16.1.9 Documentation of Statistical Methods

Original Statistical Analysis Plan (SAP) Version 1.0	14 February 2017
SAP Version 1.1	19 October 2018
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Statistical Analysis Plan

Title: A MULTICENTER OPEN-LABEL EXTENSION (OLE) STUDY TO ASSESS THE LONG-TERM SAFETY AND EFFICACY OF BEMPEDOIC ACID (ETC-1002) 180 MG
Protocol: ETC-1002-050
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Esperion Therapeutics

Table of Contents

1 List of Abbreviations

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 diseases
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
AUC_{0-24}	Area under the curve during 24 hours
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
Cl	Chloride
CNS	Central nervous system
CoA	Acetyl-coenzyme A
CO_2	Carbon dioxide
CV	Cardiovascular
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency

Abbreviation or Specialist Term	Explanation
EOS	End of Study
ETC-1002	Bempedoic acid
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FPFV	First patient first visit
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA_{1C}	Glycosylated hemoglobin, Type A_{1C}
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
Hgb	Hemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IWRS	Interactive web response system
K	Potassium
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LFT	Liver function test
LPLV	Last patient last visit
LS	Least square
MACE	Major adverse cardiac event
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume

Abbreviation or Specialist Term	Explanation
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
Na	Sodium
NA	Not applicable
NLA	National Lipid Association
NOAEL	No-observed-adverse-effect level
non-HDL-C	Non-high-density lipoprotein cholesterol
OLE	Open-label extension (study)
Parent study	Study 1002-040
PCSK9	Proprotein convertase subtilisin/kexin type 9
PE	Physical exam
PK	Pharmacokinetic(s)
PT	Prothrombin time
RBC	Red blood cell
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
SP	Safety population
SUSARS	Suspected and unexpected serious adverse reactions
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TQT	Thorough QT/QTc
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

2 Introduction

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed in ETC-1002-050. The preparation of this statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 Guidelines and in reference to Protocol ETC-1002-050 (Protocol V1.0, November 01, 2016).

The SAP will supersede the protocol in the event of any differences between the two documents in the plans for data analysis, and the protocol will be amended if appropriate. The SAP will be included as an appendix in the clinical study report for this protocol.

3 Study Objectives and Endpoints

3.1 Objectives

- The primary objective for this study is to characterize the safety and tolerability of long-term administration of bempedoic acid (ETC-1002) 180 mg

- The secondary objective is to characterize the efficacy of long-term administration of bempedoic acid 180 mg/day as assessed by changes in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol (TC), triglycerides TG and high-sensitivity C-reactive protein (hs-CRP) in patients with hyperlipidemia

3.2 Primary Endpoint

- The primary endpoint for this study is patient incidence of AEs

3.3 Secondary Endpoints

- Percent change from baseline in LDL-C at Weeks 52 and 78
- Change from baseline in LDL-C at Weeks 52 and 78
- Percent change from baseline in non-HDL-C at Weeks 52 and 78
- Percent change from baseline in TC at Weeks 52 and 78
- Percent change from baseline in ApoB at Weeks 52 and 78
- Percent change from baseline in hs-CRP at Weeks 52 and 78
- Percent change from baseline in TG at Weeks 52 and 78

- Percent change from baseline in HDL-C at Weeks 52 and 78

3.3.1 Adverse Events

The evaluation of AEs will include only incidence of treatment-emergent AEs (TEAEs), defined as AEs that begin or worsen after the first dose of study drug administration in OLE period and until 30 days after last dose of study drug. Clinical endpoints (details see section 4.2) will be collected and adjudicated by an independent Clinical Events Committee (CEC). Clinical endpoints will also be reported as SAEs. Adverse events of special interest (AESI) will further be examined (See Section 5.4.2 for more information).

3.3.2 Clinical Safety Laboratories

The evaluation of clinical safety laboratories, including blood hematology, chemistry, coagulation, and urinalysis, will be based on the observed values. Observed values and changes from baseline will be summarized for all post-baseline study visits.

3.3.3 ECG, Vital Signs and PE

The evaluation of ECG and vital signs (including heart rate, systolic blood pressure, diastolic blood pressure, height, and weight will be based on the observed values. For ECGs, shifts from baseline to end-of-study will be summarized. For vital signs, observed values and changes from baseline will be summarized for all post-baseline study visits. Listings of PE data will include only those records where the body system at the baseline PE was normal, but the body system at a post-baseline PE was marked as 'Change from previous exam, clinically significant.'

3.4 Lipids

After enrollment, patients will return to clinic at Months 12, 52, and 78. Clinical laboratory samples will be collected and analyzed for calculated LDL-C and lipid and cardiometabolic biomarkers including non-HDL-C, HDL-C, TC, ApoB, and TG at baseline and all clinic visits for evaluation of bempedoic acid effects on lipids and cardiometabolic parameters.

3.5 Pharmacokinetic (PK) and Other Biomarkers

NA.

4 Study Design

4.1 Study Design

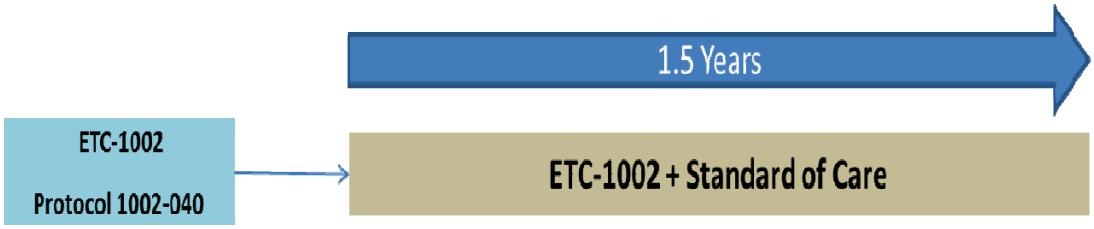
This is a multicenter OLE study designed to assess the long-term safety and efficacy of bempedoic acid (ETC-1002) 180 mg. All patients will receive open-label bempedoic acid 180 mg for up to 1.5 years after rolling over from the parent study (Study 1002-040), where they receive either bempedoic acid or placebo treatment. Investigators, site staff, patients,

and the study team will be masked to study lipid levels until the Week 12 study visit, after which time lipid values will be made available.

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety and efficacy data from this and other ongoing studies of bempedoic acid. A blinded independent expert Clinical Events Committee (CEC) will adjudicate designated clinical endpoints across the program, including all major adverse cardiac events (MACE) and non-MACE endpoints defined as: cardiovascular (CV) death (MACE), non-CV death (non-MACE), nonfatal myocardial infarction [MI] (MACE), nonfatal stroke (MACE), hospitalization for unstable angina (MACE), coronary revascularization (MACE), noncoronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE) using standardized definitions. Any clinical endpoints that meet serious adverse event (SAE) criteria will be reported as SAEs as well as a clinical endpoint.

The study will be conducted at approximately 125 clinical sites in the United States, Canada, Germany, Netherlands, Poland, and United Kingdom. The study will end when the last randomized patient completes their last study visit (last patient last visit [LPLV] for last randomized patient). The estimated overall duration of the study (first patient first visit [FPFV] to LPLV) is approximately 2.5 years.

Figure 1. Study 1002-040 Study Design



4.2 Study Treatments and Assessments

Day 1 for this study should occur on the same day as the end of study visit for the parent study (1002-040). Patients who provide informed consent and sign the ICD will be eligible to enroll in the study.

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

The investigational products were listed in Table 1 below:

Table 1: Investigational Medicinal Products

	Investigational Medicinal Product
Product Name:	Bempedoic acid
Dosage Form:	Film-coated tablets
Unit Dose:	180 mg
Container/Closure[a]	100-count bottle with screw on, child proof cap
Route of Administration:	Oral, daily with or without food
Physical Description:	[redacted]
Manufacturer (Fill/Finish):	

Study drug should be taken once a day (once every 24 hours) at approximately the same time every day and may be taken with or without food. Patients will fast (no food or drink, other than water) for a minimum of 10 hours prior to collection of all laboratory samples.

Please see Pharmacy Manual for detailed storage requirements and instructions.

Patients who withdraw from investigational medicinal product (IMP) treatment will be asked to continue to be followed for safety using the protocol-specified visit schedule and procedures. For details of study assessments, see Appendix 1: Schedule of Events (Subject Visit Schedule).

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety and efficacy data from this and other any ongoing studies of ETC-1002. All clinical endpoints, including all major cardiac events (MACE) and non-MACE endpoints defined as: CV death (MACE), non-CV death (non-MACE), nonfatal myocardial infarction (MI) (MACE), nonfatal stroke (MACE), hospitalization for unstable angina (MACE), coronary revascularization (MACE), non-coronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE), will be adjudicated by an independent blinded expert Clinical Events Committee (CEC), using standardized definitions. Any clinical endpoints that meet serious adverse event (SAE) criteria will be reported as SAEs.

4.3 Randomization and Blinding

- Randomization is not applicable for this OLE study.
- Laboratory results for lipid panel and hs-CRP will be masked to investigators, patients, and the study team until the Week 12 visit is completed. All site staff involved with this trial should refrain from obtaining lipid panels between date of last study medication (bempedoic acid or placebo) dose at end of parent study Week 52 (Visit T7) and Week 12 in this OLE trial.

4.4 Sample Size Justification

[redacted]

The number of patients entering this study will depend on the number of patients completing Study 1002-040 and their willingness to enroll.

4.5 Interim Analyses, Final Analyses and Unblinding

No formal interim analysis is planned for this study.

An interim data cut-off may occur in order to provide safety assessment to support NDA submission; the actual date will be determined by Esperion team.

The final analysis will be performed after the database is locked, and the database released.

4.6 Change from Planned Analyses

There is no change from planned analyses for this study.

5 Statistical and Analytical Plans

5.1 General Statistical Considerations

The ETC-1002 treatment group will be displayed in the tables, listings and figures (TLFs) as “bempedoic acid 180 mg.”

In general, all safety and efficacy data will be reported as observed. No imputation will be performed for missing data. Descriptive statistics (n, mean, standard deviation [SD] or Standard Error [SE], median, minimum, and maximum) will be calculated for continuous data. Minimum and maximum will be presented same number of decimal places as reported/collected, one additional decimal place for mean and median, and two additional decimal places for SD.

Categorical data will be summarized using n and percentage based on number of non-missing values. Percentage will be presented with one decimal place. The number of missing values will be presented as a separate category with no percentage, but only if 1 or more patients are missing data for the summary. Otherwise, all categories will be

presented (even if no patients are counted in the category). Counts of zero in any category will be presented without percentage. Ninety-five percent (95%) confidence intervals (CIs) will be calculated for select continuous and categorical endpoint estimates. All patients will be summarized together as well as by their prior treatment group in the parent study.

Data will be presented on listings in order of patient/subject, assessment date and assessment (in order collected on CRF, unless specified otherwise). Dates will be presented in format DDMMMYYYY.

Relative day calculations will be [date of interest – relative date + 1? (date of interest >= relative date)]. This calculation will result in dates prior to the relative date being presented as negative days, and those occurring on or after the relative date as Day 1 or later, i.e., there will be no Day 0.

For efficacy endpoint analysis, baseline is defined as the same baseline as parent study. For safety analysis, baseline is defined as the last value/result where assessment date is less than or equal to the date of first study treatment, unless otherwise specified. If last dose of study treatment is missing, then the date of last visit at which study assessments were obtained on CRF will be used in its place.

The visit schedules and window are shown below.

Visit	Day 1/Week 0	Week 12	Week 24	Week 36	Week 52	Week 64	Week 78/EOS
Month	0	3	6	9	12	15	18/EOS
Slotted Study Week	EOS Parent	Wk 12	Wk 24	Wk 36	Wk 52	Wk 64	Wk 78
Target Study Day	1	84	168	252	364	448	546
Analysis Window	1	[2,126]	[127,210]	[211,308]	[309,406]	[407,497]	[498,∞]
Protocol defined visit Windows	[30 Days, Pre M0]	84±7	168±7	252±7	364±7	448±7	546±7

5.2 Statistical Analysis Plans

5.2.1 Analysis Sets

5.2.1.1 Safety Population (SP)

The Safety Population (SP) is defined as all enrolled patients who received at least 1 dose of study medication and will be used for demographics and baseline characteristics, treatment exposure, concomitant medications, and all safety summaries.

5.2.1.2 Full Analysis Set (FAS)

The Full Analysis Set (FAS) is defined as all enrolled patients and is also known as the intention-to-treat (ITT) set of patients. FAS will be used for all of the efficacy summaries and analyses.

5.2.2 Protocol Violations and Deviations

A full list of protocol violations and deviations will be compiled and reviewed by the clinical team to identify major versus minor violations/deviations before final database

lock. For violations at study entry, patients will be assessed against the inclusion and exclusion criteria of the protocol. For on-study deviations, compliance with the protocol will be examined with regard to prohibited therapies, and timing and availability of planned assessments.

5.2.3 Subject Disposition

The number of patients enrolled, and included in each analysis population, along with study completion status, will be summarized by the treatment group in parent ETC-1002-040 study and overall. In addition, the number of patients who withdraw from the study and withdraw from study drug will be summarized by discontinuation reason.

5.2.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics collected from the parent study will be used for this study. The following demographic and baseline characteristics will be summarized by previous treatment group in parent study, as well as overall, for safety population and for FAS population: age (years), gender, race, ethnicity, region, height (cm), weight (kg), body mass index (kg/m^2), waist circumference (cm), systolic and diastolic blood pressure (mmHg), fasting lipid parameters (TC [mg/dL], calculated LDL-C [mg/dL], HDL-C [mg/dL], non-HDL-C [mg/dL] and TG [mg/dL]), apoB (mg/dL), hs-CRP (mg/dL), ASCVD only/HeFH, baseline statin intensity (low, moderate, high), eGFR category, tobacco history, alcohol history, and weekly average number of alcoholic drinks, history of diabetics, history of hypertension. Data will be summarized using descriptive statistics for continuous variables and using counts and percentages for categorical variables by treatment group and overall. Age will be summarized as a continuous variable and by age group (18-40, 41-64, 65-74, and >=75).

The baseline estimated glomerular filtration rate (eGFR) categories are: normal: ≥90 $mL/min/1.73m^2$; mild Renal Impairment: 60-89 $mL/min/1.73m^2$; moderate Renal Impairment: 30-59 $mL/min/1.73m^2$, and severe Renal Impairment (15-29 $mL/min/1.73m^2$).

The reasons for patients who are not on a highest dose of a high intensity statin will be summarized and presented in a by-patient listing.

5.2.5 Medical History

General medical history, cardiovascular history/risk factors, previous statin use and statin tolerance history will be summarized by previous treatment group in parent study, as well as overall in OLE study, for safety population and FAS population and presented in a by-patient listing. Where appropriate, terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 or later.

If a patient is entering the study beyond the 30 day rollover window, changes to medical history that occur during that period will be collected. The changes will be summarized for safety population and presented in a by-patient listing.

5.2.6 Prior and Concomitant Medications

Prior medications are defined as medications that ended prior to the initiation of study drug in this OLE study. Concomitant medications are defined as medications that were ongoing at the time of study drug initiation in this OLE study or new medications that started post study drug initiation and within 30 days following the date of the last dose of study drug.

Medications, including prior statin medications, will be coded using WHO Drug (March, 2015, or later if appropriate). The frequency of use of prior medications and use of concomitant medications will be summarized by previous treatment group in parent study, as well as overall in OLE study, for the safety population according to Anatomical Therapeutic Chemical (ATC) class and preferred term. If there is no enough prior medication data, prior medications will be presented in a by-patient listing only. Prior and concomitant medications will be listed for each patient. Prior and concomitant statin medications will be summarized and listed similarly.

5.2.7 Study Drug Exposure and Compliance

The length of exposure to study drug will be calculated as the number of days from the first dose of study drug to the last dose of study drug, regardless if the patient missed one or more doses of study drug. Length of exposure will be summarized by previous treatment group in parent study and overall in OLE study using descriptive statistics for the safety population.

The number and percentage of patients who were compliant with taking study drug will be summarized by previous treatment group in parent study and overall in OLE study and post-baseline time point for the safety population for the following categories 0 - <50%; >=50 - <80%; >= 80%. Compliance at each Visit (x)will be assessed by site staff by counting the number of tablets that are returned as unused study drug and querying the patient regarding daily intake and calculated using the formula: 100* (Number Dispensed at Visit x-1 – Number Returned at Visit x) / (Duration in days between Visit x and Visit x-1). Overall compliance during the study will be similarly calculated.

The study drug administration and compliance data, including reasons for poor compliance, will be listed for each patient.

5.3 Efficacy Endpoints and Analyses

For all efficacy endpoints and analyses, the FAS will be used. For summary by previous treatment group in parent study, patient will be summarized in their randomized group in parent study, regardless of the treatment they actually received.

For change from baseline in efficacy endpoints, baseline will be same baseline as parent study. For summaries of efficacy endpoints, only observed case data will be used (no imputation for missing data).

LDL-C, HDL-C, TG, TC, non-HDL-C, apoB and hs-CRP values at week 0, Weeks 52, and 78 will be summarized based on the FAS. For each parameter at each time point, the value

of the parameter and the percent change from baseline in the parameter will be summarized by previous treatment group in parent study and overall in OLE study. Ninety-five percent (95%) CI will be provided for the estimates at week 0, Week 52 and 78 for the change values. Lipid and cardiometabolic data from all visits will be listed.

5.4 Safety Data Endpoints and Analyses

No statistical analyses will be performed on any of the safety data in this study.

The safety and tolerability of ETC-1002 will be assessed by examination of TEAEs (including muscle related events and other AESI), physical exams, vital signs, electrocardiograms (ECGs), clinical laboratory values (serum chemistry, hematology, coagulation and urinalysis), and weight. All patients included in the SP will be evaluated in the safety analyses.

Unless otherwise stated, descriptive summaries will be displayed by previous treatment group actually received in parent study and overall and based on the SP.

5.4.1 Adverse Events (AEs)

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 or later and will be categorized by system organ class (SOC) and preferred term (PT). Patients with AEs that are ongoing at study completion or study withdrawal must be followed until resolution or for 30 days after the last study visit, whichever comes first. Summary tables will focus on TEAEs; however, listings will include all AEs (with non-TEAEs flagged). An additional listing will be provided for AEs occurred during rollover period for patients who entered the study beyond the 30-day rollover window, if data available.

In summary tables, TEAEs will be counted as “Not Related” if relationship to study drug was recorded as ‘Not Related’ or “Unlikely”. Events will be counted as “Related” if relationship to study drug was recorded as ‘Possible’, ‘Probable’, ‘Definite’ or if relationship to study drug is missing.

The severity of the AE will be characterized as mild, moderate, or severe, 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

Overviews of TEAEs will be presented by previous treatment group in parent study and overall containing the following counts and percentages for:

- patients with TEAEs
- Patients with TEAEs occurred during the rollover period for patients entered the study beyond the 30 day rollover window (if available)
- patients with TEAEs by SOC and PT
- patients with TEAEs by maximum severity
- patients with treatment-related TEAEs
- patients with treatment-emergent serious adverse events (TE SAEs)
- patients with TE SAEs (TE SAEs) by SOC and PT
- patients with TE SAEs by maximum severity
- patients with treatment-related TE SAEs
- withdrawal from study drug due to TEAEs

In addition, summary tables will be provided, by prior treatment group and overall, for the number and percent of patients experiencing:

- investigator reported major adverse cardiovascular events and mortality (MACE) by event type
- adjudicated major adverse cardiovascular events and mortality (MACE) by event type
- non-CV deaths (non-MACE),
- nonfatal myocardial infarction [MI] (MACE),
- nonfatal stroke (MACE),
- hospitalization for unstable angina (MACE),
- coronary revascularization (MACE),
- noncoronary arterial revascularization (non-MACE),
- hospitalization for heart failure (non-MACE) using standardized definitions.

