STATISTICAL ANALYSIS PLAN

Protocol Title:	A Placebo-Controlled, Double-Blind, Randomized, Phase 2 Dose Finding Study to Evaluate the Effect of Obicetrapib as an Adjunct to Stable Statin Therapy in Japanese Subjects
Protocol Number:	TA-8995-203
Protocol Version/Date:	V1.1 / 20 April 2022
Investigational Product:	Obicetrapib
Sponsor:	NewAmsterdam Pharma BV Gooimeer 2-35 1411 DC Naarden The Netherlands Telephone: +31 35 699 30 00 Fax: +31 20 240 07 79
SAP Version/Date:	V2.0 / 9 May 2023

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SIGNATURE PAGE

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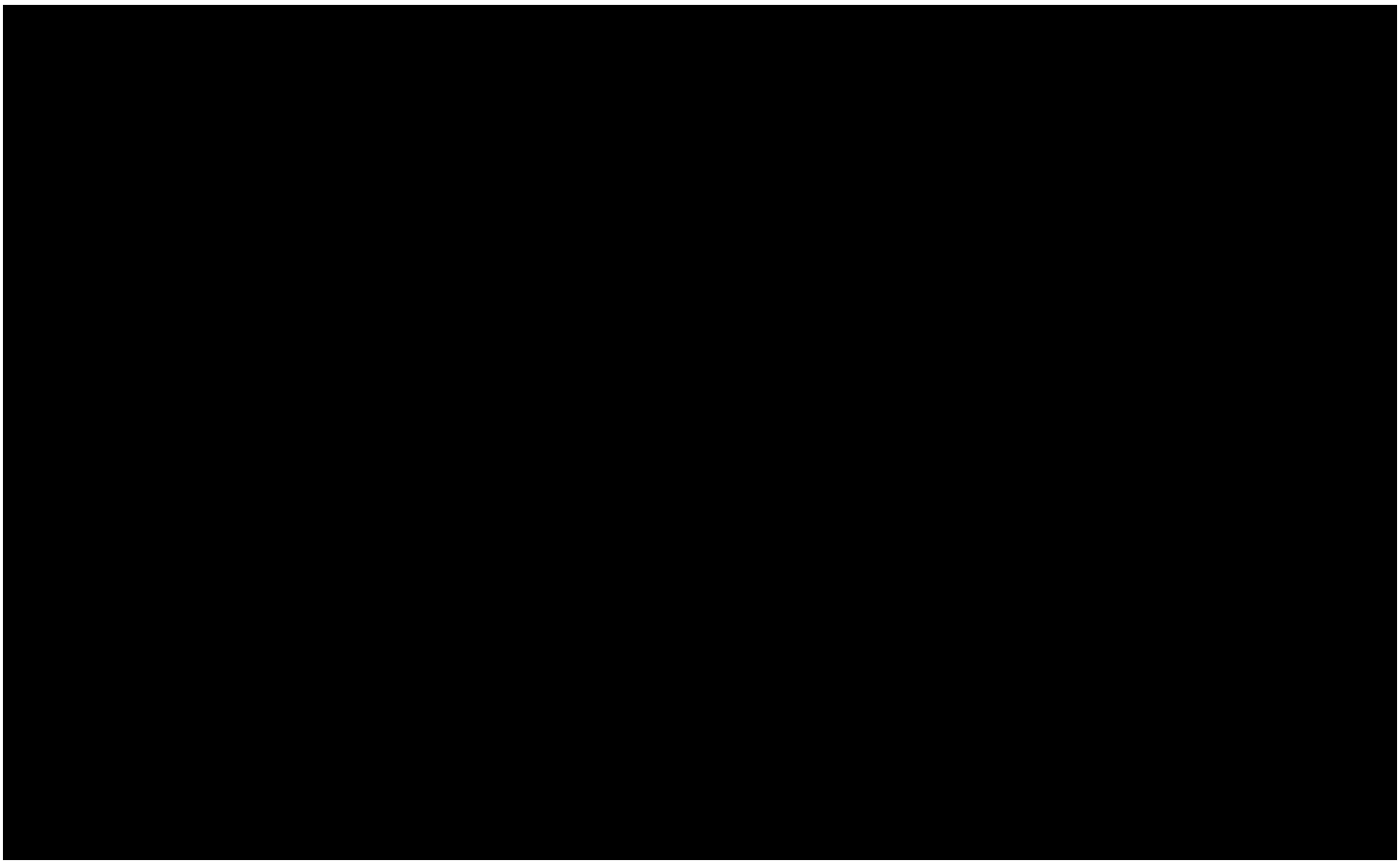
We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

Signature **Date**



VERSION HISTORY

Version	Version Date	Description
1.0	04 July 2022	Original signed version
2.0	9 May 2023	3.2.3 Added Modified Intent-to-Treat On-Treatment Population 3.3.7 Removed imputation rule for missing date of first dose of study drug 3.4 Added figures to be created 3.4.2 Removed high-density lipoprotein-ApoE from lipid profile parameter 3.7.1 Added listing for TEAEs of special interest

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
ApoB	Apolipoprotein B
ATC	Anatomical therapeutic chemical
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
ESI	Events of Special Interest
HDL-C	High Density Lipoprotein Cholesterol
ICF	Informed Consent Form
IRT	Interactive Response Technology
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-Treat
MMRM	Mixed Model for Repeated Measure
LDL-C	Low Density Lipoprotein Cholesterol
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-Protocol
PUC	Preparative Ultracentrifugation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from NewAmsterdam Pharma BV Protocol TA-8995-203. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of obicetrapib, compared to placebo, in reducing serum low density lipoprotein cholesterol (LDL-C) measured at Day 56 (Visit 5) when taken as an adjunct to a pre-existing stable statin therapy regime.

