STATISTICAL ANALYSIS PLAN

Protocol Title:	A Placebo-Controlled, Double-Blind Randomized, Phase 3 Study to Evaluate the Effect of Obicetrapib 10 mg and Ezetimibe 10 mg Fixed Dose Combination Daily on Top of Maximally Tolerated Lipid-Modifying Therapy in Participants With Heterozygous Familial Hypercholesterolemia (HeFH) and/or Atherosclerotic Cardiovascular Disease (ASCVD) or Multiple ASCVD Risk Factors
Protocol Number:	OBEZ-301
Protocol Version/Date:	4.0/09 OCT 2024
Investigational Product:	Obicetrapib 10 mg + ezetimibe 10 mg fixed dose combination (FDC)
Sponsor:	NewAmsterdam Pharma B.V. Gooimeer 2-35 1411 DC Naarden The Netherlands
SAP Version/Date:	2.0/22-OCT-2024

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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	13 May 2024	First Version
2.0	22 October 2024	Updates following protocol amendment, minor clarifications, and corrections of typing errors

Version 2.0 (22-OCT-2024): Summary of changes from SAP Version 1.0 (13-MAY-2024)

Section	Change*	Rationale
2.1 and 2.3	Adding an additional co-primary endpoint and additional secondary and exploratory endpoints	Following the protocol amendment
3.4.1	A third sensitivity analysis added for the primary efficacy endpoint	A sensitivity analysis using the last observation carried forward was added to better assess the robustness of the results of primary analysis

*Please note that minor clarification, updates, and corrections of typing errors are not listed.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case report form
CSR	Clinical Study Report
CV	Cardiovascular
CK	Creatine kinase
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
ESI	Event of special interest
ET	Early Termination
FAS	Full Analysis Set
FDC	Fixed dose combination
HbA1c	Glycated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HIS	High intensity statin
ICF	Informed consent form
ITT	Intent-to-Treat
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein (a)
LS	Least squares
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
NMR	Nuclear magnetic resonance
NODM	New-onset diabetes mellitus
Non-HDL-C	Non-high-density lipoprotein cholesterol
PK	Pharmacokinetics
PP	Per-Protocol
PT	Preferred term
PUC	Preparative ultracentrifugation

Abbreviation	Definition
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	System organ class
TC	Total cholesterol
TFL	Tables, figures, and listings
TG	Triglycerides
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
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 OBEZ-301. 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 fixed dose combination (FDC) therapy on LDL-C at Day 84, compared with each of the following:

- Placebo;
- Ezetimibe 10 mg monotherapy; and
- Obicetrapib 10 mg monotherapy.

And to evaluate the effect of obicetrapib 10 mg monotherapy on LDL-C at Day 84 compared with placebo.

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 + ezetimibe 10 mg FDC therapy compared with placebo on non-high-density lipoprotein cholesterol (non-HDL-C) at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with placebo on apolipoprotein B (ApoB) at Day 84;
- To evaluate the effect of obicetrapib 10 mg monotherapy compared with placebo on non-HDL-C at Day 84;
- To evaluate the effect of obicetrapib 10 mg monotherapy compared with placebo on ApoB at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with ezetimibe 10 mg on non-HDL-C at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with ezetimibe 10 mg on ApoB at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with obicetrapib 10 mg monotherapy on non-HDL-C at Day 84; and
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with obicetrapib 10 mg monotherapy 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 FDC therapy compared with placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy and the effect of obicetrapib 10 mg monotherapy compared with placebo on very low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), lipoprotein (a) (Lp(a)), and small dense low-density lipoprotein cholesterol (sdLDL-C) at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy and the effect of obicetrapib 10 mg monotherapy compared with placebo on LDL-C, HDL-C, and VLDL-C particle numbers and size, as measured by nuclear magnetic resonance (NMR) analysis, at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy and the effect of obicetrapib 10 mg monotherapy compared with placebo on the proportion of participants achieving predefined LDL-C targets at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy and the effect of obicetrapib 10 mg monotherapy compared with placebo on LDL-C at Day 28;
- To evaluate the safety of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy, obicetrapib 10 mg monotherapy, and ezetimibe 10 mg monotherapy, assessed by clinical laboratory values and incidence of adverse events (AEs); and
- To assess the mean trough plasma levels of obicetrapib and/or ezetimibe after obicetrapib 10 mg + ezetimibe 10 mg FDC therapy, obicetrapib 10 mg monotherapy, and ezetimibe 10 mg monotherapy on Days 28 and 84.

2.2 Study Design

2.2.1 Overview

This study is a placebo-controlled, double-blind, randomized, Phase 3 study to evaluate the efficacy, safety, and tolerability of obicetrapib 10 mg, both as an FDC with ezetimibe 10 mg and as monotherapy, on top of maximally tolerated lipid-modifying therapy. This study will take place at approximately 60 sites.

Screening Period

At Screening (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.

Treatment Period

Up to 2 weeks after Screening (Visit 1), participants will return to the site on Visit 2 (Day 1) and confirm study eligibility before being randomized and beginning treatment. Approximately 400 eligible participants (100 participants per treatment group) will be randomized in a 1:1:1:1 ratio to 1 of the following treatment groups:

- FDC therapy: Obicetrapib 10 mg + ezetimibe 10 mg;
- Obicetrapib monotherapy: Obicetrapib 10 mg;

- Ezetimibe monotherapy: Ezetimibe 10 mg; or
- Placebo.

Approximately 70% of the participants enrolled into this study should be taking high intensity statins (HIS). No more than approximately 10% of participants in this study will be completely statin intolerant.

Participants without underlying HeFH or a history of ASCVD but with multiple ASCVD risk factors will comprise a maximum of 30% of the total participants enrolled into the study. Participants with only HeFH will comprise a maximum of 20% of the total participants enrolled into the study.

