Statistical Analysis Plan

Title:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER LONG-TERM SAFETY AND TOLERABILITY STUDY OF ETC-1002 IN PATIENTS WITH HYPERLIPIDEMIA AT HIGH CARDIOVASCULAR RISK WHO ARE NOT ADEQUATELY CONTROLLED BY THEIR LIPID-MODIFYING THERAPY
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1 List of Abbreviations

Abbreviation or Specialist Term	Explanation
ADR	Adverse drug reaction
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
ASCVD	Atherosclerotic cardiovascular diseases
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CABG	Coronary artery bypass graft
CEC	Clinical Events 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
CPK	Creatine phosphokinase
CrCL	Creatinine clearance
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of Study
EU	European Union
FAS	Full analysis set

Abbreviation or Specialist Term	Explanation
FDA	U.S. Food and Drug Administration
FPFV	First patient first visit
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HbA_{1C}	Glycosylated hemoglobin, Type A1C
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HCV-AB	Hepatitis C antibodies
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
hsCRP	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
IMP	Investigational Medicinal product
IRB	Institutional Review Board
ITT	Intention-to-treat
IWRS	Interactive web response system
K	Potassium
LDH	Lactate dehydrogenase
LDL-C	Low-density lipoprotein cholesterol
LDLR	LDL receptor
LFT	Liver function test
LMT	Lipid Modifying Therapy
LPLV	Last patient last visit
LSM	Least square mean
MACE	Major adverse cardiac event
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of diet in renal disease
MED ID	Medication identification
MI	Myocardial infarction

Abbreviation or Specialist Term	Explanation
MRI	Magnetic resonance imaging
Na	Sodium
NCEP	National Cholesterol Education Program
NOAEL	No-observed-adverse-effect level
non-HDL-C	Non-high-density lipoprotein cholesterol
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PE	Physical exam
PK	Pharmacokinetic(s)
PMM	Pattern mixture model
PT	Prothrombin time
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
SOP	Standard operating procedures
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
TIA	Transient ischemic attack
TSH	Thyroid-stimulating hormone
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-1002-040. 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-1002-040 (Protocol Amendment 5, 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 evaluate the long-term safety and tolerability of ETC-1002 (bempedoic acid) versus placebo in high cardiovascular (CV) risk patients with hyperlipidemia (with underlying heterozygous familial hypercholesterolemia [HeFH] and/or atherosclerotic cardiovascular diseases [ASCVD]) who are not adequately controlled with their maximally tolerated lipid-modifying therapy.

The secondary objective is to assess the efficacy as the percent change from baseline to Week 12 in low-density lipoprotein cholesterol (LDL-C). This is the primary efficacy endpoint.

The tertiary objectives are:

• To assess percent change from baseline to Week 24 and to Week 52 in LDL-C in patients who do not receive adjunctive lipid lowering therapy.

• To assess high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol (TC), and triglycerides (TG) values at Week 12, 24 and 52.

• To assess apolipoprotein B (apoB) and high-sensitivity C reactive protein (hsCRP) values at Week 12, 24, and 52.

3.2 Primary Safety Endpoints

The primary safety endpoint for this study is general safety, which includes adverse events (AEs), clinical safety laboratories, physical examinations (PEs), vital signs, and electrocardiogram (ECGs).

3.2.1 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 IMP until 30 days after last dose of IMP. Clinical endpoints 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).

3.2.2 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 and changes from baseline will be summarized for all post-baseline study visits.

3.2.3 ECG, Vital Signs and PE

The evaluation of ECG and vital signs (including heart rate, systolic blood pressure, diastolic blood pressure, weight, height [baseline only], and body mass index [BMI]), 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.'

3.3 Primary Efficacy Endpoints

3.3.1 Primary Efficacy Endpoint

Percent change from baseline to Week 12 in LDL-C

3.3.2 Key Secondary Efficacy Endpoints

1) percent change from baseline to Week 24 in LDL-C
2) percent change from baseline to Week 12 in non-HDL-C
3) percent change from baseline to Week 12 in TC
4) percent change from baseline to Week 12 in apoB
5) percent change from baseline to Week 12 in hsCRP

3.3.3 Other Efficacy Endpoints

Percent change or change in LDL-C, HDL-C, TGs, TC, non-HDL-C, hsCRP, and apoB values at other protocol-scheduled time points will also be evaluated as secondary efficacy endpoints (See Section 5.3 for more information)

Proportion of patients achieving LDL-C < 70 mg/dL at week 12, 24 and 52 will be evaluated.

3.4 Pharmacokinetic (PK) and Other Biomarkers

Trough plasma concentrations will be collected at Weeks 12, 24, and 52 from patients randomized into the study prior to the implementation of Protocol Amendment 3 for use in further developing the population pharmacokinetic (PK) model. Trough plasma

concentrations will not be collected from patients randomized into the study after the implementation of Protocol Amendment 3 in the EU, Protocol Amendment 4 in the US. PK analysis will be based on PK concentration population using the actual treatment received.

