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STATISTICAL ANALYSIS PLAN

Protocol 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
Protocol Number:	1002-041
Protocol Version/Date:	V2.0 (Amendment 2) 13SEP2024
Investigational Product:	Bempedoic acid as 60 and 90 mg tablets and as liquid suspension (20 mg/mL, available for use through Protocol Amendment 1 only)
Sponsor:	Esperion Therapeutics, Inc. 3891 Ranchero Drive, Suite 150 Ann Arbor, MI 48108 Phone: 734-887-3903 Fax: 734-913-5344
SAP Version/Date:	V1.0: 6Jun2025

SIGNATURE PAGE

Protocol 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

Protocol Number: 1002-041

SAP Version/Date: V1.0: 6Jun2025

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

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[redacted] *Electronically signed by: [redacted] Reason: Approved Date: Jun 6, 2025 17:07 GMT+1*	06-Jun-2025
[redacted] *Electronically signed by: [redacted] Reason: Approved Date: Jun 6, 2025 11:33 EDT*	06-Jun-2025
[redacted] *Electronically signed by: [redacted] Reason: Approved Date: Jun 6, 2025 11:42 EDT*	06-Jun-2025
[redacted]	

VERSION HISTORY

Version	Version Date	Description
1.0	6Jun2025	Original signed version

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse event of special interest
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomic therapeutic chemical
AUC_{ss}	Area under the plasma concentration-time curve during the dosing interval at steady state
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
$C_{avg,ss}$	Average plasma concentration at steady state
$C_{max,ss}$	Maximum plasma drug concentration at steady state
C_{4hr}	Plasma concentration at 4 hours
CDISC	Clinical Data Interchange Standards Consortium
CK	Creatine kinase
CN	U.S. Conventional units
COVID-19	Coronavirus disease 2019
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
ET	Early termination
FH	Familial hypercholesterolemia
FU	Follow-up
HeFH	Heterozygous familial hypercholesterolemia
hs-CRP	High-sensitivity C-reactive protein
IMP	Investigational medicinal product
IWRS	Interactive web response system
LDL-C	Low-density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
non-HDL-C	Non-high-density lipoprotein cholesterol
PE	Physical examination
PD	Pharmacodynamic
PK	Pharmacokinetic
Q1	First quartile
Q3	Third quartile
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SI	Système International units
SOP	Standard operation procedure
TC	Total cholesterol
TFL	Tables, figures and listings
TG	Triglycerides

Abbreviation	Definition
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the Sponsor. Protocol 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*, Amendment 2 (13 Sep 2024). In Amendment 2 of the protocol, the liquid suspension formulation will no longer be available for use in the study and the schedule of assessments were adjusted to increase flexibility for patient visits (Protocol Appendix 6). The SAP will be finalized prior to database lock. Any deviation(s) from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to assess the pharmacokinetics (PK) of bempedoic acid (ETC1002) in pediatric patients (6 to 17 years of age) with heterozygous familial hypercholesterolemia (HeFH) treated for 8 weeks.

2.1.2 Secondary Objectives

The secondary objectives include:

- To assess the PK of ESP15228 (active metabolite);
- To assess the 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 (hs-CRP);
- To monitor the acceptability (taste and ease of swallowing) of the age-appropriate formulations; and
- 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.

2.2 Study Endpoints

2.2.1 Primary Endpoints

The primary endpoints include:

- 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 ($C_{max,ss}$).

2.2.2 Secondary Endpoints

The secondary endpoints include:

- Observed trough plasma concentration of ESP15228 (active metabolite) following 8 weeks of steady-state dosing of bempedoic acid;
- Plasma concentration at 4 hours (C4hr) of ETC-1002 and ESP15228 following first dose;
- ETC-1002 dose and exposure/LDL-C-lowering response relationship;
- Percent and absolute change from baseline to Weeks 8 and 16 in LDL-C, TC, non-HDL-C, and hs-CRP;
- Evaluation of acceptability (taste and ease of swallowing) of the age-appropriate formulations.

2.2.3 Safety Endpoints

The safety endpoints include:

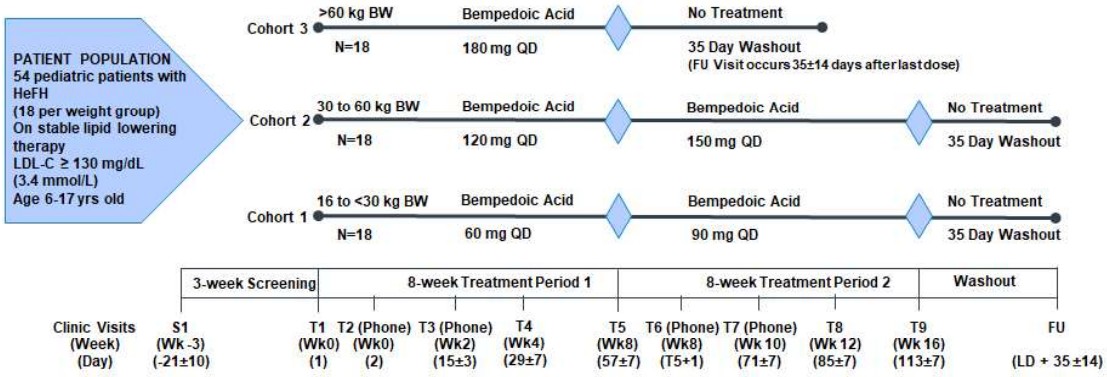
- Adverse events;
- Clinical safety laboratories (hematology, clinical chemistry, and urinalysis);
- Vital signs;
- Electrocardiogram (ECG) readings;
- Physical examinations (PEs), including growth and development assessments (height, weight, BMI, BSA, and tanner staging).