During the 12-week Treatment Period, the assigned study drugs will be administered by the participants orally with water, with or without food, once daily on Day 1 to Day 84 at approximately the same time each morning. Participants will return to the site on Visit 3 (Day 28) (±7 days) and Visit 4 (Day 84) (±7 days) for efficacy and safety assessments. Participants, Investigators, the Clinical Research Organization, and the Sponsor will be blinded to all lipid results from Day 1 (Visit 2) for the first participant until the database is locked in order to protect blinding to treatment assignment.

Safety Follow-Up Period

Participants will return to the site for a Safety Follow-up Visit (Visit 5 [Day 112]) approximately 4 weeks after the end of the Treatment Period for safety assessments.

Refer to Table 1 Schedule of Procedures for a complete list of procedures to be completed at each study visit.

2.2.2 Sample Size Determination

A sample size of at least 380 evaluable participants (ie, 95 participants per treatment group) will provide more than 90% power to detect a 30% difference in LDL-C reduction at Day 84 (SD of 25%) for the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group 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 (>90%) for the analyses of the co-primary endpoints described above. A sample size of at least 380 evaluable participants (ie, 95 participants per treatment group) will provide more than 90% power to detect a 20% difference in LDL-C reduction at Day 84 for the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with the ezetimibe 10 mg monotherapy treatment group, and it will provide more than 90% power to detect a 12% difference in LDL-C reduction at Day 84 for the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with the obicetrapib 10 mg monotherapy treatment group, assuming an SD of 25% at a 1-sided significance level of 0.025.

In addition, the sample of 95 participants in the obicetrapib 10 mg monotherapy treatment group will provide more than 90% power to detect a 15% difference in LDL-C reduction at Day 84 compared with the placebo treatment group.

Therefore, assuming an approximately 5% dropout rate, enrollment of approximately 400 participants (ie, 100 participants per treatment group) is planned for this study. This sample size will also contribute sufficient participant exposure and safety data.

Table 1 Schedule of Procedures

	Screening[a,b]	Treatment Period			Safety Follow-Up	
Visit	**1**	**2**	**3**	**4**	**5**	
Week	**Up to -2**	**0**	**4**	**12**	**16**	**EOT[c]**
Day (±Visit Window)	**-14 to -1**	**1**	**28 (±7)**	**84 (±7)**	**112 (±7)**	**–**
Informed consent[d]	X					
Inclusion/exclusion criteria	X	X[e]				
Demographic information	X					
Medical/surgical history	X					
Prior/concomitant medications	X	X	X	X	X	X
Weight and height[f]	X					
Physical examination[g]	X			X		X
Vital signs[h]	X	X	X	X	X	X
12-lead ECG[i]	X					
Urine pregnancy test[j]	X			X		X
FSH test[k]	X					
Fasting chemistry and hematology[l]	X	X	X	X	X	X
Coagulation parameters	X			X		X
Fasting lipid profile[m]	X	X	X	X		X
Fasting Lp(a)[n]		X		X		X
Urine sample for UACR	X	X	X	X	X	X
Pharmacokinetics[o]		X	X	X		X
Serum archive sample[p]		X		X[q]		X
Randomization		X				
Dispense study drugs[r]		X	X			
Study drug administration[s]		----------X----------				
Study drug compliance			X	X[q]		X
Register visit in IRT	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 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 as set forth.
Note: For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications for a minimum of 8 hours.
Note: Unscheduled visits may be scheduled as needed per the judgment of the Investigator. Procedures will be determined based on the reason for the visit.

a. If laboratory abnormalities during the Screening Period are considered by the Investigator to be transient, then the laboratory tests may be repeated once during the Screening Period. 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. Participants who discontinue study drug between Visit 2 (Day 1) and Visit 3 (Day 28) or at Visit 3 (Day 28) should complete an EOT Visit at Day 28, return to complete Visit 4 (Day 84), and return to complete the Safety Follow-up Visit (Day 112). In addition, participants who withdraw from the study should complete an EOT Visit. Participants who discontinue study drug between Visit 3 (Day 28) and Visit 4 (Day 84) will not undergo an EOT Visit but continue with study visits per protocol.
d. Participants will be required to sign an ICF before any study-related procedures are performed.
e. Confirm the participant continues to meet the inclusion and exclusion criteria and assess any updates since Screening (Visit 1).
f. Weight and height will be measured at Screening (Visit 1) 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.
g. The physical examination should comprise a focused examination, which includes general, respiratory, CV, abdominal, and extremities evaluations.
h. 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.
i. A single 12-lead ECG will be performed in the supine position after 10 minutes of rest. ECGs are to be assessed for clinical significance by a qualified medical designee at the study site.
j. For women of childbearing potential only.
k. FSH test will be performed in women <55 years of age for whom it has been ≥1 year since their last menstrual period.
l. At Screening (Visit 1), Visit 4 (Day 84), and EOT, chemistry panel will include HbA1c.
m. LDL-C, HDL-C, and VLDL-C will also be evaluated by NMR analysis for particle numbers and size. LDL-C level will be calculated using the Martin-Hopkins and Friedewald equations unless TG ≥400 mg/dL (≥4.5 mmol/L) or LDL-C ≤50 mg/dL (≤1.3 mmol/L); 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 Visit 2 (Day 1), Visit 4 (Day 84), and EOT for all participants (Sources: Martin SS, Blaha MJ, Elshazly MB, et al. LDL calculator. Johns Hopkins Medicine. https://ldlcalculator.com. Accessed 27 October 2023; Friedewald W. LDL calculated. MDCalc. https://www.mdcalc.com/ldl-calculated. Accessed 11 November 2022).
n. Samples should be collected prior to study drug administration.
o. A PK sample will be collected prior to study drug administration for trough measurements of obicetrapib and ezetimibe in plasma.
p. Serum archive samples will be collected prior to the first dose at Visit 2 (Day 1) and at Visit 4 (Day 84) (or at an EOT Visit, in cases of early discontinuation) for potential future assessment of conditions associated with cholesterol metabolism. Samples should be collected prior to study drug administration and while the participant is fasting (a minimum of 8 hours). If the samples are analyzed, it will be for non-genetic tests.
q. This assessment does not need to be repeated if the participant discontinued study drug early and has already undergone an EOT Visit.
r. At Visit 2 (Day 1), participants will receive 1 kit (containing 36 FDC tablets or matching placebo tablets, 36 obicetrapib tablets or matching placebo tablets, and 36 ezetimibe capsules or matching placebo capsules totaling 108 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. The 2 kits provide sufficient supplies for 56 days of dosing, with enough for an extra 16 days of dosing in case the participant needs to postpone Visit 4 (Day 84). Each individual kit will provide a sufficient supply for 28 days of dosing, with enough for an extra 8 days of dosing. Participants will be instructed to take 3 units from the kit each day. The kit will be clearly labelled to indicate which tablets and capsule to use on each day. Participants will be instructed to bring all unused study drugs to the site at the next visit.
s. Study drugs (2 tablets and 1 capsule) will be administered by the participant orally with water, with or without food, once daily on Day 1 to Day 84 at approximately the same time each morning. On days with visits scheduled, participants should not take the study drugs prior to the visit but should bring the study drugs with them to the site. The study drugs will be administered with water following all fasted blood samples. At Visits 3 and 4, participants will dose from the kit received at the previous visit (Visits 2 and 3, respectively). If a participant permanently discontinues study drug, he/she will continue to participate in study visits, as described in section 4.5 of the protocol, but will no longer administer study drug.

