Statistical Analysis Plan

Title:	A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg QD when Added to Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9)-Inhibitor Therapy
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Product:	ETC-1002
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REVISION HISTORY

Item No.	Version Affected	Description of change
1	1.0, 1.1	Changed analysis set/definition from FAS to mITT.
2	1.1	Repatha treatment duration calculation and compliance were written in detail.
3	1.1	A non-parametric approach for hs-CRP and TG analysis were included.

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
ANCOVA	Analysis of covariance
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CK	Creatine kinase
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of Study
ETC-1002	Bempedoic acid
FSH	Follicle-stimulating hormone
GI	Gastrointestinal
HbA_{1C}	Glycosylated hemoglobin, Type A1C
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
[redacted]	
Hgb	Hemoglobin
hs-CRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
INR	International normalized ratio
mITT	Modified Intention-to-treat
IWRS	Interactive web response system
LDL-C	Low-density lipoprotein cholesterol
LDH	Lactate dehydrogenase
LOCF	last observation carried forward
LSM	Least square mean

Abbreviation or Specialist Term	Explanation
MACE	Major adverse cardiac event
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat analysis set
non-HDL-C	Non-high-density lipoprotein cholesterol
PCSK9	Proprotein convertase subtilisin/kexin type 9
PCSK9i	PCSK9 inhibitor
PE	Physical exam
PMM	Pattern mixture model
PT	Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
SP	Safety population
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TSH	Thyroid-stimulating hormone
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-1002-039. 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 1002-039 (Protocol Amendment 1, March 05, 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 assess the 2-month efficacy of bempedoic acid 180 mg/day versus placebo in the reduction of low-density lipoprotein cholesterol (LDL-C) in patients on proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9I) therapy.

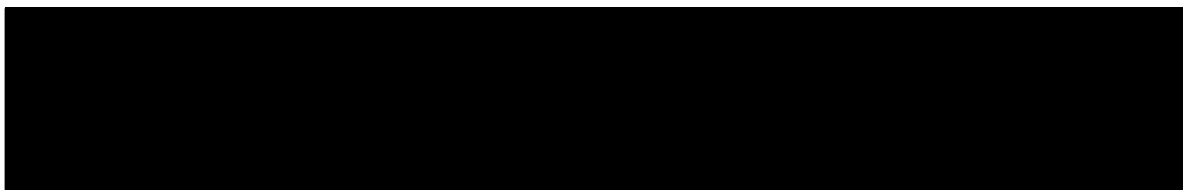
The secondary objectives are:

• To assess the 1-month efficacy of bempedoic acid 180 mg/day versus placebo in the reduction of LDL-C in patients on PCSK9i therapy

• To evaluate the effect of bempedoic acid 180 mg/day versus placebo on apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), and high-sensitivity C-reactive protein (hs-CRP) after 1 and 2 months in patients on PCSK9i therapy

• To evaluate the safety and tolerability of bempedoic acid 180 mg/day compared to placebo in patients on PCSK9i therapy

The exploratory objectives are:



3.2 Endpoints

The following endpoints will be used to evaluate the objectives of the study.

3.2.1 Primary Endpoint

• Percent change from baseline to Month 2 in LDL-C

3.2.2 Secondary Endpoints

• Percent change from baseline to Month 1 in LDL-C

• Change from baseline to Months 1 and 2 in LDL-C

• Percent change from baseline to Months 1 and 2 in ApoB, non-HDL-C, TC, and hs-CRP

• Safety and tolerability of bempedoic acid in this patient population over 2 months, as assessed by AEs and clinical laboratory values

3.2.3 Exploratory Endpoints

[redacted]

