STATISTICAL ANALYSIS PLAN

Protocol Title:	Obicetrapib on Top of Maximum Tolerated Lipid-Modifying Therapy (BROADWAY): a Placebo-Controlled, Double-Blind Randomized Phase 3 Study to Evaluate the Effect of 10 mg Obicetrapib in Participants With Underlying HeFH and/or Atherosclerotic Cardiovascular Disease (ASCVD) Who are Not Adequately Controlled by Their Lipid-Modifying Therapies
Protocol Number:	TA-8995-302
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SIGNATURE PAGE

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

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VERSION HISTORY

Version	Version Date	Description
1.0	14 June 2024	First Version
2.0	24 October 2024	Second Version

Version 2.0 (24-OCT-2024): Summary of changes from SAP Version 1.0 (14-JUN-2024)

Section	Change*	Rationale
2.3.3	Additional exploratory endpoints were added	To get a thorough understanding of the overall effect of the study drug to various cardiovascular endpoints
3.1.11	A section describing how duplicates will be handled	To provide detailed description how duplicated participants will be handled in the analysis

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

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AAA	Abdominal Aortic Aneurysm
ADaM	Analysis Data Model
ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CDISC	Clinical Data Interchange Standards Consortium
CHD	Coronary heart disease
CK	Creatine kinase
CRF	Case report form
CSR	Clinical Study Report
CV	Cardiovascular
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EOS	End of Study
EOT	End of Treatment
ESI	Event of special interest
ET	Early Termination
FAS	Full Analysis Set
HbA1c	Glycosylated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HF	Heart failure
HIS	High-intensity statin(s)
HOMA-IR	Homeostatic model assessment of insulin resistance
ICF	Informed consent form
IRT	Interactive Response Technology
ITT	Intent-to-Treat
GLP-1	Glucose-like peptide-1
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein (a)
LS	Least squares
MALE	Major Adverse Limb Events
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	Modified Intent-to-Treat
MNAR	Missing not at random

Abbreviation	Definition
NODM	New-onset diabetes mellitus
Non-HDL-C	Non-high-density lipoprotein cholesterol
PK	Pharmacokinetics
PP	Per-Protocol
PT	Preferred term
PUC	Preparative ultracentrifugation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SDTM	Study Data Tabulation Model
SGLT2	Sodium-glucose co-transporter-2
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
TIA	Transient ischemic attack
ULN	Upper limit of normal
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-8995-302, version 6.0. 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 Objective

The secondary objectives of this study include the following:

- To evaluate the effect of obicetrapib on LDL-C levels at Days 180 and 365;
- 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 lipoprotein (a) (Lp[a]) and apolipoprotein A1 (ApoA1) at Day 84; and
- To evaluate the safety and tolerability profile of obicetrapib in a representative population of adult males and females with heterozygous familial hypercholesterolemia (HeFH) and/or ASCVD of all ages, 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:
    - Proportion of participants achieving prespecified LDL-C levels at Days 84, 180, and 365; and
    - Biomarkers, including glycosylated hemoglobin (HbA1c), homeostatic model assessment of insulin resistance (HOMA-IR), and blood glucose at Day 365.
- To evaluate trough levels of obicetrapib from Baseline to Day 84, 180 and 365 in the obicetrapib group;
- To evaluate the effect of obicetrapib on cardiovascular events
    - CV death, non-fatal myocardial infarction (MI), non-fatal stroke, or non-elective coronary revascularization; and

- CV death, non-fatal myocardial infarction (MI), non-fatal stroke, or coronary revascularization; and
- CV death, non-fatal myocardial infarction (MI), non-fatal stroke
- Major Adverse Limb Events (MALE) events
- Coronary heart disease (CHD) death, non-fatal myocardial infarction (MI), non-fatal stroke, or non-elective coronary revascularization; and
- CHD death, non-fatal myocardial infarction (MI), non-fatal stroke, or coronary revascularization; and
- CHD death, non-fatal myocardial infarction (MI), non-fatal stroke
- Total CV events

- To evaluate the effect of obicetrapib on hospitalization for unstable angina and/or chest pain, hospitalization for heart failure (HF), transient ischemic attack (TIA), abdominal aortic aneurysm (AAA) and carotid revascularization.

2.2 Study Design

2.2.1 Overview

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

Approximately 2400 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.

Treatment allocation will be stratified based on CV risk (HeFH or non-HeFH) and Baseline statin dose (high-intensity statins [HIS] or non-HIS). At least 70% of the participants enrolled into this study must be taking HISs. Participants with underlying HeFH but without a history of ASCVD will comprise up to a maximum of 20% of the total participants enrolled into the study. 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. Participants will return to the site for the End Of Study (EOS) Visit (Visit 8) approximately 35 days after last dose of study drug for safety assessments.

A subset of approximately 200 participants from selected study sites who consent to participate will be enrolled in an ambulatory blood pressure monitoring (ABPM) substudy. These participants will have a 24-hour ABPM assessment conducted at Screening (Visit 1) and Visit 6 (Day 270). In order to participate in the substudy, participants must provide written informed consent in a substudy-specific informed consent form (ICF) and must be able to provide an acceptable 24-hour ABPM data collection at Screening (Visit 1).

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.

