CLINICAL STUDY PROTOCOL

A Placebo-Controlled, Double-Blind, Randomized, Phase 3 Study to Evaluate the Effect of Obicetrapib 10 mg and Ezetimibe 10 mg Fixed Dose Combination Daily on Top of Maximally Tolerated Lipid-Modifying Therapy in Participants With Heterozygous Familial Hypercholesterolemia (HeFH) and/or Atherosclerotic Cardiovascular Disease (ASCVD) or Multiple ASCVD Risk Factors

Investigational Product: Obicetrapib 10 mg + ezetimibe 10 mg fixed dose combination (FDC)
Protocol Number: OBEZ-301

Sponsor:
NewAmsterdam Pharma B.V.
Gooimeer 2-35
1411 DC
Naarden
The Netherlands
Telephone: +31 35 699 30 00
Fax: +31 20 240 07 79

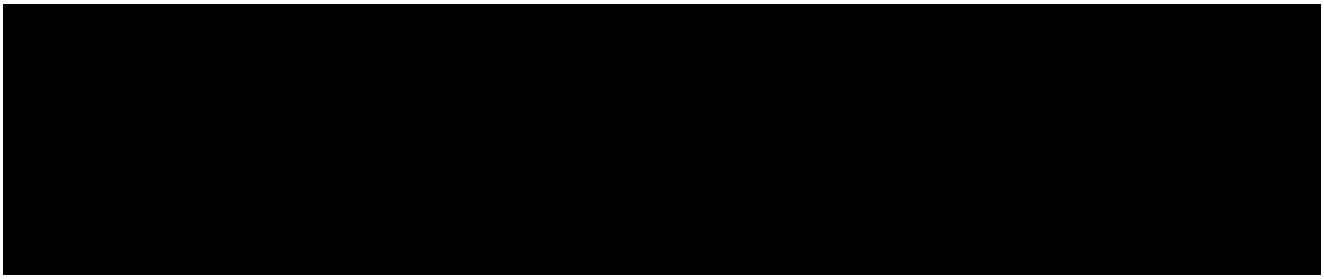
Version Number: 4.0
Original Protocol: 14 December 2022
Amendment 1: 10 August 2023
Amendment 2: 08 November 2023
Amendment 3: 09 October 2024

Sponsor's Medical Expert:	[redacted] [redacted] NewAmsterdam Pharma B.V. Gooimeer 2-35 1411 DC Naarden The Netherlands [redacted] [redacted]

SIGNATURE PAGE

STUDY TITLE: A Placebo-Controlled, Double-Blind, Randomized, Phase 3 Study to Evaluate the Effect of Obicetrapib 10 mg and Ezetimibe 10 mg Fixed Dose Combination Daily on Top of Maximally Tolerated Lipid-Modifying Therapy in Participants With Heterozygous Familial Hypercholesterolemia (HeFH) and/or Atherosclerotic Cardiovascular Disease (ASCVD) or Multiple ASCVD Risk Factors

n



INVESTIGATOR AGREEMENT

By signing below I agree that:

I have read this protocol. I approve this document and I agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by NewAmsterdam Pharma B.V. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study drugs and study procedures. I will let them know that this information is confidential and proprietary to NewAmsterdam Pharma B.V. and that it may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by NewAmsterdam Pharma B.V., with or without cause, or by me if it becomes necessary to protect the best interests of the study participants.

I agree to conduct this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation guidelines for Good Clinical Practice, and applicable regional regulations.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Placebo-Controlled, Double-Blind, Randomized, Phase 3 Study to Evaluate the Effect of Obicetrapib 10 mg and Ezetimibe 10 mg Fixed Dose Combination Daily on Top of Maximally Tolerated Lipid-Modifying Therapy in Participants With Heterozygous Familial Hypercholesterolemia (HeFH) and/or Atherosclerotic Cardiovascular Disease (ASCVD) or Multiple ASCVD Risk Factors

PROTOCOL NUMBER: OBEZ-301

INVESTIGATIONAL PRODUCT: Obicetrapib 10 mg + ezetimibe 10 mg fixed dose combination (FDC)

PHASE: 3

INDICATION: As an adjunct to diet and maximally tolerated lipid-modifying therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) and/or a history of atherosclerotic cardiovascular disease (ASCVD) or multiple ASCVD risk factors who require additional lowering of low-density lipoprotein cholesterol (LDL-C)

OBJECTIVES:

The primary objective of this study is to evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy on LDL-C at Day 84, compared with each of the following:

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

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

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

- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with placebo on non-high-density lipoprotein cholesterol (non-HDL-C) at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with placebo on apolipoprotein B (ApoB) at Day 84;
- To evaluate the effect of obicetrapib 10 mg monotherapy compared with placebo on non-HDL-C at Day 84;
- To evaluate the effect of obicetrapib 10 mg monotherapy compared with placebo on ApoB at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with ezetimibe 10 mg on non-HDL-C at Day 84;

- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with ezetimibe 10 mg on ApoB at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with obicetrapib 10 mg monotherapy on non-HDL-C at Day 84; and
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with obicetrapib 10 mg monotherapy on ApoB at Day 84.

The exploratory objectives of this study include the following:

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

POPULATION:

The population for this study will comprise participants ≥18 years of age with underlying HeFH and/or a history of ASCVD or multiple ASCVD risk factors on maximally tolerated lipid-modifying therapy. Participants must have a fasting serum LDL-C ≥70 mg/dL (≥1.8 mmol/L).

Approximately 70% of the participants enrolled into this study should be taking high-intensity statins (HIS). HIS include atorvastatin 40 and 80 mg and rosuvastatin 20 and 40 mg. No more than approximately 10% of participants in this study will be completely statin intolerant.

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

STUDY DESIGN AND DURATION:

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

Screening Period

At Screening (Visit 1), participants will be required to sign an informed consent form (ICF) before any study-related procedures are performed. After signing the ICF, participants will be assessed for study eligibility.

Treatment Period

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

- FDC therapy: Obicetrapib 10 mg + ezetimibe 10 mg;
- Obicetrapib monotherapy: Obicetrapib 10 mg;
- Ezetimibe monotherapy: Ezetimibe 10 mg; or
- Placebo.

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

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

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

Safety Follow-Up Period

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

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

Participants will be randomized in a 1:1:1:1 ratio to 1 of the following treatment groups:

- FDC therapy: Obicetrapib 10 mg + ezetimibe 10 mg (administered as 1 obicetrapib 10 mg + ezetimibe 10 mg FDC tablet, 1 obicetrapib-matched placebo tablet, and 1 ezetimibe-matched placebo capsule);
- Obicetrapib monotherapy: Obicetrapib 10 mg (administered as 1 FDC-matched placebo tablet, 1 obicetrapib 10 mg tablet, and 1 ezetimibe-matched placebo capsule);
- Ezetimibe monotherapy: Ezetimibe 10 mg (administered as 1 FDC-matched placebo tablet, 1 obicetrapib-matched placebo tablet, and 1 ezetimibe 10 mg capsule [over-encapsulated 10 mg tablet]); or
- Placebo (administered as 1 FDC-matched placebo tablet, 1 obicetrapib-matched placebo tablet, and 1 ezetimibe-matched placebo capsule).

Study drugs (2 tablets and 1 capsule) will be administered by the participant orally with water, with or without food, once daily on Day 1 to Day 84 at approximately the same time each morning.

EFFICACY ASSESSMENTS:

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

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

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

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

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

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

The exploratory efficacy endpoints include the following:

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

PHARMACOKINETIC ASSESSMENTS:

Plasma obicetrapib and ezetimibe concentrations, both in combination and each as monotherapy, will be assessed at the scheduled pharmacokinetic collection times.

SAFETY ASSESSMENTS:

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

STATISTICAL ANALYSES:

A Statistical Analysis Plan (SAP) will be finalized before database lock. Any changes to the methods described in the SAP will be described and justified as needed in the Clinical Study

Report. All study-collected data will be summarized by treatment group using descriptive statistics, graphs, and/or raw data listings. Descriptive statistics for continuous variables will include number of participants (n), mean, standard deviation (SD), median, minimum, and maximum values. Analysis of categorical variables will include frequency and percentage.

Analysis Populations

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

The Full Analysis Set (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.

The Modified ITT (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.

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

The Per-Protocol (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.

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.

Analysis of Efficacy

The ITT Population will be the primary population for the efficacy analyses. Efficacy will also be analyzed using the FAS, mITT Population, mITT On-Treatment Population, and PP Population as supportive analyses.

The primary efficacy endpoint is the percent change from Day 1 to Day 84 in LDL-C. Co-primary endpoints include the percent change from Day 1 to Day 84 in LDL-C for the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with each of the following: placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy, and for the obicetrapib 10 mg monotherapy treatment group compared with placebo. The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model with a fixed effect for the treatment group and a covariate of baseline LDL-C. 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 obtained.

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

The primary estimand will correspond to a treatment policy estimand. The target population will comprise participants who are randomized into the study. The primary summary measure to assess the treatment effect will be the LS mean difference for the primary endpoint between obicetrapib 10 mg + ezetimibe 10 mg FDC treatment and placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy based on the ANCOVA methodology. The primary estimand will be addressed using the in-study observation period (ie, including data collected post treatment discontinuation or post prohibited medication use).

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. The imputation model will be further clarified in the SAP.

Additional sensitivity analyses may be carried out under secondary estimands and/or various assumptions for missing data. Full details will be provided in the SAP.

In order to control the Type I error rate, a fixed sequential testing procedure will be implemented. In a hierarchical step-down manner, the co-primary endpoints will be tested first, followed by the secondary efficacy endpoints in the order specified. Continuous secondary efficacy endpoints will be analyzed using similar methods as in the primary efficacy analysis.

Analysis of Safety

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

SAMPLE SIZE DETERMINATION:

A sample size of at least 380 evaluable participants (ie, 95 participants per treatment group) will provide more than 90% power to detect a 30% difference in LDL-C reduction at Day 84 (SD of 25%) for the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with the placebo group at a 1-sided significance level of 0.025.

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

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

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

SITES: Approximately 60 sites

SPONSOR:

NewAmsterdam Pharma B.V.
Gooimeer 2-35
1411 DC
Naarden
The Netherlands
Telephone: +31 35 699 30 00
Fax: +31 20 240 07 79

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
ApoE	Apolipoprotein E
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
CETP	Cholesteryl ester transfer protein
CI	Confidence interval
CK	Creatine kinase
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CT	Computed tomography
CV	Cardiovascular
CVD	Cardiovascular disease
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EIU	Exposure In Utero
EOT	End of Treatment
ESI	Event of special interest
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	Fixed dose combination
FH	Familial hypercholesterolemia
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HIS	High-intensity statin(s)
HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A reductase
ICF	Informed consent form
ICH	International Council for Harmonisation

Abbreviation	Definition
IMP	Investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive response technology
ITT	Intent-to-Treat
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
Lp(a)	Lipoprotein (a)
LS	Least squares
MACE	Major adverse cardiovascular event(s)
MI	Myocardial infarction
mITT	Modified Intent-to-Treat
NMR	Nuclear magnetic resonance
NODM	New-onset diabetes mellitus
non-HDL-C	Non-high-density lipoprotein cholesterol
PCSK9	Proprotein convertase subtilisin kexin type 9
PK	Pharmacokinetic(s)
PP	Per-Protocol
QTc	Heart rate-corrected QT interval
QTcF	Heart rate-corrected QT interval using Fridericia's formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
sdLDL-C	Small dense low-density lipoprotein cholesterol
SUSAR	Suspected Unexpected Serious Adverse Reaction
TG	Triglyceride(s)
ULN	Upper limit of normal
VLDL-C	Very low-density lipoprotein cholesterol
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND INFORMATION

NewAmsterdam Pharma B.V. is developing obicetrapib (TA-8995) a selective cholesteryl ester transfer protein (CETP) inhibitor, as an adjunct to diet and maximally tolerated lipid-modifying therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) and/or a history of atherosclerotic cardiovascular disease (ASCVD) or multiple ASCVD risk factors who require additional lowering of low-density lipoprotein cholesterol (LDL-C). This study will be a placebo-controlled, double-blind, randomized, Phase 3 study to evaluate the efficacy, safety, and tolerability of obicetrapib 10 mg, both as a fixed dose combination (FDC) with ezetimibe 10 mg and as monotherapy, on top of maximally tolerated lipid-modifying therapy.

