STATISTICAL ANALYSIS PLAN

A Placebo-controlled, Randomized, Multicenter, Double-blind, Parallel-group Trial to Confirm the Superiority of ETC-1002 in Patients With Hyper-LDL Cholesterolemia

A Confirmatory Trial of ETC-1002 in Patients With Hyper-LDL Cholesterolemia

NCT Number: NCT05683340

Protocol No. 346-102-00002

Version 1.0 Date: 04/22/2024

Otsuka Pharmaceutical Co., Ltd.

Investigational New Drug
Bempedoic Acid (ETC-1002)

Protocol No. 346-102-00002
English Translation

A Placebo-controlled, Randomized, Multicenter, Double-blind, Parallel-group Trial to Confirm the Superiority of ETC-1002 in Patients With Hyper-LDL Cholesterolemia

A Confirmatory Trial of ETC-1002 in Patients With Hyper-LDL Cholesterolemia

Statistical Analysis Plan
Version: 1.0
Date: 22 Apr 2024
Protocol Date (1st Version): 04 Oct 2022
Protocol Date (2nd Version): 07 Dec 2022

Confidential

Table of Contents

List of Appendices

List of Abbreviations and Definition of Terms

Abbreviation	Definition
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
apo B	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
BMI	Body mass index
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
HbA1c	Glycosylated hemoglobin
HDL-C	High-density lipoprotein cholesterol
hsCRP	High-sensitivity C-reactive protein
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
MAR	Missing at random
MMRM	Mixed-model repeated measures
non-HDL-C	Non-high-density lipoprotein cholesterol
PAD	Peripheral Arterial Disease
PT	Preferred term
OC	Observed cases
QTc	Corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAS	Statistical Analysis System
SOC	System organ class
TC	Total cholesterol
TEAE	Treatment-emergent adverse event
TG	Triglyceride
WHODD	World Health Organization Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) documents the detailed methods for the statistical analysis planned in Trial 346-102-00002.

2 Trial Objectives

Primary:

- To confirm the superiority of ETC-1002 after 12 weeks of administration at 180 mg/day to placebo in patients with hyper-low-density lipoprotein (hyper-LDL) cholesterolemia who have inadequate control of low-density lipoprotein cholesterol (LDL-C).

Secondary:

- To assess the effects of ETC-1002 on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), apolipoprotein B (apo B), high-sensitivity C-reactive protein (hsCRP), and glycosylated hemoglobin (HbA1c). To assess the proportion of subjects achieving the lipid management goals of LDL-C by treatment with ETC-1002.
- To assess the safety of ETC-1002 when administered at 180 mg/day for 12 weeks.

3 Trial Design

3.1 Type/Design of Trial

This is a placebo-controlled, randomized, multicenter, double-blind, parallel-group trial to assess the efficacy and safety of ETC-1002 administered at 180 mg/day for 12 weeks in patients with hyper-LDL cholesterolemia who are being treated with hyper-LDL cholesterolemia drugs but have inadequate control and cannot achieve the lipid management goals. The trial population will include patients with inadequate response to statins who cannot achieve the lipid management goals despite being treated with statins, and patients with statin intolerance who have experienced safety problems that were successfully resolved after stopping or reducing the dose of statins, and cannot achieve the lipid management goals.

A schematic of the trial design is presented in Figure 3.1-1.

This trial consists of a screening period, placebo run-in period, treatment period, and follow-up period. Subjects determined to be eligible in the screening period will proceed to the placebo run-in period and continue treatment without changing the type or dosage regimen of hypercholesterolemia drugs that have been taken prior to informed consent,

and will receive placebo tablets under single-blind conditions. Subjects with less than 80% compliance with the single-blind placebo tablets during the 4-week placebo run-in period will be withdrawn during the placebo run-in period. Subjects who have no safety problems or muscle-related adverse events (AEs) during the 4-week placebo run-in period and who do not fall under the exclusion criteria as judged by the investigator or subinvestigator will be assigned either to the ETC-1002 180-mg/day group or placebo group and proceed to the treatment period. Statin response (inadequate response to statins/statin intolerance) is set as a randomization stratification factor to ensure equal allocation of subjects with inadequate response to statins and those with statin intolerance to each treatment group.

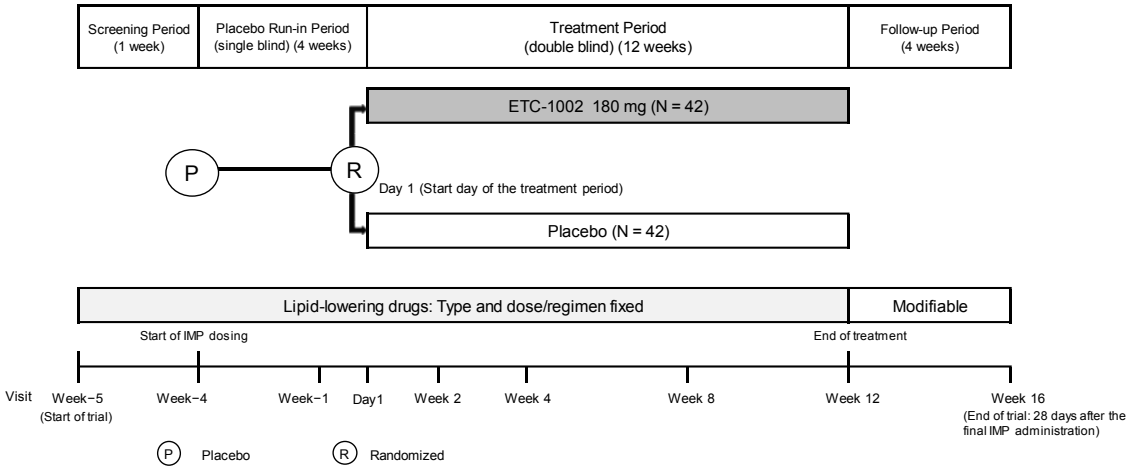

Figure 3.1-1 Trial Design Schematic

3.2 Trial Treatments

During the treatment period, subjects will receive either ETC-1002 180 mg or a placebo for 12 weeks in addition to continued hypercholesterolemia drugs that have been taken prior to informed consent. Medications to be taken in the placebo run-in period and treatment period are detailed below.

Description		Placebo Run-in Period	Treatment Period
Investigational medicinal products	Medications	Placebo tablets	ETC-1002 180-mg tablets/placebo tablets
	Dosage regimen/ Mode of administration	One tablet once daily/oral	

Lipid-lowering drugs	Medications	Lipid-lowering drugs used before informed consent (Statins and/or nonstatins)	
	Dosage regimen	Continue treatment without changing the type or dosage regimen	
Treatment duration		4 weeks	12 weeks

3.3 Trial Population

This trial will be conducted in Japanese patients with hyper-LDL cholesterolemia aged 18 to 85 years, inclusive, at the time of informed consent and who have inadequate response to statins/statin intolerance and cannot achieve the lipid management goals specified in the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2017. Subjects considered eligible by the investigator or subinvestigator during the screening period will proceed to the placebo run-in period. Among subjects with no safety problems or muscle-related AEs in the placebo run-in period, those confirmed by the investigator or subinvestigator not to fall under the exclusion criteria will be randomized. The target number of randomized subjects is 84 in total (42 in the 180-mg/day group and 42 in the placebo group). In addition to patients with inadequate response to statins, patients with statin intolerance will be enrolled at ≥20% of the total in this trial. Statin response (inadequate response to statins/statin intolerance) is set as a randomization stratification factor so that subjects with statin intolerance will be equally allocated to each treatment group.

