MEDPACE

STATISTICAL ANALYSIS PLAN

Protocol Title:	A Placebo-Controlled, Double-Blind, Randomized Phase 2 Study to Evaluate the Effect of Obicetrapib in Combination with Ezetimibe in Participants with Mild Dyslipidemia
Protocol Number:	TA-8995-303
Protocol Version/Date:	V4.0 / 14 January 2021
Investigational Product:	Obicetrapib
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SIGNATURE PAGE

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

Signature **Date**

VERSION HISTORY

Version	Version Date	Description
1.0	17 March 2021	Original signed version
2.0	24 June 2021	• Section 3.1.2 – Analysis windows updated for Protocol Version 3.0 and Version 4.0. • Section 3.3.3 – Clarification that reasons for exclusion will only be identified for the Per-Protocol Population. • Section 3.3.7 – Clarification on the definition of the calculation for the days of exposure when participants have missing dates for the first or last dose of study drug. Update to the definition of study drug compliance. • Section 4.2 – Description of the End of Double-Blind Treatment Analysis in accordance with sponsor request to unblind. • Section 4.3 – Description of the End of Study Analysis in accordance with the sponsor request to unblind. • Administrative updates as necessary throughout the SAP.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
ANCOVA	Analysis of Covariance
ApoB	Apolipoprotein B
ApoC3	Apolipoprotein C3
ApoE	Apolipoprotein E
ATC	Anatomical therapeutic chemical
CDISC	Clinical Data Interchange Standards Consortium
CETP	Cholesteryl ester transfer protein
CRF	Case report form
CSR	Clinical Study Report
ECG	Electrocardiogram
FSH	Follicle-stimulating hormone
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
ICF	Informed consent form
IRT	Interactive response technology
ITT	Intent-to-Treat
LDL-C	Low-density lipoprotein cholesterol
LOCB	Last Observation Carried Backward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMRM	Mixed model for repeated measures
Non-HDL-C	Non-high-density lipoprotein cholesterol
PK	Pharmacokinetics
PP	Per-Protocol
PUC	Preparative ultracentrifugation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFL	Tables, figures, and listings
TG	Triglycerides
TLC	Therapeutic Lifestyle Changes
VLDL-C	Very low-density lipoprotein cholesterol
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from NewAmsterdam Pharma BV Protocol TA-8995-303. 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 as follows:

- To evaluate the effect of obicetrapib in combination with ezetimibe compared to placebo on low-density lipoprotein cholesterol (LDL-C) at Day 57.

2.1.2 Secondary Objectives

The secondary objectives of this study include the following:

- To evaluate the effect of obicetrapib monotherapy compared to placebo on LDL-C at Day 57;
- To evaluate the effect of obicetrapib in combination with ezetimibe compared to placebo on apolipoprotein B (ApoB) at Day 57;
- To evaluate the effect of obicetrapib monotherapy compared to placebo on ApoB at Day 57;
- To evaluate the effect of obicetrapib in combination with ezetimibe compared to ezetimibe monotherapy on LDL-C at Day 57;
- To evaluate the effect of obicetrapib monotherapy compared to ezetimibe monotherapy on LDL-C at Day 57;
- To evaluate the effect of ezetimibe monotherapy compared to placebo on LDL-C at Day 57; and
- To evaluate the effect of obicetrapib in combination with ezetimibe compared to ezetimibe monotherapy on ApoB at Day 57.

2.1.3 Exploratory Objectives

The exploratory objectives of this study include the following:

- To evaluate the effect of ezetimibe monotherapy compared to placebo on ApoB at Day 57;
- To evaluate the effect of obicetrapib alone, ezetimibe alone, and obicetrapib in combination with ezetimibe 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), and high-density lipoprotein (HDL)-ApoE (with and without apolipoprotein C3 [ApoC3]) at Day 57;
- To evaluate the effect of obicetrapib alone, ezetimibe alone, and obicetrapib in combination with ezetimibe on the proportion of participants achieving predefined LDL-C targets at Day 57;

- To assess the mean trough plasma levels of obicetrapib alone, ezetimibe alone, and obicetrapib in combination with ezetimibe at steady state on Day 57, Week 12, and Week 16;
- To evaluate the effect of obicetrapib alone, ezetimibe alone, and obicetrapib in combination with ezetimibe on cholesteryl ester transfer protein (CETP) mass at Day 57, Week 12, and Week 16; and
- To evaluate the safety and tolerability profiles of obicetrapib alone, ezetimibe alone, and obicetrapib in combination with ezetimibe assessed by clinical laboratory values and incidence of adverse events (AEs).