COVID-19 = Coronavirus Disease 2019; CV = cardiovascular; ECG = electrocardiogram; EOT = End of Treatment; FDC = fixed dose combination; FSH = follicle-stimulating hormone; HbA1c = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; ICF = informed consent form; IRT = interactive response technology; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein (a); NMR = nuclear magnetic resonance; PK = pharmacokinetic(s); TG = triglyceride(s); UACR = urine albumin-creatinine ratio; VLDL-C = very low-density lipoprotein cholesterol.

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. Co-primary endpoints include the percent change from Day 1 to Day 84 in LDL-C for the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group as follows:

- Compared with the placebo group;
- Compared with the ezetimibe 10 mg monotherapy treatment group; and
- Compared with the obicetrapib 10 mg monotherapy treatment group.

And the percent change from Day 1 to Day 84 in LDL-C for the obicetrapib 10 mg monotherapy treatment group compared with the placebo group.

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

2.3.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include the following:

- Percent change from Day 1 to Day 84 in VLDL-C, HDL-C, TG, Lp(a), and sdLDL-C for the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with the placebo group, ezetimibe 10 mg monotherapy treatment group, and obicetrapib 10 mg monotherapy treatment group, and for the obicetarpib 10 mg monotherapy treatment group compared with the placebo group;
- Percent change from Day 1 to Day 84 in particle numbers and size, as measured by NMR analysis, of LDL-C, HDL-C, and VLDL-C for the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with the placebo group, ezetimibe 10 mg monotherapy treatment group, and obicetrapib 10 mg monotherapy treatment group, and for the obicetarpib 10 mg monotherapy treatment group compared with the placebo group
- Proportion of participants at Day 84 that achieve LDL-C <100 mg/dL (<2.6 mmol/L), LDL-C <70 mg/dL (<1.8 mmol/L), and LDL-C <55 mg/dL (<1.4 mmol/L) for the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with the placebo group, ezetimibe 10 mg monotherapy treatment group, and obicetrapib 10 mg monotherapy treatment group, and for the obicetarpib 10 mg monotherapy treatment group compared with the placebo group; and
- Percent change from Day 1 to Day 28 in LDL-C for the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with the placebo group, ezetimibe 10 mg monotherapy treatment group, and obicetrapib 10 mg monotherapy treatment group, and for obicetrapib 10 mg monotherapy treatment group compared with the placebo group.

2.3.4 Safety Endpoints

The safety endpoints include the following:

- Safety and tolerability profile of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy, obicetrapib 10 mg as monotherapy, and ezetimibe 10 mg monotherapy assessed clinical laboratory assessments (chemistry, hematology, and coagulation), vital signs, physical examinations, the incidence of AEs and events of special interest.

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 CRF.

For each analysis visit, if a scheduled visit occurs within the analysis day window, then the measurement from this scheduled visit will be used. If no scheduled visit occurs or laboratory results of the scheduled visit were unreportable, the unscheduled measurement closest to the target day will be used. If measurements are equidistant to the target day, the later measurement will be used. If laboratory measurements during the scheduled visit were taken while a participant was not in a fasting state and laboratory measurements are available from an unscheduled visit

during which the participant was in a fasting state (and the visit was done within seven days of the scheduled visit), those fasted labs will be utilized in place of the unfasted labs. Otherwise, unscheduled visits will not be re-assigned and will remain labelled as unscheduled.

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 (Visit 2)	1	NA	NA
Day 28 (Visit 3)	28	2	56
Day 84 (Visit 4)	84	57	98
Day 112 (Visit 5)	112	99	NA

3.1.3 Definition of Baseline

Baseline is defined as the last measurement prior to the first dose of study drug, unless otherwise stated.

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of subjects. 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, 1st and 3rd quartiles, minimum, and maximum.