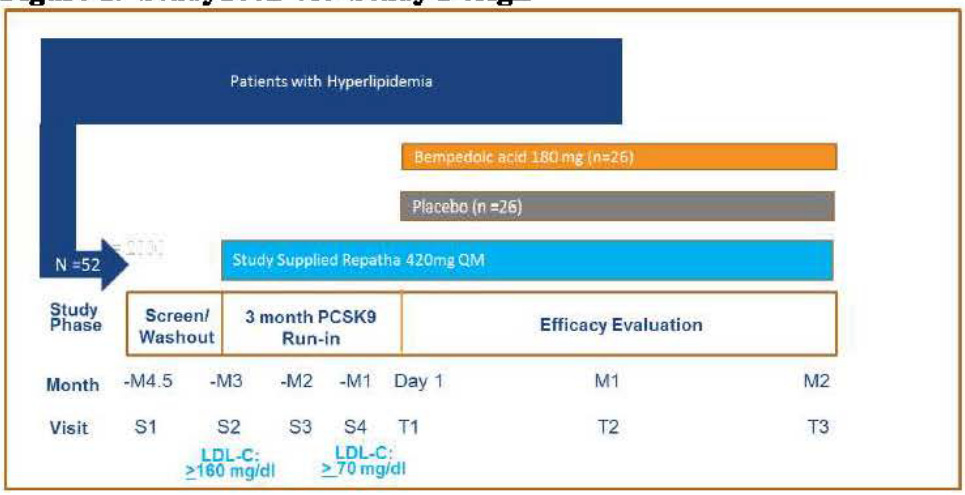
4 Study Design

4.1 Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled, parallel group multicenter study that will be conducted at approximately 20 clinical sites in North America. Screening Month -4.5 (Visit S1) will occur approximately 18 weeks prior to randomization. After providing informed consent at Visit S1, patients will stop all background lipid-lowering therapy and lipid-modifying nutritional supplements, if applicable. All patients will return to the clinic on Month -3 (Visit S2). During this visit, patients with an LDL-C value ≥160 mg/dL (via central or local lab) and triglycerides <500 mg/dL (via central or local lab) will initiate PCSK9 background therapy (Repatha 420 mg once monthly [QM]). Sites that do not use a local lab may need to bring patients back for another visit to administer PCSK9 background therapy, as a qualifying LDL value is required prior to initiating the 3-month PCSK9i run-in period. No other background lipid-modifying therapy except study provided PCSK9i will be permitted during the trial. After 1 month (at least 30 ± 3 days), patients will return to the clinic for Month -2 (Visit S3) followed by Month -1 (Visit S4) 30 ± 3 days later. During these visits, Repatha will be administered, labs will be collected, and safety assessed. At Visit S4, LDL-C will be checked a second time prior to randomization. Patients with an LDL-C ≥70 mg/dL (via central lab only) at this visit will qualify for randomization. Patients with LDL-C <70 mg/dL at Visit S4 will be screen failed and no further PCSK9i therapy will be administered. Day 1 should occur 30 days ± 3 days after Visit S4, once LDL-C eligibility is established. On Day 1, qualified patients will be randomized 1:1 to bempedoic acid 180 mg/day (n = 26) or matching placebo (n = 26). Randomized patients will return for clinic visits at Month 1 (Visit T2) and Month 2 (Visit

T3). Both study drug and PCSK9i doses will be administered on site during clinic visits after all procedures have been completed.

Figure 1. Study1002-039 Study Design



4.2 Randomization

Patients who satisfy all entry criteria, complete the 1.5-month screening period and 3-month PCSK9i run-in period and have an LDL-C ≥70 mg/dL at Visit S4 will be randomized. Randomization numbers will be assigned via IWRS on Day 1 (Visit T1). Patients will be randomized in a ratio of 1:1 to receive 1 of the following 2 treatments in a double-blind fashion in addition to monthly PCSK9i background therapy:

- Bempedoic acid 180-mg tablet
- Matching placebo tablet

4.3 Sample Size Justification

The planned total sample size for this study is 52 with 26 patients in the bempedoic acid 180 mg group and 26 in the placebo group. This sample size is expected to [redacted]

5 Statistical and Analytical Plans

5.1 General Statistical Considerations

Summary statistics for continuous variables will include the number of patients, mean, median, standard deviation or standard error, minimum, and maximum. 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.

