STATISTICAL ANALYSIS PLAN

PROTOCOL 1002-047

A LONG-TERM, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY OF BEMPEDOIC ACID (ETC-1002) IN PATIENTS WITH HYPERLIPIDEMIA AT HIGH CARDIOVASCULAR RISK NOT ADEQUATELY CONTROLLED BY THEIR LIPID-MODIFYING THERAPY

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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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.

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
ACS	acyl-CoA synthetase
ADaM	Analysis Data Model
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
apoB	apolipoprotein B
ASCVD	atherosclerotic cardiovascular diseases
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CEC	Clinical Event Committee
CHD	coronary heart disease
CI	confidence interval
CK	creatine kinase
CPK	Creatine phosphokinase
CV	cardiovascular
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	Electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
ETC-1002	Bempedoic acid
EU	European Union
FAS	full analysis set
HbA_{1C}	glycosylated hemoglobin, Type A1C
HeFH	heterozygous familial hypercholesterolemia
HDL-C	high-density lipoprotein cholesterol
Hgb	hemoglobin
hsCRP	high-sensitivity C-reactive protein
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
ITT	intention-to-treat
LDL-C	low-density lipoprotein cholesterol
LFT	liver function test
LSM	least square mean
MACE	major adverse cardiac event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction

non-HDL-C	non-high-density lipoprotein cholesterol
PCSK9	proprotein convertase subtilisin/kexin type 9
PE	physical exam
PK	pharmacokinetic(s)
PMM	pattern mixed model
PPS	per-protocol set
PT	preferred term
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SE	standard error
SOC	system organ class
SDTM	study data tabulation model
T2DM	type 2 diabetes mellitus
TB	total bilirubin
TC	total cholesterol
TEAE	treatment-emergent adverse event
TG	triglycerides
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 1002-047. 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, 2016 and amendment 1 dated 18 January 2017, amendment 2 dated 22 March 2017, and amendment 3 dated 09 May 2017.

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) 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.

2.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To evaluate the effect of 24-week treatment with bempedoic acid 180 mg/day versus placebo on LDL-C.
- To evaluate the effect of bempedoic acid 180 mg/day versus placebo on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), high-sensitivity C-reactive protein (hsCRP), and apolipoprotein B (apoB) after 12 weeks of treatment.

2.3. TERTIARY OBJECTIVES

The tertiary objectives are:

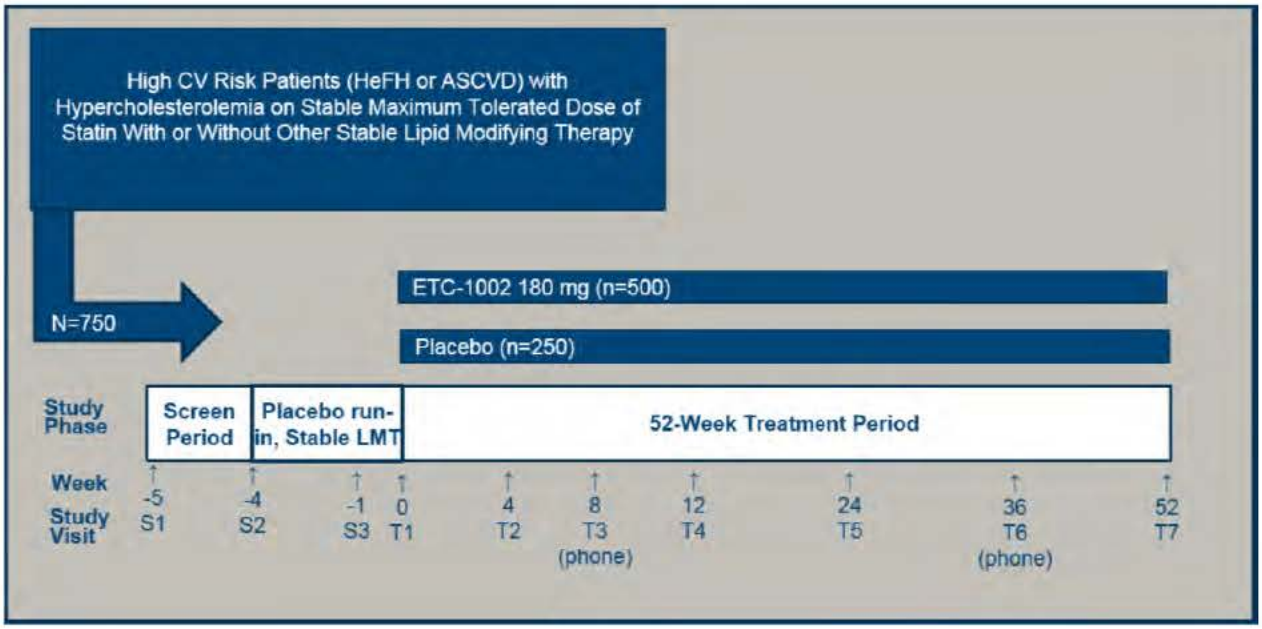
- To evaluate the long-term treatment (52 weeks) with bempedoic acid 180 mg/day versus placebo on LDL-C, non-HDL-C, TC, HDL-C, TG, hsCRP, and apoB.
- To evaluate the 52-week safety and tolerability of bempedoic acid 180 mg/day compared to placebo.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase 3, long-term randomized, double-blind, placebo-controlled, parallel group, study evaluating the efficacy of bempedoic acid in high CV risk patients with hyperlipidemia (patients with underlying HeFH and/or ASCVD) who are not adequately treated with their maximally tolerated lipid-modifying therapy. The study will be conducted at approximately 125 clinical sites in North America and Europe. Screening Week -5 (Visit S1) will be approximately 5 weeks prior to randomization, but can be extended for an additional 4 weeks if needed to adjust background medical therapy or for other reasons as specified in the protocol. Eligible patients will return to the clinical site at Week -4 (Visit S2) to initiate administration of single-blind (patient only) placebo. Eligible patients will return at Week -1 (Visit S3) for lipid and safety laboratories and an assessment of tolerability and study drug adherence. Approximately 750 eligible patients will be randomized 2:1 on Day 1 (Visit T1) to receive either bempedoic acid 180 mg (n = 500), or placebo (n = 250) once daily for 52 weeks. Randomized patients will return for clinic visits at Week 4 (Visit T2), Week 12 (Visit T4), Week 24 (Visit T5), and Week 52 (Visit T7). A phone visit will occur at Week 8 (Visit T3) and Week 36 (Visit T6).

