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STATISTICAL ANALYSIS PLAN

Protocol Title:	A Placebo-Controlled, Double-Blind, Randomized, Phase 2 Study to Evaluate the Effect of Obicetrapib 10 mg Daily in Combination With Ezetimibe 10 mg Daily as an Adjunct to High-Intensity Statin Therapy: The ROSE2 Study
Protocol Number:	TA-8995-202
Protocol Version/Date:	1.0 / 16 September 2021
Investigational Product:	Obicetrapib
Sponsor:	NewAmsterdam Pharma BV Gooimeer 2-35 1411 DC Naarden The Netherlands
SAP Version/Date:	1.0 / 20 December 2022

NCT number: NCT05266586
This NCT number has been applied to the document for the purposes of posting on clinicaltrials.gov

SIGNATURE PAGE

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

VERSION HISTORY

Version	Version Date	Description
1.0	20 December 2022	Version 1

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
ANCOVA	Analysis of Covariance
ApoB	Apolipoprotein B
ApoE	Apolipoprotein E
ATC	Anatomical therapeutic chemical
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
COVID-19	Coronavirus Disease 2019
CRF	Case report form
CRO	Clinical Research Organization
CSR	Clinical Study Report
eCRF	electronic case report form
ECG	Electrocardiogram
EOT	End of Treatment
ET	Early Termination
FSH	Follicle-stimulating hormone
FUP	Follow-Up
HbA1c	Glycosylated hemoglobin
HDL-C	High-density lipoprotein cholesterol
ICF	Informed Consent Form
IRT	Interactive response technology
ITT	Intent-to-Treat
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein (a)
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified Intent-to-Treat
MMRM	Mixed model for repeated measures
MNAR	Missing not at random
non-HDL-C	Non-high-density lipoprotein cholesterol
PK	Pharmacokinetics
PP	Per-Protocol
PT	Preferred term
PUC	Preparative ultracentrifugation
REML	Restricted maximum likelihood estimation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFL	Tables, figures, and listings
TG	Triglyceride(s)

Abbreviation	Definition
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 the study with protocol number TA-8995-202. 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 effect of obicetrapib 10 mg + ezetimibe 10 mg combination therapy compared with placebo, when used as an adjunct to high-intensity statin therapy, on low-density lipoprotein cholesterol (LDL-C) at Day 84.

2.1.2 Secondary Objectives

The secondary objectives of this study include the following, in hierarchical order:

- To evaluate the effect of obicetrapib 10 mg monotherapy compared with placebo, when used as an adjunct to high-intensity statin therapy, on LDL-C at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg combination therapy compared with placebo, when used as an adjunct to high-intensity statin therapy, on Apolipoprotein B (ApoB) at Day 84; and
- To evaluate the effect of obicetrapib 10 mg monotherapy compared with placebo, when used as an adjunct to high-intensity statin therapy, on ApoB at Day 84.

2.1.3 Exploratory Objectives

The exploratory objectives of this study include the following:

- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg combination therapy and obicetrapib 10 mg monotherapy, when used as an adjunct to high-intensity statin therapy, on non-high-density lipoprotein cholesterol (non-HDL-C), very low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), Apolipoprotein E (ApoE), Lipoprotein (a) [Lp(a)], and HDL-ApoE at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg combination therapy and obicetrapib 10 mg monotherapy, when used as an adjunct to high-intensity statin therapy, on the proportion of participants achieving predefined LDL-C targets at Day 84;
- To assess the mean trough plasma levels of obicetrapib 10 mg + ezetimibe 10 mg combination therapy and obicetrapib 10 mg monotherapy at steady state on Days 28, 84 and 112; and
- To evaluate the safety and tolerability profiles of obicetrapib 10 mg + ezetimibe 10 mg combination therapy and obicetrapib 10 mg monotherapy, when used as an adjunct to high-intensity statin therapy, assessed by clinical laboratory values and incidences of adverse events (AEs).

2.2 Study Design

2.2.1 Overview

This study is a placebo-controlled, double-blind, randomized, Phase 2 study to evaluate the efficacy, safety, and tolerability of obicetrapib 10 mg, both in combination with ezetimibe 10 mg and as monotherapy, as an adjunct to high-intensity statin therapy.