Any clinical endpoints that meet serious adverse event (SAE) criteria will be reported as SAEs as well as a clinical endpoint.

The AE overview summaries will count a patient at most once in each AE category (at the "highest/most extreme" designation of each category regardless of preferred term) and percentages will be based on the total number of patients in the safety population.

In addition to a comprehensive listing of all AEs (with non-TEAEs flagged), separate listings will be generated for SAEs, AEs resulting in withdrawal of study drug, and AEs with a fatal outcome, investigator reported major adverse cardiovascular events and mortality, and adjudicated major adverse cardiovascular events and mortality.

5.4.2 Adverse Events of Special Interest

Across clinical studies to date, the most frequently reported TEAEs associated with the experiences with ETC-1002 included musculoskeletal and connective tissue disorders (back pain, pain in extremity, myalgia, arthralgia, and muscle spasms), nervous system disorders (headache), GI disorders (nausea and diarrhea), and infections and infestations.

Adverse events of special interest (AESI) include hepatic, muscular (AE and CK evaluation), new onset diabetes/glycemia, renal, cardiovascular, metabolic acidosis and hypoglycemia and neurocognitive/neurologic events. These events will be pulled out of the AE databases with help of clinical team by SOC and PT, and will be identified as safety monitoring endpoint.

- Hepatic safety will be assessed via liver-associated enzymes and TB.
- Musculoskeletal safety will be assessed via AEs involving muscle related symptoms, CPK laboratories will also be summarized.
- New onset diabetes/glycemia will be assessed via AEs and monitoring of glucose and HbA1c.
- Renal safety will be assessed via eGFR, CK and muscle-related AEs.
- Cardiovascular safety will be assessed via AEs (note that the AESI of cardiovascular safety is broader than the MACE assessment).
- Neurocognitive events will be assessed by routine monitoring of PE findings and AEs.
- Hypoglycemia will be assessed by routine clinical laboratories and summarized based on AE evaluations
- Metabolic acidosis occurrences will be monitored by routine laboratories and summarized based on AE evaluations.

AESI will be presented in a listing and summarized by SOC, PT and previous treatment group in parent study and overall in OLE study. Muscle-related TEAEs will be summarized by SOC, PT and baseline eGFR category.

5.4.3 Clinical Cardiovascular Endpoints

Clinical cardiovascular endpoints will be monitored and adjudicated by an independent blinded expert CEC for this study and other ongoing studies the ETC-1002 program. Adjudicated clinical endpoints will be summarized by event type and previous treatment group in parent study and overall in OLE study. Additional details regarding clinical endpoints and clinical endpoint definitions will be included in CEC charter.

5.4.4 Neurocognitive Events

Neurocognitive events will be identified and evaluated by routine safety monitoring of PE findings and AEs. Summarization of neurocognitive events will occur using pre-specified MedDRA terms and will be performed by SOC, severity, and relationship to study drug by previous treatment group in parent study and overall in OLE study.

5.4.5 Laboratory Evaluations

Continuous laboratory parameters (serum chemistry, hematology, coagulation (only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0), urinalysis, urinalysis [microscopic]) listed in Table 2; glucose, and HbA1c will be summarized using descriptive statistics for the observed value and the change from baseline. Missing values for any of the laboratory evaluations will not be imputed; that is, only observed case data will be used. Baseline is defined as the last value prior to the first dose of study medication in OLE study. Categorical urinalysis data will be listed, but will not be summarized.

Table 2: Clinical Laboratory Parameters (Safety)

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; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO2) • Chloride (Cl) • Creatinine • Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total and direct bilirubin (TB)a • Total protein • Uric acid Coagulation—only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0 • Prothrombin time (PT) • International normalized ration (INR)
Urinalysis (Dipstick) • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrate • Occult blood • pH • Protein • Specific gravity • Urobilinogen	
Urinalysis (Microscopic)-only if urine dipstick abnormal • Bacteria • Casts • Crystals • Epithelial cells • RBC • WBC	Other Labs: • Urine pregnancy test • Hemoglobin A_{1C} (HbA_{1C})

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

The number and percentage of patients with laboratory abnormalities (i.e., laboratory values outside the stated laboratory normal range) will be summarized at each time point

(i.e., including baseline and post-baseline time points) for each laboratory parameter. The determination of laboratory abnormalities will take into account any unscheduled laboratory assessments. Additional lab-related summaries will be provided as follows for hepatic safety, musculoskeletal safety, diabetes and glycemia, and renal safety.

5.4.5.1 Hepatic Safety

For liver-associated enzymes and total bilirubin (TB), the number and percent of patients with abnormal values for ALT (>= 3 × ULN, >= 5 × ULN), AST (>= 3 × ULN, >= 5 × ULN), and TB (>= 2×ULN) will be summarized by overall, normal baseline ALT/AST/TB and abnormal baseline ALT/AST/TB.

Hy's law criteria (≥ 3 × upper limit of normal [ULN] for either ALT or AST, with accompanying TB > 2 × ULN, with no other known cause) will also be applied to the data; any potential Hy's law cases will be listed separately. 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.

5.4.5.2 Musculoskeletal Safety

CK levels will be summarized by the value and change from baseline in the value, by treatment group and visit as well as baseline eGFR category. In addition, the number and percent of patients with abnormal CK values (>= 5 X ULN, >= 10 × ULN) will be summarized. These summaries of patients with abnormal CK will be performed overall, normal baseline CK, and abnormal baseline CK.

5.4.5.3 Diabetes and Glycemia

For fasting glucose and HbA1C (%), a shift table from baseline with the number and percent of patients will be categorized as below:

Fasting glucose: >= 126 mg/dL; 100-125 mg/dL, and < 100 mg/dL;
HbA1C (%): >=6.5%; >5.5 to <=6.4% and <=5.5%.

5.4.5.4 Renal Safety

Shift tables of eGFR category from baseline over the study, will be provided by treatment group. If needed, post-baseline eGFR categories will be modified to include the possibility of patients with eGFR values <45 mL/min/1.73m^2 (e.g., including <30 mL/min/1.73m^2 and updating to include moderate renal impairment to 30-59 mL/min/1.73m^2).

In addition, renal function will be categorized as: (1) A creatinine change from baseline of > 1 mg/dL or occurrences of eGFR < 30mg/dL/m^2; (2) A Creatinine change <= 1 mg/dL from baseline ULN or eGFR >= 30 mg/dL/m^2. A shift table from baseline with the number and percent of patients using the two categories will be presented.

Shift tables of urine protein (negative/positive) from baseline over the study, will be provided by treatment group. Values of CK over the study will be summarized by treatment group and by baseline eGFR category. Finally, muscle-related AEs will be summarized by treatment group and by baseline eGFR category.

5.4.6 Physical Examinations (PEs)

Listings of PE data will include only those records where the body system at the baseline PE was normal, but the body system at a post-baseline PE was marked as 'Change from previous exam, clinically significant.' Baseline is defined as the last value prior to the first dose of study medication. Only changes from baseline physical examination findings that meet the definition of an AE will be recorded on the AE page of the eCRF and will be summarized with other AE outcomes.

5.4.7 Vital Signs

Actual values and changes from baseline in vital signs (heart rate, systolic blood pressure, diastolic blood pressure, weight, height [baseline only], and BMI) will be summarized using descriptive statistics by treatment group and post-baseline time point. Baseline is defined as the last value prior to the first dose of study medication.

Vital signs data will be listed for each patient, with increases from baseline of >15 mmHg in systolic or diastolic blood pressure flagged.

5.4.8 Electrocardiogram (ECG)

Shift tables for ECG data from baseline to end-of-study will be provided by treatment group. The data will be categorized as 'Normal'; 'Abnormal, not clinically significant'; and 'Abnormal, clinically significant.' Baseline is defined as the last value prior to the first dose of study medication. Listings of ECG data will include only those records where the baseline ECG was either 'Normal' or 'Abnormal, not clinically significant', but the end-of-study ECG was marked as 'Abnormal, clinically significant'.

6 DMC Analyses

Refer to DMC charter.

7 Reference

1. Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, et al. Atherosclerosis Risk in Communities Study Group. Coronary Heart Disease Prediction from Lipoprotein Cholesterol Levels, Triglycerides, Lipoprotein(A), Apolipoproteins A-I and B, and HDL Density Subfractions. The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2001;104:1108-13.
2. World Health Organization (WHO) Fact Sheet No 317 Updated January 2015.
3. Robinson JG. Management of Familial Hypercholesterolemia: A Review of the recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Managed Care Pharm. 2013;19(2):139-49.

4. Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. FDA Draft Guidance. March 2010
5. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. Curr Opin Lipidol. 2012;23:282-9.
6. Glynn RJ, Laird NM, and Rubin DB. (1986). Selection modelling versus mixture modelling with nonignorable nonresponse. In H. Wainer (ed.), Drawing Inferences from Self-Selected Samples, pp. 115–142. New York: Springer.

8 Appendices

Appendix 1: Schedule of Events (Subject Visit Schedule)

Month	**0**	**3**	**6**	**9**	**12**	**15**	**18/EOS[1]**
Week	**EOS Parent**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**	**Wk 64**	**Wk 78**
Visit Window	**30 Days pre-M0**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**
In-clinic Visit	**X**	**X**			**X**		**X**
Phone Visit			**X**	**X**		**X**	
Procedure							
Informed Consent	X						
Enrollment Criteria	X						
Medical History	X						
Concomitant Medications	X	X	X	X	X	X	X
Adverse Event Recording	X	X	X	X	X	X	X
Physical Exam	X				X		X
Weight[2]	X	X			X		X
Vital Signs[3]	X	X			X		X
Urine Pregnancy Test	X						
Clinical Safety Labs[4]	X	X			X		X
Basic Fasting Lipids[5]	X	X			X		X
Coagulation[6]	X						
ApoB and hsCRP	X	X			X		X
HbA_{1C}	X				X		X
IWRS Contact[7]	X	X			X		X
Drug Dispensing	X	X			X		
Drug Return/Compliance		X			X		X

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visit, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories, adverse events (AEs), physical examination (PE), vital signs, and electrocardiograms (ECGs). For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit week 78 will be considered the End of Study (EOS)/Early Withdrawal from study and no further visits will be scheduled.

1 All procedures will be completed for all patients at either EOS if completing the study or early withdrawal.

2 Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

3 Vital signs will include diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate (HR) and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments

4 Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Please refer to laboratory manual for detailed schedule of tests.

5 Basic fasting lipids include total cholesterol (TC), calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C,), and triglycerides (TG).

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6 Only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0

7 Interactive web response system (IWRS) contact at either an early withdrawal or an EOS visit to register study discontinuation visit date

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Statistical Analysis Plan

Title:	A MULTICENTER OPEN-LABEL EXTENSION (OLE) STUDY TO ASSESS THE LONG-TERM SAFETY AND EFFICACY OF BEMPEDOIC ACID (ETC-1002) 180 MG
Protocol:	ETC-1002-050
Clinical Phase:	3
Product:	ETC-1002
Version (Date):	Statistical Analysis Plan – Version 1.1
Status:	Final

Prepared by:

[redacted] [redacted]
22 Oct 2018 03:08:053+0000
REASON: I approve this document as author.
5e9eb6ba-ac95-46d1-aa92-422b0263855d

[redacted] Date

[redacted] [redacted]
19 Oct 2018 22:43:039+0000
REASON: I have reviewed this document and have no comments that require addressing.
17064876-dedd-4660-9752-8d3bc4287a9e

[redacted] Date

[redacted] [redacted]
22 Oct 2018 14:25:048+0000
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[redacted] Date

Esperion Therapeutics

[redacted] [redacted]
22 Oct 2018 19:07:045+0000
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fdfe4eec-c142-42c7-bf98-459047a30340

[redacted] Date

Esperion Therapeutics

Table of Contents

1 List of Abbreviations

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 diseases
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
AUC_{0-24}	Area under the curve during 24 hours
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CAS	Completer Analysis Set
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
Cl	Chloride
CNS	Central nervous system
CoA	Acetyl-coenzyme A
CO_2	Carbon dioxide
CV	Cardiovascular
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of Study

Abbreviation or Specialist Term	Explanation
ETC-1002	Bempedoic acid
EU	European Union
FDA	Food and Drug Administration
FPFV	First patient first visit
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA_{1C}	Glycosylated hemoglobin, Type A_{1C}
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
Hgb	Hemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IWRS	Interactive web response system
K	Potassium
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LFT	Liver function test
LPLV	Last patient last visit
LS	Least square
MACE	Major adverse cardiac event
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume

Abbreviation or Specialist Term	Explanation
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
Na	Sodium
NA	Not applicable
NLA	National Lipid Association
NOAEL	No-observed-adverse-effect level
non-HDL-C	Non-high-density lipoprotein cholesterol
OLE	Open-label extension (study)
Parent study	Study 1002-040
PCSK9	Proprotein convertase subtilisin/kexin type 9
PE	Physical exam
PK	Pharmacokinetic(s)
PT	Prothrombin time
RBC	Red blood cell
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
SP	Safety population
SUSARS	Suspected and unexpected serious adverse reactions
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TQT	Thorough QT/QTc
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

2 Introduction

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed in ETC-1002-050. The preparation of this statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 Guidelines and in reference to Protocol ETC-1002-050 (Protocol Amendment 2, 10 May 2017).

The SAP will supersede the protocol in the event of any differences between the two documents in the plans for data analysis, and the protocol will be amended if appropriate. The SAP will be included as an appendix in the clinical study report for this protocol.

3 Study Objectives and Endpoints

3.1 Objectives

- The primary objective for this study is to characterize the safety and tolerability of long-term administration of bempedoic acid (ETC-1002) 180 mg

- The secondary objective is to characterize the efficacy of long-term administration of bempedoic acid 180 mg/day as assessed by changes in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol (TC), triglycerides TG and high-sensitivity C-reactive protein (hs-CRP) in patients with hyperlipidemia

3.2 Primary Endpoint

- The primary endpoint for this study is patient incidence of AEs

3.3 Secondary Endpoints

- Percent change from baseline in LDL-C at Weeks 52 and 78
- Change from baseline in LDL-C at Weeks 52 and 78
- Percent change from baseline in non-HDL-C at Weeks 52 and 78
- Percent change from baseline in TC at Weeks 52 and 78
- Percent change from baseline in ApoB at Weeks 52 and 78
- Percent change from baseline in hs-CRP at Weeks 52 and 78
- Percent change from baseline in TG at Weeks 52 and 78
- Percent change from baseline in HDL-C at Weeks 52 and 78

3.3.1 Adverse Events

The evaluation of AEs will include only incidence of treatment-emergent AEs (TEAEs), defined as AEs that begin or worsen on or after the date of first dose of study drug administration in OLE period and until 30 days after last dose of study drug. Clinical endpoints (details see section 4.2) will be collected and adjudicated by an independent Clinical Events Committee (CEC). Clinical endpoints will also be reported as SAEs. Adverse events of special interest (AESI) will further be examined (See Section 5.4.2 for more information).

3.3.2 Clinical Safety Laboratories

The evaluation of clinical safety laboratories, including blood hematology, chemistry, coagulation, and urinalysis, will be based on the observed values. Observed values, changes and percent change from baseline of both the parent study and OLE study will be summarized for all post-baseline study visits.

3.3.3 Vital Signs

The evaluation of vital signs (including heart rate, systolic blood pressure, diastolic blood pressure, height, and weight will be based on the observed values. For vital signs, observed values, and changes from baseline of both the parent study and OLE study will be summarized for all post-baseline study visits.

3.3.4 PE (Physical Exam)

Listings of PE data will include only those records where the body system at the baseline PE was normal, but the body system at a post-baseline PE was marked as 'Change from previous exam, clinically significant.'

3.4 Lipids

After enrollment, patients will return to clinic at week 12, 52, 78/EOT and 82/EOS. Clinical laboratory samples will be collected and analyzed for calculated LDL-C and lipid and cardiometabolic biomarkers including non-HDL-C, HDL-C, TC, ApoB, and TG at baseline and all clinic visits for evaluation of bempedoic acid effects on lipids and cardiometabolic parameters.

3.5 Pharmacokinetic (PK) and Other Biomarkers

NA.

4 Study Design

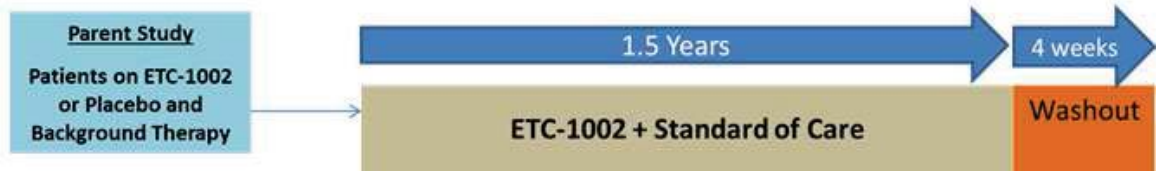
4.1 Study Design

This is a multicenter OLE study designed to assess the long-term safety and efficacy of bempedoic acid (ETC-1002) 180 mg. All patients will receive open-label bempedoic acid 180 mg for up to 1.5 years after rolling over from the parent study (Study 1002-040) followed by a follow-up period off study drug for 4 weeks. Investigators, site staff, patients, and the study team will be masked to study lipid levels until the Week 12 study visit, after which time lipid values will be made available.

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety and efficacy data from this and other ongoing studies of bempedoic acid. A blinded independent expert Clinical Events Committee (CEC) will adjudicate designated clinical endpoints across the program, including all major adverse cardiac events (MACE) and non-MACE endpoints defined as: cardiovascular (CV) death (MACE), non-CV death (non-MACE), nonfatal myocardial infarction [MI] (MACE), nonfatal stroke (MACE), hospitalization for unstable angina (MACE), coronary revascularization (MACE), noncoronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE) using standardized definitions. Any clinical endpoints that meet serious adverse event (SAE) criteria will be reported as SAEs as well as a clinical endpoint.

The study will be conducted at approximately 125 clinical sites in the United States, Canada, Germany, Netherlands, Poland, and United Kingdom. The study will end when the last randomized patient completes their last study visit (last patient last visit [LPLV] for last randomized patient). The estimated overall duration of the study (first patient first visit [FPFV] to LPLV) is approximately 2.5 years.

Figure 1. Study 1002-040 Study Design



4.2 Study Treatments and Assessments

Day 1 for this study should occur on the same day as the end of study visit for the parent study (1002-040). Patients who provide informed consent and sign the ICD will be eligible to enroll in the study.

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

The investigational products were listed in Table 1 below:

Table 1: Investigational Medicinal Products

	Investigational Medicinal Product
Product Name:	Bempedoic acid
Dosage Form:	Film-coated tablets
Unit Dose:	180 mg
Container/Closure[a]	100-count bottle with screw on, child proof cap
Route of Administration:	Oral, daily with or without food
Physical Description:	[redacted]
Manufacturer (Fill/Finish):	

Study drug should be taken once a day (once every 24 hours) at approximately the same time every day and may be taken with or without food. Patients will fast (no food or drink, other than water) for a minimum of 10 hours prior to collection of all laboratory samples.

Please see Pharmacy Manual for detailed storage requirements and instructions.

Patients who withdraw from investigational medicinal product (IMP) treatment will be asked to continue to be followed for safety using the protocol-specified visit schedule and procedures. For details of study assessments, see Appendix 1: Schedule of Events (Subject Visit Schedule).

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety and efficacy data from this and other any ongoing studies of ETC-1002. All clinical endpoints, including all major cardiac events (MACE) and non-MACE endpoints defined as: CV death (MACE), non-CV death (non-MACE), nonfatal myocardial infarction (MI) (MACE), nonfatal stroke (MACE), hospitalization for unstable angina (MACE), coronary revascularization (MACE), non-coronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE), will be adjudicated by an independent blinded expert Clinical Events Committee (CEC), using

standardized definitions. Any clinical endpoints that meet serious adverse event (SAE) criteria will be reported as SAEs.

