Statistical Analysis Plan

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Triplet Therapy with Bempedoic Acid (ETC-1002) 180 mg, Ezetimibe 10 mg, and Atorvastatin 20 mg in Patients with Elevated LDL-C

Protocol: ETC-1002-038
Clinical Phase: 2
Product: ETC-1002
Version (Date): Statistical Analysis Plan – Version 2.0 (July 03, 2017)
Status: Final

Prepared by:

[redacted]

On behalf of:

Esperion Therapeutics

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[redacted]
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I approve this document.
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Reviewed at [redacted] by:

[redacted]
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I approve this document.
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Revision History

<table>
<tr><th>Item No.</th><th>Version Affected</th><th>Description of change</th></tr>
<tr><td>1</td><td>1.0</td><td>Section 5.1 General Statistical Considerations: Changed Analysis visit window.

From

<table>
<tr><td>Visit</td><td>S1</td><td>S2</td><td>T1</td><td>T2</td><td>T3, EOS</td></tr>
<tr><td>Slotted Study Week</td><td>-6</td><td>-1</td><td>0</td><td>3</td><td>6</td></tr>
<tr><td>Target Study Day</td><td>-42</td><td>-7</td><td>1</td><td>22</td><td>43</td></tr>
<tr><td>Analysis Visit Windows</td><td>[-∞,-37]</td><td>[-10,-1]</td><td>[1,7]</td><td>[8,28]</td><td>[29,+∞]</td></tr>
<tr><td>Protocol defined visit window</td><td>-42 to -37</td><td>-10 to -7</td><td>1</td><td>22±3</td><td>43±3</td></tr>
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</table>
</td></tr>
<tr><td>2</td><td>1.0</td><td>Section 5.2.6 Medical History: Removed mITT population set.

General medical history will be summarized by treatment group, as well as overall, for safety population ~~and mITT population~~ and presented in a by-patient listing. Where appropriate, terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or later.</td></tr>
<tr><td>3</td><td>1.0</td><td>Section 5.3.1 & 5.3.2: Updated for non-parametric analysis.

An analysis of covariance (ANCOVA) with treatment group as factor and baseline LDL-C as a covariate will be performed to compare triplet therapy versus placebo for the primary endpoint using the mITT population. 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. Statistical testing of primary efficacy endpoint will be 2-sided and conducted at the 5% level of significance. To account for potential unequal variance 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. Q-Q plot will be performed to assess normality of data by treatment. If the assumptions were severely violated, non-parametric rank based approach ~~rank ANCOVA on efficacy endpoints~~ will be considered.</td></tr>
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Table of Contents

1 List of Abbreviations

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AESI	Adverse events of special interest
ALB	Albumin
ALK-P	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca	Calcium
CI	Confidence interval
CK	Creatine kinase
CO_2	Carbon dioxide
CPK	Creatine phosphokinase
CRF	Case Report Form
DBP	Diastolic blood pressure
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End of Study
FSH	Follicle-stimulating hormone
HBsAg	Hepatitis B surface antigen
Hct	Hematocrit
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
hs-CRP	High-sensitivity C-reactive protein
ICH	International Conference on Harmonisation
IMP	Investigational medicinal product
IND	Investigational New Drug Application
INR	International normalized ratio
mITT	Modified Intention-to-treat
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
LSM	Least square mean
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or Specialist Term	Explanation
non-HDL-C	Non-high-density lipoprotein cholesterol
PE	Physical exam
PK	Pharmacokinetic(s)
PMM	Pattern mixture model
PT	Prothrombin time
MedDRA PT	MedDRA Preferred term
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SE	Standard error
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
SOP	Standard operating procedures
SP	Safety population
TB	Total bilirubin
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

2 Introduction

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed in ETC-1002-038. The preparation of this statistical analysis plan (SAP) has been based on International Conference on Harmonisation (ICH) E3 and E9 Guidelines and in reference to Protocol ETC-1002-038 (Protocol Final, November 11, 2016).