1.1 Background on Cardiovascular Disease

Despite advances in treatment, cardiovascular disease (CVD) is the leading cause of death globally, resulting in over 17 million deaths annually.[1] Elevated LDL-C is a major modifiable risk factor for the development of CVD.[2,3] Lowering LDL-C has been shown to reduce the risk of death or myocardial infarction (MI), and the clinical risk reduction is linearly proportional to the absolute LDL-C reduction.[4] Approximately 100 million people worldwide are treated with lipid-modifying therapies, predominantly statins, to reduce LDL-C and the associated risk of cardiovascular (CV) events. Patients with documented ASCVD are at very high risk for events and require intensive pharmacologic intervention.[5,6] For a variety of reasons, many with ASCVD are unable to attain aggressive LDL-C treatment goals despite the addition of lipid-modifying agents to maximally tolerated statin therapy.[7]

Familial hypercholesterolemia (FH) refers to individuals with extremely elevated LDL-C due to underlying genetic mutations of the low-density lipoprotein (LDL) receptor, apolipoprotein B (ApoB), and proprotein convertase subtilisin/kexin type 9 (PCSK9). In adult patients with HeFH, LDL-C usually exceeds 190 mg/dL (4.9 mmol/L) and can be as high as 400 mg/dL (10.4 mmol/L). HeFH is the most common form of the disease with a prevalence of approximately 1 in 300 to 500 persons worldwide and as high as 1 in 100 persons in some populations. HeFH increases the risk of atherosclerosis leading to CV events. The mean age for the onset of CVD is relatively young, at 42 to 46 years in men and 51 to 52 years in women.[8] The National Lipid Association recommends that adults with HeFH use statins to achieve ≥50% reduction in LDL-C. HeFH patients at an even higher risk for CVD (such as those with a history of ASCVD, diabetes, smoking, family history, and other risk factors) have a treatment goal of ≤70 mg/dL (≤1.8 mmol/L). Those unable to achieve these treatment goals with maximally tolerated statin therapy require additional lipid-modifying therapy and still may be unable to reach LDL-C treatment goals.

Lowering LDL-C is the primary therapeutic lipid target in patients with HeFH and/or ASCVD. LDL-C is largely accepted as a valid surrogate endpoint of CV events by clinicians and regulatory authorities.[9] Chronic LDL-C elevations lead to progressive accumulation of atherosclerotic lesions in the arteries that require long-term management. While lifestyle changes are the primary intervention, these measures seldom reduce plasma LDL-C by >15%. Particularly in patients with HeFH and/or ASCVD, pharmacologic treatments are required to adequately treat hyperlipidemia.[10] Evidence supporting LDL-C as a therapeutic target and surrogate for CV outcomes comes from interventional studies with LDL-C-lowering therapies, epidemiological studies, and genetic variants (both gain of function and loss of function). Large randomized clinical studies aimed at lowering LDL-C show a consistent, logarithmic-linear relationship between LDL-C reduction and CV risk reduction, independent of the way LDL-C lowering was achieved

based on the mechanism of action.[10] A published patient-level meta-analysis, including 26 studies and more than 160,000 participants, showed a consistent relationship between LDL-C reduction and CV outcomes.[10] This analysis showed that each 1 mmol/L (38.61 mg/dL) reduction in LDL-C is associated with a 22% reduction in the 5-year incidence of major coronary events, revascularizations, and ischemic strokes. Intensive statin therapy relative to low- or moderate-intensity statin treatment confers a greater benefit in patients at high CV risk.[10] Non-statin therapies may provide additional lowering of CV risk as demonstrated in the IMPROVE-IT study adding ezetimibe to statin therapy.[11,12] Unfortunately, despite being treated with maximally tolerated lipid-modifying therapy, a substantial number of patients still do not reach their target guideline goals.[11]

Patients with HeFH and/or a history of ASCVD or multiple ASCVD risk factors who require additional lowering of LDL-C despite treatment with maximally tolerated lipid-modifying therapy, including maximally tolerated doses of statins, have an unmet medical need. Obicetrapib 10 mg + ezetimibe 10 mg FDC may offer a useful option for these patients.

1.2 Cholesteryl Ester Transfer Protein Inhibitors

CETP is a plasma glycoprotein produced in the liver and adipose tissue. It circulates in the blood, bound primarily to high-density lipoprotein cholesterol (HDL-C), and is involved in the transfer of cholesteryl esters and triglycerides (TG) between lipoproteins. In particular, it mediates the transfer of cholesteryl esters from high-density lipoprotein (HDL) to ApoB-containing particles, eg, very low-density lipoprotein and LDL-C, in exchange for TG. As a result, cholesteryl ester from HDL can be taken up by the liver through scavenger receptor class B type 1; this action also leads to decreased HDL-C and ultimately to increased LDL-C.

Inhibition of CETP activity reduces ApoB and LDL-C and increases HDL-C. CETP-inhibiting therapies were originally developed based on the premise that increasing HDL-C levels would prevent CV events. However, clinical study results and Mendelian randomization data have revealed that these effects are caused by changes in the concentration of ApoB containing particles (including LDL particles) rather than changes in the HDL-C levels.[13,14] Therefore, the LDL-C and ApoB-lowering effects, which arise from CETP inhibition and occur through upregulation of the LDL receptor, will benefit patients with elevated LDL-C and increased CV risk.

Ference and colleagues have investigated the association between changes in LDL-C levels (and other lipoproteins) and the risk of CV events related to variants in the CETP gene alone and in combination with variants in the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) gene.[13] The results of these Mendelian randomization analyses demonstrate that treatment with a CETP inhibitor has the potential to reduce the risk of CV events. Both genetic and therapeutic inhibition of CETP leads to quantitatively concordant changes in LDL-C and ApoB levels. A further Mendelian randomization analysis concluded that the clinical benefit of lower LDL-C levels per unit difference may specifically be related to the absolute reduction in ApoB-containing lipoprotein particles.[15]

The REVEAL study was a randomized, placebo-controlled trial which compared anacetrapib, a CETP inhibitor, with matching placebo on a background of atorvastatin therapy over a median 4.1-year period. Approximately 2 years after study completion, the relative reduction in major adverse CV events (MACE) in the anacetrapib group was nearly double (approximately 18%) in when compared with the reduction observed at the end of the 4-year treatment period

(approximately 9%). In addition, between-group differences in the risk of coronary death emerged in the later years of follow-up, and, importantly, no safety concerns were described for non-vascular mortality or morbidity.[16]

1.3 Obicetrapib (TA-8995)

Obicetrapib (TA-8995) is a selective CETP inhibitor. Inhibition of CETP by obicetrapib blocks the transfer of cholesteryl ester from non-atherogenic HDL particles to particles in lipoprotein fractions (including LDL) that cause atherosclerosis, and reduces the concentration of cholesterol in LDL, as well as other atherogenic lipoproteins. Obicetrapib also has several additional compound-specific activities that are hypothesized to be beneficial in patients. In a recent study, obicetrapib treatment not only reduced the number of ApoB-containing particles that constitute LDL-C, it also increased apolipoprotein E (ApoE), which leads to the removal of cholesterol via the liver and also reduced lipoprotein (a) (Lp(a)).[17] Finally, obicetrapib not only potently increases HDL-C and the concentration of apolipoprotein A1 (ApoA1)-containing lipoproteins but has been demonstrated to be a potent inducer of cholesterol efflux, which is the main driver of reverse cholesterol transport.[18] This effect is considered important because it is expected to reduce established atheroma burden.

1.4 Clinical Development of Obicetrapib

Both single-ascending dose (TA-8995-01) and multiple-ascending dose (TA-8995-02) studies of obicetrapib have been conducted in healthy volunteers. A formal, thorough QT/QTc study (TA-8995-04) demonstrated that obicetrapib has no effect on the QTcF. A drug-drug interaction study (TA-8995-05) showed no significant effect of obicetrapib on P-glycoprotein activity but showed that obicetrapib is a mild inducer of cytochrome P450 3A4. A mass balance study in healthy males concluded that obicetrapib is steadily absorbed, and the principal route of excretion was in the feces (TA-8995-07). Finally, obicetrapib capsule and tablet were determined to be bioequivalent in terms of the area under the concentration-time curve from time 0 to 72 hours, and in terms of maximum plasma concentration when wider confidence intervals (CIs) were used to due to high within-subject variability (TA-8995-08).

The first patient study conducted was a Phase 2 clinical study (TA-8995-03) in Denmark and The Netherlands where the aim was to evaluate the optimal dose of obicetrapib alone and in combination with statins in patients with mild dyslipidemia. This study concluded that a 10 mg daily dose of obicetrapib therapy resulted in an LDL-C reduction of 45.3%, an HDL-C increase of 179.0%, an ApoA1 increase of 63.4%, and a significant increase of HDL-C efflux capacity. Furthermore, given on top of atorvastatin 20 mg, obicetrapib 10 mg resulted in an additional 50.3% reduction in LDL-C. A second patient study (TA-8995-06) showed a statistically significant reduction in Lp(a) levels following 12 weeks of obicetrapib treatment.

The results of 2 additional Phase 2 studies of obicetrapib (TA-8995-303 and TA-8995-201) are available. The first study, TA-8995-303, evaluated the LDL-lowering effects of obicetrapib 5 mg in combination with ezetimibe 10 mg in participants with mild dyslipidemia. The second study, TA-8995-201, evaluated the LDL-lowering effects of obicetrapib (both 5 mg and 10 mg) as an adjunct to high-intensity statin (HIS) therapy in participants with dyslipidemia. In both studies, the primary efficacy endpoints were achieved. Another Phase 2 study, TA-8995-202, has also recently completed with pending results. This study evaluated the LDL-lowering effects of

obicetrapib 10 mg, in combination with ezetimibe 10 mg as a monotherapy, in participants on HIS therapy.

Three Phase 3 studies (TA-8995-301, TA-8995-302, and TA-8995-304) are ongoing. Two of the Phase 3 studies are investigating the LDL-C-lowering effect of 10 mg obicetrapib in participants on maximally tolerated lipid-modifying therapy. Study TA-8995-301 includes participants with HeFH and an LDL-C ≥70 mg/dL (1.8 mmol/L). Study TA-8995-302 includes participants with HeFH and/or ASCVD. Together, these 2 pivotal studies will evaluate the effects of obicetrapib 10 mg in populations requiring further LDL-C reduction across a range of baseline LDL-C values relevant to contemporary clinical practice. A third Phase 3 study (TA-8995-304) is investigating the effect of obicetrapib 10 mg on clinical outcomes (ie, MACE, including CV death, non-fatal MI, non-fatal stroke, or non-elective coronary revascularization).

1.5 Rationale

Chronic LDL-C elevation leads to progressive accumulation of arterial atherosclerotic lesions that require long-term management. While lifestyle changes are the primary intervention, these measures seldom reduce plasma LDL-C by more than 15%, and pharmacologic treatments are required to adequately treat hyperlipidemia.[10]

Statins are considered as first-line therapy for reducing LDL-C levels. However, despite lipid-modifying therapy with statins, many patients are unable to achieve acceptable levels of LDL-C.

An alternative to statin use is the use of PCSK9-targeted therapies. However, there are notable limitations with this line of therapy, including very high costs. Because PCSK9-targeted therapies are injectable, this poses a less attractive option for patients who prefer oral medications. Bempedoic acid, either as a single agent or in combination with ezetimibe, is another alternative therapy but offers only a modest reduction in LDL-C.

Accordingly, there remains an unmet need for therapies to effectively reduce elevated LDL-C levels and CV risk at an acceptable cost, a convenient dosage form, and a favorable safety and tolerability profile to encourage long-term use and patient compliance. Obicetrapib, an oral CETP inhibitor, has demonstrated safety and efficacy in the reduction of LDL-C, in addition to other beneficial effects. The combination of obicetrapib and ezetimibe, an oral cholesterol absorption inhibitor, could be a valuable alternative to a PCSK9 inhibitor in patients who require additional LDL-C lowering despite maximally tolerated lipid-modifying therapy.