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[1]
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7/EOT/ET[2]**	**V8**
Study Day	-28 to -1	1	30	84	180	270	365	35 days after last dose
Window (±days)			±3	±7	±7	±7	±7	±7
Informed consent[3]	X							
Assessment of eligibility	X[4]	X[4]						
Demographics and medical history	X							
Pregnancy test, FSH[5]	X	X			X		X	
TSH	X							
Randomization		X						
Study drug administration		X	X	X	X	X	X	
Physical examination[6]	X						X	
Weight, height, and BMI	X[7]						X	
Vital signs[8]	X	X	X	X	X	X	X	X
24-hr ABPM[9]	X[10]					X[11]		
12-lead ECG[12]		X					X	
Lipid profile/biomarkers (fasting)[13]	X	X	X	X	X	X	X	
Serum archive sample for future assessment of biomarkers related to dyslipidemia and/or CV risk (fasting)[13,14,15]		X					X	
UACR, UPCR (fasting)[13]		X					X	
Aldosterone, hsCRP (fasting)[13]	X[16]	X					X	
Lp(a), ApoA1(fasting)[13,14]	X	X		X				
Insulin for HOMA-IR (fasting)[13]	X	X		X	X	X	X	
Full serum chemistry (fasting)[13,14]		X			X		X	
Limited serum chemistry (fasting)[13,14]	X		X	X		X		
Urine dipstick analysis[17]	X	X					X	
Hematology and coagulation (fasting)[13,14]	X	X			X		X	
PK sample (central)[14,18]		X		X[20]	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	
CV events assessment[19]	X	X	X	X	X	X	X	X
AEs assessment	X	X	X	X	X	X	X	X

1. The onsite EOS Visit will include an assessment of vital signs, concomitant medications, CV events, and AEs will be completed and documented in the participant's record.
2. 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. 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. For participants who completely withdraw consent, life status will be obtained at study end through public record information according to local guidelines and as allowed by local regulations.
3. Informed consent will be obtained from participants before the initiation of any study-specific procedures. In order to participate in the ABPM substudy, participants must provide written informed consent in a substudy-specific ICF.
4. Assessment of laboratory eligibility criteria will be based on central laboratory values obtained within timeframes defined in the inclusion and exclusion criteria.
5. 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 (Visit 1) in females <55 years of age and postmenopausal, defined as ≥1 year since their last menstrual period.
6. 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.
7. Height will be measured at Screening (Visit 1) only and used to calculate BMI.
8. Vital signs (consisting of heart rate and blood pressure) will be measured as described in the clinical study protocol Section 8.9.
9. Only participants who consent to participate in the ABPM substudy will have this assessment performed.
10. The 24-hour ABPM assessment at Screening (Visit 1) should be completed after the participant's eligibility has been confirmed at that visit. It should be ensured that sufficient time is allotted during Screening (Visit 1) to allow for a repeat 24-hour ABPM assessment, if the first is not successful, prior to Visit 2. Additional details surrounding this substudy are included in a separate study manual.
11. It should be ensured that a repeat assessment (if necessary) is completed within the respective visit window and that the assessment is not done concurrently with other study procedures.
12. A single l2-lead ECG will be performed in the supine position after 10 minutes of rest.
13. Participants must fast for a minimum of 8 hours prior to samples being collected.
14. Samples should be collected prior to study drug administration.
15. Serum archive sample is not collected in China.
16. Only hsCRP will be assessed at Screening (Visit 1).
17. Urine dipstick analysis will be performed locally 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.
18. 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.
19. CV events include CV death, non-fatal myocardial infarction, non-fatal stroke, non-elective coronary revascularization, hospitalization for unstable angina and/or chest pain, hospitalization for heart failure, and transient ischemic attack.
20. 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 participants are taking study drug.

ABPM = ambulatory blood pressure monitoring; 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; HOMA-IR = homeostatic model

assessment of insulin resistance; hsCRP = high sensitivity C-reactive protein; ICF = informed consent form; 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 2400 participants globally is planned for this study.

Assuming an approximate 5% drop out rate, approximately 2280 participants will be evaluable for efficacy. This sample size of at least 2280 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.

ABPM substudy

A substudy is designed for a non-inferiority assessment in systolic blood pressure from Screening (Visit 1) to Day 270 (Visit 6) between obicetrapib and placebo. The non-inferiority margin was selected in accordance with the United States Food and Drug Administration guidelines (Assessment of Pressor Effects of Drugs, Guidance for Industry) [1]. The non-inferiority margin was chosen to assess if obicetrapib is not substantially inferior to placebo for elevations in systolic blood pressure. The assumption for the common standard deviation is determined by a literature review and the obicetrapib Phase 2 program. From the reference paper by Vollmer et al, the estimate of the standard deviation for the change in systolic blood pressure (mmHg) for hypertensive participants based on 24-hour ABPM measurements was 8.0 (95% confidence interval: 6.9, 9.4) [2].

A subset of approximately 200 participants from selected study sites who consent to participate will be enrolled in the ABPM substudy. For inclusion in the substudy analysis, participants must have an acceptable 24-hour ABPM data collection at Screening (Visit 1), as defined in a separate study manual. This sample size will allow for non-inferiority to be established between the obicetrapib group compared to the placebo group, with desired power of >80%, against a non-inferiority difference of 3 mmHg. This assumes a mean treatment difference of 0 mmHg for the obicetrapib group compared to the placebo group, with a standard deviation of 8 mmHg, at a 1-sided significance level of 0.05.

