death;

- Is life threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity, or substantial disruption of the ability to conduct normal life functions;
- Is a congenital anomaly/birth defect; or
- Is an important medical event.

Note: Hospitalization is defined as a formal inpatient admission. This will not include admissions under "23-hour Observational Status," an emergency room visit without hospital admission, or an urgent care visit and therefore such events will not be recorded as an SAE under this criterion, nor will hospitalization for an elective or outpatient procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective or outpatient surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (eg, no place to stay live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Any clinical endpoints that meet SAE criteria will be also reported as SAEs.

13.7.2.2. Definition of Adverse Events or Outcomes Not Qualifying as Serious Adverse Events

The following are not considered SAEs and therefore do not need to be reported as such:

- Preplanned or elective hospitalization, including social and/or convenience situations (eg, due to inclement weather).
- Overdose of either IMP or concomitant medication unless the event meets SAE criteria (eg, hospitalization). However, the event should still be captured as a nonserious AE on the appropriate eCRF page.

13.7.2.3. Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the Investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the local laboratory. In some cases, significant

changes in lab values within the normal range will require similar judgment. Laboratory abnormalities should be reported as an AE if they meet any of the following criteria:

- Intervention is required to treat the abnormality.
- Modification of study treatment is required due to the abnormality.
- Based on the Investigator's medical judgement.

13.7.2.4. Reporting Serious Adverse Events

All SAEs, regardless of relationship to IMP, occurring from the time of informed consent through study completion for the specific patient (defined as either the last scheduled visit attended or the last dose of bempedoic acid, whichever is later). In the event that an Investigator becomes aware of an SAEs that the Investigator considers related to IMP that occur after study completion must be reported to the Sponsor.

To report the SAE, complete the provided SAE form and submit it to the safety designee within 24 hours of becoming aware of the occurrence.

The Investigator is required to submit SAE reports to the IRB/IEC in accordance with local requirements. All Investigators involved in studies using the same investigational product will receive any safety alert notifications for onward submission to their local IRB/IEC as required. All reports sent to Investigators for ongoing studies with blinded IMP will be blinded.

All SAEs should be recorded on the eCRF and source documents. Criteria for documenting the relationship to IMP and severity will be the same as those previously described.

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form and submit any supporting documentation (eg, patient discharge summary or autopsy reports) to the safety designee.

13.7.2.5. Reporting of Serious Adverse Events to Regulatory Authorities

The Sponsor (and/or designee) is responsible for submitting expedited reports of suspected and unexpected serious adverse reactions (SUSARS) to the appropriate regulatory authorities including, but not limited to the Central Committee on Research Involving Human Subject (CCMO) web portal (the Eudravigilance database). All Investigators participating in ongoing clinical studies with the IMP will be notified by the sponsor (or designee) of SUSARs. SUSARS must be communicated as soon as possible to the appropriate IRB/IEC by the Investigator, as applicable and/or reported in accordance with local laws and regulations. Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor.

13.7.2.6. Reporting of Patient Death

The death of any patient during the study or within the 30-day follow-up period after they have completed the study (regardless of the cause) must be reported as detailed above.

13.7.2.7. Reports of Pregnancy

Although not considered an SAE (unless the event occurs with a serious outcome), pregnancy information on female patients will be collected by the authorized safety designee. If a female patient becomes pregnant during the study, study treatment should be discontinued immediately. The Principal Investigator or designee must complete and submit the Pregnancy Report Form within 24 hours of awareness of the pregnancy. In addition, patients who become pregnant will complete the remaining study evaluations according to the schedule in Appendix 1. Whenever possible, pregnancies should be followed until outcome and the Pregnancy Outcome Reporting Form submitted to the safety designee once the outcome is known.

13.7.3. Adverse Events of Special Interest

Adverse events of special interest (AESI) include metabolic acidosis (clinical laboratories) and hepatic, muscular (AE and serum CK evaluation), hyperglycemia, hypoglycemia, renal, CV, and neurocognitive/neurologic events, tendinopathy, tendon rupture and atrial fibrillation. Based on previous experience with bempedoic acid, serum uric acid, and Hgb will be closely monitored. Safety monitoring guidelines for Hgb are detailed in Section 13.6.4.3. Specific monitoring guidelines are provided for AEs that are uncovered through laboratory evaluations. Patients/caregivers are to be questioned about changes in cognition and or signs/symptoms of hypoglycemia at each study visit.

The protocol procedures that are included in clinical studies of bempedoic acid are part of standard clinical care for patients with elevated LDL-C levels and, in addition, address the potential and theoretic risks of bempedoic acid.

All bempedoic acid studies include standard pharmacovigilance including evaluation of AEs, PE findings, vital signs, and laboratory assessments. Adverse events associated with the experiences with bempedoic acid to date:

- Across clinical studies to date, the most frequently reported TEAEs included musculoskeletal and connective tissue disorders (back pain, pain in extremity, myalgia, arthralgia, and muscle spasms), nervous system disorders (headache), gastrointestinal disorders (nausea and diarrhea), and infections and infestations. Overall, AEs were generally reported with similar incidence in patients who were treated with bempedoic acid in combination with ezetimibe or statin therapy, ezetimibe, statins, or placebo.
- In general, laboratory results showed no clinically significant trends across completed clinical studies to date. Clinical chemistries, hematology, vital signs, and PEs are being routinely monitored in the bempedoic acid clinical program.
- Hyperuricemia is associated with bempedoic acid use in adults but has not been studied in pediatric populations. In clinical trials, 26% of patients treated with bempedoic acid and with normal baseline uric acid values (versus 9.5% placebo) experienced hyperuricemia one or more times, and 3.5% of patients experienced clinically significant hyperuricemia reported as an adverse reaction (versus 1.1% placebo). Increases in uric acid levels usually occurred within the first 4 weeks of treatment initiation and persisted throughout treatment. After 12 weeks of treatment,

the mean placebo-adjusted increase in uric acid compared to baseline was 0.8 mg/dL for patients treated with bempedoic acid. Elevated blood uric acid may lead to the development of gout. Gout was reported in 1.5% of patients treated with bempedoic acid and 0.4% of patients treated with placebo. The risk for gout events was higher in patients with a prior history of gout (11.2% bempedoic acid versus 1.7% placebo), although gout also occurred more frequently than placebo in patients treated with bempedoic acid who had no prior gout history (1.0% bempedoic acid versus 0.3% placebo).

- Tendon rupture or injury is associated with bempedoic acid use in adults but has not been studied in pediatric populations. Tendon rupture occurred in 0.5% of patients treated with bempedoic acid versus 0% of placebo treated patients and involved the rotator cuff (the shoulder), biceps tendon, or achilles tendon. Tendon rupture occurred within weeks to months of starting bempedoic acid. Tendon rupture may occur more frequently in patients over 60 years of age, in those taking corticosteroid or fluoroquinolone drugs, in patients with renal failure, and in patients with previous tendon disorders. Bempedoic acid treatment should be discontinued immediately if the patient experiences rupture of a tendon. At the Investigator's discretion bempedoic acid may be discontinued if the patient experiences joint pain, swelling, or inflammation. Patients should be advised to rest at the first sign of tendinitis or tendon rupture and to contact the Investigator if tendinitis or tendon rupture symptoms occur.
- Atrial Fibrillation: Bempedoic acid has been associated in some clinical studies with a small imbalance in atrial fibrillation relative to placebo. Atrial fibrillation will be identified and evaluated by routine safety monitoring of AEs.
- Potential AEs based on findings in nonclinical models:
  - Hypoglycemia and metabolic acidosis led to deaths in monkeys in nonclinical studies. Exposures in these studies were >17 times greater than those associated with the bempedoic acid 180-mg dose, which is the highest dose that will be evaluated in this study. Subsequent monkey studies proved that hypoglycemia was reversible with discontinuation of study drug and nutritional support. Patients in all clinical trials will be provided with information (in the ICF) regarding the signs and symptoms of hypoglycemia, including lightheadedness, shakiness, shaking of the hands, sweating, tingling, blurred visions, nausea or vomiting, mental confusion, difficulty concentrating, and drowsiness. Patients who experience any of these symptoms will be instructed to report them to their study doctor. Occurrence of metabolic acidosis will be monitored by clinical safety laboratory chemistries.
- Adverse events that are currently monitored for all experimental lipid-lowering therapies and have been associated with previous lipid-lowering therapies:
  - Hepatic: Hepatic function will be monitored throughout with the clinical safety labs. More detailed investigation will occur if the safety clinical laboratory results are 3 times or more than the ULN (see Section 13.6.4.1).