3.4 Trial Visit Window

For efficacy and safety endpoints (except AEs), acceptable windows of timepoints for analysis will be set, with analysis based on analysis timepoints irrespective of timepoints recorded in the case report form. Timepoints for analysis will be specified solely based on fasting data for non-HDL-C, TC, HDL-C, TG, and LDL-C (calculated using the Friedewald formula) among fasting lipid parameters in efficacy endpoints. The handling of fasting data is described in Section 5.3.

Acceptable windows of timepoints for analysis are shown in Table 3.4-1. For fasting lipid parameters (LDL-C [measured using the direct method], non-HDL-C, TC, HDL-C, TG, and LDL-C [calculated using the Friedewald formula]) in efficacy endpoints, baseline is defined as the mean of the values for Day 1 and Week −1. If only one value is obtained, that value will be used as baseline. For efficacy endpoints other than fasting lipid parameters and safety endpoints, baseline is defined as the last data point obtained prior to the initial investigational medicinal product (IMP) administration in the treatment period. The start day of IMP administration is defined as Day 1. If multiple data points

are available for a certain acceptable window, the last data point will be used for analysis. In the setting of timepoints for analysis during the treatment period (Week 2 to Week 12), data obtained from 3 days after the last IMP administration will be excluded. The last data obtained between the initial IMP administration and 2 days after the last IMP administration in the treatment period will be defined as Last Visit.

Table 3.4-1 Acceptable windows of timepoints for analysis

Week	Acceptable Window
Baseline	Fasting lipid parameters: Mean of the values for Day 1 and Week −1 (If only one value is obtained, that value will be used as baseline.) Other parameters: Last data obtained prior to initial IMP administration in the treatment period
Week 2	Day 2 to 21
Week 4	Day 22 to 42
Week 8	Day 43 to 70
Week 12	Day 71 to 92
Last Visit	Last data obtained between the initial IMP administration and 2 days after the last IMP administration in the treatment period
Week 16 (Follow up)	Timepoint recorded in case report form

4 Sample Size

In the phase 2 trial conducted in Japan, the difference in the percent change from baseline in LDL-C at Week 12 between the ETC-1002 180-mg group and the placebo group was −19%, and the standard deviation of the percent change from baseline in each group ranged from 9% to 17%. Since the between-group difference was comparable to the results estimated from phase 3 trials conducted outside Japan, the between-group difference in this trial is assumed to be −19%. Also considering the standard deviation (14% to 25%) in the phase 3 trials conducted outside Japan, in which similar populations of subjects to this trial were enrolled, the standard deviation in this trial is conservatively assumed to be 25%. Under these assumptions, a total of 76 subjects (38 subjects/group) will be required to ensure a power of 90%. Assuming a withdrawal rate of 10%, the total number of subjects in this trial will be set at 84.

5 Statistical Analysis Datasets

5.1 Full Analysis Set (FAS)

The full analysis set (FAS) will include subjects who receive at least one dose of the IMP during the treatment period, and who have LDL-C measurements at baseline and at one or more time points after IMP administration during the treatment period.

5.2 Safety Analysis Set

The safety analysis set will include subjects who receive at least one dose of the IMP during the treatment period.

5.3 Handling of Missing Data

In the primary analysis of the primary endpoint, a mixed-effects model repeated measures (MMRM) analysis assuming missing at random (MAR) will be performed using the observed case (OC) data set without imputation of missing data. Details of sensitive analyses for the handling of missing data are described in Section 8.1.2.

Analyses for non-HDL-C, TC, apo B, hsCRP, and HbA1c as secondary endpoints will be performed using the OC data set without imputation of missing data. In the analysis of the proportion of subjects achieving the lipid management goals of LDL-C (direct measurement), subjects with missing LDL-C data will be handled as having not achieved the lipid management goals.

Fasting lipid parameters will be handled as shown in the table below with regard to fasting condition.

Fasting Lipid Parameters	Handling of Data
LDL-C (direct measurement)	Parameter to be used in analysis, irrespective of fasting condition
non-HDL-C, TC, HDL-C, TG, LDL-C (Friedewald formula)	Parameters to be used in analysis only when obtained under a fasting condition

6 Primary and Secondary Outcome Variables

6.1 Primary Outcome Variables

Percent change in LDL-C from baseline at Week 12

6.2 Secondary Outcome Variables

- Percent change in non-HDL-C, TC, apo B, hsCRP, and HbA1c from baseline at Week 12

- Proportion of subjects whose LDL-C value achieves the lipid management goals based on risk assessment (<100 mg/dL [history of coronary artery disease or heterozygous familial hypercholesterolemia], <120 mg/dL [high risk], or <140 mg/dL [intermediate risk]) at Week 12

7 Disposition and Demographic Analysis

7.1 Subject Disposition

For consenting subjects, the number of subjects who provide informed consent, the number of screening failures, as well as the number and percentage (using the number of subjects who provide informed consent as the denominator) of IMP-treated subjects and discontinued subjects in the placebo run-in period will be summarized. For subjects who proceed to the placebo run-in period, the number and percentage (using the number of subjects who proceed to the placebo run-in period as the denominator) of discontinued subjects and the reasons for discontinuation in the placebo run-in period will be summarized.

For randomized subjects, the number of randomized subjects and the number and percentage (using the number of randomized subjects as the denominator) of those who receive the IMP, those who complete the trial, and those who withdraw from the trial and the reasons for withdrawal in the treatment period will be summarized by treatment group (ETC-1002 group and placebo group, the same hereinafter) and overall.

For randomized subjects, the number and percentage (using the number of randomized subjects as the denominator) of subjects included in each analysis set will be summarized by treatment group and overall.

The same analysis will also be performed by the randomization stratification factor (statin response).

7.2 Demographic and Baseline Characteristics

For the FAS and safety analysis set, descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum, the same hereinafter) of age, height, body weight, and body mass index (BMI), and estimated glomerular filtration rate (eGFR), and frequency distributions of categorized age (<65 years, ≥65 years and <75 years, ≥75 years), categorized BMI (<25 kg/m^2, ≥25 kg/m^2 and <30 kg/m^2, ≥30 kg/m^2), categorized eGFR (<60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2, ≥90 mL/min/1.73 m^2), sex, race, ethnicity, country, presence/absence of past medical history, and presence/absence of complications will be summarized by treatment group and overall. For body weight, values at screening will be used.

The same analysis will also be performed by the randomization stratification factor (statin response).

7.3 Baseline Disease Evaluation

For the FAS and safety analysis set, descriptive statistics of baseline LDL-C level and frequency distributions of LDL-C level category at baseline (<100 mg/dL, ≥100 mg/dL and <120 mg/dL, ≥120 mg/dL and <140 mg/dL, ≥140 mg/dL), presence/absence of hypercholesterolemia, presence/absence of familial hypercholesterolemia, risk assessment (history of coronary artery disease or familial hypercholesterolemia, high risk, or intermediate risk), presence/absence of diabetes mellitus, statin response (inadequate response to statins/statin intolerance), and presence/absence of atherosclerotic cardiovascular disease (ASCVD) history will be summarized by treatment group and overall. In addition, frequency distributions of subjects with diabetes who have complications of peripheral arterial disease (PAD) or microangiopathy, or who smoke, will be summarized by treatment group and overall.