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

3 Study Objectives and Endpoints

3.1 Objectives

The primary objective for this study is to assess the LDL-C lowering efficacy of triplet therapy with bempedoic acid 180 mg, ezetimibe 10 mg, and atorvastatin 20 mg versus placebo administered daily for 6 weeks in patients with elevated LDL-C.

The secondary objectives are:

• To assess the effect of triplet therapy versus placebo on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), apolipoprotein B (ApoB), high-sensitivity C-reactive protein (hs-CRP), TG, and HDL-C

• To assess the effect of triplet therapy versus placebo on percent of patients achieving LDL-C level <70 mg/dL

• To assess the effect of triplet therapy versus placebo on percent of patients achieving LDL-C reduction ≥50%

• To assess the safety and tolerability of triplet therapy versus placebo

3.2 Primary Endpoints

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

3.2.1 Primary Endpoint

• Percent change from baseline to Week 6 in LDL-C

3.2.2 Secondary Endpoints

• Percent change from baseline to Week 6 in non-HDL-C, TC, ApoB, hs-CRP, TG, and HDL-C

• Percent of patients with LDL-C <70 mg/dL at Week 6

• Percent of patients with LDL-C reduction ≥50% from baseline to Week 6

3.2.3 Safety Endpoints

• Patient incidence of adverse events

• Clinical safety laboratory (including hematology, blood chemistry, and urinalysis) results

• Vital signs and physical examination (PE) findings

4 Study Design

4.1 Study Design

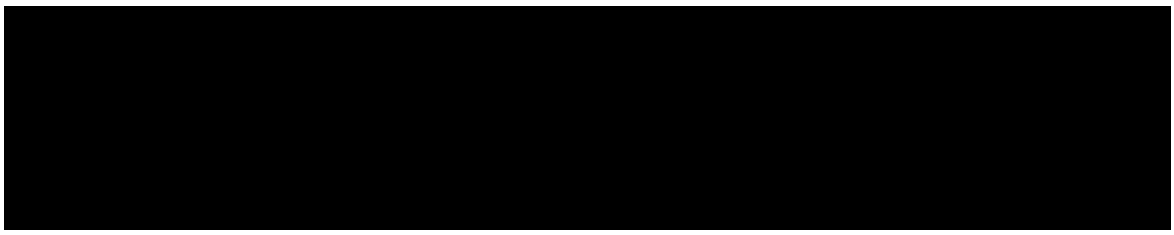
This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel group study. Patients will initially undergo screening at Week -6 (Visit S1). Eligible patients will begin washout of all LDL-C-lowering drugs and nutritional supplements at least 5 weeks prior to randomization. Patients will return at Week -1 (S2) for lipid and/or other assessments. Patients who are deemed not eligible for randomization at any point during screening will be notified by clinical site personnel and considered screen failures. At Week 0 (Visit T1), approximately 60 patients will be randomized in a ratio of 2:1 to receive either triplet therapy (bempedoic acid 180 mg + ezetimibe 10 mg + atorvastatin 20 mg) or placebo once daily for 6 weeks. Randomized patients will return for clinic visits at Week 3 (Visit T2) and Week 6 (Visit T3). Total treatment duration will be 12 weeks (6 weeks screening and 6 weeks treatment) with the option to extend screening by 1 additional week. Up to approximately 20 centers in the US will participate in this. Additional sites may be invited to participate to ensure study timelines are met.

For details of study assessments, see the Schedule of Events in Appendix 1.

4.2 Randomization

The randomization number will be determined by a computer-generated random code and will correspond to a treatment group according to patient's sequential entrance into the study. The randomization schedule for blinding of treatment assignment will be generated by the contract research organization (CRO), provided to IWRS, and released only after the study is complete and the database is locked. A patient is considered to be randomized when they have been assigned a randomization number by IWRS.

