STATISTICAL ANALYSIS PLAN

Protocol Title:	Obicetrapib on Top of Maximum Tolerated Lipid-Modifying Therapy (BROOKLYN): a Placebo-Controlled, Double-Blind Randomized Phase 3 Study to Evaluate the Effect of 10 mg Obicetrapib in Participants With a History of HeFH and LDL-C ≥70 mg/dL Who are Not Adequately Controlled by Their Lipid-Modifying Therapies
Protocol Number:	TA-8995-301
Protocol Version/Date:	3.0/18 May 2022
Investigational Product:	Obicetrapib
Sponsor:	NewAmsterdam Pharma B.V. Gooimeer 2-35 1411 DC Naarden The Netherlands
SAP Version/Date:	3.0/26-JUNE-2024

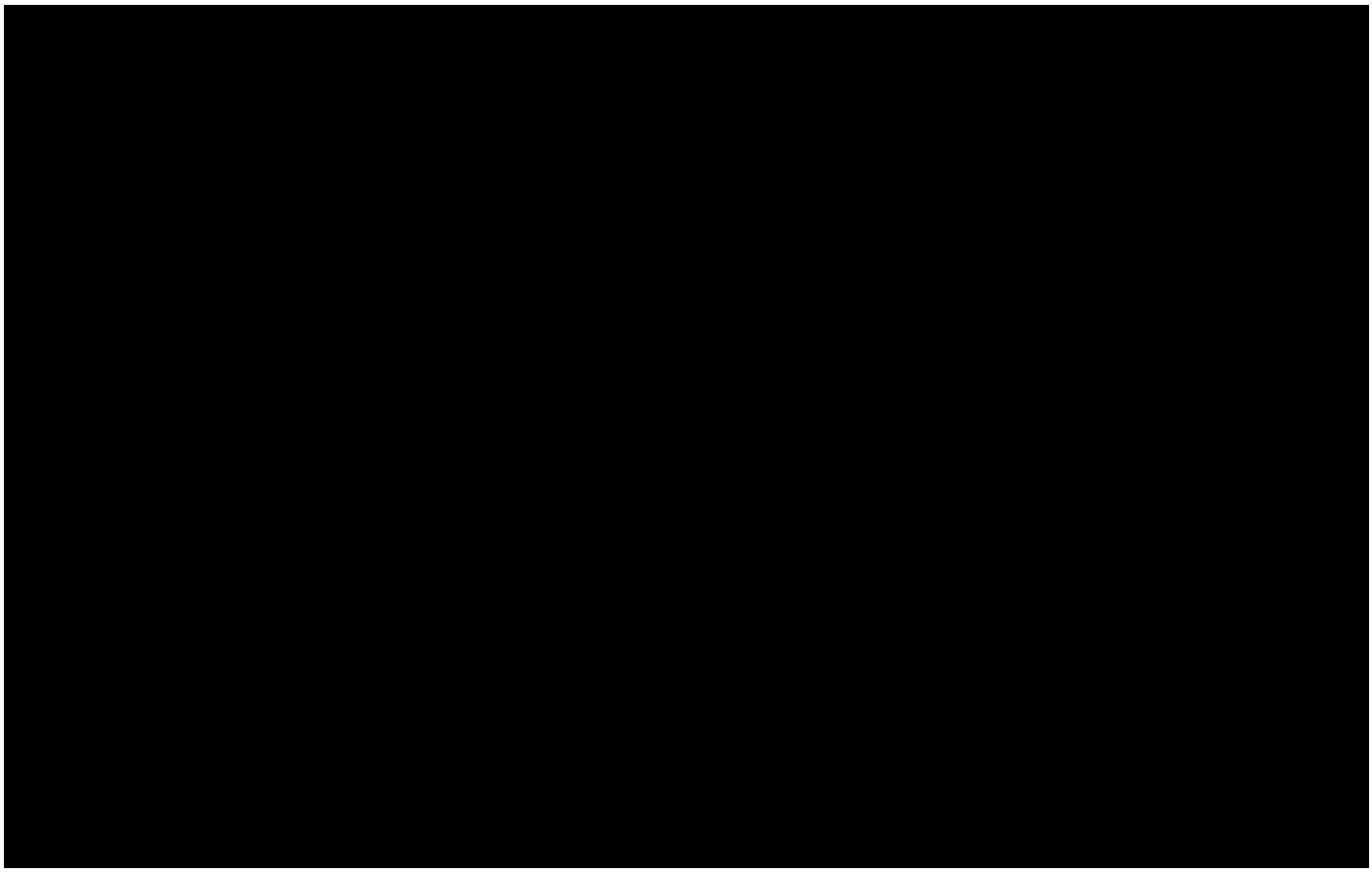
CONFIDENTIAL

SIGNATURE PAGE

Protocol Title:	Obicetrapib on Top of Maximum Tolerated Lipid-Modifying Therapy (BROOKLYN): a Placebo-Controlled, Double-Blind Randomized Phase 3 Study to Evaluate the Effect of 10 mg Obicetrapib in Participants With a History of HeFH and LDL-C ≥70 mg/dL Who are Not Adequately Controlled by Their Lipid-Modifying Therapies
Protocol Number:	TA-8995-301
SAP Version/Date:	3.0/26-JUNE-2024

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

Signature **Date**



VERSION HISTORY

Version	Version Date	Description
1.0	10 January 2024	First SAP version
2.0	13 May 2024	SAP was updated following comments from FDA
3.0	26 June 2024	Minor clarifications, updates, and corrections of typing errors

Version 2.0 (13-MAY-2024): Summary of changes from SAP Version 1.0 (10-JAN-2024)

Section	Change*	Rationale
3.1.7	More detailed description of how dropouts and missing data were handled are included	Following FDA recommendation
3.4.1	More details added for the primary analysis	If the number of retrieved dropouts will be such that the model convergence is questionable and the given parameter estimates cannot be obtained, provided additional details for analysis
3.4.1	Tipping points analysis included as sensitivity analysis	Following FDA recommendation
3.4.2	For the percentage change from Baseline to Day 180 in LDL-C, the LDL-C will be calculated using the Friedewald equation and 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.	Because PUC assessments are not performed at Day 180 as per the protocol unless the conditions for Triglycerides or LDL-C described are met at the Day 180 assessment.

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

TABLE OF CONTENTS

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
DLCN	Dutch Lipid Clinical Network
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EMEA	Europe, Middle East and Africa
EOS	End of Study
EOT	End of Treatment
ESI	Event of special interest
ET	Early Termination
FAS	Full Analysis Set
HbA1c	Glycosylated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HIS	High-intensity statin(s)