The same analysis, excluding statin response, will also be performed by the randomization stratification factor (statin response).

For subjects with statin intolerance in the FAS and safety analysis set, frequency distributions of presence/absence of statin intolerance-associated symptoms (muscle impairment, hepatic impairment, renal impairment, cognitive impairment, or other) and presence/absence of causal medication for statin intolerance (atorvastatin calcium trihydrate, fluvastatin sodium, pitavastatin calcium, pravastatin sodium, rosuvastatin calcium, or simvastatin) will be summarized by treatment group and overall.

7.4 Treatment Compliance

For the FAS, frequency distributions of IMP compliance rate (<70%, ≥70% to <80%, ≥80% to <90%, or ≥90%) in the treatment period will be summarized by treatment group and overall. The IMP compliance rate will be calculated using the following formula.

$$\text{IMP compliance rate (\%)} = \frac{\text{Actual number of days of taking IMP}}{\text{Date of final IMP administration} - \text{Date of initial IMP administration} + 1} \times 100$$

The same analysis will also be performed by the randomization stratification factor (statin response).

For the FAS, the number and percentage of subjects who do not change the type and dosage regimen of hypercholesterolemia drugs, which are mandatory concomitant medications in this trial, throughout the treatment period will be summarized by treatment group and overall.

The same analysis will also be performed by the randomization stratification factor (statin response).

7.5 Prior and Concomitant Medications

For the FAS, frequency distributions of medications used prior to or during the treatment period, including hypercholesterolemia drugs, by drug class and preferred term in the World Health Organization Drug Dictionary (WHODD) version Global B3 September 2022 will be summarized by treatment group and overall.

For the FAS and safety analysis set, frequency distributions of the presence/absence of statin use or ezetimibe use will be summarized by treatment group and overall. The preferred terms for statins and ezetimibe are shown in Appendix 4.

The same analysis will also be performed by the randomization stratification factor (statin response).

7.6 Protocol Deviations

For randomized subjects, frequency distributions of the presence/absence of the following deviations recorded in the CRF will be summarized by treatment group and overall.

- Dosing
- Inclusion/exclusion criteria
- Met withdrawal criteria but was not withdrawn
- Procedural deviations (affecting primary outcome variables)
- Prohibited concomitant medications

The same analysis will also be performed by the randomization stratification factor (statin response).

8 Efficacy Analysis

Efficacy analysis will be performed for the FAS.

8.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change in LDL-C from baseline at Week 12 obtained by direct measurement. The LDL-C values obtained by direct measurement will be used in the analyses irrespective of fasting condition.

8.1.1 Primary Efficacy Analysis

A MMRM analysis assuming MAR will be performed using the OC data set. The comparison between groups will be performed based on the least-squares mean difference between the ETC-1002 group and placebo group at Week 12. The two-sided significance level will be set at 0.05. The MMRM model will include the treatment group, randomization stratification factor, visit, and treatment group-by-visit interaction as factors, with baseline and baseline-by-visit interaction as covariates using an unstructured error covariance matrix. The Kenward-Roger method will be used to calculate the degree of freedom. If the MMRM procedure fails to converge in variance component estimation, the following error covariance structures will be used in sequence of 1) heterogeneous toeplitz, 2) heterogeneous autoregressive of order 1, and 3) heterogeneous compound symmetry, and the first structure to yield convergence will be used. If a structure other than unstructured is selected, a sandwich estimator of standard error will be used.

In the MMRM analysis described above, the least-squares mean for each treatment group and the least-squares mean difference between the ETC-1002 group and placebo group, together with the two-sided 95% confidence intervals, will be calculated for each timepoint from baseline to Week 12.

Timecourse of the least-squares mean ± standard error for the percent change from baseline in LDL-C at each visit from baseline to Week 12 will be plotted for each treatment group.

The same analysis as above will also be performed by the randomization stratification factor. The randomization stratification factor is not included in the model.

8.1.2 Sensitivity Analyses

Placebo multiple imputation assuming missing not at random (MNAR) will be performed as a sensitivity analysis for handling missing data in LDL-C (direct measurement) as the primary efficacy endpoint.

The analysis by multiple imputation will be performed in the following procedures. The number of imputations will be set at 100.

1) Missing data will be imputed using the Fully Conditional Specification method. The imputation model for LDL-C (direct measurement) at each timepoint includes the randomization stratification factor and LDL-C values (direct measurement) obtained prior to the respective timepoints. Imputation will be performed using an imputation

model based on the placebo group, assuming MNAR for missing data of the ETC-1002 group. For missing data in the placebo group, MAR will be assumed.

2) The multiply imputed dataset will be analyzed using the same MMRM as the primary efficacy endpoint.

3) The analysis results of the multiply imputed dataset will be combined using the MIANALYZE procedure in SAS, and the estimated difference between the ETC-1002 group and placebo group at Week 12, its 95% confidence interval, and p value will be calculated.

8.1.3 Technical Computational Details for Primary Efficacy Analysis

The MMRM analysis, which is the primary analysis, will be performed using the following SAS code.

```
proc mixed;
  class treatment strata visit subjid;
  model pchange = treatment visit baseline treatment*visit baseline*visit strata / ddfm=kr;
  repeated visit /type=un subject=subjid;
  lsmeans treament*visit / diff cl;
run;
```

8.2 Secondary Efficacy Analyses

- Percent change from baseline

For non-HDL-C and TC, the same MMRM analysis as the primary efficacy endpoint will be performed. The baseline value for each assessment parameter will be used as covariates.

For apo B, hsCRP, and HbA1c, analysis of covariance using OC data will be performed. The least-squares mean for each treatment group and the least-squares mean difference between the ETC-1002 group and placebo group, together with the two-sided 95% confidence intervals, will be calculated. The model includes the treatment group and statin response (inadequate response to statins/statin intolerance), which is the randomization stratification factor, as factors and the baseline value for each assessment parameter as covariates.

The timecourse of the least-squares mean ± standard error at each visit from baseline to Week 12 will be plotted for each treatment group. Least-squares mean will be calculated

based on MMRM analysis for non-HDL-C and TC, and based on analysis of covariance for apo B, hsCRP, and HbA1c.

The same analysis as above will also be performed by the randomization stratification factor. The randomization stratification factor is not included in the model for MMRM analysis and analysis of covariance.

- Lipid management goals based on risk assessment

The proportion of subjects whose LDL-C value (direct measurement) achieves the lipid management goals (<100 mg/dL [history of coronary artery disease or heterozygous familial hypercholesterolemia], <120 mg/dL [high risk], or <140 mg/dL [intermediate risk]) at Week 12 will be analyzed using the Cochran-Mantel-Haenszel test stratified by statin response (inadequate response to statins/statin intolerance). The difference between the ETC-1002 group and the placebo group will be calculated, along with the two-sided 95% confidence intervals (based on Cochran-Mantel-Haenszel). The proportion in each treatment group and the two-sided 95% interval (based on the Clopper-Pearson method) will also be calculated. Subjects with missing LDL-C data at Week 12 will be handled as having not achieved the lipid management goals. The same analysis will be performed for other timepoints (Week 2, Week 4, and Week 8).