2.3 Study Design

2.3.1 Overview

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 below.

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

T1 can be extended for an additional 14 days, if needed, to obtain written consent and records from family members for use of documented familial hypercholesterolemia (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), 120 mg (Cohort 2: 30 to 60 kg body weight), or 180 mg (Cohort 3: >60 kg body weight,). Body weight at Screening Visit S1 will be used to determine weight cohort assignment for the study. Patients enrolled under Protocol Amendment 1 were randomly assigned to receive one of the two formulations (tablet or liquid suspension) and allowed to switch the formulation after receiving their initial dose on Day 1 during the study treatment. Patients enrolled under Protocol Amendment 2 will receive the tablet formulation only. IWRS was established to ensure that approximately 25% of total patients are background ezetimibe users.

At Week 4 (Visit T4), Week 8 (Visit T5) all patients regardless of Cohort, will return to the clinic for safety and fasting laboratory assessments (including PK, efficacy, and safety). Cohort 3 patients will receive 180 mg for the duration of the trial and receive their last dose of bempedoic acid the day prior to Visit T5.

Patients in Cohort 1 and Cohort 2 will escalate dose from 60 to 90 mg and 120 to 150 mg, respectively, following safety and laboratory assessments at Visit T5 and will continue into treatment period 2 of the study. At Week 12 (Visit T8) and Week 16 (Visit T9) patients assigned to Cohort 1 and Cohort 2 will return to clinic for safety and fasting laboratory assessments (including PK, efficacy, and safety). Cohort 1 and 2 patients will receive their last dose of bempedoic acid the day prior to Visit T9.

Sites will conduct a phone or telemedicine visit with all patients, regardless of Cohort, on Day 2 (Visit T2) and Week 2 (Visit T3). Sites will conduct a phone or telemedicine visit with patients assigned to Cohort 1 or 2 at Week 8(Visit T6) and Week 10 (Visit T7).

All patients, regardless of Cohort, 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). Details of schedule of assessments refer to Protocol Appendix 1.

2.3.2 Investigational medicinal product (IMP)

Bempedoic acid 60 and 90 mg tablets will be provided by Sponsor. The tablets used in this study are in the size range that young children (≥6 years old) can swallow. The acceptability will be assessed by separate questionnaires for liquid suspension (e.g., taste and ease of measure of the dose) and tablet (e.g., ease of swallow) formulations in the study.

All IMP will be ingested orally once daily at a similar time of day with or without food. 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. 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/Week 8 for patients in Cohort 3, and the morning of the day prior to Visit T9/Week 16 for patients in Cohort 1 and Cohort 2.

2.3.3 Randomization and Blinding

This study is open label. Blinding is not applicable. Randomization for IMP formulations is only conducted under Protocol Amendment 1.

2.3.4 Sample Size Determination

The sample size in this PK/pharmacodynamic (PD) study (18 patients per cohort) was planned to provide adequate data to support the dose selection for subsequent Phase 3 studies in pediatric population. Accounting for a 10% dropout rate, 16 evaluable patients per cohort 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.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of IMP. The day of the first dose of IMP will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Study Period and Analysis Visits

This study has two treatment periods. Patients of Cohort 1 and Cohort 2 will receive a lower dose of bempedoic acid (60 mg/day and 120 mg/day) in Period 1 and escalate into a higher dose (90 mg/day and 150 mg/day) in Period 2. Patients in Cohort 3 will receive bempedoic acid 180 mg/day in Period 1 only. Each treatment period lasts for 8 weeks. All patients will have a follow-up visit about 5 weeks after the last dose of IMP.

Scheduled visits (T1, T4, T5, T8, T9, FU) will be assigned to analysis visits as recorded on the electronic case report form (eCRF) for PK, safety laboratory assessments, vital signs, ECGs, physical exams, and tanner staging scoring; analysis visit mapping will not be used.

Fasting lipids, hs-CRP data will use analysis visit mapping. Scheduled visits will be assigned to analysis visits as recorded on the eCRF. Unscheduled and early termination visits will be assigned to analysis visits based on the following, assuming the unscheduled/ET visit occurs between two nominal visits A and B:

- If data was collected at both A and B, then no analysis visit mapping is needed and the visit will not be used in analysis
- If data was not collected at both A and B, then the distance between the Unscheduled/ET visit and the two nominal visits will be calculated
    - If one of the nominal visits is closer to the Unscheduled/ET visit and data was already collected at the closer nominal visit, then no analysis visit mapping is needed, and the visit will not be used in analysis

- If one of the nominal visits is closer to the Unscheduled/ET visit and data was not collected at the closer nominal visit, then the Unscheduled/ET visit should be mapped to the closer nominal visit
- If the Unscheduled/ET visit is equal distance from both A and B and data was not collected at both A and B, then the data collected at the Unscheduled/ET visit should be mapped to B
- If the Unscheduled/ET visit is equal distance from both A and B and data was not collected at either A or B, then the data collected at the Unscheduled/ET visit should be mapped to the nominal visit without data

Unless otherwise specified above, unscheduled visits are not used for data summary and statistical analyses but are included in listings and for consideration in lab abnormalities such as for worst post-baseline value.