For categorical variables, the frequency and percentage will be given. Percentage will be presented with one decimal place. 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 in order of patient, assessment date and assessment (in order collected on CRF, unless specified otherwise). Dates will be presented in format DDMMMYYYY.

The visit schedules and window are shown below.

Visit	S1	S2	S3	S4	T1	T2	T3, EOS
Slotted Study Month	Month -4.5	Month -3	Month -2	Month -1	Week 0	Month 1	Month 2
Target Study Day	NA	Day of first 420mg PCSK9i injection	Day of 420mg PCSK9i injection during S3	Day of 420mg PCSK9i injection during S4	Day 1	Day 31	Day 61
Analysis Visit Windows	NA	within 21 days prior to 420mg PCSK9i injection	420mg PCSK9i injection during S3 visit ± 3 days	420mg PCSK9i injection during S4 visit ± 3 days	PCSK9i injection (regardless dose) during T1 visit ± 3 days	T1 injection of PCSK9i (regardless dose) + 30 ± 3 days	T2 injection of PCSK9i (regardless dose) + 30 ± 3 days
Protocol Defined Visit Window	-135	-90±3	-60±3	-30±3	1	31±3	61±3

The details of visit window derivations will be described on the programming specifications.

5.2 Statistical Analysis Plans

5.2.1 Analysis Sets

5.2.1.1 Safety Population (SP)

The Safety Population (SP), used for all of the safety summaries, is defined as all randomized patients who received at least 1 dose of double-blind study medication. Patients in the SP will be included in the treatment group that they actually received, regardless of their randomized treatment.

5.2.1.2 Modified Intent to Treat (mITT) Analysis Set

The Modified Intent to Treat (mITT) Analysis Set, used for all of the efficacy analyses, is defined as all randomized patients with a baseline lipid value, at least 1 post-baseline lipid value, and having taken 1) their study drug within 2 days prior to the lipid measurement and 2) Repatha 420 mg within 30 days +/- 3 days prior to the lipid measurement. Patients in the mITT analysis set will be included in their randomized treatment group, regardless of the treatment they actually received.

5.2.1.3 Treatment Completer Set

The treatment completer set includes patients who were in mITT analysis set, and received all planned PCSK9i dosing as well as the double-blinded treatment, as indicated on the end of treatment CRF. Sensitivity analysis for primary and secondary efficacy endpoints will be performed using the treatment completer set.

5.2.1.4 Pharmacokinetic Analysis Set (PK)

The PK Analysis Set will include all subjects in the safety analysis set who have at least one PK assessment. These patients will be evaluated for PK concentration summaries unless significant protocol deviations have affected the data or if key dosing or sampling information is missing.

5.2.2 Baseline Definition

Baseline LDL-C, TC, non-HDL-C, [redacted] is defined as the average of last two non-missing values within Visit S4 and Day 1 (including unscheduled assessments), if only 1 value is available, then that single value will be used as baseline.

Baseline value for ApoB and hs-CRP will be the Day 1 value.

If missing value presented at Visit S4 or Day 1, then the last non-missing value prior to the first dose of double-blind study medication (including unscheduled assessments) within Visit S4 and Day 1 will be used to compute the baseline for lipid measurements.

Baseline of the laboratory evaluations, vital signs and physical examination is defined as the last non-missing value prior to the first dose of study medication, except baseline of blood pressure is defined as average of measures at same visit.

5.2.3 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 using blinded review of the database with regard to prohibited therapies, and timing and availability of planned assessments. The determination of major versus minor protocol deviations will be conducted prior to the database lock. Any major protocol deviation will be summarized by treatment group, and all protocol deviation will be listed.

5.2.4 Patient Disposition

Disposition, including reason for withdrawal from the study drug and study, will be summarized by treatment group. In addition, the number of patients who withdraw from the study and withdraw from study drug will be summarized by discontinuation reason.

5.2.5 Demographic and Baseline Characteristics

Demographic information and important patient baseline characteristics including, but not limited to, gender, race, age, baseline vital sign, and baseline lipid parameter values will also be summarized by treatment group.