For the proportion of subjects having achieved the lipid management goals, the proportion in each treatment group and the two-sided 95% interval (based on the Clopper-Pearson method) will be calculated by the randomization stratification factor (statin response). Fisher's exact test will be performed for the comparison between the ETC-1002 group and the placebo group, and the difference in proportions and its exact two-sided 95% interval (based on score statistics) will be calculated.

The same analysis as above will be performed using OC data.

8.3 Other Efficacy Analyses

For HDL-C, TG, and LDL-C (Friedewald formula), the same MMRM analysis as the primary efficacy endpoint will be performed. The baseline value for each assessment parameter will be used as covariates.

The timecourse of the least-squares mean ± standard error at each visit from baseline to Week 12 will be plotted for each treatment group.

The same analysis as above will also be performed by the randomization stratification factor. The randomization stratification factor is not included in the model for MMRM analysis.

8.4 Exploratory or Other Analyses

For efficacy endpoints (LDL-C [direct method], non-HDL-C, TC, apo B, hsCRP, HbA1c, HDL-C, TG, and LDL-C [Friedewald formula]), descriptive statistics for the actual value, change from baseline, and percent change from baseline at each time point (baseline, Week 2, Week 4, Week 8, Week 12, and Week 16 [follow up]) will be calculated by treatment group. In addition, summarization at Last Visit will be performed.

For percent change from baseline at Week 12 in efficacy endpoints (LDL-C [direct method], non-HDL-C, TC, apo B, hsCRP, HbA1c, HDL-C, TG, and LDL-C [Friedewald formula]), robust regression analysis will be performed using OC data. The model includes treatment group and statin response (inadequate response to statins/statin intolerance), which is the randomization stratification factor, as factors and the baseline value for each assessment parameter as covariates.

The same analysis as above will also be performed by the randomization stratification factor. The randomization stratification factor is not included in the model for robust regression analysis.

8.5 Subgroup Analyses

Subgroup analyses will be performed by the following items for the percent change in LDL-C (direct method) from baseline at Week 12, the primary endpoint. Using the same MMRM as for the primary analysis, the least-squares mean for each treatment group and the least-squares mean difference between the ETC-1002 group and placebo group, together with the two-sided 95% confidence intervals, will be calculated for each subgroup. In the analysis for the statin response subgroup, the randomization stratification factor (statin response) will not be included in the model. Statin intensity categories and preferred terms for ezetimibe and fibrates are shown in Appendix 6 and Appendix 4, respectively.

- Statin response (Inadequate response to statins, Statin intolerance)
- Sex (Male, Female)
- Familial hypercholesterolemia (Yes, No)
- Diabetes mellitus (Yes, No)
- Age (<65 years, ≥65 years and <75 years, ≥75 years)
- Statin use (Yes, No)
- BMI (<25 kg/m^2, ≥25 kg/m^2 and <30 kg/m^2, ≥30 kg/m^2)
- eGFR (<60 mL/min/1.73 m^2, ≥60 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2, ≥90 mL/min/1.73 m^2)

- LDL-C at baseline (<100 mg/dL, ≥100 mg/dL and <120 mg/dL, ≥120 mg/dL and <140 mg/dL, ≥140 mg/dL)
- History of ASCVD (Yes, No)
- Statin intensity (Low-intensity statins, High-intensity statins, No statins)
- Ezetimibe use (Yes, No)
- Fibrate use (Yes, No)

9 Safety Analyses

Tabulation by treatment group will be performed in the safety analysis set. Baseline is defined as the last data before the start of IMP administration in the treatment period. The same tabulation will also be performed by the randomization stratification factor (statin response).

9.1 Extent of Exposure

Descriptive statistics will be calculated for the duration of IMP treatment in the treatment period (Date of final IMP administration in the treatment period – Date of initial IMP administration in the treatment period + 1) and for the total number of days of IMP administration in the treatment period (The total number of days of taking IMP in the treatment period).

9.2 Adverse Events

All AEs will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.1. The incidence of the following events will be calculated by SOC, PT, and overall. If a subject experiences the same event more than once, the more severe event will be used.

- Treatment-emergent adverse events (TEAEs) in the treatment period
- TEAEs by severity
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

TEAEs potentially causally related to the IMP will be summarized in the same manner. Summary tables (only for events occurring at ≥5% of subjects in any group) will also be prepared for TEAEs and for TEAEs potentially causally related to the IMP.

The incidence of TEAEs not judged to be adverse reactions to the COVID-19 vaccine will be calculated by SOC, PT, and overall.

9.2.1 AEs of Special Interest

The incidence of AEs of special interest will be calculated by SOC and PT. AEs of special interest potentially causally related to the IMP will be summarized in the same manner. The classification of AEs of special interest is shown in Appendix 5.

9.3 Clinical Laboratory Data

Among the urinalysis parameters in laboratory tests, parameters except for pH and specific gravity will be included in the qualitative urinalysis.

For parameters other than qualitative urinalysis, descriptive statistics of the actual value and change from baseline will be calculated at each visit (baseline, Week 4, Week 8, Week 12, Last Visit, and Week 16 [follow up]). For qualitative urinalysis parameters, shift tables at each visit from baseline will be prepared. For parameters other than qualitative urinalysis, measured values will be categorized using the reference ranges of "below the lower limit of reference range", "within the reference range" and "above the upper limit of reference range", and shift tables at each visit from baseline will be prepared.

The number and percentage of subjects meeting the criteria for identifying laboratory values of potential clinical relevance (Appendix 2: Criteria for Identifying Laboratory Values of Potential Clinical Relevance) after IMP administration during the treatment period will be calculated. All data obtained after IMP administration during the treatment period, including those at unscheduled visits, will be analyzed.

9.4 Vital Sign Data

For vital signs (blood pressure, pulse rate, and body temperature), descriptive statistics of the actual value and change from baseline will be calculated at each visit (baseline, Week 2, Week 4, Week 8, Week 12, Last Visit, and Week 16 [follow up]).

The number and percentage of subjects meeting the criteria for identifying vital signs of potential clinical relevance (Appendix 1: Criteria for Identifying Vital Signs and Weight of Potential Clinical Relevance) after IMP administration during the treatment period will be calculated. All data obtained after IMP administration during the treatment period, including those at unscheduled visits, will be analyzed.

9.5 Physical Examination Data

Physical findings recorded in the CRF will be presented in a listing of subjects.

9.6 Electrocardiogram Data

For ECG parameters (heart rate, PR interval, RR interval, QRS interval, QT interval, and QTcF), descriptive statistics of the actual value and change from baseline will be calculated at each visit (baseline, Week 4, Week 12, and Last Visit).

The number and percentage of subjects with a QTcF of >450 msec, >480 msec, or >500 msec at any postdose visit during the treatment period will be calculated. In addition, the number and percentage of subjects who have a change in QTcF from baseline of >30 msec or >60 msec at any postdose during the treatment period visit will be calculated. All data obtained after IMP administration during the treatment period, including those at unscheduled visits, will be analyzed. The number and percentage of subjects meeting these criteria at each postdose visit will also be calculated.

For assessment of normality/abnormality, shift tables at each visit from baseline will be prepared.

The number and percentage of subjects meeting the criteria for identifying ECG measurements of potential clinical relevance (Appendix 3: Criteria for Identifying ECG Measurements of Potential Clinical Relevance) after IMP administration during the treatment period will be calculated. All data obtained after IMP administration during the treatment period, including those at unscheduled visits, will be analyzed.