3.1.3 Definition of Baseline

Baseline is defined as the last measurement prior to the first dose of IMP.

3.1.4 Units

Fasting lipids will be listed and summarized using U.S. conventional (CN) units and Système International (SI) units. Safety laboratory data and hs-CRP will be summarized in CN units only. The identification of any laboratory abnormalities or shifts from baseline to worst post-baseline will be done using original conventional units only.

3.1.5 Summary Statistics

Categorical data will generally be summarized with counts and percentages of patients. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum. Geometric mean, coefficient of variance (CV%), and geometric CV% will also be provided for PK concentration data by IMP formulation, cohort, and nominal time points. Continuous PD summaries will also include first quartile (Q1) and third quartile (Q3).

3.1.6 Handling of PK and Laboratory Data Beyond the Limits of Quantification

A pre-initial-dose concentration of BLQ (Below Limit of Quantitation) will be imputed as zero; a post-initial-dose concentration of BLQ will be imputed by half of the lower limit of quantitation (LLOQ) for the purpose of quantitative summaries. If the descriptive statistics (mean, median, min, max) <BLQ, display “BLQ (< xx.x)”.

All PK concentration of BLQ values will be presented as reported, i.e., as “BLQ (<xx.x)” in the listings.

Biomarker and safety laboratory measurements reported as “<X” or “>X” will be imputed as X for the purpose of quantitative summaries, but will be presented as reported, i.e., as “<X” or “>X” in the listings.

3.1.7 Handling of Dropouts and Missing Data

Post-baseline missing data will not be imputed in this study, unless otherwise specified.

3.1.8 Definition of IMP Formulation

Patients who took IMP in liquid suspension formulation throughout the study will be summarized separately from patients who took IMP in tablet formulation. Since Protocol Amendment 1 allowed patients to switch from one formulation to the other any time during study, two types of IMP formulation variables will be created.

- **Dose Formulation** (**visit-specific**, liquid suspension vs tablet) is determined by the most recent formulation the patient was administered prior to the measurement. At T1 (Day 1) pre-dose, it is the initial formulation (randomly assigned between liquid suspension or tablet under Protocol Amendment v1.0, and tablet under Protocol Amendment v2.0). It will be used for by-visit clinical laboratory data (including lipids and hs-CRP) and PK summaries.
- **Formulation Subgroup** (**patient-level**, liquid suspension only vs tablet) will be used for all the other analysis (except PK, efficacy and Lab), which is defined as following:
    - Liquid suspension only - patients who took Liquid suspension formulation only throughout the study treatment.
    - Tablet - patients who took tablet formulation throughout the study treatment or patients who switched from Liquid suspension to tablet.

Four (4) patients who were randomized to liquid suspension but switched to tablet formulation (switchers). Their formulation will be defined at the patient-level and the visit-specific as described in Table 1.

Table 1: Patient-level and visit-specific formulation for formulation switchers

Formulation switched	Subject ID	Formulation Subgroup (Patient-Level)	Dose Formulation (Visit-specific)	
			Lab and Efficacy by-visit summaries	PK concentration by-visit summaries
Day 2	301-001 603-002 806-001	**Tablet**	**Tablet** at all scheduled visits T1, T2*, T4, T5, T6*, T8, T9, FU (whenever applicable)	• **Liquid suspension** at T1 (pre-dose, post-dose 1 hr, post-dose 4 hr), T2 (pre-dose)* • **Tablet** at all nominal timepoints of Visit T4, T5, T6*, T8 and T9 (whenever applicable)
Day 29	401-010	**Tablet**	• **Liquid suspension** at T1, T2 and T4 • **Tablet** at all scheduled visits except T2 andT4 (including T1 as baseline)	• **Liquid suspension** at T1 (pre-dose, post-dose 1 hr, post-dose 4 hr), T2 (pre-dose)*, and T4 (pre-dose) • **Tablet** at all other nominal timepoints of Visit T5, T6*, T8, T9 (whenever applicable)

* Formulation subgroup and dose formulation variables will be defined for all visits listed above in the Analysis Data Model (ADaM) (including visits T2 and T6, at which safety lab and PK data were collected only under protocol Amendment v1.0). But only T1, T4, T5, T8, T9, FU will be considered the scheduled visits for summary tables described in this SAP.

In this SAP, when it specified that a table will be summarized by formulation subgroup (e.g., disposition, demographic, baseline lipid modifying therapy, IMP exposure, treatment compliance, AE, etc.), three sections (i.e., Tablet, Liquid suspension only, and Overall) will be presented in the table. When it is specified that a table will be summarized by dose formulation (e.g., efficacy, PK concentration, lab, vital signs, etc.), three sections (i.e., Tablet, Liquid

suspension, and Overall) will be presented in the table. Otherwise, the tables will not be separated by formulations (e.g., medical history, prior/concomitant medications or procedures).