4.3 Sample Size Justification



[redacted]

5 Statistical and Analytical Plans

5.1 General Statistical Considerations

In general, summary statistics for continuous variables will include the number of patients, mean, median, standard deviation or standard error, first and third quartiles, minimum, and maximum. Minimum and maximum will be presented same number of decimal places as reported/collected, one additional decimal place for mean and median, and two additional decimal places for SD.

For categorical variables, the frequency and percentage will be given. Percentage will be presented with one decimal place. All categories will be presented (even if no patients are counted in the category). Counts of zero in any category will be presented without percentage.

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

The visit schedules and window are shown below.

Visit	S1	S2	T1	T2	T3, EOS
Slotted Study Week	-6	-1	0	3	6
Target Study Day	-42	-7	1	22	43
Analysis Visit Windows	[-∞,-37]	[-36,-1]	[1]	[2,28]	[29,+∞]
Protocol defined visit window	-42 to -37	-10 to -7	1	22±3	43±3

5.2 Statistical Analysis Plans

5.2.1 Analysis Sets

5.2.1.1 Safety Population (SP)

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

5.2.1.2 Modified Intent-to-Treat Population (mITT)

The modified Intent-to-Treat (mITT) population, used for all of the efficacy analyses, is defined as all randomized patients who received at least 1 dose of Investigational medicinal product (IMP) and have a baseline assessment and at least 1 post-baseline assessment, excluding any assessment taken more than 2 days after a dose of IMP.

Patients in the mITT will be included in their randomized treatment group, regardless of their actually received treatment.

5.2.2 Baseline Definition

Baseline for LDL-C, non-HDL-C, HDL-C, TC, and TG is defined as the mean of the values from Week -1 (Visit S2) and predose Day 1/Week 0 (Visit T1), while baseline for ApoB and hs-CRP is defined as the predose Day 1/Week 0 (Visit T1) value. If only one value is available either at Week -1 or Week 0, then that value will be used as baseline.

Baseline of other laboratory evaluations and vital signs is defined as the last value prior to the first dose of study medication, except baseline of blood pressure is defined as mean of 2 measures at same visit.

5.2.3 Protocol Violations and Deviations

A full list of protocol violations and deviations will be compiled and reviewed by the clinical team to identify major versus minor violations/deviations before final database lock. For violations at study entry, patients will be assessed against the inclusion and exclusion criteria of the protocol. For on-study deviations, compliance with the protocol will be examined using blinded review of the database with regard to prohibited therapies, and timing and availability of planned assessments. The determination of major versus minor protocol deviations will be conducted prior to the database lock. Any protocol deviation related to inclusion/exclusion criteria will be summarized in table as well as listing. Any major on-study protocol deviation will also be summarized by treatment group.

5.2.4 Patient Disposition

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

5.2.5 Demographic and Baseline Characteristics

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

The following demographic and baseline characteristics will be summarized by treatment group, as well as overall, for safety population and for mITT population: age (years), gender, race, ethnicity, height (cm), weight (kg), body mass index (kg/m2), systolic and diastolic blood pressure (mmHg), fasting lipid parameters (TC [mg/dL], calculated LDL-C [mg/dL], HDL-C [mg/dL], non-HDL-C [mg/dL] and TG [mg/dL]), apoB (mg/dL), and hs-CRP (mg/dL).

Data will be summarized using descriptive statistics for continuous variables and using counts and percentages for categorical variables by treatment group and overall. Age will be summarized as a continuous variable and by age group (18-40, 41-64, 65-74, and >=75).

5.2.6 Medical History

General medical history will be summarized by treatment group, as well as overall, for safety population and presented in a by-patient listing. Where appropriate, terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or later.

5.2.7 Prior Medications and Concomitant Medications/Procedures

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

Medications, including prior statin medications, will be coded using WHO Drug (Sept 2016, or later). The frequency of use of prior medications and use of concomitant medications will be summarized by treatment group, as well as overall, for the safety population according to Anatomical Therapeutic Chemical (ATC) class and preferred term. Prior medications, concomitant medications, and concomitant procedures will be listed for each patient.