4.3 Randomization and Blinding

- Randomization is not applicable for this OLE study.
- Laboratory results for lipid panel and hs-CRP will be masked to investigators, patients, and the study team until the Week 12 visit is completed. All site staff involved with this trial should refrain from obtaining lipid panels between date of last study medication (bempedoic acid or placebo) dose at end of parent study Week 52 (Visit T7) and Week 12 in this OLE trial.

4.4 Sample Size Justification

[redacted]

The number of patients entering this study will depend on the number of patients completing Study 1002-040 and their willingness to enroll.

4.5 Interim Analyses, Final Analyses and Unblinding

An interim analysis will be conducted in 2H, 2018 in order to provide safety assessment to support NDA submission. Another interim analysis for Day120 safety update will be approximately 120 days after the NDA cutoff. The endpoints and analyses are the same as the defined in final analysis if applicable.

The final analysis will be performed after the database is locked, and the database released.

4.6 Change from Planned Analyses

There is no change from planned analyses for this study.

5 Statistical and Analytical Plans

5.1 General Statistical Considerations

The treatment groups will be displayed as previous treatment in parent study as well as overall treatment group in OLE study.

In general, all safety and efficacy data will be reported as observed. No imputation will be performed for missing data. Descriptive statistics (n, mean, standard deviation [SD] or Standard Error [SE], median, Q1, Q3, minimum, and maximum) will be calculated for continuous data. Minimum and maximum will be presented same number of decimal places as reported/collected, one additional decimal place for mean and median, and two additional decimal places for SD.

Categorical data will be summarized using n and percentage based on number of non-missing values. Percentage will be presented with one decimal place. The number of missing values will be presented as a separate category with no percentage, but only if 1 or more patients are missing data for the summary. Otherwise, all categories will be presented (even if no patients are counted in the category). Counts of zero in any category will be presented without percentage. Ninety-five percent (95%) confidence intervals (CIs) will be calculated for select continuous and categorical endpoint estimates. All patients will be summarized together as well as by their prior treatment group in the parent study.

Data will be presented on listings in order of patient/subject, assessment date and assessment (in order collected on CRF, unless specified otherwise). Dates will be presented in format DDMMMYYYY.

Relative day calculations will be [date of interest – relative date + (date of interest >= relative date)]. This calculation will result in dates prior to the relative date being presented as negative days, and those occurring on or after the relative date as Day 1 or later, i.e., there will be no Day 0.

Two sets of baseline are defined for any laboratory parameters and vital signs: baseline in parent study (1002-040) and baseline in OLE study (1002-050). The parent baseline values will be directly extracted from parent study database and baseline for the OLE study is defined as the last non-missing value on or prior to the date of first dose in the OLE. If last dose of study treatment is missing, then the date of last visit at which study assessments were obtained on CRF will be used in its place.

The visit schedules and window are shown below.

Visit	Day 1/Week 0	Week 12	Week 24	Week 36	Week 52	Week 64	Week 78/EOT	Week 82/EOS
Month	0	3	6	9	12	15	18/EOT	19/EOS
Slotted Study Week	EOS Parent	Wk 12	Wk 24	Wk 36	Wk 52	Wk 64	Wk 78	Wk 82
Target Study Day	1	84	168	252	364	448	546	574
Analysis Window	1	[2,126]	[127,210]	[211,308]	[309,406]	[407,497]	[498,562]	[563,∞]
Protocol defined visit Windows	[30 Days, Pre M0]	84±7	168±7	252±7	364±7	448±7	546±7	574±14

5.2 Statistical Analysis Plans

5.2.1 Analysis Sets

5.2.1.1 Safety Population (SP)

The Safety Population (SP) is defined as all enrolled patients who received at least 1 dose of bempedoic acid during the OLE period and will be used for demographics and baseline characteristics, treatment exposure, concomitant medications, and all safety summaries.

5.2.1.2 Completer Analysis Set (CAS)

The completer analysis set is defined as patients who completed the full 78 weeks treatment as per end of treatment CRF page.

5.2.2 Protocol Violations and Deviations

A full list of protocol violations and deviations will be compiled and reviewed by the clinical team to identify key versus non-key violations/deviations before final database lock. For violations at study entry, patients will be assessed against the inclusion and exclusion criteria of the protocol. For on-study deviations, compliance with the protocol will be examined with regard to prohibited therapies, and timing and availability of planned assessments. The final list of protocol deviation will be approved by the study team prior to interim analysis cutoff or database lock and will be used to generate the PD deviation summary and listing.

5.2.3 Subject Disposition

The number of patients enrolled, and included in each analysis population, along with IMP and study completion status, will be summarized by the treatment group in parent ETC-1002-040 study and overall. In addition, the number of patients who withdraw from the study and withdraw from study drug will be summarized by discontinuation reason.

5.2.4 Demographic and Baseline Characteristics

Demographic collected from the parent study will be used for this study. Two sets of baseline values will be defined: baseline of parent study and OLE study. The parent study baseline will be taken directly from the parent study, and the OLE baseline is defined as last non-missing value prior to the first dose of IMP in the OLE study. The following demographic and two sets of baseline characteristics will be summarized by previous treatment group in parent study, as well as overall, for safety population:

age group (18-40, 41-64, 65-74, and >=75), gender, race, ethnicity, region (North America, and EU), height (cm), weight (kg), body mass index (kg/m^2) (< 25, 25 - < 30, ≥ 30 kg/ m^2), waist circumference, systolic and diastolic blood pressure, fasting lipid parameters (TC, LDL-C, HDL-C, non-HDL-C and TG), apoB, hs-CRP).

Cardiovascular risk factors from the parent study: ASCVD (Yes/No), HeFH (Yes/No), baseline statin intensity (derived) (low or moderate, high), eGFR category, tobacco history, alcohol history, history of diabetics, history of hypertension.

Data will be summarized using descriptive statistics for continuous variables and using counts and percentages for categorical variables.

The estimated glomerular filtration rate (eGFR) categories are: normal: ≥90 mL/min/1.73m^2; mild Renal Impairment: 60-89 mL/min/1.73m^2; moderate Renal Impairment: 30-59 mL/min/1.73m^2, and severe Renal Impairment (15-29 mL/min/1.73m^2).

5.2.5 Subgroup Variables

Subgroups defined by below variables will be evaluated for safety and the LDL-C efficacy endpoint.

1) Gender (male vs. female)
2) Age (< 65 yrs. vs. ≥65 yrs. and < 75 yrs. vs. ≥ 75 yrs.)
3) Baseline CVD risk category (HeFH (with/without ASCVD) vs. ASCVD only)
4) Baseline statin intensity (low vs. moderate vs. high)
5) Race (White vs. other)
6) Baseline LDL category (< 100 mg/dL vs. ≥100 mg/dL) (efficacy only)
7) History of diabetes (yes vs. no)
8) Body Mass Index (BMI) (< 25, 25 - < 30, ≥ 30 kg/m^2)
9) Region (North America, EU)

In case the number of patients within a subgroup is too small, e.g. less than 5% of the overall population, the analyses may not be performed or the subgroup levels may be combined.

5.2.6 Medical History

General medical history, cardiovascular history/risk factors, previous statin use and statin tolerance history will be summarized by previous treatment group in parent study, as well as overall in OLE study for safety population and presented in a by-patient listing. Where appropriate, terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or later.

If a patient is entering the study beyond the 30 day rollover window, new medical history that occur between more than 30 days after the end of the parent study and treatment start in OLE study (exclusive) that period will be collected and presented in a by-patient listing.

5.2.7 Concomitant Medications

Concomitant medications are defined as medications that were ongoing at the time of study drug initiation in this OLE study or new medications that started post study drug initiation and within 30 days following the date of the last dose of study drug.

Medications, including lipid modifying therapy (LMT) medications, will be coded using WHO Drug (March, 2017, or later if appropriate). The frequency of use of concomitant medications will be summarized by previous treatment group in parent study, as well as overall in OLE study, for the safety population according to Anatomical Therapeutic Chemical (ATC) class and preferred term. Concomitant medications will be listed for each patient. Concomitant LMT medications will be summarized by ATC class and medication name and listed separately in a similar fashion.

5.2.8 Study Drug Exposure and Compliance

The length of exposure to study drug will be calculated as the number of days from the first dose of study drug to the last dose of study drug, regardless if the patient missed one or more doses of study drug. Length of exposure in OLE study will be summarized by previous treatment group in parent study and overall in OLE study using descriptive statistics for the safety population.

The number and percentage of patients who were compliant with taking study drug will be summarized by previous treatment group in parent study and overall in OLE study for the safety population using the following categories 0 - <80%; >= 80%. Overall compliance will be calculated as: 100* (Total Number of Tablets Dispensed – Total Number of Tablets Returned) / (Treatment Duration in Days).

The study drug administration and compliance data, including reasons for poor compliance, will be listed for each patient.

5.3 Efficacy Endpoints and Analyses

Given the primary objective of the study being long term safety, efficacy analyses will be using the safety population (SP). The efficacy data will be summarized by previous treatment group in parent study as well as an overall group.

For each efficacy parameter, descriptive summary statistics at each visit will be provided for the actual value, change from baseline and percent change from baseline for both conventional and International System of Units (SI). Two sets of summaries will be provided using the baseline from the parent study and from the OLE study. The visits to be included in the overtime summary are baseline of parent study (1002-040), baseline of OLE study, week 12, week 52, week 78, and Week 82. There will be no imputation for missing data, all summaries will use observed data. Ninety-five percent (95%) CI will be provided for the estimates at post-baseline visits.

In addition, efficacy parameters will also be summarized using the Completer Analysis Set (CAS).

For LDL-C, Same descriptive summary statistics at each visit will be provided within subgroups for the actual value, change from baseline and percent change from baseline.

Efficacy data (actual value, change and percent change from baseline) from all visits will be presented using descriptive statistics using both conventional and standard units.

Figures (mean+/-se or median/IQR) supporting the summary tables will be provided for each efficacy parameter. Efficacy data from all visits will be provided in listings as well.

5.4 Safety Data Endpoints and Analyses

The safety and tolerability of ETC-1002 will be assessed by examination of TEAEs, physical exams, vital signs, clinical laboratory values (serum chemistry, hematology, coagulation and urinalysis), and weight. SP will be used for all safety analyses.

Unless otherwise stated, descriptive summaries will be displayed by previous treatment group actually received in parent study and overall group.

5.4.1 Adverse Events (AEs)

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or later and will be categorized by system organ class (SOC) and preferred term (PT). Summary tables will focus on TEAEs; however, listings will include all AEs (with non-TEAEs flagged). An additional AE listing will be provided for AEs occurred during rollover period (i.e. after completion of the parent Study, ETC1002-040 but < 30 days prior to providing consent for Study 1002-050.

In summary tables, TEAEs will be counted as “Not Related” if relationship to study drug was recorded as ‘Not Related’ or “Unlikely”. Events will be counted as “Related” if relationship to study drug was recorded as ‘Possible’, ‘Probable’, ‘Definite’ or if relationship to study drug is missing.

The severity of the AE will be characterized as mild, moderate, or severe, 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

Overviews of TEAEs will include total number of TEAEs and patient incidence of TEAE, TE SAE, related TEAE, related TE SAE, withdrew due to TEAE, AE with fatal outcome. Individual TEAE summary will be presented by previous treatment group in parent study and overall containing the following counts and percentages for:

- patients with TEAEs
- patients with TEAE by PT
- patients with TEAEs by SOC, PT and maximum severity
- patients with treatment-related TEAEs
- patients with treatment-related TEAEs by PT
- patients with treatment-related TEAEs by SOC and PT
- patients with treatment-emergent serious adverse events (TE SAEs)
- patients with TE SAEs by PT
- patients with TE SAEs by SOC, PT and maximum severity
- patients with treatment-related TE SAEs
- patients with treatment-related TE SAEs by SOC and PT
- TEAEs leading to discontinuation of IMP
- Fatal AEs by SOC and PT

In addition, summary tables will be provided, by prior treatment group and overall, for the number and percent of patients experiencing:

- adjudicated major adverse cardiovascular events and mortality (MACE) by event type
- non-CV deaths (non-MACE),
- nonfatal myocardial infarction [MI] (MACE),
- nonfatal stroke (MACE),
- hospitalization for unstable angina (MACE),
- coronary revascularization (MACE),
- noncoronary arterial revascularization (non-MACE),
- hospitalization for heart failure (non-MACE) using standardized definitions.

The TEAE, related TEAE, TE SAE, and AESI summaries by SOC, PT and maximum severity will be provided for relevant subgroups described in 5.2.5 with the exception of baseline LDL category.

The AE overview summaries will count a patient at most once in each AE category (at the "highest/most extreme" designation of each category regardless of preferred term) and percentages will be based on the total number of patients in the safety population.

In addition to a comprehensive listing of all AEs (with non-TEAEs flagged), separate listings will be generated for SAEs, AEs resulting in withdrawal of study drug, and AEs with a fatal

outcome, investigator reported major adverse cardiovascular events and mortality, and adjudicated major adverse cardiovascular events and mortality.

5.4.2 Adverse Events of Special Interest

Adverse events of special interest (AESI) will be identified based a pre-defined list of preferred terms provided by the sponsor (Appendix 2).

AESI will be presented in a listing and summarized by SOC, PT and previous treatment group in parent study and overall in OLE study.

In addition to adverse events, AESI is also being evaluated based on safety lab parameters. The details are provided in 5.4.5.

5.4.3 Clinical Cardiovascular Endpoints

Clinical cardiovascular endpoints will be monitored and adjudicated by an independent blinded expert CEC for this study and other ongoing studies the ETC-1002 program. Positively adjudicated clinical endpoints that are treatment-emergent will be summarized by event type and previous treatment group in parent study and overall in OLE study. All events that were adjudicated will be provided in a listing. Additional details regarding clinical endpoints and clinical endpoint definitions will be included in CEC charter.

5.4.4 Neurocognitive Events

Neurocognitive events will be identified and evaluated by routine safety monitoring of PE findings and AEs. Summarization of neurocognitive events will occur using pre-specified MedDRA terms and will be performed by SOC, severity, and relationship to study drug by previous treatment group in parent study and overall in OLE study.

5.4.5 Laboratory Evaluations

Two sets of baseline for safety parameters are defined, similar to that for the efficacy parameters, baseline from the parent study and the baseline from the OLE study.

Continuous laboratory parameters (serum chemistry, hematology, coagulation (only for those patients receiving anti-coagulation), urinalysis, urinalysis [microscopic]) listed in Table 4 will be summarized using descriptive statistics at each scheduled visit starting from the baseline of the parent study. The similar on-treatment and completer analysis set approach for efficacy analysis described in section 5.3 will be used for safety laboratory analysis. All analysis will use conventional unit and SI unit will be provided for selected parameters.

Fasting serum glucose and HbA1c will be summarized using descriptive statistics for the observed value and the change, percent change from baseline by history of diabetics. Missing

values for any of the laboratory evaluations will not be imputed; that is, only observed case data will be used.

Categorical urinalysis data will be listed, but will not be summarized.

As part of the AESI evaluation, below safety lab abnormality will be summarized by treatment group. All post-baseline lab values during the on-treatment period are being considered. Further details are provided in Section 5.4.6.1 through 5.4.6.4.

- ALT or AST (> 3x ULN and >5xULN)
- TB (> 2x ULN)
- Potential Hy's Law case: (ALT and/or AST > 3xULN with concurrent TB > 2xULN)
- CK (> 5x ULN) and (>10x ULN)
- Fasting Serum Glucose (mg/dL) (≤50, and ≥126) by history of diabetics
- HbA1C (≥6.5%) by history of diabetics
- Creatinine (change from baseline for >1 mg/dL)
- eGFR (< 15 mL/min/1.73m2, 15 –< 30 mL/min/1.73m2)
- Hgb (g/dL) (decrease from baseline for ≥2 g/dL)
- Hgb (<8 g/dL)

Table 2: Clinical Laboratory Parameters (Safety)

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 %)	<u>Blood Chemistry (serum, fasting)</u> • Albumin (Alb) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO2) • Chloride (Cl) • Creatinine • Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total and direct bilirubin (TB)a • Total protein • Uric acid <u>Coagulation</u>—only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0 • Prothrombin time (PT) • International normalized ration (INR)
<u>Urinalysis (Dipstick)</u> • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrate • Occult blood • pH • Protein • Specific gravity • Urobilinogen	
<u>Urinalysis (Microscopic)-only if urine dipstick abnormal</u> • Bacteria • Casts • Crystals • Epithelial cells • RBC • WBC	<u>Other Labs:</u> • Urine pregnancy test • Hemoglobin A_{1C} (HbA_{1C})

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

The number and percentage of patients with laboratory abnormalities (i.e., laboratory values outside the stated laboratory normal range) will be summarized at each time point (i.e., including baseline and post-baseline time points) for each laboratory parameter. The determination of laboratory abnormalities will take into account any unscheduled laboratory assessments. Additional lab-related summaries will be provided as follows for hepatic safety, musculoskeletal safety, diabetes and glycemia, and renal safety.

5.4.5.1 Hepatic Safety

For liver-associated enzymes and total bilirubin (TB), the number and percent of patients with abnormal values for ALT (>3 × ULN, > 5 × ULN), AST (> 3 × ULN, > 5 × ULN), and TB (> 2×ULN) will be summarized by overall, normal baseline ALT/AST/TB and abnormal baseline ALT/AST/TB.

Hy's law criteria (>3 × upper limit of normal [ULN] for either ALT or AST, with accompanying TB > 2 × ULN) will also be applied to the data; any potential Hy's law cases will be listed separately. 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.

A separate listing for direct TB will be provided for those who have Gilbert's syndrome.

5.4.5.2 Musculoskeletal Safety

CK levels will be summarized by the value and change from baseline in the value, by treatment group and visit as well as baseline eGFR category. In addition, the number and percent of patients with abnormal CK values (>5 X ULN, >10 × ULN) will be summarized. These summaries of patients with abnormal CK will be performed overall, normal baseline CK, and abnormal baseline CK.

5.4.5.3 Diabetes and Glycemia

For fasting glucose and HbA1C (%), a shift table from baseline of both parent study and OLE study with the number and percent of patients will be categorized as below:

Fasting glucose: >= 126 mg/dL; 100-125 mg/dL, and < 100 mg/dL;
HbA1C (%): >=6.5%; >5.5 to <=6.4% and <=5.5%.

These tables will be summarized by history of Diabetes.

Descriptive summary for fasting serum glucose and HbA1C will be provided by history of diabetics, previous treatment group in parent study and overall at each scheduled visit.

5.4.5.4 Renal Safety

Shift tables of eGFR category from baseline of both parent study and OLE study over the study, will be provided by previous treatment group in parent study and overall.

In addition, renal function abnormality will be identified as: (1) A creatinine change from baseline of > 1 mg/dL (2) eGFR value <30 mL/min/1.73m2. A shift table from baseline of both parent study and OLE study with the number and percent of patients using the two categories will be presented.

5.4.6 Physical Examinations (PEs)

Listings of PE data will include only those records where the body system at the baseline PE was normal, but the body system at a post-baseline PE was marked as 'Change from previous exam, clinically significant'. Baseline is defined as the last value prior to the first dose of study medication in OLE study. Only changes from baseline physical examination findings that meet the definition of an AE will be recorded on the AE page of the eCRF and will be summarized with other AE outcomes.

5.4.7 Vital Signs

Actual values and changes from baseline of both parent study and OLE study in vital signs (heart rate, systolic blood pressure, diastolic blood pressure, weight, height [baseline only], and BMI) will be summarized using descriptive statistics by previous treatment group in parent study, overall and post-baseline time point.