1.5.1 Rationale for Obicetrapib and Ezetimibe Fixed Dose Combination Therapy

Ezetimibe selectively inhibits intestinal cholesterol absorption. Ezetimibe used as monotherapy for patients with hypercholesterolemia significantly reduces serum LDL-C levels, as evidenced by a meta-analysis of 8 randomized, double-blind, placebo-controlled studies, with a statistically significant mean reduction in LDL-C of 18.58% compared with placebo.[19] Ezetimibe in combination with statin therapy further reduces LDL-C levels. A meta-analysis of 27 studies, including more than 21,000 patients, demonstrated a 15.1% greater reduction in LDL-C in patients treated with statin and ezetimibe in combination compared with statin alone.[20] The IMPROVE-IT study,[12] in which simvastatin 40 mg daily was compared with a combination of simvastatin 40 mg plus ezetimibe 10 mg in 18,144 patients with acute coronary syndrome, demonstrated a modest but statistically significant further reduction in future CV events (a 2% absolute risk reduction over

7 years) in the combination group compared with statins alone. These large long-term studies have also demonstrated an excellent safety profile for ezetimibe. Importantly, additional Mendelian randomization studies have revealed that the CETP inhibitor HMGCR inhibitor interaction does not occur when a CETP inhibitor is combined with ezetimibe. The Phase 2 study TA-8995-303, which evaluated the LDL-lowering effects of obicetrapib 5 mg in combination with ezetimibe 10 mg in participants with mild dyslipidemia, achieved its primary endpoint, demonstrating that the combination therapy of obicetrapib 5 mg + ezetimibe 10 mg markedly reduced LDL-C, non-high-density lipoprotein cholesterol (non-HDL-C), and ApoB, and increased HDL-C and ApoE. Similarly, the recently completed Phase 2 study TA-8995-202, which evaluated the LDL-lowering effects of obicetrapib 10 mg in combination with ezetimibe 10 mg in participants on HIS therapy, also achieved its primary endpoint, demonstrating that the combination therapy of obicetrapib 10 mg + ezetimibe 10 mg also markedly reduced LDL-C, non-HDL-C, ApoB, and Lp(a) and increased HDL-C and ApoE.

This study will evaluate the effect of obicetrapib 10 mg +ezetimibe 10 mg FDC in participants with HeFH and/or a history of ASCVD or multiple ASCVD risk factors on maximally tolerated lipid-modifying therapy.

1.5.2 Dose Selection Rationale

In clinical studies in healthy volunteers, obicetrapib was generally well tolerated in single doses up to 150 mg and multiple doses up to 25 mg/day for 21 days. In clinical studies in patients, obicetrapib was also well tolerated after daily dosing of 10 mg for 12 weeks, both alone and in combination with 2 different statins. Near maximal effects were observed with the 10 mg obicetrapib dose. At this dose level, CETP activity was reduced, HDL-C levels were increased, and LDL-C levels were decreased. There were no dose-related adverse events (AEs) identified and no clinically significant changes in vital signs, electrocardiograms (ECGs), or hematology or biochemistry parameters in any clinical studies. A statistically significant reduction in Lp(a) levels from baseline was also observed at the 10 mg obicetrapib dose level. Therefore, the present study will utilize a dose of 10 mg obicetrapib in participants with HeFH and/or a history of ASCVD or multiple ASCVD risk factors who are not adequately controlled by their maximally tolerated lipid-modifying therapy.

The ezetimibe dose of 10 mg is the current Food and Drug Administration (FDA)-approved dose.

1.6 Risk/Benefit

The primary pharmacology in in vitro, ex vivo, and in vivo studies have demonstrated that obicetrapib has the ability to inhibit CETP, decrease LDL-C levels, increase HDL-C levels, and importantly, reduce the number of atherogenic ApoB-containing particles in a way that is useful in the treatment of dyslipidemia.

The safety pharmacology studies have demonstrated that obicetrapib has no adverse effect on critical physiological systems (eg, central nervous system, respiratory system, gastric emptying, urinary tract, and steroidal hormonal production [including aldosterone levels]) at doses up to 300 mg/kg in rats.

In clinical studies in patients, obicetrapib was also well tolerated after daily dosing of 10 mg for 12 weeks, both alone and in combination with 2 different statins. There were no dose-related AEs

identified and no clinically significant changes in vital signs, ECGs, or hematology or biochemistry parameters in any clinical studies.

As obicetrapib is an experimental medicine, it is possible that unforeseen, unknown or unanticipated drug reactions and toxicities may occur. However, this clinical protocol is designed to mitigate risks to participants through a detailed plan for careful safety monitoring, systematic review of AEs, serious AEs (SAEs), pharmacokinetics (PK), and active pharmacovigilance review to assess for safety signals or trends. These considerations indicate the benefit/risk ratio for obicetrapib in this study to be favorable.

1.6.1 Coronavirus Disease 2019 Impacts

In March 2020, Coronavirus Disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2, was characterized as a pandemic by the World Health Organization (WHO). The COVID-19 pandemic has impacted clinical studies worldwide due to quarantines, site closures, travel limitations, diversion of resources, and/or general interruptions in study-related procedures. This study will be initiated during the ongoing COVID-19 pandemic. The Sponsor has reviewed guidance from regulatory authorities and reports from the literature while planning study start-up and conduct (ie, European Medicines Agency 2022, FDA 2021).[21,22]

The Sponsor will communicate with sites before study initiation and during the conduct of the study concerning the potential impact of COVID-19 on study-related procedures and overall conduct. The Sponsor will continue to monitor COVID-19 activity in the geographic areas and institutions where the trial will be conducted and conduct an ongoing risk assessment throughout the study. The risk assessment will be documented on an ongoing basis in the Sponsor's trial master file.

This study protocol includes contingency measures to ensure participant safety while enabling sites to generate reliable data and maintain integrity of the study and study data (see Section 3.1.4). The impacts of these implemented contingency measures on the outcomes of this study, including any protocol deviations that result from COVID-19 illness and/or COVID-19 control measures, will be discussed in the Clinical Study Report.

Treatment with standard of care and/or emergency use authorization medications, including vaccinations and boosters, for COVID-19 will be permitted during this study. There is no known negative impact of vaccination on obicetrapib efficacy and safety, nor any known negative impact of obicetrapib on vaccination efficacy and safety.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy on LDL-C at Day 84, compared with each of the following:

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

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

2.2 Secondary Objectives

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

- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with placebo on non-HDL-C at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with placebo on ApoB at Day 84;
- To evaluate the effect of obicetrapib 10 mg monotherapy compared with placebo on non-HDL-C at Day 84;
- To evaluate the effect of obicetrapib 10 mg monotherapy compared with placebo on ApoB at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with ezetimibe 10 mg on non-HDL-C at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with ezetimibe 10 mg on ApoB at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with obicetrapib 10 mg monotherapy on non-HDL-C at Day 84; and
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with obicetrapib 10 mg monotherapy on ApoB at Day 84.

2.3 Exploratory Objectives

The exploratory objectives of this study include the following:

- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy and the effect of obicetrapib 10 mg monotherapy compared with placebo on very low-density lipoprotein cholesterol (VLDL-C), HDL-C, TG, Lp(a), and small dense low-density lipoprotein cholesterol (sdLDL-C) at Day 84;

- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy and the effect of obicetrapib 10 mg monotherapy compared with placebo on LDL-C, HDL-C, and VLDL-C particle numbers and size, as measured by nuclear magnetic resonance (NMR) analysis, at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy and the effect of obicetrapib 10 mg monotherapy compared with placebo on the proportion of participants achieving predefined LDL-C targets at Day 84;
- To evaluate the effect of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy compared with placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy and the effect of obicetrapib 10 mg monotherapy compared with placebo on LDL-C at Day 28;
- To evaluate the safety of obicetrapib 10 mg + ezetimibe 10 mg FDC therapy, obicetrapib 10 mg monotherapy, and ezetimibe 10 mg monotherapy, assessed by clinical laboratory values and incidence of AEs; and
- To assess the mean trough plasma levels of obicetrapib and/or ezetimibe after obicetrapib 10 mg + ezetimibe 10 mg FDC therapy, obicetrapib 10 mg monotherapy, and ezetimibe 10 mg monotherapy on Days 28 and 84.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

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

3.1.1 Screening Period

At Screening (Visit 1), participants will be required to sign an informed consent form (ICF) before any study-related procedures are performed. After signing the ICF, participants will be assessed for study eligibility.

3.1.2 Treatment Period

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

- FDC therapy: Obicetrapib 10 mg + ezetimibe 10 mg;
- Obicetrapib monotherapy: Obicetrapib 10 mg;
- Ezetimibe monotherapy: Ezetimibe 10 mg; or
- Placebo.

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

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

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

3.1.3 Safety Follow-Up Period

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

3.1.4 Coronavirus Disease 2019 Contingency Measures

In cases of COVID-19 limitations, it is the Investigator's responsibility to assure the safety of participants. If necessary, the Sponsor will implement and document mitigation strategies. At the Investigator's discretion, the study visit(s) can be conducted in-clinic or virtually. If conducted virtually, the visit will include alternative methods for safety, efficacy, and distribution/collection of study drugs, including but not limited to phone/video contact, alternative location for biologic sample collection, alternative secure delivery of study drugs, home health care (if available), and a secured way of transferring participant data from and to home health services and the site.

If these contingency measures occur, the Sponsor will document the changes made, communicate recommendations about such changes in a timely fashion to minimize or prevent disruptions to the study, and support sites in implementing these changes. Documentation of these cases and the site's management of participants should be recorded in the Investigator study files. In the absence of a COVID-19 impact, it is expected that Investigators and participants follow the protocol requirements as set forth.

3.2 Study Indication

Obicetrapib 10 mg + ezetimibe 10 mg FDC is being developed as an adjunct to diet and maximally tolerated lipid-modifying therapy for the treatment of adults with HeFH and/or a history of ASCVD or multiple ASCVD risk factors who require additional lowering of LDL-C.

4 SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 Inclusion Criteria

Participants who meet all of the following criteria will be eligible to participate in the study:

1. Are willing and able to give written informed consent before initiation of any study-related procedures and willing to comply with all required study procedures;
2. Are male or female and ≥18 years of age at Screening (Visit 1);
   - Females may be enrolled if all 3 of the following criteria are met:
     - They are not pregnant;
     - They are not breastfeeding; and
     - They do not plan on becoming pregnant during the study.
   - Females of childbearing potential must have a negative urine pregnancy test at Screening (Visit 1);

     Note: Females are not considered to be of childbearing potential if they meet 1 of the following criteria as documented by the Investigator:
     - They have had a hysterectomy or tubal ligation at a minimum of 1 cycle prior to signing the ICF; or
     - They are postmenopausal, defined as ≥1 year since their last menstrual period for females ≥55 years of age or ≥1 year since their last menstrual period and have a follicle-stimulating hormone (FSH) level in the postmenopausal range at Screening (Visit 1) for females <55 years of age.
   - Females of childbearing potential must agree to use an effective method of avoiding pregnancy from Screening (Visit 1) until 35 days after the last dose of a study drug. Males whose partners are of childbearing potential must agree to use an effective method of avoiding pregnancy from Screening (Visit 1) until 35 days after the last dose of a study drug. Effective methods of avoiding pregnancy are contraceptive methods used consistently and correctly (including implantable contraceptives, injectable contraceptives, oral contraceptives, transdermal contraceptives, intrauterine devices, and barrier methods) or a sterile sexual partner.
3. Have underlying HeFH and/or a history of ASCVD or multiple ASCVD risk factors;

   Diagnosis of HeFH:

   Diagnosis must be made by either prior historical genotyping or by clinical assessment using either the WHO Criteria/Dutch Lipid Clinical Network Criteria with a score that is ≥3 points, as specified in Appendix C or the Simon Broome Register Diagnostic Criteria with an assessment of "Possible HeFH" or "Definite HeFH," as specified in Appendix D.[23,24] Participants with a diagnosis of HeFH may or may not have a history of ASCVD or ASCVD-risk equivalents;

History of ASCVD, defined by at least 1 of the following conditions:

- Coronary artery disease:
  - MI;
  - Prior coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting); or
  - Angiographic or computed tomography (CT) imaging (eg, multidetector CT or CT angiography) evidence of coronary atherosclerosis with >70% stenosis in at least 1 major epicardial coronary artery.
- Cerebrovascular disease:
  - Prior ischemic stroke confirmed by a brain imaging study (CT or magnetic resonance imaging), considered not to be caused by atrial fibrillation, valvular heart disease, or mural thrombus;
  - Carotid artery stenosis >70% on prior angiography or ultrasound; or
  - History of percutaneous or surgical carotid artery revascularization.
- Peripheral arterial disease:
  - History of percutaneous or surgical revascularization of an iliac, femoral, or popliteal artery; or
  - Prior non-traumatic amputation of a lower extremity due to peripheral artery disease.