9.7 Other Safety Data

9.7.1 Body Weight

Descriptive statistics of the actual value and change from baseline will be calculated at each visit (baseline, Week 4, Week 8, Week 12, and Last Visit).

The number and percentage of subjects meeting the criteria for identifying body weight of potential clinical relevance (Appendix 1: Criteria for Identifying Vital Signs and Weight of Potential Clinical Relevance) after IMP administration during the treatment period will be calculated. All data obtained after IMP administration during the treatment period, including those at unscheduled visits, will be analyzed.

10 Pharmacokinetic Analyses

No pharmacokinetic analysis is planned.

11 Pharmacodynamic Analyses

No pharmacodynamic analysis is planned.

12 Pharmacogenomic Analyses

No pharmacogenomic analysis is planned.

13 Interim Analysis

No interim analysis is planned.

14 Changes in the Planned Analyses

Not applicable.

15 References

Not applicable.

Appendix 1 Criteria for Identifying Vital Signs and Weight of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Pulse Rate	>120 bpm	≥15 bpm increase
Pulse Rate	<50 bpm	≥15 bpm decrease
Systolic Blood Pressure	>160 mmHg	≥20 mmHg increase
Systolic Blood Pressure	<90 mmHg	≥20 mmHg decrease
Diastolic Blood Pressure	>100 mmHg	≥15 mmHg increase
Diastolic Blood Pressure	<50 mmHg	≥15 mmHg decrease
Weight	N/A	≥7% increase
Weight	N/A	≥7% decrease

[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

Appendix 2 Criteria for Identifying Laboratory Values of Potential Clinical Relevance

Laboratory Tests	Criteria
Chemistry	
AST	≥3 x upper limit of normal (ULN)
ALT	≥3 x ULN
Bilirubin, Total	≥2 x ULN
ALP	≥3 x ULN
Urea Nitrogen	≥30 mg/dL
Creatinine	≥2.0 mg/dL
Creatine Kinase (CK)	≥4 x ULN
Uric Acid	≥9 mg/dL
Hematology	
Hematocrit	Males: ≤37% and ≥3 percentage points decrease from baseline Females: ≤32% and ≥3 percentage points decrease from baseline
Hemoglobin	Males: ≤11.5 g/dL Females: ≤9.5 g/dL
Leukocyte Count	≤2,800 10^6/L
Leukocyte Count	≥16,000 10^6/L
Platelet Count	≤7.5 10^{10}/L
Platelet Count	≥70 10^{10}/L
Urinalysis	
Protein	Increase of ≥2 units
Glucose	Increase of ≥2 units
Additional Criteria	
Chloride	≤90 mEq/L
Chloride	≥118 mEq/L
Potassium	≤2.5 mEq/L
Potassium	≥6.5 mEq/L
Sodium	≤126 mEq/L
Sodium	≥156 mEq/L
Calcium	≤8.2 mg/dL
Calcium	≥12 mg/dL
Glucose	Fasting: ≥126 mg/dL Non-fasting: ≥200 mg/dL
Glucose	≤50 mg/dL
Total Cholesterol	≥240 mg/dL
LDL Cholesterol	≥160 mg/dL
HDL Cholesterol	<40 mg/dL
Triglycerides, Fasting	≥150 mg/dL

Appendix 3 Criteria for Identifying ECG Measurements of Potential Clinical Relevance

Variable	Criterion Value[a]	Change Relative to Baseline[a]
Heart Rate	≥120 bpm	Increase of ≥15 bpm
Heart Rate	≤50 bpm	Decrease of ≥15 bpm
PR	≥200 msec	Increase of ≥50 msec
QRS	≥120 msec	Increase of ≥20 msec

[a]In order to be identified as potentially clinically relevant, an on-treatment value must meet the "Criterion Value" and also represent a change from the subject's baseline value of at least the magnitude shown in the "Change Relative to Baseline" column.

Appendix 4 Preferred Terms for Statins, Ezetimibe, and Fibrates

Drug	CRF Option for Drug Name (English)	Preferred Term WHODD Drug Name	Preferred Term WHODD Drug Code	WHODD Drug Code 6 Digits
Statins	Pravastatin sodium	PRAVASTATIN SODIUM	00880402001	008804
	Simvastatin	SIMVASTATIN	00848101001	008481
	Rosuvastatin calcium	ROSUVASTATIN CALCIUM	01588602001	015886
	Pitavastatin calcium	PITAVASTATIN CALCIUM	06470002001	064700
	Atorvastatin calcium trihydrate	ATORVASTATIN CALCIUM TRIHYDRATE	01326106001	013261
	Fluvastatin sodium	FLUVASTATIN SODIUM	01224502001	012245
	Caduet No. 1	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
	Caduet No. 2	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
	Caduet No. 3	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
	Caduet No. 4	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
	Amaluet No. 1	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
	Amaluet No. 2	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
	Amaluet No. 3	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
	Amaluet No. 4	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
	Atozet LD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720
	Atozet HD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720
	Rosuzet LD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410
	Rosuzet HD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410
	Other	LIPID MODIFYING AGENTS, COMBINATIONS	90083401001	900834
Ezetimibe	Ezetimibe	EZETIMIBE	01587001001	015870
	Atozet LD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720

Drug	CRF Option for Drug Name (English)	Preferred Term WHODD Drug Name	Preferred Term WHODD Drug Code	WHODD Drug Code 6 Digits
	Atozet HD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720
	Rosuzet LD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410
	Rosuzet HD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410
	Other	LIPID MODIFYING AGENTS, COMBINATIONS	90083401001	900834
Fibrates	Other	CLOFIBRATE	00001301001	000013
	Other	BEZAFIBRATE	00544101001	005441
	Other	FENOFIBRATE	00499301001	004993
	Other	PEMAFIBRATE	08922801001	089228

Appendix 5 Classification of AEs of Special Interest

AE of Special Interest	PT Code	PT Term
Hepatic dysfunction-related	10001547	Alanine aminotransferase abnormal
Hepatic dysfunction-related	10001551	Alanine aminotransferase increased
Hepatic dysfunction-related	10003477	Aspartate aminotransferase abnormal
Hepatic dysfunction-related	10003481	Aspartate aminotransferase increased
Hepatic dysfunction-related	10058477	Blood bilirubin abnormal
Hepatic dysfunction-related	10005364	Blood bilirubin increased
Hepatic dysfunction-related	10062685	Hepatic enzyme abnormal
Hepatic dysfunction-related	10060795	Hepatic enzyme increased
Hepatic dysfunction-related	10068237	Hypertransaminasaemia
Hepatic dysfunction-related	10024690	Liver function test abnormal
Hepatic dysfunction-related	10077692	Liver function test increased
Hepatic dysfunction-related	10062688	Transaminases abnormal
Hepatic dysfunction-related	10054889	Transaminases increased
Hepatic dysfunction-related	10019670	Hepatic function abnormal
Myopathy-related	10028372	Muscular weakness
Myopathy-related	10028320	Muscle necrosis
Myopathy-related	10028334	Muscle spasms
Myopathy-related	10028411	Myalgia
Myopathy-related	10028653	Myositis
Myopathy-related	10028625	Myoglobin blood increased
Myopathy-related	10059888	Myoglobin blood present
Myopathy-related	10028631	Myoglobin urine present
Myopathy-related	10058735	Myoglobinaemia
Myopathy-related	10028629	Myoglobinuria
Myopathy-related	10028641	Myopathy
Myopathy-related	10028648	Myopathy toxic
Myopathy-related	10074769	Necrotising myositis
Myopathy-related	10033425	Pain in extremity
Myopathy-related	10039020	Rhabdomyolysis
Myopathy-related	10005468	Blood creatine phosphokinase abnormal
Myopathy-related	10005470	Blood creatine phosphokinase increased