- Muscle: Muscle events have been associated with statins (FDA Press Release, 2012) and other lipid-lowering therapies and are mentioned in the product information for those products. The exact mechanism in the development of muscle events is unclear. Bempedoic acid (ETC-1002) is a prodrug which needs to be converted by an acyl-CoA synthetase (ACS) to ETC-1002-CoA. The specific ACS known to convert into its active form is not present in skeletal muscle. This suggests that bempedoic acid may not lead to an increase in muscular side effects when given in conjunction with statins. Nonetheless, muscle symptoms through AE review, elevations in serum CK levels, and symptoms of potential myopathy will be closely monitored. More detailed investigation will occur if values for serum CK exceed 5 × ULN (see Section 13.6.4.4).
- Hyperglycemia/Hypoglycemia: Clinical laboratories will be evaluated during the study, including fasting glucose.
- Renal: Nonclinical studies have demonstrated nephrotoxic effects on tubular cells of some lipid-modifying agents. Clinical laboratories will be evaluated during this study, including serum creatinine. Patients will be monitored beyond the conclusion of the study if necessary to follow abnormal renal laboratory values until resolution or stabilization.
- Neurocognitive Events: Theoretically, it is possible that lipid-lowering agents that disrupt cholesterol homeostasis in the brain could impact neurological function, and there have been reports of cognitive impairment (eg, memory loss) associated with the use of statin drugs (Dietschy 2001). The human brain has a significant requirement for cholesterol (Dietschy 2004) and dysregulation of brain cholesterol homeostasis has been linked to chronic neurodegenerative disorders, including Alzheimer's disease, Huntington's disease, Parkinson's disease, Niemann–Pick type C disease and Smith-Lemli-Opitz syndrome (Goedeke 2014). In this study, neurocognitive events will be evaluated by standard PE and AE monitoring. Summarization of events will occur using prespecified Medical Dictionary for Regulatory Activities (MedDRA) terms.

14. STATISTICS

14.1. General Considerations

The analyses described in this section will be performed as further outlined in the statistical analysis plan (SAP). The analyses specified in the SAP will supersede those specified in the protocol in the event of any differences between the 2 documents. A copy of the SAP will be included as an appendix in the clinical study report for this protocol.

14.2. Determination of Sample Size

The sample size in this PK/PD study (54 patients; approximately 18 patients per weight group) was selected to provide adequate data to support the dose selection, sample-size calculation, and

general study design considerations for subsequent Phase 3 studies in this patient population (Julious 2005). 54 male and female patients aged 6 to 17 years old (approximately 18 patients in each weight cohort: Cohort 1, 16 to <30 kg, Cohort 2, 30 to 60 kg, and Cohort 3, >60 kg) with a history of HeFH and who are on an optimal dose of statin and who meet the inclusion and exclusion criteria will be enrolled. The sample size of 54 patients accounts for at least 16 evaluable patients per cohort, accounting for a 10% dropout rate, and is expected to provide approximately 90% power to detect a difference of 25% in clearance of bempedoic acid measured by the primary endpoint of observed trough plasma concentration of ETC-1002 following 8 weeks of steady-state dosing of bempedoic acid. These power calculations are based on simulations to detect a 25% change in CL/F stratified by weight cohort using a smoothed parametric bootstrapping procedure of 1000 sets of parameters generated using the multivariate normal distribution as an approximate asymptotic posterior distribution based on the final estimates from and variance-covariance matrix from the adult base PK model output. Controls will be established to ensure that approximately 25% of total patients are taking background ezetimibe across the study to provide sufficient representation to assess patients taking concurrent bempedoic acid and ezetimibe.

14.3. Analysis Populations

The following analysis populations will be defined:

- The PK population will include all patients who receive at least 1 dose of bempedoic acid and have at least 1 evaluable PK data point.
- The full analysis population, used for all PD and safety related analysis, will include all patients enrolled into the study (all patients who receive at lease 1 dose of bempedoic acid).
- The completer population will include all patients who complete all assigned treatment-period doses.

14.4. Subgroup by IMP Formulation

Primary, secondary, and safety endpoints will be analyzed by subgroup of IMP formulation. The details will be specified in the SAP.

14.5. Disposition, Demographic, and Baseline Characteristics

Disposition, including reason for withdrawal from the study, will be summarized by cohort and formulation. Demographic and other baseline characteristics will be summarized by cohort using descriptive statistics (number, mean, median, standard deviation, minimum, and maximum) for continuous variables and counts and percentages for categorical variables.

Baseline is defined as the last assessment measurements before the first dose of IMP. No missing data of postbaseline will be imputed in this study.

14.6. Pharmacokinetic and Exposure-Response Analyses

The primary PK parameters are based on the most appropriate structural and error population model including a full covariate analysis that best describes the concentration-time relationship

through iterative model fitting using nonlinear mixed effects modeling (NONMEM). Initial model development will be based on experience gained from population PK modeling in adults.

The typical values for plasma PK parameters of ETC-1002 will be estimated using population PK analyses.

The following individual PK parameters will be determined for each patient, based on the plasma concentrations of ETC-1002:

- AUC_{ss} area under the plasma concentration-time curve over the dosing interval at steady state
- $C_{max,ss}$ maximum plasma concentration at steady state
- $C_{avg\ ss}$ average plasma concentration over the dosing interval at steady state
- C_{trough} plasma concentration observed just prior to dosing

Other parameters may be added as appropriate; the final model-based parameters and post hoc PK parameter estimates reported will be detailed in the SAP.

14.7. Pharmacodynamic and Exposure-Response Analyses

Descriptive statistics (number, mean, median, standard deviation, minimum, maximum, Q1, Q3) will be used to summarize LDL-C, TC, HDL-C, non-HDL-C, TGs, and hsCRP at each assessment by cohort and formulation to summarize the change from baseline and the percent change from baseline by cohort at each postbaseline assessment.

A model for exposure–LDL-C response will be developed that can provide simulations for dosing recommendations in subsequent pediatric trials. Clinically relevant safety observations may be included in determining an optimal dose regimen/therapeutic index for pediatric patients' therapeutic index.

14.8. Safety Analyses

Adverse Events

The summarization of AEs will include TEAEs, defined as AEs with an onset date on or after initiation of study treatment. Each AE will be coded using the latest version of MedDRA. TEAEs and SAEs will be summarized by system organ class (SOC), severity, and relationship to study drug for each cohort and formulation. These AE summaries will include cumulative incidence (percent of patients experiencing the AE) and patient-year adjusted incidence rates. Deaths and withdrawal from study treatment due to AEs will each be summarized by cohort and formulation.