Multiple risk factors for ASCVD, defined as follows:

- Type 2 diabetes plus 1 of the following risk factors or 3 of the following ASCVD risk factors:
  - Age >45 years (males) or >55 years (females);
  - Recent MI (>3 and <12 months prior to Randomization [Visit 2 (Day 1)]);
  - Family history of coronary heart disease (first degree relative with clinical coronary heart disease [males <55 years or females <65 years]);
  - Increased waist circumference (≥80 cm [women], ≥94 cm [men of non-Asian descent], or ≥90 cm [men of Asian descent]);
  - Current cigarette smoking;
  - Hypertension on active medical therapy;
  - High-sensitivity C-reactive protein ≥2.0 mg/L (≥19.0 nmol/L);
  - Lp(a) ≥50 mg/dL (≥125 nmol/L);
  - Low HDL-C (<40 mg/dL);
  - Coronary calcium score >100 Agatston units;
  - TG >175 mg/dL (>1.98 mmol/L); or
  - Ankle brachial index <0.9.

4. Are on maximally tolerated lipid-modifying therapy as an adjunct to a lipid-lowering diet and other lifestyle modifications, defined as follows:
   - A statin at a maximally tolerated stable dose;
     - A participant's maximally tolerated stable statin dose will be determined by the Investigator using his/her medical judgment and available sources, including the participant's self-reported history of lipid-modifying therapy for at least 8 weeks prior to Screening (Visit 1); and
     - For any participant not taking statin therapy due to statin intolerance, including those participants taking bempedoic acid or fibrate monotherapy, written confirmation will be required of both the participant and the Investigator stating that the participant is statin intolerant, aware of the benefit of statins to reduce the risk of a MACE, and aware that many other patients who are unable to tolerate a statin were actually able to tolerate a different statin or dose.

       Note: Statin intolerance will be defined as intolerance due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued, resulting in an inability to tolerate either 1) two or more statins at any dose, or 2) one statin at any dose and either an unwillingness to attempt a second statin or advice by a physician not to attempt a second statin.[25]
   - Bempedoic acid for at least 8 weeks in combination with a maximally tolerated statin prior to Screening (Visit 1); and/or
   - A PCSK9-targeted therapy alone or in combination with other lipid-modifying therapy for at least 4 doses prior to Screening (Visit 1).

     Note: Patients taking inclisiran must have received at least 2 stable doses prior to Screening.

   Note: Approximately 70% of the participants enrolled into this study should be taking HIS. No more than approximately 10% of participants in this study will be completely statin intolerant. Documentation in the electronic case report form (eCRF) of the reason why a participant is unable to take HIS is required. HIS include atorvastatin 40 and 80 mg and rosuvastatin 20 and 40 mg.
5. Have a fasting serum LDL-C at Screening (Visit 1) ≥70 mg/dL (≥1.8 mmol/L);

   Note: For eligibility purposes, LDL-C at Screening (Visit 1) will be calculated using the Martin-Hopkins equation unless TG ≥400 mg/dL (≥4.5 mmol/L) or LDL-C ≤50 mg/dL (≤1.3 mmol/L); in both cases, LDL-C level will be measured directly by preparative ultracentrifugation, also referred to as beta quantification.[26]
6. Have fasting TG <500 mg/dL (<5.7 mmol/L) at Screening (Visit 1); and
7. Have an estimated glomerular filtration rate (eGFR) ≥15 mL/min/1.73 m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration equation[27] at Screening (Visit 1).

4.2 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from participation in the study:

1. Have current or any previous history of New York Heart Association class III or IV heart failure or left ventricular ejection fraction <30%;
2. Have been hospitalized for heart failure within 5 years prior to Screening (Visit 1);
3. Have had any of the following clinical events within 3 months prior to Screening (Visit 1):
   - Non-fatal MI;
   - Non-fatal stroke;
   - Non-elective coronary revascularization; and/or
   - Hospitalization for unstable angina and/or chest pain.
4. Have uncontrolled severe hypertension, defined as either systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg at both Screening (Visit 1) and Randomization (Visit 2 [Day 1]) taken as the average of triplicate measurements. One triplicate retest will be allowed during the same visit, at which point if the retest result is no longer exclusionary, the participant may be randomized;
5. Have a formal diagnosis of homozygous FH;
6. Have active liver disease, defined as any known current infectious, neoplastic, or metabolic pathology of the liver; Child-Pugh score of 7 to 9 (Class B) or 10 to 15 (Class C); unexplained elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × upper limit of normal (ULN); or total bilirubin >2 × ULN at Screening (Visit 1);

   Note: An abnormal ALT, AST, or total bilirubin must be confirmed by a repeat abnormal measurement at least 1 week apart.
7. Have a glycosylated hemoglobin (HbA1c) ≥10.0% (≥0.100 hemoglobin fraction) or a fasting glucose ≥270 mg/dL (≥15.0 mmol/L) at Screening (Visit 1);
8. Have thyroid-stimulating hormone >1.5 × ULN at Screening (Visit 1);
9. Have creatine kinase (CK) >3 × ULN at Screening (Visit 1);
10. Have a history of a malignancy that required surgery (excluding local and wide local excision), radiation therapy, and/or systemic therapy during the 3 years prior to Randomization (Visit 2 [Day 1]);
11. Have a known history of alcohol and/or drug abuse within 5 years prior to Randomization (Visit 2 [Day 1]);
12. Have received treatment with other investigational products or devices within 30 days of Screening (Visit 1) or 5 half-lives of the previous investigational product, whichever is longer;

    Note: Participants who have received treatment for COVID-19 with standard of care and/or emergency use authorization medications, including vaccinations and boosters, within 30 days of Screening (Visit 1) or 5 half-lives of the previous investigational product **will** be permitted.
13. Are taking gemfibrozil or have taken gemfibrozil within 30 days of Screening (Visit 1);

14. Are taking ezetimibe or have taken ezetimibe within 14 days of Screening (Visit 1);
15. Have planned use of other investigational products or devices during the course of the study;
16. Have participated in any clinical study evaluating obicetrapib;
17. Have a known allergy or hypersensitivity to the study drugs, placebo, or any of the excipients in the study drugs or placebo; or
18. Have any participant condition that, according to the Investigator, could interfere with the conduct of the study, such as, but not limited to, the following:
    - Are unable to communicate or to cooperate with the Investigator;
    - Are unable to understand the protocol requirements, instructions and study-related restrictions, and the nature, scope, and possible consequences of the study (including participants whose cooperation is doubtful due to drug abuse or alcohol dependency);
    - Are unlikely to comply with the protocol requirements, instructions, and study-related restrictions (eg, uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study);
    - Have any medical or surgical condition which, in the opinion of the Investigator, would put the participant at increased risk from participating in the study; or
    - Are directly involved in the conduct of the study.

4.3 Retesting

If laboratory abnormalities during the Screening Period are considered by the Investigator to be transient, then the laboratory tests may be repeated once during the Screening Period. The Investigator's rationale for retesting should be documented. If the retest result is no longer exclusionary, the participant may be randomized.

4.4 Rescreening

A participant who is screened and does not meet the study eligibility criteria may be considered for rescreening upon Sponsor and/or Medical Monitor consultation and approval. Rescreened participants will be assigned a new participant number. Rescreening should occur no less than 5 days after the last screening visit.

4.5 Withdrawal Criteria

A participant may prematurely discontinue study drug and/or withdraw from the study at any time. However, a distinction must be made between premature discontinuation of study drug and withdrawal from the study. All efforts should be made to ensure the participant continues in the study per protocol. If a participant discontinues study drug prior to completion of the study, all efforts will be made to continue to follow the participant and collect data for all visits.

Only participants that request discontinuation from the study and withdraw consent will be considered withdrawn from the study. For safety reasons, it will be recommended that all participants who withdraw from the study complete an End of Treatment (EOT) Visit. Withdrawn participants will not be replaced.

Participants may need to discontinue study drug during the course of the study. All efforts will be made to restart the study drug; however, in the event of the following, participants may be permanently discontinued from study drug:

- Occurrence of any medical condition or circumstance that exposes the participant to substantial risk and/or does not allow the participant to adhere to the protocol-specified study drug treatment regimen;
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition, which indicates to the Investigator that continued treatment with study drug is not in the best interest of the participant;
- Pregnancy; or
- Requirement of prohibited concomitant medication.

If a participant permanently discontinues study drug, he/she will continue to participate in study visits as described below:

- If a participant discontinues study drug between Visit 2 (Day 1) and Visit 3 (Day 28) or at Visit 3 (Day 28), he/she should complete an EOT Visit at Day 28, return to complete Visit 4 (Day 84), and return to complete the Safety Follow-up Visit (Day 112); or
- If a participant discontinues study drug between Visit 3 (Day 28) and Visit 4 (Day 84), he/she should return for Visit 4 (Day 84) and the Safety Follow-up Visit (Day 112) as scheduled.

If a participant who discontinues study drug will not or does not return for 1 or all future visits, efforts should be made to collect as much information as possible via a telephone call, conducted at the same time as the planned study visit(s). The efforts to follow-up via telephone at each planned visit day should continue through the day of the planned Safety Follow-up Visit (Day 112).

When participants enter the study, contact information and alternative methods of contact will be collected in the event that the site loses contact with the participant. In the case of a participant lost to follow-up, attempts to contact the participant must be made and documented in the participant's medical records.

The Sponsor or regulatory agency can terminate the study at any time for any reason.

5 STUDY TREATMENTS

5.1 Treatment Groups

Participants will be randomized in a 1:1:1:1 ratio to 1 of the following treatment groups:

- FDC therapy: Obicetrapib 10 mg + ezetimibe 10 mg (administered as 1 obicetrapib 10 mg + ezetimibe 10 mg FDC tablet, 1 obicetrapib-matched placebo tablet, and 1 ezetimibe-matched placebo capsule);
- Obicetrapib monotherapy: Obicetrapib 10 mg (administered as 1 FDC-matched placebo tablet, 1 obicetrapib 10 mg tablet, and 1 ezetimibe-matched placebo capsule);
- Ezetimibe monotherapy: Ezetimibe 10 mg (administered as 1 FDC-matched placebo tablet, 1 obicetrapib-matched placebo tablet, and 1 ezetimibe 10 mg capsule [over-encapsulated 10 mg tablet]); or
- Placebo (administered as 1 FDC-matched placebo tablet, 1 obicetrapib-matched placebo tablet, and 1 ezetimibe-matched placebo capsule).

5.2 Rationale for Dosing

In clinical studies in healthy volunteers, obicetrapib was generally well tolerated in single doses up to 150 mg and multiple doses up to 25 mg/day for 21 days. In clinical studies in patients, obicetrapib was also well tolerated after daily dosing of 10 mg for 12 weeks, both alone and in combination with 2 different statins. Near maximal effects were observed with the 10 mg obicetrapib dose. At this dose level, CETP activity was reduced, HDL-C levels were increased, and LDL-C levels were decreased. There were no dose-related AEs identified and no clinically significant changes in vital signs, ECGs, or hematology or biochemistry parameters in any clinical studies. A statistically significant reduction in Lp(a) levels from baseline was also observed at the 10 mg obicetrapib dose level. Therefore, the present study will utilize a dose of 10 mg obicetrapib in participants with HeFH and/or a history of ASCVD or multiple ASCVD risk factors who are not adequately controlled by their maximally tolerated lipid-modifying therapy.

The ezetimibe dose of 10 mg is the current FDA-approved dose.

5.3 Randomization and Blinding

Participants who meet all inclusion criteria and none of the exclusion criteria will be randomized at Visit 2 (Day 1) via the [redacted] Interactive Response technology (IRT) system a 1:1:1:1 ratio to receive FDC therapy, obicetrapib monotherapy, ezetimibe monotherapy, or placebo as described in Section 5.1.

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

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

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 all study-related visits and assessments and the database has been locked for analysis.

Participants, Investigators, the Clinical Research Organization, and the Sponsor will be blinded to all lipid results from Day 1 (Visit 2) for the first participant until the database is locked in order to protect blinding to treatment assignment.

Active and placebo products will be identical as described in Section 5.5.1. Medication kits with a unique code will be assigned to participants at various points in the study by the IRT system.

5.4 Breaking the Blind

Study drugs will be managed using the IRT system. Each user will have a unique username and passcode to access the system. Investigators shall not break the study blind during the study, and Investigators should treat all participants as if they had received obicetrapib or ezetimibe. However, in situations in which knowledge of the participant's study drugs is necessary for clinical management, the Investigator should proceed with unblinding.

