CLINICAL STUDY PROTOCOL

A Placebo-Controlled, Double-Blind, Randomized, Phase 2 Dose-Finding Study to Evaluate the Effect of Obicetrapib as an Adjunct to High-Intensity Statin Therapy

Investigational Product: Obicetrapib

Protocol Number: TA-8995-201

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SIGNATURE PAGE

STUDY TITLE: A Placebo-Controlled, Double-Blind, Randomized, Phase 2 Dose-Finding Study to Evaluate the Effect of Obicetrapib as an Adjunct to High-Intensity Statin Therapy

I, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the study.

Signature Date

[redacted]

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 BV to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study drug and study procedures. I will let them know that this information is confidential and proprietary to NewAmsterdam Pharma BV 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 BV, 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 full accordance with Food and Drug Administration Regulations, Institutional Review Board Regulations, and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: A Placebo-Controlled, Double-Blind, Randomized, Phase 2 Dose-Finding Study to Evaluate the Effect of Obicetrapib as an Adjunct to High-Intensity Statin Therapy

PROTOCOL NUMBER: TA-8995-201

INVESTIGATIONAL PRODUCT: Obicetrapib

PHASE: 2

INDICATION: Dyslipidemia

OBJECTIVES:

The primary objective of this study is to evaluate the efficacy of obicetrapib, compared to placebo, at Day 56 in decreasing low-density lipoprotein cholesterol (LDL-C) as an adjunct to high-intensity statin therapy.

The secondary objectives of this study include the following:

- To evaluate the effect of obicetrapib, compared to placebo, at Day 56 on apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), and high-density lipoprotein cholesterol (HDL-C), as an adjunct to high-intensity statin therapy;
- To assess the mean plasma levels of obicetrapib at steady state on Days 56, 84, 112, and 161; and
- To evaluate the safety and tolerability profile of obicetrapib.

POPULATION:

The population for this study includes men and women 18 to 75 years of age, inclusive, with a body mass index <40 kg/m^2, fasting LDL-C levels >70 mg/dL, and triglyceride levels <400 mg/dL at the Screening Visit, who are currently receiving high-intensity statin therapy.

STUDY DESIGN AND DURATION:

This study will be a placebo-controlled, double-blind, randomized, Phase 2 dose-finding study to evaluate the efficacy, safety, and tolerability of obicetrapib as an adjunct to high-intensity statin therapy. This study will take place at approximately 20 sites in the United States.

Screening Period

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

Treatment Period

Up to 2 weeks after the Screening Visit, participants will return to the site on Day 1 (Visit 2) and confirm study eligibility before being randomized and beginning treatment.

Approximately 114 eligible participants (38 participants per treatment group) will be randomized in a 1:1:1 ratio to 1 of the following treatment groups:

- 5 mg obicetrapib (one 5 mg obicetrapib tablet + 1 placebo tablet);
- 10 mg obicetrapib (two 5 mg obicetrapib tablets); or
- Placebo (2 placebo tablets).

During the 8-week Treatment Period, the assigned study drugs will be administered by the participants orally and once daily on Day 1 to Day 56. Participants will return to the site every 4 weeks for efficacy, safety, and pharmacokinetic (PK) 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 through database lock 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) approximately 4 weeks after the end of the Treatment Period for safety and PK assessments.

Pharmacokinetic Period

Participants will return to the site for 2 PK Visits (Visits 6 and 7) approximately 8 and 15 weeks, respectively, after the end of the Treatment Period for safety and PK assessments.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

The study drugs used in this study are as follows:

- 5 mg obicetrapib tablet; and
- Matching placebo tablet.

The study drugs listed above will be packaged to provide doses of 5 or 10 mg obicetrapib or placebo only. Participants will be randomized to receive 1 of the 2 doses of obicetrapib or placebo only. Two tablets of study drugs will be administered by the participant orally and once daily on Day 1 to Day 56 at approximately the same time each morning, with food.

EFFICACY VARIABLES:

The primary efficacy endpoint is the percent change from Day 1 to Day 56 in LDL-C for each obicetrapib group compared to the placebo group.

The key secondary efficacy endpoints include the following:

- Percent change from Day 1 to Day 56 in ApoB for each obicetrapib group compared to the placebo group;
- Percent change from Day 1 to Day 56 in non-HDL-C for each obicetrapib group compared to the placebo group; and
- Percent change from Day 1 to Day 56 in HDL-C for each obicetrapib group compared to the placebo group.

SAFETY VARIABLES:

The safety and tolerability profile of obicetrapib will be assessed by clinical laboratory assessments (chemistry and hematology), vital signs, physical examinations, and the incidence of adverse events.

