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 High-Intensity Statin Therapy
Protocol Number:	TA-8995-201
Protocol Version/Date:	V2.0 / 26 January 2021
Investigational Product:	Obicetrapib
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SIGNATURE PAGE

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

Signature	**Date**
[redacted]	

VERSION HISTORY

Version	Version Date	Description
1.0	20 May 2021	Original signed version
2.0	07 July 2021	3.3.7 Definition of missing date of first dose of study drug, or last dose of study drug; The percent overall study drug compliance 4.2 End of Double-Blind Treatment Analysis 4.3 End of study analysis

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
ApoB	Apolipoprotein B
ApoC3	Apolipoprotein C3
ApoE	Apolipoprotein E
ANCOVA	Analysis of Covariance
ATC	Anatomical therapeutic chemical
CDISC	Clinical Data Interchange Standards Consortium
CETP	Cholesteryl ester transfer protein
CRF	Case report form
CRO	Clinical Research Organization
CSR	Clinical Study Report
ECG	Electrocardiogram
eCRF	Electronic case report form
FSH	Follicle-stimulating hormone
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
ICF	Informed consent form
IRT	Interactive response technology
ITT	Intent-to-Treat
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMRM	Mixed model for repeated measures
Non-HDL-C	Non-high-density lipoprotein cholesterol
PCSK9	Proprotein convertase subtilisin kexin type 9
PK	Pharmacokinetics
PP	Per-Protocol
PUC	Preparative ultracentrifugation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFLs	Tables, figures, and listings
TG	Triglycerides
VLDL-C	Very low-density lipoprotein cholesterol
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-8995-201. 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, at Day 56 in decreasing low-density lipoprotein cholesterol (LDL-C) as an adjunct to high-intensity statin therapy.

2.1.2 Secondary Objectives

The secondary objectives of this study include the following:

- To evaluate the effect of obicetrapib, compared to placebo, at Day 56 on apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), and high-density lipoprotein cholesterol (HDL-C), as an adjunct to high-intensity statin therapy;
- To assess the mean plasma levels of obicetrapib at steady state on Days 56, 84, 112, and Day 161; and
- To evaluate the safety and tolerability profile of obicetrapib.

2.2 Study Design

2.2.1 Overview

The population for this study includes men and women 18 to 75 years of age, inclusive, with a body mass index <40 kg/m^2, fasting LDL-C levels >70 mg/dL, and triglyceride levels <400 mg/dL at the Screening Visit, who are currently receiving high-intensity 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 high-intensity statin therapy. This study will take place at approximately 20 sites in the United States.

The total duration for the double-blind period for each subject will be up to 25 weeks, including up to 2 weeks for Screening, 8 weeks for blinded study treatment, 4 weeks for safety follow-up, and 11 weeks for PK assessments. Please refer to Table 1 (Schedule of Procedures) below for details.

At the Screening Visit (Visit 1), 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 114 eligible participants (38 participants per treatment group) will be randomized in a 1:1:1 ratio to 1 of the following treatment groups:

- 5 mg obicetrapib (one 5 mg obicetrapib tablet + 1 placebo tablet);

- 10 mg obicetrapib (two 5 mg obicetrapib tablets); or
- Placebo (2 placebo tablets).

During the 8-week Treatment Period, the assigned study drugs will be administered by the participants orally and once daily on Day 1 to Day 56. Participants will return to the site every 4 weeks for efficacy, safety, and pharmacokinetic (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 through database lock in order to protect blinding to treatment assignment.

Participants will return to the site for a Safety Follow-up Visit (Visit 5) approximately 4 weeks after the end of the Treatment Period for safety and PK assessments.

Participants will return to the site for 2 PK Visits (Visit 6 and 7) approximately 8 and 15 weeks, respectively, after the end of the Treatment Period for 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, including phone or video contact to assess the participant's well-being including any AE, collection of study samples and clinical data as best as possible, and direct shipment of study drug to participant, if necessary. Where available and appropriate, home health care may be considered to facilitate monitoring of safety and study continuity. Documentation of these cases and the site's management of participants should be recorded in the Investigator study files. In the absence of a COVID-19 impact, it is expected that Investigators and participants follow the protocol requirements as set forth.