Once a participant's treatment assignment has been unblinded, the Medical Monitor or designee should be notified within 24 hours of unblinding of the treatment. Information relating to unblinding (eg, date and time of the call to the Medical Monitor by the Investigator, reason for unblinding, and date and time of unblinding) shall be clearly recorded in the participant's study file and in the electronic data capture (EDC) system, as part of relevant standard operating procedures. In addition, the Investigator should consider whether the clinical event prompting unblinding should be considered an AE or SAE, according to the regulatory definitions or criteria for AEs or SAEs, and if so, submit an AE/SAE report to the Sponsor or designee (see Section 8.3). The Sponsor or designee will also unblind any SAE reports that are unexpected and considered to be related to the study drugs, in accordance with safety reporting guidance and regulations.

Each study site will be provided with a sealed envelope containing a 6-digit code that can be entered into the IRT system to unblind a participant's treatment assignment.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

The study drugs consist of obicetrapib 10 mg + ezetimibe 10 mg FDC tablets, obicetrapib 10 mg tablets, ezetimibe 10 mg capsules (over-encapsulated 10 mg tablets), and matching placebo for each. All study drugs are manufactured in accordance with current Good Manufacturing Practice.

Obicetrapib 10 mg + ezetimibe 10 mg FDC tablets are white to off-white, round, film-coated tablets with no identifying markings, containing 10 mg of obicetrapib (as obicetrapib calcium drug substance) and 10 mg of ezetimibe drug substance. [redacted]

Obicetrapib tablets are round, white film-coated tablets, with no identifying markings, containing 10 mg of obicetrapib (as obicetrapib calcium drug substance). [redacted]

[redacted].

Ezetimibe capsules are ezetimibe 10 mg tablets (Ezetrol®) filled into capsule shells, 1 tablet per capsule. Each capsule also contains lactose monohydrate, an excipient material common to the tablets, as a filler to prevent the tablet from rattling in the capsule shell.

Placebo tablets for the FDC are matching round, white film-coated tablets, with no identifying markings. [redacted]

Placebo tablets for obicetrapib are matching round, white film-coated tablets, with no identifying markings. The excipients present in the tablet cores are microcrystalline cellulose, mannitol, sodium starch glycolate, colloidal silicon dioxide, and magnesium stearate. A commercially available film-coating formula (Opadry II white, ex Colorcon) is applied to the cores.

Placebo capsules for ezetimibe are the identical capsule shells filled with the excipient filler material, lactose monohydrate (no tablets). Additionally, magnesium stearate is added to the filler.

All study drugs will be packaged into kits providing the 3 study drugs (2 tablets and 1 capsule) for each treatment group. The kits will be clearly labelled to indicate which tablets and capsule to use on each day. Each individual kit will provide a sufficient supply for 28 days of dosing, with enough for an extra 8 days of dosing. The shelf-life will be assigned based on the stability of the individual study drugs and will not be greater than the expiry date of the input ezetimibe tablets. The kits will be stored at room temperature, no higher than 77°F (25°C), protected from moisture.

The physical, chemical, and pharmaceutical formulation properties and characteristics of the obicetrapib 10 mg + ezetimibe 10 mg FDC and obicetrapib tablets are described in the Investigator's Brochure.

All study drugs will be labelled in accordance with all applicable local regulatory requirements.

5.5.2 Study Drug Preparation and Dispensing

At Visit 2 (Day 1), participants will receive 1 kit (containing 36 FDC tablets or matching placebo tablets, 36 obicetrapib tablets or matching placebo tablets, and 36 ezetimibe capsules or matching placebo capsules totaling 108 tablets/capsules per kit) with the study drugs appropriate for the participant's treatment group. At Visit 3 (Day 28), participants will receive 2 kits as described above. The 2 kits provide sufficient supplies for 56 days of dosing, with enough for an extra 16 days of dosing in case the participant needs to postpone Visit 4 (Day 84). Each individual kit will provide a sufficient supply for 28 days of dosing, with enough for an extra 8 days of dosing. Participants will be instructed to take 3 units from the kit each day. The kit will be clearly labelled to indicate which tablets and capsule to use on each day. Participants will be instructed to bring all unused study drugs to the site at the next visit.

This study protocol includes contingency measures to manage disruptions due to COVID-19 control measures, including modifications to dispensation of the study drugs specific to situations where COVID-19 is impacting study conduct. See Section 3.1.4 for details of COVID-19 contingency measures. In the absence of a COVID-19 impact, it is expected that Investigators and participants follow the protocol requirements as set forth.

5.5.3 Study Drug Administration

Study drugs (2 tablets and 1 capsule) will be administered by the participant orally with water, with or without food, once daily on Day 1 to Day 84 at approximately the same time each morning. On days with visits scheduled, participants should not take the study drugs prior to the visit but should bring the study drugs with them to the site. The study drugs will be administered with water following all fasted blood samples. At Visit 3 (Day 28) and Visit 4 (Day 84), participants will dose from the kit received at the previous visit (Visit 2 [Day 1] and Visit 3 [Day 28], respectively).

If a participant forgets to take the study drugs on a given day, he/she should take the next dose as normal and should not take a double dose to make up for the forgotten dose.

5.5.4 Treatment Compliance

Compliance with the study drug regimen will be evaluated by counting unused tablets and capsules. Participants will be instructed to bring all unused study drugs to the site at Visit 3 (Day 28) and at Visit 4 (Day 84) (or at an EOT Visit, in cases of early discontinuation of study drug or study). During the Treatment Period, if compliance is not between 80% and 120%, inclusive, the participant will be counselled about the importance of compliance with the regimen.

5.5.5 Storage and Accountability

All study drugs must be stored at room temperature, no higher than 77°F (25°C), and protected from moisture in a secure area with access limited to the Investigator and authorized site personnel.

In accordance with regulatory requirements, the Investigator or designated site personnel must document the amount of study drugs dispensed and/or administered to participants, the amount returned by participants, and the amount received from and returned to the Sponsor (or representative) when applicable. Study drug accountability records must be maintained throughout the course of the study. The accountability unit for this study is a tablet or capsule. Discrepancies are to be reconciled or resolved. At the end of the study, a final reconciliation must be made between the amount of study drug supplied, dispensed, and subsequently returned to the Sponsor (or representative) or destroyed with the written permission of the Sponsor, in accordance with applicable laws and study site's procedures. Procedures for final disposition of unused study drugs will be provided in the appropriate study manual.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Participants must not take any other investigational products or use any investigational devices within 30 days of Screening (Visit 1) or 5 half-lives of the previous investigational product, whichever is longer, or during the course of the study or they will be excluded from study participation.

Participants must not take gemfibrozil within 30 days of Screening (Visit 1) or during study participation. Participants must not take additional ezetimibe within 14 days of Screening (Visit 1) or during study participation. Participants must agree not to donate blood during study participation.

5.6.2 Restricted Medications and/or Procedures

Participants receiving maximally tolerated lipid-modifying therapy (other than PCSK9-targeted therapies) as described in Section 4.1 should be on a stable dose for at least 8 weeks prior to Screening (Visit 1). Participants taking PCSK9-targeted therapies (except for inclisiran) should have received at least 4 doses prior to Screening (Visit 1). Participants taking inclisiran must have received at least 2 stable doses prior to Screening (Visit 1). There should be no planned medication or dose changes of lipid-modifying therapy during study participation. Participants must agree not to initiate any new lipid-modifying medications (including supplements) and not to change the dose of the existing lipid-modifying medications (including supplements) during study participation. However, if there are changes to lipid-modifying therapy during the study, these data will be recorded and reported as a protocol deviation.

Participants are not required to be taking statins. Reasons for not using statin therapy must be documented as described in Section 5.6.3.

5.6.3 Documentation of Prior and Concomitant Medication Use

Any prior lipid-modifying therapies, administered at any time, must be recorded. Any non-lipid-modifying medications administered within 90 days prior to the first dose of study drug must be recorded. All prior and concomitant medications must be documented in the source documents and applicable eCRFs. Concomitant medications will continue to be assessed and recorded at every study visit from the time of informed consent until study participation is complete.

Data from all participants regarding lipid-modifying medications taken throughout the study will be recorded. The number of participants taking a statin or PCSK9-targeted therapy during the study and the number of participants who discontinue background statin therapy, along with the reasons for discontinuation of background statin therapy, will be recorded in the applicable eCRFs.

A participant's maximally tolerated stable statin dose will be determined by the Investigator using his/her medical judgment and available sources, including the participant's self-reported history of lipid-modifying therapy, for at least 8 weeks prior to Screening (Visit 1), and recorded in the applicable eCRFs.

No more than approximately 10% of participants in this study will be completely statin intolerant. For any participant not taking statin therapy due to statin intolerance (as defined in Inclusion Criterion 4), including those participants taking bempedoic acid or fibrate monotherapy, written confirmation will be required of both the participant and the Investigator stating that the participant is statin intolerant, aware of the benefit of statins to reduce the risk of a MACE, and aware that many other patients who are unable to tolerate a statin were actually able to tolerate a different statin or dose. Statin intolerance should be recorded as intolerance to any dose of any statin as historical events attributed to the statin in question, in the source documentation and eCRF as part of the medical history to confirm intolerance to statins.[25]

Documentation in the eCRF of the reason why a participant is unable to take HIS is required.

5.6.4 Dietary Guidelines

Participants will be instructed to follow a lipid-lowering diet as per local or regional guidelines throughout the study.

6 STUDY PROCEDURES

Study procedures will follow the Schedule of Procedures (Appendix A).

Unscheduled visits may be scheduled as needed per the judgment of the Investigator. Procedures will be determined based on the reason for the visit.

7 EFFICACY AND PHARMACOKINETIC ASSESSMENTS

7.1 Efficacy Assessments

7.1.1 Efficacy Endpoints

7.1.1.1 Primary efficacy endpoint

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

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

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

7.1.1.2 Secondary efficacy endpoints

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

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

7.1.1.3 Exploratory efficacy endpoints

The exploratory efficacy endpoints include the following:

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

7.1.2 Lipid Profile/Biomarkers

Blood samples for the lipid profile must be obtained under fasting conditions (ie, after the participant has fasted for a minimum of 8 hours) and before study drug administration. For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications. If a participant is not fasting, the Investigator should reschedule the visit as soon as possible.

LDL-C level will be calculated using the Martin-Hopkins and Friedewald equations unless TG ≥400 mg/dL (≥4.5 mmol/L) or LDL-C ≤50 mg/dL (≤1.3 mmol/L); in both cases, LDL-C level will be measured directly by preparative ultracentrifugation, also referred to as beta quantification.[26,28] Additionally, LDL-C will be measured by preparative ultracentrifugation at Visit 2 (Day 1), Visit 4 (Day 84), and, in cases of early discontinuation of study drug or study, at an EOT Visit, for all participants.

7.1.3 Lipoprotein (a)

A plasma sample for Lp(a) will be collected at visits specified in the Schedule of Procedures (Appendix A). Samples should be collected prior to study drug administration and while the participant is fasting (a minimum of 8 hours).

7.1.4 Nuclear Magnetic Resonance Analysis of Lipids

A plasma sample for NMR analysis will be collected at visits specified in the Schedule of Procedures (Appendix A). Samples should be collected prior to study drug administration and while the participant is fasting (a minimum of 8 hours).

7.1.5 Urine Albumin-Creatinine Ratio

A urine sample for urine albumin-creatinine ratio will be collected at visits specified in the Schedule of Procedures (Appendix A).

7.1.6 Serum Archive Samples for Future Assessment

Serum archive samples will be collected prior to the first dose at Visit 2 (Day 1) and at Visit 4 (Day 84) (or at an EOT Visit, in cases of early discontinuation of study drug or study) for potential future assessment of conditions associated with cholesterol metabolism. Samples should be collected prior to study drug administration and while the participant is fasting (a minimum of 8 hours). If the samples are analyzed, it will be for non-genetic tests.

7.2 Pharmacokinetic Assessments

Plasma obicetrapib and ezetimibe concentrations, both in combination and each as monotherapy, will be assessed at the scheduled PK collection times.

A PK sample will be collected prior to study drug administration for trough measurements of obicetrapib and ezetimibe in plasma. At Visit 2 (Day 1), Visit 3 (Day 28), Visit 4 (Day 84), and the EOT Visit, in cases of early discontinuation of study drug or study, participants should take study drug after a trough PK sample has been collected.

8 SAFETY ASSESSMENTS

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

8.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not related to the IMP. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory assessment variables, will be monitored and documented from the time of first dose of study treatment until completion of Visit 5 (Day 112). Participants should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to a study drug. Beginning at the date of the first dose of study treatment, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure itself.