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 Modified ITT (mITT) Population will include all participants in the ITT Population who receive at least 1 dose of any study drug and have a baseline value for the LDL-C assessment. Any efficacy measurement obtained during the Safety Follow-up Visit after a participant permanently discontinues the study drug or after a participant receives an excluded medication and/or procedure will be removed from the mITT analysis. Treatment classification will be based on the randomized treatment. The mITT Population will be used for the primary analysis of all efficacy endpoints.

The Per-Protocol (PP) Population will include all participants in the mITT Population who have a baseline value for the LDL-C assessment, have a Day 56 value for the LDL-C assessment, and 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 PK Population will include all participants in the mITT Population who have sufficient blood samples collected for valid estimation of PK parameters.

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 mITT Population will be the primary population for the efficacy analyses. Efficacy will also be analyzed using the ITT Population and the PP Population as supportive analyses.

The primary efficacy analysis of the percent change from Day 1 to Day 56 in LDL-C will be performed using a mixed model for repeated measures approach. The analysis will include fixed effects for treatment, visit, and treatment-by-visit interaction, along with a covariate of the baseline value. The Restricted Maximum Likelihood estimation approach will be used with an unstructured covariance matrix. The least squares means, standard errors, and 2-sided 95% confidence intervals for each treatment group and for the pairwise comparisons of each dose of obicetrapib to the

placebo group will be provided. Adjustment for multiple comparisons will be made using Dunnett's test in accordance with the power and sample size calculations utilized for the study. Missing data will be imputed using multiple imputation methodology. Results will be combined using Rubin's method. Full details of the model and imputation will be provided in the SAP.

Similar models as described for the primary efficacy analyses will be used to analyze the secondary efficacy endpoints. No adjustment will be made for multiplicity in testing the secondary efficacy endpoints. Nominal p-values will be provided when applicable. Any additional sensitivity and/or supplemental analyses will be defined in the SAP.

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.

Analysis of Pharmacokinetics

Plasma obicetrapib concentrations will be summarized with descriptive statistics based on the PK Population. Exploration of any relationships with obicetrapib exposure will be performed, as appropriate.

SAMPLE SIZE DETERMINATION:

A sample size of at least 108 evaluable participants (ie, 36 participants per treatment group) will provide >90% power to detect a 30% difference in LDL-C reduction at Day 56 (SD of 15%) for each of the obicetrapib groups compared to the placebo group at a 2-sided significance level of 0.025.

The sample size for this study was determined in order to provide sufficient power for the analyses of the primary efficacy endpoint described above. Therefore, assuming an approximately 5% dropout rate, enrollment of approximately 114 participants (ie, 38 participants per treatment group) is planned for this study. This sample size will also contribute sufficient participant exposure and safety data.

Participants will be stratified according to their Screening Visit (Visit 1) LDL-C levels (≥100 or <100 mg/dL).

SITES: Approximately 20 sites in the United States

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
ApoE	Apolipoprotein E
CETP	Cholesteryl ester transfer protein
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRO	Clinical Research Organization
CV	Cardiovascular
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
ICF	Informed consent form
ICH	International Council for Harmonisation
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)
mITT	Modified Intent-to-Treat
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

Abbreviation	Definition
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TG	Triglyceride(s)
ULN	Upper limit of normal

1 INTRODUCTION AND BACKGROUND INFORMATION

Dyslipidemias are disorders of lipoprotein metabolism, including lipoprotein overproduction or deficiency, which may be manifested by elevation of the levels of the serum total cholesterol, low-density lipoprotein (LDL) cholesterol (LDL-C) and triglyceride (TG) concentrations, and a decrease in the levels of high-density lipoprotein (HDL) cholesterol (HDL-C) concentration. These disorders are generally diagnosed by measuring the serum lipids and classified by the pattern of elevation/reduction in the lipid/lipoprotein fractions. Dyslipidemia itself does not generally cause any symptoms, but it can lead to symptomatic vascular disease including coronary artery disease and peripheral arterial disease. It is acknowledged that while there are a number of genetic and lifestyle factors which contribute to the development of vascular disease, dyslipidemia is 1 of the most prominent risk factors and normalization of the lipid profile has been a major target in cardiovascular (CV) protection strategies.[1]

Statins are generally the drug of first choice in treating dyslipidemia. Statins are considered as the most potent, most effective, and best tolerated drugs for reducing LDL-C levels. Some patients, despite treatment with high-intensity statin therapy, do not achieve acceptable levels of LDL-C with statins alone.

There is a need for chronic therapies which will robustly reduce elevated LDL-C levels when used adjunctive to high-intensity statin therapy.

1.1 Cholesteryl Ester Transfer Protein Inhibitors

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein produced in the liver and adipose tissue. It circulates in the blood, bound primarily to HDL-C, and is involved in the transfer of cholesteryl esters and TG between lipoproteins. In particular, it mediates the transfer of cholesteryl esters from HDL to apolipoprotein B (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.[2,3] Therefore, the LDL-C and ApoB-lowering effects, which arise from CETP inhibition and occurs through upregulation of the LDL receptor, would lead to large reductions in CV events and would be of great clinical importance for patients who are unable to tolerate statins.

