STATISTICAL ANALYSIS PLAN

PROTOCOL 1002-048

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BEMPEDOIC ACID (ETC-1002) 180 MG/DAY AS ADD-ON TO EZETIMIBE THERAPY IN PATIENTS WITH ELEVATED LDL-C ON LOW DOSE OR LESS THAN LOW DOSE STATINS

AUTHOR: SUSAN TIERNEY

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V0.7 (Dated 06Feb2018) for Protocol 1002-048.

	Name	Signature	Date
Author:	Susan Tierney		
Position:	Statistical Team Lead		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	John Wood		
Position:	Senior Reviewer		
Company:	IQVIA		
Approved By:	Grace Zhao		
Position:	Trial Statistician		
Company:	Esperion Therapeutics, Inc.		
Approved By:	Jeff Hanselman		
Position:	Associate Director, Clinical Development		
Company:	Esperion Therapeutics, Inc.		

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ACL	adenosine triphosphate-citrate lyase
ACS	acyl-CoA synthetase
ADaM	Analysis Data Model
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
AUC_{0-24}	area under the curve during 24 hours
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
Ca	calcium
CAS	Completer Analysis Set
CEC	Clinical Event Committee
CETP-I	Cholesteryl ester transfer protein inhibitor
CFR	Code of Federal Regulations
CHD	coronary heart disease
CI	confidence interval
CK	creatine kinase
Cl	chloride
C_{max}	time to peak maximum concentrations
CMV	cytomegalovirus
CNS	central nervous system
CoA	acetyl-coenzyme A
CO2	carbon dioxide
CRO	contract research organization
CTMS	centralized trial management system
CV	cardiovascular
CYP	cytochrome P450
DBP	diastolic blood pressure
DMC	Data Monitoring Committee

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ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
eGFR	estimated glomerular filtration rate
EOS	end of study
ETC-1002-CoA	ETC-1002-coenzyme A
EU	European Union
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FPFV	first patient first visit
FSH	follicle-stimulating hormone
GCP	good clinical practice
GI	gastrointestinal
HbA1C	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
Hgb	hemoglobin
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
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	low-density lipoprotein receptor
LFT	liver function test
LPLV	last patient last visit
LMT	lipid-modifying therapy
LS	least square
LSM	least square mean
MACE	major adverse cardiac event

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MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
MED ID	medication identification
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRI	magnetic resonance imaging
Na	sodium
NIMP	non-investigational medicinal product(s)
NLA	National Lipid Association
NOAEL	No-observed-adverse-effect level
non-HDL-C	non-high-density lipoprotein cholesterol
NYHA	New York Heart Association
PCSK9	proprotein convertase subtilisin/kexin type 9
PE	physical exam
PK	pharmacokinetic(s)
PG	pharmacogenomic
PMM	pattern mixed model
PT	prothrombin time
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
siRNA	small interfering ribonucleic acid
SOC	system organ class
SOP	standard operating procedures
SP	safety population
SDTM	study data tabulation model
SUSARS	suspected and unexpected serious adverse reactions
t½	terminal elimination half-live
T2DM	type 2 diabetes mellitus
TB	total bilirubin
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglycerides

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TSH	thyroid-stimulating hormone
TQT	thorough QT/QTc
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol 1002-048. It describes the data to be summarized and analyzed, including specifics of the statistical analysis to be performed.

This statistical analysis plan (SAP) is based on the final protocol version dated September 22, 2017 and amendments 1 and 2 dated 18JAN2017 and 10FEB2017.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to assess the 12-week efficacy of bempedoic acid 180 mg/day versus placebo in decreasing low-density lipoprotein cholesterol (LDL-C) when added to ezetimibe therapy in patients with elevated LDL-C.

2.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To evaluate the effect of 12-week treatment with bempedoic acid 180 mg/day versus placebo when added to ezetimibe therapy on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), Apo lipoprotein B (apoB), and high-sensitivity C-reactive protein (hsCRP).
- To evaluate the effect of 12-week treatment with bempedoic acid 180 mg/day versus placebo on triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C) when added to ezetimibe.
- To evaluate the 12-week safety and tolerability of bempedoic acid 180 mg/day compared to placebo when added to ezetimibe.

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2.3. TERTIARY OBJECTIVES

The tertiary objective is to evaluate 4- and 8-week treatment with bempedoic acid 180 mg/day versus placebo when added to ezetimibe therapy on LDL-C, Non-HDL-C, TC, TG, and HDL-C.

To explore the combined treatment benefit on LDL-C when bempedoic acid is used in combination with ezetimibe, percent change in LDL-C from screening visit (S1) to subsequent visits will be summarized using descriptive statistics at each time point for patients who are ezetimibe naive (no prior ezetimibe use prior to the screening) in each treatment group.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel group, multicenter study that will be conducted in North America and Europe. Patients on low dose or less than low dose statin therapy (including patients unable to tolerate a statin at any dose) and who require additional LDL lowering will be eligible for screening. Screening (Visit S1) will begin approximately 5 weeks prior to randomization. Eligible patients will return at Week -4 (Visit S2) to begin treatment with study-supplied ezetimibe 10 mg and single-blind placebo. Patients already taking ezetimibe 10 mg will switch to study-supplied ezetimibe 10 mg. Patients will continue their other background lipid-modifying therapy (LMT) for the duration of the trial. Patients will return to the clinical site at Week -1 (Visit S3) for assessment of adverse events (AEs) and adherence with study medication (study-supplied ezetimibe and single-blind placebo) and to complete lipid assessments.

Approximately 225 eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either bempedoic acid 180 mg (N = 150) or placebo (N = 75) for 12 weeks. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 8 (Visit T3), and Week 12 (Visit T4).