Table 1. Schedule of Procedures

	Screening[a,b]	Treatment Period			Safety Follow-Up	PK		Early Termination Visit
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Week	**Up to -2**	**0**	**4**	**8**	**12**	**16**	**23**	
Day (± Visit Window)	**-14 to -1**	**1**	**28 (±2)**	**56 (±2)**	**84 (±2)**	**112 (±2)**	**161 (±2)**	**Unscheduled**
Informed consent[c]	X							
Inclusion/exclusion criteria	X	X[d]						
Demographic information	X							
Medical/surgical history	X							
Prior/concomitant medications	X	X	X	X	X			X
Weight and height[e]	X							
Physical examination	X			X				
Vital signs[f]	X	X	X	X	X			X
12-lead ECG[g]	X							
Urine pregnancy test[h]	X						X	X
FSH test[i]	X							
Fasting (approximately 10 hours) chemistry and hematology[j]	X	X	X	X	X	X	X	X
Fasting (approximately 10 hours) lipid profile[k]	X	X	X	X				X
PK sample[l]		X	X	X	X[m]	X	X	X
Randomization		X						
Dispense study drug		X	X					
Study drug administration[n]		X	X	X				
Study drug compliance			X	X				
Register visit in IRT	X	X	X	X				X
Adverse events		X	X	X	X	X	X	X

Note: When several assessments are required at the same visit, samples for clinical laboratory assessments should be collected after completing other assessments, such as physical examinations, vital signs, and 12-lead ECGs.

Note: In cases of COVID-19 limitations, it is the Investigator's responsibility to assure the safety of participants, including phone or video contact to assess the participant's well-being including any adverse event, collection of study samples and clinical data as best as possible, and direct shipment of study drug to participant, if necessary. Where available and appropriate, home health care may be considered to facilitate monitoring of safety and study continuity. Documentation of these cases and the site's management of participants should be recorded in the Investigator study files. In the absence of a COVID-19 impact, it is expected that Investigators and participants follow the protocol requirements as set forth.

a. If laboratory abnormalities during screening are considered by the Investigator to be transient, then the laboratory tests may be repeated once during screening. The Investigator's rationale for retesting should be documented. If the retest result is no longer exclusionary, the participant may be randomized.
b. A participant who is screened and does not meet the study eligibility criteria may be considered for rescreening upon Sponsor and/or Medical Monitor consultation and approval. Rescreened participants will be assigned a new participant number. Rescreening should occur no less than 5 days after the last Screening Visit.
c. Signed informed consent must be obtained before any study-related procedures are performed.
d. Confirm the participant continues to meet the inclusion and exclusion criteria and assess any updates since the Screening Visit.

e. Weight and height will be measured at the Screening Visit and will be used to calculate body mass index. Measurement of weight should be performed with the participant dressed in indoor clothing, with shoes removed, and bladder empty.
f. Vital signs will include body temperature, heart rate, and triplicate blood pressure (systolic and diastolic) measurements. Participants should be in the supine position after at least 10 minutes rest prior to the vital sign measurements.
g. A single, standard 12-lead ECG will be performed by the Investigator or trained site personnel at the Screening Visit and read locally.
h. For women of childbearing potential only.
i. FSH test will be performed in women <55 years of age for whom it has been ≥1 year since their last menstrual period.
j. At the Screening Visit only, chemistry panel will include HbA1c.
k. LDL-C level will be calculated using the Friedewald equation unless TG ≥400 mg/dL or LDL-C ≤50 mg/dL; in both cases, 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 09 November 2020.) In addition, for all patients, LDL-C will be measured by preparative ultracentrifugation, also referred to as beta quantification, at baseline (Visit 2) and at the end of the 8-week Treatment Period (Visit 4).
l. 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.
m. PK samples will not be collected during the Safety Follow-up Visit for participants who discontinue study drug early without withdrawing consent or for participants who withdraw prematurely from the study.
n. Two tablets of study drugs will be administered by the participant orally and once daily on Day 1 to Day 56. Study drugs should be administered at approximately the same time each morning, with food. On days with visits scheduled, study drugs should be administered with food following all fasted blood samples.

COVID-19 = Coronavirus Disease 2019; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = glycosylated hemoglobin; IRT = interactive response technology; LDL-C = low-density lipoprotein cholesterol; PK = pharmacokinetic; TG = triglycerides.

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 ratio to the 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 3 treatment groups.

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

2.2.3 Study Drug

The study drugs used in this study are as follows:

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

The study drugs listed above will be packaged to provide doses of 5 or 10 mg obicetrapib or placebo only. Participants will be randomized to receive 1 of the 2 doses of obicetrapib or placebo only. Two tablets of study drugs will be administered by the participant orally and once daily on Day 1 to Day 56 at approximately the same time each morning, with food.

Compliance to the study drug regimen will be evaluated by counting unused tablets. Participants will be instructed to bring all unused study drugs to the site at Visits 3 and 4. During the Treatment Period, if compliance is not between 80% and 120%, inclusive, the participant will be counselled about the importance of compliance to the regimen and protocol deviation documented. If the limits are exceeded at 2 consecutive visits, a decision will be made by the Investigator and Sponsor as to whether the participant should be withdrawn from the study.