1.2 Obicetrapib

Obicetrapib has been shown to be 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 not only in LDL, but also in other atherogenic lipoproteins. On top of this, obicetrapib 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 led to the

removal of cholesterol via the liver and also reduced lipoprotein (a) (Lp[a]).[4] 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.[5] This effect is considered important because it is expected to reduce established atheroma burden.

1.3 Clinical Development of Obicetrapib

Both single ascending dose (TA-8995-01) and multiple ascending dose (TA-8995-02) studies have been conducted in healthy volunteers. A formal, thorough QT/QTc study (TA-8995-04) has been completed and obicetrapib was shown to have no effect on QTcF. A drug-drug interaction study (TA-8995-05) has also been conducted; this study showed no significant effect of obicetrapib on P-glycoprotein activity, but this study showed that obicetrapib is a mild inducer of cytochrome P450 3A4. A mass balance study (TA-8995-07) in healthy males concluded that obicetrapib is steadily absorbed, and the principal route of excretion was in the feces. Finally, bioequivalence between obicetrapib capsule and tablet formulations was investigated (TA-8995-08) and established.

A Phase 2 patient study (TA-8995-03) was conducted in Denmark and the Netherlands to evaluate the optimal dose of obicetrapib alone and in combination with medium-intensity statins in patients with mild dyslipidemia. This study concluded that a daily dose of 10 mg obicetrapib in combination with medium-intensity statins resulted in an incremental LDL-C reduction of up to 50.2% and a total LDL-C reduction of ≥63.7%, while statin monotherapy or obicetrapib monotherapy achieved an LDL-C reduction of only ≤46.4%.[4] When compared with statin treatment alone at the end of the 12-week Treatment Period, all treatment groups with obicetrapib in combination with medium-intensity statins had significantly higher mean HDL-C levels; had a significantly greater increase in ApoA1 and ApoE levels; and a greater decrease in ApoB, Lp(a), and non-high-density lipoprotein cholesterol (non-HDL-C) levels.[4] However, there is a lack of data for the safety and efficacy of obicetrapib used as an adjunct to high-intensity statin therapy, which is commonly used in patients with dyslipidemia.

Another patient study (TA-8995-06) was conducted where obicetrapib was found to result in a statistically significant reduction in Lp(a) levels following 12 weeks of treatment; however, the magnitude of the changes (approximately a 10% reduction) was not likely to be clinically relevant.

1.4 Rationale

The safety and efficacy data following 56 days of single daily dose administrations of obicetrapib as an adjunct to high-intensity statin therapy in this study will support dose selection for subsequent studies.

1.5 Risk/Benefit

Obicetrapib has undergone extensive nonclinical testing in the standard battery of tests according to International Council for Harmonisation (ICH) guidelines, including repeat-dose toxicity studies of up to 39 weeks duration. In addition, obicetrapib has been investigated in 8 completed clinical studies, of which 6 studies were in Phase 1 of clinical development and 2 studies were in Phase 2. A total of approximately 500 subjects have been exposed to obicetrapib in these studies. In Phase 1, a total of 159 subjects received single oral doses between 5 and 150 mg of obicetrapib,

and 76 subjects received consecutive doses between 1 and 25 mg of obicetrapib for periods up to 28 days. In Phase 2, a total of 268 patients received 1 to 10 mg of obicetrapib for up to 12 weeks.

In healthy volunteer studies, single doses of obicetrapib up to 150 mg and multiple doses up to 25 mg/day over 28 days were generally well tolerated. In patient studies, 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 adverse events (AEs) identified and no clinically significant changes in vital signs, 12-lead electrocardiograms (ECGs), hematology, or biochemistry in any clinical trials. Most treatment-emergent AEs (TEAEs) were mild or moderate in severity. None of the severe TEAEs were considered related to study drug. The number of patients experiencing TEAEs and their severity were similar across all treatment groups. Incidence rates of drug-related TEAEs were also comparable for all treatment groups; the number of TEAEs in the obicetrapib treatment groups did not display a dose-dependent effect. There were 7 patients, who were randomized to receive obicetrapib alone or in combination with statin, with a treatment-emergent serious AE (SAE), none of which were suspected to be related to study drug. One patient had a treatment-emergent SAE that resulted in study discontinuation.

1.6 Coronavirus Disease 2019 Impacts

In March 2020, the 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. 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 protocol includes contingency measures to manage disruptions due to COVID-19 control measures, see Section 3.1.5 for details. 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.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of obicetrapib, compared to placebo, at Day 56 in decreasing LDL-C as an adjunct to high-intensity statin therapy.