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
NODM	New-onset diabetes mellitus
Non-HDL-C	Non-high-density lipoprotein cholesterol
PK	Pharmacokinetics
PP	Per-Protocol
PT	Preferred term

Abbreviation	Definition
PUC	Preparative ultracentrifugation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SI	Statin intolerant
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
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number TA-8995-301. 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 on low-density lipoprotein cholesterol (LDL-C) levels at Day 84.

2.1.2 Secondary Objectives

The secondary objectives of this study include the following:

- To evaluate the effect of obicetrapib on apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TG) at Days 84, 180, and 365;
- To evaluate the effect of obicetrapib on LDL-C levels at Days 180 and 365;
- To evaluate the effect of obicetrapib on lipoprotein (a) (Lp[a]) at Days 84 and 365; and
- To evaluate the safety and tolerability profile of obicetrapib in a representative population of adult males and females with heterozygous familial hypercholesterolemia (HeFH), assessed by adverse events (AEs), events of special interest (ESIs), vital signs (including blood pressure), electrocardiogram (ECG) measurements, and clinical laboratory values.

2.1.3 Exploratory Objectives

The exploratory objectives of this study include the following:

- To evaluate the effect of obicetrapib on the following:
    - Number of participants achieving prespecified LDL-C, non-HDL-C, and ApoB levels at Days 84 and 365; and
    - Fasting Apolipoprotein A1 (ApoA1) at Days 84 and 365.
- To evaluate trough levels of obicetrapib from Baseline to Day 84, 180 and 365 in the obicetrapib group.

2.2 Study Design

2.2.1 Overview

This study is a multisite, placebo-controlled, double-blind, randomized Phase 3 study in approximately 300 participants with a history of HeFH who are not adequately controlled by their lipid-modifying therapy to evaluate the efficacy, safety, and tolerability of obicetrapib.

Approximately 300 eligible participants will be randomized in a 2:1 ratio, respectively, to the

following treatment groups:

- Obicetrapib group: one 10 mg obicetrapib tablet once daily; or
- Placebo group: 1 placebo tablet once daily.

At least 70% of the participants enrolled into this study must be taking high intensity statins (HISs). HeFH diagnosis is defined by existing confirmation via genetic testing, WHO Criteria/Dutch Lipid Clinical Network (DLCN) Criteria with a score of >8 points, and/or Simon Broome Register Diagnostic Criteria [1,2].