Table A: 1002-047 Study Design



3.2. SCHEDULE OF EVENTS

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

4. PLANNED ANALYSIS

The following analysis will be performed for this study:

- Analysis 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.

4.2. FINAL ANALYSIS

All final, planned analysis identified in this SAP will be performed by IQVIA 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 subjects 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 analysis, 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. PK ANALYSIS SET [PKS]

The PK Analysis Set will include all patients in the safety analysis set who have at least one non-missing PK assessment. These patients will be summarized for PK concentrations unless major protocol deviations are identified during the protocol deviation review or if key dosing or sampling information is missing.

6. GENERAL CONSIDERATIONS

6.1. 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 double-blind study medication (Day 1 is the day of the first dose of study medication. In case the first dose date is missing, the 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.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken on or 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 pre-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.

6.3. 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.

6.4. 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.

Analysis Visit	S1	S2	S3	T1	T2	T3	T4	T5	T6	T7
Study Week	-5	-4	-1	week 0	4	8	12	24	36	52/EOS
Target Study Day	-35	-28	-7	1	29	57	85	168	252	365
Analysis Visit Windows	[-∞,-32]	[-31 ,-18]	[-17, -1]	[1,1]	[2,43]	[44,71]	[72,127]	[128, 211]	[212, 309]	[310,∞]

6.5. 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 analysis.

6.6. 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

6.7. SOFTWARE VERSION

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

7. STATISTICAL CONSIDERATIONS

7.1. 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 500 randomized patients in the bempedoic acid 180 mg group and 250 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 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 ($\alpha = 0.05$) and a common standard deviation of 15%. The sample size of 500 randomized patients in the bempedoic acid 180 mg group and 250 randomized patients in the placebo group gives a total study sample size of 750.

7.2. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSIS

The following covariates and factors are used in the analysis. For details of their inclusion in the models, see the specific analysis section.

- treatment group (bempedoic acid 180 mg/day; placebo)
- CV risk (ASCVD only; HeFH with or without ASCVD)
- baseline statin intensity (high intensity; moderate intensity; low intensity)
- baseline laboratory value of interest

- treatment by subgroup interaction term for subgroup analyses of efficacy variables

7.3. MULTICENTER STUDIES

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

7.4. MISSING DATA

Missing efficacy data will be handled as described in section 15.1.2 of this analysis plan.