Vital signs data will be listed for each patient, with increases from baseline of >15 mmHg in systolic or diastolic blood pressure flagged.

6 DMC Analyses

Refer to DMC charter.

7 Reference

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2. World Health Organization (WHO) Fact Sheet No 317 Updated January 2015.
3. Robinson JG. Management of Familial Hypercholesterolemia: A Review of the recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Managed Care Pharm. 2013;19(2):139-49.

4. Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. FDA Draft Guidance. March 2010
5. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. Curr Opin Lipidol. 2012;23:282-9.
6. Glynn RJ, Laird NM, and Rubin DB. (1986). Selection modelling versus mixture modelling with nonignorable nonresponse. In H. Wainer (ed.), Drawing Inferences from Self-Selected Samples, pp. 115–142. New York: Springer.

8 Appendices

8.1 Appendix 1: Schedule of Events (Subject Visit Schedule)

Month	**0**	**3**	**6**	**9**	**12**	**15**	**18/EOT[1]**	**19/EOS[2]**
Week	**EOS Parent**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**	**Wk 64**	**Wk 78**	**Wk 82**
Visit Window	**30 Days pre-M0**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**+14 days**
In-clinic Visit	**X**	**X**			**X**		**X**	**X**
Phone Visit			**X**	**X**		**X**		
Procedure								
Informed Consent	X							
Enrollment Criteria	X							
Medical History	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording	X	X	X	X	X	X	X	X
Physical Exam	X				X		X	
Weight[3]	X	X			X		X	X
Vital Signs[4]	X	X			X		X	X
Urine Pregnancy Test[5]	X							
Clinical Safety Labs[6]	X	X			X		X	X
Basic Fasting Lipids[7]	X	X			X		X	X
Coagulation[8]	X							
ApoB and hsCRP	X	X			X		X	X
HbA_{1C}	X				X		X	X
IWRS Contact[9]	X	X			X		X	
Drug Dispensing	X	X			X			
Drug Return/ Compliance		X			X		X	

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visit, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories, adverse events (AEs), physical examination (PE), and vital signs. For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit Week 78/End of Treatment (EOT) will be scheduled as soon as possible and the patient will be asked to come back 4 weeks after last investigational medicinal product (IMP) dose for Visit Week 82/End of Study (EOS). No further visits will be scheduled.

[1] All procedures will be completed for all patients at either EOT or early withdrawal.

[2] All procedures will be completed for all patients 4 weeks after last IMP dose if completing the study or early withdrawal.

[3] Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

[4] Vital signs will include diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate (HR) and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments
[5] Urine pregnancy test in women of childbearing potential only
[6] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Please refer to laboratory manual for detailed schedule of tests.
[7] Basic fasting lipids include total cholesterol (TC), calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C,), and triglycerides (TG).
[8] Only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0
[9] Interactive web response system (IWRS) contact at either an early withdrawal or an EOS visit to register study discontinuation visit date

8.2 Appendix 2: Adverse Event of Special Interest (AESI)

Adverse Event Terms per Protocol	Associated MedDRA Preferred Terms
Creatine kinase elevations	Blood creatine phosphokinase abnormal
Creatine kinase elevations	Blood creatine phosphokinase increased
Creatine kinase elevations	Blood creatine phosphokinase MM abnormal
Creatine kinase elevations	Blood creatine phosphokinase MM increased
New onset or worsening diabetes mellitus	Blood glucose abnormal
New onset or worsening diabetes mellitus	Blood glucose increased
New onset or worsening diabetes mellitus	Diabetes mellitus
New onset or worsening diabetes mellitus	Diabetes mellitus inadequate control
New onset or worsening diabetes mellitus	Diabetic ketoacidosis
New onset or worsening diabetes mellitus	Glucose tolerance impaired
New onset or worsening diabetes mellitus	Glucose urine present
New onset or worsening diabetes mellitus	Glycosuria
New onset or worsening diabetes mellitus	Glycosylated haemoglobin increased
New onset or worsening diabetes mellitus	Hyperglycaemia
New onset or worsening diabetes mellitus	Impaired fasting glucose
New onset or worsening diabetes mellitus	Ketoacidosis
New onset or worsening diabetes mellitus	Ketosuria
New onset or worsening diabetes mellitus	Ketosis
New onset or worsening diabetes mellitus	Type 2 diabetes mellitus
New onset or worsening diabetes mellitus	Urine ketone body present
Hepatic disorders	Alanine aminotransferase abnormal
Hepatic disorders	Alanine aminotransferase increased
Hepatic disorders	Aspartate aminotransferase abnormal
Hepatic disorders	Aspartate aminotransferase increased
Hepatic disorders	Blood bilirubin abnormal
Hepatic disorders	Blood bilirubin increased
Hepatic disorders	Hepatic enzyme abnormal
Hepatic disorders	Hepatic enzyme increased
Hepatic disorders	Hypertransaminaseaemia
Hepatic disorders	Liver function test abnormal
Hepatic disorders	Liver function test increased
Hepatic disorders	Transaminases abnormal
Hepatic disorders	Transaminases increased
Hypoglycemia	Blood glucose abnormal
Hypoglycemia	Blood glucose decreased
Hypoglycemia	Hypoglycaemia
Hypoglycemia	Hypoglycaemic coma
Hypoglycemia	Hypoglycaemic encephalopathy
Hypoglycemia	Hypoglycaemic seizure
Hypoglycemia	Shock hypoglycaemic
Metabolic acidosis	Metabolic acidosis
Muscular disorders	Muscular weakness
Muscular disorders	Muscle necrosis

Muscular disorders	Muscle spasms
Muscular disorders	Myalgia
Muscular disorders	Myoglobin blood increased
Muscular disorders	Myoglobin blood present
Muscular disorders	Myoglobin urine present
Muscular disorders	Myoglobinaemia
Muscular disorders	Myoglininuria
Muscular disorders	Myopathy
Muscular disorders	Myopathy toxic
Muscular disorders	Necrotizing myositis
Muscular disorders	Pain in extremity
Muscular disorders	Rhabdomyolysis
Neurocognitive/Neurologic disorders	Amnesia
Neurocognitive/Neurologic disorders	Cognitive disorder
Neurocognitive/Neurologic disorders	Confusional state
Neurocognitive/Neurologic disorders	Disorientation
Neurocognitive/Neurologic disorders	Memory impairment
Neurocognitive/Neurologic disorders	Mental status changes
Renal disorders	Acute kidney injury
Renal disorders	Acute prerenal failure
Renal disorders	Blood creatinine abnormal
Renal disorders	Blood creatinine increased
Renal disorders	Blood urea abnormal
Renal disorders	Blood urea increased
Renal disorders	Blood urea nitrogen/Creatinine ratio increased
Renal disorders	Creatinine renal clearance abnormal
Renal disorders	Creatinine renal clearance decreased
Renal disorders	Glomerular filtration rate abnormal
Renal disorders	Glomerular filtration rate decreased
Renal disorders	Gout
Renal disorders	Oliguria
Renal disorders	Prerenal failure
Renal disorders	Renal failure
Renal disorders	Renal function test abnormal
Renal disorders	Renal impairment

Statistical Analysis Plan

Title: A MULTICENTER OPEN-LABEL EXTENSION (OLE) STUDY TO ASSESS THE LONG-TERM SAFETY AND EFFICACY OF BEMPEDOIC ACID (ETC-1002) 180 MG
Protocol: ETC-1002-050
Clinical Phase: 3
Product: ETC-1002
Version (Date): Statistical Analysis Plan – Version 1.2
Status: Final

Prepared by:

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Esperion Therapeutics

Table of Contents

1 List of Abbreviations

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 diseases
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
AUC_{0-24}	Area under the curve during 24 hours
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CAS	Completer Analysis Set
CEC	Clinical Event Committee
CFR	Code of Federal Regulations
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
Cl	Chloride
CNS	Central nervous system
CoA	Acetyl-coenzyme A
CO_2	Carbon dioxide
CV	Cardiovascular
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate

Abbreviation or Specialist Term	Explanation
EMA	European Medicines Agency
EOS	End of Study
ETC-1002	Bempedoic acid
EU	European Union
FDA	Food and Drug Administration
FPFV	First patient first visit
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA_{1C}	Glycosylated hemoglobin, Type A_{1C}
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
Hgb	Hemoglobin
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug Application
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intention-to-treat
IUD	Intrauterine device
IWRS	Interactive web response system
K	Potassium
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LFT	Liver function test
LPLV	Last patient last visit
LS	Least square
MACE	Major adverse cardiac event
MCH	Mean corpuscular hemoglobin

Abbreviation or Specialist Term	Explanation
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
MRI	Magnetic resonance imaging
Na	Sodium
NA	Not applicable
NLA	National Lipid Association
NOAEL	No-observed-adverse-effect level
non-HDL-C	Non-high-density lipoprotein cholesterol
OLE	Open-label extension (study)
Parent study	Study 1002-040
PCSK9	Proprotein convertase subtilisin/kexin type 9
PE	Physical exam
PK	Pharmacokinetic(s)
PT	Prothrombin time
RBC	Red blood cell
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
SP	Safety population
SUSARS	Suspected and unexpected serious adverse reactions
T2DM	Type 2 diabetes mellitus
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TQT	Thorough QT/QTc
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

2 Introduction

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed in ETC-1002-050. The preparation of this statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 Guidelines and in reference to Protocol ETC-1002-050 (Protocol Amendment 2, 10 May 2017).

The SAP will supersede the protocol in the event of any differences between the two documents in the plans for data analysis, and the protocol will be amended if appropriate. The SAP will be included as an appendix in the clinical study report for this protocol.

3 Study Objectives and Endpoints

3.1 Objectives

- The primary objective for this study is to characterize the safety and tolerability of long-term administration of bempedoic acid (ETC-1002) 180 mg

- The secondary objective is to characterize the efficacy of long-term administration of bempedoic acid 180 mg/day as assessed by changes in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol (TC), triglycerides TG and high-sensitivity C-reactive protein (hs-CRP) in patients with hyperlipidemia

3.2 Primary Endpoint

- The primary endpoint for this study is patient incidence of AEs

3.3 Secondary Endpoints

- Percent change from baseline in LDL-C at Weeks 52 and 78
- Change from baseline in LDL-C at Weeks 52 and 78
- Percent change from baseline in non-HDL-C at Weeks 52 and 78
- Percent change from baseline in TC at Weeks 52 and 78
- Percent change from baseline in ApoB at Weeks 52 and 78
- Percent change from baseline in hs-CRP at Weeks 52 and 78
- Percent change from baseline in TG at Weeks 52 and 78

- Percent change from baseline in HDL-C at Weeks 52 and 78

3.3.1 Adverse Events

The evaluation of AEs will include only incidence of treatment-emergent AEs (TEAEs), defined as AEs that begin or worsen on or after the date of first dose of study drug administration in OLE period and until 30 days after last dose of study drug. Clinical endpoints (details see section 4.2) will be collected and adjudicated by an independent Clinical Events Committee (CEC). Clinical endpoints will also be reported as SAEs. Adverse events of special interest (AESI) will further be examined (See Section 5.4.2 for more information).

3.3.2 Clinical Safety Laboratories

The evaluation of clinical safety laboratories, including blood hematology, chemistry, coagulation, and urinalysis, will be based on the observed values. Observed values, changes and percent change from baseline of both the parent study and OLE study will be summarized for all post-baseline study visits.

3.3.3 Vital Signs

The evaluation of vital signs (including heart rate, systolic blood pressure, diastolic blood pressure, height, and weight will be based on the observed values. For vital signs, observed values, and changes from baseline of both the parent study and OLE study will be summarized for all post-baseline study visits.

3.3.4 PE

Listings of PE data will include only those records where the body system at the baseline PE was normal, but the body system at a post-baseline PE was marked as 'Change from previous exam, clinically significant.'

3.4 Lipids

After enrollment, patients will return to clinic at week 12, 52, 78/EOT and 82/EOS. Clinical laboratory samples will be collected and analyzed for calculated LDL-C and lipid and cardiometabolic biomarkers including non-HDL-C, HDL-C, TC, ApoB, and TG at baseline and all clinic visits for evaluation of bempedoic acid effects on lipids and cardiometabolic parameters.

3.5 Pharmacokinetic (PK) and Other Biomarkers

NA.

4 Study Design

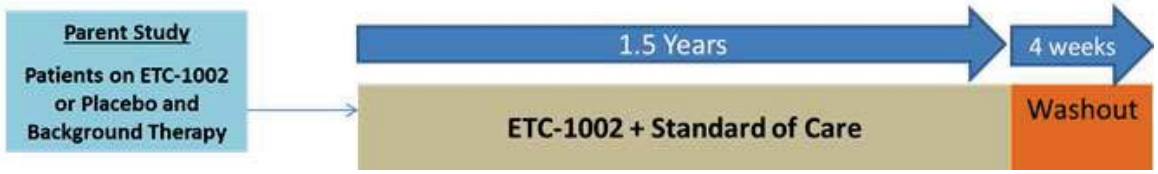
4.1 Study Design

This is a multicenter OLE study designed to assess the long-term safety and efficacy of bempedoic acid (ETC-1002) 180 mg. All patients will receive open-label bempedoic acid 180 mg for up to 1.5 years after rolling over from the parent study (Study 1002-040) followed by a follow-up period off study drug for 4 weeks. Investigators, site staff, patients, and the study team will be masked to study lipid levels until the Week 12 study visit, after which time lipid values will be made available.

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety and efficacy data from this and other ongoing studies of bempedoic acid. A blinded independent expert Clinical Events Committee (CEC) will adjudicate designated clinical endpoints across the program, including all major adverse cardiac events (MACE) and non-MACE endpoints defined as: cardiovascular (CV) death (MACE), non-CV death (non-MACE), nonfatal myocardial infarction [MI] (MACE), nonfatal stroke (MACE), hospitalization for unstable angina (MACE), coronary revascularization (MACE), noncoronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE) using standardized definitions. Any clinical endpoints that meet serious adverse event (SAE) criteria will be reported as SAEs as well as a clinical endpoint.

The study will be conducted at approximately 125 clinical sites in the United States, Canada, Germany, Netherlands, Poland, and United Kingdom. The study will end when the last randomized patient completes their last study visit (last patient last visit [LPLV] for last randomized patient). The estimated overall duration of the study (first patient first visit [FPFV] to LPLV) is approximately 2.5 years.

Figure 1. Study 1002-040 Study Design



4.2 Study Treatments and Assessments

Day 1 for this study should occur on the same day as the end of study visit for the parent study (1002-040). Patients who provide informed consent and sign the ICD will be eligible to enroll in the study.

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

The investigational products were listed in Table 1 below:

Table 1: Investigational Medicinal Products

	Investigational Medicinal Product
Product Name:	Bempedoic acid
Dosage Form:	Film-coated tablets
Unit Dose:	180 mg
Container/Closure[a]	100-count bottle with screw on, child proof cap
Route of Administration:	Oral, daily with or without food
Physical Description:	[redacted]
Manufacturer (Fill/Finish):	

Study drug should be taken once a day (once every 24 hours) at approximately the same time every day and may be taken with or without food. Patients will fast (no food or drink, other than water) for a minimum of 10 hours prior to collection of all laboratory samples.

Please see Pharmacy Manual for detailed storage requirements and instructions.

Patients who withdraw from investigational medicinal product (IMP) treatment will be asked to continue to be followed for safety using the protocol-specified visit schedule and procedures. For details of study assessments, see Appendix 1: Schedule of Events (Subject Visit Schedule).

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety and efficacy data from this and other any ongoing studies of ETC-1002. All clinical endpoints, including all major cardiac events (MACE) and non-MACE endpoints defined as: CV death (MACE), non-CV death (non-MACE), nonfatal myocardial infarction (MI) (MACE), nonfatal stroke (MACE), hospitalization for unstable angina (MACE), coronary revascularization (MACE), non-coronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE), will be adjudicated by an independent blinded expert Clinical Events Committee (CEC), using

standardized definitions. Any clinical endpoints that meet serious adverse event (SAE) criteria will be reported as SAEs.

4.3 Randomization and Blinding

- Randomization is not applicable for this OLE study.
- Laboratory results for lipid panel and hs-CRP will be masked to investigators, patients, and the study team until the Week 12 visit is completed. All site staff involved with this trial should refrain from obtaining lipid panels between date of last study medication (bempedoic acid or placebo) dose at end of parent study Week 52 (Visit T7) and Week 12 in this OLE trial.

4.4 Sample Size Justification

[redacted]

The number of patients entering this study will depend on the number of patients completing Study 1002-040 and their willingness to enroll.

4.5 Interim Analyses, Final Analyses and Unblinding

An interim analysis will be conducted in 2H, 2018 in order to provide safety assessment to support NDA submission. Another interim analysis for Day120 safety update will be approximately 120 days after the NDA cutoff. The endpoints and analyses are the same as the defined in final analysis if applicable.

The final analysis will be performed after the database is locked, and the database released.

4.6 Change from Planned Analyses

There is no change from planned analyses for this study.

5 Statistical and Analytical Plans

5.1 General Statistical Considerations

The treatment groups will be displayed as previous treatment in parent study as well as overall treatment group in OLE study.

In general, all safety and efficacy data will be reported as observed. No imputation will be performed for missing data. Descriptive statistics (n, mean, standard deviation [SD] or Standard Error [SE], median, Q1, Q3, minimum, and maximum) will be calculated for continuous data. Minimum and maximum will be presented same number of decimal places as reported/collected, one additional decimal place for mean and median, and two additional decimal places for SD.

Categorical data will be summarized using n and percentage based on number of non-missing values. Percentage will be presented with one decimal place. The number of missing values will be presented as a separate category with no percentage, but only if 1 or more patients are missing data for the summary. Otherwise, all categories will be presented (even if no patients are counted in the category). Counts of zero in any category will be presented without percentage. Ninety-five percent (95%) confidence intervals (CIs) will be calculated for select continuous and categorical endpoint estimates. All patients will be summarized together as well as by their prior treatment group in the parent study.

Data will be presented on listings in order of patient/subject, assessment date and assessment (in order collected on CRF, unless specified otherwise). Dates will be presented in format DDMMMYYYY.

Relative day calculations will be [date of interest – relative date + (date of interest >= relative date)]. This calculation will result in dates prior to the relative date being presented as negative days, and those occurring on or after the relative date as Day 1 or later, i.e., there will be no Day 0.

Two sets of baseline are defined for any laboratory parameters and vital signs: baseline in parent study (1002-040) and baseline in OLE study (1002-050). The parent baseline values will be directly extracted from parent study database and baseline for the OLE study is defined as the last non-missing value on or prior to the date of first dose in the OLE. If last dose of study treatment is missing, then the date of last visit at which study assessments were obtained on CRF will be used in its place.

The visit schedules and window are shown below.

Visit	Day 1/Week 0	Week 12	Week 24	Week 36	Week 52	Week 64	Week 78/EOT	Week 82/EOS
Month	0	3	6	9	12	15	18/EOT	19/EOS
Slotted Study Week	EOS Parent	Wk 12	Wk 24	Wk 36	Wk 52	Wk 64	Wk 78	Wk 82
Target Study Day	1	84	168	252	364	448	546	574
Analysis Window	1	[2,126]	[127,210]	[211,308]	[309,406]	[407,497]	[498,562]	[563,∞]
Protocol defined visit Windows	[30 Days, Pre M0]	84±7	168±7	252±7	364±7	448±7	546±7	574±14

5.2 Statistical Analysis Plans

5.2.1 Analysis Sets

5.2.1.1 Safety Population (SP)

The Safety Population (SP) is defined as all enrolled patients who received at least 1 dose of bempedoic acid during the OLE period and will be used for demographics and baseline characteristics, treatment exposure, concomitant medications, and all safety summaries.