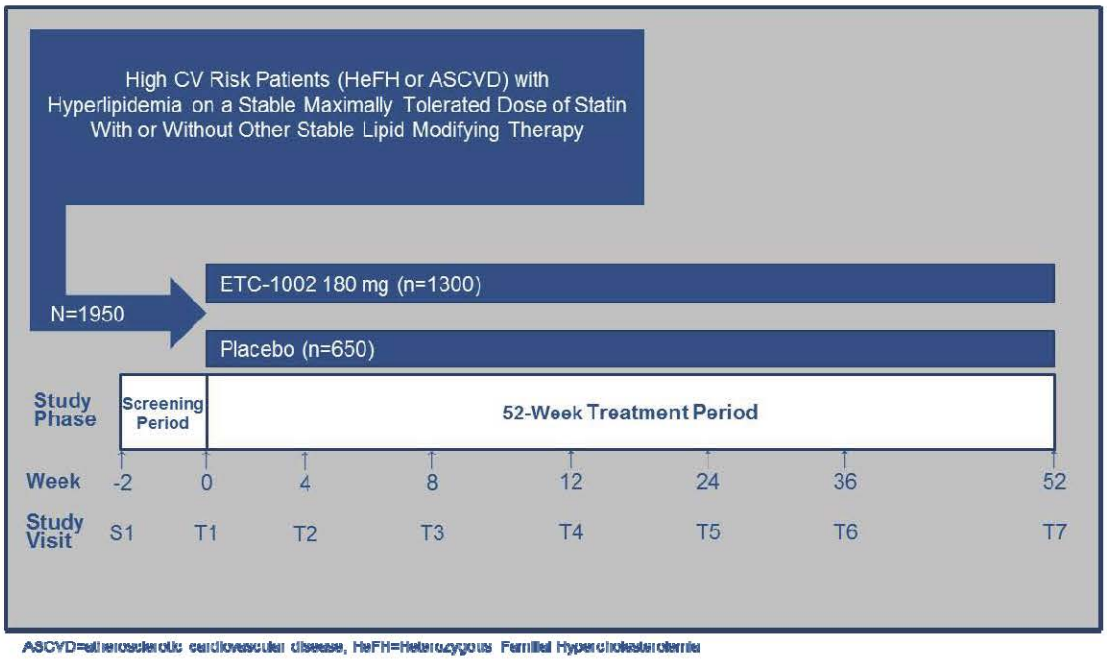
4 Study Design

4.1 Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group study evaluating the long-term safety and tolerability of ETC-1002 in high cardiovascular (CV) risk patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who are not adequately treated with their maximally tolerated lipid-modifying therapy. Maximally tolerated lipid-lowering therapy includes a maximally tolerated statin alone or in combination with other lipid-lowering therapies, in patients with hyperlipidemia. A patient's maximally tolerated lipid-modifying therapy will be determined by the investigator using their medical judgment and available sources, including the patient's self-reported history of lipid-modifying therapy.

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 28 months.

Figure 1. Study 1002-040 Study Design



ASCVD=atherosclerotic cardiovascular disease, HeFH=Heterozygous Familial Hypercholesterolemia

4.2 Study Treatments and Assessments

Screening (Visit S1) will occur approximately 2 weeks prior to Day 1 (Visit T1). Patients on maximally tolerated lipid-lowering therapy, as determined by the investigator, will be stratified based on CV risk (HeFH and ASCVD diagnosis) and baseline statin dose category defined in Table 1, where baseline statin dose category is defined in Table 2. There will be no cap placed on randomization into any particular stratum. Patients will be placed in the baseline statin dose category based on their average daily statin dose (some patients do not take a daily statin; for those who do not, their baseline statin category will be based on the average daily statin dose rather than on the actual statin dose).

Table 1: Randomization Strata

HeFH (with or without ASCVD)	ASCVD (without HeFH)
HeFH+ Low Intensity Statins	ASCVD + Low Intensity Statins
HeFH+ Moderate Intensity Statins	ASCVD + Moderate Intensity Statins
HeFH+ High Intensity Statins[a]	ASCVD + High Intensity Statins[a]

ASCVD = Atherosclerotic cardiovascular diseases; HeFH = Heterozygous familial hypercholesterolemia.

[a] Simvastatin with doses ≥40 mg/day are not allowed in this study.

Table 2: Baseline Statin Dose Categories

High Intensity Statins	Moderate Intensity Statins	Low Intensity Statins[a]
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin 20-40[b] mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

[a] Low intensity statins also include those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week)

[b] Simvastatin with doses ≥40 mg/day are not allowed in this study.