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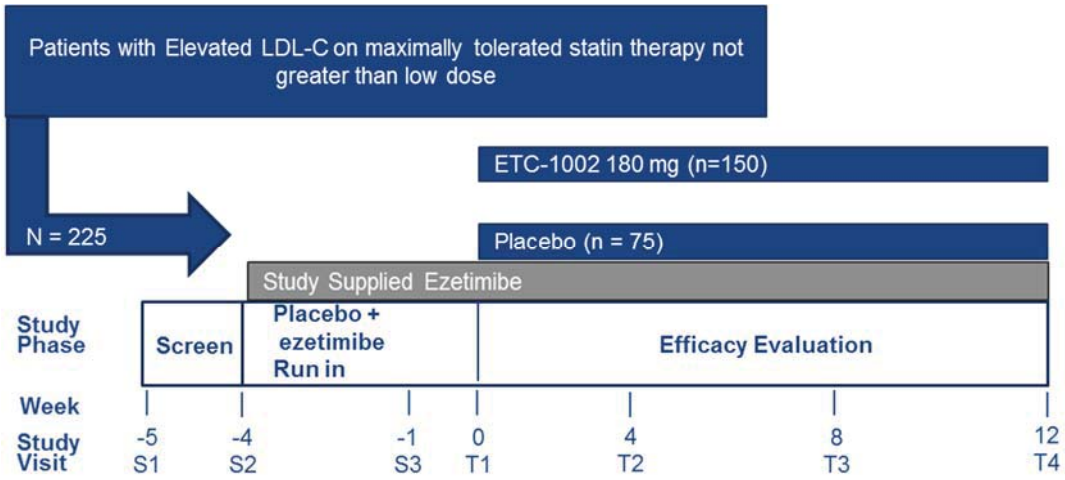
Table A: 1002-048 Study Design



3.2. SCHEDULE OF EVENTS

The schedule of events can be found in Appendix 1 of the protocol.

4. PLANNED ANALYSIS

The following analyses will be performed for this study:

- Analyses for Data Monitoring Committee (DMC) meetings
- Final Analysis

4.1. DATA MONITORING COMMITTEE (DMC)

The subset of outputs for the DMC is listed in Appendix 3. Access to results will be provided by Quintiles in a separate unblinding plan.

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4.2. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by Quintiles Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of Treatment.

5. ANALYSIS SETS

Agreement and authorization of patients included/ excluded from each analysis set will be conducted prior to the unblinding of the study.

5.1. SAFETY ANALYSIS SET [SAF]

The Safety Analysis Set (SAF), 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 SAF will be included in the treatment group that they actually received, regardless of their randomized treatment.

5.2. FULL ANALYSIS SET [FAS]

The Full Analysis Set (FAS), used for all of the efficacy analyses, is defined as all randomized patients. The FAS is also known as the intention-to-treat (ITT) set of patients. Patients in the FAS will be included in their randomized treatment group, regardless of the treatment they actually received.

5.3. COMPLETER ANALYSIS SET [CAS]

The Completer Analysis Set (CAS), used for all of the primary, and secondary efficacy analysis, is defined as patients in the FAS who completed both IMP and Ezetimibe treatment per the end of treatment CRF page and have non-missing week 12 LDL-C value.

5.4. PK ANALYSIS SET [PKS]

The PK Analysis Set will include all patients in the safety analysis set who have at least one 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, i.e. the time between the PK sampling and last study drug dose prior to PK sample is not

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within 18-30 hours or sampling time information is missing.

5.5. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication (Day 1 is the day of the first dose of study medication). In case the first dose date is missing, randomization date will be used instead.

- If the date of the event is on or after the reference date then:

Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix 2; Partial Date Conventions.

5.6. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered as baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

Baseline for calculated LDL-C, HDL-C, non-HDL-C, TG, and TC is defined as the mean of the values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1) (i.e., the last two non-missing values on or prior to Day 1). If only one value is available then that single value will be used as baseline.

Baseline for apoB and hsCRP is defined as the predose Day 1/Week 0 (Visit T1) value (i.e. the last non-missing value on or prior to Day 1). If this is not available, then the last non-missing value prior to the first dose of double-blind study medication (including unscheduled assessments) will be used as baseline.

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5.7. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In the event of a missing value at a scheduled visit, and if an unscheduled visit falls within the protocol-defined window of that visit (see table below), the value from the unscheduled visit will be used for that visit.

In the case of a retest (same visit number assigned), the later available measurement for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

5.8. VISIT WINDOWING

Protocol-defined assessments will be "slotted" to study weeks based on collection date and applying the rules summarized in the following table. If there is more than one scheduled visit in a visit window, the visit closest to the target date will be used. If there is a tie between the numbers of days from the target date, the visit after the target date will be used. Unscheduled visits that fall within the protocol-defined visit windows will be summarized in the by-visit analyses if there is no scheduled visit available. If there is more than one unscheduled visit within the protocol-defined visit window and no scheduled visit available, the unscheduled visit closest to the scheduled visit date will be used. If there is a tie between the numbers of days from the target date, the visit after the target date will be used.

However, exposure data obtained from the drug accountability and administration CRF will be summarized and listed according to nominal visit information

Visit	S1	S2	S3	T1	T2	T3	T4, EOS
Slotted Study Week	-5	-4	-1	0	4	8	12
Target Study Day	-35	-28	-7	1	29	57	85
Analysis Visit Windows	[-∞,-32]	[-31,-18]	[-17,-1]	[1,1]	[2,43]	[44,71]	[72, ∞]

5.9. STATISTICAL TESTS

The default significance level will be (5%); confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

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5.10. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

Percent change from baseline will be calculated as:

- [(Test Value at Visit X – Baseline Value)/Baseline Value] x 100

5.11. STUDY MEDICATION AND INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

For the purpose of this document, IMP is defined as either bempedoic acid 180 mg or placebo. Study medication includes both IMP and ezetimibe supplied by the sponsor per protocol.

5.12. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

6. STATISTICAL CONSIDERATIONS

6.1. SAMPLE SIZE

The primary efficacy endpoint for this study is the percent change from baseline to Week 12 in LDL-C.