5.2.1.2 Completer Analysis Set (CAS)

The completer analysis set is defined as patients who completed the full 78 weeks treatment as per end of treatment CRF page.

5.2.2 Protocol Violations and Deviations

A full list of protocol violations and deviations will be compiled and reviewed by the clinical team to identify key versus non-key violations/deviations before final database lock. For violations at study entry, patients will be assessed against the inclusion and exclusion criteria of the protocol. For on-study deviations, compliance with the protocol will be examined with regard to prohibited therapies, and timing and availability of planned assessments. The final list of protocol deviation will be approved by the study team prior to interim analysis cut of or database lock and will be used to generate the PD deviation summary and listing.

5.2.3 Subject Disposition

The number of patients enrolled, and included in each analysis population, along with IMP and study completion status, will be summarized by the treatment group in parent ETC-1002-040 study and overall. In addition, the number of patients who withdraw from the study and withdraw from study drug will be summarized by discontinuation reason.

5.2.4 Demographic and Baseline Characteristics

Demographic collected from the parent study will be used for this study. Two sets of baseline values will be defined: baseline of parent study and OLE study. The parent study baseline will be taken directly from the parent study, and the OLE baseline is defined as last non-missing value prior to the first dose of IMP in the OLE study. The following demographic and both baseline characteristics will be summarized by previous treatment group in parent study, as well as overall, for safety population:

age group (18-40, 41-64, 65-74, and >=75), gender, race, ethnicity, region (North America, and EU), height (cm), weight (kg), body mass index (kg/m^2) (< 25, 25 - < 30, ≥ 30 kg/ m^2), waist circumference, systolic and diastolic blood pressure, fasting lipid parameters (TC, LDL-C, HDL-C, non-HDL-C and TG), apoB, hs-CRP).

Cardiovascular risk factors from the parent study: ASCVD (Yes/No), HeFH (Yes/No), baseline statin intensity (derived) (low or moderate, high), eGFR category, tobacco history, alcohol history, history of diabetics, history of hypertension.

Data will be summarized using descriptive statistics for continuous variables and using counts and percentages for categorical variables by treatment group and overall.

The baseline estimated glomerular filtration rate (eGFR) categories are: normal: ≥90 mL/min/1.73m^2; mild Renal Impairment: 60-89 mL/min/1.73m^2; moderate Renal Impairment: 30-59 mL/min/1.73m^2, and severe Renal Impairment (15-29 mL/min/1.73m^2).

5.2.5 Subgroup Variables

Subgroups defined by below variables will be evaluated for safety and the LDL-C efficacy endpoint.

1) Gender (male vs. female)
2) Age (< 65 yrs. vs. ≥ 65 yrs. and < 75 yrs. vs. ≥ 75 yrs.)
3) Baseline CVD risk category (HeFH (with/without ASCVD) vs. ASCVD only)
4) Baseline statin intensity (low vs. moderate vs. high)
5) Race (White vs. other)
6) Baseline LDL category (< 100 mg/dL vs. ≥100 mg/dL) (efficacy only)
7) History of diabetes (yes vs. no)
8) Body Mass Index (BMI) (< 25, 25 - < 30, ≥ 30 kg/m^2)
9) Region (North America, EU)

In case the number of patients within a subgroup is too small, e.g. less than 5% of the overall population, the analyses may not be performed or the subgroup levels may be combined.

5.2.6 Medical History

General medical history, cardiovascular history/risk factors, previous statin use and statin tolerance history will be summarized by previous treatment group in parent study, as well as overall in OLE study for safety population and presented in a by-patient listing. Where appropriate, terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or later.

If a patient is entering the study beyond the 30 day rollover window, new medical history that occur between more than 30 days after the end of the parent study and treatment start in OLE study (exclusive) that period will be collected and presented in a by-patient listing.

5.2.7 Concomitant Medications

Concomitant medications are defined as medications that were ongoing at the time of study drug initiation in this OLE study or new medications that started post study drug initiation and within 30 days following the date of the last dose of study drug.

Medications, including lipid modifying therapy (LMT) medications, will be coded using WHO Drug (March, 2017, or later if appropriate). The frequency of use of concomitant medications will be summarized by previous treatment group in parent study, as well as overall in OLE study, for the safety population according to Anatomical Therapeutic Chemical (ATC) class and preferred term. Concomitant medications will be listed for each patient. Concomitant LMT medications will be summarized by ATC class and medication name and listed separately in a similar fashion.

5.2.8 Study Drug Exposure and Compliance

The length of exposure to study drug will be calculated as the number of days from the first dose of study drug to the last dose of study drug, regardless if the patient missed one or more doses of study drug. Length of exposure will be summarized by previous treatment group in parent study and overall in OLE study using descriptive statistics for the safety population.

The number and percentage of patients who were compliant with taking study drug will be summarized by previous treatment group in parent study and overall in OLE study and post-baseline time point for the safety population for the following categories 0 - <80%; >= 80%. Overall compliance will be calculated as: 100* (Total Number of Tablets Dispensed – Total Number of Tablets Returned) / (Treatment Duration in Days).

The study drug administration and compliance data, including reasons for poor compliance, will be listed for each patient.

5.3 Efficacy Endpoints and Analyses

Given the primary objective of the study being long term safety, efficacy analyses will be using the safety population (SP). The efficacy data will be summarized by previous treatment group in parent study as well as an overall group.

For each efficacy parameter, descriptive summary statistics at each visit will be provided for the actual value, change from baseline and percent change from baseline for both conventional and International System of Units (SI). Two sets of summaries will be provided using the baseline from the parent study and from the OLE study. The visits to be included in the overtime summary are baseline of parent study (1002-040), baseline of OLE study, week 12, week 52, week 78, and Week 82. There will be no imputation for missing data, all summaries will use observed data. Ninety-five percent (95%) CI will be provided for the estimates at post-baseline visits.

In addition, efficacy parameters will also be summarized using the Completer Analysis Set (CAS).

For LDL-C, Same descriptive summary statistics at each visit will be provided within subgroups for the actual value, change from baseline and percent change from baseline.

Efficacy data (actual value, change and percent change from baseline) from all visits will be presented using descriptive statistics using both conventional and standard units.

Figures (mean+/-se or median/IQR) supporting the summary tables will be provided for each efficacy parameter. Efficacy data from all visits will be provided in listings as well.

5.4 Safety Data Endpoints and Analyses

The safety and tolerability of ETC-1002 will be assessed by examination of TEAEs, physical exams, vital signs, clinical laboratory values (serum chemistry, hematology, coagulation and urinalysis), and weight. SP will be used for all safety analyses.

Unless otherwise stated, descriptive summaries will be displayed by previous treatment group actually received in parent study and overall group.

5.4.1 Adverse Events (AEs)

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or later and will be categorized by system organ class (SOC) and preferred term (PT). Summary tables will focus on TEAEs; however, listings will include all AEs (with non-TEAEs flagged). An additional AE listing will be provided for AEs occurred during rollover period.

In summary tables, TEAEs will be counted as “Not Related” if relationship to study drug was recorded as ‘Not Related’ or “Unlikely”. Events will be counted as “Related” if relationship to study drug was recorded as ‘Possible’, ‘Probable’, ‘Definite’ or if relationship to study drug is missing.

The severity of the AE will be characterized as mild, moderate, or severe, 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

Overviews of TEAEs will include total number of TEAEs and patient incidence of TEAE, TE SAE, related TEAE, related TE SAE, withdrew due to TEAE, AE with fatal outcome. Individual TEAE summary will be presented by previous treatment group in parent study and overall containing the following counts and percentages for:

- patients with TEAEs
- patients with TEAE by PT
- patients with TEAEs by SOC, PT and maximum severity
- patients with treatment-related TEAEs
- patients with treatment-related TEAEs by PT
- patients with treatment-related TEAEs by SOC and PT
- patients with treatment-emergent serious adverse events (TE SAEs)
- patients with TE SAEs by PT
- patients with TE SAEs by SOC, PT and maximum severity
- patients with treatment-related TE SAEs
- patients with treatment-related TE SAEs by SOC and PT
- TEAEs leading to discontinuation of IMP
- Fatal AEs by SOC and PT

In addition, summary tables will be provided, by prior treatment group and overall, for the number and percent of patients experiencing:

- adjudicated major adverse cardiovascular events and mortality (MACE) by event type
- non-CV deaths (non-MACE),
- nonfatal myocardial infarction [MI] (MACE),
- nonfatal stroke (MACE),
- hospitalization for unstable angina (MACE),
- coronary revascularization (MACE),
- noncoronary arterial revascularization (non-MACE),
- hospitalization for heart failure (non-MACE) using standardized definitions.

The TEAE, related TEAE, TE SAE, and AESI summaries by SOC, PT and maximum severity will be provided for relevant subgroups described in 5.2.5 with the exception of baseline LDL category.

The AE overview summaries will count a patient at most once in each AE category (at the "highest/most extreme" designation of each category regardless of preferred term) and percentages will be based on the total number of patients in the safety population.

In addition to a comprehensive listing of all AEs (with non-TEAEs flagged), separate listings will be generated for SAEs, AEs resulting in withdrawal of study drug, and AEs with a fatal outcome, investigator reported major adverse cardiovascular events and mortality, and adjudicated major adverse cardiovascular events and mortality.

5.4.2 Adverse Events of Special Interest

Adverse events of special interest (AESI) will be identified based on a pre-defined list of preferred terms provided by the sponsor (Appendix 2).

AESI will be presented in a listing and summarized by SOC, PT and previous treatment group in parent study and overall in OLE study. A separate table for treatment emergent AESI resulting in the discontinuation of study drug will be summarized by SOC, PT, and previous treatment group in the parent study and overall in OLE study.

In addition to adverse events, AESI is also being evaluated based on safety lab parameters. The details are provided in 5.4.5.

5.4.3 Clinical Cardiovascular Endpoints

Clinical cardiovascular endpoints will be monitored and adjudicated by an independent blinded expert CEC for this study and other ongoing studies the ETC-1002 program. Adjudicated clinical endpoints that are treatment-emergent will be summarized by event type and previous treatment group in parent study and overall in OLE study. All events will be provided in a listing. Additional details regarding clinical endpoints and clinical endpoint definitions will be included in CEC charter.

5.4.4 Neurocognitive Events

Neurocognitive events will be identified and evaluated by routine safety monitoring of PE findings and AEs. Summarization of neurocognitive events will occur using pre-specified MedDRA terms and will be performed by SOC, severity, and relationship to study drug by previous treatment group in parent study and overall in OLE study.

5.4.5 Laboratory Evaluations

Two sets of baseline for safety parameters are defined, similar to that for the efficacy parameters, baseline from the parent study and the baseline from the OLE study.

Continuous laboratory parameters (serum chemistry, hematology, coagulation (only for those patients receiving anti-coagulation), urinalysis, urinalysis [microscopic]) listed in Table 4 will be summarized using descriptive statistics at each scheduled visit starting from the baseline of the parent study. The similar on-treatment and completer analysis set approach for efficacy analysis described in section 5.3 will be used for safety laboratory analysis. All analysis will use conventional unit and SI unit will be provided for selected parameters.

Fasting serum glucose and HbA1c will be summarized using descriptive statistics for the observed value and the change, percent change from baseline by history of diabetics. Missing values for any of the laboratory evaluations will not be imputed; that is, only observed case data will be used.

Categorical urinalysis data will be listed, but will not be summarized.

As part of the AESI evaluation, below safety lab abnormality will be summarized by treatment group. All post-baseline lab values during the on-treatment period are being considered. Further details are provided in Section 5.4.6.1 through 5.4.6.4.

- ALT or AST (> 3 × ULN and >5 × ULN)
- TB (> 2 × ULN)
- Potential Hy's Law case: (ALT and/or AST > 3 × ULN with concurrent TB > 2 × ULN)
- CK (> 5 × ULN) and (>10 × ULN)
- Fasting Serum Glucose (mg/dL) (≤ 50, and ≥ 126) by history of diabetics
- HbA1C (≥ 6.5%) by history of diabetics
- Creatinine (change from baseline for >1 mg/dL)
- eGFR (< 15 mL/min/1.73m^2, 15 –29 mL/min/1.73m^2)
- Hgb (g/dL) (decrease from baseline for ≥ 2 g/dL)
- Hgb (< 8 g/dL)

The number and percentage of patients with the following laboratory abnormalities will be summarized by the parent study baseline statin intensity, previous treatment group in the parent study, and overall in the OLE study:

- ALT or AST (> 3 × ULN and >5 × ULN)
- TB (> 2 × ULN)
- Potential Hy's Law case: (ALT and/or AST > 3 × ULN with concurrent TB > 2 × ULN)
- CK (> 5 × ULN) and (>10 × ULN)
- Creatinine (change from baseline for > 1 mg/dL)
- eGFR (< 15 mL/min/1.73m^2, 15 –29 mL/min/1.73m^2)
- Hgb (g/dL) (decrease from baseline for ≥ 2 g/dL)
- Hgb (< 8 g/dL)

Table 2: Clinical Laboratory Parameters (Safety)

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 %)	<u>Blood Chemistry (serum, fasting)</u> • Albumin (Alb) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO2) • Chloride (Cl) • Creatinine • Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total and direct bilirubin (TB)a • Total protein • Uric acid <u>Coagulation</u>—only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0 • Prothrombin time (PT) • International normalized ration (INR)
<u>Urinalysis (Dipstick)</u> • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrate • Occult blood • pH • Protein • Specific gravity • Urobilinogen	
<u>Urinalysis (Microscopic)-only if urine dipstick abnormal</u> • Bacteria • Casts • Crystals • Epithelial cells • RBC • WBC	<u>Other Labs:</u> • Urine pregnancy test • Hemoglobin A_{1C} (HbA_{1C})

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

The number and percentage of patients with laboratory abnormalities (i.e., laboratory values outside the stated laboratory normal range) will be summarized at each time point (i.e., including baseline and post-baseline time points) for each laboratory parameter. The determination of laboratory abnormalities will take into account any unscheduled laboratory assessments. Additional lab-related summaries will be provided as follows for hepatic safety, musculoskeletal safety, diabetes and glycemia, and renal safety.

5.4.5.1 Hepatic Safety

For liver-associated enzymes and total bilirubin (TB), the number and percent of patients with abnormal values for ALT (>3 × ULN, > 5 × ULN), AST (> 3 × ULN, > 5 × ULN), and TB (> 2×ULN) will be summarized by overall, normal baseline ALT/AST/TB and abnormal baseline ALT/AST/TB.

Hy's law criteria (> 3 × upper limit of normal [ULN] for either ALT or AST, with accompanying TB > 2 × ULN) will also be applied to the data; any potential Hy's law cases will be listed separately. 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.

The number and percentage of patients experiencing a single incident or confirmed and repeated incidence of abnormal liver function test values for ALT (>3 × ULN, >5 × ULN), AST (>3 × ULN, >5 x ULN), CK (>5 × ULN, >10 × ULN) and either ALT and/or AST (>3 × ULN, >5 × ULN) will be summarized by the previous treatment group in the parent study and overall in the OLE study. A single incident is defined as the patient experiencing only one abnormal incident of the liver function test value. Repeated and confirmed incidence is defined as the patient experiencing at least one of the following: the last on-study liver function test value is abnormal, the last on-treatment liver function test value is abnormal, or an abnormal liver function test value is followed by another abnormal liver function test value for the same test.

A separate listing for direct TB will be provided for those who have Gilbert's syndrome.

5.4.5.2 Musculoskeletal Safety

CK levels will be summarized by the value and change from baseline in the value, by treatment group and visit as well as baseline eGFR category. In addition, the number and percent of patients with abnormal CK values (>5 X ULN, >10 × ULN) will be summarized. These summaries of patients with abnormal CK will be performed overall, normal baseline CK, and abnormal baseline CK.

5.4.5.3 Diabetes and Glycemia

For fasting glucose and HbA1C (%), a shift table from baseline with the number and percent of patients will be categorized as below:

Fasting glucose: >= 126 mg/dL; 100-125 mg/dL, and < 100 mg/dL;
HbA1C (%): >=6.5%; >5.5 to <=6.4% and <=5.5%.

These tables will be summarized by history of Diabetes.

Descriptive summary for fasting serum glucose and HbA1C will be provided by history of diabetics, previous treatment group in parent study and overall at each scheduled visit.

5.4.5.4 Renal Safety

Shift tables of eGFR category from baseline over the study, will be provided by previous treatment group in parent study and overall.

In addition, renal function abnormality will be identified as: (1) A creatinine change from baseline of > 1 mg/dL (2) eGFR value <30 mL/min/1.73m2. A shift table from baseline with the number and percent of patients using the two categories will be presented.

5.4.6 Physical Examinations (PEs)

Listings of PE data will include only those records where the body system at the baseline PE was normal, but the body system at a post-baseline PE was marked as 'Change from previous exam, clinically significant'. Baseline is defined as the last value prior to the first dose of study medication in OLE study. Only changes from baseline physical examination findings that meet the definition of an AE will be recorded on the AE page of the eCRF and will be summarized with other AE outcomes.

5.4.7 Vital Signs

Actual values and changes from baseline of both parent study and OLE study in vital signs (heart rate, systolic blood pressure, diastolic blood pressure, weight, height [baseline only], and BMI) will be summarized using descriptive statistics by previous treatment group in parent study, overall and post-baseline time point.

Vital signs data will be listed for each patient, with increases from baseline of >15 mmHg in systolic or diastolic blood pressure flagged.

6 DMC Analyses

Refer to DMC charter.

7 Reference

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8 Appendices

8.1 Appendix 1: Schedule of Events (Subject Visit Schedule)

Month	**0**	**3**	**6**	**9**	**12**	**15**	**18/EOT[1]**	**19/EOS[2]**
Week	**EOS Parent**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**	**Wk 64**	**Wk 78**	**Wk 82**
Visit Window	**30 Days pre-M0**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**+14 days**
In-clinic Visit	**X**	**X**			**X**		**X**	**X**
Phone Visit			**X**	**X**		**X**		
Procedure								
Informed Consent	X							
Enrollment Criteria	X							
Medical History	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording	X	X	X	X	X	X	X	X
Physical Exam	X				X		X	
Weight[3]	X	X			X		X	X
Vital Signs[4]	X	X			X		X	X
Urine Pregnancy Test[5]	X							
Clinical Safety Labs[6]	X	X			X		X	X
Basic Fasting Lipids[7]	X	X			X		X	X
Coagulation[8]	X							
ApoB and hsCRP	X	X			X		X	X
HbA_{1C}	X				X		X	X
IWRS Contact[9]	X	X			X		X	
Drug Dispensing	X	X			X			
Drug Return/ Compliance		X			X		X	

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visit, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories, adverse events (AEs), physical examination (PE), and vital signs. For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit Week 78/End of Treatment (EOT) will be scheduled as soon as possible and the patient will be asked to come back 4 weeks after last investigational medicinal product (IMP) dose for Visit Week 82/End of Study (EOS). No further visits will be scheduled.

[1] All procedures will be completed for all patients at either EOT or early withdrawal.

[2] All procedures will be completed for all patients 4 weeks after last IMP dose if completing the study or early withdrawal.