Starting on Day 1, each participant will self-administer their assigned study drug once daily until Day 365. During the Treatment Period, participants will return to the study site for efficacy and safety assessments. Blood samples for pharmacokinetic (PK) assessment will be collected at specified visits throughout the study. The End Of Study (EOS) Visit will be conducted approximately 35 days after the participant's last dose of study drug, during which vital signs; limited serum chemistry, hematology, and coagulation parameters; pharmacokinetics; concomitant medications; and AEs will be assessed.

The study drug blind will be maintained through the EOS Visit (Visit 8). Participants, the Sponsor, Investigators, and all study site personnel involved in the study, including personnel carrying out study procedures, evaluating participants, entering study data, and/or evaluating study data, will remain blinded to treatment allocations until all participants have completed the EOS Visit assessments and the database has been locked for analysis.

Active and placebo products will be identical. Medication bottles with a unique code will be assigned to participants at various points in the study by the Medpace Interactive Response Technology system.

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

Table 1 Schedule of Procedures

	Screening	Treatment Period						EOS
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7/EOT/ET[1]**	**V8**
Study Day	-14 to -1	1	30	84	180	270	365	35 days after last dose
Window (±days)	±3		±3	±7	±7	±7	±7	±7
Informed consent	X							
Assessment of eligibility	X[2]	X[2]						
Demographics and medical history	X							
Pregnancy test, FSH[3]	X	X	X	X	X	X	X	
TSH	X							
Randomization		X						
Study drug administration		X	X	X	X	X	X	
Physical examination[4]	X						X	
Weight, height, and BMI	X[5]						X	
Vital signs[6]	X	X	X	X	X	X	X	X
12-lead ECG[7]		X					X	
Lipid profile/biomarkers (fasting)[8]	X	X	X	X	X	X	X	
Serum archive sample for future assessment of biomarkers related to dyslipidemia and/or CV risk (fasting)[8,9]		X					X	
UACR, UPCR (fasting)[8]		X	X	X	X	X	X	
Aldosterone, hsCRP (fasting)[8]		X	X	X	X	X	X	
Lp(a), ApoA1(fasting)[8,9]	X	X		IX				
Full serum chemistry (fasting)[8,9]		X			X		X	
Limited serum chemistry (fasting)[8,9]	X		X	X		X		X
Urinalysis (local)[10]	X	X					X	
Hematology and coagulation (fasting)[8,9]	X	X			X		X	X
PK sample (central)[9,11]		X		X[12]	X		X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X
Study drug dispensation		X	X	X	X	X		
Study drug return/compliance calculations			X	X	X	X	X	
AEs assessment	X	X	X	X	X	X	X	X

1. For participants who permanently discontinue from study treatment **and who decline continued study participation**, an ET Visit will be scheduled as soon as possible followed by an onsite EOS Visit 35 days later. The ET Visit procedures are identical to the EOT Visit procedures. If the discontinuation occurs at a specific onsite visit, this visit will become the ET Visit and EOT Visit procedures should be followed. Participants who withdraw consent to all follow-up will be asked about the reason(s) and will be assessed for the presence of any AEs..
2. Assessment of laboratory eligibility criteria will be based on central laboratory values obtained within timeframes defined in the inclusion and exclusion criteria.
3. Urine pregnancy tests will be performed for females of childbearing potential only (performed locally using central laboratory kit supplies). FSH will only be performed at Screening in females <55 years of age and postmenopausal, defined as ≥1 year since their last menstrual period.

4. The physical examination should comprise a focused examination, which includes general, respiratory, CV, abdominal, and extremities evaluations; ophthalmological examination and recording of weight and height.
5. Height will be measured at Screening only and used to calculate BMI.
6. Vital signs (consisting of heart rate and blood pressure) will be measured as described in Section 8.8.
7. A single l2-lead ECG will be performed in the supine position after 10 minutes of rest.
8. Participants must fast for a minimum of 8 hours prior to samples being collected.
9. Samples should be collected prior to study drug administration.
10. Urinalysis will be performed locally by dipstick analyses from a sample of mid-stream urine. In case of abnormal results, microscopy and other assessments will be performed at the local laboratory and the abnormality recorded as an AE.
11. A PK sample will be collected prior to study drug administration for trough measurement of obicetrapib in plasma. At Visits 2, 5, and 7, participants should take study drug after a trough PK sample has been drawn.
12. The PK sample at Visit 4 is not designated in the protocol, however the PK will be assessed using residual serum from the Day 84 limited chemistry panel to confirm patients are taking IP.