5.2.8 Study Drug Exposure and Compliance

The length of exposure to study drug (triplet therapy or placebo) will be calculated as the number of days from the first dose of double-blind study drug to the last dose of double-blind study drug, regardless if the patient missed one or more doses of study drug. If last dose of study treatment is missing, then the last IMP return date will be used for imputation of end of treatment date. Length of exposure will be summarized by treatment group using descriptive statistics for the safety population.

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

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

5.3 Efficacy Endpoints and Analyses

For all efficacy endpoints and analyses, the modified Intent-to-Treat (mITT) population will be used.

5.3.1 Primary Endpoint Analysis

The primary efficacy endpoint is the percent change from baseline to Week 6 in LDL-C.

LDL-C value will be measured directly if TG are >400 mg/dL or LDL-C is <50 mg/dL. Baseline is defined as the mean of the values from Week -1 (Visit S2) and predose Day 1/Week 0 (Visit T1). Percent change from baseline is defined as (observed value-baseline)/baseline*100.

An analysis of covariance (ANCOVA) with treatment group as factor and baseline LDL-C as a covariate will be performed to compare triplet therapy versus placebo for the primary endpoint using the mITT population. 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. Statistical testing of primary efficacy endpoint will be 2-sided and conducted at the 5% level of significance. To account for potential unequal variance 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. Q-Q plot will be performed to assess normality of data by treatment. If the assumptions were severely violated, non-parametric rank based approach will be considered.

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

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

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

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

5.3.2 Secondary Efficacy Endpoint Analyses

Secondary endpoints based on percent change from baseline to Week 6 in additional lipid and cardiometabolic biomarkers, will be analyzed in a similar manner as the primary efficacy endpoint. Baseline for non-HDL-C, HDL-C, TC, and TG is defined as the mean of the values from Week -1 (Visit S2) and predose Day 1/Week 0 (Visit T1), while baseline for ApoB and hs-CRP is defined as the predose Day 1/Week 0 (Visit T1) value.

An analysis of covariance (ANCOVA) with treatment group as factor and baseline as a covariate will be performed to compare triplet therapy versus placebo for the secondary endpoints using the mITT population. Missing values at Week 6 will be imputed using the last observation carried forward (LOCF) procedure (only post-baseline values will be carried forward). 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. Q-Q plot will be performed to assess normality of data by treatment. If the assumptions were severely violated, non-parametric rank based approach will be considered.

Statistical testing of secondary efficacy endpoints will be 2-sided and conducted at the 5% level of significance with no adjustment for multiple comparisons, and all p-values will be considered descriptive only.

Analyses using observed data only for the secondary efficacy endpoints will also be performed.

Percent of patients with LDL-C <70 mg/dL at Week 6 and LDL-C reduction ≥50% from baseline at Week 6 will be summarized by treatment group. Comparisons between treatment groups will be performed using Fisher's exact test or Pearson's chi-square test on observed data and LOCF data.

Lipid and cardiometabolic data from all visits will be listed.

5.4 Safety Endpoints and Analyses

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

The summarization of AEs will include only TEAEs (defined as AEs that begin or worsen after the first dose of double-blind IMP until 30 days after last dose of IMP). All TEAEs, SAEs, AEs leading to withdrawal of IMP, fatal AEs and AEs of special interest will be summarized by MedDRA SOC and preferred term in descending order of frequency by treatment group.

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

5.4.1 Adverse Events (AEs)

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1 or later and will be categorized by system organ class (SOC) and preferred term (PT). Patients with AEs that are ongoing at study completion or study withdrawal must be followed until resolution, until determined to be stable/chronic, or for 30 days after the last study visit, whichever comes first. Summary tables will focus on TEAEs; however, listings will include all AEs (with non-TEAEs flagged).