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 30, 180, 270 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 in Lp(a) and ApoA1 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:

- Proportion of participants at Days 84, 180, and 365 who achieved LDL-C <70 mg/dL (<1.8 mmol/L) in the obicetrapib group compared to the placebo group;
- Proportion of participants at Days 84, 180, and 365 who achieved LDL-C <55 mg/dL (<1.4 mmol/L) in the obicetrapib group compared to the placebo group;
- Proportion of participants at Days 84, 180, and 365 who achieved LDL-C <40mg/dL (<1.0 mmol/L) in the obicetrapib group compared to the placebo group;
- Percentage change from Baseline to Day 365 in HbA1c in the obicetrapib group compared to the placebo group;
- Percentage change from Baseline to Day 365 in HOMA-IR in the obicetrapib group compared to the placebo group;
- Percentage change from Baseline to Day 365 in blood glucose in the obicetrapib group compared to the placebo group;
- Percentage change from Baseline to Day 30, 84, 180, 270 and 365 in LDL-C in the obicetrapib group compared to the placebo group in participants who are statin intolerant;
- Trough levels of obicetrapib from Baseline to Days 84, 180 and 365 in the obicetrapib group;
- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, or non-fatal stroke, or non-elective coronary revascularization;
- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, or non-fatal stroke, or coronary revascularization;
- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, or non-fatal stroke; and
- The time from Randomization until the first confirmed occurrence of hospitalization for unstable angina and/or chest pain, hospitalization for HF, and TIA;
- The time from Randomization until the first confirmed occurrence of MALE event. The MALE event will include acute limb ischemia, major amputation, urgent revascularization.
- The time from Randomization until the first confirmed occurrence of a composite of CHD death, non-fatal MI, or non-fatal stroke, or non-elective coronary revascularization;

- The time from Randomization until the first confirmed occurrence of a composite of CHD death, non-fatal MI, or non-fatal stroke, or coronary revascularization;
- The time from Randomization until the first confirmed occurrence of a composite of CHD death, non-fatal MI, or non-fatal stroke;
- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, or non-elective coronary revascularization;
- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, or coronary revascularization;
- The time from Randomization until the first confirmed occurrence of a composite of CHD death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, or non-elective coronary revascularization;
- The time from Randomization until the first confirmed occurrence of a composite of CHD death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, or coronary revascularization;
- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE, or non-elective coronary revascularization;
- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE, or coronary revascularization;
- The time from Randomization until the first confirmed occurrence of a composite of CHD death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE, or non-elective coronary revascularization;
- The time from Randomization until the first confirmed occurrence of a composite of CHD death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE, or coronary revascularization;
- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE, other atherosclerotic events (AAA, TIA, carotid revascularization), or non-elective coronary revascularization;
- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE, other atherosclerotic events (AAA, TIA, carotid revascularization), or coronary revascularization;
- The time from Randomization until the first confirmed occurrence of a composite of CHD death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE, other atherosclerotic events (AAA, TIA, carotid revascularization), or non-elective coronary revascularization;

- The time from Randomization until the first confirmed occurrence of a composite of CHD death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE, other atherosclerotic events (AAA, TIA, carotid revascularization), or coronary revascularization;
- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, or non-fatal stroke;
- The time from Randomization until the first confirmed occurrence of a composite of CHD death, non-fatal MI, or non-fatal stroke;
- The time from Randomization until the confirmed occurrence of CV death;
- The time from Randomization until the confirmed occurrence of non-fatal MI;
- The time from Randomization until the confirmed occurrence of non-fatal stroke;
- The time from Randomization until the confirmed occurrence of non-elective coronary revascularization ;
- The time from Randomization until the confirmed occurrence of all cause death;
- The number of total events: CV death, non-fatal MI, non-fatal stroke;
- The number of total events: CHD death, non-fatal MI, non-fatal stroke;
- The number of total events: CV death, non-fatal MI, non-fatal stroke, or non-elective coronary revascularization;
- The number of total events: CV death, non-fatal MI, non-fatal stroke, or all coronary revascularization;
- The number of total events: CHD death, non-fatal MI, non-fatal stroke, or non-elective coronary revascularization;
- The number of total events: CHD death, non-fatal MI, non-fatal stroke, or all coronary revascularization;
- The number of total events: CV death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, or non-elective coronary revascularization;
- The number of total events: CV death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, or all coronary revascularization;
- The number of total events: CHD death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, or non-elective coronary revascularization;
- The number of total events: CHD death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, or all coronary revascularization;
- The number of total events: CV death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE or non-elective coronary revascularization;
- The number of total events: CV death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE or all coronary revascularization;

- The number of total events: CHD death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE or non-elective coronary revascularization;
- The number of total events: CHD death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE or all coronary revascularization;
- The number of total events: CV death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE, other atherosclerotic events (AAA, TIA, carotid revascularization) or non-elective coronary revascularization;
- The number of total events: CV death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE, other atherosclerotic events (AAA, TIA, carotid revascularization) or all coronary revascularization;
- The number of total events: CHD death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE, other atherosclerotic events (AAA, TIA, carotid revascularization) or non-elective coronary revascularization;
- The number of total events: CHD death, non-fatal MI, non-fatal stroke, hospitalization of unstable angina, MALE, other atherosclerotic events (AAA, TIA, carotid revascularization) or all coronary revascularization; and
- The number of total CV events.

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, and
- Assessment of ABPM measured at Baseline and at Day 270.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study drug. The day of the first dose of study drug will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Analysis Visits

Scheduled visits will be assigned to analysis visits as recorded on the CRF.