Any medical condition already present at the date of the first dose of study treatment should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination findings (eg, ECG) that are detected during the study or are present at the date of the first dose of study treatment and significantly worsen during the study should be reported as AEs, as described below. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Abnormal test results that are determined to be an error should not be reported as an AE. Laboratory abnormalities or other abnormal clinical findings (eg, ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality;
- If action taken with a study drug is required as a result of the abnormality; or

- Based on the clinical judgment of the Investigator.

8.1.1 Adverse Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, ie, the relationship cannot be ruled out.

8.1.2 Unexpected Adverse Drug Reaction

An Unexpected Adverse Drug Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

For the obicetrapib 10 mg + ezetimibe 10 mg FDC, the reference safety information is included in Section 6 of the Investigator’s Brochure currently in force. The reference safety information will be reviewed annually by the Sponsor and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report, where possible.

For ezetimibe, the reference safety information is included in the Summary of Product Characteristics.

8.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to the study drugs using the categories of yes or no.

Assessment of severity

Mild – An event that is easily tolerated and generally not interfering with normal daily activities.

Moderate – An event that is sufficiently discomforting to interfere with normal daily activities.

Severe – An event that is incapacitating with inability to work or perform normal daily activities.

Causality assessment

The relationship of an AE to the administration of the study drugs is to be assessed according to the following definitions:

No (unrelated, not related, unlikely to be related) – The time course between the administration of study drugs and the occurrence or worsening of the AE is not consistent with a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study drugs and the occurrence or worsening of the AE is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc) can be identified.

The definition implies a reasonable possibility of a causal relationship between the event and the study drugs. This means that there are facts (evidence) or arguments to suggest a causal relationship.

The following factors should also be considered:

- The temporal sequence from a study drug administration-

  The event should occur after a study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.

- Underlying, concomitant, intercurrent diseases-

  Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the participant may have.

- Concomitant drug-

  The other drugs the participant is taking or the treatment the participant receives should be examined to determine whether any of them might be recognized to cause the event in question.

- Known response pattern for this class of study drug-

  Clinical and/or preclinical data displayed in the Investigator's Brochure may indicate whether a particular response is likely to be a class effect.

- Exposure to physical and/or mental stresses-

  The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.

- The pharmacology and PK of the study drugs-

  The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drugs should be considered.

8.1.4 Events of Special Interest

ESIs will be monitored, regardless of whether these events were reported as AEs. Any events that qualify as an AE or SAE will be reported accordingly (see Sections 8.1, 8.2, and 8.3).

ESIs will 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 ophthalmic events (ie, macular degeneration), described as follows:

- AST or ALT >3 × ULN;
- Total bilirubin >2 × ULN;
- CK >5 × ULN;
- NODM or worsening of glycemic control;

  Note: NODM is defined by 1 or more of the following criteria, based upon information from AE, medication, and laboratory data:

  - AE indicating new type 1 or type 2 diabetes;
  - Initiation of anti-diabetes medication with confirmation of the diagnosis of diabetes by blinded external review by experts in diabetology;

- HbA1c ≥6.5% (≥0.065 hemoglobin fraction); and/or
- Two consecutive values of fasting plasma glucose that are ≥126 mg/dL (≥7.0 mmol/L).

Note: Worsening of glycemic control will be defined as an 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 <15 mL/min/1.73 m^2, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, and/or an increase in serum creatinine of ≥0.3 mg/dL (≥26.5 μmol/L) from baseline;
- Changes to antihypertensive medication(s) due to changes in blood pressure in those participants receiving antihypertensive medication(s) treatment at baseline, and new antihypertensive medication prescriptions for participants not previously treated for hypertension; and
- Macular degeneration.

These ESIs will be monitored through review of the AE and laboratory databases.

8.1.4.1 Guidelines for management of elevated liver enzymes

Participants with signs or symptoms consistent with liver injury (eg, nausea, vomiting, anorexia, fatigue, or right upper abdominal pain or discomfort) should undergo immediate testing of ALT, AST, gamma-glutamyl transferase, bilirubin, alkaline phosphatase, prothrombin time, and international normalized ratio.

In the absence of clinical symptoms, participants with ALT or AST >3 × ULN (if normal at baseline) or >2-fold change (if abnormal at baseline) should be retested within 48 to 72 hours for the usual serum measurements (ALT, AST, alkaline phosphatase, and bilirubin) to confirm the abnormalities and to determine if the associated values are increasing or decreasing. There should also be an inquiry about symptoms at the time of follow-up.

If the above abnormalities are confirmed:

- Repeat liver enzyme and serum bilirubin tests 2 or 3 times weekly. The frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the participant is asymptomatic;
- Obtain a more detailed history of symptoms and prior or concurrent diseases;
- Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diet;
- Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease;
- Obtain a history of exposure to environmental chemical agents;
- Obtain additional tests to evaluate liver function, as appropriate (eg, international normalized ratio, direct bilirubin); and
- Consider gastroenterology or hepatology consultations.

Study drug discontinuation should occur if:

- ALT or AST >8 × ULN;
- ALT or AST >5 × ULN for more than 2 weeks;
- ALT or AST >3 × ULN and total bilirubin >2 × ULN or international normalized ratio >1.5; or
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

8.1.4.2 Guidelines for monitoring and management of creatine kinase

If at any time after Randomization (Visit 2 [Day 1]) a participant experiences a CK elevation >5 × ULN, the participant will undergo a repeat confirmatory assessment as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available.

A repeat CK assessment will include query for related symptoms.

If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK abnormality >5 × ULN and the participant is asymptomatic, he/she should receive further assessment and investigation into the cause, assessment of whether there is renal injury, and measurement of CK approximately weekly, or more frequently if clinically indicated, until resolution. If CK levels continue to rise, the study drug should be discontinued.

If the participant experiences a CK elevation >5 × ULN and is symptomatic, the following should be completed:

- Interruption of study drug;
- Clarification of the nature, duration, and intensity of muscle symptoms;
- Review of possible predisposing factors, such as unaccustomed exercise, heavy alcohol intake, and viral illness (consider performing serology);
- Evaluation for additional diagnoses or other conditions which can cause myopathy, including muscle tenderness (by physical examination), weakness, rash, measurement of serum creatinine, and/or urine dipstick analysis with microscopy if indicated;
- Measurement of clinical chemistries to assess the possibility of lactic acidosis; and
- Follow-up of symptoms and CK until the abnormality has resolved.

If, based on the above evaluation, an alternative explanation is suspected, consideration can be given to resuming study drug once CK returns to baseline levels.

If no alternative explanation exists, consideration should be given to discontinuing study drug treatment.

If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK >10 × ULN, the participant should be discontinued from study drug, even in the absence of symptoms. The signs and symptoms and laboratory assessments as outlined above should also be evaluated. The participant should continue being followed in the study for safety.

Any event of rhabdomyolysis, regardless of CK level, should lead to study drug interruption or discontinuation until the contribution of obicetrapib has been excluded.

8.1.4.3 Guidelines for monitoring and management of new-onset diabetes mellitus

Diabetes mellitus may be newly diagnosed during the study as described in Section 8.1.4. If a participant is newly diagnosed with diabetes mellitus during the course of the study, the Investigator will recommend referral for initial diabetes education and management by an appropriate healthcare provider (eg, diabetologist, endocrinologist, or primary care provider). Interventions for management may include diet and lifestyle counseling, self-monitoring of blood glucose, oral glucose-lowering medications, injectable medications, or insulin as deemed necessary by the treating physician based on the level of hyperglycemia and relevant symptoms.

8.1.4.4 Guidelines for monitoring and management of significant changes in renal function

If at any time after Randomization (Visit 2 [Day 1]) a participant experiences ANY of the following, the participant will undergo a repeat confirmatory assessment as soon as is reasonably possible, preferably within 3 to 7 days of the laboratory result becoming available:

- A >25% decrease in eGFR from baseline, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation;
- An eGFR <15 mL/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.

In consultation with the Medical Monitor and/or nephrologist, if no alternative etiology is determined, the study drug should be discontinued if participants experience an unexplained, confirmed increase in serum creatinine of ≥0.3 mg/dL (≥26.5 µmol/L) from baseline or an unexplained, confirmed >25% decrease in eGFR from baseline.

If any of these individual laboratory parameters are confirmed, such events of decline in renal function should be recorded as an ESI.

8.1.4.5 Guidelines for monitoring and management of changes to antihypertensive medication(s)

Any changes to antihypertensive medication(s) due to changes in blood pressure in those participants receiving antihypertensive medication(s) treatment at baseline will be assessed by the Investigator, primary care physician, or other appropriate health care provider to assess for etiologies of blood pressure change, to confirm clinical safety of the participant, to assess the need for any AE or SAE reporting, and to arrange for appropriate medical follow-up.

8.1.4.6 Guidelines for management of macular degeneration

In cases of suspected macular degeneration or acute vision loss, participants will be referred for an ophthalmological consultation.

8.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the participant at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

  Note: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as a SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a pre-existing condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (ie, no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- An important medical event.

  Note: Important medical events that do not meet any of the above criteria may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent 1 of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial reports

All SAEs occurring from the time of the first dose of study treatment until 30 days following the last administration of study drug must be reported to [redacted] within 24 hours of the knowledge of the occurrence. After the 30-day reporting window, any SAE that the Investigator considers related to a study drug must be reported to the [redacted] or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the EDC system for the study. When the form is completed, [redacted] personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to [redacted] at [redacted] or call the [redacted] SAE

reporting line (phone number listed below), and fax/email the completed paper SAE form to [redacted] (contact information listed in Section 8.6) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Follow-up reports

The Investigator must continue to follow the participant until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the participant dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (eg, participant discharge summary or autopsy reports) to [redacted] via fax or email. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

8.4 Pregnancy Reporting

If a participant becomes pregnant during the study or within the Safety Follow-up Period defined in the protocol, the Investigator is to stop dosing with the study drug immediately. The participant should complete an EOT Visit as soon as possible. The participant will continue to participate in study visits as described in Section 4.5.

A pregnancy is not considered to be an AE or SAE; however, it must be reported to [redacted] within 24 hours of knowledge of the event. [redacted] will then provide the Investigator/site the Exposure In Utero (EIU) form for completion. The Investigator/site must complete the EIU form and fax/email it back to [redacted]

If the female partner of a male participant becomes pregnant while the participant is receiving study drugs or within the Safety Follow-up Period defined in the protocol, the Investigator should notify [redacted] as described above.

The pregnancy should be followed until the outcome of the pregnancy, whenever possible. Once the outcome of the pregnancy is known, the EIU form should be completed and faxed/emailed to [redacted]. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

8.5 Expedited Reporting

The Sponsor/designee will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening as soon as possible to the FDA and to applicable Institutional Review Boards (IRBs), and in any case no later than 7 days after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 days.

All other SUSARs will be reported to the FDA, other regulatory authorities, as applicable, and to applicable IRBs as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor/designee.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

The requirements above refer to the requirements relating to study drugs.

8.6 Special Situation Reports

Special situation reports include reports of overdose, misuse, abuse, medication error, and reports of adverse reactions associated with product complaints.

- **Overdose:** Refers to the administration of a quantity of a medicinal product given per administration or cumulatively (accidentally or intentionally), which is above the maximum recommended dose according to the protocol. Clinical judgement should always be applied. In cases of a discrepancy in the drug accountability, overdose will be established only when it is clear that the participant has taken additional dose(s) or the Investigator has reason to suspect that the participant has taken additional dose(s).
- **Misuse:** Refers to situations where the medicinal product is intentionally and inappropriately used not in a way that is not in accordance with the protocol instructions or local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- **Abuse:** Is defined as persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.
- **Medication error:** Is any unintentional error in the prescribing, dispensing, or administration of a medicinal product by a healthcare professional, participant, or consumer, respectively. The administration or consumption of the unassigned treatment and administration of an expired product are always reportable as medication errors, cases of participants missing doses of investigational product are not considered reportable as medication error.
- **Product complaint:** Is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a drug or device after it is released for distribution. A special situations form will only be completed if a complaint is associated with an adverse drug reaction.

All special situation events as described above must be reported on the Special Situations Report form and faxed/emailed to [redacted] (contact information listed below) within 24 hours of knowledge of the event. All AEs associated with these Special Situation reports should be reported as AEs or SAEs as well as recorded on the AE eCRF and/or the SAE report form. Details of the symptoms and signs, clinical management, and outcome should be provided, when available.