2.1.2 Secondary Objectives

The secondary objectives of this study include the following:

- To evaluate the effect of obicetrapib, compared to placebo, on serum apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), and high density lipoprotein cholesterol (HDL-C) concentrations at Day 56 (Visit 5), when taken as an adjunct to pre-existing stable statin therapy;
- To assess the mean plasma levels of obicetrapib at steady state on Day 56 (Visit 5) and Day 84 (Visit 6); and
- To evaluate the safety and tolerability profile of obicetrapib in Japanese subjects.

2.2 Study Design

2.2.1 Overview

The population for this study includes Japanese men and women, 18 to 75 years of age, inclusive, with a body mass index <35 kg/m2, fasting LDL-C levels >70 mg/dL, and triglyceride levels <400 mg/dL at the Screening Visit, who are currently receiving stable statin therapy.

This study will be a placebo-controlled, double-blind, randomized, Phase 2 dose-finding study to evaluate the efficacy, safety, and tolerability of obicetrapib as an adjunct to stable statin therapy in Japanese participants. This study will take place at approximately 10 sites in Japan.

The total duration for the double-blind period for each subject will be up to 14 weeks, including up to 2 weeks for Screening, 8 weeks for blinded study treatment, and 4 weeks for safety follow-up. Please refer to Appendix A (Schedule of Procedures) of the study protocol for details.

At the Screening Visit (Visit 1), and up to 2 weeks before the start of the treatment period, participants will be required to sign an informed consent form (ICF) before any study-related procedures are performed. After signing the ICF, participants will be assessed for study eligibility.

Up to 2 weeks after the Screening Visit, participants will return to the site on Day 1 (Visit 2) and confirm study eligibility before being randomized and beginning treatment. Approximately 100

eligible participants (25 participants per treatment group) will be randomized in a 1:1:1:1 ratio to 1 of the following treatment groups:

- 2.5 mg obicetrapib (one 2.5 mg obicetrapib tablet);
- 5 mg obicetrapib (one 5 mg obicetrapib tablet);
- 10 mg obicetrapib (one 10 mg obicetrapib tablet); or
- Placebo (1 placebo tablet).

During the 8-week Treatment Period, the assigned study drugs will be administered by the participants orally once daily from Day 1 (Visit 2) to Day 56 (Visit 5). Participants will return to the site on Day 14 (Visit 3), Day 28 (Visit 4), and Day 56 (Visit 5) for efficacy, safety, and Pharmacokinetics (PK) assessments. Participants, Investigators, the Clinical Research Organization (CRO), and the Sponsor will be blinded to all lipid results from Day 1 (Visit 2) for the first participant and continuing to database lock in order to protect blinding to treatment assignment.

Participants will return to the site for a Safety Follow-up Visit on Day 84 (Visit 6), approximately 4 weeks after the end of the Treatment Period, for final safety and PK assessments.

Coronavirus Disease 2019 Contingency Measures

In cases of COVID-19 limitations, it is the Investigator's responsibility to assure the safety of participants. If investigators need to implement contingency measures, the investigators will communicate with the Sponsor and discuss the best practice with the sponsor. In the absence of a COVID-19 impact, it is expected that Investigators and participants follow the protocol requirements as set forth.

2.2.2 Randomization and Blinding

Participants who meet all eligibility criteria will be randomized into the study. Participants will be randomized in a 1:1:1:1 ratio to the 2.5 mg obicetrapib, 5 mg obicetrapib, 10 mg obicetrapib, or placebo treatment groups. At randomization, participants will be stratified according to their Screening Visit (Visit 1) LDL-C level (≥100 or <100 mg/dL). An automated interactive response technology (IRT) system will be used to assign the participant to 1 of the 4 treatment groups, and visits will be registered in the IRT for Screening and Visits 1 through 5 as well as Early Termination, if applicable.

Participants, Investigators, the CRO, and the Sponsor will be blinded to all lipid results from Day 1 (Visit 2) for the first participant and continuing to database lock in order to protect blinding to treatment assignment.

2.2.3 Study Drug

The study drugs to be used in this study include the following:

- 2.5 mg obicetrapib tablet;
- 5 mg obicetrapib tablet;
- 10 mg obicetrapib tablet; and
- Matching placebo tablet.

The study drugs listed above will be packaged to provide doses of 2.5 mg, 5 mg, 10 mg obicetrapib, or placebo only. Placebo tablets will be visually identical. Participants will be randomized to receive 1 of the 3 doses of obicetrapib or placebo only. One tablet of study drug will be administered by the participant orally once daily from Day 1 (Visit 2) to Day 56 (Visit 5) at approximately the same time each morning.