Safety narratives will be generated for deaths, AEs leading to discontinuation of bempedoic acid or study, pregnancies, SAEs, and SUSARs. These safety events will also be summarized overall and by cohort and formulation.

All AEs of Special Interest (AESI) will be identified and evaluated by routine safety monitoring of AEs and laboratory values (where appropriate) and will be summarized by severity and relationship to IMP for each.

The following are considered AESI for this study:

- Hepatic Safety, including liver-associated enzymes, TB, and any Hy's law cases (≥3 × ULN for either ALT or AST, with accompanying TB >2 × ULN in the setting of no known other cause)
- Musculoskeletal Safety, including CK
- Diabetes and Glycemia, including new onset of diabetes and worsening of diabetes
- Hypoglycemia Associated with Metabolic Acidosis
- Renal Impairment, including lab measures of renal function
- Neurocognitive Events
- Atrial Fibrillation
- Tendon rupture

Laboratory Values, Physical Exam, ECG and Vital Signs

Clinical safety laboratories, including hematology and blood chemistry; PE findings, ECG and vital signs will be summarized by the value and by change from baseline in the value (where appropriate) at each postbaseline time point for each cohort and formulation.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

15.1. Study Monitoring

The Sponsor (or its authorized representative) has the obligation to follow this study closely to ensure that the study is conducted in accordance with the protocol, International Council for Harmonization (ICH) and Good Clinical Practice (GCP) guidelines, Regulation (EU) No. 536/2014, national and international regulatory requirements, and the current Declaration of Helsinki throughout its duration by means of personal visits to the Investigator's facilities and other communications.

These visits will be conducted to evaluate the progress of the study, to verify that the rights and well-being of the patients are protected, and to verify that the reported clinical study data are accurate, complete, and verifiable from source documents. This includes review of ICFs, results of tests performed as a requirement for participation in this study, and any other medical records (eg, laboratory reports, clinic notes, investigational medicinal product dispensing log, pharmacy records, patient sign-in sheets, patient-completed questionnaires, telephone logs) that are required to confirm information contained on the eCRFs.

The monitoring strategy for the study foresees a risk-based monitoring approach, in line with the relevant Food and Drug Administration (FDA) and European Medicines Agency (EMA) recommendations and will be described in detail by the study-specific risk-based-monitoring plan.

A monitoring visit should include a review of the essential clinical study documents (regulatory documents, eCRFs, medical records and source documents, drug disposition records, ICFs, etc.),

as well as discussion on the conduct of the study with the investigator and staff. These documents should be redacted by the site in accordance with local law.

The monitor should conduct these visits as frequently as appropriate for the clinical study. The Investigator and staff should be available during these visits for discussion of the conduct of the study, as well as to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the clinical site by signature and date on the study-specific monitoring log.

15.2. Audits and Inspections

Representatives of the Sponsor or its authorized clinical quality assurance group may visit a clinical site at any time during the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Patient privacy must be respected. The Investigator and clinical site personnel are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the Sponsor or its authorized representative.

The clinical study may also be inspected by the FDA or EMA (or other regulatory authority) to verify that the study was conducted in accordance with protocol requirements, as well as the applicable regulations and guidelines.

In the event the Investigator is contacted by regulatory authorities who wish to conduct an inspection of the clinical site, the Investigator will promptly notify the Sponsor of all such requests and will promptly forward a copy of all such inspection reports.

16. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor/designee may conduct a quality assurance audit (see Section 15.2).

17. ETHICS

17.1. Institutional Review Board/Independent Ethics Committee Approval

Before initiation of the study, approval or favorable opinion of the research protocol, ICF, and any material related to patient recruitment from an IRB or IEC must be obtained. For locations participating within the US, the IRB must comply with the provisions specified in 21 Code of Federal Regulations (CFR) Part 56, ICH and GCP guidelines, and applicable pertinent state and federal requirements. For locations participating outside of the US, the IRB or IEC must comply with the applicable requirements of each participating location, including ICH and GCP guidelines, except where a waiver is applicable.

IRBs and IECs must be constituted according to the applicable laws. It is the responsibility of the Sponsor or their designee to obtain the approval of the responsible ethics committees

according to the national regulations. The study will start in the respective sites only once the respective ethics committee's written approval has been given. Documents to submit for review and approval are based on regional requirements and may include the protocol, Investigator's Brochure, patient ICF for the study, patient recruitment materials (if applicable), and other documentation as required to its IRB/IEC for review and approval. A copy of the written approval must be provided to the Sponsor.

The documentation should clearly mention the approval/favorable opinion of the protocol, the patient ICF, and patient recruitment materials (if applicable), including respective version dates. The written approval and a list of the voting members, their titles or occupations, and their institutional affiliations must be obtained from the IRBs or IECs and provided to the Sponsor before the release of clinical study supplies to the investigational site and commencement of the study. If any member of the IRB or IEC has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained.

Clinical sites must adhere to all requirements stipulated by the respective IRB or IEC. This includes notification to the IRB or IEC of protocol amendments, updates to the patient ICF, recruitment materials intended for viewing by patients, aggregate safety reports required by regulatory competent authorities, serious and unexpected AEs, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of final study reports and summaries to the IRB or IEC. Depending on national regulations, reporting may be done by the Sponsor or their designee.

Submission of information to the appropriate IRB or IEC for annual review and annual re-approval must be done by the clinical site; or depending on national regulations may be done by the Sponsor or their designee.

IRBs and IECs must be promptly informed of all SAEs or other safety information reported from the patient or Sponsor.

17.2. Ethical Conduct of the Study

The Investigator agrees, when signing the protocol, to conduct the study in accordance with ethical principles that have their origin in the current revision of the Declaration of Helsinki and that are consistent with ICH/GCP, applicable regulatory requirements, and policies and procedures as outlined by the ethical requirements for IRB or IEC review and ICFs.

The Investigator agrees to allow monitoring and auditing of all essential clinical study documents by the Sponsor or its authorized representatives and inspection by the FDA, EMA, or other appropriate regulatory authorities. Monitoring and auditing visits by the Sponsor or authorized designee will be scheduled with the appropriate staff at mutually agreeable times periodically throughout the study.

The Investigator will ensure proper implementation and conduct of the study, including those study-related duties delegated to other appropriately qualified individuals. The Investigator will ensure that the study staff cooperates with monitoring and audits and will demonstrate due diligence in recruiting and screening study patients. The Investigator must sign the "Investigator Signature" page (Appendix 3) and return it and a copy of a current curriculum vitae to the Sponsor. For this study and all studies conducted under an Investigational New Drug application

(IND), the Investigator must sign and return a completed Form FDA 1572 "Statement of Investigator" to the Sponsor (or designee). For EU Investigators, equivalent information contained within the FDA 1572 may be requested unless a waiver has been requested and received by the Sponsor from the FDA.

17.3. Written Informed Consent/Assent

The Principal Investigator(s) will ensure that the patient and the patient's parent/legal guardian are given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study. Patients and their parent/legal guardian must also clearly understand that they are free to discontinue from the study at any time. The patient and parent/legal guardian should be given the opportunity to ask questions and allowed time to consider the information provided.

The patient's and their parent/legal guardian's signed and dated informed assent and consent, respectively, must be obtained before conducting any study procedures on the Sponsor-approved ICF. Updates to the ICF during the conduct of the study will be communicated by written letter from the Sponsor to the Investigator. The ICF and informed assent should be provided in the appropriate language of the patient and their parent/legal guardian.

The Principal Investigator(s) must maintain the original, signed ICF. A copy of the signed ICF must be given to the patient and their parent/legal guardian.