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:

- Combination therapy: Obicetrapib 10 mg + ezetimibe 10 mg (administered as one 10 mg obicetrapib tablet and one 10 mg ezetimibe capsule);
- Obicetrapib monotherapy: Obicetrapib 10 mg (administered as one 10 mg obicetrapib tablet and 1 placebo capsule); or
- Placebo (administered as 1 placebo tablet and 1 placebo capsule).

Randomization will be stratified according to LDL-C levels (≥100 or <100 mg/dL).

During the 12-week Treatment Period, the assigned study drugs will be administered by the participants, once daily on Day 1 to Day 84 at approximately the same time each morning. Participants will return to the site on Day 28 (±2 days), Day 84 (±2 days) and Day 112 (±2 days) for efficacy, safety, and pharmacokinetic (PK) assessments. Participants, Investigators, and the Clinical Research Organization (CRO), and the Sponsor will be blinded to all lipid results from Day 1 (Visit 2) for the first participant until all enrolled participants complete the Day 84 (End of Treatment [EOT]) visit or are withdrawn from the study, in order to protect blinding to treatment assignment.

Participants will return to the site for a Safety Follow-Up (FUP) Visit (Day 112; Visit 5) approximately 4 weeks after the end of the Treatment Period for safety and PK assessments.

Refer to Table 1 Schedule of Procedures for further details.

2.2.2 Sample Size Determination

A sample size of at least 108 evaluable participants (i.e., 36 participants per treatment group) will provide >90% power to detect a 30% difference in LDL-C reduction at Day 84 (SD of 15%) for each of the obicetrapib treatment groups compared with the placebo group at a 1-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 and first secondary efficacy endpoints. Therefore, assuming an approximately 5% dropout rate, enrollment of approximately 114 participants (i.e., 38 participants per treatment group) was planned for this study. This sample size will also contribute sufficient participant exposure and safety date.

Table 1 Schedule of Procedures

	Screening[a,b]	Treatment Period			Safety FUP	Early Termination (ET) Visit
Visit	**1**	**2 (Baseline)**	**3**	**4 (EOT)**	**5**	
Week	**Up to -2**	**0**	**4**	**12**	**16**	
Day (± Visit Window)	**-14 to -1**	**1**	**28 (±2)**	**84 (±2)**	**112 (±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
FSH test[i]	X					
Fasting (approximately 10 hours) chemistry and hematology[j]	X	X	X	X	X	X
Fasting (approximately 10 hours) lipid profile[k]	X	X	X	X	X	X
PK sample[l]		X	X	X	X[m]	X
Fasting (approximately 10 hours) aldosterone		X	X	X	X	X
Fasting (approximately 10 hours) Lp(a)		X		X		
Serum archive sample[n]		X		X		
Randomization		X				
Dispense study drug[o]		X	X			
Study drug administration[p]		---------- X ----------				
Study drug compliance			X	X		
Register visit in IRT	X	X	X	X	X	X
Adverse events		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 all 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. If necessary , the Sponsor will implement, and document mitigation strategies as described in Section 3.1.4 of the Protocol. In the absence of a COVID-19 impact, it is expected that Investigators and participants follow the protocol requirements set forth.
Note: For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications.

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 can 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. Participants will be required to sign an Informed Consent Form (ICF) 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 (BMI). 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 vial sign measurements.
g. A single, standard 12-lead Electrocardiogram (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 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 (PUC), also referred to as beta quantification. Additionally, LDL-C will be measured by preparative ultracentrifugation, also referred to as beta quantification, at baseline (Visit 2; Day 1) and at the end of the 12-week Treatment Period (Visit 4; Day 84) for all participants.
l. At visits with dosing scheduled (i.e., Visits 2, 3 and 4; Days 1, 28 and 84), PK samples will be collected with fasting laboratory samples (pre-dose). At Visits 3 and 4 (Days 28 and 84), the time between the last dose of study drug and PK sampling will be > 24 hours. The subsequent post-dose PK sample at Visit 5 (Safety FUP) should be collected at approximately the same time as the previous visits.
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. A serum archive sample will be obtained and stored for future analysis. If the sample is analyzed, it will be for non-genetic tests.
o. At Visit 2 (Day 1) , participants will receive 1 kit (containing 32 obicetrapib tablets or matching placebo tablets and 32 ezetimibe capsules or matching placebo capsules totaling 64 tablets/capsules per kit) with the study drugs appropriate for the participant's treatment group. At Visit 3 (Day 28), participants will receive 2 kits as described above. Each kit will provide a sufficient supply for 28 days of dosing, with enough for an extra 4 days of dosing in case the participant needs to postpone the next visit. Participants will be instructed to take 2 units from the kit each day. The kit will be clearly labelled to indicate which tablets/capsules to use one each day/ Participants will be instructed to bring all unused study drugs to the site at the next visit.
p. Study drugs (1 tablet and 1 capsule) will be administered by the participant orally with water, once daily on Day 1 to Day 84 at approximately the same time each morning. On days with visits scheduled, study drugs should be administered with water following all fasted blood samples. At Visits 3 and 4 (Days 28 and 84), participants will dose form the kit received at the previous visit (Visits 2 and 3 [Days 1 and 28], respectively).