2.2.4 Sample Size Determination

A sample size of at least 100 evaluable participants (i.e., 25 participants per treatment group) will provide >90% power to detect a 30% difference in LDL-C reduction at Day 56 (standard deviation (SD) of 25%) for each of the obicetrapib groups compared to the placebo group at a 2-sided significance level of 0.05.

The sample size for this study was determined in order to provide sufficient power for the analyses of the primary efficacy endpoint described in Section 3.4. Therefore, assuming a dropout rate of approximately 7%, an estimated enrollment target of approximately 108 participants (i.e., 27 participants per treatment group) is planned for this study. This sample size will also contribute sufficient participant exposure and safety data.

Participants will be stratified according to their Screening Visit (Visit 1) LDL-C levels (≥100 or <100 mg/dL).

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the percent change from Day 1 to Day 56 in LDL-C for each obicetrapib group compared to the placebo group.

2.3.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoints include the following:

- Percent change from Day 1 to Day 56 in ApoB for each obicetrapib group compared to the placebo group;
- Percent change from Day 1 to Day 56 in non-HDL-C for each obicetrapib group compared to the placebo group; and
- Percent change from Day 1 to Day 56 in HDL-C for each obicetrapib group compared to the placebo group.

2.3.3 Safety Endpoints

The safety and tolerability profile of obicetrapib will be assessed by clinical laboratory assessments (chemistry and hematology), vital signs, physical examinations, and the incidence of adverse events and events of special interest (ESIs).

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

Scheduled visits will be assigned to analysis visits as recorded on the case report form (CRF). Early termination visits will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 1	1	NA	NA
Week 2	14	2	21
Week 4	28	22	42
Week 8	56	43	70
Safety Follow-up	84	71	

Unscheduled visits recorded on the CRF will not be re-assigned and remain labeled as unscheduled.

3.1.3 Definition of Baseline

Unless otherwise stated, Baseline will be defined as the last measurement prior to the first dose of study drug.

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of participants. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, minimum, and maximum.

3.1.5 Evaluation of Site Effect

This is a multi-center study. Sites will not be pooled for any planned inferential analysis but may be pooled for subgroup analysis to assess the heterogeneity of treatment effects among pooled sites. The final pooling algorithm, if needed, will be specified before treatment unblinding and will be provided as an addendum to the SAP. Additionally, a review of by-site effects will be performed in the context of data listing review.

3.1.6 Handling of Dropouts and Missing Data

Date Values

In cases of incomplete dates (e.g. adverse event (AE), concomitant medication, and medical history start and/or stop dates), the missing component(s) will be assumed as the most conservative value possible. For example, if the start date is incomplete, the first day of the month will be imputed for the missing day and January will be imputed for the missing month. If a stop date is incomplete, the last day of the month will be imputed for the missing day and December will be imputed for the missing month. Incomplete start and stop dates will be listed as collected without imputation.

Date imputation will only be used for computational purposes such as treatment-emergent status. Actual data values, as they appear in the original CRFs, will be presented within the data listings.

Non-Date Values

For sensitivity analyses of the primary efficacy endpoint, missing values will be imputed using multiple imputation (see Section 3.4.1). For the analyses of secondary and exploratory efficacy endpoints, no imputation will be made for missing values. Safety data will be used according to availability, with no imputation for missing data.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) Population will include all participants randomized into the study. Treatment classification will be based on the randomized treatment.

3.2.2 Modified Intent-to-Treat (mITT) Population

The Modified ITT (mITT) Population will include all participants in the ITT Population who receive at least 1 dose of any study drug and have a Baseline value for the LDL-C assessment. Any efficacy measurement obtained during the Safety Follow-up Visit after a participant

permanently discontinues the study drug or after a participant receives an excluded medication and/or procedure will be removed from the mITT analysis. Treatment classification will be based on the randomized treatment. The mITT Population will be used for the primary analysis of all efficacy endpoints.

3.2.3 Modified Intent-to-Treat (mITT) On-Treatment Population

The mITT On-Treatment Population will include all randomized participants who have a Baseline value for LDL-C assessment, have a Day 56 value for the LDL-C assessment, and plasma obicetrapib concentration at Day 56 is >100 ng/mL. Treatment classification will be based on the randomized treatment.

Rationale: <100 ng/mL is more than three standard deviations from the mean plasma obicetrapib concentration observed in both the ROSE (TA-8995-201) and TULIP (TA-8995-03) [with a very similar patient population compared to ROSE2 (TA-8995-202)] at respectively week 4 and week 12. In addition, in none of the previous conducted studies (3 clinical studies and 2 Phase 1 PK / PD studies the minimal observed obicetrapib concentration for C_{max} was below 100 ng/mL.

3.2.4 Per-Protocol (PP) Population

The Per-Protocol (PP) Population will include all participants in the mITT Population who have a Baseline value for the LDL-C assessment, have a Day 56 value for the LDL-C assessment, and who do not experience a major protocol deviation that would potentially impact the primary efficacy endpoint. Major protocol deviations will be defined in the Protocol Deviation Plan within the trial master file to align with International Conference on Harmonization guidelines. The PP Population, along with the reason for exclusion, will be finalized prior to study unblinding. The PP Population will be a secondary population for analysis of the primary efficacy endpoint.