AE = adverse event; ApoA1 = apolipoprotein A1; BMI = body mass index; CV = cardiovascular; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; ET = Early Termination; FSH = follicle-stimulating hormone; hsCRP = high sensitivity C-reactive protein; Lp(a) = lipoprotein (a); PK = pharmacokinetic(s); TSH = thyroid-stimulating hormone; UACR = urine albumin-creatinine ratio; UPCR = urine protein-creatinine ratio; V = Visit.

2.2.2 Sample Size Determination

Enrollment of approximately 300 participants globally is planned for this study.

Assuming an approximate 5% drop out rate, approximately 285 participants will be evaluable for efficacy. This sample size of at least 285 evaluable participants will provide more than 90% power to detect a 30% reduction of LDL-C (standard deviation 15%) levels in the obicetrapib group compared to the placebo group at a 1-sided significance level of 0.025. This sample size will also contribute to sufficient participant exposure and safety data.

2.3 Study Endpoints

2.3.1 Primary Efficacy Endpoints

The primary efficacy endpoint is the percentage change from Baseline to Day 84 in LDL-C in the obicetrapib group compared to the placebo group.

2.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- Percentage change from Baseline to Days 180 and 365 in LDL-C in the obicetrapib group compared to the placebo group;
- Percentage change from Baseline to Days 84, 180, and 365 in ApoB in the obicetrapib group compared to placebo group;
- Percentage change from Baseline to Days 84, 180, and 365 in non-HDL-C in the obicetrapib group compared to placebo group;
- Percentage change from Baseline to Days 84, 180, and 365 in HDL-C in the obicetrapib group compared to placebo group;
- Percentage change from Baseline to Days 84 and 365 in Lp(a) in the obicetrapib group compared to placebo group;
- Percentage change from Baseline to Days 84, 180, and 365 in TC in the obicetrapib group compared to placebo group;
- Percentage change from Baseline to Days 84, 180, and 365 in TG in the obicetrapib group compared to placebo group.

2.3.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include the following:

- Individual responsiveness defined as the number of participants reaching on treatment LDL-C levels of <40 mg/dL (<1.04 mmol/L), <55 mg/dL (<1.42 mmol/L), <70 mg/dL (1.81 mmol/L), and <100 mg/dL (<2.59 mmol/L) at Days 84 and 365;
- Individual responsiveness defined as the number of participants reaching on treatment non-HDL-C levels of <85 mg/dL (<2.20 mmol/L), <100 mg/dL (<2.59 mmol/L), and <130 mg/dL (<3.37 mmol/L) at Days 84 and 365;

- Individual responsiveness defined as the number of participants reaching on treatment ApoB levels of <65mg/dL (<0.65 mmol/L), <80 mg/dL (<0.80 mmol/L), and <130 mg/dL (<1.30 mmol/L) at Days 84 and 365;
- Percentage change from Baseline to Day 84 and 365 in ApoA1 in the obicetrapib group compared to the placebo group; and
- Trough levels of obicetrapib from Baseline to Days 84, 180 and 365 in the obicetrapib group;

2.3.4 Safety Endpoints

The safety endpoints include the following:

- Safety and tolerability profile of obicetrapib assessed by AEs, ESIs, vital signs (including blood pressure as assessed by office blood pressure measurements), ECG, and clinical laboratory values.

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 latter will be used. Otherwise, unscheduled visits will not be re-assigned and will remain labelled as unscheduled. If laboratory measurements for 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 occurred within seven days of the scheduled visit), those fasted labs will be utilized in place of the unfasted labs.

Early termination (ET) visits will be assigned to analysis visits according to the following visit windows in Table 2:

Table 2 Analysis Visit Windows

Analysis Visit	**Target Analysis Day**	**Low Analysis Day**	**High Analysis Day**
Day 1 (Visit 2)	1	NA	NA
Day 30 (Visit 3)	30	2	57
Day 84 (Visit 4)	84	58	132
Day 180 (Visit 5)	180	133	225

Day 270 (Visit 6)	270	226	317
Day 365 (EOT)/(Visit 7)	365	318	N/A

3.1.3 Handling of missed/delayed visits due to COVID-19

Due to the pandemic of Coronavirus Disease 2019 (COVID-19), study visits for some participants may be partially completed, delayed, or cancelled, with the corresponding information collected on the CRF. The sites were given the following instructions:

- If the visit window is exceeded by more than 7 days for the Visit 3 (Day 30) assessment, the visit should be recorded as an unscheduled visit.
- If the visit window is exceeded by more than 14 days for Visit 4 (Day 84), Visit 5 (Day 180), Visit 6 (Day 270), or Visit 7 (Day 365); then the visit should be recorded as an unscheduled visit.