The following demographic and baseline characteristics will be summarized by treatment group, as well as overall, for safety population and for mITT: age (years), gender, race, ethnicity, height (cm), weight (kg), body mass index (kg/m^2), systolic and diastolic blood pressure (mmHg), heart rate (bpm), fasting lipid parameters (TC [mg/dL], calculated LDL-C [mg/dL], [redacted] non-HDL-C [mg/dL] and [redacted] ApoB (mg/dL), and hs-CRP (mg/dL). 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).

5.2.6 Medical History

General medical history will be summarized by treatment group, as well as overall, for safety population and mITT population and presented in a by-patient listing. Where appropriate, terms will be coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA).

5.2.7 Prior Medications and Concomitant Medications/Procedures

Prior medications are defined as medications that ended prior to the initiation of double-blind study drug. Concomitant medications are defined as medications that were ongoing at the time of double-blind study drug initiation or new medications that started post double-blind 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 (Sept 2016, or later). The frequency of use of prior medications and use of concomitant medications will be summarized by treatment group, as well as overall, for the safety population according to Anatomical Therapeutic Chemical (ATC) class and preferred term. Prior medications, concomitant medications, and concomitant procedures will be listed for each patient.

5.2.8 Study Drug (ETC-1002 or placebo) Exposure and Compliance

The length of exposure to study drug (ETC-1002 or placebo) will be calculated as the number of days from the first dose of double-blind study drug to the last dose of double-blind study drug, regardless if the patient missed one or more doses of study drug. Length of exposure to study drug during the double-blinded period will be summarized by treatment group using descriptive statistics for the safety population.

The number and percentage of patients who were compliant with taking study drug will be summarized by treatment group and post-baseline time point for the safety population for the following categories <80%; >= 80%. Compliance for study drug will be assessed 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–Number Returned) / (Duration in days between study drug dispensed and study drug returned). Overall compliance during the study will be calculated by programmer.

Administration and compliance data of the study drug, including reasons for poor compliance, will be listed for each patient.

5.2.9 Repatha Exposure and Compliance

The length of exposure to Repatha for run-in and double-blinded period will be calculated as the number of days from the first dose of Repatha to the last dose of Repatha + 30 days within run-in and double-blinded period, respectively, regardless if the patient missed one or more doses of study drug. The exposure to Repatha (in total doses) will be summarized during the run-in period in an overall group, as well as within the treatment group during the double-blind period. Length of exposure to Repatha (in total doses) for overall group during run-in and by treatment group during double-blinded period will be summarized using descriptive statistics for the safety population.

The number and percentage of patients who were compliant with taking Repatha will be summarized by treatment group for the safety population for the following categories <80%; >= 80%. For Repatha Compliance, it will be calculated using the formula: 100 * (Total number of Repatha administration with 420 mg/number of planned injections). The number of planned injections are 3 and 2 for run-in and double-blinded period, respectively.

Administration and compliance data of Repatha, including reasons for poor compliance, will be listed for each patient.

5.3 Efficacy Endpoints and Analyses

5.3.1 For all efficacy endpoints and analyses, the Modified Intent to Treat (mITT) analysis set will be used. Primary Endpoint Analysis

The primary efficacy endpoint is the percent change from baseline to Month 2 in LDL-C. If triglycerides (TG) > 400 mg/dL or LDL-C < 50 mg/dL, LDL-M instead of LDL-C will be used as primary efficacy endpoint. The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group as a factor and baseline LDL-C as a covariate. The ANCOVA will be performed using the mITT, with patients included in their randomized treatment group regardless of the treatment they actually received. Patients who are missing their Month 2 LDL-C will have their Month 2 value imputed by last post-baseline observation carried forward (LOCF). The least squares mean (LSM) and standard error (SE) for percent change estimate will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% confidence interval (CI) and associated p-value.

The ANCOVA assumptions will be examined and nonparametric test or transformation of the data will be considered if these assumptions are not met. A non-parametric approach using Wilcoxon rank sum test will be performed on percent change from baseline for hs-CRP and TG. The median treatment difference (location shift) and 95% CI from Hodges-Lehmann estimates will be also presented.