3.2.5 PK Population

The PK Population will include all participants in the mITT Population who have sufficient blood samples collected for valid estimation of PK parameters.

3.2.6 Safety Population

The Safety Population will include all participants who receive at least 1 dose of any study drug. Treatment classification will be based on the actual treatment received. The Safety Population will be the primary population used for the safety analyses.

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Subject disposition will be presented for ITT Population. Counts and percentages of participants who are randomized, complete the study, complete the treatment, prematurely discontinue from the study, reasons for study discontinuation, and primary reason for early termination was due to COVID-19 will be summarized by treatment and overall. For each scheduled visit, counts and percentages of participants who do not complete the visit, partially complete the visit in-person, or complete the visit virtually will be summarized by treatment. The denominator for calculating percentages will be based on the number of randomized participants.

Data listings for subject disposition and exclusion and inclusion criteria violations will be provided.

3.3.2 Protocol Deviations

Protocol deviations will be identified based on the clinical data as defined in the Protocol Deviation Plan. The Protocol Deviation Plan will define all protocol deviations as either CSR reportable or non-CSR reportable deviations. Counts and percentages of participants with CSR reportable protocol deviations by deviation category will be summarized by treatment and in total based on ITT Population. A listing of CSR-reportable protocol deviations will be generated.

3.3.3 Analysis Populations

Counts and percentages of participants in each analysis population will be summarized by treatment and in total based on ITT Population. Reasons for exclusion from PP Population will also be summarized.

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (<65 years, 65-75 years)
- Sex
- Childbearing potential
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2) and BMI categories (<30 kg/m^2, ≥30 kg/m^2)
- Stratification group (LDL-C value ≥100 or <100 mg/dL)
- Current statin therapy (Atorvastatin 10 mg, 20mg/day, Rosuvastatin 5, 10 mg/day)

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of participants as appropriate by treatment and in total for the mITT Population and each of the ITT Population, the PP Population, the mITT On-Treatment Population and the Safety Population if they differ from the mITT.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) with the version specified in Data Management Plan. Counts and percentages of participants with medical history by system organ class and preferred term will be summarized by treatment and in total based on ITT Population.

3.3.6 Prior and Concomitant Medications

Medication start and stop dates that are recorded on the Prior & Concomitant Medications case report form will be used to determine whether the medications are prior or concomitant to the study treatment. Concomitant medications are defined as those used on or after the first dose of study treatment. Prior medications are defined as those used prior to and stopped before the first dose of study treatment. All prior and concomitant medication verbatim terms will be coded using the World Health Organization (WHO) Drug Dictionary with the version specified in Data Management Plan. The numbers and percentages of participants taking prior and concomitant medications in each treatment and in total will be summarized by anatomical therapeutic chemical (ATC) class and preferred term for the Safety Population.

3.3.7 Study Drug Exposure and Compliance

Participants' exposure to randomized study medication will be summarized with descriptive statistics by treatment for the Safety Population. Days of exposure is defined as:

$$Exposure\ (days) = \ date\ of\ last\ dose\ of\ study\ drug - date\ of\ first\ dose + 1$$

For those who failed to provide the date of last dose of study drug, the earliest date between the end of treatment date and the date of end of study/early termination will be used.

A summary will be provided to display counts and percentages of participants in each treatment with exposure in the following categories: <4 weeks, 4 – <8 weeks, and 8+ weeks.

Summary statistics will be presented for percent overall compliance to study medication by treatment. Counts and percentages of participants will also be tabulated by groups with overall compliance < 80%, 80% to 120%, and > 120%.

The percent overall compliance to study medication will be calculated as:

$$Compliance\ (\%) = \frac{(\#\ tablets\ dispensed - \#\ tablets\ returned)}{\#\ expected\ dosing\ days} \times 100$$

The number of expected dosing days = (the earliest date between the end of treatment date and the date of early termination – the date of randomization + 1).

A separate listing of derived exposure and compliance will be provided for ITT Population.

3.4 Efficacy Assessment

The mITT Population will be the primary population for the efficacy analyses. Efficacy will also be analyzed using the ITT Population, the mITT On-Treatment Population, and the PP Population as supportive analyses for selected endpoints.

LDL-C will be collected using the following two approaches:

1. LDL-C level will be calculated using the Friedewald equation unless TG ≥400 mg/dL or LDL-C ≤50 mg/dL. If TG ≥400 mg/dL or LDL-C ≤50 mg/dL, then LDL-C level will be measured directly by preparative ultracentrifugation (PUC), also referred to as beta quantification.
2. In addition, for all participants, LDL-C will be measured by PUC at Baseline (Visit 2) and at the end of the 8-week Treatment Period (Visit 5).

3.4.1 Primary Efficacy Endpoint

Primary Analysis

The primary efficacy endpoint is the percent change from Day 1 to Day 56 in LDL-C (as determined by approach 1) for each obicetrapib group compared to the placebo group. The percent change will be calculated from Day 1 (Baseline) to each measurement taken at Day 14, Day 28, and Day 56.