3.1.5 Hypothesis Testing

The percentage change in LDL-C from Baseline to Day 84 for each treatment group is defined mathematically as μ_j, where j stands for the j^{th} treatment (j=0,1,2,3) and the subscript 0 refers to the placebo, 1 refers to obicetrapib 10 mg monotherapy, 2 refers to ezetimibe 10 mg monotherapy, and 3 refers to the FDC treatment group. The hypothesis testing to the percent change in LDL-C from Baseline to Day 84 is then defined statistically as following:

$$H_0: \mu_3-\mu_j = 0 \text{ (where j=0,1,2) and } \mu_1-\mu_0 = 0$$

$$H_1: \mu_3-\mu_j \neq 0 \text{ (where j=0,1,2) and } \mu_1-\mu_0 \neq 0.$$

Each of the comparisons within the co-primary endpoint family will be conducted at a significance level of 0.05. If and only if all 4 testing achieve statistical significance, the study is claimed to meet its primary objective and the hypothesis testing will continue to secondary endpoints, otherwise all statistical comparisons for secondary endpoints are considered descriptive only.

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.

3.1.7 Handling of Dropouts and Missing Data

The objective is for missing data to be kept to a minimum. Continued efforts will be made to measure endpoints on all subjects, including those who may have discontinued study drug. Accordingly, site investigators have been robustly trained about the importance of participant retention and multiple approaches will be implemented to retain participants who fail to actively maintain contact with the investigator.

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 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.

3.1.8 Laboratory Values Above or Below Limits of Quantification

For laboratory values less than the lower limit of quantification (LLQ), half of the lower limit value (i.e. LLQ/2) will be used in the analysis. For values greater than the upper limit of quantification (ULQ), the upper limit value (i.e., ULQ) will be used in the analysis.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

The ITT Population will include all participants who are randomized into the study. Treatment classification will be based on the randomized treatment.

3.2.2 The Full Analysis Set (FAS)

The FAS will include all participants who are randomized into the study, take any study drug, and have at least 1 post-treatment lipid data assessment. Treatment classification will be based on the randomized treatment.

3.2.3 Modified Intent-to-Treat (mITT) Population

The mITT Population will include all randomized participants who receive at least 1 dose of any study drug and have data for both the Day 1 and Day 84 LDL-C assessments. Treatment classification will be based on the randomized treatment.

3.2.4 The mITT On-Treatment Population

The mITT On-Treatment Population will include all randomized participants who receive at least 1 dose of any study drug, have data for both the Day 1 and Day 84 LDL-C assessments, are in the placebo or ezetimibe only arm or, if in the fixed dose combo or obicetrapib only arms have an obicetrapib plasma concentration at Visit 4 (Day 84) that was >100 ng/mL. Treatment classification will be based on the randomized treatment.

Rationale: <100 ng/mL is more than three standard deviations from the mean obicetrapib concentration observed in both the ROSE (protocol number TA-8995-201) and TULIP (protocol number TA-8995-03) studies (with a very similar participant population compared to TANDEM (protocol number OBEZ-301) at respectively Week 4 and Week 12 [1-3]. In addition, in none of the previous conducted studies (3 clinical studies and 2 Phase 1) PK / PD studies the minimal observed obicetrapib concentration for Cmax was below 100 µg/mL.

3.2.5 Per-Protocol (PP) Population

The PP Population will include all participants in the mITT Population who did not experience a major protocol deviation that potentially impacted the primary efficacy endpoint. The PP Population, along with the reason for exclusion, will be finalized prior to study unblinding.

3.2.6 Safety Population

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

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

Counts and percentages of subjects who were randomized, completed the treatment period, discontinued treatment (including primary reason for discontinuation), completed the study, and prematurely discontinued from the study (including primary reason for discontinuation) will be summarized by treatment group and overall.

For each scheduled visit, counts and percentages of subjects who did not complete the visit, completed in-clinic, completed in-clinic and remote, or completed will be summarized by treatment group and overall. The denominator for calculating percentages will be based on the number of randomized participants.

3.3.2 Protocol Deviations

Protocol deviations will be identified based on clinical data as defined in the Protocol Deviation Plan, where all protocol deviations will be defined as either CSR reportable or non-CSR reportable deviations. The CSR reportable protocol deviations will be categorized and separated by treatment group. The CSR reportable deviations will include all randomized subjects using counts and percentages.

3.3.3 Analysis Populations

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

3.3.4 Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment group and overall, for the ITT Population:

- Age and age categories (<65 years, 65 to 74 years, and 75+ years)
- Sex
- Race
- Ethnicity
- Height
- Weight
- Body Mass Index (BMI)
- HIS, non-HIS. HIS include atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg. Participants will be defined as having HIS therapy based on the data collected in the eCRF and if any following were used at baseline: average daily dose of atorvastatin ≥40 mg or average daily dose of rosuvastatin of ≥20 mg. Participants having any other doses of statin or another statin or no statin will be defined as having non-HIS therapy.
- The history of ASCVD (Yes, No).

If they differ from the ITT Population, summaries will also be provided for the FAS, the mITT Population, the mITT On-Treatment Population, the PP Population, and the Safety Population. Demographic characteristics 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 current Medical Dictionary for Regulatory Activities (MedDRA) version. Counts and percentages of subjects with medical history by system organ class (SOC) and preferred term (PT) will be summarized by treatment group and in total based on all randomized subjects.

A listing of all medical history data will be provided.

3.3.6 Concomitant Medications

The Prior & Concomitant Medications case report form where medication start and stop dates are recorded, 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 the study drug. Prior medications are defined as those used prior to and stopped before the first dose of study drug. All prior and concomitant medications will be coded using the current World Health Organization (WHO) Drug Dictionary. Counts and percentages of subjects taking prior and concomitant medications will be summarized by anatomical therapeutic chemical (ATC) class and preferred term by treatment group and overall, for the Safety Population.

Concomitant medications will be listed.