For each analysis visit, if a scheduled visit occurs within the analysis day window, then the measurement from this scheduled visit will be used. If no scheduled visit occurs or laboratory results of the scheduled visit were unreportable, the unscheduled measurement closest to the target day will be used. If measurements are equidistant to the target day, the later measurement will be used. 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 visit windows in Table 2 and Table 3.

Table 2 Analysis Visit Windows (excluding Japan)

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

Table 3 Analysis Visit Windows (Japan Only)

Analysis Visit	Target Analysis Day	Low Analysis Day	High Analysis Day
Day 1 (Visit 2)	1	NA	NA
Day 14 (Visit 3)	14	2	22
Day 30 (Visit 4)	30	23	57
Day 84 (Visit 5)	84	58	132
Day 180 (Visit 6)	180	133	225
Day 270 (Visit 7)	270	226	317
Day 365 (EOT/Visit 8)	365	318	N/A

3.1.3 Handling of missed/delayed visits dues 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 could do the following:

- If the visit window is exceeded by more than 7 days for the Visit 3 (Day 30) assessment, the visit may 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 may 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 subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, 1st and 3rd quartiles, minimum, and maximum.

3.1.6 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.

The hypothesis testing of the change in average systolic blood pressure (SBP) measured by 24-hour ABPM from Baseline to Day 270 is defined as follows:

$$H_0: \mu_T-\mu_P \geq 3 \text{ mmHg}, H_1: \mu_T-\mu_P < 3 \text{ mmHg}$$

where μ_P - the change in average SBP in the placebo group,

μ_T- the change in average SBP in the obicetrapib group.

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 subjects, including those who may have discontinued study drug. Accordingly, site investigators have been robustly trained about the importance of participant retention and multiple approaches will be implemented to retain participants who fail to actively maintain contact with the investigator.

Date Values

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

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

Non-Date Values

For 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 continuous 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.

3.1.10 Discrepancies Between Interactive Response Technology (IRT) and eCRF Stratification Variables

Summary tables by treatment group for stratification variables (CV risk and Baseline statin dose) will be provided to show any discrepancies between what was reported through IRT vs data collected in the study eCRF. The stratification variables based on data collected in the eCRF will be defined as follows:

- HIS includes atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg. Participants will be defined as having HIS 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. For Japan only, HIS includes atorvastatin 10 or 20 mg for non-familial hypercholesterolemia, atorvastatin 20 or 40 mg for heterozygous familial hypercholesterolemia, and rosuvastatin 10 or 20 mg. Participants will be defined as having HIS treatment, for Japan only, if any following were used at baseline: average daily dose of atorvastatin ≥10 mg or average daily dose of rosuvastatin of ≥10 mg. Participants having other doses of statin or other statin treatment, or no statin will be defined as non-HIS therapy.
- Participants will be defined as having CV risk (HeFH, non-HeFH) based on the CV history collected in the eCRF.

3.1.11 Handling of Duplicate Enrollment

The list of confirmed duplicate participants will be directly incorporated into Analysis Data Model (ADaM) dataset as a variable to identify a duplicate participant. Duplicate participants will be excluded from all analysis.

3.2 Analysis Populations

3.2.1 Intent-to-Treat (ITT) Population

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

3.2.2 The Full Analysis Set (FAS)

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

3.2.3 Modified Intent-to-Treat (mITT) Population

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

3.2.4 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) and 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.

3.2.7 24-hours ABPM Population

The 24-hour ABPM Population will include all participants in the ITT Population who received at least 1 dose of any study drug and have valid data for both the baseline and Day 270 24-hour ABPM assessments and have 80% to 120% treatment compliance.

3.3 Subject Data and Study Conduct

3.3.1 Participant Disposition

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

For each scheduled visit, counts and percentages of subjects who did not complete the visit, 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.

Participants disposition and exclusion and inclusion criteria violations will be listed.

3.3.2 Protocol Deviations

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

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 group and in total based on all randomized subjects. Reasons for exclusion from PP Population will also be summarized.

3.3.4 Demographic and Baseline Characteristics

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

- Age and age categories (<65 years, 65 to 74 years, and 75+ years)
- Sex
- Race
- Ethnicity
- Height
- Weight
- Body Mass Index (BMI)
- Region (Asia, Eastern Europe, Western Europe and North America)
- Country (USA, Japan, China, Other)
- 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%, ≥5.7 to ≤6.4%, >6.4%)
- Urinary albumin:creatinine ratio (normal, micro-albuminuria, macro-albuminuria)
- eGFR (<30ml/min/1.73 m^2, ≥30 to <45ml/min/1.73 m^2, ≥45 to <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). High dose statin will be defined as atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg. Participants will be defined as having high dose statin 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. For Japan only, high dose statin includes atorvastatin 10 or 20 mg for non-familial hypercholesterolemia, atorvastatin 20 or 40 mg for heterozygous

familial hypercholesterolemia, rosuvastatin 10 or 20 mg. Participants will be defined as having high dose statin treatment, for Japan only, if any following were used at baseline: average daily dose of atorvastatin ≥10 mg or average daily dose of rosuvastatin of ≥10 mg. Participants having other doses of statin or other statin treatment will be defined as low or moderate.

- Ezetimibe use (yes, no)
- Glucose-like peptide-1 (GLP1) use (yes, no)
- Sodium-glucose co-transporter-2 (SGLT2) use (yes, no)
- A high-sensitivity C-reactive protein [hs-CRP] (<2mg/dL, ≥2mg/dL)
- HeFH (yes, no)
- HIS, non-HIS
- HeFH (Genotyping confirmed or DLCN>8 points or 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, mITT On-Treatment Population, the PP Population, and the Safety Population. Demographic characteristics data will be provided in participants listings.