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the percent change from Day 1 to Day 84 in LDL-C for the obicetrapib 10 mg + ezetimibe 10 mg combination treatment group compared with the placebo group.

Blood samples for the lipid profile must be obtained under fasting conditions (i.e., after the participant has fasted for approximately 10 hours).

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. Additionally, LDL-C will be measured by preparative ultracentrifugation at baseline (Visit 2; Day 1) and at the end of the 12-week Treatment Period (Visit 4; Day 84) for all participants.

2.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following, in hierarchical order:

- Percent change from Day 1 to Day 84 in LDL-C for the obicetrapib monotherapy treatment group compared with the placebo group;
- Percent change from Day 1 to Day 84 in ApoB for the obicetrapib 10 mg + ezetimibe 10 mg combination treatment group compared with the placebo group; and
- Percent change from Day 1 to Day 84 in ApoB for the obicetrapib 10 mg monotherapy treatment group compared with the placebo group.

2.3.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include the following:

- Percent change from Day 1 to Day 84 in non-HDL, VLDL-C, HDL-C, TG, ApoE, Lp(a), and HDL-APOE for the obicetrapib 10 mg + ezetimibe 10 mg combination treatment group compared with the placebo group and for the obicetrapib 10 mg monotherapy group compared with the placebo group;
- Proportion of participants at Day 84 that achieve LDL-C <2.6 mmol/L (<100 mg/dL), LDL-C <1.8 mmol/L (<70 mg/dL), and LDL-C <1.4 mmol/L (<55 mg/dL) for the obicetrapib 10 mg + ezetimibe combination treatment group compared with the placebo group and for the obicetrapib 10 mg monotherapy treatment group compared with the placebo group;
- Percent change from Day 1 to Day 84 in HDL particles (total), IDL particles, LDL particles (total) and VLDL/Chylomicron particles for the obicetrapib 10 mg + ezetimibe 10 mg combination treatment group compared with the placebo group and for the obicetrapib 10 mg monotherapy group compared with the placebo group; and
- Percent change from Day 1 to Day 84 in PCSK9 for the obicetrapib 10 mg + ezetimibe 10 mg combination treatment group compared with the placebo group and for the obicetrapib 10 mg monotherapy group compared with the placebo group.

2.3.4 Pharmacokinetic Endpoints

The PK endpoint is plasma obicetrapib concentrations in combination with ezetimibe and as monotherapy at Days 28, 84 and 112. PK samples will be collected with fasting laboratory samples (pre-dose on Days 28 and 84 and >24 hours after last dose of study drug).

2.3.5 Safety Endpoints

The safety and tolerability profiles of the obicetrapib 10 mg + ezetimibe 10 mg combination treatment group, obicetrapib 10 mg monotherapy treatment group, and the placebo group will be assessed by clinical laboratory values and the incidence of 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 (ET) 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
Day 28	28	2	56
Day 84 (EOT)	84	57	98
Day 112 (Safety FUP)	112	99	

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

3.1.3 Definition of Baseline

Unless otherwise stated, baseline is 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-centre 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., 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 date 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 methods (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 ITT Population is defined as 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 mITT Population is defined as 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 (Visit 5; Day 112) 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 PP Population is defined as all participants in the mITT Population who have a Day 84 value for the LDL-C assessment, and who did not experience a major protocol deviation that could potentially impact the primary efficacy endpoint. The PP Population, along with the reason for exclusion, will be finalized prior to study unblinding.

3.2.4 Pharmacokinetic (PK) Population

The PK Population is defined as 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 is defined as 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 analysis.