3.1.4 Definition of Baseline

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

3.1.5 Summary Statistics

Categorical data will generally be summarized with counts and percentages of participants. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, 1st and 3rd quartiles, minimum, and maximum.

3.1.6 Hypothesis Testing

The hypothesis testing of the percentage change in LDL-C from Baseline to Day 84 is statistically defined as:

$$H_0: \mu_1-\mu_0 = 0, H_1: \mu_1-\mu_0 \neq 0,$$

where μ_0 - the percentage change in LDL-C in the placebo group,

μ_1 - the percentage change in LDL-C in the obicetrapib group.

A fixed sequential testing procedure will be implemented in order to control the Type I error rate. In a hierarchical step-down manner, the primary endpoint will be tested first, followed by the secondary efficacy endpoints in a pre-specified order (see Section 3.4.2). No adjustment for multiple comparison will be made for the exploratory efficacy endpoints.

3.1.7 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.

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

3.1.9 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 analyses.

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

The mITT On-Treatment Population will include all randomized participants who have data for both the Day 1 and Day 84 LDL-C assessments. Participants in the obicetrapib group with PK values less than 3 standard deviations from the mean obicetrapib concentration should be excluded. Treatment classification will be based on the randomized treatment.

Rationale: in previous studies, such as ROSE (protocol number TA-8995-201), TULIP (protocol number TA-8995-03), and ROSE2 (protocol number TA-8995-202), it was demonstrated that the minimally observed obicetrapib concentration for C_{max} was less than three standard deviations from the mean at respectively Week 4 and Week 12 [3-5].

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 Participant Data and Study Conduct

3.3.1 Participant Disposition

Counts and percentages of participants 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 participants who did not complete the visit, partially completed the visit in-person, or completed the visit via virtual method 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. The CSR reportable protocol deviations will be categorized and separated by treatment group. The CSR reportable deviations will include all randomized participants using counts and percentages.

3.3.3 Analysis Populations

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

3.3.4 Demographic and Baseline Characteristics

The following demographic and Baseline characteristics will be summarized with descriptive statistics or counts and percentages of participants 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)
- Region (North America and EMEA (Europe, Middle East, and Africa))
- Diabetes (yes, no)
- HDL-C (<40mg/dL, 40 - <60 mg/dL, ≥60mg/dL)
- ApoB (<60mg/dL, 60 - <90 mg/dL, ≥90mg/dL)
- ApoA1 (<110 mg/dL, ≥110 and <125 mg/dL, ≥125mg/dL)
- Lipoprotein(a) (<75nmol/L, ≥75 and <125 nmol/L, ≥125nmol/L)
- Non-HDL-C (<100 mg/dL, ≥100 and <130 mg/dL, ≥130mg/dL)
- LDL-C (<70mg/dL, ≥70 and <100 mg/dL, ≥100mg/dL)
- TG (<150 mg/dL, ≥150mg/dL)
- HbA1c (<5.7%, ≥5.75 to ≤6.4%, >6.4%)
- Urinary albumin:creatinine ratio (normal, micro-albuminuria, macro-albuminuria)
- eGFR (<60ml/min/1.73 m^2, ≥60 to <90ml/min/1.73 m^2, ≥90ml/min/1.73 m^2)
- Statin treatment (high dose (HIS), low or moderate dose (non-HIS), none (SI)). High dose statin includes atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg. Participants will be defined as having high dose statin treatment 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. Additionally, these medications can be a part of combination medications (e.g. Rosuzet 10/20mg; combination of ezetimibe 10mg and Rosuvastatin 20mg). Participants having other doses of statin or other statin treatment will be defined as low or moderate (non-HIS). Participants that are not taking statin are defined as statin intolerant (SI).
- Ezetimibe use (yes, no)
- A high-sensitivity C-reactive protein [hs-CRP] (<2mg/dL, ≥2mg/dL)
- HeFH (Genotyping confirmed or DLCN>8 points of Simon Broome definite; Simon Broome possible Familial Hypercholesterolemia (FH) diagnosis)

If they differ from the ITT Population, summaries will also be provided for the FAS, the mITT Population, the mITT On-Treatment, 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 participants

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 participants.

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 participants 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

Participants' 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 bottle dispensed was not available, the date of randomization will be used to assign the date of first dose. For participants 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 participants with exposure in the following categories:

- <3 weeks
- 3 – <5 weeks
- 5 – <7 weeks
- 7 – <9 weeks
- 9 – <11 weeks
- 11 – <13 weeks
- 13 – <19 weeks
- 19 – <25 weeks
- 25 – <28 weeks
- 28 – <34 weeks
- 34 – <40 weeks
- 40 – <50 weeks
- 50 – <54 weeks
- >=54 weeks

The percentage overall compliance to study drug will be calculated using the following formula:

$$\frac{\#\ tablets\ dispensed - \#tablets\ returned}{\#\ expected\ dosing\ days} \times 100$$

If study drug is not returned, the number of tablets returned and lost will be considered 0 for the compliance calculation. The expected dosing days 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)*.