AE of Special Interest	PT Code	PT Term
Myopathy-related	10005477	Blood creatine phosphokinase MM increased
Tendon rupture/disorder-related	10043248	Tendon rupture
Tendon rupture/disorder-related	10028331	Muscle rupture
Tendon rupture/disorder-related	10039227	Rotator cuff syndrome
Tendon rupture/disorder-related	10074599	Tendon discomfort
Tendon rupture/disorder-related	10043239	Tendon disorder
Tendon rupture/disorder-related	10043242	Tendon injury
Tendon rupture/disorder-related	10069650	Tendon necrosis
Tendon rupture/disorder-related	10066371	Tendon pain
Tendon rupture/disorder-related	10043255	Tendonitis
Diabetes-related	10005554	Blood glucose abnormal
Diabetes-related	10005557	Blood glucose increased
Diabetes-related	10012601	Diabetes mellitus
Diabetes-related	10012607	Diabetes mellitus inadequate control
Diabetes-related	10012671	Diabetic ketoacidosis
Diabetes-related	10018429	Glucose tolerance impaired
Diabetes-related	10018478	Glucose urine present
Diabetes-related	10018473	Glycosuria
Diabetes-related	10018484	Glycosylated haemoglobin increased
Diabetes-related	10020635	Hyperglycaemia
Diabetes-related	10056997	Impaired fasting glucose
Diabetes-related	10023379	Ketoacidosis
Diabetes-related	10023388	Ketonuria
Diabetes-related	10023391	Ketosis
Diabetes-related	10067585	Type 2 diabetes mellitus
Diabetes-related	10057597	Urine ketone body present
Renal dysfunction-related	10069339	Acute kidney injury
Renal dysfunction-related	10005481	Blood creatinine abnormal
Renal dysfunction-related	10005483	Blood creatinine increased
Renal dysfunction-related	10005846	Blood urea abnormal
Renal dysfunction-related	10005851	Blood urea increased
Renal dysfunction-related	10050760	Blood urea nitrogen/creatinine ratio increased
Renal dysfunction-related	10068447	Creatinine renal clearance abnormal

AE of Special Interest	PT Code	PT Term
Renal dysfunction-related	10011372	Creatinine renal clearance decreased
Renal dysfunction-related	10018356	Glomerular filtration rate abnormal
Renal dysfunction-related	10018358	Glomerular filtration rate decreased
Renal dysfunction-related	10030302	Oliguria
Renal dysfunction-related	10072370	Prerenal failure
Renal dysfunction-related	10038435	Renal failure
Renal dysfunction-related	10061480	Renal function test abnormal
Renal dysfunction-related	10062237	Renal impairment
Metabolic acidosis	10027417	Metabolic acidosis
Hypoglycemia-related	10005554	Blood glucose abnormal
Hypoglycemia-related	10005555	Blood glucose decreased
Hypoglycemia-related	10020993	Hypoglycaemia
Hypoglycemia-related	10021000	Hypoglycaemic coma
Hypoglycemia-related	10021002	Hypoglycaemic encephalopathy
Hypoglycemia-related	10048803	Hypoglycaemic seizure
Hypoglycemia-related	10040576	Shock hypoglycaemic
Cognitive dysfunction-related	10057668	Cognitive disorder
Cognitive dysfunction-related	10010305	Confusional state
Cognitive dysfunction-related	10013395	Disorientation
Cognitive dysfunction-related	10027175	Memory impairment
Cognitive dysfunction-related	10048294	Mental status changes
Cognitive dysfunction-related	10001949	Amnesia
Elevated uric acid-related	10005861	Blood uric acid increased
Elevated uric acid-related	10020903	Hyperuricaemia
Elevated uric acid-related	10018627	Gout
Decreased hemoglobin-related	10018884	Haemoglobin decreased
Decreased hemoglobin-related	10018838	Haematocrit decreased
Decreased hemoglobin-related	10002034	Anaemia

Appendix 6 Statin Intensity

Item	Category	CRF Option for Drug Name (English)	Preferred Term WHODD Drug Name	Preferred Term WHODD Drug Code	WHODD Drug Code 6 digits
Statin Intensity	Low-intensity	Pravastatin sodium	PRAVASTATIN SODIUM	00880402001	008804
		Simvastatin	SIMVASTATIN	00848101001	008481
		Fluvastatin sodium	FLUVASTATIN SODIUM	01224502001	012245
	High-intensity	Rosuvastatin calcium	ROSUVASTATIN CALCIUM	01588602001	015886
		Pitavastatin calcium	PITAVASTATIN CALCIUM	06470002001	064700
		Atorvastatin calcium trihydrate	ATORVASTATIN CALCIUM TRIHYDRATE	01326106001	013261
		Caduet No.1	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
		Caduet No.2	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
		Caduet No.3	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
		Caduet No.4	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM	12872303001	128723
		Amaluet No.1	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
		Amaluet No.2	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
		Amaluet No.3	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
		Amaluet No.4	AMLODIPINE BESILATE; ATORVASTATIN CALCIUM TRIHYDRATE	12872304001	128723
		Atozet LD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720
		Atozet HD	ATORVASTATIN CALCIUM; EZETIMIBE	12872002001	128720
		Other	LIPID MODIFYING AGENTS, COMBINATIONS	90083401001	900834
		Other	LIPID MODIFYING AGENTS, COMBINATIONS	90083401001	900834
		Rosuzet LD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410

Item	Category	CRF Option for Drug Name (English)	Preferred Term WHODD Drug Name	Preferred Term WHODD Drug Code	WHODD Drug Code 6 digits
		Rosuzet HD	EZETIMIBE; ROSUVASTATIN CALCIUM	10641002001	106410

Appendix 7 List of Figures and Tables

CT-3.3.1 Symptoms and Medications of Statin Intolerance (Full Analysis Set with Statin Intolerance)

CT-3.3.2 Symptoms and Medications of Statin Intolerance (Safety Analysis Set with Statin Intolerance)

CT-4.1.1-1 Prior Medications (Full Analysis Set)

CT-4.1.1-2 Prior Medications by Statin Response (Full Analysis Set)

CT-4.1.2-1 Concomitant Medications (Full Analysis Set)

CT-4.1.2-2 Concomitant Medications by Statin Response (Full Analysis Set)

CT-4.2-1 Concomitant Hypercholesterolemic Treatment Medications (Full Analysis Set)

CT-4.2-2 Concomitant Hypercholesterolemic Treatment Medications by Statin Response (Full Analysis Set)

CT-4.3-1 Concomitant Hypercholesterolemic Treatment Medications (Safety Analysis Set)

CT-4.3-2 Concomitant Hypercholesterolemic Treatment Medications by Statin Response (Safety Analysis Set)

CT-5.1 Primary Analysis: Percent Change From Baseline in LDL-C at Week 12 (MMRM) (Full Analysis Set)