2.2 Study Design

2.2.1 Overview

This study will be a placebo-controlled, double-blind, randomized Phase 2 study in participants with mild dyslipidemia to evaluate the efficacy, safety, and tolerability of obicetrapib and ezetimibe combination therapy. The study will take place at approximately 10 to 15 sites in North America and Europe as appropriate.

This study consists of a Screening Visit (Visit 1), a Treatment Period (8 weeks, Visits 2 to 4), a Safety Follow-up Visit (Visit 5), and a Pharmacokinetic Visit (Visit 6). The expected study duration for participants entering on the study since Screening Visit is approximately 20-weeks. Please refer to Table 1. Schedule of Procedures) below for details.

At the Screening Visit (Visit 1), participants will be required to sign an informed consent form (ICF) before any study-related procedures are performed. After signing the ICF, participants will be assessed for study eligibility. Participants will also receive counselling regarding the Therapeutic Lifestyle Changes diet and will receive instructions on how to follow this diet. Participants will be required to begin the diet starting at the Screening Visit.

Up to 2 weeks after the Screening Visit, participants will return to the site on Day 1 (Visit 2) to be randomized and begin treatment. Approximately 100 eligible participants (25 participants per treatment group) will be randomized in a 1:1:1:1 ratio to 1 of the following treatment groups:

- Combination therapy: 5 mg obicetrapib + 10 mg ezetimibe;
- Obicetrapib monotherapy: 5 mg obicetrapib + placebo ezetimibe;
- Ezetimibe monotherapy: placebo obicetrapib + 10 mg ezetimibe; or
- Placebo: placebo obicetrapib + placebo ezetimibe.

During the 8-week Treatment Period, the assigned study drugs will be administered by the participant orally and once daily on Days 1 through 57. Participants will return to the site every 4 weeks for efficacy, safety, pharmacokinetics (PK), and CETP mass assessments.

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

Participants will return to the site for a PK Visit (Visit 6) approximately 8 weeks after the end of the Treatment Period for PK and CETP mass assessments.

Table 1. Schedule of Procedures

	Screening	Treatment Period			Safety Follow-up	PK	Early Termination Visit
Visit	1	2	3	4	5	6	
Week	Up to -2	0	4	8	12	16	
Day (±Visit Window)	-14 to -1	1	29 (±3)	57 (±3)	85 (±3)	113 (±7)	Unscheduled
Informed consent[a]	X						
Inclusion/exclusion criteria	X	X[b]					
Demographic information	X						
Medical/surgical history	X						
Prior/concomitant medications	X	X	X	X	X		X
Weight and height[c]	X			X			X
Physical examination	X			X			X
Vital signs[d]	X	X	X	X	X		X
12-lead ECG[e]	X						
Urine pregnancy test[f]	X						
FSH test[g]	X						
Fasting (≥10 hours) chemistry and hematology[h]	X	X	X	X	X		X
Urinalysis	X	X	X	X	X		X
Fasting (≥10 hours) lipid profile[i]	X	X	X	X			X
PK sample[j]		X		X	X	X	
CETP mass sample[j]		X		X	X	X	
Randomization		X					
Dispense study drugs, as appropriate		X	X				
Study drug administration[k]		X	X	X			
Study drug compliance check			X	X			X
TLC diet counseling[l]	X	X	X				
Register visit in IRT	X	X	X	X			X
Adverse event assessment		X	X	X	X	X	X

Note:

a. Signed informed consent must be obtained before any study-related procedures are performed.

b. Any updates since the Screening Visit will be assessed.

c. Height and weight will be measured at the Screening Visit and will be used to calculate body mass index. Weight only will be measured at all other visits as indicated. Measurement of weight should be performed with the participant dressed in indoor clothing, with shoes removed, and bladder empty.

d. Vital signs will include body temperature, heart rate, and triplicate blood pressure (systolic and diastolic) measurements.

e. A single, standard 12-lead ECG will be performed by the Investigator or trained site personnel at the Screening Visit and centrally read by [redacted]

f. For women of childbearing potential only.