7.5. 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:

- Test the primary efficacy endpoint: percent change from baseline to Week 12 in LDL-C
- Test the percent change from baseline to Week 24 in LDL-C
- Test the percent change from baseline to Week 12 in non-HDL-C
- Test the percent change from baseline to Week 12 in TC
- Test the percent change from baseline to Week 12 in apoB
- 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 24 in LDL-C will be tested; and so forth.

8. 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. Unless otherwise specified all outputs will be presented by randomized treatment group.

9. 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 or exclusion criteria violation, the criteria category will be presented. Patient disposition and withdrawals (both from study treatment and the study) will be summarized for the FAS. The number of patients in each analysis set and by visit will be presented for all randomized patients.

10. PROTOCOL DEVIATIONS

All protocol deviations will be provided in a listing with type and description. Major protocol deviations will be summarized by treatment group. The protocol deviations are recorded and tracked in the trial monitoring platform CTMS. The final protocol deviations will be determined before treatment group is unblinded.

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be summarized by treatment group for the FAS.

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
- Region (US vs. Canada vs. EU)
- Stratification factor
- CV risk (ASCVD only; HeFH (with or without ASCVD))
- Baseline statin intensity (high intensity; moderate intensity; low intensity)
- 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, Apolipoprotein B, and hsCRP)
- Baseline LDL-C category (<130 mg/dL, ≥130 and < 160 mg/dL, or ≥160 mg/dL)
- Baseline eGFR (normal: ≥90 mL/min/1.73m2; mild Renal Impairment: 60-89 mL/min/1.73m2; moderate Renal Impairment: 30-59 mL/min/1.73m2, and severe Renal Impairment (15-29 mL/min/1.73m2)
- 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 (Non-Drinker, Former Drinker, or Current Drinker)
- Tobacco use (Never Used, Former User, or Current User)

11.1. DERIVATIONS

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

12. 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 started prior to signing the inform consent form (ICF) and stopped prior to or at screening. Medical History will be coded using MedDRA Version 20.1.

13. 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 signing ICF and are ongoing at the date of randomization. Concomitant Illnesses will be coded using MedDRA Version 20.1

14. CARDIOVASCULAR HISTORY/RISK FACTORS

Cardiovascular history/risk factors collected at screening will be presented in a table by treatment group and data listing.

15. 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).

Medications will be summarized by ATC classification and preferred term by treatment group. Prior and concomitant lipid modifying therapy including statin, PCSK9i, ezetimibe and others will be tabulated and listed separately.

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.

15.1. BACKGROUND LIPID MODIFYING THERAPY

Baseline background lipid modifying therapy is defined as any lipid modifying agents that are on-going at the time of randomization. It will be presented by treatment group in separate table and listing by category , ATC class 4 and coded medication name.

15.2. ADDITIONAL POST-RANDOMIZATION ADJUNCTIVE TRIGLYCERIDE-LOWERING THERAPY

The number and percent of patients requiring additional (post-randomization) TG-lowering therapy (only when TG>1000) will be summarized by treatment group, ATC class 4 and medication name, as well as provided in a listing. The TG lowering medication will be identified as post-randomization concomitant medications with indication of 'hypertriglyceridemia'.

15.3. ADDITIONAL POST-RANDOMIZATION LIPID MODIFYING THERAPY

The number and percent of patients in each treatment group requiring additional (post-randomization) lipid-lowering therapy will be summarized by treatment group, ATC class 4 and medication name as well as provided in a listing. The lipid-lowering therapy includes all post-randomization concomitant medications based on ATC class 2 = lipid-modifying agent.

16. STUDY MEDICATION COMPLIANCE AND EXPOSURE

Compliance to study medication will be presented for the SAF. At visit Week -1 (S3) 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.

16.1. 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 on treatment within each of the 2 periods.

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), Week 12 (Visit T4), and two 100-day supply bottles at Week 24 (Visit T5).

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 day of their last medication return date. For example, if the initial dispense date is Day 1 and the last return date 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.

For subjects who did not return any bottle during the run-in or double-blind period, their compliance will be set to missing.

Treatment exposure will be calculated in weeks as (date of last dose of study medication – first date of first dose of study medication +1)/7. Descriptive statistics will be presented for exposure as well as categorization into time periods. (e.g., <12weeks, 12-<24 weeks, 24-<48 weeks and >=48 weeks, etc.).

17. EFFICACY OUTCOMES

17.1. PRIMARY EFFICACY

17.1.1. 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.

17.1.2. 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.