The sample size of 150 randomized patients in the bempedoic acid 180 mg group and 75 randomized patients in the placebo group is expected to provide more than 95% power to detect a difference of 15% in the percent change from baseline to Week 12 in calculated LDL-C between the bempedoic acid treatment group and the placebo group. This calculation is based on a 2-sided t-test at the 5% level of significance and a common standard deviation of 15%. The sample size of 150 randomized patients in the bempedoic acid 180 mg group and 75 randomized patients in the placebo group gives a total study sample size of 225.

6.2. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors are used in the analyses. For details of their inclusion in the

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models, see the specific analysis section.

- treatment group (bempedoic acid 180 mg/day; placebo)
- baseline laboratory value of interest
- treatment by subgroup interaction term for subgroup analyses of efficacy variables

6.3. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers in North America and Europe.

6.4. MISSING DATA

Missing efficacy data will be handled as described in section 16.1.3 of this analysis plan.

6.5. MULTIPLE COMPARISONS/ MULTIPLICITY

In terms of controlling the overall Type I error rate, a gatekeeping or stepdown approach will be used to test the primary efficacy endpoint and then specific secondary efficacy endpoints sequentially in order to preserve the study-wise Type I error rate. The sequence for the stepdown procedure in this study is as follows:

1. Test the primary efficacy endpoint: percent change from baseline to Week 12 in LDL-C
2. Test the percent change from baseline to Week 12 in non-HDL-C
3. Test the percent change from baseline to Week 12 in TC
4. Test the percent change from baseline to Week 12 in apoB
5. Test the percent change from baseline to Week 12 in hsCRP

In this hierarchical testing structure, each hypothesis is tested at a significance level of 0.05, two-sided. Statistical significance at each step is required in order to test the next hypothesis. If the primary endpoint meets the criteria for statistical significance, then the percent change from baseline to Week 12 in non-HDL-C will be tested; and so forth.

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7. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by IQVIA Biostatistics.

8. DISPOSITION AND WITHDRAWALS

All patients who were screened will be accounted for in this study. Reasons for screen failure will be summarized by pre-defined categories per CRF. For screen fail due to inclusion and exclusion criteria, the criteria category will be presented. Patient disposition and withdrawals (both from study treatment and the study) will be presented for the FAS. The number of patients in each analysis set will be presented for all randomized patients.

9. PROTOCOL DEVIATIONS

All protocol deviations will be provided in a listing. Major protocol deviations will be summarized by treatment group. The protocol deviations are recorded and tracked in the trial monitoring platform CTMS.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the FAS and CAS.

No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) - calculated relative to date of randomization
- Age category (<65 years vs. ≥65 years and < 75 years vs. ≥75 years)
- Gender
- Race
- Ethnicity

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- Region (US vs. Canada vs. EU)
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- BMI category (< 25 vs. 25 - < 30 vs. ≥ 30 kg/ m2)
- Baseline Laboratory Results (Total Cholesterol, LDL-C, HDL-C, Triglycerides, Non-HDL-C, ApoB, and hsCRP)
- Baseline LDL-C category (<130 mg/dL, ≥130 and < 160 mg/dL, or ≥160 mg/dL)
- History of diabetes (Yes vs. No)
- History of hypertension (Yes vs. No)
- Baseline Vital Signs (systolic blood pressure (SBP) and diastolic blood pressure (DBP))
- Alcohol consumption
- Tobacco use
- Background Lipid-Modifying Therapy
- Baseline eGFR (>=90 mL/min/1.73m2; 60-<90 mL/min/1.73m2; 30-<60 mL/min/1.73m2; 15-<30 mL/min/1.73m2)

10.1. DERIVATIONS

- Age (years) = (date of randomization – date of birth)/365.25
- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$

11. MEDICAL AND SURGICAL HISTORY

Medical and Surgical History information will be presented by MedDRA SOC (System Organ Class) and PT (Preferred Term) for the FAS. Medical History conditions are defined as those conditions which

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stopped prior to or at Screening. Medical History will be coded using MedDRA Version 20.1.

12. CONCOMITANT ILLNESSES

Concomitant Illnesses will be presented by SOC (System Organ Class) and PT (Preferred Term) for the FAS. Concomitant Illnesses are conditions (other than the indication being studied) which started prior to the date of randomization and are ongoing at the date of randomization. Concomitant Illnesses will be coded using MedDRA Version 20.1

13. MEDICATIONS

Prior and concomitant medications will be presented for the SAF and coded using the September 2017 version of the World Health Organization Drug Dictionary Enhanced (WHO-DDE). Tables excluding lipid-modifying therapies will be presented. Separate prior and concomitant medication tables will be presented for lipid-modifying therapy.

Medications will be summarized by ATC classification and preferred term by treatment group. Prior and concomitant lipid modifying therapy including statin (low dose), and others will be tabulated and listed separately. See protocol 8.4.1 for the list of LMT allowed in the study.

See Appendix 2 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior or concomitant to treatment, the medication will be classified by the worst case, i.e. concomitant.

Prior medications are medications which started and stopped prior to the first dose of double-blind study medication.

Concomitant medications are medications which: started prior to, on or after the first dose of double-blind study medication and started no later than 30 days following end of study medication, and ended on or after the date of first dose of study medication or were ongoing at the end of the study.

13.1. BACKGROUND LIPID MODIFYING THERAPY

Lipid modifying therapy started prior to randomization date will be presented in separate tables and listings by category (as defined in protocol section 8.4.1) and coded medication name and by treatment group.

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13.2. ADDITIONAL POST-RANDOMIZATION ADJUNCTIVE TRIGLYCERIDE-LOWERING THERAPY

The number and percent of patients in each treatment group requiring additional (post-randomization) TG-lowering therapy (when TG>1000) will be summarized by treatment group as well as provided in a listing. The TG lowering medication will be identified as post-randomization concomitant medications with indication of 'hypertriglyceridemia'.

14. STUDY MEDICATION COMPLIANCE AND EXPOSURE

Compliance to study medication will be presented for the SAF. At visits Week -1 (S1), Week 0 (T1), and each patient visit during the study, clinical site staff will count the number of tablets that are returned as unused and query the patient with regards to daily intake.