Listings for by-visit data will include a column of dose formulation, other listings will be presented by formulation subgroup (Tablet vs Liquid suspension only), when needed.

3.2 Analysis Populations

3.2.1 Full Analysis Population

The Full Analysis Population will include all patients enrolled into the study which are defined as patients who receive at least 1 dose of IMP. This is the population used for all efficacy and safety related analysis.

3.2.2 PK Population

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.

3.3 Patient Data and Study Conduct

3.3.1 Patient Disposition

Counts and percentages of patients who were screened, failed screening (including reason for screen failure), eligible but left the study before enrollment (including reason for withdrawal prior to enrollment), enrolled, completed the study treatment, discontinued early from the study treatment (including reason for treatment discontinuation), completed the study, and withdrew early from the study (including reason for early withdrawal) will be summarized by formulation subgroup and cohort. For the patients who screen failed, who discontinued study treatment, and/or withdrew early from the study, related information will be listed. For this open-label study, the patients who received the initial dose of IMP are considered as enrolled.

3.3.2 Protocol Deviations

The terminology of CSR Reportable and not CSR Reportable cannot be changed within Medpace's ClinTrak system used for the study protocol deviation management. To align with the ICH E3 guidelines, CSR Reportable will be considered as *Important* and not CSR reportable will be considered as *Not Important in the ADaM dataset*.

Counts and percentages of patients with important protocol deviations by deviation category will be summarized by formulation subgroup (and overall), cohort (and in total) based on all enrolled patients. Important protocol deviations will also be listed and sorted by site, subject ID, and deviation start date. All protocol deviations (important and non-important) will be included in ADaM dataset.

3.3.3 Demographic and Baseline Characteristics

Descriptive summaries of demographic baseline characteristics will be summarized by formulation subgroup, cohort and in total for the Full Analysis Population. A subset analysis of patients with background ezetimibe use will also be summarized by cohort and in total for the Full Analysis Population. The demographics and baseline characteristics will also be summarized based on the PK Population.

Demographic and baseline characteristics include but are not limited to age at informed consent, sex, childbearing potential, ethnicity, race, height, weight, body mass index (BMI), body surface area (BSA), fasting lipid parameters and hs-CRP. baseline lipid modifying therapy [statin only, statin and other lipid modifying therapy, other lipid modifying therapy without statin, or no lipid modifying therapy], baseline statin intolerance, baseline ezetimibe use stratification group, whether or not the patient is taking the highest approved statin dose, whether or not the patient reported a history of statin related adverse event(s), and whether or not the patient diagnosed HeFH with positive genetic test.

3.3.4 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.1. Counts and percentages of patients with medical history by system organ class and preferred term will be summarized by cohort and in total based on the Full Analysis Population. All medical history will be listed.

History of hypercholesterolemia and the genetic testing for hypercholesterolemia are collected in separate CRFs and will be listed.

3.3.5 Prior and Concomitant Medications and Baseline Lipid Modifying Therapies

If a medication, lipid modifying therapy, or procedure has incomplete start or stop dates, dates will be imputed to determine whether a medication/lipid modifying therapy/procedures should be considered prior or concomitant. Missing date is imputed as described in Appendix C.

Prior and Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the World Health Organization (WHO) Drug Dictionary version WHO Drug Global B3/C3 March 2022. For summary purposes, medications will be considered prior medications if they stopped prior to the day of the first dose of IMP and concomitant medications if they were taken at any time on or after the day of first dose of IMP (i.e., started prior to the first dose of IMP and were ongoing or started after the first dose of IMP). Based on these definitions, a medication may be considered prior *or* concomitant, not both.

Counts and percentages of patients taking prior and concomitant medications by ATC class and preferred term will be summarized by cohort and in total based on the Full Analysis Population.

All prior and concomitant medications will be listed.

Baseline LMTs

LMTs as collected on a separate CRF will be coded to ATC class and preferred term using the WHO Drug Dictionary version WHO Drug Global B3/C3 March 2022. Baseline LMTs are those that the patient is receiving on the day of dosing.

For summary purposes, LMTs will be classified as following categories and sub-categories:

- Statins: preferred term contains any of the stain sub-type
    - Atorvastatin
    - Pitavastatin
    - Pravastatin
    - Rosuvastatin
    - Simvastatin

    - Other Statin
- Non-statins LMTs:
    - Ezetimibe
    - PCSK9 inhibitor
        - Alirocumab
        - Evolocumab
        - Inclisiran
    - Other non-statin LMT (exclude dietary supplements)
        - Niacin Derivatives:
        - Fibrates
        - Bile Acid Sequestrants

LMTs of combination of multiple components will be counted under individual categories and sub-categories of each component. e.g. LMT contains both Atorvastatin and ezetimibe should be counted under both Statins/Atorvastatin and Non-statin/Ezetimibe.

Baseline LMTs are defined as LMT ongoing at the time of initial dose of IMP.

Counts and percentages of patients taking baseline LMTs by category and sub-category will be summarized by formulation subgroup cohort and total based on the Full Analysis Population.

A separate prior Lipid Modifying Therapy (LMT) summary table will be created for each cohort and the total FAS population.