Percent compliance to the study drug regimen will be summarized by treatment group and in total based on the Safety Population and mITT On-Treatment with descriptive statistics and with counts and percentages of participants with compliance in the following categories:

- <80%
- 80% to 120%
- >120%

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 in the FAS, mITT Population, mITT On-Treatment Population, and PP Population as supportive analyses.

3.4.1 Primary Efficacy Endpoints

Primary Analysis

The primary efficacy endpoint is the percentage change from Baseline to Day 84 in LDL-C in the obicetrapib group compared to placebo group.

The LDL-C values measured by preparative ultracentrifugation (PUC) will be used. If the latter 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 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 treatment groups

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 mean difference compared to placebo will be estimated. The model will be fit assuming unequal variances for each treatment group. 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 (ie, 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 variables for the imputation model will consist of the LDL-C values from Baseline and Day 84, along with 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 (obicetrapib vs. placebo) 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)
LDLC_BASE = Baseline LDL_C value

```
  LDLC_Day84 = LDL_C value at Day 84
**********************************************************************************************************
proc mi data=LDL_C seed=154264 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)
  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 / ddfm=satterth  solution cl;
  repeated / group=TREATMENT;
  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 treatment group 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 (obicetrapib vs. placebo) 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 a tipping point approach in the following steps [6-7]:

1. The missing data will be imputed using multiple imputation assuming MAR with a shift parameter in each treatment group.
2. The multiply imputed data will be analyzed using a standard multiple imputation method combining rule (Rubin's Rule).
3. Step 1 and 2 will be repeated such that the shift parameter for each treatment group will be increased in the negative and /or positive direction by a certain amount in each step until the "tipping point" is reached (i.e., where statistical significance is lost). The more the tipping point diverges from the observed data, the more robust the conclusions from the primary analysis.

The same analysis method as specified for primary analysis will be applied when analyzing adjusted data generated under each plausible shift parameter.

The third 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.

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 LDL-C values measured by preparative ultracentrifugation will be used. 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 group to the placebo group will be provided. The MMRM approach will include all available assessments of percent change in LDL-C from Day 1, Day 30, Day 84, Day 180, Day 270, and Day 365. The model assumes that the data are missing at random (MAR). For missing data, 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.

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

Note:

```
  USUBJID = unique participant identifier
  TREATMENT = 0 (Placebo),  1 (Obicetrapib)
  VISIT = visit
  LDLC_BASE = Baseline LDL_C value
  PCHG = Percent change from Baseline
*************************************************************************************************

proc mixed;
  class USUBJID TREATMENT VISIT CVRISK  STATIN;
  model PCHG = TREATMENT  LDLC_BASE  VISIT  TREATMENT*VISIT / solution cl;
  Repeated VISIT / TYPE=UN sub=USUBJID;
  lsmeans VISIT*TREATMENT / cl diffs;

run;

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

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 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 treatment groups.

This hypothetical estimand represents the treatment effect of obicetrapib 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:

- Percentage change from Baseline to Days 180 and 365 in LDL-C in the obicetrapib group compared to the placebo group;
- Percentage change from Baseline to Days 84, 180, and 365 in ApoB in the obicetrapib group compared to placebo group;
- Percentage change from Baseline to Days 84, 180, and 365 in non-HDL-C in the obicetrapib group compared to placebo group;
- Percentage change from Baseline to Days 84, 180, and 365 in HDL-C in the obicetrapib group compared to placebo group;
- Percentage change from Baseline to Days 84 and 365 in Lp(a) in the obicetrapib group compared to placebo group;
- Percentage change from Baseline to Days 84, 180, and 365 in TC in the obicetrapib group compared to placebo group;
- Percentage change from Baseline to Days 84, 180, and 365 in TG in the obicetrapib group compared to placebo group.

For the percentage change from Baseline to Day 180 in LDL-C, the LDL-C will be calculated using the Friedewald 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 180 as per the protocol, unless the conditions for Triglycerides or LDL-C described above are met at the Day 180 assessment. The analysis will be repeated using the Martin-Hopkins equation as described in the Section 3.4.1 above.