The investigational products were listed in Table 3 below:

Table 3: Investigational Medicinal Products

	Investigational Medicinal Product	
Product Name:	ETC-1002	Placebo
Dosage Form:	Film-coated tablets	Film-coated tablets
Unit Dose:	180 mg	Not applicable
Container/Closure[a]	35- and/or 100-count bottle (depending upon visit) with screw on, non-child proof cap	35- and/or 100-count bottle (depending upon visit) with screw on, non-child proof cap
Route of Administration:	Oral, daily (once every 24 hours, at approximately the same time each day), with or without food	Oral, daily (once every 24 hours, at approximately the same time each day), with or without food
Physical Description:	Oval, white to off-while film-coated tablet debossed with "ABC" on one face and debossed with "000" on the opposite face	Oval, white to off-while film-coated tablet debossed with "ABC" on one face and debossed with "000" on the opposite face
Manufacturer (Fill/Finish):	Norwich Pharma Services 6826 State Highway 12 Norwich, New York 13815 AND: Patheon 2100 Syntex Court Mississauga, Ontario L5N 7K9 Canada	Norwich Pharma Services 6826 State Highway 12 Norwich, New York 13815 AND: Patheon 2100 Syntex Court Mississauga, Ontario L5N 7K9 Canada

[a] A 100-day supply of IMP will be included in the 100-count bottle and a 35-day supply of IMP will be included in the 35-count bottle.

Randomized patients will continue in the study until they have completed Week 52 (Visit T7). Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 8 (Visit T3), Week 12 (Visit T4), Week 24 (Visit T5), Week 36 (Visit T6), and Week 52 (Visit T7).

Patients on an average daily dose of simvastatin 40 mg will be scheduled for the additional Visit T4.1 (Week 16) and T5.1 (Week 28) for clinical safety laboratory evaluations specifically to monitor changes in creatine phosphokinase (CPK) and liver function tests (LFTs). On Visit T4.2 (Week 20, phone only), and T5.2 (Week 32, phone only), these patients will be monitored for AE and SAE occurrences.

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 (Patient 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 cardiovascular 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

For patients who satisfy all entry criteria and complete the 2-week screening period, randomization will occur and their randomization number will be assigned via IWRS at Week 0 (Visit T1). Patients will be stratified on CV risk (HeFH and ASCVD diagnosis) and baseline statin dose and randomized in a ratio of 2:1 to receive 1 of the 2 following treatments in a double-blind fashion:

- ETC-1002 180-mg tablet
- Matching placebo tablet

For details regarding the randomization strata see Table 1.

The randomization code for treatment and IMP packaging will be generated by the Clinical Supply Chain (CSC) department following specifications from the Biostatistics Department. Patients will be randomly assigned to treatment and IMP packing through Interactive Web-based Response System (IWRS). This system is used to ensure a balance across treatment groups within each randomization stratum; no effort will be made to maintain a balance among treatment groups within an investigational center.

4.4 Sample Size Justification

A total of 1950 patients will be enrolled in this study with 1300 patients randomized to ETC 1002 and 650 patients randomized to placebo. Using an anticipated overall dropout rate of 7.5% at 6 months exposure and 10.0% at 12 months exposure in each treatment group, the expected number of patients exposed to treatment during the study is as follows:

	Patients ≥6 Months	Patients ≥12 Months
ETC-1002	1,202	1,170
Placebo	601	585

Absolute risk will be addressed by 1300 patients randomized to ETC-1002 and will provide at least 95% power to detect AEs that occur at rates similar to those seen in the placebo group for the AEs of interest in the recently completed long-term safety study entitled Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events [5]. In this study, adverse event rates ranged from 0.5% to 13.6%. Additional assumptions include a two-sided test with significance level at 0.05.

When AEs occur at a range of rates similar to those seen in the placebo group in the above referenced alirocumab study (0.5% to 13.6%), the sample size of 1300 patients randomized to ETC 1002 and 650 patients randomized to placebo will allow for detection of relative risks of 1.0 and of 2.0 (ETC-1002: placebo) with the following approximate 95% confidence limits:

% Placebo Patients Experiencing AE	% ETC-1002 Patients Experiencing AE	Relative Risk	Approximate 95% Confidence Interval
0.5%	0.5%	1.0	(0.3, 3.8)
0.5%	1.0%	2.0	(0.6, 6.7)
13.6%	13.6%	1.0	(0.8, 1.3)
13.6%	27.2%	2.0	(1.6, 2.5)

4.5 Interim Analyses, Final Analyses and Unblinding

No interim analysis is planned for this study.

The final analysis will be performed after the database is locked, the treatment assignments are unblinded using the actual randomization, and the database released.

An independent external Data Monitoring Committee (DMC) has been established for this study. Detailed information about the responsibilities and operation of the DMC were provided in the DMC Charter.

4.6 Changes from Protocol Planned Analyses

1) Additional subgroup analysis and sensitivity analyses are proposed and described in this SAP.
2) It is clarified in the SAP that study objectives are supported by both primary safety and primary efficacy endpoints.
3) Multiplicity adjustment amongst efficacy endpoints is implemented and described in this SAP.

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 PK data will be reported as observed. No imputation will be performed for missing data, except for the missing lipid efficacy data (Please refer to Section 5.3.2 for more details). Descriptive statistics (n, mean, standard deviation [SD], Q1, Q3, 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.

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.

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.