14.1. DERIVATIONS

Compliance with placebo-run in (as an overall group) and double-blind study medication by treatment group—based on the drug accountability data—will be calculated as the number of tablets taken (total dispensed – total returned) divided by the number of days within each of the 2 periods.

In addition, compliance with ezetimibe will also be calculated using the same tablets counting method as described above. During the run-in period, the compliance will be summarized as a single overall group and during the double-blind period, compliance will be summarized by treatment group (bempedoic acid and placebo).

Compliance will not be computed by visit.

A 35-day supply of single-blind placebo drug will be dispensed one time at Week -4 (Visit S2) for the 4-week placebo run-in period of the study. Double-blind IMP will be dispensed in 100-day supply increments to patients by appropriate clinical site personnel. Patients will receive one 100-day supply bottle at Week 0 (Visit T1)).

The treatment is taken once daily and it is assumed that the patient takes medication on the visit day at which their medication is initially dispensed to the date of last dose as captured on the End of Treatment eCRF page. For example, if the initial dispense date is Day 1 and the last dose is Day 84, then the patient should have taken the first tablet at Day 1, once a day on Days 2 to 83 and 1 tablet on Day 84; hence, the total number of prescribed tablets would be 84.

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In cases where the last dispensed bottle(s) were not returned due to lost to follow up or death, the last bottle return date will be imputed with EOS date. The number of tablets returned for those unreturned bottles will be '0'.

Treatment exposure will be calculated in weeks as (date of last dose of study medication – first date of first dose of study medication +1). Descriptive statistics will be presented for exposure as well as categorization into time periods (<4 weeks, >=4- <8 weeks, >=8 weeks).

Exposure to ezetimibe during the double-blind period will be calculated in days as (date of last dose of ezetimibe medication –date of first dose of ezetimibe during the double-blind period +1). Descriptive statistics will be presented for exposure as well as categorization into time periods (<4 weeks, >=4- <8 weeks, >=8 weeks). Exposure to ezetimibe (in weeks) during the run-in period will be calculated in a similar fashion and presented as an overall group using descriptive statistics.

15. EFFICACY OUTCOMES

15.1. PRIMARY EFFICACY

15.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy endpoint is the percent change from baseline to Week 12 in LDL-C. Baseline LDL-C is defined as the mean of the LDL-C values from Week -1 (Visit S3) and predose Day 1/Week 0 (Visit T1) (last two non-missing values on or prior to Day 1).

In cases where triglycerides (TG) 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, the LDL-M will be used.

15.1.2. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The null hypothesis, H_0, will be that there is no difference between bempedoic acid 180 mg/day and placebo in mean percent change from baseline to Week 12 in LDL-C. The alternative hypothesis, H_1, will be that bempedoic acid 180 mg/day is different from placebo:

$H_0: \mu_p = \mu_b$

$H_1: \mu_p \neq \mu_b$

where μ_p and μ_b denote the mean percent change from baseline to Week 12 in LDL-C on placebo and bempedoic acid 180 mg/day respectively.

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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 FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. 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. Model assumptions for performing ANCOVA will be assessed and if the assumptions are severely violated, non-parametric method will be considered.

In addition, descriptive statistics will be presented for LDL-C at each visit and for change from baseline.

15.1.3. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE

For the primary endpoint of percent change from baseline to Week 12 in LDL-C values, a pattern mixture model (PMM) will be used 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 (defined by date of last dose of study medication is < Week 12 visit date -7 days) can be assumed to no longer be benefitting from study medication, and their missing value(s) can be assumed to be similar to those in placebo group who remained on study and have data. To account for uncertainty, missing values will be imputed using multiple imputation via a regression based model including baseline data from placebo subjects 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 ≥ Week 12 visit date -7 days) 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, lipid values will be imputed based on the observed values in their randomized treatment group at Week 12. To account for uncertainty, missing values will be imputed using multiple imputation via a regression based model. Only baseline values will be included in the imputation model. Imputed datasets will be analyzed using an ANCOVA model with treatment as a factor and baseline LDL-C as a covariate. Approximately 200 imputed datasets will be created, with results from the analysis of each imputed dataset combined using Rubin's method. The least squares mean (LSM) and standard error (SE) will be provided for both treatment groups, along with the placebo-corrected LSM, its 95% confidence interval (CI) and associated p-value. To account for possibility of unequal variances between the groups, the ANCOVA model will be implemented within mixed model framework where <repeated/group=> option will be used to allow separate estimation of residual variance between the groups.

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Further information on the multiple imputation method is presented in Appendix 4.

15.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed for the full analysis set (FAS).

15.2.1. KEY SECONDARY EFFICACY ENDPOINTS

The key secondary endpoints, which are included in the hierarchical analysis described in Section 7.5, are:

- percent change from baseline to Week 12 in non-HDL-C
- percent change from baseline to Week 12 in TC
- percent change from baseline to Week 12 in apoB
- percent change from baseline to Week 12 in hsCRP

Key secondary endpoints will be analyzed using the same ANCOVA model described in 16.1.2. An additional non-parametric (Wilcoxon rank-sum test) analysis will be performed for hsCRP.

Similar to the primary endpoint, missing data will be imputed using multiple imputation method as described in 16.1.3.

A by-visit graphic presentation (mean+/-SE) will also be provided.

15.2.2. OTHER SECONDARY EFFICACY ENDPOINTS

Other Secondary efficacy endpoints are:

- percent change from baseline to Week 12 in TGs
- percent change from baseline to Week 12 in HDL-C

Other secondary endpoints will be analyzed using the same ANCOVA model described in 16.1.2.

An additional non-parametric (Wilcoxon rank-sum test) analysis will be performed for triglycerides.

Observed data from the full analysis set will be used for other secondary efficacy endpoints.In addition, descriptive statistics for all efficacy endpoints and change from baseline will be presented at each visit.