An example sas code for ANCOVA analysis is shown as below:

```
PROC MIXED DATA=adxx method=reml;
    class usubjid armcd;
    model pchg = blres armcd  / solution ddfm=kenwardroger;
    repeated/group=armcd;
    lsmeans armcd / diff  cl;
```

Missing data for the primary endpoint will be imputed using the last post-baseline observation carried forward (LOCF) procedure (only post-baseline values will be carried forward).

A secondary analysis for the primary endpoint will be conducted use observed data only.

The same analysis will be performed as sensitivity analysis on treatment completer set for primary efficacy endpoint.

The mean (± SE) will be plotted for primary efficacy endpoint by visit.

5.3.2 Secondary Efficacy Endpoint Analyses and Exploratory Endpoint Analyses

The secondary efficacy endpoints (percent change from baseline to Month 1 in LDL-C; change from baseline to Months 1 and 2 in LDL-C; percent change from baseline to Months 1 and 2 in ApoB, non-HDL-C, TC, and hs-CRP) will be analyzed using the ANCOVA method similar to the primary endpoint. Each ANCOVA will be performed using the mITT, with patients included in their randomized treatment group regardless of the treatment they actually received. Missing values will be imputed using LOCF, where

applicable. For each parameter and analysis time point, the LSM and SE will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% CI and associated p value.

All efficacy endpoints will be analyzed at a significance level of 0.05, no multiplicity adjustment will be implemented. We will analyze observed data and LOCF data separately.

The same analysis will be performed as sensitivity analysis on treatment completer set for secondary efficacy endpoints.

The mean (± SE) will be plotted for secondary efficacy endpoints by visit.

Exploratory endpoints [redacted] will be summarized by descriptive statistics.

5.3.3 Pharmacokinetics

Plasma concentrations of bempedoic acid and ESP15228 will be expressed in ng/mL. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the lower limit of quantification will be treated as zero in summary statistics.

PK observations with missing concentration, missing dose, missing elapsed time will be flagged as such in the concentration data listings and excluded from PK statistical summary.

PK concentration with elapsed time less than 18 or more than 30 hours post-dose (most recent dose) will be flagged as "out of sampling window" in the concentration data listings and excluded from descriptive statistics.

Three trough plasma concentrations of bempedoic acid and ESP15228 will be summarized from patients at pre-dose (T1), T2, and T3 using descriptive statistics, including subject numbers, mean, standard deviation, CV, median and range.

Population PK analysis may be performed if needed. The result will be reported separately from the clinical study report (CSR).

5.4 Safety Endpoints and Analyses

For all safety endpoints, the safety population (SP) will be used. Descriptive summaries will be provided for safety endpoints.

The summarization of AEs will include TEAEs defined as AEs that begin or worsen after the first dose of double-blind study drug administration and ingestion of the first dose of study drug until 30 days after last dose of study drug. The AEs reported during the Repatha run-in period will be summarized separately by overall group. All TEAEs, SAEs, related AEs (to IMP or to Repatha), AEs leading to withdrawal of the study drug or Repatha and study, fatal AEs and AEs of special interest will be summarized by MedDRA System

Organ Class (SOC) and Preferred Term (PT) in descending order of frequency by treatment group.

Clinical safety laboratories, including hematology, blood chemistry, HbA1C, glucose, and urinalysis; PE findings; vital signs; and weight will be summarized by the value and by change from baseline in the value (where appropriate) at each post-baseline time point.

5.4.1 Adverse Events (AEs)

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or later and will be categorized by MedDRA SOC and preferred term (PT). Patients with AEs that are ongoing at study completion or study withdrawal must be followed until resolution, until stable/chronic, 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).

In summary tables, TEAEs will be counted as "Not Related" if relationship to IMP was assessed as 'Not Related' or "Unlikely". Events will be counted as "Related" if relationship to IMP was assessed as 'Possible', 'Probable', 'Definite', or if relationship to IMP is missing. TEAEs related to the Repatha will be summarized in the similar fashion.