3.4.3 Exploratory Efficacy Endpoints

Similar ANCOVA models as described for the primary analyses will be used to assess the percentage change from Baseline to Day 84 and 365 in fasting ApoA1 in the obicetrapib group compared to the placebo group.

The proportion of participants at Days 84 and 365 who achieved

- LDL-C levels of <40 mg/dL (<1.04 mmol/L), <55 mg/dL (<1.42 mmol/L), <70 mg/dL (1.81 mmol/L), and <100 mg/dL (<2.59 mmol/L) at Days 84 and 365;
- non-HDL-C levels of <85 mg/dL (<2.20 mmol/L), <100 mg/dL (<2.59 mmol/L), and <130 mg/dL (<3.37 mmol/L) at Days 84 and 365;
- ApoB levels of <65mg/dL (<0.65 mmol/L), <80 mg/dL (<0.80 mmol/L), and <130 mg/dL (<1.30 mmol/L) at Days 84 and 365

in the obicetrapib group compared to the placebo 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)
 BASE          = Baseline LDL_C value
 LDLC40      = LDL_C value less than 40mg/dL at DAY84 (YES/NO) for example
*************************************************************************************************************
proc logistic data= LDL_C;
    Class TREATMENT(ref=0) / Param= Ref;
    Model LDLC70= TREATMENT BASE / alpha=0.05 expb plcl plrl orpvalue lackfit;
   Ods output
        ParameterEstimates= Log_LDLC40_ParameterEstimates
        CLoddsPL= Log_ LDLC40_OddsRatios
        ;
Run;
*************************************************************************************************************
```

3.4.4 Subgroup Analysis

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

- Age categories (<65 years, 65 to 74 years, and 75+ years)
- Sex (male, female)
- Race (white, Asian, Black or African American, Other)
- Ethnicity (Hispanic/Latino, Not Hispanit/Latino)
- BMI (<25 kg/m^2, 25 -30 kg/m^2, ≥30 kg/m^2)
- Region (North America and EMEA (Europe, Middle East, and Africa))
- Diabetes (yes, no)
- HDL-C (<40mg/dL, 40 - <60 mg/dL, ≥60mg/dL)
- ApoB (<60mg/dL, 60 - <90 mg/dL, ≥90mg/dL)
- ApoA1 (<110 mg/dL, ≥110 and <125 mg/dL, ≥125mg/dL)
- Lipoprotein(a) (<75nmol/L, ≥75 and <125 nmol/L, ≥125nmol/L)
- Non-HDL-C (<100 mg/dL, ≥100 and <130 mg/dL, ≥130mg/dL)
- LDL-C (<70mg/dL, ≥70 and <100 mg/dL, ≥100mg/dL)
- TG (<150 mg/dL, ≥150mg/dL)
- HbA1c (<5.7%, ≥5.75 to ≤6.4%, >6.4%)
- Urinary albumin:creatinine ratio (normal, micro-albuminuria, macro-albuminuria)
- eGFR (<60ml/min/1.73 m^2, ≥60 to <90ml/min/1.73 m^2, ≥90ml/min/1.73 m^2)
- Statin treatment (high dose, low or moderate dose, none)
- Ezetimibe use (yes, no)
- Hs-CRP (<2mg/dL, ≥2mg/dL)
- HeFH (Genotyping confirmed or DLCN>8 points of Simon Broome definite; Simon Broome possible FH diagnosis)

The ANCOVA model with 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 be performed

using only observed data. For the primary efficacy endpoint, the LDL-C values measured by PUC 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 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 and 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 those participants not receiving antihypertensive medication(s) treatment at Baseline; and
- Macular degeneration.

An overview of ESIs described above will be provided including counts, percentages of participants by treatment group, and a listing of each ESI.

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. Hy's Law criteria (>3 ×ULN for either ALT or AST, with accompanying total bilirubin >2 × ULN) will also be applied to the data. Any potential Hy's Law cases will be listed separately.

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. Fasting plasma glucose and HbA1c will be monitored as specified in Table 1 Schedule of Procedures.

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 and urine protein-creatinine ratio from Baseline to EOT will be provided by treatment group.

Participants will be identified as those who had a diagnosis of hypertension in their medical history and received antihypertensive medication(s) at Baseline. If participants had an adverse event related to hypertension after Baseline (see Appendix B for preferred terms) and had any change in antihypertension medication within 30 days of the start date of the adverse event, that change

in antihypertension medication will be considered as due to a change in blood pressure. The number and percentage of participants will be summarized by treatment group.

Participants will be identified who did not have a prior diagnosis of hypertension in their medical history and did not receive antihypertensive medication(s) at Baseline. If participants had an adverse event of hypertension and initiated antihypertension medication within 30 days of the start date of the adverse event, the adverse event will be classified as a change in blood pressure. The number and percentage of participants 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 and urine samples for clinical laboratory evaluations (including a full serum chemistry panel, hematology, coagulation, and urine dipstick analysis) will be collected at visits specified in Table 1. A limited serum chemistry panel will also be collected as specified in Table 1. All safety laboratory samples should be collected while the participant is fasting (a minimum of 8 hours) and prior to the next dose of study drug (at applicable visits). Urinalysis will be performed locally by dipstick analysis from a sample of mid-stream urine. See clinical protocol (Appendix B) for a complete list of analytes.