Baseline for fasting lipid parameters including LDL-C, TC, HDL-C, non-HDL-C, and Triglycerides are defined as the average of S1 and T1 values (last two non-missing values on or prior to Day 1). If only one value is available, the single value will be used as baseline. For other parameters including apoB and hsCRP, the 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	S1	T1	T2	T3	T4	T5	T6	T7, EOS
Slotted Study Week	-2	0	4	8	12	24	36	52
Target Study Day	-16	1	29	57	85	169	253	365
Visit Windows	[-∞,-1]	[1,1]	[2,43]	[44,71]	[72,127]	[128,211]	[212,309]	[310,∞]
Study Day Range	-16 to -4	1	29±3	57±3	85±3	169±7	253±7	365±7

For Patients on an average daily dose of simvastatin 40 mg, the visit schedules and windows are shown below only for clinical safety laboratory evaluations in creatine phosphokinase (CPK) and LFT related listings and tables.

Visit	S1	T1	T2	T3	T4	T4.1	T4.2	T5	T5.1	T5.2	T6	T7, EOS
Slotted Study Week	-2	0	4	8	12	16	20	24	28	32	36	52
Target Study Day	-16	1	29	57	85	112	140	169	196	224	253	365
Visit Windows	[-∞, -1]	[1, 1]	[2, 43]	[44, 71]	[72, 99]	[100, 127]	[128, 155]	[156, 183]	[184, 211]	[212, 239]	[240, 309]	[310, ∞]
Study Day Range	-16 to -4	1	29±3	57±3	85±3	112±3	140±3	169±7	196±7	224±7	253±7	365±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 randomized patients who received at least 1 dose of IMP and will be used for demographics and baseline characteristics, treatment exposure, concomitant medications, and all safety summaries. Patients in the SP will be included in the treatment group that they actually received, regardless of their randomized treatment.

5.2.1.2 Full Analysis Set (FAS)

The Full Analysis Set (FAS) is defined as all randomized patients and is also known as the intention-to-treat (ITT) set of patients. FAS will be used for all efficacy analyses. In addition, FAS will be also used for summary for disposition, demographics, and baseline characteristics. Patients in the FAS will be included in their randomized treatment group.

5.2.1.3 PK Concentration Population

The PK concentration population is defined as all patients in the safety population who have at least one non-missing PK assessment. These patients will be summarized for PK concentration summaries unless major protocol deviations identified during the protocol deviation review or if key dosing or sampling information is missing. PK concentration population will be used for PK concentration summary and listing.

5.2.2 Protocol Deviations

A full list of protocol deviations will be compiled and reviewed by the clinical team to identify key versus non-key deviations before final database lock. For deviations 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 final list of protocol deviation will be approved by the study team prior to database lock and will be used to generate the PD deviation summary and listing.

5.2.3 Patient Disposition

The number of patients screened, randomized and included in each analysis population, along with study completion status, will be summarized by treatment group as well as overall. In addition, the number of patients who withdraw from the study and withdraw from IMP will be summarized by discontinuation reason.
Patient disposition will also be summarized for patients who are on simvastatin 40 mg/day or higher dose at any time during the study. The identification of these patients will be based on the concomitant statin medication use.

5.2.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized by treatment group, as well as overall, for safety population and for FAS population: age (years), age will be summarized as a continuous variable and by age group (18-40, 41-64, 65-74, and >=75), gender, race, ethnicity, height (cm), weight (kg), body mass index (kg/m^2), BMI group (< 25, 25 - < 30, ≥ 30 kg/ m^2), Region (North America, and EU), 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 TGs [mg/dL]), apoB (mg/dL), hsCRP (mg/dL), stratification factors: ASCVD only/HeFH (with or without ASCVD), and baseline statin intensity (low, moderate, high), history of diabetics and hypertension, eGFR category, tobacco history, alcohol history, and weekly average number of alcoholic drinks. Data will be summarized using descriptive statistics for continuous variables and using counts and percentages for categorical variables by treatment group and overall. Demographic and baseline characteristics will be summarized for patients who are on simvastatin 40 mg/day or higher dose at any time during the study.

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, and cardiovascular history/risk factors will be summarized by treatment group, as well as overall, for 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.

5.2.7 Baseline Serology, Serum and Urine Pregnancy Test and TSH

Hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV), and serum pregnancy test (only for females of childbearing potential), follicle stimulating hormone ([FSH], only for females who are < 55 years old and > 1 year without menses), urine pregnancy test Day 1 prior to randomization (only in Canada for females prior to amendment 3 and in all women who are of childbearing potential after amendment 3, and thyroid-stimulating hormone (TSH) will be presented in a by-patient listing.

5.2.8 Prior and Concomitant Medications

Prior medications are defined as medications that ended prior to the initiation of double-blind IMP. Concomitant medications are defined as medications that were ongoing at the time of double-blind IMP initiation or new medications that started post double-blind IMP initiation and within 30 days following the date of the last dose of IMP.

Medications, including prior statin medications, will be coded using WHO Drug (March, 2015, or later). The use of prior or concomitant medications will be summarized by treatment group, as well as overall, for the safety population according to Anatomical Therapeutic Chemical (ATC) class and coded medication name. Statin medications will be summarized separately. Prior and concomitant medications will be listed for each patient.

Number of patients receiving additional (post-randomization) adjunctive lipid-modifying therapy will be identified by medication class and will be summarized by the reasons for their additional treatment (hyperlipidemia or. hypertriglyceridemia) per concomitant medication CRF.