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

The run-un period will be defined as the period subjects receive Repatha prior to Visit T1. It's 3 months prior to Visit T1.

Overviews of TEAEs will be presented by treatment group containing the following counts and percentages for:

- Patients with AE during the run-in period
- patients with TEAEs
- patients with TEAEs by SOC and PT
- patients with AEs during run-in period by SOC and PT
- patients with TEAEs by maximum severity
- patients with treatment-related TEAEs by IMP or by Repatha
- patients with SAE during the run-in period
- patients with treatment-emergent serious adverse events (TE SAEs)
- patients with TE SAEs by SOC and PT
- patients with SAEs during the run-in period by SOC and PT

- patients with TE SAEs by maximum severity
- patients with treatment-related TE SAEs by IMP or by Repatha
- withdrawal from study drug due to TEAEs
- patients with TEAE by PT
- patients with TE SAEs by PT
- patients with study drug-related TEAEs by PT

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.

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 (pain in extremity, myalgia, arthralgia, and muscle spasms), nervous system disorders (headache), and gastrointestinal disorders (nausea and diarrhea).

As with other lipid lowering medications, adverse events of special interest (AESI) include hepatic disorders (including changes in hepatic aminotransferases), musculoskeletal events (AE and CK evaluation), new onset diabetes/hyperglycemia, renal events, and neurocognitive/neurologic events. These events will be evaluated from the AE database by SOC and PT, and will be identified as safety monitoring endpoints.

- AEs of muscle-related symptoms will be summarized by treatment group. In addition, the number and percent of patients with abnormal CK values will be summarized.

- New onset diabetes/hyperglycemia will be recorded as AEs and will be summarized using the appropriate SOC. The events will be summarized by severity and relationship to study drug for each treatment group.

- Baseline eGFR and values of CK will be summarized by treatment group and by baseline eGFR categories. Shift tables of eGFR category from baseline over the study, will be provided by treatment group.

- Neurocognitive events will be identified and evaluated by routine monitoring of PE findings and AEs. Summarization of neurocognitive events will occur using pre-specified MedDRA terms and will be performed by treatment group.

- Hypoglycemia/Metabolic acidosis occurrences will be summarized based on AE evaluations.

AESI will be presented in a listing and summarized by SOC, PT and treatment group.

5.4.3 Laboratory Evaluations

Continuous laboratory parameters (serum chemistry, hematology), urinalysis, urinalysis [microscopic]) listed in Table 4; glucose, and HbA1c will be summarized using descriptive statistics for the observed value and the change from baseline for all post-baseline study visits. 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.

Table 4: Clinical Laboratory Parameters (Safety)

Hematology • 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 %) 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 • Red blood cell (RBC) • WBC	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) • Total protein • Uric acid Coagulation (only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Visit T1 and 3 to 5 days post Visit T1) • Prothrombin time (PT) • International normalized ration (INR) Additional samples • Hemoglobin A1C (HbA1C) • PK

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 hyperglycemia, and renal safety.

5.4.3.1 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 treatment group and overall, normal baseline ALT/AST/TB and abnormal baseline ALT/AST/TB.

Potential 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.

5.4.3.2 Renal Safety

Baseline eGFR and values of CK will be summarized by treatment group and by baseline eGFR categories. Shift tables of eGFR category from baseline over the study, will be provided by treatment group.

5.4.4 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.' 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.

5.4.5 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 on the observed values. 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.

For vital signs, observed values and changes from baseline will be summarized for all post-baseline study visits.

6 Changes in Statistical Analysis Plan Based on the Study-Specific Protocol

1. To be consistent with other Esperion studies, the LDL-M will be used as primary endpoint where triglycerides (TG) > 400 mg/dL or LDL-C < 50 mg/dL for primary efficacy endpoint analysis.