The mean percent change from Day 1 to Day 56 in LDL-C for each treatment is defined mathematically as μ_j, where j stands for jth treatment (j=0,1,2,3) and the subscripts 0, 1, 2, and 3 refer to the placebo, Obicetrapib 10 mg, 5 mg, and 2.5 mg group, respectively. The hypotheses

testing to the difference in the mean percent change in LDL-C from Day 1 to Day 56 between the j[th] obicetrapib group and the placebo group is then defined statistically as following:

$$H_0: \mu_j - \mu_0 = 0, H_1: \mu_j - \mu_0 \neq 0, \text{ where j = 1,2,3}$$

The primary efficacy analysis of the percent change from Day 1 to Day 56 in LDL-C will be performed using a mixed model for repeated measure (MMRM) approach. The analysis will include fixed effects for treatment, visit, and treatment-by-visit interaction, along with a covariate of the Baseline value as a continuous covariate. It is to note that randomization was stratified by categories of LDL-C value (≥100 or <100 mg/dL) only to ensure similar distribution of LDL-C values across all treatment. However, the MMRM model will include the original scale of the LDL-C value as a continuous covariate, not categorical.

The Restricted Maximum Likelihood estimation approach will be used with an unstructured covariance matrix. The least squares means, standard errors, and 2-sided 95% confidence intervals for each treatment group and for the pairwise comparisons of each dose of obicetrapib to the placebo group will be provided. The least squares means for the pairwise comparison and its standard error will be used for the hypothesis testing. The ratio of estimate to standard error will be approximately t distributed. The null hypothesis of no treatment effect will be rejected if the p-value, the probability of obtaining the observed or more extreme value of t statistic under the null hypothesis, is less than or equal to 0.05.

In order to maintain the overall alpha level on the primary endpoint, the hypothesis testing will be performed sequentially at the 2-sided alpha=0.05 significance level. The first comparison will be the 10 mg obicetrapib group versus placebo; if significant, comparison of the 5 mg obicetrapib group versus placebo will be performed, followed by the 2.5 mg obicetrapib group versus placebo. Hypothesis testing will proceed in this hierarchical step-down fashion until a comparison is not significant. At that point, all remaining sequential tests will be deemed not significant.

The MMRM approach will include all available assessments of percent change in LDL-C from Baseline to Day 14, Day 28, and Day 56. The model assumes the data are missing at random (MAR). If any data are missing, the model will use all information from the other time points as well as Baseline covariate values to estimate the mean treatment difference at the given time point. No imputation of missing data will be performed for the primary efficacy endpoint analysis.

In order to address the effect of intercurrent events, “While-on-Treatment Strategies” will be employed[1]. For participants who are withdrawn from the study because of the use of an excluded medication and/or procedure, data occurring after the intercurrent event of excluded medications use will be excluded from the primary analysis. For participants who are withdrawn from the trial, data occurring after the intercurrent event of failure to adhere to treatment dosing will be excluded from the primary analysis. Failure to adhere to treatment dosing will be defined as study drug compliance <75% at the time of study withdrawal.

The MMRM analysis will be implemented using SAS® Proc Mixed. Example SAS code can be found below:

```
**************************************************************************************************
Note:
  USUBJID = unique subject identifier
  TREATMENT = 0 (Placebo), 1 (2.5 mg obicetrapib), 2 (5 mg obicetrapib), 3 (10 mg
  obicetrapib)
```

```
  VISIT = Visit
  BASE = Baseline value
  PCHG = Percent change from Baseline
**********************************************************************************************************
proc mixed;
  class USUBJID TREATMENT VISIT;
  model PCHG = TREATMENT BASE VISIT TREATMENT*VISIT / solution cl;
  repeated VISIT / TYPE=UN sub=USUBJID;
  lsmeans VISIT*TREATMENT / cl diffs;
run;
**********************************************************************************************************
```

Values, changes from Baseline, and percent change from Baseline of LDL-C will be summarized using descriptive statistics at scheduled visits and Baseline by treatment group.

Counts and percentages of participants will be summarized by treatment for each type of data pattern. There will be 16 data patterns for four time points (Baseline, Day 14, Day 28 and Day 56) each having two possible outcomes (LDL-C data reported or missing).

Waterfall plot of percent change in LDL-C from Baseline to each scheduled visit will be created. Line plot of the mean (+/- 2 * SE) and the median (and IQR) percent change in LDL-C from Baseline to each scheduled visit will be created. Figures will be created for LDL-C values collected using two approaches described above.

The main analyses for the primary efficacy endpoint will be repeated for the ITT Population, the mITT On-Treatment Population, and PP Population.

Sensitivity Analyses

Three sensitivity analyses will be performed for the primary efficacy endpoint:

1. MMRM with imputation
2. Analysis covariance (ANCOVA)
3. ANCOVA using LDL-C by PUC

All sensitivity analyses will be conducted on the mITT Population.

Sensitivity Analysis 1

The first sensitivity analysis will be performed in two steps. In the first step, missing data will be assumed missing not at random (MNAR). Missing data at Days 14, 28 and 56 will be imputed using multiple imputation methodology in two steps. Initially, 25 data sets will be imputed for non-monotone missing values in the original dataset. In the second step the remaining monotone missing values in the 25 data sets will be imputed based on the observations in the Placebo group. Upon completion of the trial, if the percentage of cases with incomplete data is larger than initially anticipated then the number of imputations will be increased for the final analysis.