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 treatment, discontinue treatment (including primary reason for discontinuation), complete the study, prematurely discontinue from the study (including primary reason for discontinuation) will be summarized by treatment group 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 group and overall. 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 group 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 group and overall based on all randomized participants. Reasons for exclusion from the PP Population will also be summarized.

A listing detail participants inclusion in each of the study populations will be provided.

3.3.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics including age, race, ethnicity, sex, height, weight, body mass index (BMI), and stratification group (LDL-C value ≥100 or <100 mg/dL) will be summarized with descriptive statistics or counts and percentages of participants as appropriate by treatment group and overall, 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.

All demographic and baseline characteristic data will be provided in participant listings.

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 24.1. Counts and percentages of participants with medical history by system organ class (SOC) and preferred term (PT) will be summarized by treatment and overall based on all randomized participants.

A listing of all medical history data will be provided.

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 drug. Prior medications are defined as those used prior to and stopped before the first dose of study drug. All prior and concomitant medication verbatim terms will be coded using the World Health Organization (WHO) Drug Dictionary (WHO Drug B3 Global, September 2021). The numbers and percentages of participants taking prior and concomitant medications in each treatment group and overall will be summarized by anatomical therapeutic chemical (ATC) class and preferred term for the Safety Population.

All medications will be listed and flagged as either prior or concomitant.

3.3.7 Study Drug Exposure and Compliance

Participants' exposure to randomized study drug 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, 8 - <12 weeks and 12+ weeks.

Summary statistics will be presented for overall compliance to study drug by treatment group 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 obicetrapib tablets will be calculated as:

$$100 \times \frac{actual\ tablets\ taken}{expected\ study\ drug\ taken},$$

The percent overall compliance to ezetimibe capsules will be calculated as:

$$100 \times \frac{actual\ capsules\ taken}{expected\ study\ drug\ taken},$$

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

$$100 \times \frac{actual\ study\ drug\ taken}{expected\ study\ drug\ taken\ x\ 2},$$

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

The actual study drug taken is reported on the electronic case report form (eCRF). If no kits are returned, it will be assumed that all study drug from that kit were used.

Listings of drug accountability and 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 approaches:

1. At each scheduled visit, LDL-C will be calculated using the Friedewald equation unless triglycerides ≥400 mg/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.
2. In addition, for all participants, LDL-C will be measured by PUC, at baseline (Visit 2, Day 1) and at the end of the 12-week Treatment Period (Visit 4, Day 84).

3.4.1 Primary Efficacy Endpoints

Primary Analysis

The primary efficacy endpoint is the percent change from Day 1 to Day 84 in LDL-C (as determined by approach 1 above) for the combination treatment group compared to the placebo group. The percent change will be calculated from Day 1 (Baseline) to each measurement taken at Day 28 and Day 84.

The percent change in LDL-C from Day 1 to Day 84 for each treatment group is defined mathematically as μ_j, where j stands for the jth 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 84 is then defined statistically as following:

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

LDL-C values will be summarized by visit and treatment group; visit values, change from baseline and percent change from baseline will be summarized. Missing data patterns in the LDL-C values will also be summarized by treatment group.

The analysis of the percent change from Day 1 to Day 84 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. Randomization was stratified according to Screening Visit LDL-C value (≥100 or <100 mg/dL) to ensure a similar distribution of LDL-C values across all treatment groups. However, the MMRM model will include the original scale of the baseline LDL-C values as continuous covariate.

The Restricted Maximum Likelihood estimation approach (REML) will be used with an unstructured covariance matrix. The least-squares means (LSMean), standard errors, and 2-sided 95% confidence intervals for the combination treatment group and for the comparison of the combination treatment group to the placebo group will be provided.

The MMRM approach will include all available assessments of percent change in LDL-C from Day 1 to Day 28 and Day 84. The model assumes that 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 analysis.

The primary analysis will be conducted for the mITT, ITT, and PP Populations.

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

```
**************************************************************************************************
Note:
  USUBJID = unique subject identifier
  TREATMENT = 0 (Placebo),  1 (Obicetrapib monotherapy), 2 (Combination therapy)
  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;

**************************************************************************************************
```

Sensitivity Analyses

Four 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
4. MMRM (no imputation) using LDL-C by Martin/Hopkins Calculation

All sensitivity analyses will be conducted on the mITT Population.