The primary efficacy endpoint will be analyzed using analysis of covariance (ANCOVA), with treatment group and randomization stratification factors (CV risk and baseline statin intensity) as factors and baseline LDL-C as a covariate. In case the of number of subjects within a stratum is too small for a meaningful analysis, the strata may be combined to obtain larger cell size. 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. Assumptions for ANCOVA model will be assessed and if the assumptions are severely violated, a non-parametric rank based method will be performed.

In addition, descriptive statistics will be presented for LDL-C at each visit and for change/percent change from baseline by treatment group for overall population and for each stratification factor.

17.1.3. 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) 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 stratification and 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) 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 including treatment, stratification and baseline data.

Imputed datasets will be analyzed using an ANCOVA model with treatment, CV risk, baseline statin intensity as a factors 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.

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

17.2. SECONDARY EFFICACY

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

17.2.1. 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 24 in LDL-C

- 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 of LDL-C, non-HDL-C, TC, and apoB will be analyzed using the same ANCOVA model described in 17.1.2.

Similar to the primary endpoint, missing data will be imputed using multiple imputation method as described in 17.1.3.

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 etc., 2006) and recent data available, hsCRP is known to be skewed by extreme values and have non-normal distribution.

Graphic presentations (mean+/-SE) or median (IQR) for efficacy parameters will be provided.

17.2.2. OTHER SECONDARY EFFICACY VARIABLES & DERIVATIONS

- change from baseline to Week 12 in LDL-C
- change from baseline to Week 24 in LDL-C

Other secondary endpoints will be analyzed using descriptive statistics by treatment group using observed data as well as on-treatment approach.

17.2.3. SENSITIVITY ANALYSIS OF PRIMARY AND KEY SECONDARY EFFICACY VARIABLES

17.2.3.1. Analysis Using Derived Stratification Factors

In order to assess any potential impact to the efficacy result from mis-stratification, the stratification factors of disease characters and statin intensity will be derived in cases there is a known stratification error. The primary endpoint will be re-analyzed using the same method as described in section 17.1.2 using derived stratification factors.

17.2.3.2. Adjunctive Lipid-modifying Therapy (LMT) Analysis

To explore the potential impact from adjunctive lipid-modifying therapy use during the study, a sensitivity analysis will be performed for primary and key secondary endpoints using data prior to the change of the post-baseline LMT only, i.e., lab test date <=change date of LMT. There will be no imputation for missing data.

17.2.3.3. On-treatment Analysis

To explore the impact to efficacy from patient discontinue study medication, an on-treatment analysis will also be conducted for primary and key secondary endpoints using data collected from the on-treatment period, i.e. lab test date <= of last dose of double-blind IMP+7 days. On-treatment analysis will be based on FAS. There will be no imputation for missing data.

17.2.3.4. Observed Data Analysis

The observed case data with no imputation for missing data will be used in sensitivity analyses for primary and key secondary endpoints to explore any difference between a observed analysis vs. missing data imputation using PMM method.

17.2.4. SUBGROUP ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary endpoint for LDL-C 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 subjects 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 variable will also be presented.

- CV risk category (HeFH (with or without ASCVD) vs. ASCVD only)
- Baseline statin intensity (Low or Moderate, vs. High)
- Baseline LDL category (<130mg/dL, ≥130 mg/dL and < 160 mg/dL, ≥160mg/dL) (efficacy only)
- History of diabetes (yes vs.no)
- Age (< 65 yrs. vs. ≥65 yrs. and <75 yrs vs. ≥75 yrs)
- Race (White vs. other)
- Gender (male vs. female)
- Region (North America vs. EU)
- BMI category (< 25 vs. 25 - < 30 vs. ≥ 30 kg/ m2)

17.3. TERTIARY EFFICACY

17.3.1. TERTIARY EFFICACY VARIABLES & DERIVATIONS

The tertiary efficacy endpoints are:

- Absolute change and percent change from baseline to Week 52 in LDL-C
- Percent change from baseline to Weeks 24 and 52 in non-HDL-C, TC, apoB, and hsCRP
- Percent change from baseline to Weeks 12, 24, and 52 in TG and HDL-C

17.3.2. MISSING DATA METHODS FOR TERTIARY EFFICACY VARIABLES

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

17.3.3. ANALYSIS OF TERTIARY EFFICACY VARIABLES

Tertiary efficacy endpoints of LDL-C, non-HDL-C, TC and ApoB will be analyzed using the same ANCOVA model described in 17.1.2. Each statistical comparison will be conducted at significant level of 0.05.

hsCRP will be analysed using non-parametric Wilcoxon rank sum test as described in 17.2.1.