[3] Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

[4] Vital signs will include diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate (HR) and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments

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[5] Urine pregnancy test in women of childbearing potential only
[6] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Please refer to laboratory manual for detailed schedule of tests.
[7] Basic fasting lipids include total cholesterol (TC), calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C,), and triglycerides (TG).
[8] Only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0
[9] Interactive web response system (IWRS) contact at either an early withdrawal or an EOS visit to register study discontinuation visit date

8.2 Appendix 2: Adverse Event of Special Interest (AESI)

Adverse Event Terms per Protocol	Associated MedDRA Preferred Terms
Creatine kinase elevations	Blood creatine phosphokinase abnormal
Creatine kinase elevations	Blood creatine phosphokinase increased
Creatine kinase elevations	Blood creatine phosphokinase MM abnormal
Creatine kinase elevations	Blood creatine phosphokinase MM increased
New onset or worsening diabetes mellitus	Blood glucose abnormal
New onset or worsening diabetes mellitus	Blood glucose increased
New onset or worsening diabetes mellitus	Diabetes mellitus
New onset or worsening diabetes mellitus	Diabetes mellitus inadequate control
New onset or worsening diabetes mellitus	Diabetic ketoacidosis
New onset or worsening diabetes mellitus	Glucose tolerance impaired
New onset or worsening diabetes mellitus	Glucose urine present
New onset or worsening diabetes mellitus	Glycosuria
New onset or worsening diabetes mellitus	Glycosylated haemoglobin increased
New onset or worsening diabetes mellitus	Hyperglycaemia
New onset or worsening diabetes mellitus	Impaired fasting glucose
New onset or worsening diabetes mellitus	Ketoacidosis
New onset or worsening diabetes mellitus	Ketosuria
New onset or worsening diabetes mellitus	Ketosis
New onset or worsening diabetes mellitus	Type 2 diabetes mellitus
New onset or worsening diabetes mellitus	Urine ketone body present
Hepatic disorders	Alanine aminotransferase abnormal
Hepatic disorders	Alanine aminotransferase increased
Hepatic disorders	Aspartate aminotransferase abnormal
Hepatic disorders	Aspartate aminotransferase increased
Hepatic disorders	Blood bilirubin abnormal
Hepatic disorders	Blood bilirubin increased
Hepatic disorders	Hepatic enzyme abnormal
Hepatic disorders	Hepatic enzyme increased
Hepatic disorders	Hypertransaminaseaemia
Hepatic disorders	Liver function test abnormal
Hepatic disorders	Liver function test increased
Hepatic disorders	Transaminases abnormal
Hepatic disorders	Transaminases increased
Hypoglycemia	Blood glucose abnormal
Hypoglycemia	Blood glucose decreased
Hypoglycemia	Hypoglycaemia
Hypoglycemia	Hypoglycaemic coma
Hypoglycemia	Hypoglycaemic encephalopathy
Hypoglycemia	Hypoglycaemic seizure
Hypoglycemia	Shock hypoglycaemic
Metabolic acidosis	Metabolic acidosis
Muscular disorders	Muscular weakness
Muscular disorders	Muscle necrosis

Muscular disorders	Muscle spasms
Muscular disorders	Myalgia
Muscular disorders	Myoglobin blood increased
Muscular disorders	Myoglobin blood present
Muscular disorders	Myoglobin urine present
Muscular disorders	Myoglobinaemia
Muscular disorders	Myoglininuria
Muscular disorders	Myopathy
Muscular disorders	Myopathy toxic
Muscular disorders	Necrotizing myositis
Muscular disorders	Pain in extremity
Muscular disorders	Rhabdomyolysis
Neurocognitive/Neurologic disorders	Amnesia
Neurocognitive/Neurologic disorders	Cognitive disorder
Neurocognitive/Neurologic disorders	Confusional state
Neurocognitive/Neurologic disorders	Disorientation
Neurocognitive/Neurologic disorders	Memory impairment
Neurocognitive/Neurologic disorders	Mental status changes
Renal disorders	Acute kidney injury
Renal disorders	Acute prerenal failure
Renal disorders	Blood creatinine abnormal
Renal disorders	Blood creatinine increased
Renal disorders	Blood urea abnormal
Renal disorders	Blood urea increased
Renal disorders	Blood urea nitrogen/Creatinine ratio increased
Renal disorders	Creatinine renal clearance abnormal
Renal disorders	Creatinine renal clearance decreased
Renal disorders	Glomerular filtration rate abnormal
Renal disorders	Glomerular filtration rate decreased
Renal disorders	Gout
Renal disorders	Oliguria
Renal disorders	Prerenal failure
Renal disorders	Renal failure
Renal disorders	Renal function test abnormal
Renal disorders	Renal impairment

Statistical Analysis Plan for Study 1002-050, 120 Day Safety Update Interim Analysis

Title:	A MULTICENTER OPEN-LABEL EXTENSION (OLE) STUDY TO ASSESS THE LONG-TERM SAFETY AND EFFICACY OF BEMPEDOIC ACID (ETC-1002) 180 MG
Protocol:	ETC-1002-050
Clinical Phase:	3
Product:	ETC-1002
Date:	23-May-2019

[redacted] 28 May 2019 13:50:037+0000
REASON: I approve this document
f1330a26-8e65-4f1a-b28b-172f4186890d

[redacted] Date

[redacted] 29 May 2019 15:43:036+0000
REASON: I approve this document

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Esperion Therapeutics

[redacted] 30 May 2019 20:06:038+0000
REASON: I approve this document
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[redacted] Date
Esperion Therapeutics

Statistical Analysis Plan for Study 1002-050, Day 120 Safety Update Interim Analysis

An interim analysis for Day120 safety update will happen ≥ 4 months after the cutoff for the NDA submission (15-Mar-2019). The set of tables, listings and figures that were run for the NDA submission will be run again for the Day 120 safety update with additional tables and listings as described here. In addition, all of the subject incidence treatment-emergent adverse event (TEAE) tables as specified in the original SAP (dated as 05-Dec-2018), will be replaced with exposure-adjusted tables.

The lipid modifying treatment (LMT) use at the study baseline will be summarized by anatomic therapeutic chemical class and preferred term by treatment group in the parent study (1002-040) for the safety population.

The summary tables will be generated for incremental adverse events, serious adverse events, death, adverse events leading to discontinuation of investigational product and major adverse cardiac event by treatment group in the parent study (1002-040) for the safety population.

To calculate exposure-adjusted subject incidence, the number of subjects with at least one incidence of a given treatment-emergent adverse event (TEAE) will be used as the numerator, and the exposure-years for all the subjects for that treatment-emergent adverse event will be used as the denominator. The exposure-years will be calculated as total person time (in person-years) at risk from on or after the first dose of IMP and up to last date of IMP+30 days or end of study date or analysis cut-off date whichever is earlier for subjects who did not have a given TEAE. For a subject with the TEAE, the exposure-year will be calculated as total person time from on or after first dose of IMP to the onset date of first occurrence of the given TEAE. In the tables by maximum severity, the first occurrence to the maximum severity of the TEAE will be used for the exposure calculation.

The tables and listings for the Day 120 analyses:

Number	Title	Population
Table 14.1.1.1	Patient Disposition	The Enrolled Patients
Table 14.1.1.2	Major Protocol Deviation	Safety Population
Table 14.1.2.1	Demographic and Baseline Characteristics from the Parent ETC-1002-040 Study	Safety Population
Table 14.1.2.1.1	Demographic and Baseline Characteristics from OLE Study	Safety Population
Table 14.1.3.1	Medical History	Safety Population
Table 14.1.4.1	Cardiovascular History	Safety Population
Table 14.1.6.1	Concomitant Non-statin Medications by Anatomic Therapeutic Chemical Class and Preferred Term	Safety Population
Table 14.1.6.2	Concomitant Statin Medications by Anatomic Therapeutic Chemical Class and Preferred Term	Safety Population
Table 14.1.6.3	LMT Category at OLE Study (ETC-1002-050) Baseline by Anatomic Therapeutic Chemical Class and Preferred Term	Safety Population
Table 14.1.7	IMP Exposure	Safety Population
Table 14.2.1	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Observed Data, Conventional Unit)	Safety Population
Table 14.2.1.1	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline by Gender (Observed Data, Conventional Unit)	Safety Population

Table 14.2.1.2	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline by Age (Observed Data, Conventional Unit)	Safety Population
Table 14.2.1.3	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline by Baseline CVD Risk Category (Observed Data, Conventional Unit)	Safety Population
Table 14.2.1.4	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline by Baseline Statin Intensity Category (Observed Data, Conventional Unit)	Safety Population
Table 14.2.1.5	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline by Race (Observed Data, Conventional Unit)	Safety Population
Table 14.2.1.6	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline by Baseline LDL Category (Observed Data, Conventional Unit)	Safety Population
Table 14.2.1.7	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline by History of Diabetes (Observed Data, Conventional Unit)	Safety Population
Table 14.2.1.8	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline by Baseline BMI Group (Observed Data, Conventional Unit)	Safety Population

Table 14.2.1.9	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline by Region (Observed Data, Conventional Unit)	Safety Population
Table 14.2.2	High-density Lipoprotein Cholesterol (HDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Observed Data, Conventional Unit)	Safety Population
Table 14.2.3	Non-High-density Lipoprotein Cholesterol (Non - HDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Observed Data, Conventional Unit)	Safety Population
Table 14.2.4	Total Cholesterol (TC) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Observed Data, Conventional Unit)	Safety Population
Table 14.2.5	Triglycerides (TG) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Observed Data, Conventional Unit)	Safety Population
Table 14.2.6	Apolipoprotein B (apo-B) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Observed Data, Conventional Unit)	Safety Population
Table 14.2.7	High-sensitivity C-reactive Protein (hs-CRP) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Observed Data, Conventional Unit)	Safety Population
Table 14.2.8.1	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Safety Population
Table 14.2.8.2	High-density Lipoprotein Cholesterol (HDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Safety Population

Table 14.2.8.3	Non-High-density Lipoprotein Cholesterol (Non-HDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Safety Population
Table 14.2.8.4	Total Cholesterol (TC) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Safety Population
Table 14.2.8.5	Triglycerides (TG) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Safety Population
Table 14.2.8.6	Apolipoprotein B (apo-B) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Safety Population
Table 14.2.8.7	High-sensitivity C-reactive Protein (phCRP) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Safety Population
Table 14.2.9.1	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Conventional Unit)	Completer Analysis Set
Table 14.2.9.2	High-density Lipoprotein Cholesterol (HDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Conventional Unit)	Completer Analysis Set
Table 14.2.9.3	Non-High-density Lipoprotein Cholesterol (Non-HDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline by Age (Standard Unit)	Completer Analysis Set
Table 14.2.9.4	Total Cholesterol (TC) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Completer Analysis Set
Table 14.2.9.5	Triglycerides (TG) Values and Changes and Percent Changes from Parent Study (ETC-1002-	Completer Analysis Set

	040) Baseline (Conventional Unit)	
Table 14.2.9.6	Apolipoprotein B (apo-B) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Conventional Unit)	Completer Analysis Set
Table 14.2.9.7	High-sensitivity C-reactive Protein (phCRP) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Conventional Unit)	Completer Analysis Set
Table 14.2.10.1	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Completer Analysis Set
Table 14.2.10.2	High-density Lipoprotein Cholesterol (HDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Completer Analysis Set
Table 14.2.10.3	Non-High-density Lipoprotein Cholesterol (Non-HDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Completer Analysis Set
Table 14.2.10.4	Total Cholesterol (TC) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Completer Analysis Set
Table 14.2.10.5	Triglycerides (TG) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Completer Analysis Set
Table 14.2.10.6	Apolipoprotein B (apo-B) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Completer Analysis Set
Table 14.2.10.7	High-sensitivity C-reactive Protein (phCRP) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Standard Unit)	Completer Analysis Set

Table 14.2.11.1	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Observed Data, Conventional Unit)	Safety Population
Table 14.2.11.2	High-density Lipoprotein Cholesterol (HDL-C) Values and Changes and Percent Changes from Baseline (Baseline in OLE Study) (Observed Data, Conventional Unit)	Safety Population
Table 14.2.11.3	Non-High-density Lipoprotein Cholesterol (Non - HDL-C) Values and Changes and Percent Changes from Baseline (Baseline in OLE Study) (Observed Data, Conventional Unit)	Safety Population
Table 14.2.11.4	Total Cholesterol (TC) Values and Changes and Percent Changes from Baseline (Baseline in OLE Study) (Observed Data, Conventional Unit)	Safety Population
Table 14.2.11.5	Triglycerides (TG) Values and Changes and Percent Changes from Baseline (Baseline in OLE Study) (Observed Data, Conventional Unit)	Safety Population
Table 14.2.11.6	Apolipoprotein B (apo-B) Values and Changes and Percent Changes from Baseline (Baseline in OLE Study) (Observed Data, Conventional Unit)	Safety Population
Table 14.2.11.7	High-sensitivity C-reactive Protein (hs-CRP) Values and Changes and Percent Changes from Baseline (Baseline in OLE Study) (Observed Data, Conventional Unit)	Safety Population
Table 14.2.12.1	Low-density Lipoprotein Cholesterol (LDL-C) Values and Changes and Percent Changes from Parent Study (ETC-1002-040) Baseline (Observed Data, Standard Unit)	Safety Population
Table 14.2.12.2	High-density Lipoprotein Cholesterol (HDL-C) Values and Changes and Percent Changes from Baseline (Baseline in OLE Study) (Observed Data, Standard Unit)	Safety Population

Table 14.2.12.3	Non-High-density Lipoprotein Cholesterol (Non - HDL-C) Values and Changes and Percent Changes from Baseline (Baseline in OLE Study) (Observed Data, Standard Unit)	Safety Population
Table 14.2.12.4	Total Cholesterol (TC) Values and Changes and Percent Changes from Baseline (Baseline in OLE Study) (Observed Data, Standard Unit)	Safety Population
Table 14.2.12.5	Triglycerides (TG) Values and Changes and Percent Changes from Baseline (Baseline in OLE Study) (Observed Data, Standard Unit)	Safety Population
Table 14.2.12.6	Apolipoprotein B (apo-B) Values and Changes and Percent Changes from Baseline (Baseline in OLE Study) (Observed Data, Standard Unit)	Safety Population
Table 14.2.12.7	High-sensitivity C-reactive Protein (hs-CRP) Values and Changes and Percent Changes from Baseline (Baseline in OLE Study) (Observed Data, Standard Unit)	Safety Population
Table 14.3.1.1.1.1	Overview of Treatment-emergent Adverse Events	Safety Population
Table 14.3.1.1.1.2	Overview of Treatment-emergent Adverse Events by Gender	Safety Population
Table 14.3.1.1.1.3	Overview of Treatment-emergent Adverse Events by Age	Safety Population
Table 14.3.1.1.1.4	Overview of Treatment-emergent Adverse Events by Baseline CVD risk Category	Safety Population
Table 14.3.1.1.1.5	Overview of Treatment-emergent Adverse Events by Baseline Statin Intensity	Safety Population
Table 14.3.1.1.1.6	Overview of Treatment-emergent Adverse Events by Race	Safety Population
Table 14.3.1.1.1.7	Overview of Treatment-emergent Adverse Events by History of Diabetes	Safety Population
Table 14.3.1.1.1.8	Overview of Treatment-emergent Adverse Events by Baseline BMI Group	Safety Population

Table 14.3.1.1.1.9	Overview of Treatment-emergent Adverse Events by Region	Safety Population
Table 14.3.1.1.2.1	Overview of Treatment-emergent Serious Adverse Events (TE SAE)	Safety Population
Table 14.3.1.1.2.2	Overview of Treatment-emergent Serious Adverse Events (TE SAE) by Gender	Safety Population
Table 14.3.1.1.2.3	Overview of Treatment-emergent Serious Adverse Events (TE SAE) by Age	Safety Population
Table 14.3.1.1.2.4	Overview of Treatment-emergent Serious Adverse Events (TE SAE) by Baseline CVD risk category	Safety Population
Table 14.3.1.1.2.5	Overview of Treatment-emergent Serious Adverse Events (TE SAE) by Baseline Statin Intensity	Safety Population
Table 14.3.1.1.2.6	Overview of Treatment-emergent Serious Adverse Events (TE SAE) by Race	Safety Population
Table 14.3.1.1.2.7	Overview of Treatment-emergent Serious Adverse Events (TE SAE) by History of Diabetes	Safety Population
Table 14.3.1.1.2.8	Overview of Treatment-emergent Serious Adverse Events (TE SAE) by Baseline BMI Group	Safety Population
Table 14.3.1.1.2.9	Overview of Treatment-emergent Serious Adverse Events (TE SAE) by Region	Safety Population
Table 14.3.1.2.2	Overview of Treatment-emergent Adverse Events Resulting in Withdrawal of Study Drug	Safety Population
Table 14.3.1.3.1.1a	Incremental Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety Population
Table 14.3.1.3.2.1a	Incremental Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population
Table 14.3.1.3.3.3a	Incremental Treatment-emergent Adverse Events Resulting in Discontinuation of IMP by System Organ Class, Preferred Term and Maximum Severity	Safety Population

Table 14.3.1.3.3.4a	Incremental Treatment-emergent Fatal Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety Population
Table 14.3.2.2.1a	Incremental Treatment-emergent and Positively Adjudicated Adverse Cardiovascular Events by Event Type	Safety Population
Table 14.3.2.2.2	Exposure-Adjusted Subject Incidence of Treatment-emergent and Positivrely Adjudicated Adverse Cardiovascular Events by Event Type	Safety Population
Table 14.3.3.1.1	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population
Table 14.3.3.1.2	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population - by Gender
Table 14.3.3.1.3	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population - by Age
Table 14.3.3.1.4	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Baseline CVD risk Category
Table 14.3.3.1.5	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Baseline Statin Intensity
Table 14.3.3.1.6	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Race
Table 14.3.3.1.7	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by History of

		Diabetes
Table 14.3.3.1.8	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Baseline Body Mass Index (BMI) Group
Table 14.3.3.1.9	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Region
Table 14.3.3.2.1	Exposure-Adjusted Incidence of Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population
Table 14.3.3.2.2	Exposure-Adjusted Incidence of Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population - by Gender
Table 14.3.3.2.3	Exposure-Adjusted Incidence of Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population - by Age
Table 14.3.3.2.4	Exposure-Adjusted Incidence of Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Baseline CVD risk Category
Table 14.3.3.2.5	Exposure-Adjusted Incidence of Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Baseline Statin Intensity

Table 14.3.3.2.6	Exposure-Adjusted Incidence of Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Race
Table 14.3.3.2.7	Exposure-Adjusted Incidence of Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by History of Diabetes
Table 14.3.3.2.8	Exposure-Adjusted Incidence of Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Baseline Body Mass Index (BMI) Group
Table 14.3.3.2.9	Exposure-Adjusted Incidence of Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Region
Table 14.3.3.3.3	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events Resulting in Discontinuation of IMP by System Organ Class, Preferred Term and Maximum Severity	Safety Population
Table 14.3.3.4.1	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events of Special Interest (AESIs) by System Organ Class, Preferred Term and Maximum Severity	Safety Population
Table 14.3.3.4.2	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events of Special Interest (AESIs) by System Organ Class, Preferred Term and Maximum Severity	Safety Population - by Gender
Table 14.3.3.4.3	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events of Special Interest (AESIs) by System Organ Class, Preferred Term	Safety Population - by Age

	and Maximum Severity	
Table 14.3.3.4.4	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events of Special Interest (AESIs) by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Baseline CVD risk Category
Table 14.3.3.4.5	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events of Special Interest (AESIs) by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Baseline Statin Intensity
Table 14.3.3.4.6	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events of Special Interest (AESIs) by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Race
Table 14.3.3.4.7	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events of Special Interest (AESIs) by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by History of Diabetes
Table 14.3.3.4.8	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events of Special Interest (AESIs) by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Baseline Body Mass Index (BMI) Group
Table 14.3.3.4.9	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events of Special Interest (AESIs) by System Organ Class, Preferred Term and Maximum Severity	Safety Population – by Region
Table 14.3.3.5.1	Exposure-Adjusted Incidence of Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term	Safety Population