All baseline lipid modifying therapies will be listed.

3.3.6 Prior and Concomitant Procedures

Concomitant procedures will be coded to system organ class and preferred term using the MedDRA version 25.1. For summary purposes, procedures will be considered prior procedures if they stopped prior to the day of the first dose of IMP and concomitant procedures if they were performed at any time on or after the day of first dose of IMP (i.e., started prior to the first dose of IMP and were ongoing or started after the first dose of IMP). Based on these definitions, a procedure may consider prior *or* concomitant, not both.

Counts and percentages of patients with prior procedures by system organ class and preferred term will be summarized by cohort and in total based on the Full Analysis Population. Counts and percentages of patients with concomitant procedures by system organ class and preferred term will be summarized by cohort based on the Full Analysis Population. All prior and concomitant procedures will be listed.

3.3.7 IMP Exposure

Days of exposure to IMP will be calculated as date of last dose of IMP – date of first dose of IMP + 1 of each dose level. Note that the exposure calculation is intended to describe the length of time a patient was exposed to IMP and therefore does not take IMP interruptions into account.

Days of exposure to IMP will be summarized by formulation subgroup and cohort for each treatment period based on the Full Analysis Population with descriptive statistics.

Individual data related to IMP administration will be listed.

3.3.8 Study Treatment Compliance

Estimated treatment compliance will be presented for the Full Analysis Population by formulation subgroup and Cohort. Patients will be grouped as compliance ≥80% versus compliance <80% compliance for study treatment Period 1 and Period 2, respectively and for the whole study treatment.

Per protocol, patients will take the IMP once daily, starting from the visit day at which their IMP is initially dispensed to the day of last dose of the period. Compliance will be calculated based on IMP accountability data if available, otherwise on the self-reported drug administration data from the patient diary, and calculated by the following formula:

% Compliance of Study = [days of full dose taken in the period] ×100 / [treatment duration (days) in the period], where

- Days of full dose taken will be calculated by tablet dispensed and tablet returned when drug accountability data is available (note that patients in Cohort 1 take one tablet daily, Cohort 2 and 3 take two tablets daily), otherwise (e.g. when IMP bottle was not returned or only partially returned, or for the days patients took liquid suspension formulation) using the reported days of full dose and days of missing dose (if any) from patient exposure CRF.
- The treatment duration is defined as (last dose date - first dose date +1) for each period.

The percentage compliance will be capped as a maximum of 100%. Patients who do not have any “full dose” day will be counted as noncompliant (0%).

3.4 Pharmacokinetic Assessment

Pharmacokinetic data will be collected at following nominal time points:

- T1 (Day 1), T4 (Week 4), T5 (Week 8), T8 (Week 12), T9 (Week 16), FU (Week 21 for Cohort 1 and 2, Week 13 for Cohort 3)

PK concentration data will be summarized by visit-level IMP formulation, cohort, dose level and the nominal timepoint based on the PK Population. All PK concentration data will be listed. The detailed PK analysis plan and report will be developed by the Sponsor’s pharmacometrics vendor, who will conduct the model-based PK parameters estimates.

Analysis visits will be labeled as following and used in the PK concentration summary tables:

Table 2: Analysis Visit for PK concentration

Analysis Visit Label Nominal Time	Dose Level 1 (Period 1)	Dose Level 2 (Period 2)
Day 1 of the Dose	T1 (Day 1)	
Pre-dose	Pre-dose	
Post-dose 1 hr	Post-dose 1 hr	Post-dose 1 hr
Post-dose 4 hr	Post-dose 4 hr	Post-dose 4 hr
Week 4 of the Dose	T4 (Week 4)	T8 (Week 12)

Pre-dose	Pre-dose	Pre-dose
Week 8 of the Dose	T5 (Week 8)	T9 (Week 16)
Pre-dose	Pre-dose*	Pre-dose
Follow-up	FU (Week 21 for Cohort 1 and 2, Week 13 for Cohort 3)	
Pre-dose	Pre-dose	Pre-dose

* Week 8 Pre-dose PK concentrations of Dose Level 1 also serve as the Day 1 Pre-dose PK concentrations of Dose Level 2.

3.5 Pharmacodynamic/Efficacy Assessment

Basic fasting lipids (direct LDL-C, calculated TC, calculated non-HDL-C,) and hs-CRP will be collected at Screening, T1 (Day 1), T4 (Week 4), T5 (Week 8), T8 (Week 12), T9 (Week 16), FU (Week 21 for Cohort 1 and 2, Week 13 for Cohort 3).