17.4. Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained.

The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs or other records that are provided to or retained by the Sponsor (or designee). If a patient's name appears on any document, it must be redacted and replaced with the patient identifier before a copy of the document is supplied to the Sponsor (or designee). The ICF must include appropriate statements explaining that patient data will be confidential and the actions that will be taken to ensure patient confidentiality.

Any other confidentiality requirements specified by the site, IRB or IEC, or national or local regulations will be adhered to and detailed appropriately in the ICF.

17.5. Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will review accumulating unblinded safety data from this and other ongoing studies of bempedoic acid in regularly scheduled intervals approximately 4 times per year to ensure there is no avoidable increased risk of harm to patients. Safety data reviewed by the DMC will include AEs, clinical endpoints, and lipids. The DMC will be chaired by an external academic cardiologist who is an expert in this therapeutic area and who has no conflicts of interest. Analysis for the DMC will be provided by an independent Statistical Analysis Data Center, which is external to the Sponsor. Additional details will be provided in a DMC Charter.

18. DATA HANDLING AND RECORD KEEPING

18.1. Inspection of Records

Applicable regulations require the Sponsor (or designee) to inspect all documents and records to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) for the patients in this study. These regulations also allow the Sponsor's records to be inspected by authorized representatives of the regulatory agencies. The Investigator will permit study-related monitoring, audits, IRB or IEC review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

18.2. Retention of Records

In compliance with the ICH/GCP guidelines, the Investigator/Institution agrees to retain and maintain all study records that support the data collected from each patient, as well as all study documents, as specified in ICH/GCP, Section 8 Essential Documents for the Conduct of a Clinical Trial. The Investigator agrees to contact the Sponsor before destroying or relocating any study documentation and is expected to take measures to prevent accidental or premature destruction of these documents.

If the Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept responsibility. The Sponsor must be contacted in writing regarding the name and address of the new person responsible as well as the disposition of document storage. Under no circumstances shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

Essential records (including eCRFs, source documents, study drug disposition records, signed patient ICFs, AE reports, and other regulatory documents), as required by the applicable regulations, must be maintained for 2 years after a marketing application is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the investigational product.

It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

18.3. Electronic Case Report Forms and Study Records

Access to eCRFs will be provided to the clinical site. As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The Investigator agrees to maintain accurate source documentation and eCRFs as part of the case histories.

Study records are comprised of source documents, eCRFs, and all other administrative documents (eg, IRB or IEC correspondence, clinical study materials and supplies shipment

manifests, monitoring logs, and correspondence). A study-specific binder will be provided with instructions for the maintenance of study records.

Source documentation is defined as any handwritten or computer-generated document that contains medical information or test results that have been collected for or is in support of the protocol specifications (eg, laboratory reports, clinic notes, drug disbursement log, pharmacy records, patient sign in sheets, patient-completed questionnaires, telephone logs, x-rays, ECGs). All draft, preliminary and pre/final iterations of a final report are also considered to be source documents (eg, faxed and hard copy of laboratory reports, faxed and hard copy of initial results, and final report).

The Investigator agrees to allow direct access to all essential clinical study documents for purposes of monitoring and/or auditing by the Sponsor or its authorized representatives and inspection by the appropriate regulatory authorities.

Data reflecting the patient's participation with the IMP under investigation are to be reported to the Sponsor. The data is to be recorded on the eCRFs and/or other media provided or approved by the Sponsor.

A completed eCRF must be submitted for each patient who receives IMP, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and patient number. Any personal information, including patient name, should be removed or rendered illegible to preserve individual confidentiality. The eCRF should not be used as a source document unless otherwise specified by the Sponsor.

Neither the Sponsor nor a service provider contracted to analyze data and complete the study report is permitted to interpret a blank answer; therefore, all fields should be completed. All requested information must be entered on the eCRFs. If an item is not available or is not applicable, this fact should be indicated as (N/A) not available or (N/D) not done; do not leave a field blank.

Each set of completed eCRFs must be signed and dated by the Investigator acknowledging review of data is accurate and complete. The completed database is to be returned to the Sponsor as soon as practical after completion by the mechanism prescribed for the protocol.

It is essential that all dates appearing on the Sponsor's patient data collection forms for laboratory tests, cultures, etc., be the dates on which the specimens were obtained, or the procedures performed. The eCRFs will be signed or countersigned by the Investigator and dated as verification of the accuracy of the recorded data. All data collection forms should be completed within a timely manner, according to the eCRF Completion Guidelines.

18.4. Handling of Data and Data Protection

Data will be collected and processed by the study investigator and investigative site staff in compliance with applicable data protection laws, including but not limited to the General Data Protection Regulation (GDPR), also known as Regulation (EU) 2106/679. The lawful basis for collecting and processing the study participants personal information is the study Sponsor's legitimate interest in conducting the clinical research.

In order to protect the privacy of study participants' health information, the participant data will be pseudonymized in accordance with Article 4(5) of the GDPR. Pseudonymization of the study data will be achieved by assigning a unique identifier to each study participant, that is not derived from the participant's identifiable personal information. This unique identifier will replace all direct identifiers of the study participant, such as name, address, government issued ID number, phone number, email address, etc. The study Sponsor will only receive pseudonymized data, which is not considered personal data under the GDPR as long as the study Sponsor has no access to the key to re-identify the data. Only the investigator and site staff will have access to the key that allows for re-identification of the study participant's pseudonymized data.

In addition to pseudonymization, participant data will be encrypted in transit and at rest and access controls will be employed to ensure that only authorized individuals will have access to the data. All individuals handling participant data will receive appropriate data protection training.

The pseudonymized study data will be transferred to the study Sponsor and its representatives in the United States, in compliance with applicable data protection laws, including the GDPR, utilizing standard contractual clauses or other comparable data transfer mechanisms.

The study Sponsor's data protection officer (DPO) will oversee compliance with the GDPR.

The participant's parent(s)/legal representative(s) and to the extent possible (given his/her understanding) the participant must be informed that participant's pseudonymized data will transferred to the study Sponsor and its representatives in the United States, in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant's parent(s)/legal representative(s) (and to the extent possible (given his/her understanding).

The participant's parent(s)/legal representative(s) and to the extent possible (given his/her understanding) the participant must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The study Sponsor has appropriate processes and policies in place to handle personal data breaches according to applicable privacy laws. Any data security breach that may impact the confidentiality and protection of study participants' data is recorded and investigated by Sponsor as required by applicable laws or regulations and as adequate to the nature of the breach. Upon identification of any potential data security breach, an appropriate Sponsor team (depending on nature of the breach) performs an initial assessment. Depending on the nature and type of breach, including the categories of data impacted, the data security breach management process may include investigation of the root cause of the incident, and, on a basis of its outcome, determination of the adequate mitigation actions to address any immediate impact, and corrective and preventive measures to prevent recurrence and mitigate any adverse effects, as applicable. The data security breach will be reported to the regulatory authorities and Ethics Committees or IRBs, to the extent required by the applicable data protection laws.

19. ADMINISTRATIVE CONSIDERATIONS

19.1. Investigators

The Investigator must agree to the responsibilities and obligations listed below, as specified by the appropriate FDA/EMA regulatory requirements or ICH/GCP guidelines:

- Agree to conduct the study in accordance with the relevant current protocol;
- Agree to personally conduct or supervise the described investigation(s);
- Agree to inform any patients, or persons used as controls, that the investigational medicinal products are being used for investigational purposes and ensure that the requirements relating to obtaining informed consent and IRB/IEC review and approval are met;
- Agree to report adverse experiences that occur during the investigation;
- Read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the investigational medicinal product;
- Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments;
- Maintain adequate and accurate records and make those records available for inspection;
- Ensure that an appropriate IRB/IEC will be responsible for the initial and continuing review and approval of the clinical investigation;
- Agree to promptly report to the IRB/IEC all changes in the research activity and all unanticipated problems involving risks to patients or others;
- Agree not to make changes in the research without IRB/IEC approval, except where necessary to eliminate apparent hazards to patients;
- Comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements.