3.3.5 Medical History

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

A listing of all medical history data will be provided.

3.3.6 Concomitant Medications

The Prior & Concomitant Medications case report form where medication start and stop dates are recorded, will be used to determine whether the medications are prior or concomitant to the study treatment. Concomitant medications are defined as those used on or after the first dose of the study drug. Prior medications are defined as those used prior to and stopped before the first dose of study drug. All prior and concomitant medications will be coded using the current World Health Organization (WHO) Drug Dictionary. Counts and percentages of 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

Subjects' exposure to randomized study drug will be summarized with descriptive statistics for the Safety and mITT On-Treatment Populations. 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 subjects 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 subjects who failed to provide the date of last dose of study drug, the earliest date between the end of treatment date and the date of the end of study/early termination will be used.

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

- <3 weeks
- 3 – <5 weeks
- 5 – <7 weeks
- 7 – <9 weeks
- 9 – <11 weeks
- 11 – <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 – any 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 with descriptive statistics and with counts and percentages of subjects 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 using 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 later 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, CV risk (HeFH or non-HeFH), and Baseline statin therapy (HIS or non-HIS) will be used to analyze the primary efficacy endpoint. The CV risk and Baseline statin therapy covariates, that were used in the stratification of the randomization scheme, will be classified according to the IRT stratification levels (meaning, the stratification categorization at the time of the randomization). 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 as non-parametric assessments, will be considered. The primary efficacy analysis will be conducted based on the ITT Population.

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, CV risk (HeFH or non-HeFH) and Baseline statin therapy (HIS or non-HIS). 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
  CVRISK = 1 (HeFH), 0 (non-HeFH)
  STATIN = 1 (HIS), 0 (non-HIS)
**********************************************************************************************************
proc mi data=LDL_C seed=8267356 nimpute=100 out= LDL_C_IMP;
  class TREATMENT CVRISK STATIN;
  monotone method=reg;
  var TREATMENT CVRISK STATIN 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, CV risk (HeFH or non-HeFH), and Baseline statin therapy (HIS
or non-HIS).
  TREATMENT = 0 (Placebo),  1 (Obicetrapib)
  BASE = Baseline LDL_C value
  PCHG = Percent change from Baseline to Day 84
```

```
  CVRISK = 1 (HeFH), 0 (non-HeFH)
  STATIN = 1 (HIS), 0 (non-HIS)
*************************************************************************************************
proc mixed data= TEMP;
  by _imputation_;
  class TREATMENT  CVRISK  STATIN;
  model PCHG = TREATMENT  BASE  CVRISK  STATIN /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, along with CV risk (HeFH or non-HeFH) and Baseline statin therapy (HIS or non-HIS). 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]. The same analysis method as specified for primary analysis will be applied when analyzing adjusted data generated under each plausible shift parameter:

1. The missing data will be imputed using multiple imputation assuming missing at random (MAR) with a shift parameter in each treatment group.

2. The multiple 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 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.

The fourth sensitivity analysis will be performed using the eCRF data for stratification variables. This analysis will be performed only if stratification variables at IRT and in the eCRF disagree for more than 10% of the randomized participants.

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, CV risk (HeFH or non-HeFH), Baseline statin therapy (HIS or non-HIS). 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). If any data are missing, the model will use all information from the other time points to estimate the mean treatment difference at the given time point. No imputation of missing data will be performed. The analysis will be conducted for ITT Population.

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

```
*************************************************************************************************
Note:
  USUBJID = unique subject identifier
  TREATMENT = 0 (Placebo),  1 (Obicetrapib)
  VISIT = visit
  LDLC_BASE = Baseline LDL_C value
  PCHG = Percent change from Baseline
            CVRISK = 1 (HeFH), 0 (non-HeFH)
            STATIN = 1 (HIS), 0 (non-HIS)
*************************************************************************************************
proc mixed;
  class USUBJID TREATMENT VISIT CVRISK  STATIN;
  model PCHG = TREATMENT  LDLC_BASE  CVRISK  STATIN  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 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 an 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.

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 30, 180, 270 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 in Lp(a) and ApoA1 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 30, 180 and 270 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 30, 180 and 270 as per the protocol, unless the conditions for Triglycerides or LDL-C described above are met at the Day 30, 180 and 270 assessments. 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 365 in HbA1c, HOMA-IR and blood glucose in the obicetrapib group compared to the placebo group.

To assess the percentage change from Baseline to Day 30, 84, 180, 270 and 365 in LDL-C in the obicetrapib group compared to the placebo group in participants who were statin intolerant a similar ANCOVA model as for the primary analyses will be used. For the percentage change from Baseline to Day 84 and 365, the LDL-C will be calculated using PUC. For the percentage change from Baseline to Day 30, 84, 180, 270 and 365, analysis will be performed using the Martin-Hopkins equation as described in Section 3.4.1 above.

The proportion of participants at Days 84, 180, and 365 who achieved LDL-C < 70 mg/dL (<1.8 mmol/L), LDL-C < 55 mg/dL (<1.4 mmol/L), and LDL-C < 40mg/dL (<1.0 mmol/L) in the obicetrapib group compared to the placebo group, will be examined using logistic regression models with covariates of treatment group, Baseline LDL-C value, CV risk (HeFH or non-HeFH), and Baseline statin therapy (HIS or non-HIS). 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
  CVRISK = 1 (HeFH), 2 (non-HeFH)
  STATIN = 1 (HIS), 2 (non-HIS)
  LDLC70 = LDL_C value less than 70mg/dL at DAY84 (YES/NO) for example
*************************************************************************************************************
proc logistic data= LDL_C;
     Class TREATMENT(ref=0) CVRISK STATIN / Param= Ref;
     Model LDLC70= TREATMENT BASE CVRISK STATIN / alpha=0.05 expb plcl plrl orpvalue lackfit;
    Ods output
          ParameterEstimates= Log_LDLC70_ParameterEstimates
          CLoddsPL= Log_ LDLC70_OddsRatios
          ;
Run;
```