5.2.9 IMP Exposure and Compliance

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

The number and percentage of patients who were compliant with taking IMP will be summarized by treatment group 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 IMP administration and compliance data, including reasons for poor compliance, if noted in CRF will be listed for each patient.

5.3 Primary Efficacy Endpoints and Analyses

For all efficacy analyses, the FAS will be used, with patients included in their randomized group, regardless of the treatment they actually received.

The primary and key secondary efficacy endpoints will be included in a step-down testing procedure to control overall type I error. Below endpoints will be tested sequentially at alpha level of 0.05. Each endpoint will be tested only if the previous endpoint achieved statistical significance.

1. percent change from baseline to Week 12 in LDL-C (primary efficacy)
2. percent change from baseline to Week 24 in LDL-C
3. percent change from baseline to Week 12 in non-HDL-C
4. percent change from baseline to Week 12 in TC
5. percent change from baseline to Week 12 in apoB
6. percent change from baseline to Week 12 in hsCRP

The clinical hypothesis being tested for each respective endpoint is that a treatment regimen with bempedoic acid 180mg daily in addition to other lipid modifying therapies (including statin) will result in higher reduction in respective lipid value than that from the lipid modifying therapy alone.

5.3.1 Analysis for the Efficacy Parameters

Percent change in LDL-C, non-HDL-C, TC, and apoB at week 12 or week 24 will be analyzed using the analysis of covariance (ANCOVA) method. The ANCOVA model will include treatment, randomization stratum (from IWRS) as factors, and baseline value as covariate. In case of number of subjects within a stratum is too small for a meaningful analysis, the strata may be combined to obtain larger cell size. To account for the likelihood of unequal variances between the treatment groups, the ANCOVA model will be implemented within mixed model framework and the <repeated/group=> option will

be used to allow estimating the residual variances separately between the groups. The model assumptions for ANCOVA will be assessed and if these assumptions are severely violated, alternative non-parametric approach will be performed.

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

```
PROC MIXED DATA=adeff;
  class armcd stratum;
  model chg = blres armcd stratum/ solution ddfm=kenwardroger;
 repeated /group=armcd;
  lsmeans armcd / diff=control ('0') cl;
```

For hsCRP, a non-parametric (Wilcoxon rank-sum test) analysis with Hodges-Lehmann estimates and confidence interval will be performed because based on historical knowledge, publication precedence (Brendan et al., 2006) and recent data available, hsCRP is known to be skewed by extreme values and have non-normal distribution.

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. A figure of mean (+/- SE) value or median (IQR) as appropriate, over time will be provided for these efficacy parameters.

5.3.2 Missing Data Imputation

Missing data in efficacy endpoints included in the step-down procedure will be imputed using a pattern mixture model (PMM) to specify different imputation strategies depending on whether the patient is still on study treatment. Patients with missing lipid data at Week 12 who are no longer taking study treatment (date of last dose of IMP is < week 12 visit date -7) can be assumed to no longer be benefitting from study medication, and their missing value(s) can be assumed to be similar to those from the placebo patients who have data. To account for uncertainty, missing values will be imputed using multiple imputation via a regression based model including stratification factor, baseline value and week 12 value using data from placebo patients only. In this imputation model, treatment group will not be included as a factor.

Patients with missing lipid data at Week 12 who are still taking study treatment (date of last dose of study medication is ≥ date of week 12 visit -7) can be assumed to continue to benefit from study medication, and their missing value(s) can be assumed to be similar to those who remain on study treatment and have data and as a result, missing lipid values will be imputed based on the observed values in their randomized treatment group. To account for uncertainty, missing values will be imputed using multiple imputation via a regression based model including data from both treatment groups. In this imputation model, treatment group will be included as a factor.

5.3.3 Other Efficacy Endpoints

Percent change from baseline to week 52 in LDL-C will be analyzed using the ANCOVA method as described in section 5.3.1., using observed data (no imputation for missing data).

In addition, the same endpoint will be analyzed with patients in the FAS who did not receive additional lipid-lowering therapy by that time point (by week 24 and 52). Only observed case data will be used. Non-HDL-C, TC, ApoB and hsCRP at week 24 and 52 will be analyzed similarly using observed data.

The proportion of patients achieving LDL-C < 70 mg/dL at week 12, 24, and 52 will be summarized by treatment group and compared by Chi-sq test or fisher exact test. Only observed data will be used, i.e. the denominator will be number of patients who have LDL-C value at perspective time point.

TGs and HDL-C values at week 12, 24 and 52 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 treatment group.

In cases where triglycerides (TGs) is >400 mg/dL or LDL-C is ≤50 mg/dL, a measured LDL (LDL-M) will be used instead of LDL-C for the analysis of that time point. If both values are available, LDL-M will be used.

Baseline for each lipid is defined as the average of S1 (week -2) and predose Day 1/Week 0 values (the last two non-missing values on or prior to Day 1) with exception for apoB and hsCRP, for which predose Day 1 value will be used.