2.2 Secondary Objectives

The secondary objectives of this study include the following:

- To evaluate the effect of obicetrapib, compared to placebo, at Day 56 on ApoB, non-HDL-C, and HDL-C, as an adjunct to high-intensity statin therapy;
- To assess the mean plasma levels of obicetrapib at steady state on Days 56, 84, 112, and 161; and
- To evaluate the safety and tolerability profile of obicetrapib.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This study will be a placebo-controlled, double-blind, randomized, Phase 2 dose-finding study to evaluate the efficacy, safety, and tolerability of obicetrapib as an adjunct to high-intensity statin therapy. This study will take place at approximately 20 sites in the United States.

3.1.1 Screening Period

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

3.1.2 Treatment Period

Up to 2 weeks after the Screening Visit, participants will return to the site on Day 1 (Visit 2) and confirm study eligibility before being randomized and beginning treatment. Approximately 114 eligible participants (38 participants per treatment group) will be randomized in a 1:1:1 ratio to 1 of the following treatment groups:

- 5 mg obicetrapib (one 5 mg obicetrapib tablet + 1 placebo tablet);
- 10 mg obicetrapib (two 5 mg obicetrapib tablets); or
- Placebo (2 placebo tablets).

During the 8-week Treatment Period, the assigned study drugs will be administered by the participants orally and once daily on Day 1 to Day 56. Participants will return to the site every 4 weeks for efficacy, safety, and pharmacokinetic (PK) assessments. Participants, Investigators, the Clinical Research Organization (CRO), and the Sponsor will be blinded to all lipid results from Day 1 (Visit 2) for the first participant through database lock 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) approximately 4 weeks after the end of the Treatment Period for safety and PK assessments.

3.1.4 Pharmacokinetic Period

Participants will return to the site for 2 PK Visits (Visits 6 and 7) approximately 8 and 15 weeks, respectively, after the end of the Treatment Period for safety and PK assessments.

3.1.5 Coronavirus Disease 2019 Contingency Measures

In cases of COVID-19 limitations, it is the Investigator's responsibility to assure the safety of participants, including phone or video contact to assess the participant's well-being including any AE, collection of study samples and clinical data as best as possible, and direct shipment of study drug to participant, if necessary. Where available and appropriate, home health care may be considered to facilitate monitoring of safety and study continuity. 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

The indication for this study is dyslipidemia.

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. Understanding of the study procedures, willingness to adhere to the study schedules, and agreement to participate in the study by giving written informed consent prior to screening procedures;
2. Men or women 18 to 75 years of age, inclusive, at the Screening Visit;
   - Women 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;
   - Women of childbearing potential must have a negative urine pregnancy test at the Screening Visit. Note: Women 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 women ≥55 years of age or ≥1 year since their last menstrual period and have a follicle-stimulating hormone (FSH) level in the postmenopausal range for women <55 years of age; and
   - Women of childbearing potential must agree to use an effective method of avoiding pregnancy from screening to 90 days after the last visit. Men whose partners are of childbearing potential must agree to use an effective method of avoiding pregnancy from screening to 90 days after the last visit. Effective methods of avoiding pregnancy are contraceptive methods with a Pearl index of <1 used consistently and correctly (including implantable contraceptives, injectable contraceptives, oral contraceptives, transdermal contraceptives, intrauterine devices, diaphragm with spermicide, male or female condoms with spermicide, or cervical cap) or a sterile sexual partner;
3. Fasting LDL-C levels >70 mg/dL and TG levels <400 mg/dL at the Screening Visit; and
4. Currently receiving high-intensity statin therapy (atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg) at a stable dose for 8 weeks prior to screening and intending to remain at the same stable dose throughout the study duration.

4.2 Exclusion Criteria

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

1. Body mass index ≥40 kg/m^2 at the Screening Visit;
2. Current clinically significant CV disease, including but not limited to:
   - Major adverse CV event within 3 months prior to randomization; or
   - New York Heart Association Functional Classification Class III or IV heart failure;
3. Glycosylated hemoglobin (HbA1c) ≥10% at the Screening Visit;
4. Uncontrolled hypertension, ie, sitting systolic blood pressure >160 mmHg and/or sitting diastolic blood pressure >90 mmHg. One retest will be allowed, at which point if the retest result is no longer exclusionary, the participant may be randomized;
5. Active muscle disease or persistent creatine kinase concentration >3 × the upper limit of normal (ULN). One retest will be allowed after 1 week to verify the result, at which point if the retest result is no longer exclusionary, the participant may be randomized;
6. Estimated glomerular filtration rate <60 mL/min, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation;[6]
7. Hepatic dysfunction as evidenced by any laboratory abnormality as follows: gamma-glutamyl transferase, alanine aminotransferase, or aspartate aminotransferase >2 × ULN, or total bilirubin >1.5 × ULN;
8. Anemia, defined as hemoglobin concentration <11 g/dL for men and hemoglobin concentration <9 g/dL for women;
9. History of malignancy within 5 years prior to screening, with the exception of non-melanoma skin cancers;
10. History of alcohol and/or drug abuse within 5 years prior to screening;
11. Treatment with other investigational products or devices within 30 days or 5 half-lives, whichever is longer, prior to screening;
12. Treatment with any proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitor within 10 weeks prior to randomization or bempedoic acid within 2 weeks prior to randomization;
13. Evidence of any other clinically significant, non-cardiac disease or condition that, in the opinion of the Investigator, would preclude participant in the study; or
14. Known CETP inhibitor allergy or intolerance.