****

For the time from Randomization until the first confirmed occurrence of event

the following analysis will be performed. The participants who withdraw from the study before the occurrence of event or event did not occur will be censored. For these participants the time-to-event will be defined as time between Randomization and ET/EOS. Other atherosclerotic events such as AAA and carotid revascularization will be identified using the preferred terms (see Appendix C). The Clinical Events Committee (CEC) adjudicated date of event will be used to identify the first confirmed occurrence of event where appropriate, otherwise the date of event as recorded in eCRF will be used. In case when CEC cannot provide adjudicated date of death, the latest date of the last dose of study drug or date of last visit will be imputed as date of death for analysis.

The Log-rank Test

The log-rank test, stratified by CV risk (HeFH or non-HeFH), and Baseline statin therapy (HIS or non-HIS) will be used to compare differences in the time-to-event between obicetrapib and placebo.

The sample SAS code can be found below:

```
**********
Note:
  TREATMENT  = 0 (Placebo),  1 (Obicetrapib)
  CVRISK        = 1 (HeFH), 2 (non-HeFH)
  STATIN        = 1 (HIS), 2 (non-HIS)
  TIME          = Time from Randomization until the first occurrence of event
  CENSOR     = 0 (Event occurred), 1 (Event did not occurred)
**********
proc lifetest data= time_to_event method=KM
     strata CVRISK STATIN/test=logrank group=TREATMENT;
     time TIME*CENSOR;
Run;
**********
```

Cox Proportional Hazard Model

A Stratified Cox proportional hazard model will be used to estimate hazard ratio between treatment groups along with the 95% confidence intervals. The model will include treatment group, CV risk (HeFH or non-HeFH), and Baseline statin therapy (HIS or non-HIS).

The Cox proportional hazard model will be implemented using SAS® Proc PHREG. The sample SAS code can be found below:

```
**********
Note:
  TREATMENT  = 0 (Placebo),  1 (Obicetrapib)
  CVRISK        = 1 (HeFH), 2 (non-HeFH)
  STATIN        = 1 (HIS), 2 (non-HIS)
  TIME          = Time from Randomization until the first occurrence of event
  CENSOR     = 0 (Event occurred), 1 (Event did not occurred)
**********
proc phreg data= time_to_event ;
     model TIME*CENSOR=TREATMENT;
     strata CVRISK STATIN;
```

```
Run;
**********************************************************************************************************
```

The proportional hazard assumption will be evaluated via examination of complementary log-log (event time) versus log (time) plots. If the proportional hazard assumption raises concerns, the non-parametric Peto-Peto-Prentice test will be applied. Nominal p-values will be provided when applicable.

The number of occurrences of CV events will be analyzed using a Poisson regression model including covariates of treatment group, CV risk (HeFH or non-HeFH), and Baseline statin therapy (HIS or non-HIS). Rate ratio with 95% confidence intervals will be estimated. The model assumption for equidispersion will be tested and if this assumption is not supported, alternative analysis and models such as negative binomial or zero-inflated Poisson model will be explored.

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

```
**********************************************************************************************************
Note:
  TREATMENT  = 0 (Placebo),  1 (Obicetrapib)
  COUNT      = Number of events
  TIME       = Follow up time for each participant measured in days
  LOGT       =log(TIME)
**********************************************************************************************************
proc genmod data= events ;
    class TREATMENT;
    model COUNT=TREATMENT/offset=logt disp=poisson link=log;
run;
**********************************************************************************************************
```

Descriptive and graphical summaries will be presented by treatment group. Adjudicated clinical events will be presented in participants listing.

Plasma obicetrapib concentrations will be summarized with descriptive statistics based on the Safety Population.

3.4.4 Subgroup Analysis

The primary efficacy endpoints 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 Hispanic/Latino)
- BMI (<25 kg/m^2, 25 -30 kg/m^2, ≥30 kg/m^2)
- Region (Asia, Eastern Europe, Western Europe and North America)
- Country (USA vs Other, Japan vs Other, China vs Other)
- 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%, ≥5.7 to ≤6.4%, >6.4%)
- Urinary albumin:creatinine ratio (normal, micro-albuminuria, macro-albuminuria)
- eGFR (<30ml/min/1.73 m^2, ≥30 to <45ml/min/1.73 m^2, ≥45 to <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)
- GLP1 use (yes, no)
- SGLT2 use (yes, no)
- Hs-CRP (<2mg/dL, ≥2mg/dL)
- HeFH (Genotyping confirmed or DLCN>8 points or Simon Broome definite; Simon Broome possible FH diagnosis).