g. FSH test will be performed in peri-menopausal women, defined as women <55 years of age for whom it has been ≥1 year since

their last menstrual period.
h. At Screening Visit only, hematology panel will include HbA1c.
i. At all visits, LDL-C will be calculated using the Friedewald formula. In addition, at Visit 2 and Visit 4, LDL-C will also be measured by preparative ultracentrifugation, also referred to as beta quantification.
j. Samples will be stored for future analysis.
k. Study drugs will be administered by the participant orally and once daily on Days 1 through 57. Study drugs should be administered at approximately the same time each morning, with food. On days with visits scheduled, study drugs should be administered with food following all fasted blood samples.
l. Participants will be instructed to begin the TLC diet at the Screening Visit.
CETP = cholesteryl ester transfer protein; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = glycosylated hemoglobin; IRT = interactive response technology; PK = pharmacokinetic; TLC = Therapeutic Lifestyle Changes.

2.2.2 Randomization and Blinding

Participants who meet all eligibility criteria will be randomized into the study. Participants will be randomized in a 1:1:1:1 ratio to the combination therapy, obicetrapib monotherapy, ezetimibe monotherapy, or placebo treatment groups. At randomization, participants will be stratified according to their Screening Visit (Visit 1) LDL-C value (<3.5 mmol/L [<135 mg/dL] or ≥3.5 mmol/L [≥135 mg/dL]). An automated interactive response technology (IRT) system will be used to assign the participant to 1 of the 4 treatment groups.

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 through the PK Visit (Visit 6) for the last participant in order to protect blinding to treatment assignment.

2.2.3 Study Drug

The study drugs used in this study are as follows:

- 5 mg obicetrapib tablet;
- 10 mg ezetimibe tablet, over-encapsulated into a capsule;
- Placebo tablet for obicetrapib; and
- Placebo capsule for ezetimibe.

Participants will be randomized to receive 2 of the study drugs listed above for the duration of the study.

At each appropriate visit (Visits 2 and 3), participants will receive a kit containing blister cards with the 2 study drugs appropriate for the participant's treatment group. Participants will be instructed to take 2 units (1 tablet + 1 capsule) from the blister cards in the kit each day. The blister cards will be clearly labelled to indicate which blisters to use on each day. Each kit will provide a sufficient supply for 1 month of dosing. Participants will be instructed to return all unused study drugs at the next visit.

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

2.2.4 Sample Size Determination

A sample size of at least 100 evaluable participants (ie, 25 participants per treatment group) will provide >90% power to detect a 30% difference in LDL-C reduction at Day 57 (SD 15%) for the combination therapy group compared to the placebo group at a 2-sided significance level of 0.05.

The sample size for this study was determined in order to provide sufficient power (>80%) for the analyses of the primary efficacy endpoint and secondary efficacy endpoints described in Section 2.3. The sample size calculations used values reported from a previous clinical trial involving obicetrapib (TA-8995) as a starting point for the assumptions of the treatment difference and standard deviation[1]. This sample size will also contribute sufficient participant exposure and safety data.

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is percent change from Day 1 to Day 57 in LDL-C, for the combination therapy group compared to 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 57 in LDL-C for the obicetrapib monotherapy group compared to the placebo group;
- Percent change from Day 1 to Day 57 in ApoB for the combination therapy group compared to the placebo group;
- Percent change from Day 1 to Day 57 in ApoB for the obicetrapib monotherapy group compared to the placebo group;
- Percent change from Day 1 to Day 57 in LDL-C for combination therapy group compared to the ezetimibe monotherapy group;
- Percent change from Day 1 to Day 57 in LDL-C for the obicetrapib monotherapy group compared to the ezetimibe monotherapy group;
- Percent change from Day 1 to Day 57 in LDL-C, for the ezetimibe monotherapy group compared to the placebo group; and
- Percent change from Day 1 to Day 57 in ApoB for the combination therapy group compared to the ezetimibe monotherapy group.

2.3.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include the following:

- Percent change from Day 1 to Day 57 in ApoB for the ezetimibe monotherapy group compared to the placebo group;
- Pairwise comparisons among the various treatment groups for the percent change from Day 1 to Day 57 in non-HDL-C, VLDL-C, HDL-C, TG, ApoE, and HDL-ApoE (with and without ApoC3);
- Pairwise comparisons among the various treatment groups for the proportion of participants at Day 57 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);

- Pairwise comparisons among the various treatment groups for the change from Day 1 to Day 57, Day 1 to Week 12, and Day 1 to Week 16 in the mean trough plasma levels of obicetrapib; and
- Pairwise comparisons among the various treatment groups for the change from Day 1 to Day 57, Day 1 to Week 12, and Day 1 to Week 16 in CETP mass.