Analysis visits will be labeled as following and used in the efficacy summary tables:

Table 3: Analysis Visit for Efficacy summary

Analysis Visit Label	Dose Level 1 (Period 1)	Dose Level 2 (Period 2)
Baseline	T1 (Day 1)	
Week 4 of the Dose	T4 (Week 4)	T8 (Week 12)
Week 8 of the Dose	T5 (Week 8)	T9 (Week 16)
Follow-up	FU (Week 21 for Cohort 1 and 2, Week 13 for Cohort 3)	

Descriptive statistics (n, mean, median, standard deviation, minimum, maximum, Q1 and Q3) and the 95% confidence interval for mean of fasting lipids and median of hs-CRP values, change from baseline and percent change from baseline will be summarized by visit-level IMP formulation, cohort and analysis visit based on the Full Analysis Population. The 95% confidence interval will be calculated using Student's t distribution. A subgroup of patients with baseline ezetimibe use will be summarized in a similar manner based on the Full Analysis Population. Plots of mean values over time by visit-level IMP formulation and cohort will be generated. hs-CRP plot will use the median and the 95% confidence interval of the median by free-distribution method. Similar plots for change from baseline and percent change from baseline will also be generated. Non-fasting lipids will be excluded from summary analysis. All lipids and hs-CRP results (fasting and non-fasting) will be listed.

A model for exposure-LDL-C response will be developed in a separate analysis plan and with a separate report provided by the Sponsor's pharmacometrics vendor, which can provide simulations for dosing recommendations in subsequent pediatric trials.

3.6 Safety Assessment

3.6.1 Adverse Events (AEs)

All adverse events (AEs) will be coded to system organ class and preferred term using MedDRA version 25.1. Treatment-emergent adverse events (TEAEs) are defined as AEs with an onset date on or after the initiation of IMP and before the end of study.

For AEs with a partial date, available date parts (year, month, and day) of the partial date will be compared with the corresponding date components of the start date of the IMP to determine if the event is treatment emergent. The rules to impute partial dates for AEs are included in Appendix C.

Incomplete start and stop dates will be listed as collected without imputation.

Adverse Events of Special Interest (AESIs)

AESIs determined by AE preferred terms will be identified using a list of preferred terms provided by the Sponsor (See Appendix B) and will be finalized prior to database lock.

AESI preferred terms will be categorized into the following:

- Hepatic Safety
- Musculoskeletal Safety
- New onset Diabetes Mellitus
- Hypoglycemia Associated with Metabolic Acidosis
- Renal Impairment
- Neurocognitive Events
- Atrial Fibrillation
- Tendon rupture

Counts and percentages of patients with treatment-emergent AESI will be classified by category and preferred term, and summarized by formulation subgroup, cohort and total.

AE Overview

An overview of AEs will be provided including counts and percentages of patients (and event counts) with the following:

- At least one TEAE (overall and by maximum severity)
- At least one TEAE related to the IMP (overall and by strongest relationship)
- At least one serious TEAE
- At least one serious TEAE related to the IMP
- At least one TEAE of Special Interest
- A TEAE leading to IMP discontinuation
- A TEAE leading to study discontinuation
- A TEAE leading to death

Counts and percentages of patients will be presented by formulation subgroup (and overall), cohort (and in total), system organ class, and preferred term, for TEAEs, TEAEs related to IMP, serious TEAEs, serious TEAEs related to IMP, TEAEs leading to IMP discontinuation, TEAEs leading to study discontinuation, and TEAEs leading to death. Counts and percentages of

patients will be presented by formulation subgroup (and overall), cohort (and in total), system organ class, preferred term, and maximum severity for TEAEs as well.

All AEs, whether treatment-emergent or not, will be listed sorted by formulation subgroup, cohort and patient. TEAEs related to IMP, serious TEAEs, AESIs, and TEAEs leading to IMP discontinuation or death will also be listed separately.

3.6.2 Clinical Laboratory Tests

Blood and urine samples for clinical laboratory tests will be collected at Screening, T1 (Day 1), T4 (Week 4), T5 (Week 8), T8 (Week 12), T9 (Week 16), FU (Week 21 for Cohort 1 and 2, Week 13 for Cohort 3). A list of laboratory tests to be performed is included in Appendix A.

Chemistry, hematology, laboratory numeric data will be summarized by dose formulation, cohort, and scheduled visit for the Full Analysis Population. Change from baseline to post-dose visits and percent change from baseline to post-dose visits at each scheduled visit will also be summarized by dose formulation, cohort and visit for chemistry and hematology laboratory data.

All clinical laboratory tests will be listed. Abnormal lab tests will be indicated in the listings.

Shifts from baseline to worst post-baseline value within each treatment period will be presented for specified lab tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], creatine kinase [CK]), estimated glomerular filtration rate [eGFR], total bilirubin and hemoglobin) by formulation subgroup and cohort. Results will be categorized based on the criteria in the table below.

Table 4: Description of Criteria for Selected Lab Tests

Parameter	Categories			
ALT	Low/Normal (≤ULN)		High (>ULN)	
AST	Low/Normal (≤ULN)		High (>ULN)	
ALP	Low/Normal (≤ULN)		High (>ULN)	
CK	Low/Normal (≤ULN)		High (>ULN)	
Total Bilirubin	Low/Normal (≤ULN)		High (>ULN)	
Hemoglobin	Normal/High (≥LLN)		Low (<LLN)	
eGFR (mL/min/1.73m2)	≥90	≥60 to <90	≥30 to <60	<30

A summary table of specified lab abnormalities, based on the worst post-baseline value (including unscheduled visits), by formulation subgroup and cohort will also be provided for the Full Analysis Population. The criteria evaluated in the table includes:

- ALP >1.5× ULN
- ALT or AST >3× ULN
- ALT or AST >5× ULN
- Blood urea nitrogen (BUN) ≥2× Baseline and > ULN