3.3.7 Study Drug Exposure and Compliance

Participant' exposure to randomized study drug will be summarized with descriptive statistics for the Safety Population and mITT On-Treatment Population. Days of exposure to study drug will be calculated as

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

For participants whose date of first dose from the initial kit dispensed was not available, the date of randomization will be used to assign the date of first dose. For subjects 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 the end of study/early termination will be used.

Days of exposure to study drug will be summarized by treatment group based on the Safety Population with counts and percentages of subjects with exposure in the following categories:

- <3 weeks
- 3 – <5 weeks
- 5 – <7 weeks
- 7 – <9 weeks
- 9 – <11 weeks
- >=11 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 percentage overall compliance to obicetrapib tablets will be calculated as:

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

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

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

The percentage overall compliance to FDC tablet will be calculated as:

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

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

$$\frac{actual\ study\ drug\ taken}{expected\ study\ drug\ taken * 3} \times 100$$

The expected study drug taken will be calculated as the earliest date between the end of treatment date and the date of early termination – the date of randomization- missed doses +1 (missed

doses defined as number of doses missed during IP interruptions due to AE or IP interruptions that are longer than 14 days).

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.

Study drug interruptions due to AE or IP interruptions longer than 14 days will be listed.

3.4 Efficacy Assessment

The ITT Population will be the primary population for the efficacy analysis. Efficacy will also be analyzed using the FAS, the mITT Population, mITT On-Treatment Population, and PP Population as supportive analyses. Primary and secondary efficacy endpoints will be presented in listings.

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. Co-primary endpoints include the percent change from Day 1 to Day 84 in LDL-C for the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with each of the following: placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy, and for the obicetrapib 10 mg monotherapy treatment group compared with placebo.

Each of the comparisons within the co-primary endpoint family will be conducted at a significance level of 0.05. If and only if all 4 testing achieve statistical significance, the study is claimed to meet its primary objective and the hypothesis testing will continue to secondary endpoints, otherwise all statistical comparisons for secondary endpoints are considered descriptive only.

The LDL-C values measured by preparative ultracentrifugation (PUC) will be used. If the later measurement is not available, the LDL-C values will be assumed missing.

All the analysis for primary efficacy endpoint will be repeated with LDL-C values calculated as follows:

1. LDL-C will be calculated using the Friedewald equation unless triglycerides ≥400 mg/dL or LDL-C ≤50 mg/dL; where, LDL-C level will be measured directly by PUC.
2. LDL-C will be calculated using the Martin-Hopkins equation unless triglycerides ≥400 mg/dL or LDL-C ≤50 mg/dL; where, LDL-C level will be measured directly by PUC.

Primary Estimand

To assess the primary efficacy endpoint, the primary estimand is defined by the following key attributes:

- **Treatment**: obicetrapib 10 mg + ezetimibe 10 mg FDC treatment versus placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy, and obicetrapib 10 mg monotherapy versus placebo
- **Target Population**: participants who are randomized into the study
- **Analysis Population**: The ITT Population
- **Intercurrent events**: treatment discontinuation, prohibited medication use

- **Analysis set and handling of intercurrent events**: Treatment policy strategy will be used. All available values of LDL-C at Baseline and Day 84 will be included in the calculation of the percentage change from Baseline to Day 84.
- **Population level summary**: The difference in LS mean percentage change in LDL-C from Baseline to Day 84 between obicetrapib 10 mg + ezetimibe 10 mg FDC treatment versus placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy, and obicetrapic 10 mg monotherapy versus placebo

The analysis of covariance (ANCOVA) model with a fixed effect for the treatment group and covariates of Baseline LDL-C will be used to analyze the primary efficacy endpoint. The least squares (LS) mean, standard errors, and 2-sided 95% confidence intervals for each treatment group and for the treatment comparison (FDC treatment – placebo, FDC treatment – ezetimibe 10 mg, and FDC treatment- obicetrapib 10 mg, and obicetrapib 10 mg - placebo) will be provided. Model diagnostics for the ANCOVA model will be computed that include assessment for homogeneity of variance, normality of the residual, and residual outliers. If substantial deviations from the model assumptions are observed, then supportive analyses, such non-parametric assessments, will be considered.

Missing data will be imputed for the primary efficacy analysis based on a pattern mixture model that uses a multiple imputation technique analyzed with ANCOVA with pre-specified fixed factors and covariates. If appropriate, based on the number of retrieved dropouts, missing measurements of non-retrieved dropouts will be modeled by known measurements from retrieved dropouts (i.e., participants who remain in the study after treatment discontinuation) in the same treatment group. If the number of retrieved dropouts is such that the model convergence is questionable and the given parameter estimates cannot be obtained, then missing data at the Day 84 assessment will be estimated based on the placebo treatment group as described in subsequent sections of the SAP corresponding to the first sensitivity analysis.

Missing data at Day 84 will be imputed using a retrieved dropout imputation model assuming the data are missing not at random (MNAR). At Day 84, the data will be split into two groups as follows: (1) all participants that did not discontinue treatment and had a non-missing value at Day 84; and (2) either participants that had a missing value at Day 84, or participants that had discontinued treatment and had a non-missing value at Day 84. For the second group, 100 data sets will be imputed. The imputation model will include LDL-C Baseline and Day 84 values, treatment group. Each data set will be combined with the first group to obtain 100 imputed data sets with no missing values at Day 84. For each imputation data set, the percent change from baseline to Day 84 will be analyzed using the ANCOVA model described above. The results of these 100 analyses will be combined to construct the treatment estimates using the parameter estimates and associated standard errors. Similarly, the difference of the adjusted treatment means will be presented with the associated standard error and two-sided 95% confidence interval. Randomly chosen seed numbers will be selected for the analysis and will be retained.