5.3.4 Sensitivity Analysis for Efficacy Endpoints

- A sensitivity analysis for primary and key secondary endpoints included in the step-down procedure will be performed using the ANCOVA model with derived stratum instead of IWRS randomized stratum. For details of how the stratum are derived using concomitant medication and medical history, please see Appendix 3.
- The observed case data only (no imputations for missing data) analyses will also be used for sensitivity analyses for primary and key secondary endpoints. Observed data analysis will be conducted using FAS.
- On-treatment analysis will be using data collected during the treatment period only, i.e. up to the date of last dose of IMP +7 days (e.g. any efficacy data collected after 7 days post last dose of IMP will be excluded for efficacy analysis). On-treatment analysis will be conducted using SP for primary and key secondary endpoints
- By-visit summary for all efficacy endpoints (LDL-C, non-HDL-C, TC, ApoB, hsCRP, HDL-C and TGs) using on-treatment approach will be provided for both conventional and standard units.

5.3.5 Subgroup Analysis for Efficacy Endpoints

The LDL-C efficacy endpoints at week 12 will be analyzed within subgroups described in section 5.2.5. No imputation will be performed on missing data for subgroup analyses. Subgroups based on stratification factors will be derived from corresponding eCRFs such as targeted CV history or concomitant statin medication.

A forest plot of treatment effect for the LDL-C endpoint within each subgroup will be provided.

5.4 Primary Safety Endpoints and Analyses

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. These endpoints identified in Section 3.2 with exception of PK-related endpoints, will be addressed as a result of the analysis description. All patients included in the SP will be evaluated in the safety analyses.

Unless otherwise stated, descriptive summaries will be displayed by treatment group actually received 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).

In summary tables, TEAEs will be counted as "Not Related" if relationship to IMP was recorded as 'Not Related' or "Unlikely". Events will be counted as "Related" if relationship to IMP was recorded as 'Possible', 'Probable', 'Definite' or if relationship to IMP 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, AESI, withdrew due to TEAE, Fatal

TEAE. Individual TEAE summary will be presented by treatment group containing the following counts and percentages for:

- patients with TEAEs
- 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, PT and maximum severity
- 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
- Fatal AEs by SOC and PT
- withdrawal from IMP due to TEAEs

Patient incidence (percent of patients experiencing the AE) will be provided for overall TEAE, treatment related TEAE, TE SAE, treatment related TE SAE, and AESI.

The TEAE, related TEAE, TE SAE, and AESI summaries by SOC and 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 IMP, and AEs with a fatal outcome.

5.4.2 Adverse Events of Special Interest

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

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

In addition to adverse events, AESI is also being evaluated based on safety lab parameters. The details are provided in 5.4.6.

5.4.3 Muscle Related Adverse Events

Muscle related adverse events as reported on the general AE CRF will be summarized by SOC, PT, and maximum severity. All muscle related events and details associated with it including cause and location will be provided in a listing.

5.4.4 Adverse Events among Simvastatin 40mg Patients

TEAE and Serious TEAE by SOC and PT will be summarized by treatment group for patients who are on simvastatin 40mg or higher dose at any time during the study.

5.4.5 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 treatment group. All events will be provided in a listing. Additional details regarding clinical endpoints and clinical endpoint definitions will be included in CEC charter.

5.4.6 Laboratory Evaluations

Continuous laboratory parameters (serum chemistry, hematology, coagulation (only at screening after amendment 3 and for those patients receiving anti-coagulation), urinalysis, urinalysis [microscopic]) listed in Table 4; fasting serum glucose, and HbA1c will be summarized using descriptive statistics for the observed value and the 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. Baseline is defined as the last value prior to the first dose of study medication. 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 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 4: Clinical Laboratory Parameters (Safety)

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 (In all patients at screening, then 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)

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.

5.4.6.1 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 for overall safety population and patients who were on simvastatin 40mg or higher dose at any time during the study.

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.

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

5.4.6.2 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 x ULN) will be summarized for overall safety population and patients who were on simvastatin 40mg or higher dose at any time during the study. These summaries of patients with abnormal CK will be performed overall, normal baseline CK, and abnormal baseline CK.

5.4.6.3 Diabetes and Glycemia

For fasting serum 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 and treatment group at each scheduled visit.

5.4.6.4 Renal Safety

By-visit summary and shift tables of eGFR by baseline category will be provided by treatment group.

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.

5.4.7 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.

5.4.8 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.

5.4.9 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.' 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'.

5.5 Pharmacokinetic Endpoints and Other Biomarkers

Plasma concentrations of ETC-1002 and its metabolite ESP15228 will be determined from 6 mL whole blood samples collected from patients at Weeks 12, 24, and 52 for those patients randomized prior to Amendment 3 in the EU and Amendment 4 in the US. At the time of sample collection, the date and time of blood draw and the last 2 doses of study medication will be collected. Any PK concentration with sample draw time outside of the 18-30 hours from last dose of IMP will be excluded from the summary.

In all data presentations (except listings), concentrations below the limit of quantitation (BLQ) will be set to zero. In listings, BLQ values will be reported as less than the lower limit of quantification (<LLQ).

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.
7. Brendan M.Everett, TobiasKurth, Julie E.Buring, Paul M.Ridker. "The Relative Strength of C-Reactive Protein and Lipid Levels as Determinants of Ischemic Stroke Compared With Coronary Heart Disease in Women." Journal of the American College of Cardiology (2006), Volume 48, Issue 11, Pages 2235-2242.