Laboratory values will be summarized descriptively, including the change from Baseline. In addition, shift tables for all parameters will be presented to describe the change in laboratory parameter values at end of treatment visit using normal range categories (low, normal, and high).

Chemistry and hematology laboratory parameters will be listed.

3.5.4 Vital Signs

Vital signs (heart rate and blood pressure) measured in triplicate prior to study administration 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.

Additional summaries of blood pressure measurements will be performed, within treatment group and time point, using counts of triplicate means that meet the following criteria:

- Systolic blood pressure:
  - ≥160 mmHg
  - ≥180 mmHg
  - change from Baseline by ≥20 mmHg
- Diastolic blood pressure:
  - ≥100 mmHg
  - ≥110 mmHg
  - change from Baseline by ≥15 mmHg.

As described above, the number and percentage of participants receiving antihypertensive medications at Baseline with changes to antihypertensive medications due to change in blood pressure will be summarized by treatment group. The number of participants who were not hypertensive or on any antihypertensive medications at Baseline, but started one or more antihypertensive drugs during the treatment period, will be summarized by treatment group.

Vital signs will be listed.

3.5.5 Electrocardiograms

A single 12-lead ECG will be performed at Visit 2 and Visit 7/EOT/ET and will be read locally.

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

3.5.6 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 7/EOT/ET. 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 DATA SAFETY MONITORING BOARD

An independent Data Safety Monitoring Board (DSMB) will monitor unblinded safety data, including blood pressure changes over time and the occurrence of ESIs during the study on a bi-annual basis (ie, approximately every 6 months). Participants, investigators, site staff and in general all personnel directly involved in the conduct of the study will remain blinded to the participants' treatment assignment until the completion of the study.

Details related to the DSMB responsibilities, authorities, and procedures will be documented in a DSMB Charter.

5 ANALYSIS TIMING

5.1 Interim Analysis

No interim analysis is planned.

5.2 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.

5.3 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.

6 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

There have been four changes from the protocol v3.0.

The first change is in the description of the study objectives and endpoints, the term ‘fasting’ from version 3.0 of the protocol, which precedes the specified lipid parameter, has been removed. The Schedule of Procedures, along with Section 8.7 of the protocol, specifies that all laboratory samples should be collected while the participant is fasting; therefore, the corresponding language was removed from the objective and endpoint descriptions in the SAP. Additionally, the primary efficacy endpoint for the LDL-C assessment will utilize values collected via preparative ultracentrifugation (PUC), also referred to as beta quantification, which is not sensitive to fasting status.

The second change is the inclusion of subgroup analysis.

The third change is the inclusion of the evaluation of trough levels of obicetrapib from Baseline to Day 84 and 180 in the obicetrapib group.

The fourth change is the change in the variance for the primary analysis. The model will assume unequal variances for each treatment group. Therefore, supportive analysis of the primary efficacy assessment will not require consideration of an ANCOVA model assuming unequal variances, as described in v3.0 of the protocol.

7 PROGRAMMING SPECIFICATIONS

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

APPENDIX A: REFERENCES

1. World Health Organization. Familial hypercholesterolaemia (FH): report of a second WHO consultation 04 September 1998 https://apps.who.int/iris/handle/10665/66346. Accessed 21 April 2022.

2. Austin MA, Hutter Cm, Zimmern RL, et al. Rationale and design of the CLEAR-outcomes trial: evaluating the effect of bempedoic acid on cardiovascular events in patients with statin intolerance. *Am Heart J*. 2021; 235:104-112.

3.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.

4.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.

5. 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.

6. Ratitch B, O'Kelly M, Tosiello R. Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharmaceutical statistics 2013; 12 (6):337-347.

7. Yuan Y. Sensitivity analysis in multiple imputation for missing data. In Proceedings of the SAS Global Forum 2014 conference (https://support.sas.com/resources/papers/proceedings14/SAS270-2014.pdf).

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