In addition, the LDL-C endpoint at week 52 will be analyzed with patients in the FAS who did not receive additional lipid-lowering therapy by that time point (by week 52). Only observed case data will be used (no imputation for missing data).

For endpoint of HDL-C and TG at week 12, 24, and 52 summary statistics will be provided for actual value, change and percent change at each visit by treatment group.

17.3.1. ADDITIONAL ANALYSIS

Proportion of patients achieve hsCRP <2 mg/L at Weeks 12, 24, and 52 for whom baseline hsCRP >2 mg/L will be analysed by Cochran–Mantel–Haenszel (CMH) method adjusted by stratification factor. Summary statistics and treatment difference estimates are based on observed data with no imputation for the missing data.

18. SAFETY OUTCOMES

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

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

18.1. 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 after the first dose of double-blind study medication and prior to the last date of study medication + 30 days. AEs that occurred on day 1 will be only be determined as TEAE if the site indicated it occurred after first dose 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 scenario, 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.

18.1.1. ALL TEAES

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and relationship to study medication. TEAEs will also be presented by PT in descending frequency. Adverse events by the subgroups in Section 17.2.4 with the exception of baseline LDL subgroup will also be presented.

18.1.2. SEVERITY

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of double-blind study medication with a missing severity will be classified according to worst case scenario, ie, as severe. If a subject 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.

18.1.3. RELATIONSHIP TO STUDY MEDICATION

Relationship, 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. If a subject reports the 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.

18.1.4. TEAES LEADING TO DISCONTINUATION OF STUDY MEDICATION

TEAEs leading to permanent discontinuation of study medication will be identified by using the

response of 'Drug Withdrawn/Permanently discontinued' on the Action Taken With Study Drug Field on the AE eCRF page. For TEAEs leading to discontinuation of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

18.1.5. 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 will be prepared. Serious TEAEs will also be presented by PT in descending frequency.

18.1.6. ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

Adverse events of special interest 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 18.4.

18.2. 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).

18.3. 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:

- 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)
- Hospitalization for heart failure (non-MACE)

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

18.4. SAFETY LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for Hematology, Blood Chemistry, Lipids, Coagulation, HbA1C, hsCRP 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 SI Units and conventional 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).

Shift from baseline by visit according to normal ranges.

Shift from baseline according to normal ranges 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 , >5xULN)

TB (>2x ULN)

CK (> 5x ULN) and (>10x ULN)

Fasting Blood Glucose (≤50 mg/dL, ≥126 mg/dL) by history of diabetes

HbA1c (≥6.5%) by history of diabetes

Creatinine (change from baseline for >1 mg/dL)

eGFR (< 15 mL/min/1.73m2, 15 –< 30 mL/min/1.73m2)

Hgb (decrease from baseline for ≥2 g/dL)

Hgb (<8 g/dL)

18.4.1. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units 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.

18.5. 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.

18.6. 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/m2) (calculated automatically by the EDC system)

The following summaries will be provided for vital signs data:

- Observed and change from baseline by visit

18.7. PHYSICAL EXAMINATION

Abnormalities in physical examinations will be presented in a listing.

18.8. PHARMACOKINETICS

A PK blood sample will be collected prior to dosing at Weeks 24 and 52. Descriptive statistics for concentrations of bempedoic acid and its metabolite ESP15228 will be presented for each visit for the PK Analysis Set as defined in section 5.4. All concentration data will also be presented in a listing.

All concentrations below the limit of quantification or missing data will be labelled as such in the concentration data listings. Concentrations below the lower limit of quantification will be treated as zero in summary statistics.

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

19. 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.

20. REFERENCES

Demets, David L., and K. K. Lan. "Interim analysis: the alpha spending function approach." Statistics in medicine 13.13-14 (1994): 1341-1352.

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Liang, K., Zeger, S., Longitudinal Data Analysis for Continuous and Discrete Responses for Pre-Post Designs. Sankhyta: The Indian Journal of Statistics. 2000. 62(B): 134-148.

Little, R. & Rubin, D.(1987) Statistical Analysis with Missing Data, Wiley, New York.

Ratitch, B. and O'Kelley, M., "Implementation of Pattern-Mixture Models Using Standard SAS/STAT Procedures," in Proceedings of PharmaSUG 2011 (Pharmaceutical Industry SAS Users Group), SP04, Nashville.

O'Brien, Peter C., and Thomas R. Fleming. "A multiple testing procedure for clinical trials." Biometrics (1979): 549-556.

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,

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.