8 Appendices

Appendix 1: Schedule of Events (Patient Visit Schedule)

Visit	Screen	Treatment										
	S1[1,2]	T1	T2	T3	T4	*T4.1*	*T4.2 phone*	T5	*T5.1*	*T5.2 phone*	T6	T7 EOS[3]
Week	Wk -2	Wk 0	Wk 4	Wk 8	Wk 12	*Wk 16*	*Wk 20*	Wk 24	*Wk 28*	*Wk 32*	Wk 36	Wk 52
Procedure	Day -16 to -4	Day 1	Day 29±3	Day 57±3	Day 85±3	*Day 112±3*	*Day 140±3*	Day 169±7	*Day 196±7*	*Day 224±7*	Day 253±7	Day 365±7
Informed Consent	X											
Enrollment Criteria	X											
Demographics	X											
Medical History	X											
HeFH Status Determination	X											
Concomitant Medications	X	X	X	X	X	*X*	*X*	X	*X*	*X*	X	X
Adverse Event Recording		X	X	X	X	*X*	*X*	X	*X*	*X*	X	X
Physical Exam		X										X
Weight[4]	X	X	X	X	X			X			X	X
Height/BMI	X											
12-Lead ECG[5]		X										X
Vital Signs[6]	X	X	X	X	X			X			X	X
Serology[7]	X											
Serum Pregnancy *and/or FSH*[8]	X											
Urine Pregnancy Test[8]		*X*										
TSH	X											
Clinical Safety Labs[9]	X	X	X	X	X			X			X	X
Additional Clinical Safety Labs[10]						*X*			*X*			
Basic Fasting Lipids[11]	X	X	X	X	X			X			X	X
HbA_{1C}	X	X			X							X
10 mL reserve sample		X			X			X				X
Genetic sample		*X*										
apoB		X			X			X				X
hsCRP		X			X			X				X
Diet and exercise counseling[12]	X	X	X	X	X	*X*		X	*X*		X	
Plasma PK[13]					X			X				X
Establish Patient Eligibility		X										
Randomization		X										
IWRS Contact	X	X			X			X			X	X[14]
Double-blind Drug Dispensing[15]		X			X			X			X	
Drug Return/Compliance			X	X	X			X			X	X
Schedule next visit	*X*	*X*	*X*	*X*	*X*			*X*			*X*	*X*[16]

NOTE: For patients who withdraw from IMP 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 (except for apoB and hsCRP), adverse events, PE, vital signs, and ECGs. For patients who withdraw from IMP 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 T7 will be considered the EOS/Early Withdrawal from study and no further visits will be scheduled.

[1] An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of lipid values from both visits will be used to determine eligibility.

[2] An optional visit between Visits S1 and T1 may be completed if the patient's DBP and/or 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. An optional visit between Visit S1 and T1 may be completed to determine eligibility if the patient's eGFR, ALT, AST, and/or TB meet exclusion criteria levels. If this optional visit is completed, the repeated value will be used to determine eligibility.

[3] All procedures will be completed for all patients at either End of Study (EOS) if completing the study or early withdrawal.

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

[5] Single 12-lead ECG will be collected prior to any blood sample collection.

[6] Vital signs will include DBP, SBP, *and* 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

[8] *Serum p*regnancy test completed in premenopausal women only. *Urine pregnancy test is completed in premenopausal women who are able to become pregnant. FSH test is completed in women <55 years old and >1 year without menses*

[9] Clinical safety labs include hematology, blood chemistry, and urinalysis at all visits. *These will also be conducted 4 weeks after any changes in the patient's lipid-modifying treatment.* Coagulation is included at Screening (Visit S1) *for all patients, and then only in patients receiving anticoagulant therapy that in the investigator's judgement requires monitoring at* Baseline (Visit T1*) and 3 to 5 days post Visit T1.* Please refer to ICON laboratory manual for detailed schedule of tests.

[10] *Patients on an average daily dose of simvastatin 40 mg will be scheduled for additional Visits T4.1 and T5.1 to monitor clinical laboratory assessments and AE and SAE occurrence. These patients will also be contacted by telephone at Visits T4.2 and T5.2 to monitor AE and SAE occurrence.*

[11] Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides. Repeat within 1 week if exceed protocol-specified criteria.

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

[13] *Patients randomized after Protocol Amendment 3 and subsequent amendments are excluded from PK sampling.*

[14] IWRS contact at either an early withdrawal or an EOS visit to register study discontinuation visit date.

[15] Depending upon the length of time between visits, 1 or 2 bottles of study medication will be dispensed as instructed by IWRS. The bottle dispensed at Visit T1 will be returned to clinic at Visits T2 and T3 for evaluation of compliance and returned for continued use.

[16] *If patient is discontinuing treatment and completing the EOS visit, but will be continuing in the study either by returning to clinic or by phone, continue to schedule study visits for the patient according to the protocol Schedule of Events*

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

Appendix 3: Derived Randomization Stratum

Randomization stratum contains two factors: baseline statin intensity and cardiovascular history/risk factor. Derived randomization stratum will be based on available records in concomitant medication and medical history.