The variables for the imputation model will consist of LDL-C values from Baseline and Days 14, 28 and 56. For each imputation dataset, the percent change from Baseline to Day 56 will be analyzed using the MMRM model described for the primary analysis. The results from these 25 analyses will be combined using Rubin’s method to construct the treatment estimates using the parameter estimates and associated standard errors. Similarly, the difference of the adjusted

treatment means (the three doses of obicetrapib therapy – Placebo) will be presented with the associated standard error and 95% confidence interval. Randomly chosen seed numbers will be selected for the analysis and will be retained.

Example SAS code to create a dataset for non-monotone missing values is shown below:

```
**************************************************************************************************************
Note:
  non-MONOTONE missing values
  TREATMENT = 0 (Placebo), 1 (2.5 mg obicetrapib), 2 (5 mg obicetrapib), 3 (10 mg
  obicetrapib)
  LDLC_BASE = LDL_C Baseline value
  LDLC_Day14 = LDL_C value at Day 14
  LDLC_Day28 = LDL_C value at Day 28
  LDLC_Day56 = LDL_C value at Day 56
**************************************************************************************************************
proc mi data=LDLC_Wide seed=20220101 out=LDLC_25MCMC nimpute=25;
  var TREATMENT LDLC_base LDLC_Day14 LDLC_Day28 LDLC_Day56;
  mcmc impute=monotone chain=multiple;
run;
**************************************************************************************************************
```

In the second step, the remaining monotone missing values will be imputed. Example SAS code to complete this step is shown below:

```
**************************************************************************************************************
Note:
MONOTONE missing values
TREATMENT = 0 (Placebo), 1 (2 mg obicetrapib), 2 (5 mg obicetrapib), 3 (10 mg obicetrapib)
LDLC_BASE = LDL_C Baseline value
LDLC_Day14 = LDL_C value at Day 14
LDLC_Day28 = LDL_C value at Day 28
LDLC_Day56 = LDL_C value at Day 56
**************************************************************************************************************
proc mi data= LDLC_25MCMC seed=810456 out= LDLC_Mono nimpute=1 simple;
  by _Imputation;
  class TREATMENT;
  monotone method=reg;
  mnar model (LDLC_Day14 LDLC_Day28 LDLC_Day56 / modelobs=(TREATMENT=”0”));
  var LDLC_base LDLC_Day14 LDLC_Day28 LDLC_Day56;
run;
**************************************************************************************************************
```

For each imputation dataset, the percent change from Baseline to Day 14, Day 28 and Day 56 will be analyzed using similar MMRM approach. Then the parameter estimates will be combined using Rubin’s method. Example SAS code to combine the parameter estimates is shown below:

```
**************************************************************************************************************
Note:
  MIANALYZE to combine imputations
**************************************************************************************************************
proc mianalyze parms(classvar=full)=mixLSM;
  class TREATMENT;
```

```
  modeleffects TREATMENT;
  ods output parameterestimates=mi_LSM;
run;
proc mianalyze parms(classvar=full)=mixDIFF;
  class TREATMENT;
  modeleffects TREATMENT;
  ods output parameterestimates=minus_mi_DIFF;
run;
**********************************************************************************************************
```

Sensitivity Analysis 2

In the second sensitivity analysis, the percent change from Day 1 to Day 56 in LDL-C, via approach 1, for the obicetrapib groups compared to the placebo group will be analyzed using an Analysis of Covariance (ANCOVA) model with fixed effects of treatment group and the Baseline LDL-C value as a continuous covariate. The least squares means, standard errors, and 2-sided 95% confidence intervals for each treatment group, for the pairwise comparisons of three obicetrapib will be provided. The treatment comparison will be performed using a 2-sided test at the $\alpha = 0.05$ level of significance. No imputation of missing data will be performed for this sensitivity analysis.

Example SAS code can be found below:

```
**********************************************************************************************************
Note:
  USUBJID = unique subject identifier
  TREATMENT = 0 (Placebo), 1 (2.5 mg obicetrapib), 2 (5 mg obicetrapib), 3 (10 mg
  obicetrapib)
  BASE = Baseline value
  PCHG = Percent change from Baseline
**********************************************************************************************************
proc glm data=LDL_C;
  class TREATMENT;
  model PCHG = TREATMENT BASE / ss1 ss3;
  means TREATMENT;
  lsmeans TREATMENT / cov stderr pdiff cl;
  estimate " 2.5 mg obicetrapib - Placebo" TREATMENT -1 1 0 0;
  estimate " 5 mg obicetrapib - Placebo"    TREATMENT -1 0 1 0;
  estimate " 10 mg obicetrapib - Placebo"  TREATMENT -1 0 0 1;
run;
**********************************************************************************************************
```

Sensitivity Analysis 3

In the final sensitivity analysis, the percent change from Day 1 to Day 56 in LDL-C will be assessed where the LDL-C values were determined by approach 2. The percent change from Day 1 to Day 56 in LDL-C by PUC for the obicetrapib groups compared to the placebo group will be analyzed using an ANCOVA similar to the model described in the second sensitivity analysis. No imputation of missing data will be performed for this sensitivity analysis.