2. The treatment completer set will be used for sensitivity analyses of primary and secondary efficacy endpoints.

3. AEs during run-in period will be summarized.

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. 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)

	Schedule of Events						
Visit	**S1[1,2]**	**S2**	**S3**	**S4**	**T1**	**T2**	**T3/EOS[3]**
Month	**Month -4.5**	**Month -3**	**Month -2**	**Month -1**	**Week 0**	**Month 1**	**Month 2**
Day **Procedure**	**Day -135**	**Day-90 ±3**	**Day -60 ±3**	**Day -30 ±3**	**Day 1***	**Day31 ±3**	**Day61 ±3**
Informed Consent	X						
Enrollment Criteria	X	X	X	X			
Demographics	X						
Medical History	X						
Concomitant Medications	X	X	X	X	X	X	X
Adverse Event Recording		X	X	X	X	X	X
Physical Exam		X					X
Weight[4]	X				X		X
Height	X						
Vital Signs[6]	X	X	X	X	X	X	X
Serology[7]	X						
Serum Pregnancy/FSH[8]	X						
Urine pregnancy test for women of childbearing potential only					X		

	Schedule of Events						
Visit	**S1[1,2]**	**S2**	**S3**	**S4**	**T1**	**T2**	**T3/EOS[3]**
Month	**Month -4.5**	**Month -3**	**Month -2**	**Month -1**	**Week 0**	**Month 1**	**Month 2**
Day **Procedure**	**Day -135**	**Day-90 ±3**	**Day -60 ±3**	**Day -30 ±3**	**Day 1***	**Day31 ±3**	**Day61 ±3**
TSH	X						
Clinical Safety Labs[9]	X				X	X	X
Basic Fasting Lipids[10]	X	X**	X	X***	X	X	X
ApoB and hs-CRP		X			X	X	X
HbA_{1C}	X				X		X
PK – predose trough					X	X	X
Diet and exercise counseling[11]	X	X			X	X	X
Establish Patient Eligibility					X		
Randomization					X		
IWRS Contact[12]	X				X	X	X
PCSK9i administered at site		X	X	X	X	X	
Double-blind Drug Dispensing					X	X	
IMP Return/Compliance						X	X
PCSK9i Return/Accountability		X	X	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. 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 T4 will be considered the End of Study (EOS)/Early Withdrawal from study and no further visits will be scheduled.

1 An optional basic fasting lipid MAY be completed prior to S2, but must occur just prior to the next witnessed PCSK9i dose if patient fails to meet lipid entry criterion at Visit S1. If this optional basic fasting lipid is completed, the average of the 2 lipid values will be used to determine eligibility.

2 A recheck of blood pressure may be completed prior to T1 if the patient's diastolic blood pressure (DBP) and/or systolic blood pressure (SBP) meet the exclusion criteria levels. Patients may randomize after blood pressure medications have been adjusted, the patients have been on stable doses of blood pressure medications for at least 2 weeks, and the repeat blood pressure values (DBP and/or SBP) do not meet exclusionary values. Repeat labs may be completed prior to T1 to determine eligibility if the patient's estimated glomerular filtration rate (eGFR), alanine aminotransferase (ALT), aspartate aminotransferase (AST) or other labs meet exclusion criteria levels. If this optional lab is completed, the repeated value will be used to determine eligibility.

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

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

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

7 Serology for HBsAg, HCV-ABVivi

8 Pregnancy test completed in women of child-bearing age only. FSH in naturally postmenopausal women ≥1 year without menses and <55 years;

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

10 Basic fasting lipids include total cholesterol (TC), calculated low-density lipoprotein cholesterol (LDL-C), [redacted] non-HDL-C,), and [redacted].

11 Diet and exercise counseling per local and/or regional guidelines for the management of hyperlipidemia.

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

*Patients must be on PCSK9 for 30± ***3*** days during each month of the PCSK9 run-in period before initiating Day 1.

** LDL-C must be ≥160 mg/dL and TG <500 mg/dL before initiating PCSK9i. A local lab may be used to assess LDL-C and TG for eligibility prior to initiating Repatha, but a central lab must also be conducted at this visit.

*** LDL-C must be ≥70 mg/dL to qualify for randomization. Only a central lab may be used to assess entry LDL-C.