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
- 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:
  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.

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.
- 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

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)

Long Name (default)	Short Name
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)
Week 16 (Visit T4.1)	W16 (VT4.1)
Week 20 (Visit T4.2)	W20 (VT4.2)
Week 24 (Visit T5)	W24 (VT5)
Week 28 (Visit T5.2)	W28 (VT5.2)
Week 32 (Visit T5.3)	W32 (VT5.3)
Week 36 (Visit T6)	W36 (VT6)
Week 52 (Visit T7)	W52 (VT7)

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 labelled ‘Not Randomized’.

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	Known	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 start date < study med start date, then not TEAE If start date >= study med start date and <=study med end date + 30, then TEAE
	Missing	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, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date and <=study med end date + 30, then TEAE
	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, then not TEAE If stop date >= study med start date and <=study med end date + 30, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date and <=study med end date + 30, then TEAE
	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 and <=study med end date + 30, then not TEAE

START DATE	STOP DATE	ACTION
		If stop date >= study med start date and <=study med end date + 30, then TEAE
	Missing	Assumed TEAE

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

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. LIST OF DMC TABLES, LISTINGS, AND FIGURES

TABLES

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 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

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

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. Missing Week 24 values will be imputed in the same way.

	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 strata;
 monotone regression;
 var trt01pn strata base aval;
run;
```

Imputation code for Cohort 4.

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

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

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
Hepatic disorders	Liver function test abnormal
Hepatic disorders	Liver function test increased
Hepatic disorders	Transaminases abnormal

Adverse Event Terms per Protocol	Associated MedDRA Preferred Terms
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

Adverse Event Terms per Protocol	Associated MedDRA Preferred Terms
	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
Gout	Gout

Addendum to Statistical Analysis Plan

Title:	A LONG-TERM, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY OF BEMPEDOIC ACID (ETC-1002) IN PATIENTS WITH HYPERLIPIDEMIA AT HIGH CARDIOVASCULAR RISK NOT ADEQUATELY CONTROLLED BY THEIR LIPID-MODIFYING THERAPYE
Protocol:	ETC-1002-047
Clinical Phase:	3
Product:	ETC-1002
Date:	Dec 17, 2018

Addendum to the Statistical Analysis Plan for Study 1002-047

Post-hoc Analyses

Esperion completed the planned analysis as described in Study 1002-047 SAP for all data collected in the study. After unblinding, additional tables and figures were generated to address some issues of clinical interest.

The tables and figures may be presented in the manuscript, presented in the top line results press release, reported in the CSR, and included the communications with the regulatory agencies for the NDA/MAA submissions.

The listing of tables and figures for the post-hoc analyses is provided in the table below.

Table 17.2.4.1a	Efficacy Subgroup Analysis: Percent Change from Baseline to Week 12 in Low Density Lipoprotein Cholesterol (LDL-C) by Derived Baseline Statin Intensity / Full Analysis Set
Table 17.2.4.1b	Efficacy Subgroup Analysis: Percent Change from Baseline to Week 12 in Low Density Lipoprotein Cholesterol (LDL-C) by Baseline Lipid-modifying / Therapies (LMT) Medications Full Analysis Set
Table 17.2.2.6a	Key Secondary Efficacy Non-parameteric Analysis: Wilcoxon Rank Sum Test on Percent Change from Baseline to Week 12 and 52 in High-Sensitivity C-reactive Protein (hsCRP) by Derived Baseline Statin Intensity /Full Analysis Set
Table 17.2.2.6b	Key Secondary Efficacy Non-parameteric Analysis: Wilcoxon Rank Sum Test on Percent Change from Baseline to Week 12 and 52 in High-Sensitivity C-reactive Protein (hsCRP) by Baseline Lipid-modifying Therapies (LMT) Medications / Full Analysis Set
Table 17.2.2.6c	Key Secondary Efficacy Non-parametric Analysis: Wilcoxon Rank Sum Test on Percent Change from Baseline to Week 24 and 52 in High-Sensitivity C-reactive Protein (hsCRP) On-Treatment Analysis / Full Analysis Set
Table 17.3.1.1	Incidence of Positively Adjudicated Treatment-Emergent Composite Clinical Endpoints / Safety Analysis Set
Table 17.4.1.1	Post-Randomization Abnormal Liver Function Summary / Safety Analysis Set
Figure 19.1.1	Waterfall Plot of Percent Change from Baseline to Week 12 in Low Density Lipoprotein Cholesterol (LDL-C) / Full Analysis Set