2.3.4 Safety Endpoints

The safety and tolerability profiles of obicetrapib alone, ezetimibe alone, and obicetrapib in combination with ezetimibe 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 (Visit 2), 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). For participants who will be enrolled with Protocol Version 3.0 (02 September 2020), early termination visits will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 1	1	NA	NA
Day 29	29	2	43
Day 57	57	44	71
Day 85	85	72	99
Safety Follow-up	113	100	126
PK Visit	141	127	

For participants who will be enrolled with Protocol Version 4.0 (14 January 2021), early termination visits will be assigned to analysis visits according to the following visit windows:

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 1	1	NA	NA
Day 29	29	2	43
Day 57	57	44	71
Safety Follow-up	85	72	99
PK Visit	113	100	

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

3.1.3 Definition of Baseline

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

3.1.4 Summary Statistics

Categorical data will generally be summarized with counts and percentages of 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, minimum, and maximum.

3.1.5 Missing Data

Date Values

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

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

Non-Date Values

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

3.1.6 Evaluation of Site Effect

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

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

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

3.2.2 Modified Intent-to-Treat (ITT) Population

The Modified ITT (mITT) Population will include all participants in the ITT Population who receive at least 1 dose of any study drug and have a Baseline value for the LDL-C assessment. Any

efficacy measurement obtained after a participant receives a restricted lipid altering therapy[1], outside of the current study design, will be removed from the mITT analysis. Treatment classification will be based on the randomized treatment. The mITT Population will be used for the primary analysis of all efficacy endpoints.

3.2.3 Per-Protocol (PP) Population

The Per-Protocol (PP) Population will include all participants in the mITT Population who have a Baseline value for the LDL-C assessment, have a Day 57 value for the LDL-C assessment, and who did not experience a major protocol deviation that potentially impacted the primary efficacy endpoint. Major protocol deviations will be defined in the Protocol Deviation Plan within the trial master file to align with International Conference on Harmonization guidelines. The determination of membership in the PP Population will be made prior to study unblinding. The PP Population will be a secondary population for analysis of the primary efficacy endpoint.

3.2.4 Safety Population

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

3.3 Subject Data and Study Conduct

3.3.1 Subject Disposition

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

Data listing for subject disposition and exclusion and inclusion criteria violation 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 subjects with CSR reportable protocol deviations by deviation category will be summarized by treatment and in total based on all randomized subjects. A listing of CSR-reportable protocol deviations will be generated.

3.3.3 Analysis Populations

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

[1] Any lipid-altering therapy other than the investigational study drugs will be prohibited during the study.

3.3.4 Demographic and Baseline Characteristics

Subjects demographic and Baseline characteristics include, but are not limited to, the following:

- Age in years
- Sex
- Ethnicity
- Height (cm)
- Weight (kg)
- Stratification group: LDL-C value (<3.5 mmol/L [<135 mg/dL] or ≥3.5 mmol/L [≥135 mg/dL])
- Whether or not used statin therapy in the past

Demographic and Baseline characteristics will be summarized descriptively by treatment and in total for the mITT Population. If they differ from the mITT Population, summaries will also be provided for the ITT Population, the PP Population and the Safety Population.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0. Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by treatment and in total based on all randomized subjects.

3.3.6 Concomitant Medications

Medication start and stop dates that are recorded on the Prior & Concomitant Medications case report form will be used to determine whether the medications are prior or concomitant to the study treatment. Concomitant medications are defined as those used on or after the first dose of study treatment. Prior medications are defined as those used prior to and stopped before the first dose of study treatment. All prior and concomitant medication verbatim terms will be coded using the World Health Organization (WHO) Drug Dictionary (WHO Drug Mar 2020G B). The numbers and percentages of subjects taking prior and concomitant medications in each treatment and in total will be summarized by anatomic and therapeutic chemical (ATC) class and preferred term for the Safety Population.