Refer also to:

- FDA Regulations Related to GCP and Clinical Trials: http://www.fda.gov/oc/gcp/regulations.html
- Guidance and Information Sheets on GCP in FDA-Regulated Clinical Trials: http://www.fda.gov/oc/gcp/guidance.html
- Guidance for IRBs and Clinical Investigators: http://www.fda.gov/oc/ohrt/irbs/default.htm
- Guidance for Industry – E6 Good Clinical Practice: Consolidated Guidance: http://www.fda.gov/cder/guidance/959fnl.pdf
- Regulation (EU) No. 536/2014

19.2. Study Administrative Structure

Medical and Safety Monitoring: [redacted]

Central Laboratory: Details are provided in the laboratory manual

Bioanalytical Laboratory: [redacted]

Clinical Supply Details are provided in the pharmacy manual

eCRF and Database: Details are provided in the CRF Completion Guidelines

19.3. Amendments

Changes to the research covered by this protocol must be implemented by formal protocol amendment. All amendments to the protocol must be initiated by the Sponsor and signed and dated by the Investigator. Protocol amendments must not be implemented without prior IRB or IEC approval. Documentation of amendment approval by the Investigator and IRB or IEC must be provided to the Sponsor or its authorized representative. When the change(s) involve only logistic or administrative aspects of the study, the IRB or IEC only needs to be notified.

During the course of the study, in situations in which a departure from the protocol is unavoidable, the Investigator will contact the Medical Monitor. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the Medical Monitor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded on the eCRF and source documents will reflect any departure from the protocol and the source documents will describe the departure and the circumstances requiring it.

19.4. Financial Disclosure

Prior to the start of the study, Investigators will release sufficient and accurate financial information that permits the Sponsor to demonstrate that an Investigator and all study relevant assigned personnel have no personal or professional financial incentive regarding the future approval or disapproval of the study drug such that his or her research might be biased by such incentive. In addition, the Investigator is responsible for providing any changes to this information that occur during the conduct of this study to the Sponsor.

20. PUBLICATION AND DISCLOSURE POLICY

It is understood by the Investigator that the information and data included in this protocol may be disclosed to and used by the Investigator's staff and associates as may be necessary to conduct this clinical study.

All information derived from this clinical study will be used by the Sponsor (or designee) and, therefore, may be disclosed by the Sponsor (or designee), as required, to other clinical Investigators, to the FDA, EMA, to other government agencies, or in connection with intellectual property filings or publications. To allow for the use of the information derived from this clinical study, it is understood by the Investigator that there is an obligation to provide the Sponsor with complete test results and all data from this clinical study. The Investigator agrees to maintain this information in confidence, to use the information only to conduct the study, and to use the information for no other purpose without the Sponsor's prior written consent (or as otherwise may be permitted pursuant to a written agreement with the Sponsor or its designee).

The results of the study will be reported in a clinical study report prepared by the Sponsor (or designee), which will contain eCRF data from all clinical sites that conducted the study.

The Sponsor shall have the right to publish data from the study without approval from the Investigator(s). Manuscript(s) and abstract(s) may only be prepared through cooperation between the Sponsor (or designee) and the study Investigator(s). If an Investigator wishes to publish information from the study, a copy of the manuscript must be provided to the Sponsor for review in accordance with the provisions of such Investigator's written agreement with the Sponsor (or designee) before submission for publication or presentation. If requested by the Sponsor in writing, the Investigator will withhold such publication in accordance with the provisions of such agreement.

21. LIST OF REFERENCES

Akioyamen LE, Genest J, Shan SD, et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ Open. 2017;7(9):e016461.

Avis HJ, Hutten BA, Gagné C, Langslet G, McCrindle BW, Wiegman A, et al. Efficacy and safety of rosuvastatin therapy for children with familial hypercholesterolemia. J Am Coll Cardiol. 2010;55:1121-6.

Benn M, Watts GF, Tybjaerg-Hansen, Nordestgaard BG. Familial hypercholesterolemia in the Danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab. 2012;97:3956-64.

Bhatt DK, Mehrotra A, Gaedigk A,Chapa R, Basit A, Zhang H, et al. Age- and genotype-dependent variability in the protein abundance and activity of six major uridine diphosphate-glucuronosyltransferases in human liver. Clin Pharmacol Ther. 2019;105(1):131-141.

Daniels SR, Gidding SS, deFerranti SD. Pediatric aspects of familial hypercholesterolemia's: Recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5:S30-7.

De Jongh S, Ose L, Szamosi T, Gagné C, Lambert M, Scott R, et al. Efficacy and safety of statin therapy in children with familial hypercholesterolemia. Circulation. 2002a;106:2231-7.

De Jongh S, Lilien MR, Op't Roodt J, Stroes ES, Bakker HD, Kastelein JJP. Early statin therapy restores endothelial function in children with familial hypercholesterolemia. J Am Coll Cardiol. 2002b;40:2117-21.

Dietschy JM, Turley SD. Cholesterol metabolism in the brain. Curr Opin Lipidol. 2001(12):105-12.

Dietschy JM, Turley SD. Cholesterol metabolism in the central nervous system during early development and in the mature animal. J Lipid Res. 2004(45):1375-97.

Emmanuel M, Bokor BR. Tanner Stages. [Updated 2019 May 13]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK470280.

Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics. 2011;128:S213-56.

Flynn JT, Kaelber DC, Baker-Smith CM, Blowey D, Carroll AE, Daniels SR, et al. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics. 2017;140(3):e20171904.

Food and Drug Administration (2012). FDA announces safety changes in labeling for some cholesterol-lowering drugs [Press release]. Available from http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm293623.htm.

Food and Drug Administration Guidance Document: General clinical pharmacology considerations for pediatric studies for drugs and biological products. Dec 2014.

Fouchier S, Defesche J, Umans-Eckenhausen M, Kastelein JP. The molecular basis of familial hypercholesterolemia in the Netherlands. Hum Genet. 2001;109:602-15.

Gaudet D, Langslet G, Gidding SS, Luirink IK, Ruzza A, Kurtz C, et al. Efficacy, safety, and tolerability of evolocumab in pediatric patients with heterozygous familial hypercholesterolemia: Rationale and design of the HAUSER-RCT study. J Clin Lipidol. 2018; 12:1199-207.

Gidding SS, Allen NB. Cholesterol and atherosclerotic cardiovascular disease: A lifelong problem. J Am Heart Assoc. 2019;8(11):e012924.

Goedeke L, Fernandez-Hernando C. microRNAs: A connection between cholesterol metabolism and neurodegeneration. Neurobiol Dis. 2014;72(a):48-53.

Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. 2011;5:S1-8.

Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019 Jun 25;73(24):3237-41.

Howie SR. Blood sample volumes in child health research: review of safe limits. Bull World Health Organ. 2011 Jan 1;89(1):46-53.

Humphries SE, Cooper J, Dale P, Ramaswami U, FH Paediatric Register Steering Group. The UK paediatric familial hypercholesterolemia register: Statin-related safety and 1-year growth data. J Clin Lipidol. 2018;12(1):25-32.