2.2.4 Sample Size Determination

A sample size of at least 108 evaluable participants (ie, 36 participants per treatment group) will provide >90% power to detect a 30% difference in LDL-C reduction at Day 56 (standard deviation of 15%) for each of the obicetrapib groups compared to the placebo group at a 2-sided significance level of 0.025.

The sample size for this study was determined in order to provide sufficient power for the analyses of the primary efficacy endpoint described above. Therefore, assuming an approximately 5% dropout rate, enrollment of approximately 114 participants (ie, 38 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 (AEs).

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 28	28	2	42
Week 56	56	43	71
Safety Follow-up	84	72	98
PK Visit 1	112	99	137
PK Visit 2	161	138	

Unscheduled visits recorded on the CRF will not be re-assigned and will 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 Handling of Dropouts and Missing Data

Date Values

In cases of incomplete dates (e.g. 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.

3.1.6 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.

3.2 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 ITT (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 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 did not experience a major protocol deviation that potentially impacted 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.

3.2.4 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.

3.2.5 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 all randomized participants. 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 all randomized participants. 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 all randomized participants. Reasons for exclusion from PP population will also be summarized.

3.3.4 Demographic and Baseline Characteristics

Demographic and Baseline characteristics including age, race, ethnicity, sex, height, weight, body mass index, and stratification group (LDL-C value $\geq$100 or <100 mg/dL) will be summarized with descriptive statistics or counts and percentages of participant as appropriate by treatment and in total for the mITT Population. If they differ from the mITT Population, summaries will also be provided for the ITT Population, the PP Population and the Safety Population.

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) version 23.1. 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 all randomized participants.

3.3.6 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 (WHO Drug_Sept 2020G B3). 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 for the Safety Population. Days of exposure is defined as:

date of last dose of study drug – date of first dose + 1

For those whose date of first dose from the initial blister card dispensed was not available, the date of randomization will be used to assign the date of first dose. 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 and in total. 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:

$$100 \times \frac{number\ of\ actual\ tablets\ taken}{expected\ tablets\ taken},$$

Expected tablets taken = 2 × (the earliest date between the end of treatment date and the date of early termination – the date of randomization +1).

The number of actual tablets taken is the sum of number administered from each blister pack. If number administered from a blister pack is missing, the number administered is considered 16 for the compliance calculation.

A separate listing of derived exposure and compliance will be provided for all randomized participants.

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 and the PP Population as supportive analyses for selected endpoints.

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

1. At each scheduled visit, LDL-C will be calculated using the Friedewald equation unless TG≥400mg/dL or LDL-C≤50 mg/dL; in both cases, LDL-C level will be measured directly by preparative ultracentrifugation (PUC), also referred to as beta quantification [LDL calculated, 2020].
2. In addition, at Baseline (Day 1) and at the end of the 8-week Treatment Period (Day 56), LDL-C will be measured for all patients by PUC.

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 Baseline to each measurement taken at Day 28 and Day 56.

The percent change in LDL-C from Day 1 to Day 56 for each treatment is defined mathematically as μ_j, where j stands for the j^{th} treatment (j=0,1,2) and the subscript 0 refers to the placebo group. The hypotheses testing to the percent change in LDL-C from Day 1 to Day 56 is then defined statistically as following:

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

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 measures (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. Adjustment for multiple comparisons will be made using Dunnett's test in accordance with the power and sample size calculations utilized for the study.

The MMRM approach will include all available assessments of percent change in LDL-C from Baseline to 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 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.

For participants who are withdrawn from the study because of the use of a prohibited medication, data occurring after the intercurrent event of prohibited 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 (5 mg obicetrapib), 2 (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;
  adjust=DUNNETT;
run;
**************************************************************************************************
```

Sensitivity Analyses

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

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

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 Day 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 will be imputed. 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 28 and 56. For each imputation dataset, the percent change from baseline to Day 56 will be analyzed using the MMRM model described above. 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 two 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 (5 mg obicetrapib), 2 (10 mg obicetrapib)
  LDLC_BASE = LDL_C Baseline value
  LDLC_Day28 = LDL_C value at Day 28
  LDLC_Day56 = LDL_C value at Day 56
*************************************************************************************************************
proc mi data=LDLC_Wide seed=18032021 out=LDLC_25MCMC nimpute=25;
    var TREATMENT LDLC_base LDLC_Day28 LDL_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 (5 mg obicetrapib), 2 (10 mg obicetrapib)
  LDLC_BASE = LDL_C Baseline value
  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;
    monotone method=reg;
    var TREATMENT LDLC_base LDLC_Day28 LDL_Day56;
    by _Imputation_;
run;
*************************************************************************************************************
```

For each imputation dataset, the percent change from Baseline to 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 two obicetrapib will be provided. The treatment comparison will be performed using a 2-sided test at the α = 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 (5 mg obicetrapib), 2 (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 " 5 mg obicetrapib - Placebo"      TREATMENT -1 1 0;
  estimate " 10 mg obicetrapib - Placebo"     TREATMENT -1 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 will be measured by PUC. 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.