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15.2.3. SENSITIVITY ANALYSIS OF PRIMARY AND KEY SECONDARY EFFICACY VARIABLES

15.2.3.1. Completer Analysis

The completer analysis set (CAS) will be used as a sensitivity analysis for all primary and key secondary efficacy endpoints. There will be no imputation for missing data.

15.2.3.2. On-treatment Analysis

An on-treatment analysis will also be conducted for primary and key secondary endpoints using data from the on-treatment period, i.e. up to the date of last dose of double-blind study medication. On-treatment analysis will be based on FAS. There will be no imputation for missing data.

15.2.3.3. Observed Data Analysis

The observed case data with no imputation for missing data will be used as sensitivity analyses for primary and key secondary endpoints.

15.2.4. SUBGROUP ANALYSIS OF PRIMARY EFFICACY VARIABLES

The primary endpoints will be analysed within subgroups below using the same analysis method previously described. The treatment and subgroup interaction will be examined by including the interaction term in the ANCOVA model for the overall population first. No imputation will be performed on missing data for subgroup analyses. 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. Forest plots for the primary efficacy variables will also be presented.

- Baseline LDL category (<130mg/dL, ≥130 mg/dL and < 160 mg/dL, ≥160mg/dL)
- History of diabetes (yes vs.no)
- Age (< 65 yrs. vs. ≥65 yrs. and <75 yrs vs. ≥75 yrs)
- Race (White vs.Non-White)
- Gender (male vs. female)
- Region (North America (US and Canada) vs. EU)
- BMI category (< 25 vs. 25 - < 30 vs. ≥ 30 kg/ m2)
- Background lipid modifying therapy (statin vs. other)

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15.3. TERTIARY EFFICACY

15.3.1. TERTIARY EFFICACY VARIABLES & DERIVATIONS

The tertiary efficacy endpoints are:

- Percent change from Baseline to weeks 4 and week 8 in LDL-C, non-HDL-C, TC, TG, and HDL-C.
- Absolute change from Baseline to weeks 4, 8, and 12 in LDL-C
- Percent change from S1 to subsequent time point in LDL-C in ezetimibe naive patients
- Absolute change from S1 to subsequent time point in LDL-C in ezetimibe naive patients

15.3.2. MISSING DATA METHODS FOR TERTIARY EFFICACY VARIABLES

No missing data imputation will be used for the tertiary analyses.

15.3.3. ANALYSIS OF TERTIARY EFFICACY VARIABLES

Tertiary efficacy endpoints related to change or percent change from baseline will be analyzed using the same ANCOVA model described in 16.1.2. Estimates for change from baseline, standard errors and 95% CIs will be presented by treatment group and visit. Contrast estimates for between-group (Bempedoic Acid vs. placebo) comparisons, standard errors, 95% CIs, and p-values will be presented for each visit.

For the percent change In LDL-C from S1 to subsequent visits, only patients who are ezetimibe naïve will be included. The actual value, change and percent change will be presented using summary statistics. The comparison of percent change in LDL-C to week 12 between the two treatment groups will be performed using an ANCOVA model with treatment group as a factor and S1 value as covariate. Ezetimibe naïve is defined as no prior ezetimibe use as per recorded on the concomitant medication page. Observed data will be used for this analysis, no imputation for the missing data will be performed.

For the tertiary efficacy endpoints, a significance level of 0.05 will be used; given the large number of remaining endpoints, the p-values for those endpoints will be considered descriptive.

16. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.

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There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified with the relevant section.

16.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA, Version 20.1.

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of IMP (double-blind study medication) and prior to the last dose date of double-blind study medication + 30 days. AEs that occurred on day 1 will be only determined as TEAE if determined to be after first dose as recorded by the site on the AE CRF.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e. treatment emergent.

An overall summary of number of patients within each of the categories described in the sub-section below, will be provided as specified in the templates. Listings will include TEAEs and Non-TEAEs.

16.1.1. ALL TEAEs

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) as well as by PT in descending frequency and also broken down further by maximum severity and relationship to IMP and Ezetimibe. Adverse events by the subgroups in Section 15.2.4, with exception of baseline LDL category, will also be presented.

16.1.1.1. Severity

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of IMP with a missing severity will be classified as severe. If a patients reports a TEAE more than once within that SOC/ PT, the AE with the worst case severity will be used in the corresponding severity summaries.

16.1.1.2. Relationship to Study Medication

Relationship to study medication (IMP and ezetimibe), as indicated by the Investigator, is “not related” if the TEAE is “not related” or “unlikely related”. A ”related” TEAE is defined as a TEAE with a relationship of ”possibly related”, ”probably related”, or “definitely related” to study medication. TEAEs with a missing relationship to study medication will be regarded as ”related” to study medication.

TEAEs that are related to IMP and ezetimibe will be summarized separately. If a patient reports the

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same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries.

16.1.2. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of IMP or ezetimibe will be identified by using the response of 'Drug Withdrawn/Permanently discontinued' on the Action Taken With Study Drug or ezetimibe Field on the AE eCRF page. For TEAEs leading to discontinuation of study IMP or ezetimibe, summaries of incidence rates (frequencies and percentages) by SOC and PT will be summarized and presented separately.

16.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the (e)CRF. A summary of serious TEAEs by SOC and PT as well as by PT in descending frequency will be presented.

16.1.4. Adverse Events Of Special Interest (AESI)

Adverse events of special interest include but not limited to muscle related symptoms, worsening or new onset diabetes, and neurocognitive events and will be identified by pre-specified MedDRA preferred terms provided by Esperion Therapeutics Inc. (see Appendix 5). These events will be summarized by AESI category, SOC and PT. All AESI will be summarized by severity and relationship to study medication. In addition, AESI will be evaluated by monitoring safety labs as detailed in section 17.4.

16.1.5. Muscle Related Adverse Events

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

16.2. Deaths

If any patients die during the study, as recorded on the Death Event page of the eCRF, the information will be presented in a data listing. Deaths will be categorized as cardiovascular (CV) death (MACE) or non-CV death (non-MACE).