Values, changes from Baseline, and percent change from Baseline of LDL-C by PUC will be summarized using descriptive statistics at scheduled visits and Baseline by treatment group.

Counts and percentages of participants will be summarized by treatment for each type of data pattern. There will be four data patterns for two time points (Baseline and Day 56) each having two possible outcomes (LDL-C data reported or missing).

3.4.2 Secondary Efficacy Endpoints

Similar MMRM models as described for the primary efficacy analyses will be used to analyze the secondary efficacy endpoints based on the mITT Population. No adjustment will be made for multiplicity in testing the secondary efficacy endpoints. Nominal p-values will be provided when applicable.

Values, changes from Baseline, and percent change from Baseline of each lipid profile will be summarized using descriptive statistics at scheduled visits and Baseline by treatment group. The following endpoints will be examined:

- Percent change from Day 1 to Day 56 in ApoB for each obicetrapib group compared to the placebo group;
- Percent change from Day 1 to Day 56 in non-HDL-C for each obicetrapib group compared to the placebo group; and
- Percent change from Day 1 to Day 56 in HDL-C for each obicetrapib group compared to the placebo group.

Waterfall plot of percent change in ApoB from Baseline to each scheduled visit will be created.

3.4.3 Other Efficacy Endpoints

The percent change from Day 1 to Day 56 in Apolipoprotein E (ApoE), Triglycerides, and Very low-density lipoprotein cholesterol will be examined through similar MMRM models as described for the primary efficacy analyses based on the mITT Population. Values, changes from Baseline, and percent change from Baseline of each lipid profile will be summarized using descriptive statistics at scheduled visits and Baseline by treatment group.

3.4.4 Subgroups

Not applicable.

3.5 Pharmacokinetic Assessment

Plasma obicetrapib concentrations will be summarized with descriptive statistics based on the PK Population. Exploration of any relationships with obicetrapib exposure will be performed, as appropriate.

On Day 1, a PK sample will be collected pre-dose. The subsequent post-dose PK samples should be collected once at approximately the same time at each visit.

3.6 Pharmacodynamic Assessment

Not applicable.

3.7 Safety Assessment

The Safety Population will be the primary population for the safety analyses. All safety endpoints will be summarized descriptively. No statistical inference will be applied to the safety endpoints.

3.7.1 Adverse Events (AEs)

AEs will be categorized by primary system organ class and preferred term as coded using the MedDRA (with the version specified in Data Management Plan) category designations.

Treatment-emergent adverse events (TEAEs) are defined as AEs that start after the first dose of study drug.

Adverse events of special interest will be flagged in CRF.

An overview of AEs will be provided including counts and percentages of participants (and event counts) by treatment and in total with the following:

- Any TEAEs overall and by maximum severity
- Any study drug related TEAEs overall and by maximum severity
- Any TEAEs of special interest
- Any treatment-emergent serious AEs (TESAEs)
- Any study drug related TESAEs
- Any TEAEs leading to discontinuation of study drug
- Any AEs leading to death

Counts and percentages of participants (and event counts) will also be presented by system organ class and preferred term for each of the categories in the overview.

Listings will be presented specifically for TEAEs, TESAEs, TEAEs leading to discontinuation of study drug, and TEAEs of special interest.

3.7.2 Clinical Laboratory Tests

Blood and urine samples for clinical laboratory tests will be collected at timepoints indicated in Appendix A (Schedule of Procedures) of the study protocol and processed by a central laboratory. See Appendix B for a complete list of analytes.

Blood samples for chemistry and hematology must be obtained under fasting conditions (i.e., after the participant has fasted for approximately 8 hours). For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications. If a participant is not fasting, the Investigator should reschedule the visit as soon as possible. Estimated glomerular filtration rate will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. At the Screening Visit only, the chemistry panel will include HbA1c.

A urine pregnancy test will be performed for women of childbearing potential at the Screening Visit (Visit 1) prior to their participation in the study and at the Safety Follow-Up Visit (Visit 6), and the Early Termination Visit, if appropriate.

An FSH test will be performed at the Screening Visit prior to participation in the study in women <55 years of age for whom it has been ≥1 year since their last menstrual period to confirm a postmenopausal state.

For each laboratory test, values, changes from Baseline, percent change from Baseline will be presented at each scheduled visit and Baseline by treatment and in total. According to the availability of laboratory data, additional shift tables will be presented to describe the change in laboratory parameter values at post-Baseline visits using normal range categories (low, normal, and high).

3.7.3 Vital Signs

Vital signs will include body temperature, heart rate, and triplicate blood pressure (systolic and diastolic) measurements and measured at all scheduled timepoints. Participants should be in the supine position after at least 10 minutes rest prior to the vital sign measurements.

Weight and height will be measured at the Screening Visit and will be used to calculate body mass index as following:

$$BMI(kg/m^2) = weight(kg)/(height(m))^2$$

Measurement of weight should be performed with the participant dressed in indoor clothing, with shoes removed, and bladder empty.