- CK >5× ULN
- CK >10× ULN
- Creatinine Change from Baseline >0.5 mg/dL and > ULN
- eGFR <15 mL/min/1.73 m²
- eGFR ≥15 to <30 mL/min/1.73 m²
- eGFR ≥30 to <60 mL/min/1.73 m²
- Glucose <54 mg/dL
- Glucose ≥54 mg/dL and <70 mg/dL
- Hemoglobin A1C (HbA1C) ≥6.5%
- Hgb <11.0 g/dL
- Hgb decrease from Baseline >2.0 g/dL and <LLN
- Potential Hy's Law (ALT or AST >3× ULN and concomitant Total Bilirubin >2× ULN)
- Total Bilirubin >2× ULN

3.6.3 Vital Signs

Vital signs, including blood pressure and heart rate, will be collected at scheduled visit per protocol Appendix 1. Vital signs will be summarized using descriptive statistics at each post-dose scheduled visit by formulation subgroup, and cohort for the Full Analysis Population. Change from baseline and percent change from baseline to each scheduled post-dose visit will also be summarized. All vital sign results will be listed by patient.

3.6.4 Electrocardiograms

ECGs will be conducted at Screening, Weeks 4 and 12 for Cohorts 1 and 2 and at Screening and Week 4 for Cohort 3.

ECG interpretations will be summarized using counts and percentages at each scheduled visit by formulation subgroup and cohort based on the Full Analysis Population. All ECG results will be listed by patient.

3.6.5 Physical Examinations

Physical examinations will be conducted at scheduled visit per protocol Appendix 1. Full physical examinations will include the following body systems: general appearance, skin, head, ears, eyes, nose, throat, neck, lungs, heart, abdomen, musculoskeletal, extremities, and neurological systems. All physical examination findings will be listed by formulation subgroup and patient, visit and body system.

3.6.6 Height, Weight, BMI, BSA and Tanner Staging

Height, weight, BMI, and BSA values will be used as collected on the eCRF. BMI will be calculated on the eCRF as: body weight (kg) / [height (m)] ². BSA will be calculated on the eCRF as: square root of ([weight(kg) x height(cm)]/3600).

Height, weight, BMI and BSA will be summarized using descriptive statistics by formulation subgroup (and overall), cohort (and in total) and scheduled visit (T1 [Baseline], T4, T5, T8, T9, FU) for the Full Analysis Population. Change from baseline and percent change from baseline to each scheduled post-dose visit will also be summarized. All related results will be listed by patient.

Tanner staging scoring will be conducted at visit T1 (Day 1), T5 (Week 8) and T9 (Week 16) for Cohorts 1 and 2 and at T1 (Day 1) and T5 (Week 8) for Cohort 3. All Tanner staging scoring results will be listed by formulation subgroup, cohort and patient.

3.6.7 Dosing Acceptability

Dosing acceptability responses for liquid suspension and tablet will be summarized separately using counts and percentages at each visit by cohort and in total based on the Full Analysis Population. All dosing acceptability responses for liquid suspension and tablet will also be listed by patient, visit, and dosing acceptability question. Patients who switched from one formulation to the other will complete acceptability questionnaires for both formulations.

4 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will review accumulating unblinded safety data from this and other ongoing pediatric 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. Data reviewed by the DMC will include inclusion/exclusion, disposition, demographics and baseline characteristics, medical history, prior and concomitant medications, AEs, clinical safety assessments (e.g. safety lab tests, vital signs, ECG), IMP exposure, and lipids. The committee has a separate charter that includes additional details.

5 ANALYSIS TIMING

5.1 Dry Runs

Two sets of dry run analysis tables, figures, and listings (TFLs) will be provided prior to the scheduled database lock.

5.2 Interim Analysis

Study data will be reviewed periodically by the DMC as described in the DMC Charter. No other interim analysis is planned for this study.

5.3 Final Analysis

After the database is locked, the final analysis will be generated. The topline tables (important tables selected as a subset of the full set of tables) will be provided approximately 1 week after database lock. Final tables, figures, and listings (TFLs) will be provided approximately 3 weeks after database lock.

If there are any comment(s) and/or edit(s) needed in the database or final TFLs, then the TFLs cannot be considered final until all updates are resolved.

In addition to TFLs, study data tabulation model (SDTM) data and ADaM data along with associated files will be provided. Associated files may include annotated eCRFs, SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, and TFL programs. Clinical data interchange standards consortium (CDISC) define packages for both SDTM and ADaM data will be provided approximately 5 weeks after final database and TFLs.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

The Analysis Populations section 14.3 of the protocol states “The completer population will include all patients who complete all assigned treatment period doses.”. This analysis population will not be used.