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16.3. CLINICAL ENDPOINTS

Clinical endpoints will be monitored and adjudicated by an independent blinded expert CEC for this study. The following clinical endpoints will be tabulated and listed:

CV death (MACE)

Nonfatal myocardial infarction [MI] (MACE)

Nonfatal stroke (MACE)

Hospitalization for unstable angina (MACE)

Coronary revascularization (MACE)

Non-coronary arterial revascularization (non-MACE)

Hospitalization for heart failure (non-MACE)

Additional details regarding clinical endpoints and clinical endpoint definitions will be included in CEC charter. The number of incidences and percentage of patients with each outcome will be presented in a table.

16.4. SAFETY LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for Hematology, Blood Chemistry, Coagulation (for subjects taking Vitamin K antagonists only), HbA_{1C}, and Urinalysis. A list of laboratory assessments to be included in the outputs is included in Protocol, Section 11.1.6.1.

Presentations will use both conventional and SI Units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The formula to calculate eGFR is: eGFR = 186 x (Creatinine / 88.4)-1.154 x (Age)-0.203 x (0.742 if female) x (1.210 if black), where creatinine is in mmol/L.

Summaries for all lab results, including unscheduled visit values, will be included for below analyses:

- Observed and change/percent change from baseline by visit (for quantitative measurements).
- Observed and change/percent change from baseline for HbA1c and Glucose by history of diabetes and visit.

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- Shift from baseline by visit according to normal ranges.
- Shift from baseline according to predefined categories for HbA1c and Glucose by history of diabetes and visit.eGFR and values of CK will be summarized by treatment group and by baseline eGFR categories (low, normal, high).
- Potential Hy's law cases (>3 × ULN for either ALT or AST AND Total Bilirubin >2 × ULN in the setting of no known other cause) will be tabulated and listed.

Laboratory abnormalities in parameters of interest:

- ALT or AST (> 3x ULN and ≥5xULN)
- TB (> 2x ULN)
- CK (> 5x ULN) and (>10x ULN)
- Fasting Blood Glucose (mg/dL) (≤50, ≥126)
- HbA1C (≥6.5%)
- Creatinine (change from baseline for >1 mg/dL)
- eGFR (< 15 mL/min/1.73m^2, 15 –< 30 mL/min/1.73m^2)
- Hgb (g/dL) (decrease from baseline for ≥2 g/dL)
- Hgb (<8 g/dL)

16.4.1. Laboratory Reference Ranges and Markedly Abnormal Criteria

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units or conventional units as appropriate and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

In addition to the high and low quantitative laboratory assignments, Hy's law criteria (>3 × ULN for either ALT or AST, with accompanying total bilirubin >2 × ULN in the absence of other known causes) will be used to identify potential Hy's law cases.

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16.5. ECG EVALUATIONS

The Investigator's judgment of overall assessment of ECG (Normal, Abnormal, Not Clinically Significant (ANCS), and Abnormal, Clinically Significant (ACS)) will be recorded at baseline and end of study. A summary of shift from baseline to end of study in overall assessment will be provided.

16.6. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Sitting Systolic Blood Pressure (mmHg)
- Sitting Diastolic Blood Pressure (mmHg)
- Sitting Heart Rate (bpm)
- Weight (kg)
- Height (cm) (at Screening only)
- BMI (kg/m^2) (calculated automatically by the EDC system)

The following summaries will be provided for vital signs data:

- Observed and change from baseline by visit

16.7. PHYSICAL EXAMINATION

Abnormalities in physical examinations will be presented in a listing.

16.8. PHARMACOKINETICS

Descriptive statistics for concentrations of bempedoic acid and its metabolite ESP15228 will be presented for each visit weeks 4, 8, and 12. If the time between the PK sampling and last study drug dose prior to PK sample is not within 18-30 hours or the sampling time information is missing the concentration value is not analyzed. Concentrations below the lower limit of quantification will be

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treated as zero in summary statistics.

All concentration data will also be presented in a listing. Concentrations below the limit of quantification data will be labelled as such in the concentration.

17. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments
- Variables used by the data entry system to direct user to proper page (e.g., patient visit status, patient health status)
- Inclusion/Exclusion Criteria that are not violated
- Normal Physical Examination Results

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

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18. REFERENCES

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APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUT

QUINTILES OUTPUT CONVENTIONS

OUTPUT FILE NAMING CONVENTIONS

File names should only consist of uppercase letters, lowercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.

As far as possible, output files should be in RTF format, although .DOC files are also permitted.

The program, program log and output file name should reflect the type and number of the statistical output. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('T' for table, 'L' for listing and 'F' for figure). If there is only 1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (eg T14_3_01_1.RTF)

PAPER SIZE, ORIENTATION AND MARGINS

The size of paper will be Letter for the United States, otherwise A4.
The page orientation should preferably be landscape, but portrait is also permitted.
Margins should provide at least 1 inch (2.54 centimeters) of white space all around the page, regardless of the paper size.
The number of columns per page (linesize) should be 145 for A4 and 134 for Letter.
The number of rows per page (pagesize) should be 49 for A4 and 51 for Letter.

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FONTS

The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8. The font color should be black. No **bolding**, underlining *italics* or subscripting should be permitted. Try to avoid using super-scripts, unless absolutely necessary. Single spacing should be used for all text.
Figures should have a default font of "Times Roman", "Helvetica", or "Courier New" .
This can be achieved by using the following options in SAS:

```
goptions
gunit = pct
cback = white
colors = (black)
hby = 2.4
ftext = "TimesRoman"
htext = 2.5
device = cgmof97l
gaccess = gsasfile;
filename gsasfile "….cgm";
```

HEADER INFORMATION

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing
- The customer name and protocol number should appear in row 1, left-aligned
- The output identification number should appear in row 2, centered
- The output title should start in row 3, centered
- The output population should appear in row 4, centered. The population should be spelled out in full, e.g. Intention-to-Treat in preference to ITT.
- Row 5 should be a continuous row of underscores ('_') (the number of underscores should equal the linesize)
- Row 6 should be a blank line
- Mixed case should be used for titles
- The output titles should be designed so that they are arranged consistently through all outputs. For example, content (eg Vital Signs) followed by metric (eg Change from Baseline) e.g. Vital Signs – Change from Baseline.
- Titles should not contain quotation marks or footnote references
- The column headings should be underlined with a row of underscores ('_')
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered

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- Column headings containing numbers should be centered
- Column headings should be in sentence case
- In general, the population count should appear in the column header in the form "(N=XXX)"
- "Statistic" should be the column header over n, Mean, SE, n (%) etc.
- As a rule, all columns should have column headings.