4.3 Retesting

If laboratory abnormalities during screening are considered by the Investigator to be transient, then the laboratory tests may be repeated once during screening. 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

Participation in this study may be discontinued for any of the following reasons:

- The participant withdraws consent or requests discontinuation from the study for any reason;
- 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 requirements of the protocol;
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition, which indicates to the Investigator that continued participation is not in the best interest of the participant;
- Pregnancy;
- Requirement of prohibited concomitant medication;
- Participant failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor or the regulatory authority.

Unless the participant withdraws consent, participants who discontinue study drug early should be encouraged to complete the full panel of assessments scheduled for the Early Termination Visit promptly and complete a Safety Follow-up Visit 4 weeks after the last dose. If a participant withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the Early Termination Visit and complete a Safety Follow-up Visit 4 weeks after the last dose. PK samples will not be collected during the Safety Follow-up Visit for participants who discontinue study drug early without withdrawing consent or for participants who withdraw prematurely from the study. The reason for participant withdrawal must be documented in the electronic case report form (eCRF).

In the case of participant lost to follow-up, attempts to contact the participant must be made and documented in the participant's medical records.

Withdrawn participants will not be replaced.

5 STUDY TREATMENTS

5.1 Treatment Groups

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

- 5 mg obicetrapib (one 5 mg obicetrapib tablet + 1 placebo tablet);
- 10 mg obicetrapib (two 5 mg obicetrapib tablets); or
- Placebo (2 placebo tablets).

5.2 Rationale for Dosing

In previous clinical studies of obicetrapib in healthy volunteers and patients, near maximal effects were observed at the 5 mg obicetrapib dose level with increased HDL-C levels and decreased LDL-C levels. 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 doses of 5 and 10 mg obicetrapib in participants currently receiving high-intensity statin therapy.

5.3 Randomization and Blinding

Participants who meet all eligibility criteria will be randomized into the study. Participants will be randomized in a 1:1:1 ratio to the 5 mg obicetrapib, 10 mg obicetrapib, or placebo treatment groups. At randomization, participants will be stratified according to their Screening Visit (Visit 1) LDL-C level (≥100 or <100 mg/dL). An automated interactive response technology (IRT) system will be used to assign the participant to 1 of the 3 treatment groups.

Participants, Investigators, the CRO, and the Sponsor will be blinded to all lipid results from Day 1 (Visit 2) for the first participant through database lock in order to protect blinding to treatment assignment.

5.4 Breaking the Blind

Unblinding by request of an Investigator should occur only in the event of an emergency or AE, for which it is necessary to know the study drugs to determine an appropriate course of therapy for the participant. If the Investigator or qualified designee must identify the treatment assignment of an individual participant, the Investigator or qualified designee should request the treatment assignment from the IRT system. The Investigator is advised not to reveal the treatment assignment to other sites or Sponsor personnel.

Prior to unblinding, and if the situation allows, the Investigator should consult with the Sponsor's Medical Monitor. If this is impractical, the Investigator must notify the Sponsor's Medical Monitor as soon as possible, without revealing the treatment assignment of the unblinded participant. The Investigator must document the participant identification and the date and time for breaking the blind and must clearly explain the reasons for breaking the blind.

Medically necessary care should not be delayed for unblinding information (ie, the Investigator should treat the participant based on the participant's signs/symptoms without waiting for the unblinding process to be completed).

For participants who are unblinded and withdrawn from the study, study staff should make every effort to complete the full panel of assessments scheduled for the Early Termination Visit and complete a Safety Follow-up Visit 4 weeks after the last dose.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

The study drugs will consist of 5 mg obicetrapib tablets and matching placebo tablets. All study drugs are manufactured in accordance with current Good Manufacturing Practice.

Obicetrapib tablets are round, 6 mm in diameter, white film-coated tablets, with no identifying markings, containing 5 mg of obicetrapib drug substance. Matching placebo tablets will also be provided. [redacted]

Obicetrapib and placebo tablets will be packaged into foil blisters and assembled into blister cards providing the study drugs for each treatment group. The blister cards will be clearly labelled to indicate which blisters to use on each day. The tablets should be stored at ambient conditions below 25 °C (77 °F).