The ANCOVA model with fixed effects for the treatment group, subgroup variable, treatment-by-subgroup variable, along with CV risk (HeFH or non-HeFH) and Baseline statin therapy (HIS or non-HIS) and covariates of Baseline LDL-C will be used. The CV risk and Baseline statin therapy covariates may be excluded from the model in cases where inclusion causes the model not to converge. The least squares (LS) mean, standard errors, and 2-sided 95% confidence intervals for each treatment group and for the mean difference compared to placebo, within each level of the subgroup, will be estimated. No imputation of missing data will be performed; therefore, the subgroup analysis will perform using only observed data. For the primary efficacy endpoint, the LDL-C values measured by preparative ultracentrifugation will be used. However, if the analysis for the primary efficacy endpoint specified above will show a difference between the 3 LDL-C approaches, then Friedewald and Martin-Hopkins equations may be considered for subgroup analysis.

3.5 Safety Assessment

Safety Population will be the primary population for the safety analyses. All safety endpoints will be summarized descriptively by treatment group and overall. No statistical inference will be applied to the safety endpoints.

3.5.1 Adverse Events (AEs)

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

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

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

- Any study drug related TESAEs
- Any TEAEs leading to death.

The TEAEs described above will be summarized separately by system organ class and preferred term. The non-serious TEAEs occurring in more than 2% of participants in any treatment group and preferred term will be summarized.

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

3.5.2 Event of Special Interest

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

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

Muscle-related abnormalities will be summarized by treatment group and by Baseline eGFR category.

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 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.
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 had initiation of antihypertension medication within 30 days of the start date of the adverse event, that initiation of an antihypertension medication will be considered as due to a change in blood pressure.
The number and percentage of participants receiving/not receiving antihypertensive medication(s) at Baseline with changes to or initiation of new antihypertensive medication(s) due to changes in blood pressure will be summarized by treatment group.

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

3.5.3 Clinical Laboratory Tests

Blood 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. Only urine dipstick analysis will be performed locally, while the rest of clinical laboratory test will be processed by a central laboratory. See Appendix A of the protocol for a complete list of analytes. Blood samples (a full serum chemistry panel, hematology, coagulation) must be collected under fasting conditions (a minimum of 8 hours) and prior to the next dose of study drug (at applicable visits).

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

Chemistry and hematology laboratory parameters will be listed.

3.5.4 Vital Signs

Vital signs (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.

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; ophthalmological examination; 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.

Physical examination will be listed.

3.5.7 24-hour ABPM

Participants who consent to participate in the ABPM substudy will have a 24-hour ABPM assessment conducted at Screening (Visit 1, Baseline) and at Day 270 (Visit 6). If necessary, a repeated assessment can be completed within the respective visit window and performed such that the assessment is not done concurrently with other study procedures.

Blood pressure and heart rate measurements will be obtained every 20 minutes during the interval of 06:00 hours to 21:59:59 hours (daytime period), and every 30 minutes during the interval of 22:00:00 hours to 05:59:59 hours (nighttime period). Within a 24-hour recording, 64 measurements would be expected (16 hours of 3 recordings/hour and 8-hours of 2 recordings/hour). A valid ABPM will have no more than 2 consecutive hours without a measured and recorded blood pressure reading and have at least 70% (≥45 recordings) of the overall readings with a measured and recorded blood pressure reading.

Counts and percentage of participants with non-missing blood pressure measurements will be presented by time, visit and treatment group.

Descriptive statistics for 24-hour average systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate values, including the change from baseline, will be presented at each visit by treatment groups and overall. Additionally, hourly average summaries of diastolic and systolic blood pressure will be provided by visit and treatment group.

Summaries of blood pressure measurements that meet the following criteria will be performed by time daytime period average, and nighttime average, visit and treatment group:

- 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.

The change in average 24-hour SBP from Baseline to Day 270 will be analyzed using an ANCOVA model with a fixed effect for the treatment group and covariates of Baseline average SBP, Age, Sex and background diagnosis of hypertension. The change in average 24-hour SBP from Baseline to Day 270 will be presented by treatment group with a 2-sided 95% CI (1-sided α = 0.025) for the difference between the treatment groups. Obicetrapib will be considered non-inferior to placebo if the upper bound of the 2-sided 95% CI (1-sided α = 0.025) for the difference between the treatment groups is less than the non-inferiority margin corresponding to 3 mmHg.

The model will be fit assuming unequal variances for each treatment group. The primary analysis will be conducted based on the 24-hour ABPM Population.

A sensitivity analysis will be performed using all randomized participants from ITT Population who received at least 1 dose of study drug and had either a Baseline or Day 270 ABPM assessment. If the participant only had an assessment at one of these two visits, the value at the missing visit will be imputed. Similarly, if a participant had an invalid ABPM assessment (following the definition of a valid ABPM assessment described previously), the records at that visit will be set to missing and the overall assessment value will be imputed. Missing data will be imputed based on multiple imputation methodology assuming the data are MAR. The variables for the imputation model will consist of the SBP values from Baseline and Day 270, along with treatment group, Age, Sex and background diagnosis of hypertension. For the imputation methodology, 100 imputed data sets will be generated with no missing values at Day 270. For each imputation data set, the change from baseline to Day 270 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 sample SAS code can be found in Appendix D.

A supplemental analysis will be performed consisting of participants in the 24-hour ABPM Population who did not discontinue study drug prior to the Day 270 assessment. The change in average 24-hour SBP from Baseline to Day 270 will be analyzed using a similar ANCOVA model as the primary ABPM assessment.