Sensitivity Analysis 1

The first sensitivity analysis will impute missing data using a control-based pattern imputation model assuming the data are missing not at random (MNAR). The multiple imputation will be performed such that only observations from the placebo group are used to derive the imputation model for missing LDL-C values. Missing data at Day 28 and 84 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 84. For each imputation dataset, the percent change from baseline to Day 84 will be analyzed using the MMRM model described above 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 (combination treatment – 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 (Obicetrapib monotherapy), 2 (Combination therapy)
  LDLC_BASE = LDL_C Baseline value
  LDLC_Day28 = LDL_C value at Day 28
  LDLC_Day84 = LDL_C value at Day 84
*************************************************************************************************************
proc mi data=LDLC_Wide seed=18032021 out=LDLC_25MCMC nimpute=25;
    var TREATMENT LDLC_base LDLC_Day28 LDL_Day84;
    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 (Obicetrapib monotherapy), 2 (Combination therapy)
  LDLC_BASE = LDL_C Baseline value
  LDLC_Day28 = LDL_C value at Day 28
  LDLC_Day84 = LDL_C value at Day 84
*************************************************************************************************************
proc mi data= LDLC_25MCMC seed=810456 out= LDLC_Mono nimpute=1 simple;
    monotone method=reg;
    class TREATMENT;
    var LDLC_base LDLC_Day28 LDL_Day84;
    by _Imputation_;
    mnar model (LDLC_Day28 LDL_Day84 / modelobs=(TREATMENT=0);
run;
*************************************************************************************************************
```

For each imputation dataset, the percent change from baseline to Day 84 will be analyzed using a 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 84 in LDL-C (as determined by approach 1 above) for the combination treatment group compared to the placebo group will be analyzed using an 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 the combination treatment group and for the comparison of the combination treatment group to the placebo group will be provided. The treatment comparison (combination treatment – placebo) 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 (Obicetrapib monotherapy), 2 (Combination therapy)
  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 " Combination - Placebo"        TREATMENT -1 0  1;
run;
**************************************************************************************************
```

Sensitivity Analysis 3

In the third sensitivity analysis, the percent change from Day 1 to Day 84 in LDL-C will be assessed where the LDL-C values will be measured by PUC. The percent change from Day 1 to Day 84 in LDL-C by PUC for the combination treatment group compared to the placebo group will be analyzed using an ANCOVA model similar to the model described in the second sensitivity analysis. No imputation of missing data will be performed for this sensitivity analysis.

Sensitivity Analysis 4

In the fourth sensitivity analysis, the percent change from Day 1 to Day 84 in LDL-C will be assessed where the LDL-C values will be derived using the Martin/Hopkins calculation. A similar MMRM model as described for the primary analysis will be used.

3.4.2 Secondary Efficacy Endpoints

Similar MMRM models as described for the primary analyses will be used to analyze the secondary efficacy endpoints. In order to maintain the overall Type 1 error rate, the secondary efficacy endpoints will be tested sequentially at the 0.05 significance level according to the order of hierarchy specified below:

- Percent change from Day 1 to Day 84 in LDL-C for the obicetrapib monotherapy treatment group compared with the placebo group;
- Percent change from Day 1 to Day 84 in ApoB for the combination treatment group compared with the placebo group; and

- Percent change from Day 1 to Day 84 in ApoB for the obicetrapib monotherapy treatment group compared to the placebo group.

3.4.3 Exploratory Efficacy Endpoints

Similar MMRM models as described for the primary analyses will be used to assess the percent change from Day 1 to Day 84 in non-HDL-C, VLDL-C, HDL-C, TG, ApoE and Lp(a).

The proportion of participants at Day 84 that achieve LDL-C <2.6 mmol/L (<100 mg/dL), LDL-C <1.8 mmol/L (<70 mg/dL), and LDL-C <1.4 mmol/L (<55 mg/dL) will be examined through Logistic Regression Models with covariates of treatment group and the baseline LDL-C value.