CT-5.2-1 Primary Analysis: Percent Change From Baseline in LDL-C (MMRM) (Full Analysis Set)

CT-5.2-2 Primary Analysis: Percent Change From Baseline in LDL-C (MMRM) by Statin Response (Full Analysis Set)

CT-5.3 Sensitivity Analysis of MNAR using Placebo Based Imputation in Percent Change From Baseline in LDL-C at Week 12 (Full Analysis Set)

CT-6.1 Secondary Analysis: Percent Change From Baseline in Efficacy Parameters and Incidence of Subjects who Achieved the Target Value in LDL-C at Week 12 (Full Analysis Set)

CT-6.2 Other Efficacy Analysis: Percent Change From Baseline in Efficacy Parameters at Week 12 (Full Analysis Set)

CT-6.3-1 Secondary Analysis: Percent Change From Baseline in Efficacy Parameters (MMRM) (Full Analysis Set)

CT-6.3-2 Secondary Analysis: Percent Change From Baseline in Efficacy Parameters (MMRM) by Statin Response (Full Analysis Set)

CT-6.4-1 Secondary Analysis: Percent Change From Baseline in Efficacy Parameters (ANCOVA) (Full Analysis Set)

CT-6.4-2 Secondary Analysis: Percent Change From Baseline in Efficacy Parameters (ANCOVA) by Statin Response (Full Analysis Set)

CT-6.5-1 Secondary Analysis: Incidence of Subjects who Achieved the Target Value in LDL-C (Full Analysis Set)

CT-6.5-2 Secondary Analysis: Incidence of Subjects who Achieved the Target Value in LDL-C by Statin Response (Full Analysis Set)

CT-6.6-1 Secondary Analysis: Incidence of Subjects who Achieved the Target Value in LDL-C (OC) (Full Analysis Set)

CT-6.6-2 Secondary Analysis: Incidence of Subjects who Achieved the Target Value in LDL-C by Statin Response (OC) (Full Analysis Set)

CT-6.7-1 Other Efficacy Analysis: Percent Change From Baseline in Efficacy Parameters (MMRM) (Full Analysis Set)

CT-6.7-2 Other Efficacy Analysis: Percent Change From Baseline in Efficacy Parameters (MMRM) by Statin Response (Full Analysis Set)

CT-6.8-1 Exploratory Analysis: Descriptive Statistics for Efficacy Parameters Values, Change and Percent Change From Baseline (Full Analysis Set)

CT-6.8-2 Exploratory Analysis: Descriptive Statistics for Efficacy Parameters Values, Change and Percent Change From Baseline by Statin Response (Full Analysis Set)

CT-6.9-1 Exploratory Analysis: Robust Regression for Efficacy Parameters (Full Analysis Set)

CT-6.9-2 Exploratory Analysis: Robust Regression for Efficacy Parameters by Statin Response (Full Analysis Set)

CT-6.10-1 Subgroup Analysis: Percent Change From Baseline in LDL-C at Week 12 (MMRM) by Statin Response (Full Analysis Set)

CT-6.10-2 Subgroup Analysis: Percent Change From Baseline in LDL-C at Week 12 (MMRM) by Sex (Full Analysis Set)

CT-6.10-3 Subgroup Analysis: Percent Change From Baseline in LDL-C at Week 12 (MMRM) by Familial Hypercholesterolemia (Full Analysis Set)

CT-6.10-4 Subgroup Analysis: Percent Change From Baseline in LDL-C at Week 12 (MMRM) by Diabetes Mellitus (Full Analysis Set)

CT-6.10-5 Subgroup Analysis: Percent Change From Baseline in LDL-C at Week 12 (MMRM) by Age (Full Analysis Set)

CT-6.10-6 Subgroup Analysis: Percent Change From Baseline in LDL-C at Week 12 (MMRM) by Statin Therapy (Full Analysis Set)

CT-6.10-7 Subgroup Analysis: Percent Change From Baseline in LDL-C at Week 12 (MMRM) by BMI (Full Analysis Set)

CT-6.10-8 Subgroup Analysis: Percent Change From Baseline in LDL-C at Week 12 (MMRM) by eGFR (Full Analysis Set)

CT-6.10-9 Subgroup Analysis: Percent Change From Baseline in LDL-C at Week 12 (MMRM) by Baseline LDL-C (Full Analysis Set)

CT-6.10-10 Subgroup Analysis: Percent Change From Baseline in LDL-C at Week 12 (MMRM) by ASCVD (Full Analysis Set)

CT-6.10-11 Subgroup Analysis: Percent Change From Baseline in LDL-C at Week 12 (MMRM) by Baseline Statin Intensity (Full Analysis Set)

CT-6.10-12 Subgroup Analysis: Percent Change From Baseline in LDL-C at Week 12 (MMRM) by Ezetimibe Therapy (Full Analysis Set)

CT-6.10-13 Subgroup Analysis: Percent Change From Baseline in LDL-C at Week 12 (MMRM) by Fibrate Therapy (Full Analysis Set)

CT-7.1-1 Extent of Exposure to Investigational Medicinal Product (Safety Analysis Set)

CT-7.1-2 Extent of Exposure to Investigational Medicinal Product by Statin Response (Safety Analysis Set)

CT-7.2-1 Treatment Compliance (Full Analysis Set)

CT-7.2-2 Treatment Compliance by Statin Response (Full Analysis Set)

CT-7.3-1 Hypercholesterolemic Treatment Compliance (Full Analysis Set)

CT-7.3-2 Hypercholesterolemic Treatment Compliance by Statin Response (Full Analysis Set)

CT-8.1-1 Overall Summary of Adverse Events (Safety Analysis Set)

CT-8.1-2 Overall Summary of Adverse Events by Statin Response (Safety Analysis Set)

CT-8.2-1 Incidence of TEAEs by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.2-2 Incidence of TEAEs by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-8.2-3 Incidence of TEAEs of at Least 5% in Any Group by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.2-4 Incidence of TEAEs of at Least 5% in Any Group by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-8.3-1 Incidence of IMP-related TEAEs by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.3-2 Incidence of IMP-related TEAEs by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-8.3-3 Incidence of IMP-related TEAEs of at Least 5% in Any Group by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.3-4 Incidence of IMP-related TEAEs of at Least 5% in Any Group by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-8.4-1 Incidence of TEAEs by Severity by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.4-2 Incidence of TEAEs by Severity by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-8.5-1 Incidence of IMP-related TEAEs by Severity by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.5-2 Incidence of IMP-related TEAEs by Severity by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-8.6-1 Incidence of TEAEs With an Outcome of Death by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.6-2 Incidence of TEAEs With an Outcome of Death by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-8.7-1 Incidence of IMP-related TEAEs With an Outcome of Death by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.7-2 Incidence of IMP-related TEAEs With an Outcome of Death by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-8.8-1 Incidence of Serious TEAEs by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.8-2 Incidence of Serious TEAEs by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-8.9-1 Incidence of IMP-related Serious TEAEs by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.9-2 Incidence of IMP-related Serious TEAEs by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-8.10-1 Incidence of TEAEs Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.10-2 Incidence of TEAEs Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-8.11-1 Incidence of IMP-related TEAEs Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.11-2 Incidence of IMP-related TEAEs Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-8.12-1 Incidence of AESIs by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.12-2 Incidence of AESIs by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-8.13-1 Incidence of IMP-related AESIs by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.13-2 Incidence of IMP-related AESIs by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-8.14-1 Incidence of TEAEs of Non-Side Effect From COVID-19 Vaccine by MedDRA System Organ Class and Preferred Term (Safety Analysis Set)