TABLE AND LISTING OUTPUT CONVENTIONS

General:

- The first row in the body of the table or listing should be blank
- The left hand column should start in column 1. No indenting or centering of the output should occur.
- Rounding should be done with the SAS function ROUND.
- Numbers in tables should be rounded, not truncated.
- Alphanumeric output should be left aligned.
- Numbers should be decimal point aligned.
- Whole numbers should be right aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized
- Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
- The study drug should appear first in tables with treatments as columns
- In general, only present totals (across treatment groups) at baseline/randomization, and do not present them post randomization, unless the customer specifically requests it.
- If possible, include 100% frequencies in the table shell, so that it is clear what the denominator is for percentage calculations.
- All listing outputs should be sorted (preferably by Treatment, Site Number and Subject Number).
- Do not use superscripts and subscripts
- Exponentiation will be expressed using a double asterisk, i.e., mm3 will be written as mm**3.
- All variables that are output in the CRF (which have data present) should appear in the listings, along with all derived data appearing in the corresponding tables
- The width of the entire output should match the linesize

Univariate Statistics:

- Statistics should be presented in the same order across tables (i.e., n, Mean, SD, Q1, Median, Q3, Minimum, Maximum)
- Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.
- If the original data has N decimal places, then the summary statistics should have the following decimal places:

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Minimum and maximum: N
Mean, median and CV%: N + 1
SD: N + 2

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:
  77 (100.0%)
  50 (64.9%)
  0 (0.0%)
- Percentages will be reported to one decimal place, except percents <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percents < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule.
  Eg (<0.1%)
  (6.8%)
  (>99.9%)
  Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
- Where counts are zero, percentages of 0.0% should appear in the output.

Confidence Intervals:

- As a rule confidence intervals are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data
- Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up".
- Boundary values of confidence intervals should be separated by a comma.
- Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
- An example is given below:
  (-0.12, -0.10)
  (9.54, 12.91)

P-values:

- P-values should be reported to three decimal places, except values <1.000 but >0.999 will be presented as '>0.999' (e.g., 0.9998 is presented as >0.999); and values <0.001 will be presented as '<0.001' (e.g., 0.0009 is presented as <0.001). Rounding will be applied after the <0.001 and >0.999 rule

Ratios:

- Ratios should be reported to one more decimal place than the original data.

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Spacing:
• There must be a minimum of 1 blank space between columns (preferably 2)
Denominators:
• If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
• Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values
• A "0" should be used to indicate a zero frequency.
• A blank will be used to indicate missing data in an end-of-text table or subject listing.

FIGURE OUTPUT CONVENTIONS

• Figures should be provided in RTF files using the SAS Output Delivery System (ODS), as Computer Graphics Metafile (CGM) formatted graphical output generated by SAS.
• The CGM file itself should contain the title or footer.
• The image should be clear and of high quality when viewed in the Word document, and when printed.
• In general, boxes around the figures should be used.

FOOTNOTE INFORMATION

Footers should be defined as follows:
• A continuous line of underscores ('_') will follow the body of the table or listing prior to any footnotes at the bottom of the page
• Table footnotes should be defined using compute statements in the proc report, and should appear directly after the body of the table
• The program path and name and version number (if applicable) should appear as footnote 1 at the bottom of the page
• The date/time stamp should appear as footnote 2 at the bottom of the page
• Footnotes should be left-aligned.
• Footnotes should be in sentence case.
• Only "typewriter" symbols are permitted – eg "*", "$", "#", "@", "&" and "+".
• The choice of footnote symbols should be consistent. E.g. if you have the footnote "# indicates last observation carried forward" for one table, the same symbol and footnote should indicate LOCF for all tables.
• If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line.

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• The page identification in the format Page X of Y (where Y is the total number of pages for the output) should appear in the first footnote, right aligned

Ordering of footnotes should be as follows:

1.) Source data listing reference, if necessary
2.) Abbreviations and definitions
3.) Formulae
4.) P-value significance footnote
5.) Symbols
6.) Specific notes
• Common notes from table to table should appear in the same order.
• The symbols should appear in the same order as what they are defined in the table or listing, from left to right.

PROGRAMMING INSTRUCTIONS

Programming instructions must appear in blue font at the end of each table or listing shell. Programming instructions, where necessary, should follow the table or listing shells in blue font, beginning with the words “Programming Note” followed by a colon. These include notes on the output, reminders of how to handle missing values, repeat shells for similar tables etc.

DATES & TIMES

Depending on data available, dates and times will take the form yyyy-mm-ddThh:mm:ss.

PRESENTATION OF TREATMENT GROUPS

For outputs, treatment groups will be represented as follows and in that order:

Treatment Group	For Tables and Graphs	For Listings
Placebo	Placebo	Placebo
Bempedoic Acid 180 mg	Bempedoic Acid 180 mg	Bempedoic Acid 180 mg
Not Randomized	Not Randomized	Not Randomized

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PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Week -5 (Visit S1)	W-5 (VS1)
Week -4 (Visit S2)	W-4 (VS2)
Week -1 (Visit S3)	W-2 (VS3)
Week 0 (Visit T1)/Baseline	W0 (VT1)
Week 4 (Visit T2)	W4 (VT2)
Week 8 (Visit T3)	W8 (VT3)
Week 12 (Visit T4)	W12 (VT4)

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- randomized treatment
- center-subject ID,
- date (where applicable),
- For listings where non-randomized patients are included, these will appear in a category after the randomized treatment groups labeled 'Not Randomized'.