7 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in patient data listings which will be sorted by patient and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: CLINICAL SAFETY LABORATORY EVALUATIONS

Clinical Laboratory Test	***Clinical Laboratory Test***
Hematology	***Blood Chemistry (serum, fasting)***
• 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 %)	• 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)	**Urinalysis (Microscope) – only if urine dipstick abnormal**
• Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrate • Occult Blood • pH • Protein • Specific Gravity • Urobilinogen	• Bacteria • Casts • Crystals • Epithelial cells • RBC • WBC

[a] *eGFR will be calculated (by central laboratory) using the Revised ("Bedside") Schwartz formula.*
[b] *If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin will be obtained.*

APPENDIX B: ADVERSE EVENTS OF SPECIAL INTEREST

AESI Category	MedDRA Preferred Terms
New onset diabetes mellitus (NODM) (Patients without medical history of diabetes mellitus)	• Acquired lipoatrophic diabetes • Blood glucose abnormal • Blood glucose fluctuation • Blood glucose increased • Blood insulin abnormal • Blood insulin decreased • Blood insulin increased • Decreased insulin requirement • Diabetes complicating pregnancy • Diabetes mellitus • Diabetes mellitus inadequate control • Diabetes mellitus malnutrition-related • Diabetes with hyperosmolarity • Diabetic arteritis • Diabetic coma • Diabetic complication • Diabetic coronary microangiopathy • Diabetic hepatopathy • Diabetic hyperglycaemic coma • Diabetic hyperosmolar coma • Diabetic ketoacidosis • Diabetic ketoacidosis hyperglycaemic coma • Diabetic ketosis • Diabetic wound • Diabetic metabolic decompensation • Euglycaemic diabetic ketoacidosis • Fulminant type I diabetes mellitus • Glycosylated haemoglobin abnormal • Glycosylated haemoglobin decreased • Glycosylated haemoglobin increased • Hyperglycaemia • Hyperglycaemic hyperosmolar nonketotic syndrome • Insuline resistant diabetes • Insulin-resistant type 2 diabetes mellitus • Ketosis-prone diabetes mellitus • Metabolic syndrome • Monogenic diabetes • New onset diabetes after transplantation • Pancreatogenous diabetes • Steroid diabetes • Type 1 diabetes mellitus • Type 2 diabetes mellitus • Diabetic endorgan damage
Hypoglycemia associated with metabolic acidosis	• Level 3 Hypoglycemia: hypoglycaemic coma, hypoglycaemic encephalopathy, hypoglycaemic seizure, shock hypoglycaemic, hypoglycaemic unconsciousness • lactic acidosis, metabolic acidosis, diabetic ketoacidosis
Hepatic enzymes elevated	• Alanine aminotransferase abnormal • Alanine aminotransferase increased • Aspartate aminotransferase abnormal • Aspartate aminotransferase increased • Blood bilirubin abnormal • Blood bilirubin increased • Hepatic enzyme abnormal • Hepatic enzyme increased • Hypertransaminasaemia • Liver function test abnormal • Liver function test increased • Transaminases abnormal • Transaminases increased
Muscular disorders	• Muscular weakness • Muscle necrosis

	• Muscle spasms • Myalgia • Myositis • Myoglobin blood increased • Myoglobin blood present • Myoglobin urine present • Myoglobinaemia • Myoglobinuria • Myopathy • Myopathy toxic • Necrotising myositis • Pain in extremity • Rhabdomyolysis • Blood creatine phosphokinase increased • Musculoskeletal discomfort • Red blood cells urine positive • Muscle fatigue • Muscle tightness
Neurocognitive disorders	• Cognitive disorder • Memory impairment • Mental impairment • Confusional state • Disorientation • Mental status changes
Renal impairment	• Acute kidney injury • Acute prerenal failure • Blood creatinine abnormal • Blood creatinine increased • Blood urea abnormal • Blood urea increased • Blood urea nitrogen/creatinine ratio increased • Creatinine renal clearance abnormal • Creatinine renal clearance decreased • Glomerular filtration rate abnormal • Glomerular filtration rate decreased • Oliguria • Prerenal failure • Renal failure • Renal function test abnormal • Renal impairment • Blood urine present • Proteinuria • Nephropathy • Protein urine present • Red blood cells urine positive • Haematuria
Tendon rupture and Tendinopathies	• Tendon rupture • Muscle rupture • Rotator cuff syndrome • Tendon discomfort • Tendon disorder • Tendon injury • Tendon necrosis • Tendon pain • Tendonitis

APPENDIX C: MISSING DATA IMPUTATION

Imputation of missing date for Prior and Concomitant Medications and Procedures and Baseline Cross-in Lipid Modifying Therapies

If a medication/lipid modifying therapy/procedure start date is incomplete, then the first day of the month will be imputed for missing day and January will be imputed for missing month. If a medication/lipid modifying therapy/procedure stop date is incomplete, then the last day of the month will be imputed for missing day and December will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation

Imputation of AE dates:

If start date of an AE is partially missing, then the following imputation rules will be applied:

- If both Month and Day are missing and Year = Year of IMP start date, then set to IMP start date.
- If both Month and Day are missing and Year ≠ Year of IMP start date, then set to January 1.
- If Day is missing and Month and Year = Month and Year of IMP start date, then set to IMP start date.
- If Day is missing and Month and Year ≠ Month and Year of IMP start date, then set to first day of the month.
- If start date is completely missing, set to IMP start date if AE end date is not prior to IMP start date.

If end date of an AE is partially missing, then following imputation rules will be applied:

- If both Month and Day are missing but Year is not missing, then set to December 31.
- If only Day is missing, then set to last day of the month.
- If end date is completely missing, then do not impute.