Table 14.3.3.5.2	Exposure-Adjusted Incidence of Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term	Safety Population - by Gender
Table 14.3.3.5.3	Exposure-Adjusted Incidence of Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term	Safety Population - by Age
Table 14.3.3.5.4	Exposure-Adjusted Incidence of Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term	Safety Population – by Baseline CVD risk Category
Table 14.3.3.5.5	Exposure-Adjusted Incidence of Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term	Safety Population – by Baseline Statin Intensity
Table 14.3.3.5.6	Exposure-Adjusted Incidence of Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term	Safety Population – by Race
Table 14.3.3.5.7	Exposure-Adjusted Incidence of Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term	Safety Population – by History of Diabetes
Table 14.3.3.5.8	Exposure-Adjusted Incidence of Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term	Safety Population – by Baseline Body Mass Index (BMI) Group
Table 14.3.3.5.9	Exposure-Adjusted Incidence of Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term	Safety Population – by Region
Table 14.3.3.6.2	Exposure-Adjusted Incidence of Related Treatment-emergent Adverse Events of Special	Safety Population

	Interest (AESIs) by System Organ Class and Preferred Term	
Table 14.3.3.6.3	Exposure-Adjusted Incidence of Related Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.3.6.4	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events of Special Interest (AESIs) Resulting in Discontinuation of IMP by System Organ Class and Preferred Term	Safety Population
Table 14.3.3.7.1	Exposure-Adjusted Incidence of Treatment-emergent Adverse Events by Preferred Term	Safety Population
Table 14.3.3.7.2	Exposure-Adjusted Incidence of Treatment-emergent Serious Adverse Events by Preferred Term	Safety Population
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Statistical Analysis Plan

Title:	A MULTICENTER OPEN-LABEL EXTENSION (OLE) STUDY TO ASSESS THE LONG-TERM SAFETY AND EFFICACY OF BEMPEDOIC ACID (ETC-1002) 180 MG
Protocol:	ETC-1002-050
Clinical Phase:	3
Product:	ETC-1002
Version (Date):	Statistical Analysis Plan – Version 1.3
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Table of Contents

1 List of Abbreviations

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AESI	Adverse events of special interest
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
ApoB	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular diseases
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CAS	Completer Analysis Set
CEC	Clinical Event Committee
CI	Confidence interval
CK	Creatine kinase
Cl	Chloride
CO_2	Carbon dioxide
CV	Cardiovascular
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EOS	End of Study
ETC-1002	Bempedoic acid
FDA	Food and Drug Administration
FPFV	First patient first visit
HbA_{1C}	Glycosylated hemoglobin, Type A_{1C}
Hct	Hematocrit
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
Hgb	Hemoglobin
hs-CRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonisation

Abbreviation or Specialist Term	Explanation
IMP	Investigational medicinal product
ITT	Intention-to-treat
IWRS	Interactive web response system
K	Potassium
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LMT	Lipid modifying therapy
LPLV	Last patient last visit
LS	Least square
MACE	Major adverse cardiac event
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
Na	Sodium
non-HDL-C	Non-high-density lipoprotein cholesterol
OLE	Open-label extension
Parent study	Study 1002-040
PE	Physical exam
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SI	International system of units
SOC	System organ class
SP	Safety population
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TG	Triglycerides
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

2 Introduction

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed in ETC-1002-050. The preparation of this statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 Guidelines and in reference to Protocol ETC-1002-050 (Protocol Amendment 2, 15Jan2018).

The SAP will supersede the protocol in the event of any differences between the two documents in the plans for data analysis, and the protocol will be amended if appropriate. The SAP will be included as an appendix in the clinical study report for this protocol.

3 Study Objectives and Endpoints

3.1 Objectives

- The primary objective for this study is to characterize the safety and tolerability of long-term administration of bempedoic acid (ETC-1002) 180 mg

- The secondary objective is to characterize the efficacy of long-term administration of bempedoic acid 180 mg/day as assessed by changes in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (ApoB), total cholesterol (TC), triglycerides TG, and high-sensitivity C-reactive protein (hs-CRP) in patients with hyperlipidemia

3.2 Endpoint

Primary Endpoint (Safety)

- The primary endpoint for this study is patient incidence of treatment-emergent adverse events (TEAEs)

Secondary Endpoints (Efficacy)

- Percent change from baseline in LDL-C at Weeks 52 and 78
- Change from baseline in LDL-C at Weeks 52 and 78
- Percent change from baseline in non-HDL-C at Weeks 52 and 78
- Percent change from baseline in TC at Weeks 52 and 78
- Percent change from baseline in ApoB at Weeks 52 and 78

- Percent change from baseline in hs-CRP at Weeks 52 and 78
- Percent change from baseline in TG at Weeks 52 and 78
- Percent change from baseline in HDL-C at Weeks 52 and 78

Other Safety Endpoints

- Laboratory Results
- Physical Measurements
- Vital Signs
- Hepatic Safety
- Musculoskeletal Safety
- Diabetes and Hyperglycemia
- Renal Safety
- Neurocognitive Events
- Clinical Endpoints

3.2.1 Adverse Events

The evaluation of adverse events (AEs) will include only incidence of TEAEs, defined as AEs that begin or worsen on or after the date of first dose of study drug administration in open-label extension (OLE) period and until 30 days after last dose of study drug. AESI will be examined further (See Section 5.4.2 for more information).

Clinical endpoints (details see section 4.2) will be collected and adjudicated by an independent Clinical Events Committee (CEC). Clinical endpoints will also be reported as AEs.

3.2.2 Clinical Safety Laboratories

The evaluation of clinical safety laboratories, including blood hematology, chemistry, coagulation, and urinalysis will be based on the observed values. Observed values, change from baseline, and percent change from baseline of both the parent study and OLE study will be summarized for all the scheduled post-baseline visits.

3.2.3 Vital Signs

The evaluation of vital signs (including heart rate, systolic blood pressure, and diastolic blood pressure, and weight and BMI) will be based on the observed values. The summary of the observed values and change from baseline will be performed for all the scheduled visits based on the baseline of the parent study and OLE study. Baseline height will be summarized and will be used in the BMI calculations over time.

3.2.4 Physical Exam

Listings of PE data will include only those records where the body system at the baseline PE was normal, but the body system at a post-baseline PE was marked as 'Change from previous exam, clinically significant.'

3.2.5 Lipids

After enrollment, patients will return to clinic at Weeks 12, 52, 78/EOT, and 82/EOS. Clinical laboratory samples will be collected and analyzed for calculated LDL-C and lipid and cardiometabolic biomarkers including non-HDL-C, HDL-C, TC, ApoB, and TG at baseline and all clinic visits for evaluation of bempedoic acid effects on lipids and cardiometabolic parameters.

4 Study Design

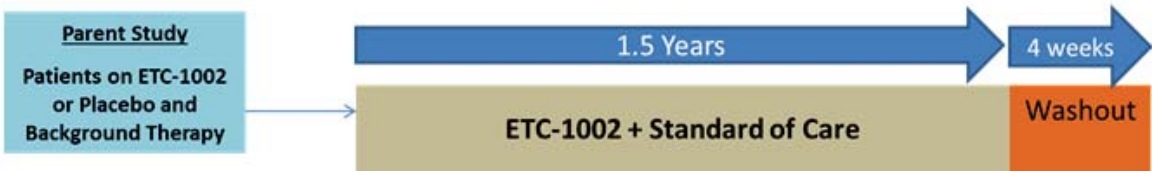
4.1 Study Design

This is a multicenter OLE study designed to assess the long-term safety and efficacy of bempedoic acid (ETC-1002) 180 mg. All patients will receive open-label bempedoic acid 180 mg for up to 1.5 years after rolling over from the parent study (Study 1002-040) followed by a follow-up period off study drug for 4 weeks. Investigators, site staff, patients, and the study team will be masked to study lipid levels until the Week 12 study visit, after which time lipid values will be made available.

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety and efficacy data from this and other ongoing studies of bempedoic acid. A blinded independent expert Clinical Events Committee (CEC) will adjudicate designated clinical endpoints across the program, including all major adverse cardiac events (MACE) and non-MACE endpoints defined as: cardiovascular (CV) death (MACE), non-CV death (non-MACE), nonfatal myocardial infarction [MI] (MACE), nonfatal stroke (MACE), hospitalization for unstable angina (MACE), coronary revascularization (MACE), noncoronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE) using standardized definitions. Any clinical endpoints that meet serious adverse event (SAE) criteria will be reported as SAEs as well as a clinical endpoint.

The study will be conducted at approximately 125 clinical sites in the United States, Canada, Germany, Netherlands, Poland, and United Kingdom. The study will end when the last randomized patient completes their last study visit (last patient last visit [LPLV] for last randomized patient). The estimated overall duration of the study (first patient first visit [FPFV] to LPLV) is approximately 2.5 years.

Figure 1. Study 1002-050 Study Design



4.2 Study Treatments and Assessments

Day 1 for this study should occur on the same day as the end of study visit for the parent study (1002-040). Patients who provide informed consent will be eligible to enroll in the study.

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

The investigational products were listed in Table 1 below:

Table 1: Investigational Medicinal Products

	Investigational Medicinal Product
Product Name:	Bempedoic acid
Dosage Form:	Film-coated tablets
Unit Dose:	180 mg
Container/Closure[a]	100-count bottle with screw on, child proof cap
Route of Administration:	Oral, daily with or without food
Physical Description:	[redacted]
Manufacturer (Fill/Finish):	

Study drug should be taken once a day (once every 24 hours) at approximately the same time every day and may be taken with or without food. Patients will fast (no food or drink, other than water) for a minimum of 10 hours prior to collection of all laboratory samples.

Please see Pharmacy Manual for detailed storage requirements and instructions.

Patients who withdraw from investigational medicinal product (IMP) treatment will be asked to continue to be followed for safety using the protocol-specified visit schedule and procedures. For details of study assessments, see Appendix 1: Schedule of Events (Subject Visit Schedule).

An independent expert Data Monitoring Committee (DMC) will formally review accumulating unblinded safety and efficacy data from this and other any ongoing studies of ETC-1002. All clinical endpoints, including all major cardiac events (MACE) and non-MACE endpoints defined as: CV death (MACE), non-CV death (non-MACE), nonfatal myocardial infarction (MI) (MACE), nonfatal stroke (MACE), hospitalization for unstable angina (MACE), coronary revascularization (MACE), non-coronary arterial revascularization (non-MACE), and hospitalization for heart failure (non-MACE), will be adjudicated by an independent blinded expert Clinical Events Committee (CEC), using standardized definitions. Any clinical endpoints that meet serious adverse event (SAE) criteria will be reported as SAEs.

4.3 Randomization and Blinding

Randomization is not applicable for this OLE study.

Laboratory results for lipid panel and hs-CRP will be masked to investigators, patients, and the study team until the Week 12 visit is completed. All site staff involved with this trial should refrain from obtaining lipid panels between date of last study medication (bempedoic acid or placebo) dose at end of parent study Week 52 (Visit T7) and Week 12 in this OLE trial.

4.4 Sample Size Justification

[redacted]

The number of patients entering this study will depend on the number of patients completing Study 1002-040 and their willingness to enroll.

4.5 Interim Analyses, Final Analyses, and Unblinding

An interim analysis will be conducted in 2H 2018 in order to provide safety assessment to support NDA submission. Another interim analysis for Day120 safety update will be approximately 120 days after the NDA cutoff. The endpoints and analyses are the same as those defined in final analysis if applicable.

The final analysis will be performed after the database is locked.

4.6 Change from Planned Analyses in Protocol

There is no change from planned analyses for this study.

5 Statistical and Analytical Plans

5.1 General Statistical Considerations

The treatment groups will be displayed as previous treatment in parent study as well as overall treatment group in OLE study.

In general, all safety and efficacy data will be reported as observed. No imputation will be performed for missing data. Descriptive statistics (n, mean, standard deviation, median, Q1, Q3, minimum, and maximum) will be calculated for continuous data. Minimum and maximum will be presented same number of decimal places as reported/collected, one additional decimal place for mean and median, and two additional decimal places for standard deviation. Ninety-five percent (95%) confidence intervals (CIs) will be calculated for select continuous endpoint estimates.

Categorical data will be summarized using n and percentage based on number of non-missing values. Percentage will be presented with one decimal place. The number of missing values will be presented as a separate category with no percentage, but only if 1 or more patients are missing data for the summary. Otherwise, all categories will be presented (even if no patients are counted in the category). Counts of zero in any category will be presented without percentage.

Data will be presented on listings by prior treatment group in the parent study, subject ID, assessment (in order collected on CRF, unless specified otherwise), and assessment date. Dates will be presented in format DDMMMYYYY.

Relative day calculations will be [date of interest – relative date + (date of interest >= relative date)]. This calculation will result in dates prior to the relative date being presented as negative days, and those occurring on or after the relative date as Day 1 or later, i.e., there will be no Day 0.

Two sets of baseline are defined for applicable endpoints: baseline in parent study (1002-040) and baseline in OLE study (1002-050). The parent baseline values will be directly extracted from parent study database. The baseline for the OLE study is defined as the last non-missing value on or prior to the date of first dose in the OLE.

If last dose of study treatment is missing, then the end of study date or death date, whichever occurs earlier, will be used in its place.

The visit schedules and windows are shown below:

Visit	Day 1/Week 0	Week 12	Week 24	Week 36	Week 52	Week 64	Week 78/EOT	Week 82/EOS

Month	0	3	6	9	12	15	18/EOT	19/EOS
Slotted Study Week	EOS Parent	Wk 12	Wk 24	Wk 36	Wk 52	Wk 64	Wk 78	Wk 82
Target Study Day	1	84	168	252	364	448	546	574
Analysis Window	1	[2,126]	[127,210]	[211,308]	[309,406]	[407,497]	[498,562]	[563,∞]
Protocol defined visit Windows	[30 Days, Pre M0]	84±7	168±7	252±7	364±7	448±7	546±7	574±14

5.2 Statistical Analysis Plans

5.2.1 Analysis Sets

5.2.1.1 Safety Population (SP)

The SP is defined as all enrolled patients who received at least 1 dose of bempedoic acid during the OLE period and will be used for demographics and baseline characteristics, treatment exposure, concomitant medications, safety and efficacy summaries. If all subjects receive at least one dose of bempedoic acid in this study, the SP will be used for all efficacy analyses as well.

5.2.1.2 Completer Analysis Set (CAS)

The CAS is defined as the patients who completed the full 78 weeks treatment as per End of Treatment CRF page.

5.2.2 Protocol Violations and Deviations

A full list of protocol violations and deviations will be compiled and reviewed by the clinical team to identify key versus non-key violations/deviations before final database lock. For violations at study entry, patients will be assessed against the inclusion and exclusion criteria of the protocol. For on-study deviations, compliance with the protocol will be examined with regard to prohibited therapies, and timing and availability of planned assessments. The final list of protocol deviation will be approved by the study team prior to interim analysis cut of or final database lock, and will be used to generate the protocol deviation summary and listing.

5.2.3 Subject Disposition

The number of patients enrolled, and included in each analysis population, along with IMP and study completion status, will be summarized by the treatment group in parent ETC-1002-040 study and overall. In addition, the number of patients who withdraw from the study and withdraw from study drug will be summarized by discontinuation reason.

5.2.4 Demographic and Baseline Characteristics

Two sets of baseline values will be defined: baseline of parent study and OLE study. The parent study baseline will be taken directly from the parent study, and the OLE baseline is defined as last non-missing value prior to the first dose of IMP in the OLE study. The following demographic and both baseline characteristics will be summarized using descriptive statistics by previous treatment group in parent study, as well as overall, for safety population:

- Age group (18-40, 41-64, 65-74, and >=75 years), gender, race, ethnicity, region (North America, and Europe), height (cm), weight (kg), body mass index (BMI) (kg/m^2) (< 25, 25 - < 30, ≥ 30 kg/ m^2), , systolic and diastolic blood pressure, fasting lipid parameters (TC, LDL-C, HDL-C, non-HDL-C, and TG), apoB, and hs-CRP.

- Cardiovascular risk factors from the parent study: ASCVD (Yes/No), HeFH (Yes/No), baseline statin intensity (derived) (low or moderate, high), eGFR category, tobacco history, alcohol history, history of diabetics, and history of hypertension.

- The baseline estimated glomerular filtration rate (eGFR) categories are: normal: ≥90 $mL/min/1.73m^2$; mild Renal Impairment: 60-89 $mL/min/1.73m^2$; moderate Renal Impairment: 30-59 $mL/min/1.73m^2$, and severe Renal Impairment (15-29 $mL/min/1.73m^2$).

5.2.5 Subgroup Variables

Subgroups defined by below variables will be evaluated for safety and the LDL-C efficacy endpoint.

1) Gender (male vs. female)
2) Age (< 65 yrs. vs. ≥ 65 yrs. and < 75 yrs. vs. ≥ 75 yrs.)
3) Baseline CVD risk category (HeFH (with/without ASCVD) vs. ASCVD only)
4) Baseline statin intensity (low vs. moderate vs. high)
5) Race (White vs. other)
6) Baseline LDL category (< 100 mg/dL vs. ≥100 mg/dL) (efficacy only)
7) History of diabetes (yes vs. no)
8) Body Mass Index (BMI) (< 25, 25 - < 30, ≥ 30 kg/m^2)
9) Region (North America, Europe)

In case the number of patients within a subgroup is too small, e.g. less than 5% of the overall population, the analyses may not be performed or the subgroup levels may be combined.

5.2.6 Medical History

General medical history, cardiovascular history/risk factors, previous statin use and statin tolerance history will be summarized by previous treatment group in parent study, as well as overall in OLE study for safety population and presented in a by-patient listing. Where appropriate, terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or later.

If a patient is entering the study beyond the 30-day rollover window, new medical history that occur between more than 30 days after the end of the parent study and treatment start in OLE study (exclusive) that period will be collected and presented in a by-patient listing.

5.2.7 Concomitant Medications

Concomitant medications are defined as medications that were ongoing at the time of study drug initiation in this OLE study or new medications that started post study drug initiation and within 30 days following the date of the last dose of study drug.

Medications, including lipid modifying therapy (LMT) medications, will be coded using WHO Drug (March, 2017, or later if appropriate). The frequency of use of concomitant medications will be summarized by previous treatment group in parent study, as well as overall in OLE study, for the safety population according to Anatomical Therapeutic Chemical (ATC) class and preferred term. Concomitant medications will be listed for each patient. Concomitant LMT medications will be summarized by ATC class and medication name and listed separately in a similar fashion.

5.2.8 Study Drug Exposure and Compliance

For each patient, the length of exposure to study drug will be calculated as the number of days from the first dose of study drug to the last dose of study drug, regardless if the patient missed one or more doses of study drug. Length of exposure will be summarized by previous treatment group in parent study and overall in OLE study using descriptive statistics for the safety population.

For each patient, overall compliance (%) will be calculated as: (Total Number of Tablets Dispensed – Total Number of Tablets Returned)*100/ (Treatment Duration in Days). The number and percentage of patients who were compliant with taking study drug will be summarized by previous treatment group in parent study and overall in OLE study for the safety population for the following categories 0 - <80%; >= 80%.

The study drug administration and compliance data will be listed for each patient.

5.3 Efficacy Endpoints and Analyses

Given the primary objective of the study being long term safety, efficacy analyses will be using the safety population (SP). The efficacy data will be summarized by previous treatment group in parent study as well as an overall group.

For each efficacy parameter, descriptive summary statistics at each visit will be provided for the observed value, change from baseline, and percent change from baseline in both conventional and International System of Units (SI). Two sets of summaries will be provided using the baseline from the parent study and from the OLE study. The visits to be included in the overtime summary are baseline of parent study (1002-040), baseline of OLE study, week 12, week 52, week 78, and Week 82. There will be no imputation for missing data, all summaries will use the observed data. Ninety-five percent (95%) CI will be provided for the estimates at post-baseline visits.

In addition, efficacy parameters will also be summarized using the Completer Analysis Set (CAS).

For LDL-C, the same descriptive summary statistics at each scheduled visit will be provided within each subgroup for the observed value, change from baseline, and percent change from baseline.