Julious SA. Sample size of 12 per group rule of thumb for a pilot study. Pharm Stat. 2005;4:287-91.

Knipscheer HC, Boelen CC, Kastelein JJ, van Diermen DE, Groenemeijer BE, van den Ende A, et al. Short-term efficacy and safety of pravastatin in 72 children with familial hypercholesterolemia. Pediatr Res. 1996;39:867-71. Erratum in Pediatr Res 1996;40(6):866.

Lambert M, Lupien PJ, Gagné C, Levy E, Blaichman S, Langlois S, et al. Treatment of familial hypercholesterolemia in children and adolescents: effect of lovastatin. Canadian Lovastatin in Children Study Group. Pediatrics. 1996;97:619-28.

Langslet G, Bogsrud MP, Halvorsen I, Fjeldstad H, Retterstøl K, Veierød MB, et al. Long-term follow-up of young adults with familial hypercholesterolemia after participation in clinical trials during childhood. J Clin Lipidol. 2015;9(6):778-85.

Luirink IK, Wiegman A, Kusters DM, Hof MH, Groothoff JW, de Groot E, et al. 20-year follow-up of statin in children with familial hypercholesterolemia. N Engl J Med. 2019 Oct 17;381(16):1547-56.

McCrindle BW, Ose L, Marais AD. Efficacy and safety of atorvastatin in children and adolescents with familial hypercholesterolemia or severe hyperlipidemia: a multicenter, randomized, placebo-controlled trial. J Pediatr. 2003;143:74–80.

Nexletol [Highlights of Prescribing Information]. Ann Arbor, MI, Esperion The Lipid Management Company: 2020.

Nexlizet [Highlights of Prescribing Information]. Ann Arbor, MI, Esperion The Lipid Management Company: 2020.

Nielson J, Chapel S. Memo (on file) outlining initial 10- to 17-year-old dose estimates of bempedoic acid based on Adult Population PK/PD model for bempedoic acid. 18 Sep 2015.

Nilemdo [Summary of Product Characteristics]. Pfaffenhofen, Germany, Daiichi Sankyo Europe: 2020.

Nustendi [Summary of Product Characteristics]. Pfaffenhofen, Germany, Daiichi Sankyo Europe: 2020.

Pottel H, Hoste L, Delanaye P. Abnormal glomerular filtration rate in children, adolescents and young adults starts below 75 mL/min/1.73 m(2). Pediatr Nephrol. 2015;30(5):821-828.

Report 1002-073. Population Modeling Report: Simulations to Predict Bempedoic acid exposure and assess sample size for initial studies in pediatric patients. Esperion Therapeutics, Inc. March 24, 2020.

Risk of fatal coronary heart disease in familial hypercholesterolemia. Scientific Steering Committee on behalf of the Simon Broome Register Group. BMJ. 1991;303(6807):893-6.

Stein EA, Illingworth DR, Kwiterovich PO Jr, Liacouras CA, Siimes MA, Jacobson MS, et al. Efficacy and safety of lovastatin in adolescent males with heterozygous familial hypercholesterolemia: a randomized controlled trial. JAMA. 1999;281:137-44.

Tada H, Kawashiri MA, Ohtani R, et al. A novel type of familial hypercholesterolemia: double heterozygous mutations in LDL receptor and LDL receptor adaptor protein 1 gene. *Atherosclerosis*. 2011;219(2):663-666.

Tsume Y, Langguth P, Garcia-Aieta A, Amidon GL. In silico prediction of drug dissolution and absorption with variation in intestinal pH for BCS class II weak acid drugs: ibuprofen and ketoprofen. Biopharm Drug Dispos. 2012;33(7):366-77.

Tubic-Grozdanis M, Bolger MB, Langguth P. Application of gastrointestinal simulations for extensions of biowaivers of highly permeable compounds. AAPS Journal. 2008;10(1);213-26.

Tuleu C. The School of Pharmacy, University of London Workshop on Paediatric Formulations II for Assessors in National Regulatory Agencies. 8 Nov 2011; available from:https://www.ema.europa.eu/documents/presentation/presentation-acceptability-palatability-methods-available-assessment_en.pdf.

Vuorio A, Kuoppala J, Kovanen PT, Humphries SE, Tonstad S, Wiegman A, et al. Statins for children with familial hypercholesterolemia. Cochrane Database Syst Rev. 2019 Nov 7;2019(11).

Wald DS, Bestwick JP, Morris JK, Whyte K, Jenkins L, Wald NJ. Child-parent familial hypercholesterolemia screening in primary care. N Engl J Med. 2016 Oct 27;375(17):1628-37.

Wiegman A, de Groot E, Hutten BA, Rodenburg J, Gort J, Bakker HD, et al. Arterial intima-media thickness in children heterozygous for familial hypercholesterolemia. Lancet. 2004;363:369-70.

Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, et al. Familial hypercholesterolemia in children and adolescents: gaining decades of life by optimizing detection and treatment. Eur Heart J. 2015;36:2425-37.

Williams RR, Hunt SC, Schumacher M, Hegele RA, Leppert MF, Ludwig EH, et al. Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. Am J Cardiol. 1993;72(2):171-6.

World Health Organization. Familial hypercholesterolemia (FH): report of a second WHO consultation, WHO publication no: WHO/HGN/FH/CONS/99.2. Geneva, 1998.

Yazdanian M, Briggs K, Jankovsky C, Hawi A. The “high solubility” definition of the current FDA Guidance on Biopharmaceutical Classification System may be too strict for acidic drugs. Pharm Res. 2004;21(2):293-99.

Youngblom E, Knowles JW. Familial Hypercholesterolemia. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 02 Jan 2014.

22. APPENDICES

Appendix 1	Schedule of Assessments
Appendix 2	Sponsor Signature
Appendix 3	Investigator Signature
Appendix 4	Stage 2 Hypertension Assessment Criteria
Appendix 5	Tanner Stage Criteria
Appendix 6	Summary of Changes in Amendment 2.1 (applies to European Union sites only)
Appendix 7	Summary of Changes in Amendment 2
Appendix 8	Summary of Changes in Amendment 1

[Appendices 6 through 8 have been removed in this redacted protocol]

APPENDIX 1. SCHEDULE OF ASSESSMENTS

Study Period:	**Screen**	**Treatment Period 1 (Cohorts 1, 2 and 3) [a]**					**Treatment Period 2 (Cohorts 1 &2 Only) [b]**				**Follow-up**
Study Visit:	**S1**	**T1**	**T2 [c]**	**T3[c]**	**T4**	**T5**	**T6 [c]**	**T7[c]**	**T8**	**T9**	**FU**
Study Week:	**-3**	**0**	**0**	**2**	**4**	**8**	**8**	**10**	**12**	**16**	**Cohort 1&2: 21 Cohort 3: 13**
Procedure Study Days:	**-21 ± 10**	**1**	**2**	**15** ± 3	**29 ± 7**	**57 ± 7**	**T5 + 1**	**71 ± 7**	**85 ± 7**	**113 ± 7**	**Cohort 1&2: 148±14 Cohort 3: 92±14**
Informed consent/assent	X										
Inclusion/Exclusion criteria[d]	X	X									
Demographics	X										
Medical history	X										
Enrollment		X									
Prior and/or Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Adverse event recording	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X				X				X	X
Tanner Staging Score		X				X				X	
Weight, height [e]	X	X			X	X			X	X	X
Vital signs [f]	X	X			X	X			X	X	X
12-Lead ECG	X				X				X		
Urine pregnancy test [g]	X	X				X				X	
Basic fasting lipid panel and hsCRP [h]	X	X			X	X			X	X	X
Specialty Laboratories [i]	X	X				X				X	
Serology [j]	X										
Clinical safety laboratories [k]	X	X			X	X			X	X	X
Optional Blood and Urine Exploratory Samples for Storage	X				X				X		X
Optional Genetic Sample	X										
Urine drug screen	X										
Diet and exercise counseling	X	X	X	X	X	X	X	X	X		
Dose escalation [l]						X					
PK sampling[m]		X			X	X			X	X	