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

The severity of the AE will be characterized as mild, moderate, or severe, to the following definitions:

- Mild: Events are usually transient and do not interfere with the patient's daily activities
- Moderate: Events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities
- Severe: Events interrupt the patient's usual daily activity, are incapacitating with inability to do usual activities, or significantly affect clinical status and warrant intervention and/or close follow-up

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

- patients with TEAEs
- patients with TEAEs by SOC and PT
- patients with TEAEs by maximum severity
- patients with treatment-related TEAEs
- patients with treatment-emergent serious adverse events (TE SAEs)
- patients with TE SAEs by SOC and PT
- patients with TE SAEs by maximum severity
- patients with treatment-related TE SAEs
- withdrawal from study drug due to TEAEs

AE summaries will include cumulative incidence (percent of patients experiencing the AE). If appropriate, absolute and relative risk differences will be calculated using both cumulative incidence and incidence rates.

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

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

5.4.2 Adverse Events of Special Interest

Adverse events of special interest (AESI) include hepatic disorders (including changes in hepatic aminotransferases), musculoskeletal events (AE and CK evaluation), new onset diabetes/hyperglycemia, renal events, metabolic acidosis and/or hypoglycemia, and

neurocognitive/neurologic events. These events will be pulled out of the AE databases by SOC and PT, and will be identified as safety monitoring endpoints.

- Hepatic safety will be assessed via liver-associated enzymes (eg, ALT, AST) and total bilirubin.
- Musculoskeletal safety will be assessed via AEs involving muscle related symptoms. Changes in creatine kinase (CK) values will also be summarized.
- New onset diabetes/hyperglycemia will be assessed via AEs and monitoring of glucose.
- Renal safety will be assessed via eGFR measurements, changes in serum creatinine and blood urea nitrogen values, as well as CK values.
- Neurocognitive events will be assessed by routine monitoring of PE findings and AEs.
- Hypoglycemia will be assessed by routine clinical laboratories and AEs and summarized based on AE evaluations
- Metabolic acidosis occurrences will be monitored by routine laboratories and summarized based on AE evaluations.

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

5.4.3 Laboratory Evaluations

Continuous laboratory parameters (serum chemistry, hematology), urinalysis, urinalysis [microscopic]) listed in Table 4; and glucose will be summarized using descriptive statistics for the observed value and the change from baseline for all post-baseline study visits. Missing values for any of the laboratory evaluations will not be imputed; that is, only observed case data will be used. Baseline is defined as the last value prior to the first dose of study medication. Categorical urinalysis data will be provided in the listing.

Table 4: Clinical Laboratory Parameters (Safety)

Hematology • Hematocrit (Hct) • Hemoglobin (Hgb) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Mean corpuscular volume (MCV) • Platelet count • Red blood (RBC) cell count • White blood (WBC) cell count with differential (absolute and %) Urinalysis (Dipstick) • Clarity • Bilirubin • Color • Glucose • Ketones • Leukocyte esterase • Nitrate • Occult blood • pH • Protein • Specific gravity • Urobilinogen Urinalysis (Microscopic)-only if urine dipstick abnormal • Bacteria • Casts • Crystals • Epithelial cells • Red blood cell (RBC) • WBC	Blood Chemistry (serum, fasting) • Albumin (Alb) • Alkaline phosphatase (Alk-P) • Alanine aminotransferase (ALT; SGPT) • Aspartate aminotransferase (AST; SGOT) • Blood urea nitrogen (BUN) • Calcium (Ca) • Carbon dioxide (CO2) • Chloride (Cl) • Creatinine • Creatine kinase (CK) • Glucose • Lactate dehydrogenase (LDH) • Phosphorus • Potassium (K) • Sodium (Na) • Total and direct bilirubin (TB) • Total protein • Uric acid Coagulation (In all patients at screening, then only in patients receiving anticoagulant therapy that in the investigator's judgment require monitoring at Visit T1 and 3 to 5 days post Visit T1) • Prothrombin time (PT) • International normalized ration (INR)

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

5.4.4 Physical Examinations (PEs)

Listings of PE data will include only those records where the body system at the baseline PE was normal, but the body system at a post-baseline PE was marked as 'Change from previous exam, clinically significant.' Only changes from baseline physical examination findings that meet the definition of an AE will be recorded on the AE page of the eCRF and will be summarized with other AEs.