The physical, chemical, and pharmaceutical formulation properties and characteristics of the 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

The study drugs used in this study are as follows:

- 5 mg obicetrapib tablet; and
- Matching placebo tablet.

The study drugs listed above will be packaged to provide doses of 5 or 10 mg obicetrapib or placebo only. Participants will be randomized to receive 1 of the 2 doses of obicetrapib or placebo only on Day 1 to Day 56.

At each appropriate visit (Visits 2 and 3), participants will receive 4 blister cards with the study drugs appropriate for the participant's treatment group. Each blister card will provide a sufficient supply for 1 week of dosing, with enough for an extra day of dosing in case the participant needs to postpone the next visit. Participants will be instructed to take 2 units from the blister cards each day. The blister cards will be clearly labelled to indicate which blisters 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 study drug dispensation specific to situations where COVID-19 is impacting study conduct. See Section 3.1.5 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

Two tablets of study drugs will be administered by the participant orally and once daily on Day 1 to Day 56. Study drugs should be administered at approximately the same time each morning, with food. On days with visits scheduled, study drugs should be administered with food following all fasted blood samples. If a participant forgets to take study drug on a given day, they 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 to the study drug regimen will be evaluated by counting unused tablets. Participants will be instructed to bring all unused study drugs to the site at Visits 3 and 4. During the Treatment Period, if compliance is not between 80% and 120%, inclusive, the participant will be counselled about the importance of compliance to the regimen. If the limits are exceeded at 2 consecutive visits, a decision will be made by the Investigator and Sponsor as to whether the participant should be withdrawn from the study.

5.5.5 Storage and Accountability

All study drugs must be stored below 25 °C (77 °F) 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 drug 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. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused study drug 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 receive treatment with other investigational products or devices within 30 days or 5 half-lives, whichever is longer, prior to screening.

Participants must abstain from taking any PCSK9 inhibitor within 10 weeks prior to randomization or bempedoic acid within 2 weeks prior to randomization.

5.6.2 Allowed Medications and/or Procedures

Participants must be currently receiving high-intensity statin therapy (atorvastatin 40 or 80 mg or rosuvastatin 20 or 40 mg) at a stable dose for 8 weeks prior to screening and intending to remain at the same stable dose throughout the study duration.

5.6.3 Documentation of Prior and Concomitant Medication Use

Medications used within 28 days prior to the Screening Visit will be recorded. Any medications administered in addition to the study drugs, whether allowed per the protocol or not, must be documented on the concomitant medication eCRF.

6 STUDY PROCEDURES

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

This study protocol includes contingency measures to manage disruptions due to COVID-19 control measures, including modifications to visit schedules and procedures specific to situations where COVID-19 is impacting study conduct. See Section 3.1.5 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.

7 EFFICACY ASSESSMENTS

The primary efficacy endpoint is the percent change from Day 1 to Day 56 in LDL-C for each obicetrapib group compared to the placebo group.

The key secondary efficacy endpoints include the following:

- Percent change from Day 1 to Day 56 in ApoB for each obicetrapib group compared to the placebo group;
- Percent change from Day 1 to Day 56 in non-HDL-C for each obicetrapib group compared to the placebo group; and
- Percent change from Day 1 to Day 56 in HDL-C for each obicetrapib group compared to the placebo group.

Blood samples for the lipid profile must be obtained under fasting conditions (ie, after the participant has fasted for approximately 10 hours). For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications. If a participant is not fasting, the Investigator should reschedule the visit as soon as possible. LDL-C level will be calculated using the Friedewald equation unless TG ≥400 mg/dL or LDL-C ≤50 mg/dL; in both cases, LDL-C level will be measured directly by preparative ultracentrifugation, also referred to as beta quantification.[7] In addition, for all patients, LDL-C will be measured by preparative ultracentrifugation, also referred to as beta quantification, at baseline (Visit 2) and at the end of the 8-week Treatment Period (Visit 4).

8 SAFETY ASSESSMENTS

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 an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. 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 7. Participants should be instructed to report any AE that they experience to the Investigator, whether or not they think the event is due to 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 the study drug is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

8.1.1 Adverse (Drug) 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.

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 study drug 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 drug 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 drug and the occurrence or worsening of the AE rules out 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 drug 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 drug. 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 study drug administration-

  The event should occur after the 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 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 drug-

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

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 study drug must be reported to the [redacted] or the Sponsor/designee.

To report the SAE, complete the SAE form electronically in the electronic data capture (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] or call the [redacted] (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 study drug(s) immediately and the participant should be withdrawn from the study. Early termination procedures should be implemented at that time.

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 drug 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 Food and Drug Administration (FDA), 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, applicable competent authorities concerned, and to the Central Ethics Committee concerned 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 investigational medicinal product.