3.3.7 Study Drug Exposure and Compliance

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

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

For those whose date of first dose from the initial blister card dispensed was not available, the date of randomization will be used to assign the date of first dose. For those who failed to provide the date of last dose of study drug, the earliest date between the end of treatment date and the date of end of study/early termination will be used.

A summary will be provided to display the count and percentage of subjects 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 percent overall compliance to study medication by treatment and in total. The count and percentage of subjects 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 study drug compliance will be calculated as:

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

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 number of actual study drug taken is the total number of study drug dispensed minus the total number of study drug returned, as reported on the CRF. If blister cards are not returned, it will be assumed that all tablets/capsules from that blister cards were used.

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 select endpoints.

It is to highlight that LDL-C level will be collected using the following two approaches:

1. At each scheduled visit, LDL-C level will be calculated using the Friedewald formula;
2. In addition, at Baseline (Day 1) and at the end of the 8-week Treatment Period (Day 57), LDL-C will be measured for all patients by PUC[1].

3.4.1 Primary Efficacy Endpoint

Primary Analysis

The primary efficacy analysis is to evaluate the percent change from Day 1 to Day 57 in LDL-C (as determined by the Friedewald formula) for the combination therapy group compared to the placebo group. The percent change is calculated from Baseline to each measurement taken at Day 29, Day 57, and Day 85.

The percent change in LDL-C from Day 1 to Day 57 for each treatment is defined mathematically as μ_{jt}, where j stands for the j[th] treatment (j=0,1,2,3) and the subscript 0 refers to the placebo group; and t stands for time to visit at Day 29, Day 57, and Day 85 (t=1,2,3). The hypotheses testing to the percent change in LDL-C from Day 1 to Day 57 is then defined statistically as following:

$$H_0: \mu_{jt} - \mu_{0t} = 0,\ H_1: \mu_{jt} - \mu_{0t} \neq 0,\ \text{where } j=1,2,3$$

The primary efficacy analysis of the percent change from Day 1 to Day 57 in LDL-C will be performed using a mixed model for repeated measures (MMRM) approach. The analysis will include fixed effects for treatment, visit, and treatment-by-visit interaction, along with a covariate of the Baseline value as a continuous covariate. It is to note that randomization was stratified by categories of LDL-C value (<3.5 mmol/L [<135 mg/dL] or ≥3.5 mmol/L [≥135 mg/dL]) only to ensure similar distribution of LDL-C across all treatment groups; however, the MMRM model will include the original scale of the LDL-C value as a continuous covariate. The Restricted Maximum Likelihood estimation approach will be used with an unstructured covariance matrix. The least squares means, standard errors, and 2-sided 95% confidence intervals for each treatment group, for the pairwise comparisons of the combination therapy, obicetrapib monotherapy, and ezetimibe monotherapy to placebo, and for the pairwise comparisons of combination therapy and obicetrapib monotherapy versus ezetimibe monotherapy will be provided. The treatment comparison will be performed using a 2-sided test at the $\alpha = 0.05$ level of significance.

The MMRM approach will include all available assessments of percent change in LDL-C from Baseline to Day 29, Day 57, and Day 85. The model assumes the data are missing at random (MAR). If any data are missing, the model will use all information from the other time points to estimate the mean treatment difference at the given time point. No imputation of missing data will be performed for the primary efficacy endpoint analysis.

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 (Ezetimibe monotherapy), 2 (Obicetrapib monotherapy),
              3 (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 Analysis

Sensitivity analysis will be performed for the primary efficacy endpoint. In the first analysis, missing data will be imputed 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 29, 57, and 85 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 29, 57, and 85. For each imputation dataset, the percent change from baseline to Day 57 will be analyzed using the MMRM model described above. The results from these 25 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 (Combination therapy – Placebo) will be presented with the associated standard error and 95% confidence interval. Randomly chosen seed numbers will be selected for the analysis and will be retained.

In the second sensitivity analysis, the percent change from Day 1 to Day 57 in LDL-C, via the Friedewald formula, for the combination therapy group compared to the placebo group will be analyzed using an Analysis of Covariance (ANCOVA) model with fixed effects of treatment group and the Baseline LDL-C value as a continuous covariate. The least squares means, standard errors, and 2-sided 95% confidence intervals for each treatment group, for the pairwise comparisons of the combination therapy, obicetrapib monotherapy, and ezetimibe monotherapy to placebo will be provided. The treatment comparison will be performed using a 2-sided test at the α = 0.05 level of significance. No imputation of missing data will be performed for this sensitivity analysis.