Sample SAS code is shown below:

```
1.1
**********************************************************************************************
```

```
Note: Missing value imputation only using participant group (2): participants that had a
missing value at Day 84, or participants that had discontinued treatment and had a non-
missing value at Day 84
  TREATMENT = 0 (Placebo),  1 (Obicetrapib), 3(Ezetimibe), 4 (FDC Treatment)
  LDLC_BASE = Baseline LDL_C value
  LDLC_Day84 = LDL_C value at Day 84
*************************************************************************************************
proc mi data=LDL_C seed=382794 nimpute=100 out= LDL_C_IMP;
  class TREATMENT;
  monotone method=reg;
  var TREATMENT LDLC_BASE LDLC_DAY84;
run;
*************************************************************************************************
1.2
*************************************************************************************************
Note:  LDL_C_IMP dataset must be merged with dataset containing participants from
group (1): participants that did not discontinue treatment and had a non-missing value at
Day 84.
Note:  For each imputation dataset, the percentage change from Baseline to Day 84 will
be analyzed using an ANCOVA approach with a fixed effect for the treatment group and
covariates of Baseline LDL-C.
  TREATMENT = 0 (Placebo),  1 (Obicetrapib) , 3(Ezetimibe), 4 (FDC Treatment)
  BASE = Baseline LDL_C value
  PCHG = Percent change from Baseline to Day 84

*************************************************************************************************
proc mixed data= TEMP;
  by _imputation_;
  class TREATMENT ;
  model PCHG = TREATMENT  BASE / solution cl;
  lsmeans  TREATMENT / cl diffs;
run;
*************************************************************************************************
1.3
*************************************************************************************************
Note:  MI Analyze 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 Analyses

The first sensitivity analysis will be performed imputing missing LDL-C values at Day 84 based on the assumption the data are MNAR using a control-based pattern mixture method. At Day 84, the data will be split into two groups as follows: (1) all participants randomized to the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy treatment groups that had a non-missing value at Day 84; and (2) either participants randomized to the placebo treatment group, or participants that had a missing value at Day 84. For the second group, 100 data sets will be imputed. The variables for the imputation model will consist of the LDL-C values from Baseline and Day 84. In this manner, missing data at the Day 84 assessment will be estimated from the placebo treatment group. Each data set will be combined with the first group to obtain 100 imputed data sets with no missing values at Day 84. For each imputation data set, the percent change from baseline to Day 84 will be analyzed using the ANCOVA model described above. The results of these 100 analyses will be combined to construct the treatment estimates using the parameter estimates and associated standard errors. Similarly, the difference of the adjusted treatment means will be presented with the associated standard error and two-sided 95% confidence interval. Randomly chosen seed numbers will be selected for the analysis and will be retained.

The second sensitivity analysis will be performed using the ANCOVA model from the primary analysis for the ITT Population using only observed cases with no imputation for missing data.

The third sensitivity analysis will be performed using ANCOVA model from the primary analysis for the ITT Population using the last observation carried forward (LOCF), i.e. if the Day 84 measurement is missing, then the last on-treatment measurement will be used.

Supplemental Analyses

Supplemental analyses will be performed for the primary efficacy endpoint in order to assess any differences with the results from the primary analysis and investigate what effect, if any, protocol violations have on the trial results. In the first supplemental analysis, a mixed model for repeated measures (MMRM) approach will be utilized. The analysis will include fixed effects for treatment group, visit, and treatment-by-visit interaction, along with covariates of the Baseline LDL-C value as a continuous covariate. The restricted maximum likelihood estimation approach will be used with an unstructured covariance matrix. The LS mean, standard errors, and 2-sided 95% confidence intervals for the treatment group and for the comparison of the treatment groups (FDC treatment vs. placebo, FDC treatment vs. ezetimibe 10 mg, and FDC treatment vs. obicetrapib 10 mg, and obicetrapib 10 mg vs. placebo) will be provided. The MMRM approach will include all available assessments of percent change in LDLC from Day 1, 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. The analysis will be conducted for ITT Population.

Additional supplementary analysis will be performed using the ANCOVA model from the primary analysis based on the FAS, mITT, mITT On-Treatment, and PP populations. No imputation for missing data will be performed for the analysis.

Secondary Estimand

A secondary estimand will be assessed for the primary efficacy endpoint. The secondary estimand is defined by the following key attributes:

- **Treatment**:

- obicetrapib 10 mg + ezetimibe 10 mg FDC treatment versus placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy, and obicetrapib 10 mg monotherapy versus placebo
- **Target Population**: participants who are randomized into the study
- **Analysis Population**: The ITT Population
- **Intercurrent events**: treatment discontinuation, prohibited medication use
- **Analysis set and handling of intercurrent events**: A hypothetical strategy will be used. All available values of LDL-C at Baseline and Day 84 will be included in the calculation of the percentage change from Baseline to Day 84.
- **Population level summary**: The difference in LS mean percentage change in LDL-C from Baseline to Day 84 between obicetrapib 10 mg + ezetimibe 10 mg FDC treatment versus placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy, and obicetrapic 10 mg monotherapy versus placebo.

This hypothetical estimand represents the treatment effect of FDC treatment relative to placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy, and the treatment effect of obicetrapib 10 mg monotherapy relative to placebo at Day 84 in the randomized participants had they remained on their randomized treatment for the entire planned treatment period. This estimand uses a hypothetical strategy to handle intercurrent events and is intended to provide an estimation of the achievable study treatment effect if participants take the treatment as planned. The resulting missing values (corresponding to unobserved values or excluded values following study drug discontinuation or the use of prohibited medication) will be implicitly handled by using a MMRM approach under the assumption of missing at random. The model will be similar to the MMRM approach described previously for the supplemental analysis of the primary efficacy endpoint. The supplementary analysis for the primary efficacy endpoint assessed by secondary estimand will be performed using the mITT On-Treatment populations.

3.4.2 Secondary Efficacy Endpoints

Similar ANCOVA models as described for the primary analyses will be used to analyze the secondary efficacy endpoints and will be tested sequentially at the 0.05 significant level according to the order specified below, if all 3 co-primary endpoints achieved statistical significance. Otherwise, all statistical comparisons for secondary endpoints are considered descriptive only:

- Percent change from Day 1 to Day 84 in non-HDL-C for the obicetrapib 10 mg + ezetimibe 10 mg FDC 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 FDC treatment group compared with the placebo group;
- Percent change from Day 1 to Day 84 in non-HDL-C for the obicetrapib 10 mg monotherapy treatment group compared with the placebo group;
- Percent change from Day 1 to Day 84 in ApoB for the obicetrapib 10 mg monotherapy compared with the placebo group;

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

3.4.3 Exploratory Efficacy Endpoints

Similar ANCOVA models as described for the primary analyses will be used to assess in obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with the placebo treatment group, ezetimibe 10 mg monotherapy treatment group, and obicetrapib 10 mg monotherapy treatment group, and obocetrapib 10 mg monotherapy treatment group compared with the placebo treatment group for the following:

- Percent change from Day 1 to Day 84 in VLDL-C, HDL-C, TG, Lp(a), and sdLDL-C
- Percent change from Day 1 to Day 84 in particle numbers and size, as measured by NMR analysis, of LDL-C, HDL-C, and VLDL-C
- Percent change from Day 1 to Day 28 in LDL-C.

For the percentage change from Day 1 to Day 28 in LDL-C, the LDL-C will be calculated using the Martin-Hopkins equation unless the Triglyceride value is ≥400 mg/dL or the LDL-C value is ≤50 mg/dL; in which case, the LDL-C level measured directly by PUC will be used in the analysis. The latter approach will be used because PUC assessments are not performed at Day 28 as per the protocol, unless the conditions for Triglycerides or LDL-C described above are met at the Day 28 assessment. The analysis will be repeated using the Friedewald equation as described in the Section **Error! Reference source not found.** above.

The proportion of participants at Days 84 who achieved

- LDL-C levels of <55 mg/dL (<1.4 mmol/L), <70 mg/dL (1.8 mmol/L), and <100 mg/dL (<2.6 mmol/L)

in the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with the placebo treatment group, ezetimibe 10 mg monotherapy treatment group, and the obicetrapib 10 mg monotherapy treatment group, and obicetrapib 10 mg monotherapy compared with the placebo treatment group will be examined using logistic regression models with covariates of treatment group and respective baseline values as covariates. Odds ratio with 95% confidence intervals will be estimated.

The logistic regression model will be implemented using SAS® Proc LOGISTIC. The sample SAS code can be found below:

```
Note:
 TREATMENT =  0 (Placebo),  1 (Obicetrapib), 3(Ezetimibe), 4 (FDC Treatment)
 BASE          = Baseline LDL_C value
 LDLC55      = LDL_C value less than 55mg/dL at DAY84 (YES/NO) for example
*************************************************************************************************************
proc logistic data= LDL_C;
    Class TREATMENT;
    Model LDLC55= TREATMENT BASE / alpha=0.05 expb plcl plrl orpvalue lackfit;
   Ods output
        ParameterEstimates= Log_LDLC55_ParameterEstimates
        CLoddsPL= Log_ LDLC55_OddsRatios
        ;
Run;
*************************************************************************************************************
```

3.4.4 Subgroup Analysis

The primary efficacy endpoint also may be analyzed by the following subgroups:

- Sex (male, female)
- HIS, non-HIS. HIS include atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg. Participants will be defined as having HIS therapy based on the data collected in the eCRF and if any following were used at baseline: average daily dose of atorvastatin ≥40 mg or average daily dose of rosuvastatin of ≥20 mg. Participants having any other doses of statin or another statin or no statin will be defined as having non-HIS therapy;
- The history of ASCVD (Yes, No).

The ANCOVA model with a fixed effects for the treatment group, subgroup variable, treatment-by-subgroup variable and covariates of Baseline LDL-C will be used. The least squares (LS) mean, standard errors, and 2-sided 95% confidence intervals for each treatment group and for the mean difference compared to placebo, within each level of the subgroup, will be estimated. No imputation of missing data will be performed; therefore, the subgroup analysis will perform using only observed data. For the primary efficacy endpoint, the LDL-C values measured by preparative ultracentrifugation will be used. However, if the analysis for the primary efficacy endpoint specified above will show a difference between the 3 LDL-C approaches, then Friedewald and Martin-Hopkins equations may be considered for subgroup analysis.

3.5 Safety Assessment

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.

3.5.1 Adverse Events (AEs)

AEs will be categorized by primary system organ class and preferred term as coded using the current MedDRA version category designation.

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

- Any TEAEs (overall and by maximum severity)
- Any TEAEs (non-serious)
- Any study drug related TEAEs (overall and by maximum severity)
- Any TEAEs leading to discontinuation of study drug
- Any drug related 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. The non-serious TEAEs occurring in more than 2% of participants in any treatment group and preferred term will be summarized.

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

3.5.2 Event of Special Interest

Events of special interest (ESIs) include the following: hepatic abnormalities, muscle-related abnormalities, new-onset diabetes mellitus (NODM) and/or hyperglycemia, renal abnormalities, changes to antihypertensive medication(s) due to changes in blood pressure, and macular degeneration described as follows:

- AST or ALT > 3×ULN;
- Total bilirubin > 2×ULN;
- Creatine kinase (CK) > 5 × ULN;
- NODM or worsening of glycemic control;
  Note: NODM is defined by 1 or more of the following criteria, based upon information from AE, medication, and laboratory data:
  - AE indicating new type 1 or type 2 diabetes;
  - Initiation of anti-diabetes medication with confirmation of the diagnosis of diabetes by blinded external review by experts in diabetology;
  - HbA1c ≥6.5% (≥0.065 hemoglobin fraction); and/or
  - Two consecutive values of fasting plasma glucose that are ≥126 mg/dL (≥7.0 mmol/L).

  Note: Worsening of glycemic control will be defined as HbA1c increase from baseline >0.5% (>0.005 hemoglobin fraction) and/or a new concomitant medication or increase in current antidiabetic therapy in a participant with a baseline HbA1c≥6.5% (≥0.065 hemoglobin fraction)
- A >25% decrease in eGFR from Baseline or an eGFR<30mL/min/1.73 m^2, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, and/or an increase in serum creatinine of ≥0.3 mg/dL (≥26.5 µmol/L) from baseline;
- Changes to antihypertensive medication(s) due to changes in blood pressure in those participants receiving antihypertensive medication(s) treatment at baseline, and new

antihypertensive medication prescriptions for participants not previously treated for hypertension; and
- Macular degeneration.

Values and changes from baseline will be summarized for ALT, AST, and total bilirubin by visit and treatment group. The number and percent of participants with abnormal values for ALT, AST, and total bilirubin will be summarized. These summaries of participants with abnormal values will be performed overall; by normal Baseline; and by abnormal Baseline for ALT, AST, and total bilirubin individually.

Values and changes from baseline will be summarized for CK levels by visit and treatment group and visit. In addition, the number and percent of participants with abnormal CK values will be summarized. These summaries of participants with abnormal CK values will be performed overall, by normal Baseline CK, and by abnormal Baseline CK. Values of CK from Baseline to EOT will be summarized by treatment group and by Baseline eGFR category.