Values and changes from Baseline will be summarized with descriptive statistics at each visit by treatment.

3.7.4 Electrocardiograms

A single, standard 12-lead ECG will be performed by the Investigator or trained site personnel at the Screening Visit and read locally. Summary statistics will be provided for the overall interpretation by treatment and in total. A separate data listing by participant will be provided for ECG data.

3.7.5 Physical Examinations

Physical examinations will be performed at Screening Visit and Visit 5. Data collected related to physical examinations will be listed.

3.7.6 Events of Special Interest

Liver-associated enzymes and total bilirubin will be summarized by the value and change from Baseline in the value, by treatment group and visit. In addition, the number and percent of participants with abnormal values for ALT, AST, and total bilirubin will be summarized. These summaries of participants with abnormal values will be performed overall; by normal Baseline; and by abnormal Baseline for ALT, AST, and total bilirubin individually. Hy's Law criteria (>3 × ULN for either ALT or AST, with accompanying total bilirubin >2 × ULN) will also be applied to the data. Any potential Hy's Law cases will be listed separately.

Muscle-related abnormalities will be summarized by treatment group. CK levels will be summarized by the value and change from Baseline in value, by treatment group and visit. In addition, the number and percent of participants with abnormal CK values will be summarized. These summaries of participants with abnormal CK values will be performed overall, by normal Baseline CK, and by abnormal Baseline CK.

Cases of NODM will be recorded and summarized using the appropriate system organ class. These events will be summarized by severity and relationship to study drug for each treatment group. Fasting plasma glucose and HbA1c will be monitored as specified in Appendix A (Schedule of Procedures) of the study protocol.

Baseline eGFR will be summarized by treatment group for actual value and for Baseline eGFR categories. Shift tables of eGFR category from Baseline to End of Treatment (EOT) will be provided by treatment group. Shift tables of urine albumin-creatinine ratio and urine protein creatinine ratio from Baseline to EOT will be provided by treatment group. Values of CK from Baseline to EOT will be summarized by treatment group and by Baseline eGFR category. Muscle related abnormalities will be summarized by treatment group and by Baseline eGFR category.

Cases of macular degeneration will be recorded and summarized using the appropriate system organ class. These events will be summarized by severity and relationship to study drug for each treatment group.

4 ANALYSIS TIMING

4.1 Interim Analysis

No interim analysis is planned for this study.

4.2 Final Analysis

Upon completion of the study (all enrolled participants have completed the double-blind treatment and Safety Follow-up periods or are withdrawn from the study), the database will be locked and the final analysis will be generated. The final analysis will be performed on all available efficacy and safety data as described in the above sections of the SAP. The corresponding TFLs will be provided after database lock. In addition to TFLs, SDTM data and ADaM data along with associated files will be provided. Associated files may include the following: annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and CDISC Define packages for both SDTM and ADaM data.

The result of this analysis will be used for the clinical study report.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

Following changes are made to the statistical analysis described in v1.1 of the protocol.

- mITT On-Treatment Population has been added to supportive analyses for the primary efficacy endpoint
- High-density lipoprotein-ApoE has been removed from lipid profile parameters.

Any deviations from the protocol or SAP will be described in the CSR.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in participant data listings which will be sorted by participant and visit date as applicable. Detailed Programming Specifications will be provided in a separate document.

APPENDIX A: REFERENCES

ICH guidance for industry E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials, 2017

APPENDIX B: LABORATORY TESTS

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate [1]
Gamma-glutamyl transferase	Glucose (fasting)
Glycosylated hemoglobin [2]	High-sensitivity C-reactive protein
Inorganic phosphorus	Lactate dehydrogenase
Lipase	Potassium
Sodium	Total bilirubin
Total protein	Uric acid

1. Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. (Source: CKD-EPI equations for glomerular filtration rate [GFR]. MDCalc. https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr. Accessed 19 November 2021.)
2. Screening Visit only.

Endocrinology

Follicle-stimulating hormone [1]

1. A follicle-stimulating hormone test will be performed in women <55 years of age for whom it has been ≥1 year since their last menstrual period.

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count

White blood cell count and differential [1]

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.

Pregnancy Test

Urine [1]

1. For women of childbearing potential only.

Lipid Profile

Apolipoprotein B
Low-density lipoprotein cholesterol [1]
Triglycerides
Apolipoprotein E (ApoE)
High-density lipoprotein cholesterol
Non-high-density lipoprotein cholesterol
Very low-density lipoprotein cholesterol

1. Calculated using the Friedewald equation unless triglycerides (TGs) ≥400 mg/dL or low-density lipoprotein cholesterol (LDL-C) ≤50 mg/dL. If TG ≥400 mg/dL or LDL-C ≤50 mg/dL, then LDL-C level will be measured directly by preparative ultracentrifugation, also referred to as beta quantification. (Source: LDL calculated. MDCalc. https://www.mdcalc.com/ldl-calculated. Accessed 19 November 2021.) In addition, for all participants, LDL-C will be measured by preparative ultracentrifugation, also referred to as beta quantification, at Baseline (Day 1; Visit 2) and at the end of the 8-week Treatment Period (Day 56; Visit 5).