In the third sensitivity analysis, the percent change from Day 1 to Day 57 in LDL-C will be assessed where the LDL-C values will be measured by preparative ultracentrifugation (PUC), also referred to as beta quantification. The percent change from Day 1 to Day 57 in LDL-C by PUC for the combination therapy group compared to the placebo group will be analyzed using an ANCOVA similar to the model described in the second sensitivity analysis. No imputation of missing data will be performed for this sensitivity analysis.

In the fourth sensitivity analysis, a similar ANCOVA model as described above will be utilized for the assessment of percent change from Baseline to Day 57 in LDL-C as measured by PUC. In this analysis, missing data at Day 57 will be imputed using a last observation carried backward (LOCB) approach in which the next available LDL-C measurement, as measured by PUC, following Day 57 will be used in the analysis. The previous TULIP trial[1] observed similar values of percent change in LDL-C at Week 8 and 12, providing a rationale for the LOCB approach in this trial.

The ANCOVA model will be implemented using SAS® Proc GLM. The sample SAS code can be found below:

```
**********************************************************************************************************
Note:
  USUBJID = unique subject identifier
  TREATMENT = 0 (Placebo), 1 (Ezetimibe monotherapy), 2 (Obicetrapib monotherapy),
              3 (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 " Ezetimibe monotherapy: Placebo"      TREATMENT -1 1 0 0;
 estimate " Obicetrapib monotherapy: Placebo"  TREATMENT -1 0 1 0;
 estimate " Combination therapy: Placebo"        TREATMENT -1 0 0 1;
run;
*************************************************************************************************************
```

3.4.2 Secondary Efficacy Endpoints

Similar MMRM models will be developed to examine the percent change from Day 1 to Day 57 in LDL-C (by Friedewald formula) or ApoB. In order to maintain the overall Type I error rate, the secondary efficacy endpoints will be tested sequentially at the 0.05 significance level according to the pre-specified order of hierarchy.

- Percent change from Day 1 to Day 57 in LDL-C for the obicetrapib monotherapy group compared to the placebo group;
- Percent change from Day 1 to Day 57 in ApoB for the combination therapy group compared to the placebo group;
- Percent change from Day 1 to Day 57 in ApoB for the obicetrapib monotherapy group compared to the placebo group;
- Percent change from Day 1 to Day 57 in LDL-C for combination therapy group compared to the ezetimibe monotherapy group;
- Percent change from Day 1 to Day 57 in LDL-C for the obicetrapib monotherapy group compared to the ezetimibe monotherapy group;
- Percent change from Day 1 to Day 57 in LDL-C, for the ezetimibe monotherapy group compared to the placebo group; and
- Percent change from Day 1 to Day 57 in ApoB for the combination therapy group compared to the ezetimibe monotherapy group.

3.4.3 Exploratory Efficacy Endpoints

Similar MMRM models will be used for the following analysis:

- Percent change from Day 1 to Day 57 in ApoB for the ezetimibe monotherapy group compared to the placebo group;
- Pairwise comparisons among the various treatment groups for the percent change from Day 1 to Day 57 in non-HDL-C, VLDL-C, HDL-C, TG, ApoE, and HDL-ApoE (with and without ApoC3);
- Pairwise comparisons among the various treatment groups for the change from Day 1 to Day 57, Day 1 to Week 12, and Day 1 to Week 16 in the mean trough plasma levels of obicetrapib; and
- Pairwise comparisons among the various treatment groups for the change from Day 1 to Day 57, Day 1 to Week 12, and Day 1 to Week 16 in CETP mass.

The proportion of subjects at Day 57 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) will be examined through Logistic Regression Models for binary variables with covariates of the treatment groups and the Baseline variable.