[redacted]
Telephone: [redacted]
Fax: [redacted]
Email: [redacted]

8.7 Clinical Laboratory Evaluations

8.7.1 Chemistry, Hematology, and Coagulation Assessments

Blood for chemistry, hematology, and coagulation will be obtained as indicated in Appendix A and sent to a central laboratory for analysis. See Appendix B for a complete list of clinical laboratory analytes. Blood samples for chemistry and hematology must be obtained under fasting conditions (ie, after the participant has fasted for a minimum of 8 hours) and before study drug administration. For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications. If a participant is not fasting, the Investigator should reschedule the visit as soon as possible. eGFR will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[27] At Screening (Visit 1), Visit 4 (Day 84), and, in cases of early discontinuation of study drug or study, at an EOT Visit, chemistry panel will include HbA1c.

8.7.2 Endocrinology Assessments

A urine pregnancy test will be performed for women of childbearing potential at Screening (Visit 1) prior to their participation in the study, at Visit 4 (Day 84), and at an EOT Visit, in cases of early discontinuation of study drug or study.

An FSH test will be performed at Screening (Visit 1) prior to participation in the study in women <55 years of age for whom it has been ≥1 year since their last menstrual period.

8.8 Vital Signs

Vital signs will be taken as indicated in Appendix A. Vital signs will include body temperature, heart rate, and triplicate blood pressure (systolic and diastolic) measurements. Participants should be in the supine position after at least 10 minutes rest prior to the vital sign measurements.

8.9 Weight and Height

Weight and height will be measured at Screening (Visit 1) and will be used to calculate body mass index. Measurement of weight should be performed with the participant dressed in indoor clothing with shoes removed.

8.10 Demographics

Participant demographic data (eg, gender, race, ethnicity, and birth date/year) will be collected at Screening (Visit 1).

8.11 Electrocardiograms

A single 12-lead ECG will be performed in the supine position after 10 minutes of rest at visits specified in Appendix A. ECGs are to be assessed for clinical significance by a qualified medical designee at the study site.

8.12 Physical Examinations

A physical examination will be performed as indicated in Appendix A. The physical examination should comprise a focused examination, which includes general, respiratory, CV, abdominal, and extremities evaluations.

9 STATISTICS

9.1 Analysis Populations

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

The Full Analysis Set (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.

The Modified ITT (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.

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

The Per-Protocol (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.

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.

9.2 Statistical Methods

A Statistical Analysis Plan (SAP) will be finalized before database lock. Any changes to the methods described in the SAP will be described and justified as needed in the Clinical Study Report. All study-collected data will be summarized by treatment group using descriptive statistics, graphs, and/or raw data listings. Descriptive statistics for continuous variables will include number of participants (n), mean, standard deviation (SD), median, minimum, and maximum values. Analysis of categorical variables will include frequency and percentage.

Unless otherwise stated, baseline values will be the last non-missing measurements taken prior to the participant receiving any study drug.

9.2.1 Analysis of Efficacy

The ITT Population will be the primary population for the efficacy analyses. Efficacy will also be analyzed using the FAS, mITT Population, mITT On-Treatment Population, and PP Population as supportive analyses.

9.2.1.1 Primary efficacy analysis

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

will be analyzed using an analysis of covariance (ANCOVA) model with a fixed effect for the treatment group and a covariate of baseline LDL-C. 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 obtained.

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

The primary estimand will correspond to a treatment policy estimand. The target population will comprise participants who are randomized into the study. The primary summary measure to assess the treatment effect will be the LS mean difference for the primary endpoint between obicetrapib 10 mg + ezetimibe 10 mg FDC treatment and placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy based on the ANCOVA methodology. The primary estimand will be addressed using the in-study observation period (ie, including data collected post treatment discontinuation or post prohibited medication use).

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. The imputation model will be further clarified in the SAP.

Additional sensitivity analyses may be carried out under secondary estimands and/or various assumptions for missing data. Full details will be provided in the SAP.

9.2.1.2 Secondary efficacy analyses

In order to control the Type I error rate, a fixed sequential testing procedure will be implemented. In a hierarchical step-down manner, the co-primary endpoints will be tested first, followed by the secondary efficacy endpoints in the order specified. Continuous secondary efficacy endpoints will be analyzed using similar methods as in the primary efficacy analysis.

9.2.1.3 Exploratory analyses

No adjustment for multiple comparisons will be made for the exploratory efficacy endpoints.

Exploratory efficacy endpoints corresponding to continuous variables will be analyzed using a similar ANCOVA model as in the primary efficacy analysis. The 2-sided 95% CI for LS means will be provided for continuous variables. Odds ratio and 95% CI for the odds ratio will be provided for exploratory efficacy endpoints corresponding to binary variables. Descriptive and graphical summaries by treatment group will also be presented.

Full details of the models and analyses to be performed will be provided in the SAP.

9.2.2 Analysis of Safety

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

AEs will be categorized by primary system organ class and preferred term as coded using the Medical Dictionary for Regulatory Activities category designations. Summaries of AEs, including the number and percentage of participants who experience an AE, will be provided.

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

9.2.3 Interim Analysis

No interim analysis is planned for this study.

9.2.4 Sample Size Determination

A sample size of at least 380 evaluable participants (ie, 95 participants per treatment group) will provide more than 90% power to detect a 30% difference in LDL-C reduction at Day 84 (SD of 25%) for the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with the placebo group at a 1-sided significance level of 0.025.

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

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

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

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed, per the monitoring plan, by the Clinical Research Associate (CRA) during monitoring visits. The CRAs will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for.

10.1.2 Computer Systems

Data will be processed using a validated computer system conforming to regulatory requirements.

10.1.3 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations Part 11 and other appropriate international regulations. All passwords will be strictly confidential.

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

- Medical Dictionary for Regulatory Activities (latest) for medical history and AEs; and
- WHO Drug Dictionary for prior and concomitant medications.

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator.

10.2 Record Keeping

Records of participants, source documents, monitoring visit logs, eCRFs, inventory of study drugs, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last participant in the study.

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human participants. Compliance with this standard provides public assurance that the rights, safety, and wellbeing of study participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

11.2 Institutional Review Board

The IRB will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of participants. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, ICF, advertisements (if applicable), written information given to the participants, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

Federal regulations and International Council for Harmonisation (ICH) Guidelines require that approval be obtained from an IRB prior to participation of participants in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for participant recruitment, and any other written information regarding this study to be provided to a participant or participant's legal guardian must be approved by the IRB.

No study drugs will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent Procedures

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure that each study participant is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure that the participant has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each participant before any study-related activity is performed and should document in the source documentation that consent was obtained prior to enrollment in the study. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, their representatives, auditors, the IRB, and/or regulatory agencies. A copy of the signed ICF will be given to the participant.

11.4 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, applicable regulatory requirements, Declaration of Helsinki, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized, and easily retrievable data. Before the enrollment of any participant in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, Investigator's

Brochure, eCRFs and procedures for their completion, informed consent process, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. Study monitoring may include onsite, remote, or a combination of both onsite and remote monitoring. During the monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data is entered by the site, the CRA will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the Sponsor or their designee and provide any missing information, whenever possible.

All monitoring activities will be reported and archived.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, regulatory authorities, and the IRB as appropriate. Participants or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Participant medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

11.6 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participants (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

11.7 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

11.8 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 Code of Federal Regulations Part 54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

12 STUDY ADMINISTRATIVE INFORMATION

12.1 Protocol Amendments

Any amendments to the study protocol will be communicated to the Investigators by [redacted] or the Sponsor. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB, unless immediate implementation of the change is necessary for participant safety. In this case, the situation must be documented and reported to the IRB within 5 working days.

13 REFERENCES

1. World Health Organization. Cardiovascular diseases (CVDs). http://www.who.int/mediacentre/factsheets/fs317/en/. Accessed 30 March 2021.
2. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation.* 2014;129(3):e28-e292.
3. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *J Am Coll Cardiol.* 2004;44(3):720-732.
4. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet.* 2005;366(9493):1267-1278.
5. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2019;140(11):e596-e646.
6. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J*. 2020;41(1):111-188.
7. Jacobson TA. NLA Task Force on Statin Safety--2014 update. *J Clin Lipidol*. 2014;8(3 Suppl):S1-S4.
8. Robinson JG. Management of familial hypercholesterolemia: a review of the recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Manag Care Pharm*. 2013;19(2):139-149.
9. Lansberg P, Lee A, Lee ZV, et al. Nonadherence to statins: individualized intervention strategies outside the pill box. *Vasc Health Risk Manag*. 2018;14:91-102.
10. Cholesterol Treatment Trialists' (CTT) Collaboration. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376(9753):1670-1681.
11. Banach M, Rizzo M, Toth PP, et al. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. *Arch Med Sci*. 2015;11(1):1-23.
12. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372(25):2387-2397.
13. Ference BA, Kastelein JJP, Ginsberg HN, et al. Association of genetic variants related to CETP inhibitors and statins with lipoprotein levels and cardiovascular risk. *JAMA*. 2017;318(10):947-956.
14. Tall AR, Rader DJ. Trials and tribulations of CETP inhibitors. *Circ Res*. 2018;122(1):106-112.
15. Ference BA, Kastelein JJP, Ray KK, et al. Association of triglyceride-lowering LPL variants and LDL-C-lowering LDLR variants with risk of coronary heart disease. *JAMA*. 2019;321(4):364-373.

16. American Heart Association Scientific Sessions, 2019. MDP477. The effects of anacetrapib therapy on occlusive vascular events during post-trial follow-up of the REVEAL randomized trial. https://www.ctsu.ox.ac.uk/files/research/reveal_aha_ptfu_slides_2019_11_12.pdf. Accessed 22 November 2021.
17. Hovingh GK, Kastelein JJP, van Deventer SJ, et al. Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet*. 2015;386(9992):452-460.
18. van Capelleveen JC, Kastelein JJP, Zwinderman AH, et al. Effects of the cholesteryl ester transfer protein inhibitor, TA-8995, on cholesterol efflux capacity and high-density lipoprotein particle subclasses. *J Clin Lipidol*. 2016;10(5):1137-1144.e3.
19. Pandor A, Ara RM, Tumur I, et al. Ezetimibe monotherapy for cholesterol lowering in 2,722 people: systematic review and meta-analysis of randomized controlled trials. *J Intern Med*. 2009;265(5):568-580.
20. Morrone D, Weintraub WS, Toth PP, et al. Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials. *Atherosclerosis*. 2012;223(2):251-261.
21. European Medicines Agency. Guidance on the management of clinical trials during the COVID-19 (coronavirus) pandemic. Version 5. 10 February 2022. Accessed 27 June 2022. https://health.ec.europa.eu/system/files/2022-02/guidanceclinicaltrials_covid19_en_1.pdf.
22. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), et al. Conduct of clinical trials of medical products during the COVID-19 public health emergency. Guidance for industry, investigators, and institutional review boards. US Dept of Health and Human Services, Food and Drug Administration. 30 August 2021. Accessed 03 December 2021. https://www.fda.gov/media/136238/download.
23. World Health Organization. Familial hypercholesterolaemia (FH): report of a second WHO consultation. 04 September 1998. http://whqlibdoc.who.int/hq/1999/WHO_HGN_FH_CONS_99.2.pdf. Accessed 21 April 2022.
24. Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. *N Engl J Med.* 2020;382(16):1520-1530.
25. Nicholls SJ, Lincoff AM, Bays HE, et al. Rationale and design of the CLEAR-outcomes trial: evaluating the effect of bempedoic acid on cardiovascular events in patients with statin intolerance. *Am Heart J.* 2021;235:104-112.
26. Martin SS, Blaha MJ, Elshazly MB, et al. LDL calculator. Johns Hopkins Medicine. https://ldlcalculator.com. Accessed 27 October 2023.
27. Levey AS and Inker LA. CKD-EPI equations for glomerular filtration rate (GFR). MDCalc. https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr. Accessed 11 November 2022.
28. Friedewald W. LDL calculated. MDCalc. https://www.mdcalc.com/ldl-calculated. Accessed 11 November 2022.