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.

8.7 Clinical Laboratory Evaluations

Blood for chemistry and hematology will be obtained as indicated in Appendix A and sent to a central laboratory for analysis. See Appendix B for a complete list of analytes. Blood samples for chemistry and hematology must be obtained under fasting conditions (ie, after the participant has fasted for approximately 10 hours). For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications. If a participant is not fasting, the Investigator should reschedule the visit as soon as possible. Estimated glomerular filtration rate will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.[6] At the Screening Visit only, the chemistry panel will include HbA1c.

A urine pregnancy test will be performed for women of childbearing potential at the Screening Visit prior to their participation in the study, the last PK Visit (Visit 7), and the Early Termination Visit.

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

Blood samples for PK assessment will be collected as indicated in Appendix A. On Day 1, a PK sample will be collected pre-dose. The subsequent post-dose PK samples should be collected once at approximately the same time at each visit.

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 the Screening Visit 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, and bladder empty.

8.10 Demographics

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

8.11 Electrocardiograms

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

8.12 Physical Examinations

A physical examination will be performed as indicated in Appendix A.

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 Modified ITT (mITT) Population will include all participants in the ITT Population who receive at least 1 dose of any study drug and have a baseline value for the LDL-C assessment. Any efficacy measurement obtained during the Safety Follow-up Visit after a participant permanently discontinues the study drug or after a participant receives an excluded medication and/or procedure will be removed from the mITT analysis. Treatment classification will be based on the randomized treatment. The mITT Population will be used for the primary analysis of all efficacy endpoints.

The Per-Protocol (PP) Population will include all participants in the mITT Population who have a baseline value for the LDL-C assessment, have a Day 56 value for the LDL-C assessment, and 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 PK Population will include all participants in the mITT Population who have sufficient blood samples collected for valid estimation of PK parameters.

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.

9.2.1 Analysis of Efficacy

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

9.2.1.1 Primary efficacy analysis

The primary efficacy analysis of the percent change from Day 1 to Day 56 in LDL-C will be performed using a mixed model for repeated measures approach. The analysis will include fixed effects for treatment, visit, and treatment-by-visit interaction, along with a covariate of the baseline value. The Restricted Maximum Likelihood estimation approach will be used with an unstructured covariance matrix. The least squares means, standard errors, and 2-sided 95% confidence intervals for each treatment group and for the pairwise comparisons of each dose of obicetrapib to the placebo group will be provided. Adjustment for multiple comparisons will be made using Dunnett's test in accordance with the power and sample size calculations utilized for the study.

Missing data will be imputed using multiple imputation methodology. Results will be combined using Rubin's method. Full details of the model and imputation will be provided in the SAP.

9.2.1.2 Secondary efficacy analysis

Similar models as described for the primary efficacy analyses will be used to analyze the secondary efficacy endpoints. No adjustment will be made for multiplicity in testing the secondary efficacy endpoints. Nominal p-values will be provided when applicable. Any additional sensitivity and/or supplemental analyses will be defined 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 Analysis of Pharmacokinetics

Plasma obicetrapib concentrations will be summarized with descriptive statistics based on the PK Population. Exploration of any relationships with obicetrapib exposure will be performed, as appropriate.

9.2.4 Interim Analysis

No interim analysis is planned for this study.

9.2.5 Sample Size Determination

A sample size of at least 108 evaluable participants (ie, 36 participants per treatment group) will provide >90% power to detect a 30% difference in LDL-C reduction at Day 56 (SD of 15%) for each of the obicetrapib groups compared to the placebo group at a 2-sided significance level of 0.025.

The sample size for this study was determined in order to provide sufficient power for the analyses of the primary efficacy endpoint described in Section 7. Therefore, assuming an approximately 5% dropout rate, enrollment of approximately 114 participants (ie, 38 participants per treatment group) is planned for this study. This sample size will also contribute sufficient participant exposure and safety data.

Participants will be stratified according to their Screening Visit (Visit 1) LDL-C levels (≥100 or <100 mg/dL).

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 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
- World Health Organization 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 investigative 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 product, 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 Institutional Review Board (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 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 drug will be released to the site for dosing until written IRB authorization has been received by the Sponsor.

11.3 Informed Consent

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, Declaration of Helsinki, ICH GCP, and applicable regulatory requirements, and that valid data are entered into the eCRFs.

To achieve this objective, the monitor'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. 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 monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the investigational site by signature and date on the study-related monitoring log.

11.5 Disclosure of Data

Data generated by this study must be available for inspection by the FDA, the Sponsor or their designee, applicable foreign health 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

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4. Hovingh GK, Kastelein JJ, van Deventer SJ, et al. Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet*. 2015;386(9992):452-460.
5. van Capelleveen JC, Kastelein JJ, 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.
6. CKD-EPI equations for glomerular filtration rate (GFR). MDCalc. https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr. Accessed 09 November 2020.
7. LDL calculated. MDCalc. https://www.mdcalc.com/ldl-calculated. Accessed 09 November 2020.