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

Baseline eGFR will be summarized by treatment group for actual value and for baseline eGFR categories. Shift tables of eGFR category from baseline to EOT will be provided by treatment group. Shift tables of urine albumin-creatinine ratio from baseline to EOT will be provided by treatment group.

Participants will be identified as those who have a diagnosis of hypertension in their medical history and received antihypertensive medication(s) at Baseline. If a participant has an adverse event related to hypertension after Baseline (see Appendix B for preferred terms) and has any change in antihypertension medication within 30 days of the start date of the adverse event, that change in antihypertension medication will be considered due to a change in blood pressure.
Participants will be identified as those who did not have a prior diagnosis of hypertension in their medical history but had an adverse event of hypertension (see Appendix B) after Baseline. If participants had an adverse event of hypertension and had initiation of antihypertension medication within 30 days of the start date of the adverse event, that initiation of an antihypertension medication will be considered due to a change in blood pressure.
The number and percentage of participants receiving/not receiving antihypertensive medication(s) at Baseline with changes to or initiation of new antihypertensive medication(s) due to changes in blood pressure will be summarized by treatment group.

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

3.5.3 Clinical Laboratory Tests

Blood samples for clinical laboratory evaluations (chemistry, hematology, and coagulation) will be collected at visits specified in Table 1. Blood samples for chemistry and hematology must be obtained under fasting conditions (ie, after the participant has fasted for a minimum of 8 hours) and before study drug administration. For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications. See Appendix B of the protocol for a complete list of analytes.

Laboratory values will be summarized descriptively, including the change from baseline. In addition, shift tables for select parameters will be presented to describe the change in laboratory parameter values at post-baseline visits using normal range categories (low, normal, and high).

Chemistry and hematology laboratory parameters will be listed.

3.5.4 Vital Signs

Vital signs (body temperature, heart rate and triplicate blood pressure) will be measured at applicable visits as indicated in Table 1. Values will be summarized with descriptive statistics, including the change from baseline at each visit by treatment group and overall.

Vital signs will be listed.

3.5.5 Physical Examinations

Physical examinations (with focused examination on general, respiratory, CV, abdominal, and extremities evaluations) and recording of weight and height will be performed at Screening Visit and Visit 4/EOT. Height will be measured at Screening Visit only and used to calculate body mass index. BMI will be calculated as weight/(height/100)^2 (kg/m^2); rounded and displayed to 1 decimal place.

Physical examination parameters will be recorded as normal, abnormal or not done. Abnormal values will be assessed as clinically significant or not clinically significant. Count and percentages for physical parameters will be summarized by treatment group and in total.

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. 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 has been one change from the protocol v3.0:

- The inclusion of subgroup analysis.

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: REFERENCES

1.Hovingh GK, Kastelein JJ, van Deventer SJ et al. Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomized, double-blind, placebo-controlled phase 2 trial. *The Lancet* 2015; 386 (9992):452-460.

2.Nicholls SJ, Ditmarsch M, Kastelein JJ et el. Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial. Nature Medicine 2022; 28 (8): 1672-1678.

3. Ballantyne CM, Ditmarsch M, Kastelein JJ et al. Obicetrapib plus ezetimibe as an adjunct to high-intensity statin therapy: a randomized phase 2 trial. *Journal of Clinical Lipidology*; 2023 June 3.

4.Martin SS, Blaha MJ, Elshazly MB, et al. LDL calculator. John Hopkins Medicine. https://ldlcalculator.com. Accessed 27 October 2023.

APPENDIX B: PREFFERED TERMS FOR HYPERTENSION

Preferred Term
Accelerated hypertension
Blood pressure ambulatory increased
Blood pressure diastolic increased
Blood pressure inadequately controlled
Blood pressure increased
Blood pressure orthostatic increased
Blood pressure systolic increased
Diastolic hypertension
Essential hypertension
Hypertension
Malignant hypertension
Mean arterial pressure increased
Systolic hypertension
Blood pressure abnormal
Blood pressure ambulatory abnormal
Blood pressure diastolic abnormal
Blood pressure orthostatic abnormal
Blood pressure systolic abnormal
Labile blood pressure
Hypertensive crisis
Hypertensive emergency
Hypertensive urgency
Orthostatic hypertension