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APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known and AESTART=study med start date		If AEPRIOR=Y then not TEAE If AEPRIOR=N then TEAE
Known and AESTART>or < study med start date		If start date < study med start date, then not TEAE If start date > study med start date and <=study med end date + 30 , then TEAE
Partial		If AEPRIOR=Y then not TEAE Otherwise, If Impute 1st of month if date is missing; impute 1st of Jan if both date and month are missing. If resulting imputed start date is prior to study med start date, set as study med start date. If imputed start date is <= study med end date + 30 days, then TEAE; otherwise NOT TEAE
Missing		If AEPRIOR=Y then not TEAE Otherwise, Assumed TEAE

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ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post treatment

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START DATE	STOP DATE	ACTION
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

APPENDIX 3. **DMC TABLES, LISTINGS AND FIGURES**

TABLES

14.1.1.1 Patient Disposition – All Patients

14.1.2.1a Demographic and Other Baseline Characteristics – Full Analysis Set

14.1.3.1 Medical/Surgical History – Full Analysis Set

14.1.3.3 Targeted Cardiovascular History/Risk Factors – Full Analysis Set

14.1.5.1 Study Drug Compliance – Safety Analysis Set

14.3.1.1 Overview of Treatment-Emergent Adverse Events – Safety Analysis Set

14.3.1.2 Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term – Safety Analysis Set

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14.3.1.3 Serious Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term – Safety Analysis Set

14.3.1.4 Related Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term – Safety Analysis Set

14.3.1.5 Related Serious Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term – Safety Analysis Set

14.3.1.6 Treatment-Emergent Adverse Events That Led to Discontinuation of Study Drug by Maximum Severity, System Organ Class and Preferred Term – Safety Analysis Set

14.3.1.8 Treatment-Emergent AESIs by Maximum Severity, System Organ Class and Preferred Term – Safety Analysis Set

14.3.1.15 Investigator-reported Major Cardiac Events (MACE) by Event Type – Safety Analysis Set

14.3.1.16 Adjudicated Major Cardiac Events (MACE) by Event Type – Safety Analysis Set

14.3.2.8 Laboratory Parameters of Interest: Observed and Change from Baseline – Safety Analysis Set

14.3.2.9 Laboratory Parameters of Interest: Laboratory Abnormalities – Safety Analysis Set

14.3.2.10 Quantitative Clinical Laboratory Evaluations: Lipids – Safety Analysis Set (note that this table is produced for DMC only)

FIGURES

14.3.1 Boxplots of Hematology Parameters

14.3.2 Boxplots of Chemistry Parameters

The next 2 listings will be created at the same time frame as DMC TLFs above. However, these 2 listings will be sent to Esperion Team only for monitoring thresholds for protocol deviations and for evaluable patients, but not sent to DMC members.

Listing 16.2.3 Patient Inclusion per Analysis Population – All Screened Patients

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Listing 16.2.4 Screen Failures – All Screened Patients (note that this listing is produced for DMC only)

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APPENDIX 4. DETAILS OF MULTIPLE IMPUTATION METHOD

Missing Week 12 values will be imputed based on baseline values. The following table details the possible cohorts and which cohorts will be used for imputation.

	Treatment	Week 12 Value	On Treatment at Week 12	Imputation Cohort(s)
1	Placebo	Missing	Yes	Cohort 5: Placebo patients with non-missing Week 12
2	BA	Missing	Yes	Cohorts 6 and 8 BA patients with non-missing Week 12
3	placebo	Missing	No	Cohort 5: Placebo patients with non-missing Week 12
4	BA	Missing	No	Cohorts 5 and 7 Placebo patients with non-missing Week 12 and not on treatment
5	placebo	Non-missing	Yes	
6	BA	Non-missing	Yes	
7	placebo	Non-missing	No	
8	BA	Non-missing	No	

Imputation code for Cohorts 1-3.

```
proc mi;
where cohort in(1,2,3,5,6,8);
 class trt01pn;
 monotone regression;
 var trt01pn base aval;
run;
```

Imputation code for Cohort 4.

```
proc mi;
where cohort in(4,5,7);
monotone regression;
 var base aval;
```


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```
run;
```

Two hundred imputed datasets will be created, with results from the analysis of each imputed dataset (ANCOVA) combined using Rubin's method.

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APPENDIX 5. LIST OF ADVERSE EVENTS OF SPECIAL INTEREST

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

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Adverse Event Terms per Protocol	Associated MedDRA Preferred Terms
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

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Adverse Event Terms per Protocol	Associated MedDRA Preferred Terms
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	Oliguria
Renal disorders	Prerenal failure
Renal disorders	Renal failure
Renal disorders	Renal function test abnormal
Renal disorders	Renal impairment

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Addendum to Statistical Analysis Plan

Title:	A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BEMPEDOIC ACID (ETC-1002) 180 MG/DAY AS ADD-ON TO EZETIMIBE THERAPY IN PATIENTS WITH ELEVATED LDL-C ON LOW DOSE OR LESS THAN LOW DOSE STATINS
Protocol:	ETC-1002-048
Clinical Phase:	3
Product:	ETC-1002
Date:	Dec 17, 2018

Addendum to the Statistical Analysis Plan for Study 1002-048

Ad-hoc Analyses

Esperion completed the planned analysis as described in Study 1002-048 SAP for all data collected in the study. After the review of the results, it was suggested by the internal clinical team that a waterfall plot was generated to visually show percent change from baseline in Low Density Lipoprotein Cholesterol (LDL-C) Percent for the different treatment groups.

The waterfall plot was not included in the CSR, but may be included in communications with the regulatory agencies for the NDA/MAA submissions.

The Figure for Study 1002-048 Post-hoc Analyses.

Figure 14.2.5	Low Density Lipoprotein Cholesterol (LDL-C) Percent Change from Baseline to Week 12 / Full Analysis Set