5.4.5 Vital Signs

Actual values and changes from baseline in vital signs (heart rate, systolic blood pressure, diastolic blood pressure, weight, height [baseline only], and BMI) will be summarized using descriptive statistics by treatment group and post-baseline time point on the observed values. Baseline is defined as the last value prior to the first dose of study medication, except baseline of blood pressure is defined as mean of 2 measures at same visit.

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

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

6 Reference

1. Sharrett AR, Ballantyne CM, Coady SA, Heiss G, Sorlie PD, Catellier D, et al. Atherosclerosis Risk in Communities Study Group. Coronary Heart Disease Prediction from Lipoprotein Cholesterol Levels, Triglycerides, Lipoprotein(A), Apolipoproteins A-I and B, and HDL Density Subfractions. The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. 2001;104:1108-13.
2. World Health Organization (WHO) Fact Sheet No 317 Updated January 2015.
3. Robinson JG. Management of Familial Hypercholesterolemia: A Review of the recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Managed Care Pharm. 2013;19(2):139-49.
4. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. Curr Opin Lipidol. 2012;23:282-9.
5. Glynn RJ, Laird NM, and Rubin DB. (1986). Selection modelling versus mixture modelling with nonignorable nonresponse. In H. Wainer (ed.), Drawing Inferences from Self-Selected Samples, pp. 115–142. New York: Springer.

7 Appendices

Appendix 1: Schedule of Events (Patient Visit Schedule)

	Screen		Treatment		
Visit	**S1**	**S2**[1]	**T1**	**T2**	**T3**
Week	**-6**	**-1**	**0**	**3**	**6/EOS/ET**[2]
Procedure	**Day -42 to -37**	**Day -10 to -7**	**Day 1**	**Day 22 ± 3**	**Day 43 ± 3**
Informed Consent	X				
Enrollment Criteria	X	X	X		
Demographics	X				
Medical History	X				
Concomitant\Prohibited Medications	X	X	X	X	X
Adverse Event Recording		X	X	X	X
Physical Exam		X			X
Weight[3]	X		X		X
Height/BMI	X				
Vital Signs[4]	X	X	X	X	X
Serology[5]		X			
Serum Pregnancy *and/or FSH*[6]	X				
Urine Pregnancy[6]			X		
TSH	X				
Clinical Safety Labs[7]	X		X	X	X
Basic Fasting Lipid[8]	X	X	X	X	X
Special Fasting Lipids and Other Biomarkers[9]			X		X
Dietary and Lifestyle Counselling	X	X	X	X	
Randomization			X		
Double-blind IMP Dispensing			X	X	
IMP Drug Return				X	X

BMI = body mass index; FSH = follicle-stimulating hormone, TSH = thyroid-stimulating hormone, EOS = End of Study, ET = Early Termination.

1 An optional visit approximately 1 week later MAY be completed if patient fails to meet a lipid entry criterion. If this optional visit is completed, the mean of the LDL-C values, or TG values, will be used to determine eligibility.

2 All procedures will be completed at end of study or early termination.

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

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

5 Serology for Hep B antigen, Hep C antibody.

6 FSH completed in appropriate postmenopausal women only; pregnancy test completed in non-postmenopausal women only.

7 Clinical safety labs include hematology, blood chemistry, and urinalysis. Coagulation panel ONLY in patients receiving anticoagulants measured only at T1 and repeat 3-5 days after starting IMP.

8 Basic fasting lipids include total cholesterol, calculated LDL-C, HDL-C, non-HDL-C, and triglycerides.

9 Includes ApoB and hs-CRP