The Logistic Regression Model will be implemented using SAS® Proc LOGISTIC. The sample SAS code can be found below:

```
**********************************************************************************************************
Note:
  USUBJID = unique subject identifier
  TREATMENT = = 0 (Placebo),  1 (Obicetrapib monotherapy), 2 (Combination therapy)
  BASE = Baseline value
  LDLC100 = LDL_C value less than 100mg/dL at DAY84 (YES/NO) for example
**********************************************************************************************************
proc logistic data= LDL_C;
     Class TREATMENT(ref=0) / Param= Ref;
     Model LDLC100= TREATMENT BASE / alpha=0.05 expb plcl plrl orpvalue lackfit;
    Ods output
          ParameterEstimates= Log_LDLC100_ParameterEstimates
          CLoddsPL= Log_ LDLC100_OddsRatios
          ;
Run;
**********************************************************************************************************
```

Similar ANCOVA models as described in the secondary sensitivity analysis for the primary analyses will be used to assess the percent change from Day 1 to Day 84 in HDL particles (total), IDL particles, LDL particles (total), VLDL/Chylomicron particles and PCSK9.

No adjustments will be made for multiplicity in testing the exploratory endpoints. Nominal p-values will be provided.

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.

3.6 Safety Assessment

The Safety Population will be the primary population for the safety analyses. All safety endpoints will be summarized descriptively by treatment group and overall. 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 24.1) category designations.

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

The TEAEs described above will be summarized separately by System Organ Class and Preferred Term.

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

3.6.2 Clinical Laboratory Tests

Blood for chemistry and hematology will be obtained as indicated in Table 1 Schedule of Procedures and sent to a central laboratory for analysis. See Appendix A 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 ≥10 hours).

Laboratory values will be summarized descriptively, including the change and percent change from baseline. In addition, 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).

All safety laboratory data will be presented in participants listings.

3.6.3 Vital Signs

Vital signs including body temperature, heart rate, and triplicate blood pressure will be measured at all scheduled visits. Triplicate blood pressure measurements will be averaged for analysis.

Values and changes from baseline will be summarized with descriptive statistics at each visit.

Separate plots will be provided for the change from baseline in systolic and diastolic blood pressure by visit.

Height and weight will be measured at the Screening Visit only. Body Mass Index (BMI) will be derived as $\mathrm{weight}/(\mathrm{height}/100)^2$ (kg/m^2); rounded and displayed to 1 decimal place.

3.6.4 Electrocardiograms

A single, standard 12-lead ECG will be performed on-site at the Screening Visit and read locally.

ECG data will be summarized with descriptive statistics and presented in participant listings.

3.6.5 Physical Examinations

Physical examinations will be performed at the Screening Visit and at Day 84. Data collected related to physical examinations will be listed.

4 ANALYSIS TIMING

4.1 Interim Analysis

No interim analysis is planned.

4.2 Pre-Final Analysis

After the database is locked and exclusions from analysis populations have been finalized, the randomized treatment assignments will be unblinded and the pre-final analysis will be generated. Pre-final tables, figures, and listings (TFLs) will be provided approximately 3 weeks after database lock.

4.3 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. Final TFLs will be provided approximately 1 week after the study database is declared final. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final. In addition to TFLs, SDTM data and ADaM data along with associated files will be provided. Associated files may include 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.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

There have been three changes from the protocol defined exploratory endpoints.

The first change relates to the LDL-C response definition. The protocol includes:

- Proportion of participants at Day 84 that achieve LDL-C <2.6 mmol/L (<100 mg/dL), LDL-C <1.8 mmol/L (<70 mg/dL), and LDL-C <1.3 mmol/L (<50 mg/dL) for the obicetrapib 10 mg + ezetimibe combination treatment group compared with the placebo group and for the obicetrapib 10 mg monotherapy treatment group compared with the placebo group.

Within the SAP, the lower threshold has been updated to LDL-C <1.4 mmol/L (<55 mg/dL) to reflect the targets described in the 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk.

The second changes relates to the exploratory endpoint, HDL-ApoE. The laboratory assessment corresponding to the protocol defined exploratory endpoint of HDL-ApoE was determined to be invalid. As a result, the planned assessment of this endpoint was not performed.

The third change is the addition of the exploratory endpoints – HDL particles (total), IDL particles, LDL particles (total), VLDL/Chylomicron particles and PCSK9.

6 PROGRAMMING SPECIFICATIONS

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

APPENDIX A: 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.
2. Screening Visit only

Endocrinology

Aldosterone	Follicle-stimulating hormone [1]
Urine pregnancy test [2]	

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.
2. For women of childbearing potential only.

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.

Lipid Profile

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

1. LDL-C will be 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 (PUC), also referred to as beta quantification.

Other Laboratory Analytes

Lipoprotein (a)