APPENDIX A: SCHEDULE OF PROCEDURES

	Screening[a,b]	Treatment Period			Safety Follow-Up	PK		Early Termination Visit
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	
Week	**Up to -2**	**0**	**4**	**8**	**12**	**16**	**23**	
Day (± Visit Window)	**-14 to -1**	**1**	**28 (±2)**	**56 (±2)**	**84 (±2)**	**112 (±2)**	**161 (±2)**	**Unscheduled**
Informed consent[c]	X							
Inclusion/exclusion criteria	X	X[d]						
Demographic information	X							
Medical/surgical history	X							
Prior/concomitant medications	X	X	X	X	X			X
Weight and height[e]	X							
Physical examination	X			X				
Vital signs[f]	X	X	X	X	X			X
12-lead ECG[g]	X							
Urine pregnancy test[h]	X						X	X
FSH test[i]	X							
Fasting (approximately 10 hours) chemistry and hematology[j]	X	X	X	X	X	X	X	X
Fasting (approximately 10 hours) lipid profile[k]	X	X	X	X				X
PK sample[l]		X	X	X	X[m]	X	X	X
Randomization		X						
Dispense study drug		X	X					
Study drug administration[n]		X	X	X				
Study drug compliance			X	X				
Register visit in IRT	X	X	X	X				X
Adverse events		X	X	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, including phone or video contact to assess the participant's well-being including any adverse event, collection of study samples and clinical data as best as possible, and direct shipment of study drug to participant, if necessary. Where available and appropriate, home health care may be considered to facilitate monitoring of safety and study continuity. 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.

a. If laboratory abnormalities during screening are considered by the Investigator to be transient, then the laboratory tests may be repeated once during screening. 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. Signed informed consent must be obtained before any study-related procedures are performed.
d. Confirm the participant continues to meet the inclusion and exclusion criteria and assess any updates since the Screening Visit.
e. Weight and height will be measured at the Screening Visit 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, and bladder empty.
f. 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.
g. A single, standard 12-lead ECG will be performed by the Investigator or trained site personnel at the Screening Visit and read locally.
h. For women of childbearing potential only.
i. FSH test will be performed in women <55 years of age for whom it has been ≥1 year since their last menstrual period.
j. At the Screening Visit only, chemistry panel will include HbA1c.
k. LDL-C level will be calculated using the Friedewald equation unless TG ≥400 mg/dL or LDL-C ≤50 mg/dL; in both cases, LDL-C level will be measured directly by preparative ultracentrifugation, also referred to as beta quantification. (Source: LDL calculated. MDCalc. https://www.mdcalc.com/ldl-calculated. Accessed 09 November 2020.) In addition, for all patients, LDL-C will be measured by preparative ultracentrifugation, also referred to as beta quantification, at baseline (Visit 2) and at the end of the 8-week Treatment Period (Visit 4).
l. On Day 1, a PK sample will be collected pre-dose. The subsequent post-dose PK samples should be collected once at approximately the same time at each visit.
m. PK samples will not be collected during the Safety Follow-up Visit for participants who discontinue study drug early without withdrawing consent or for participants who withdraw prematurely from the study.
n. Two tablets of study drugs will be administered by the participant orally and once daily on Day 1 to Day 56. Study drugs should be administered at approximately the same time each morning, with food. On days with visits scheduled, study drugs should be administered with food following all fasted blood samples.

COVID-19 = Coronavirus Disease 2019; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = glycosylated hemoglobin; IRT = interactive response technology; LDL-C = low-density lipoprotein cholesterol; PK = pharmacokinetic; TG = triglycerides.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

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

1. Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. (Source: CKD-EPI equations for glomerular filtration rate [GFR]. MDCalc. https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr. Accessed 09 November 2020.)
2. Screening Visit only.

Endocrinology

Follicle-stimulating hormone [1]

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.

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.

Pregnancy Test

Urine [1]

1. For women of childbearing potential only.

Lipid Profile

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

1. With and without apolipoprotein C3.
2. Calculated using the Friedewald equation unless triglycerides ≥400 mg/dL or low-density lipoprotein cholesterol (LDL-C) ≤50 mg/dL; in both cases, LDL-C level will be measured directly by preparative ultracentrifugation, also referred to as beta quantification. (Source: LDL calculated. MDCalc. https://www.mdcalc.com/ldl-calculated. Accessed 09 November 2020.) In addition, for all patients, LDL-C will be measured by preparative ultracentrifugation, also referred to as beta quantification, at baseline (Visit 2) and at the end of the 8-week Treatment Period (Visit 4).