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. No adjustment will be made for multiplicity in testing the secondary efficacy endpoints. Nominal p-values will be provided when applicable. 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.

3.4.3 Other Efficacy Endpoints

The percent change from Day 1 to Day 56 in Apolipoprotein E (ApoE), High-density lipoprotein-ApoE, Triglycerides, and Very low-density lipoprotein cholesterol will be examined through similar MMRM models as described for the primary efficacy analyses.

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.

Blood samples for PK assessment will be collected as indicated in Table 1. 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 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.

3.6.1 Adverse Events (AEs)

AEs will be categorized by primary system organ class and preferred term as coded using the MedDRA (version 23.1) category designations. Summaries of AEs, including the count and percentage of participants who experience an AE, will be provided.

An overview of treatment-emergent AEs (TEAEs) will be provided including counts and percentages of participants (and event counts) with the following:

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

Listings will be presented for TEAEs, TESAEs and TEAEs leading to discontinuation of study drug. Counts and percentages of participants will also be presented by system organ class and preferred term for TEAEs, study drug related TEAEs and TESAEs.

3.6.2 Clinical Laboratory Tests

Blood samples for chemistry and hematology will be obtained as indicated in Table 1 and sent to a central laboratory for analysis. See Appendix B for a complete list of analytes. Blood samples for chemistry and hematology must be obtained under fasting conditions (ie, after the participant has fasted for approximately 10 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 [CKD-EPI equations for glomerular filtration rate (GFR), 2020]. 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 prior to their participation in the study, the last PK Visit (Visit 7), and the Early Termination Visit.

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

For each laboratory test, values and changes 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).

3.6.3 Vital Signs

Vital signs including body temperature, heart rate, and triplicate blood pressure will be measured at all scheduled visits except for Week 16 and 23 (the PK Visits). Height and weight will be measured at Screening only. Body mass index will be derived as $\mathrm{weight}/(\mathrm{height}/100)^2$ (kg/m^2) and displayed to 1 decimal place. Triplicate blood pressure measurements will be averaged for summary.

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

3.6.4 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.

3.6.5 Physical Examinations

Physical examinations will be performed at Screening Visit and Visit 4 (see Table 1). Data collected related to physical examinations will be listed.

4 ANALYSIS TIMING

4.1 Interim Analysis

No interim analysis is planned.

4.2 End of Double-Blind Treatment Analysis

An end of double-blind treatment analysis will be performed when all enrolled participants have completed the double-blind treatment and Safety Follow-up periods or are withdrawn from the study. The end of treatment analysis will be performed on all available efficacy and safety data as described in the above sections of the SAP.

The database, for the primary efficacy endpoint, will be locked before the end of treatment analysis is generated. After exclusions from analysis populations have been finalized, the randomized treatment assignments will be unblinded and the analysis will be generated. 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, and TFL programs.

The result of this analysis will be used to support regulatory submissions interactions.

4.3 End of Study Analysis

Upon completion of the study, the database will be locked and the final analysis will be generated. The end of study 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

This SAP does not deviate from the statistical analysis described in v2.0 of the protocol. 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. 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

LDL calculated. MDCalc. https://www.mdcalc.com/ldl-calculated. Accessed 09 November 2020.

CKD-EPI equations for glomerular filtration rate (GFR). MDCalc. https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr. Accessed 09 November 2020.

APPENDIX B: CLINICAL LABORATORY ANALYTES

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

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 09 November 2020.)

Screening Visit only.

Endocrinology

Follicle-stimulating hormone [1]

1. 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	Apolipoprotein E (ApoE)
High-density lipoprotein-ApoE [1]	High-density lipoprotein cholesterol
Low-density lipoprotein cholesterol [2]	Non-high-density lipoprotein cholesterol
Triglycerides	Very low-density lipoprotein cholesterol

1. With and without apolipoprotein C3.
2. Calculated using the Friedewald equation unless triglycerides ≥400 mg/dL or low-density lipoprotein cholesterol (LDL-C) ≤50 mg/dL; in both cases, 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 09 November 2020.) In addition, for all patients, LDL-C will be measured by preparative ultracentrifugation, also referred to as beta quantification, at Baseline (Visit 2) and at the end of the 8-week Treatment Period (Visit 4).