CT-8.14-2 Incidence of TEAEs of Non-Side Effect From COVID-19 Vaccine by MedDRA System Organ Class and Preferred Term by Statin Response (Safety Analysis Set)

CT-9.1 Listing of Deaths (Safety Analysis Set)

CT-9.2 Listing of Serious Adverse Events Other Than Death (Safety Analysis Set)

CT-9.3 Listing of Discontinuations Due to Adverse Events (Safety Analysis Set)

CT-10.1.1-1 Descriptive Statistics for Clinical Laboratory Test Results - Serum Chemistry (Safety Analysis Set)

CT-10.1.1-2 Descriptive Statistics for Clinical Laboratory Test Results by Statin Response - Serum Chemistry (Safety Analysis Set)

CT-10.1.2-1 Descriptive Statistics for Clinical Laboratory Test Results - Hematology (Safety Analysis Set)

CT-10.1.2-2 Descriptive Statistics for Clinical Laboratory Test Results by Statin Response - Hematology (Safety Analysis Set)

CT-10.1.3-1 Descriptive Statistics for Clinical Laboratory Test Results - Urinalysis (Safety Analysis Set)

CT-10.1.3-2 Descriptive Statistics for Clinical Laboratory Test Results by Statin Response - Urinalysis (Safety Analysis Set)

CT-10.2.1-1 Shift Tables of Clinical Laboratory Test Results - Serum Chemistry (Safety Analysis Set)

CT-10.2.1-2 Shift Tables of Clinical Laboratory Test Results by Statin Response - Serum Chemistry (Safety Analysis Set)

CT-10.2.2-1 Shift Tables of Clinical Laboratory Test Results - Hematology (Safety Analysis Set)

CT-10.2.2-2 Shift Tables of Clinical Laboratory Test Results by Statin Response - Hematology (Safety Analysis Set)

CT-10.2.3-1 Shift Tables of Clinical Laboratory Test Results - Urinalysis (Safety Analysis Set)

CT-10.2.3-2 Shift Tables of Clinical Laboratory Test Results by Statin Response - Urinalysis (Safety Analysis Set)

CT-10.2.4-1 Shift Tables of Clinical Laboratory Test Results - Qualitative Urinalysis (Safety Analysis Set)

CT-10.2.4-2 Shift Tables of Clinical Laboratory Test Results by Statin Response - Qualitative Urinalysis (Safety Analysis Set)

CT-10.3-1 Incidence of Potentially Clinically Significant Abnormalities in Laboratory Tests (Safety Analysis Set)

CT-10.3-2 Incidence of Potentially Clinically Significant Abnormalities in Laboratory Tests by Statin Response (Safety Analysis Set)

CT-10.4 Listing of Abnormal Laboratory Findings (Safety Analysis Set)

CT-11.1-1 Descriptive Statistics for Vital Signs (Safety Analysis Set)

CT-11.1-2 Descriptive Statistics for Vital Signs by Statin Response (Safety Analysis Set)

CT-11.2-1 Incidence of Potentially Clinically Significant Abnormalities in Vital Signs (Safety Analysis Set)

CT-11.2-2 Incidence of Potentially Clinically Significant Abnormalities in Vital Signs by Statin Response (Safety Analysis Set)

CT-11.3-1 Descriptive Statistics for Body Weight (Safety Analysis Set)

CT-11.3-2 Descriptive Statistics for Body Weight by Statin Response (Safety Analysis Set)

CT-11.4-1 Incidence of Potentially Clinically Significant Abnormalities in Body Weight (Safety Analysis Set)

CT-11.4-2 Incidence of Potentially Clinically Significant Abnormalities in Body Weight by Statin Response (Safety Analysis Set)

CT-12.1-1 Descriptive Statistics for ECG Parameters (Safety Analysis Set)

CT-12.1-2 Descriptive Statistics for ECG Parameters by Statin Response (Safety Analysis Set)

CT-12.2-1 Categorical Analysis of ECG - QTcF (Safety Analysis Set)

CT-12.2-2 Categorical Analysis of ECG by Statin Response - QTcF (Safety Analysis Set)

CT-12.3-1 Shift Table of ECG Findings (Normal/Abnormal Assessments) (Safety Analysis Set)

CT-12.3-2 Shift Table of ECG Findings (Normal/Abnormal Assessments) by Statin Response (Safety Analysis Set)

CT-12.4-1 Incidence of Potentially Clinically Significant Abnormalities in ECG Parameters (Safety Analysis Set)

CT-12.4-2 Incidence of Potentially Clinically Significant Abnormalities in ECG Parameters by Statin Response (Safety Analysis Set)

CF-1-1 Percent Change From Baseline by Visit in Efficacy Parameters (LSMean+-SE) (Full Analysis Set)

CF-1-2 Percent Change From Baseline by Visit in Efficacy Parameters (LSMean+-SE) by Statin Response (Full Analysis Set)

Appendix 8 List of Subject Data Listings

DREAS-1 Discontinued Subjects and Reason for Discontinuation (Screened Subjects)

SUBEX-1 Subjects Excluded From Analysis Set (Randomized Subjects)

DEMOG-1 Demographic Characteristics (Screened Subjects)

SMED-1 Investigational Medicinal Product Compliance (Screened Subjects)

SMED-2.1 Prior Hypercholesterolemic Treatment (Screened Subjects)

SMED-2.2 Hypercholesterolemic Treatment Compliance (Screened Subjects)

EFF-1.1 Listing of Primary Efficacy Endpoint - LDL-C (Randomized Subjects)

EFF-1.2 Listing of Efficacy Endpoints Other Than LDL-C (Randomized Subjects)

AE-1 Adverse Events (Informed Subjects)

LAB-1.1 Laboratory Values (Hematology) (Screened Subjects)

LAB-1.2 Laboratory Values (Blood Chemistry) (Screened Subjects)

LAB-1.3 Laboratory Values (Urinalysis) (Screened Subjects)

LAB-2 Laboratory Values (Fasting Lipid) (Screened Subjects)

PDATA-1 Study Completion Status and Reason for Discontinuation (Screened Subjects)

PDATA-2 Inclusion Criteria and Exclusion Criteria Not Met

PDATA-3.1 Medical History (Hypercholesterolemia) (Informed Subjects)

PDATA-3.2 Medical History (Screened Subjects)

PDATA-4 Physical Examination (Screened Subjects)

PDATA-5.1 Prior and Concomitant Medication (Screened Subjects)

PDATA-5.2 Prior and Concomitant Therapy (Screened Subjects)

PDATA-6 Vital Signs and Body Weight (Screened Subjects)

PDATA-7 12-Lead ECG Parameters and Findings (Screened Subjects)

PDATA-8 Pregnancy Test (Screened Subjects)

PDATA-9 TSH and Virus Test (Screened Subjects)

PDATA-10 Blood Draw Time for Biomarker and DNA storage (Screened Subjects)

PDATA-11 Screen Failures

PDATA-12 Post-treatment Follow-up (Randomized Subjects)

PDATA-13 Randomization (Randomized Subjects)

PDEV-1 Protocol Deviations (Screened Subjects)