Study Period:	Screen	Treatment Period 1 (Cohorts 1, 2 and 3) [a]					Treatment Period 2 (Cohorts 1 &2 Only) [b]				Follow-up
Study Visit:	**S1**	**T1**	**T2 [c]**	**T3[c]**	**T4**	**T5**	**T6 [c]**	**T7[c]**	**T8**	**T9**	**FU**
Study Week:	**-3**	**0**	**0**	**2**	**4**	**8**	**8**	**10**	**12**	**16**	**Cohort 1&2: 21 Cohort 3: 13**
Procedure Study Days:	**-21 ± 10**	**1**	**2**	**15** ± 3	**29 ± 7**	**57 ± 7**	**T5 + 1**	**71 ± 7**	**85 ± 7**	**113 ± 7**	**Cohort 1&2: 148±14 Cohort 3: 92±14**
Dispense bempedoic acid		X				X					
Return bempedoic acid						X				X	
Review Patient Dosing Log		X			X	X			X	X	
Dosing acceptability (taste and ease of swallowing) questionnaire		X	X	X	X	X	X	X	X	X	

eGFR = estimated glomerular filtration rate; HbA_{1C} = glycosylated hemoglobin, type A_{1C}; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; bempedoic acid = investigational medicinal product; LDL-C = low-density lipoprotein cholesterol; PK = pharmacokinetic; TC = total cholesterol; TG = triglycerides; TSH = thyroid-stimulating hormone.

[a] Cohorts 1, 2, and 3 participate in Treatment Period 1 visits; no dosing or postdosing assessments for Cohort 3.

[b] Cohorts 1 and 2 participate in Treatment Period 2.

[c] Visit T2, T3, T6 and T7 are telephone/telehealth device interviews. If needed based on adverse events reported, unscheduled visits may be arranged by the site to assess safety laboratories and other relevant safety evaluations.. Per provisions outlined in the protocol, any visit may be conducted at-home with appropriate site and IRB/EC approved policy approved by the sponsor.

[d] Patient must have a fasting direct LDL-C level ≥130 mg/dL (3.4 mmol/L) during Screening prior to Visit T1. If TG level is >400 mg/dL (4.5 mmol/L) or if the patient needs to complete 4 weeks dosing with optimal statin a repeat assessment may be obtained; the repeat assessment will be used to determine study eligibility and screening may be extended by 2 week.

[e] Weight (kg) will be measured on a calibrated scale in the morning while fasting, in street clothing, and after voiding. Height (cm) will be measured without shoes. Weight at Visit S1 will be used to determine weight cohort assignment for the study.

[f] Systolic blood pressure, diastolic blood pressure, and pulse rate will be obtained after the patient has been seated quietly for at least 5 minutes in a chair with the back supported, the feet flat on the ground, and the arms bared and supported at heart level.

[g] Urine pregnancy tests will be obtained for female patients of childbearing potential only

[h] Basic fasting lipid panel includes direct LDL-C, calculated TC, calculated HDL-C, calculated non-HDL-C, and TGs.

[i] Specialty Laboratories of Cortisol, Dihydroepiandroestrone, FSH, HbA1c, LH, Estradiol (females), Testrosterone (Males), and Urine pregnancy (for female patients of childbearing potential) to be assessed at Visits S1, T1, T5 and T9. PT and INR assessed as-needed accompanying repeat LFT elevation assessment per Section 14.6.4.1.

[j] The serology assessment includes HbsAg (hepatitis B surface antigen) and HCV-AB (hepatitis C virus antibody)

[k] Clinical safety laboratories include hematology, clinical chemistry and urinalysis and eGFR; the required assays are listed in Table 4:Clinical Safety Laboratory Evaluations

[l] At Visit T5, patients in Cohorts 1 and 2 will dose escalate to 90 and 150 mg, respectively. Patients in Cohort 3 will take last dose of bempedoic acid the day prior to Visit T5.

[m] PK samples will be collected at prior to first dose, 1 hour ± 10 minutes and 4 hours ± 15 minutes post-dose at Visit T1; pre-dose at Visits T4 and T5 for all patients; additionally for patients in Cohorts 1 and 2 PK samples will be collected at 1 hour ± 10 minutes and 4 hours ± 15 minutes post-dose at Visit T5; pre-dose at Visits T8, and T9.

APPENDIX 2. SPONSOR SIGNATURES

Study Title: An Open-Label Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Bempedoic Acid in Pediatric Patients (6 to 17 Years of Age) with Heterozygous Familial Hypercholesterolemia

Study Number: 1002-041

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following contributed to writing and/or approving this protocol:

[redacted]

Date

Study Title: An Open-Label Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Bempedoic Acid in Pediatric Patients (6 to 17 Years of Age) with Heterozygous Familial Hypercholesterolemia

Study Number: 1002-041

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following contributed to writing and/or approving this protocol:

[redacted] Date

APPENDIX 3. INVESTIGATOR SIGNATURE

Study Title: An Open-Label Study to Evaluate the Pharmacokinetics, Pharmacodynamics, and Safety of Bempedoic Acid in Pediatric Patients (6 to 17 Years of Age) with Heterozygous Familial Hypercholesterolemia

Study Number: 1002-041

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

_____ _____

Name: Date
Title:
Affiliation:
Address:
Phone:
Fax:

APPENDIX 4. STAGE 2 HYPERTENSION ASSESSMENT CRITERIA

Minimal systolic blood pressure and/or diastolic blood pressure characterizing Stage 2 hypertension in boys and girls aged 6-17 years according to height.

	Height Percentile						
	5%	10%	25%	50%	75%	90%	95%
Boy, Age 6 Years							
Height (cm)	110.3	112.2	115.3	118.9	122.4	125.6	127.5
SBP: Stage 2 HTN (mm Hg)	120	121	122	123	124	125	126
DBP: Stage 2 HTN (mm Hg)	81	82	82	83	84	84	85
Boy, Age 7 Years							
Height (cm)	116.1	118.0	121.4	125.1	128.9	132.4	134.5
SBP: Stage 2 HTN (mm Hg)	122	122	123	124	126	127	128
DBP: Stage 2 HTN (mm Hg)	83	83	84	85	85	86	86
Boy, Age 8 Years							
Height (cm)	121.4	123.5	127.0	131.0	135.1	138.8	141.0
SBP: Stage 2 HTN (mm Hg)	123	124	124	126	127	128	129
DBP: Stage 2 HTN (mm Hg)	84	85	85	86	87	87	87
Boy, Age 9 Years							
Height (cm)	126.0	128.3	132.1	136.3	140.7	144.7	147.1
SBP: Stage 2 HTN (mm Hg)	124	124	125	127	128	130	131
DBP: Stage 2 HTN (mm Hg)	86	86	87	88	88	89	89
Boy, Age 10 Years							
Height (cm)	130.2	132.7	136.7	141.3	145.9	150.1	152.7
SBP: Stage 2 HTN (mm Hg)	124	125	126	128	130	132	133
DBP: Stage 2 HTN (mm Hg)	88	88	89	89	90	90	90
Boy, Age 11 Years							
Height (cm)	134.7	137.3	141.5	146.4	151.3	155.8	158.6
SBP: Stage 2 HTN (mm Hg)	126	126	128	130	132	135	136
DBP: Stage 2 HTN (mm Hg)	89	90	90	90	90	90	90