For cardiovascular history/risk factors: "ASCVD Only" vs. "HeFH with/without ASCVD". It will be derived from medical history. If a patient has a medical history of HeFH noted on the cardiovascular history page, then this patient will be categorized as "HeFH (with/without ASCVD)"; if a patient doesn't have medical history of HeFH, but with a history of cardiovascular history/risk factor (as collected on the CV history CRF), then this patient will be categorized as "ASCVD only"; if a patient doesn't have medical history of either HeFH or cardiovascular disease, the patient will be considered as not qualified.

Baseline statin intensity was categorized as High, Moderate and Low Intensity. It will be derived from concomitant medication using the latest Statin record prior to randomization. Average daily dose is calculated and the statin intensity is determined based on below table. The patient will be considered as "Low Intensity Statin" if the patient has no record of statin use.

High Intensity Statins	**Moderate Intensity Statins**	**Low Intensity Statins**
Atorvastatin 40-80 mg	Atorvastatin 10-<40 mg	Atorvastatin <10mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-<20 mg	Rosuvastatin <5mg
	Simvastatin 20-40 mg	Simvastatin <20 mg
	Pravastatin 40-80 mg	Pravastatin <40 mg
	Lovastatin 40 mg	Lovastatin <40 mg
	Fluvastatin XL 80 mg	Fluvastatin <80 mg
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	Pitavastatin <2 mg

SUMMARY OF CHANGES
STATISTICAL ANALYSIS PLAN

Study Number:	ETC 1002-040
Study Title:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER LONG-TERM SAFETY AND TOLERABILITY STUDY OF ETC-1002 IN PATIENTS WITH HYPERLIPIDEMIA AT HIGH CARDIOVASCULAR RISK WHO ARE NOT ADEQUATELY CONTROLLED BY THEIR LIPID-MODIFYING THERAPY
Final SAP Version:	22 Mar 2018
Original SAP Version:	21 Mar 2016

The original SAP dated 22Mar2016 was completed subsequent to the protocol amendment 2, dated 23Feb2016. Since then, the SAP was revised during the course of the study to:

1. Incorporate changes due to protocol amendments.
2. Improve the clarity and organization of the analyses.
3. Incorporate recommendations from the FDA and external experts.

The main changes are summarized below:

1. Per protocol amendment 3 dated 28 July 2016, the sample size was increased from 900 to 1950. The number of subjects to be enrolled and sample size determination section was updated to reflect such change. The rational for increased sample size was to provide adequate exposure to assess safety for the bempedoic acid (ETC-1002) program.
2. Per protocol amendment 3, the eGFR category definition was changed to include eGFR 30 - < 45 mL/min/1.73m^2
3. General language in the laboratory evaluation section was updated to reflect changed language in hepatic parameters monitoring in protocol amendment 3.
4. PK analysis set was updated to reflect PK assessments being removed in protocol amendment 3.
5. Per protocol amendment 4 dated 14 Oct 2016, simva 40 mg daily dose or higher were allowed. Additional visits for safety assessment were added in the protocol for these patients. As a result, the analysis window mapping and laboratory summary were updated accordingly.
6. Clarified in the SAP that the study objective is supported by both safety and efficacy. Defined the safety endpoints to be primary safety and efficacy endpoints to be primary

efficacy. The rationale for this change is because while the study was designed to provide the largest safety database and the longest exposure for safety evaluation for the program, this is a double-blind and placebo-controlled study and the efficacy parameters were collected in a similar fashion to other phase 3 studies, the efficacy data from this study is important to understand the effectiveness of bempedoic acid

7. The efficacy endpoints were organized in a hierarchical order to match other phase 3 studies and type I error control testing procedure (gatekeeping) was proposed to control the family-wise type I error. The purpose was to strengthen the rigor of the efficacy analyses and allow better integration with other phase 3 studies.
8. Incorporated more details (no method change) around missing data imputation using patterns mixed model (PMM). The reference publication for PMM was provided.
9. Specified non-parametric analysis will be used for hsCRP due to known skewed distribution, which was also confirmed by historical knowledge, publication precedence and recent data available,
10. In protocol amendment 5 dated 10 May 2017, patients who were on simva 40 mg/day or higher dose were withdrew from the study treatment. Subgroup analyses for adverse events and safety laboratory were added in order to gain further understanding of this group of patients.
11. Definition for baseline lipid parameters was updated to use the mean of screening and T1 instead of single value on T1. This change was made to be consistent with other phase 3 studies.
12. Added subgroup analysis for efficacy and safety. Subgroup analysis for large phase 3 study is expected.
13. Added sensitivity analysis for efficacy endpoints. This change was made to assess the robustness of the primary analysis result.
14. Added exploratory analysis for proportion of patients achieve LDL-C < 70 mg/dL at each visit.
15. Updated the list of preferred terms for AESI and abnormal lab cutoff. This change was made based on further understanding of the safety profile for bempedoic acid from recent data and DMC recommendation.
16. Administrative and editorial changes were made throughout the document.

The final SAP dated 22Mar2018 was completed and signed off prior to the database lock for Study 1002-040.