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 (Ezetimibe monotherapy), 2 (Obicetrapib monotherapy),
             3 (Combination therapy)
 BASE = Baseline value
 LDLC100 = LDL_C value less than 100mg/dL at DAY57 (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;
**********************************************************************************************************
```

3.5 Safety Assessment

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

3.5.1 Adverse Events (AEs)

AEs will be categorized by primary system organ class and preferred term as coded using the MedDRA (version 23.0) category designations. Summaries of AEs, including the count and percentage of participants who experience an AE, will be provided.

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

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

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

3.5.2 Clinical Laboratory Tests

Blood for chemistry and hematology will be obtained as indicated in Table 1 and sent to a central laboratory for analysis. See Appendix B for a complete list of analytes. Blood samples for chemistry and hematology must be obtained under fasting conditions (ie, after the participant has fasted for ≥10 hours). For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications. If a participant is not fasting, the Investigator will reschedule the visit as soon as possible. At the Screening Visit only, the hematology panel will include HbA1c.

Laboratory values will be summarized descriptively, including the change from Baseline, by treatment and in total. 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).

3.5.3 Vital Signs

Vital signs including body temperature, heart rate, and triplicate blood pressure will be measured at all scheduled visits except for Week 16 (the PK Visit). Height and weight will be measured at Screening and Week 8 or End of Treatment. Body mass index will be derived as $\text{weight}/(\text{height}/100)^2$ (kg/m^2) and displayed to 1 decimal place. Triplicate blood pressure measurements will be averaged for summary.

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

3.5.4 Electrocardiograms

A single, standard 12-lead ECG will be performed by the Investigator or trained site personnel at the Screening Visit and centrally read by Medpace Core Labs. Summary statistics will be provided for continuous results (PR, QRS, Heart Rate, RR, QT, QTc, QTcF) and the overall interpretation by treatment and in total. A separate data listing by subject will be provided for ECG data.

3.5.5 Physical Examinations

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

4 ANALYSIS TIMING

4.1 Interim Analysis

No interim analysis is planned.

4.2 End of Double-Blind Treatment Analysis

An end of double-blind treatment analysis will be performed when all enrolled participants have completed the double-blind treatment and Safety Follow-up periods, or are withdrawn from the study. For participants enrolled under protocol amendment version 3.0 and earlier, the Safety Follow-up period will correspond to Visit 6 / Week 16. For participants enrolled under protocol amendment version 4.0, the Safety Follow-up period will correspond to Visit 5 / Week 12. The end of treatment analysis will be performed on all available efficacy and safety data as described in the above sections of the SAP.

After all enrolled participants have completed the double-blind treatment and Safety Follow-up periods and exclusions from analysis populations have been finalized, the randomized treatment assignments will be unblinded and the analysis will be generated. Following sponsor request to unblind after end of treatment, a subset of personnel at the Clinical Research Organization (Medpace, Inc.) who are not involved with the day-to-day operations of the study will be unblinded in order to generate the end of double-blind treatment analysis. In accordance with the protocol, the Sponsor will only receive end of treatment analysis containing unblinded information following the final participant completing the PK Visit (Visit 6). In addition to TFLs, SDTM data and ADaM data along with associated files will be provided. Associated files may include the following: annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, and TFL programs.

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

4.3 End of Study Analysis

Upon completion of the study, the database will be locked and the final analysis will be generated. The end of study analysis will be performed on all available efficacy and safety data as described in the above sections of the SAP. The corresponding TFLs will be provided approximately 3 weeks after database lock. In addition to TFLs, SDTM data and ADaM data along with associated files will be provided. Associated files may include the following: annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and CDISC Define packages for both SDTM and ADaM data.

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

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

This SAP does not deviate from the statistical analysis described in v4.0 of the protocol. Any deviations from the protocol or SAP will be described in the CSR.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4. All available data will be presented in 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 randomised, double-blind, placebo-controlled phase 2 trial. *Lancet*. 2015;386(9992):452-460.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate [1]
Gamma-glutamyl transferase	Glucose (fasting)
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: https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr.

Endocrinology

Follicle-stimulating hormone [1]

[1] Follicle-stimulating hormone test will be performed in peri-menopausal women, defined as women <55 years of age for whom it has been ≥1 year since their last menstrual period.

Hematology

Glycosylated hemoglobin (HbA1c) [1]	Hematocrit
Hemoglobin	Platelets
Red blood cell count	White blood cell count and differential [2]

[1] Screening Visit only.

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

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]

Nitrite	pH
Protein	Specific gravity
Urobilinogen	

[1] Microscopy is performed only as needed based on positive dipstick test results.

Pregnancy Test

Urine

Lipid Profile

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

[1] With and without apolipoprotein C3.

[2] At all visits, LDL-C will be calculated using the Friedewald formula. In addition, at Visit 2 and Visit 4, LDL-C will also be measured by preparative ultracentrifugation, also referred to as beta quantification