	Height Percentile						
	5%	10%	25%	50%	75%	90%	95%
Boy, Age 12 Years							
Height (cm)	140.3	143.0	147.5	152.7	157.9	162.6	165.5
SBP: Stage 2 HTN (mm Hg)	128	129	130	133	136	138	140
DBP: Stage 2 HTN (mm Hg)	90	90	90	90	90	90	90
Boy, Age 13 Years							
Height (cm)	147.0	150.0	154.9	160.3	165.7	170.5	173.4
SBP: Stage 2 HTN (mm Hg)	140	140	140	140	140	140	140
DBP: Stage 2 HTN (mm Hg)	90	90	90	90	90	90	90
Boy, Age 14 Years							
Height (cm)	153.8	156.9	162.0	167.5	172.7	177.4	180.1
SBP: Stage 2 HTN (mm Hg)	140	140	140	140	140	140	140
DBP: Stage 2 HTN (mm Hg)	90	90	90	90	90	90	90
Boy, Age 15 Years							
Height (cm)	159.0	162.0	166.9	172.2	177.2	181.6	184.2
SBP: Stage 2 HTN (mm Hg)	140	140	140	140	140	140	140
DBP: Stage 2 HTN (mm Hg)	90	90	90	90	90	90	90
Boy, Age 16 Years							
Height (cm)	162.1	165.0	169.6	174.6	179.5	183.8	186.4
SBP: Stage 2 HTN (mm Hg)	140	140	140	140	140	140	140
DBP: Stage 2 HTN (mm Hg)	90	90	90	90	90	90	90
Boy, Age 17 Years							
Height (cm)	163.8	166.5	170.9	175.8	180.7	184.9	187.5
SBP: Stage 2 HTN (mm Hg)	140	140	140	140	140	140	140
DBP: Stage 2 HTN (mm Hg)	90	90	90	90	90	90	90
Girl, Age 6 Years							
Height (cm)	110.0	111.8	114.9	118.4	122.1	125.6	127.7
SBP: Stage 2 HTN (mm Hg)	121	121	122	123	124	125	126
DBP: Stage 2 HTN (mm Hg)	82	83	84	84	85	86	86

	Height Percentile						
	5%	10%	25%	50%	75%	90%	95%
Girl, Age 7 Years							
Height (cm)	115.9	117.8	121.1	124.9	128.8	132.5	134.7
SBP: Stage 2 HTN (mm Hg)	121	122	123	124	125	126	127
DBP: Stage 2 HTN (mm Hg)	84	84	85	85	86	86	87
Girl, Age 8 Years							
Height (cm)	121.0	123.0	126.5	130.6	134.7	138.5	140.9
SBP: Stage 2 HTN (mm Hg)	122	123	124	125	127	128	129
DBP: Stage 2 HTN (mm Hg)	84	85	86	86	87	87	87
Girl, Age 9 Years							
Height (cm)	125.3	127.6	131.3	135.6	140.1	144.1	146.6
SBP: Stage 2 HTN (mm Hg)	124	124	125	126	128	129	130
DBP: Stage 2 HTN (mm Hg)	86	86	87	87	87	87	87
Girl, Age 10 Years							
Height (cm)	129.7	132.2	136.3	141.0	145.8	150.2	152.8
SBP: Stage 2 HTN (mm Hg)	125	126	126	128	129	131	132
DBP: Stage 2 HTN (mm Hg)	87	87	88	88	88	88	88
Girl, Age 11 Years							
Height (cm)	135.6	138.3	142.8	147.8	152.8	157.3	160.0
SBP: Stage 2 HTN (mm Hg)	127	128	129	130	132	135	136
DBP: Stage 2 HTN (mm Hg)	88	89	89	89	89	89	89
Girl, Age 12 Years							
Height (cm)	142.8	145.5	149.9	154.8	159.6	163.8	166.4
SBP: Stage 2 HTN (mm Hg)	130	131	132	134	136	137	138
DBP: Stage 2 HTN (mm Hg)	90	90	90	90	90	90	90
Girl, Age 13 Years							
Height (cm)	148.1	150.6	154.7	159.2	163.7	167.8	170.2
SBP: Stage 2 HTN (mm Hg)	140	140	140	140	140	140	140
DBP: Stage 2 HTN (mm Hg)	90	90	90	90	90	90	90

	Height Percentile						
	5%	10%	25%	50%	75%	90%	95%
Girl, Age 14 Years							
Height (cm)	150.6	153.0	156.9	161.3	165.7	169.7	172.1
SBP: Stage 2 HTN (mm Hg)	140	140	140	140	140	140	140
DBP: Stage 2 HTN (mm Hg)	90	90	90	90	90	90	90
Girl, Age 15 Years							
Height (cm)	151.7	154.0	157.9	162.3	166.7	170.6	173.0
SBP: Stage 2 HTN (mm Hg)	140	140	140	140	140	140	140
DBP: Stage 2 HTN (mm Hg)	90	90	90	90	90	90	90
Girl, Age 16 Years							
Height (cm)	152.1	154.5	158.4	162.8	167.1	171.1	173.4
SBP: Stage 2 HTN (mm Hg)	140	140	140	140	140	140	140
DBP: Stage 2 HTN (mm Hg)	90	90	90	90	90	90	90
Girl, Age 17 Years							
Height (cm)	152.4	154.7	158.7	163.0	167.4	171.3	173.7
SBP: Stage 2 HTN (mm Hg)	140	140	140	140	140	140	140
DBP: Stage 2 HTN (mm Hg)	90	90	90	90	90	90	90

Stage 2 hypertension (Stage 2 HTN) value presented is the value for systolic blood pressure (SBP) or diastolic blood pressure (DBP) that if equal to or greater than characterizes the individual as having Stage 2 HTN based on gender, age, and height. For children aged 6 through <13 Stage 2 HTN values represent ≥95th percentile +12 mm Hg, or SBP of 140 mm Hg or DBP of 90 mm Hg (whichever is lower). For children aged 13 through 17 Stage 2 HTN values represent SBP of 140 mm Hg or DBP of 90 mm Hg. Height (cm) should be rounded to the nearest listed height percentile category. (Adapted from Flynn 2017).

APPENDIX 5. TANNER STAGE CRITERIA*

Pubic Hair Scale (both males and females)

- Stage 1: No hair
- Stage 2: Downy hair
- Stage 3: Scant terminal hair
- Stage 4: Terminal hair that fills the entire triangle overlying the pubic region
- Stage 5: Terminal hair that extends beyond the inguinal crease onto the thigh

Female Breast Development Scale

- Stage 1: No glandular breast tissue palpable
- Stage 2: Breast bud palpable under areola (1st pubertal sign in females)
- Stage 3: Breast tissue palpable outside areola; no areolar development
- Stage 4: Areola elevated above contour of the breast, forming "double scoop" appearance
- Stage 5: Areolar mound recedes back into single breast contour with areolar hyperpigmentation, papillae development and nipple protrusion

Male External Genitalia Scale

- Stage 1: Testicular volume < 4 ml or long axis < 2.5 cm
- Stage 2: 4 ml-8 ml (or 2.5-3.3 cm long), 1st pubertal sign in males
- Stage 3: 9 ml-12 ml (or 3.4-4.0 cm long)
- Stage 4: 15-20 ml (or 4.1-4.5 cm long)
- Stage 5: > 20 ml (or > 4.5 cm long)

* Adapted from Emmanuel and Bokor (2020)