APPENDIX A: SCHEDULE OF PROCEDURES

	Screening[a,b]	Treatment Period			Safety Follow-Up	
Visit	**1**	**2**	**3**	**4**	**5**	
Week	**Up to -2**	**0**	**4**	**12**	**16**	**EOT[c]**
Day (±Visit Window)	**-14 to -1**	**1**	**28 (±7)**	**84 (±7)**	**112 (±7)**	**–**
Informed consent[d]	X					
Inclusion/exclusion criteria	X	X[e]				
Demographic information	X					
Medical/surgical history	X					
Prior/concomitant medications	X	X	X	X	X	X
Weight and height[f]	X					
Physical examination[g]	X			X		X
Vital signs[h]	X	X	X	X	X	X
12-lead ECG[i]	X					
Urine pregnancy test[j]	X			X		X
FSH test[k]	X					
Fasting chemistry and hematology[l]	X	X	X	X	X	X
Coagulation parameters	X			X		X
Fasting lipid profile[m]	X	X	X	X		X
Fasting Lp(a)[n]		X		X		X
Urine sample for UACR	X	X	X	X	X	X
Pharmacokinetics[o]		X	X	X		X
Serum archive sample[p]		X		X[q]		X
Randomization		X				
Dispense study drugs[r]		X	X			
Study drug administration[s]		----------X----------				
Study drug compliance			X	X[q]		X
Register visit in IRT	X	X	X	X		X
Adverse events		X	X	X	X	X

Note: When several assessments are required at the same visit, samples for clinical laboratory assessments should be collected after completing other assessments, such as physical examinations, vital signs, and 12-lead ECGs.
Note: In cases of COVID-19 limitations, it is the Investigator's responsibility to assure the safety of participants. If necessary, the Sponsor will implement and document mitigation strategies as described in Section 3.1.4. In the absence of a COVID-19 impact, it is expected that Investigators and participants follow the protocol requirements as set forth.
Note: For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications for a minimum of 8 hours.
Note: Unscheduled visits may be scheduled as needed per the judgment of the Investigator. Procedures will be determined based on the reason for the visit.

a. If laboratory abnormalities during the Screening Period are considered by the Investigator to be transient, then the laboratory tests may be repeated once during the Screening Period. The Investigator's rationale for retesting should be documented. If the retest result is no longer exclusionary, the participant may be randomized.
b. A participant who is screened and does not meet the study eligibility criteria may be considered for rescreening upon Sponsor and/or Medical Monitor consultation and approval. Rescreened participants will be assigned a new participant number. Rescreening should occur no less than 5 days after the last screening visit.
c. Participants who discontinue study drug between Visit 2 (Day 1) and Visit 3 (Day 28) or at Visit 3 (Day 28) should complete an EOT Visit at Day 28, return to complete Visit 4 (Day 84), and return to complete the Safety Follow-up Visit (Day 112). In addition, participants who withdraw from the study should complete an EOT Visit. Participants who discontinue study drug between Visit 3 (Day 28) and Visit 4 (Day 84) will not undergo an EOT Visit but continue with study visits per protocol.
d. Participants will be required to sign an ICF before any study-related procedures are performed.
e. Confirm the participant continues to meet the inclusion and exclusion criteria and assess any updates since Screening (Visit 1).
f. Weight and height will be measured at Screening (Visit 1) and will be used to calculate body mass index. Measurement of weight should be performed with the participant dressed in indoor clothing, with shoes removed.
g. The physical examination should comprise a focused examination, which includes general, respiratory, CV, abdominal, and extremities evaluations.
h. Vital signs will include body temperature, heart rate, and triplicate blood pressure (systolic and diastolic) measurements. Participants should be in the supine position after at least 10 minutes rest prior to the vital sign measurements.
i. A single 12-lead ECG will be performed in the supine position after 10 minutes of rest. ECGs are to be assessed for clinical significance by a qualified medical designee at the study site.
j. For women of childbearing potential only.
k. FSH test will be performed in women <55 years of age for whom it has been ≥1 year since their last menstrual period.
l. At Screening (Visit 1), Visit 4 (Day 84), and EOT, chemistry panel will include HbA1c.
m. LDL-C, HDL-C, and VLDL-C will also be evaluated by NMR analysis for particle numbers and size. LDL-C level will be calculated using the Martin-Hopkins and Friedewald equations unless TG ≥400 mg/dL (≥4.5 mmol/L) or LDL-C ≤50 mg/dL (≤1.3 mmol/L); in both cases, LDL-C level will be measured directly by preparative ultracentrifugation, also referred to as beta quantification. Additionally, LDL-C will be measured by preparative ultracentrifugation at Visit 2 (Day 1), Visit 4 (Day 84), and EOT for all participants (Sources: Martin SS, Blaha MJ, Elshazly MB, et al. LDL calculator. Johns Hopkins Medicine. https://ldlcalculator.com. Accessed 27 October 2023; Friedewald W. LDL calculated. MDCalc. https://www.mdcalc.com/ldl-calculated. Accessed 11 November 2022).
n. Samples should be collected prior to study drug administration.
o. A PK sample will be collected prior to study drug administration for trough measurements of obicetrapib and ezetimibe in plasma.
p. Serum archive samples will be collected prior to the first dose at Visit 2 (Day 1) and at Visit 4 (Day 84) (or at an EOT Visit, in cases of early discontinuation) for potential future assessment of conditions associated with cholesterol metabolism. Samples should be collected prior to study drug administration and while the participant is fasting (a minimum of 8 hours). If the samples are analyzed, it will be for non-genetic tests.
q. This assessment does not need to be repeated if the participant discontinued study drug early and has already undergone an EOT Visit.
r. At Visit 2 (Day 1), participants will receive 1 kit (containing 36 FDC tablets or matching placebo tablets, 36 obicetrapib tablets or matching placebo tablets, and 36 ezetimibe capsules or matching placebo capsules totaling 108 tablets/capsules per kit) with the study drugs appropriate for the participant's treatment group. At Visit 3 (Day 28), participants will receive 2 kits as described above. The 2 kits provide sufficient supplies for 56 days of dosing, with enough for an extra 16 days of dosing in case the participant needs to postpone Visit 4 (Day 84). Each individual kit will provide a sufficient supply for 28 days of dosing, with enough for an extra 8 days of dosing. Participants will be instructed to take 3 units from the kit each day. The kit will be clearly labelled to indicate which tablets and capsule to use on each day. Participants will be instructed to bring all unused study drugs to the site at the next visit.
s. Study drugs (2 tablets and 1 capsule) will be administered by the participant orally with water, with or without food, once daily on Day 1 to Day 84 at approximately the same time each morning. On days with visits scheduled, participants should not take the study drugs prior to the visit but should bring the study drugs with them to the site. The study drugs will be administered with water following all fasted blood samples. At Visits 3 and 4, participants will dose from the kit received at the previous visit (Visits 2 and 3, respectively). If a participant permanently discontinues study drug, he/she will continue to participate in study visits, as described in Section 4.5, but will no longer administer study drug.

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

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Amylase
Aspartate aminotransferase	Bicarbonate
Bilirubin (total, direct, and indirect)	Blood urea nitrogen
Calcium	Chloride
Creatine kinase	Creatinine
Estimated glomerular filtration rate [1]	Gamma-glutamyl transferase
Glucose (fasting)	Glycosylated hemoglobin [2]
High-sensitivity C-reactive protein	Inorganic phosphorus
Lactate dehydrogenase	Lipase
Potassium	Sodium
Total protein	Uric acid

1. Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. (Source: Levey AS and Inker LA. CKD-EPI equations for glomerular filtration rate (GFR). MDCalc. https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr. Accessed 11 November 2022).
2. Screening (Visit 1), Visit 4 (Day 84), and EOT only.

Coagulation Parameters

International normalized ratio	Prothrombin time

Endocrinology

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

1. Follicle-stimulating hormone test will be performed in women <55 years of age for whom it has been ≥1 year since their last menstrual period.
2. For women of childbearing potential only.

Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count
White blood cell count and differential [1]	

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

Lipid Profile

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

1. LDL-C level will be calculated using the Martin-Hopkins and Friedewald equations unless TG ≥400 mg/dL (≥4.5 mmol/L) or LDL-C ≤50 mg/dL (≤1.3 mmol/L); in both cases, LDL-C level will be measured directly by preparative ultracentrifugation, also referred to as beta quantification. Additionally, LDL-C will be measured by preparative ultracentrifugation at Visit 2 (Day 1), Visit 4 (Day 84), and EOT for all participants (Sources: Martin SS, Blaha MJ, Elshazly MB, et al. LDL calculator. Johns Hopkins Medicine. https://ldlcalculator.com. Accessed 27 October 2023; Friedewald W. LDL calculated. MDCalc. https://www.mdcalc.com/ldl-calculated. Accessed 11 November 2022).

Other Laboratory Analytes

- Lipoprotein (a)
- Urine albumin-creatinine ratio

APPENDIX C: DIAGNOSTIC SCORING TABLE FOR FAMILIAL HYPERCHOLESTEROLEMIA (CONSTRUCTED BY THE DUTCH LIPID CLINIC NETWORK)

Criteria	Score
Family history	
a) First-degree relative known with premature (men <55 years, women <60 years) coronary and vascular disease; OR b) First-degree relative known with LDL-C >95th percentile; AND/OR	1
c) First-degree relative with tendon xanthomata and/or arcus cornealis; OR d) Children <18 years with LDL-C >95th percentile.	2
Clinical history	
a) Patient has premature (men <55 years, women <60 years) coronary artery disease	2
b) Patient has premature (men <55 years, women <60 years) cerebral or peripheral vascular disease	1
Physical examination	
a) Tendon xanthomata	6
b) Arcus cornealis below the age of 45 years	4
Laboratory analysis[1]	
a) LDL-C >330 mg/dL (>8.5 mmol/L)	8
b) LDL-C 250 to 329 mg/dL (6.5 to 8.5 mmol/L)	5
c) LDL-C 190 to 249 mg/dL (4.9 to 6.4 mmol/L)	3
d) LDL-C 155 to 189 mg/dL (4.0 to 4.9 mmol/L)	1
DNA analysis	
a) Presence of functional LDL-R mutation (in the LDL-R, ApoB, or PCSK9 gene)	8
Diagnosis of familial hypercholesterolemia is:	
Certain when	>8 points
Probable when	6 to 8 points
Possible when	3 to 5 points

1. High-density lipoprotein cholesterol and triglycerides are normal.

ApoB = apolipoprotein B; DNA = deoxyribonucleic acid; LDL-C = low-density lipoprotein cholesterol; LDL-R = low-density lipoprotein receptor; PCSK9 = proprotein convertase subtilisin/kexin type 9.

Sources:

World Health Organization. Familial hypercholesterolaemia (FH): report of a second WHO consultation. 04 September 1998. http://whqlibdoc.who.int/hq/1999/WHO_HGN_FH_CONS_99.2.pdf. Accessed 11 November 2022

Nordestgaard BG, Chapman MJ, Humphries SE, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J.* 2013;34(45):3478-3490a. Erratum in: *Eur Heart J.* 2020;41(47):4517

McGowan MP, Hosseini Dehkordi SH, Moriarty PM, et al. Diagnosis and treatment of heterozygous familial hypercholesterolemia. *J Am Heart Assoc.* 2019;8(24):e013225

APPENDIX D: SIMON BROOME REGISTER DIAGNOSTIC CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA

Definite Familial Hypercholesterolemia:

Required laboratory = high cholesterol levels:

- Adult = Total cholesterol (TC) levels >290 mg/dL (>7.5 mmol/L) or low-density lipoprotein (LDL) cholesterol (LDL-C) >190 mg/dL (>4.9 mmol/L).

  Note: Qualifying TC and LDL-C values for the Simon Broome Register Diagnostic Criteria for Familial Hypercholesterolemia may be fulfilled by historical values.

Plus at least 1 of the 2:

- Physical finding = tendon xanthomas, or tendon xanthomas in first- or second-degree relative;

  OR

- DNA-based evidence of an LDL-receptor mutation, familial defective apolipoprotein B-100, or a proprotein convertase subtilisin/kexin type 9 mutation.

Possible Familial Hypercholesterolemia:

Laboratory = high cholesterol levels:

- Adult = TC levels >290 mg/dL (>7.5 mmol/L) or LDL-C >190 mg/dL (>4.9 mmol/L).

  Note: Qualifying TC and LDL-C values for the Simon Broome Register Diagnostic Criteria for Familial Hypercholesterolemia may be fulfilled by historical values.

Plus at least 1 of the 2:

- Family history of at least 1 of the following:
  - Family history of myocardial infarction at:
    - Age 60 years or younger in first-degree relative; or
    - Age 50 years or younger in second-degree relative.

  OR

- Family history of elevated TC:
  - >290 mg/dL (>7.5 mmol/L) in adult first- or second-degree relative; or
  - >260 mg/dL (>6.7 mmol/L) in child, brother, or sister aged younger than 16 years.

Source: Raal FJ, Kallend D, Ray KK, et al. Inclisiran for the treatment of heterozygous familial hypercholesterolemia. *N Engl J Med*. 2020;382(16):1520-1530.