Similar ANCOVA models as described for SBP will be used to assess the change from Baseline to Day 270 in average SBP daytime period and average SPB nighttime period in the obicetrapib group compared to the placebo group.

Forest plots of daytime period, nighttime period, and 24-hour change from Baseline with 95% confidence interval will be displayed for SBP.

The change in average 24-hour DBP from Baseline to Day 270 will be analyzed using similar methods as for SBP.

24-hour ABPM data will be presented in participants listing.

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). Subjects, 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 three changes from the protocol v6.0.

The first change is the addition of time points to the exploratory endpoint, Day 84 and Day 180, to evaluate trough levels of obicetrapib from Baseline.

The second change relates to the effect of obicetrapib on cardiovascular events. Additional exploratory endpoints were added:

- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, or non-fatal stroke, or coronary revascularization
- The time from Randomization until the first confirmed occurrence of a composite of CHD death, non-fatal MI, or non-fatal stroke, or non-elective coronary revascularization
- The time from Randomization until the first confirmed occurrence of a composite of CHD death, non-fatal MI, or non-fatal stroke, or coronary revascularization
- The time from Randomization until the first confirmed occurrence of a composite of CHD death, non-fatal MI, or non-fatal stroke
- MALE events
- Number of total CV events.

The third change is the inclusion of subgroup analysis.

7 PROGRAMMING SPECIFICATIONS

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

APPENDIX A: REFERENCES

1. United States Food and Drug Administration. Assessment of pressor effects of drugs. Guidance for industry. February 2022. https://www.fda.gov/media/113477/download. Accessed 14 June 2022.

2. Vollmer WM, Appel LJ, Svetkey LP, et al. Comparing office-based and ambulatory blood pressure monitoring in clinical trials. *J Hum Hypertens*. 2005;19(1):77-82.

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; 17: 491-503.

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: PREFERRED 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

APPENDIX C: PREFERRED TERMS FOR AAA AND CAROTID REVASCULARIZATION

Preferred Term for AAA	**Preferred Term for carotid revascularization**
Acute aortic syndrome	Carotid angioplasty
Aortic aneurysm	Carotid artery bypass
Aortic aneurysm repair	Carotid artery stent insertion
Aortic aneurysm rupture	Carotid artery stent removal
Aortic aneurysm syphilitic	Carotid endarterectomy
Aortic dilatation	Carotid revascularisation
Aortic dissection	
Aortic dissection rupture	
Aortic intramural haematoma	
False lumen dilatation of aortic dissection	
Penetrating aortic ulcer	

APPENDIX D: SAS EXAMPLE CODE 24 HOUR ABPM ANALYSIS

ANCOVA ANALYSIS

```
**********************************************************************************************
Note:
  TREATMENT  = 0 (Placebo),  1 (Obicetrapib)
  BASE          = Baseline average SBP 24-hour ABPM value
  CHG           = Change from Baseline at Day 270
  AGE           = Age
  SEX           = Sex
  HP            = Background diagnosis of hypertension
**********************************************************************************************
proc mixed data=SBP_24HR;
  class TREATMENT SEX HP;
  model CHG = TREATMENT BASE AGE SEX HP / ddfm=satterth solution cl;
  lsmeans  TREATMENT /diffs cl alpha=0.05;
run;
**********************************************************************************************
```

SENSITIVITY ANALYSIS

1. Missing data will be imputed 100 times to generate 100 datasets. Multiple imputation will be performed in two steps:

   1.1 Non-monotone values will be imputed to create a monotone missing pattern.

```
**********************************************************************************************
Note:
  TREATMENT  = 0 (Placebo),  1 (Obicetrapib)
  BASE          = Baseline average SBP 24-hour ABPM value
  Day270        = Day 270 average SBP 24-hour ABPM value
  AGE           = Age
  SEX           = Sex
  HP            = Background diagnosis of hypertension
**********************************************************************************************

          proc mi data=SBP_24HR seed=63974 nimpute=100 out= SBP_24HR_imp1;
            class TREATMENT;
            mcmc impute=monotone;
            var BASE DAY270;
          run;
**********************************************************************************************
```

   1.2 The remaining monotome missing values will be imputed.

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

```
proc sort data= SBP_24HR_imp1; by _Imputation_;run;

proc mi data=SBP_24HR_imp1 nimpute=1 out= SBP_24HR_imp2;
  by _Imputation_;
  class TREATMENT SEX HP;
  var TREATMENT SEX HP BASE DAY270;
  monotone reg(BASE= TREATMENT SEX HP);
  monotone reg(DAY270= TREATMENT SEX HP BASE);
run;
*******************************************************************************************
```

2. For each imputed dataset, the percent change from baseline to Day 270 will be analyzed using Ancova model.

```
*******************************************************************************************
Note:
  TREATMENT  = 0 (Placebo),  1 (Obicetrapib)
  BASE          = Baseline average SBP 24-hour ABPM value
  CHG           = Change from Baseline at Day 270
  AGE           = Age
  SEX           = Sex
  HP            = Background diagnosis of hypertension
*******************************************************************************************

        proc mixed data= SBP_24HR_imp2;
          by _Imputation_;
          class TREATMENT SEX HP;
          model CHG = TREATMENT BASE AGE SEX HP / ddfm=satterth solution cl;
          lsmeans  TREATMENT /diffs cl alpha=0.05;
        run;

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

3. The parameter estimates will be combined using Rubin's method.

```
*******************************************************************************************
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;

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