Efficacy data (observed value, change from baseline, and percent change from baseline) from all visits will be summarized using descriptive statistics in both conventional and standard units.

Figures (mean ± standard deviation or median/interquartile range) supporting the summary tables will be provided for each efficacy parameter.

Efficacy data from all visits will be provided in listings as well.

By-visit summary for efficacy endpoints (LDL-C, non-HDL-C, TC, HDL-C, TG, ApoB, and hs-CRP,) using the CAS will be provided in conventional and standard units.

5.4 Safety Data Endpoints and Analyses

The safety and tolerability of ETC-1002 will be assessed by examination of TEAEs, PEs, vital signs, clinical laboratory values (serum chemistry, hematology, coagulation, and urinalysis), and weight. SP will be used for all safety analyses.

Unless otherwise stated, descriptive summaries will be performed by previous treatment group actually received in parent study and overall group.

5.4.1 Adverse Events (AEs)

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.1 or later and will be categorized by system organ class (SOC) and preferred

term (PT). Summary tables will focus on TEAEs; however, listings will include all AEs (with non-TEAEs flagged). An additional AE listing will be provided for AEs occurred during rollover period.

In summary tables, TEAEs will be counted as "Not Related" if relationship to study drug was recorded as 'Not Related' or "Unlikely". Events will be counted as "Related" if relationship to study drug was recorded as 'Possible', 'Probable', 'Definite' or if relationship to study drug is missing.

The severity of the AE will be characterized as mild, moderate, or severe, 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

Overviews of TEAEs will include total number of TEAEs, and patient incidence of TEAEs, TESAEs, treatment-related TEAEs, treatment-related TESAEs, IMP withdrawal due to TEAEs, TEAEs with fatal outcome. Individual TEAE summary will be presented by previous treatment group in parent study and overall containing the following counts and percentages for:

- patients with TEAEs by SOC and PT
- patients with TEAEs by PT
- patients with TEAEs by SOC, PT, and maximum severity
- patients with treatment-related TEAEs
- patients with treatment-related TEAEs by PT
- patients with treatment-related TEAEs by SOC and PT
- patients with treatment-emergent serious adverse events (TESAEs) by SOC and PT
- patients with TESAEs by PT
- patients with TESAEs by SOC, PT, and maximum severity
- patients with treatment-related TESAEs
- patients with treatment-related TESAEs by SOC and PT
- TEAEs leading to withdrawal of IMP by SOC and PT
- fatal TEAEs by SOC and PT

Preferred terms for TEAEs that occurred in more than 1% of subjects overall will be plotted using the overall group. This plot will be repeated for TESAEs in the overall group.

In addition, summary tables will be provided, by prior treatment group and overall, for the number and percent of patients experiencing:

- adjudicated major adverse cardiovascular events and mortality (MACE) by event type
- non-CV deaths (non-MACE),
- nonfatal myocardial infarction [MI] (MACE),
- nonfatal stroke (MACE),
- hospitalization for unstable angina (MACE),
- coronary revascularization (MACE),
- noncoronary arterial revascularization (non-MACE),
- hospitalization for heart failure (non-MACE) using standardized definitions.

The TEAE, treatment-related TEAE, TESAE, and AESI summaries by SOC, PT and maximum severity will be provided for relevant subgroups described in 5.2.5 with the exception of baseline LDL category.

The AE overview summaries will count a patient at most once in each AE category (at the "highest/most extreme" designation of each category regardless of preferred term) and percentages will be based on the total number of patients in the safety population.

In addition to a comprehensive listing of all AEs (with non-TEAEs flagged), separate listings will be generated for serious adverse events, TEAEs resulting in withdrawal of study drug, and TEAEs with a fatal outcome, investigator reported major adverse cardiovascular events and mortality, and adjudicated major adverse cardiovascular events and mortality.

5.4.2 Adverse Events of Special Interest

Adverse events of special interest (AESI) will be identified based on a pre-defined list of preferred terms provided by the sponsor (Appendix 2).

AESI will be presented in a listing and summarized by SOC, PT, and previous treatment group in parent study and overall in OLE study. A separate table for treatment-emergent AESI resulting in the discontinuation of study drug will be summarized by SOC, PT, and previous treatment group in the parent study and overall in OLE study.

In addition to adverse events, AESI is also being evaluated based on safety lab parameters. The details are provided in 5.4.5.

5.4.2.1 Neurocognitive Events

Neurocognitive events will be identified and evaluated by routine safety monitoring of PE findings and AEs. Summarization of neurocognitive events will occur using pre-specified MedDRA terms and will be performed by SOC, severity, and relationship to study drug by previous treatment group in parent study and overall in OLE study.

5.4.3 Clinical Cardiovascular Endpoints

Clinical cardiovascular endpoints will be monitored and adjudicated by an independent blinded expert CEC for this study and other ongoing studies the ETC-1002 program. Adjudicated clinical endpoints that are treatment-emergent will be summarized by event type and previous treatment group in parent study and overall in OLE study. All events will be provided in a listing. Additional details regarding clinical endpoints and clinical endpoint definitions will be included in CEC charter.

5.4.4 Laboratory Evaluations

Continuous laboratory parameters (serum chemistry, hematology, coagulation (only for those patients receiving anti-coagulation), urinalysis, urinalysis [microscopic]) listed in Table 4 will be summarized in conventional unit and SI unit using descriptive statistics at each scheduled visit starting from the baseline of the parent study. The similar completer analysis set approach for efficacy analysis described in section 5.3 will be used for selected parameters. Missing values for any of the laboratory evaluations will not be imputed; that is, only observed case data will be used.

Fasting serum glucose and HbA1c will be summarized using descriptive statistics for the observed value, change from baseline, and percent change from baseline at each scheduled visit by history of diabetics.

Categorical urinalysis data will be listed, but will not be summarized.

As part of the AESI evaluation, below safety lab abnormality will be summarized by treatment group. All post-baseline lab values during the on-treatment period are being considered. Further details are provided in Section 5.4.6.1 through 5.4.6.4.

- ALT or AST (> 3 × Upper limit of normal (ULN) and >5 × ULN)
- Total bilirubin (TB) (> 2 × ULN)
- Potential Hy's Law case: (ALT and/or AST > 3 × ULN with concurrent TB > 2 × ULN)
- CK (> 5 × ULN) and (>10 × ULN)
- Fasting Serum Glucose (mg/dL) (≤ 50, and ≥ 126) by history of diabetics
- $HbA1_C$ (≥ 6.5%) by history of diabetics
- Creatinine (change from baseline for >1 mg/dL)
- eGFR (< 15 mL/min/1.73m^2, 15 –29 mL/min/1.73m^2)
- Hgb (g/dL) (decrease from baseline for ≥ 2 g/dL)
- Hgb (< 8 g/dL)

The number and percentage of patients with the following laboratory abnormalities will be summarized by the parent study baseline statin intensity, previous treatment group in the parent study, and overall in the OLE study:

- ALT or AST (> 3 × ULN and >5 × ULN)
- TB (> 2 × ULN)
- Potential Hy's Law case: (ALT and/or AST > 3 × ULN with concurrent TB > 2 × ULN)
- CK (> 5 × ULN) and (>10 × ULN)
- Creatinine (change from baseline for > 1 mg/dL)
- eGFR (< 15 mL/min/1.73m^2, 15 –29 mL/min/1.73m^2)
- Hgb (g/dL) (decrease from baseline for ≥ 2 g/dL)
- Hgb (< 8 g/dL)

For labs of interest (such as uric acid, hemoglobin, creatinine, BUN, and Fasting glucose by diabetes history), a line plot will be generated to visualize the mean values over time.

A matrix display of liver dysfunction shift from baseline to maximum value will be used to visualize the abnormal values of labs including AST, ALK-P ALT, and TB.

Table 2: Clinical Laboratory Parameters (Safety)

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 %)	<u>Blood Chemistry (serum, fasting)</u> • Albumin (Alb) • Alkaline phosphatase (ALK-P) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO2) • Chloride (Cl) • Creatinine • Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total and direct bilirubin (TB)a • Total protein • Uric acid <u>Coagulation</u>—only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0 • Prothrombin time • International normalized ration (INR)
<u>Urinalysis (Dipstick)</u> • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrate • Occult blood • pH • Protein • Specific gravity • Urobilinogen	
<u>Urinalysis (Microscopic)-only if urine dipstick abnormal</u> • Bacteria • Casts • Crystals • Epithelial cells • RBC • WBC	<u>Other Labs:</u> • Urine pregnancy test • Hemoglobin A_{1C} (HbA_{1C})

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

The number and percentage of patients with laboratory abnormalities (i.e., laboratory values outside the stated laboratory normal range) will be summarized at each time point (i.e., including baseline and post-baseline time points) for each laboratory parameter. The determination of laboratory abnormalities will take into account any unscheduled laboratory assessments. Additional lab-related summaries will be provided as follows for hepatic safety, musculoskeletal safety, diabetes and glycemia, and renal safety.

5.4.4.1 Hepatic Safety

For liver-associated enzymes and total bilirubin (TB), the number and percent of patients with abnormal values for ALT (>3 × ULN, > 5 × ULN), AST (> 3 × ULN, > 5 × ULN), and TB (> 2×ULN) will be summarized by overall, normal baseline ALT/AST/TB and abnormal baseline ALT/AST/TB.

Hy's law criteria (> 3 × upper limit of normal [ULN] for either ALT or AST, with accompanying TB > 2 × ULN) will also be applied to the data; any potential Hy's law cases will be listed separately. 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.

The number and percentage of patients experiencing a single incident or confirmed and repeated incidence of abnormal liver function test values for ALT (>3 × ULN, >5 × ULN), AST (>3 × ULN, >5 x ULN), CK (>5 × ULN, >10 × ULN) and either ALT and/or AST (>3 × ULN, >5 × ULN) will be summarized by the previous treatment group in the parent study and overall in the OLE study. A single incident is defined as the patient experiencing only one abnormal incident of the liver function test value. Repeated and confirmed incidence is defined as the patient experiencing at least one of the following: the last on-study liver function test value is abnormal, the last on-treatment liver function test value is abnormal, or an abnormal liver function test value is followed by another abnormal liver function test value for the same test.

A separate listing for direct bilirubin will be provided for those who have Gilbert's syndrome.

5.4.4.2 Musculoskeletal Safety

CK levels will be summarized by the value and change from baseline in the value, by treatment group and visit as well as baseline eGFR category. In addition, the number and percent of patients with abnormal CK values (>5 X ULN, >10 × ULN) will be summarized. These summaries of patients with abnormal CK will be performed overall, normal baseline CK, and abnormal baseline CK.

5.4.4.3 Diabetes and Glycemia

For fasting glucose and $HbA1_C$ (%), a shift table from baseline with the number and percent of patients will be categorized as below:

Fasting glucose: >= 126 mg/dL; 100-125 mg/dL, and < 100 mg/dL;

$HbA1_C$ (%): >=6.5%; >5.5 to <=6.4% and <=5.5%.

These tables will be summarized by history of Diabetes.

Descriptive summary for fasting serum glucose and $HbA1_C$ will be provided by history of diabetics, previous treatment group in parent study and overall at each scheduled visit.

5.4.4.4 Renal Safety

Shift tables of eGFR category from baseline over the study, will be provided by previous treatment group in parent study and overall.

In addition, renal function abnormality will be identified as: (1) A creatinine change from baseline of > 1 mg/dL (2) eGFR value <30 mL/min/1.73m^2. A shift table from baseline with the number and percent of patients using the two categories will be presented.

5.4.5 Physical Examination (PE)

Listings of PE data will include only those records where the body system at the baseline PE was normal, but the body system at a post-baseline PE was marked as 'Change from previous exam, clinically significant'. Baseline is defined as the last value prior to the first dose of study medication in OLE study. Only changes from baseline PE findings that meet the definition of an AE will be recorded on the AE page of the eCRF and will be summarized with other AE outcomes.

5.4.6 Vital Signs and Weight

The observed values and changes from baseline of both parent study and OLE study in vital signs (heart rate, systolic blood pressure, diastolic blood pressure) and weight will be summarized using descriptive statistics by previous treatment group in parent study, overall and post-baseline time point.

Vital sign data will be listed for each patient, with increases from baseline of > 15 mmHg in systolic or diastolic blood pressure flagged.

6 DMC Analyses

Refer to DMC charter.

7 Reference

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3. Robinson JG. Management of Familial Hypercholesterolemia: A Review of the recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Managed Care Pharm. 2013;19(2):139-49.
4. Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling. FDA Draft Guidance. March 2010
5. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. Curr Opin Lipidol. 2012;23:282-9.
6. Glynn RJ, Laird NM, and Rubin DB. (1986). Selection modelling versus mixture modelling with nonignorable nonresponse. In H. Wainer (ed.), Drawing Inferences from Self-Selected Samples, pp. 115–142. New York: Springer.

8 Appendices

8.1 Appendix 1: Schedule of Events (Subject Visit Schedule)

Month	**0**	**3**	**6**	**9**	**12**	**15**	**18/EOT[1]**	**19/EOS[2]**
Week	**EOS Parent**	**Wk 12**	**Wk 24**	**Wk 36**	**Wk 52**	**Wk 64**	**Wk 78**	**Wk 82**
Visit Window	**30 Days pre-M0**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**±7 days**	**+14 days**
In-clinic Visit	**X**	**X**			**X**		**X**	**X**
Phone Visit			**X**	**X**		**X**		
Procedure								
Informed Consent	X							
Enrollment Criteria	X							
Medical History	X							
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Event Recording	X	X	X	X	X	X	X	X
Physical Exam	X				X		X	
Weight[3]	X	X			X		X	X
Vital Signs[4]	X	X			X		X	X
Urine Pregnancy Test[5]	X							
Clinical Safety Labs[6]	X	X			X		X	X
Basic Fasting Lipids[7]	X	X			X		X	X
Coagulation[8]	X							
ApoB and hsCRP	X	X			X		X	X
HbA_{1C}	X				X		X	X
IWRS Contact[9]	X	X			X		X	
Drug Dispensing	X	X			X			
Drug Return/ Compliance		X			X		X	

NOTE: For patients who withdraw from study drug treatment, but consent to be followed for safety assessments and return to clinic for these visit, the visits will occur according to the protocol schedule. Safety assessments should include clinical safety and basic lipid laboratories, adverse events (AEs), physical examination (PE), and vital signs. For patients who withdraw from study drug treatment, but consent to be followed for safety assessments by phone, the telephone contacts will occur according the protocol schedule with information regarding current health status and to collect information on AEs (eg, recent procedures, hospitalizations, and if the patient has died, the cause of death). If a patient does not provide consent to be followed for safety assessments per the protocol (either by returning to clinic or by phone), Visit Week 78/End of Treatment (EOT) will be scheduled as soon as possible and the patient will be asked to come back 4 weeks after last investigational medicinal product (IMP) dose for Visit Week 82/End of Study (EOS). No further visits will be scheduled.

[1] All procedures will be completed for all patients at either EOT or early withdrawal.

[2] All procedures will be completed for all patients 4 weeks after last IMP dose if completing the study or early withdrawal.

[3] Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

[4] Vital signs will include diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate (HR) and will be collected prior to any blood sample collection. Patient will rest for 5 minutes prior to assessments

[5] Urine pregnancy test in women of childbearing potential only
[6] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. Please refer to laboratory manual for detailed schedule of tests.
[7] Basic fasting lipids include total cholesterol (TC), calculated low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C,), and triglycerides (TG).
[8] Only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Month 0 and 3 to 5 days post-Month 0
[9] Interactive web response system (IWRS) contact at either an early withdrawal or an EOS visit to register study discontinuation visit date

8.2 Appendix 2: Adverse Event of Special Interest (AESI)

Adverse Event Terms per Protocol	Associated MedDRA Preferred Terms
Creatine kinase elevations	Blood creatine phosphokinase abnormal
Creatine kinase elevations	Blood creatine phosphokinase increased
Creatine kinase elevations	Blood creatine phosphokinase MM abnormal
Creatine kinase elevations	Blood creatine phosphokinase MM increased
New onset or worsening diabetes mellitus	Blood glucose abnormal
New onset or worsening diabetes mellitus	Blood glucose increased
New onset or worsening diabetes mellitus	Diabetes mellitus
New onset or worsening diabetes mellitus	Diabetes mellitus inadequate control
New onset or worsening diabetes mellitus	Diabetic ketoacidosis
New onset or worsening diabetes mellitus	Glucose tolerance impaired
New onset or worsening diabetes mellitus	Glucose urine present
New onset or worsening diabetes mellitus	Glycosuria
New onset or worsening diabetes mellitus	Glycosylated haemoglobin increased
New onset or worsening diabetes mellitus	Hyperglycaemia
New onset or worsening diabetes mellitus	Impaired fasting glucose
New onset or worsening diabetes mellitus	Ketoacidosis
New onset or worsening diabetes mellitus	Ketosuria
New onset or worsening diabetes mellitus	Ketosis
New onset or worsening diabetes mellitus	Type 2 diabetes mellitus
New onset or worsening diabetes mellitus	Urine ketone body present
Hepatic disorders	Alanine aminotransferase abnormal
Hepatic disorders	Alanine aminotransferase increased
Hepatic disorders	Aspartate aminotransferase abnormal
Hepatic disorders	Aspartate aminotransferase increased
Hepatic disorders	Blood bilirubin abnormal
Hepatic disorders	Blood bilirubin increased
Hepatic disorders	Hepatic enzyme abnormal
Hepatic disorders	Hepatic enzyme increased
Hepatic disorders	Hypertransaminaseaemia
Hepatic disorders	Liver function test abnormal
Hepatic disorders	Liver function test increased
Hepatic disorders	Transaminases abnormal
Hepatic disorders	Transaminases increased
Hypoglycemia	Blood glucose abnormal
Hypoglycemia	Blood glucose decreased
Hypoglycemia	Hypoglycaemia
Hypoglycemia	Hypoglycaemic coma
Hypoglycemia	Hypoglycaemic encephalopathy
Hypoglycemia	Hypoglycaemic seizure
Hypoglycemia	Shock hypoglycaemic
Metabolic acidosis	Metabolic acidosis
Muscular disorders	Muscular weakness
Muscular disorders	Muscle necrosis

Muscular disorders	Muscle spasms
Muscular disorders	Myalgia
Muscular disorders	Myoglobin blood increased
Muscular disorders	Myoglobin blood present
Muscular disorders	Myoglobin urine present
Muscular disorders	Myoglobinaemia
Muscular disorders	Myoglininuria
Muscular disorders	Myopathy
Muscular disorders	Myopathy toxic
Muscular disorders	Necrotizing myositis
Muscular disorders	Pain in extremity
Muscular disorders	Rhabdomyolysis
Neurocognitive/Neurologic disorders	Amnesia
Neurocognitive/Neurologic disorders	Cognitive disorder
Neurocognitive/Neurologic disorders	Confusional state
Neurocognitive/Neurologic disorders	Disorientation
Neurocognitive/Neurologic disorders	Memory impairment
Neurocognitive/Neurologic disorders	Mental status changes
Renal disorders	Acute kidney injury
Renal disorders	Acute prerenal failure
Renal disorders	Blood creatinine abnormal
Renal disorders	Blood creatinine increased
Renal disorders	Blood urea abnormal
Renal disorders	Blood urea increased
Renal disorders	Blood urea nitrogen/Creatinine ratio increased
Renal disorders	Creatinine renal clearance abnormal
Renal disorders	Creatinine renal clearance decreased
Renal disorders	Glomerular filtration rate abnormal
Renal disorders	Glomerular filtration rate decreased
Renal disorders	Gout
Renal disorders	Oliguria
Renal disorders	Prerenal failure
Renal disorders	Renal failure
Renal disorders	Renal function test abnormal
Renal disorders	Renal impairment