CLINICAL STUDY PROTOCOL

A Placebo-Controlled, Double-Blind, Randomized Phase 2 Study to Evaluate the Effect of Obicetrapib in Combination with Ezetimibe in Participants with Mild Dyslipidemia

Investigational Product: Obicetrapib

Protocol Number: TA-8995-303

EudraCT Number: 2019-004935-22

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SIGNATURE PAGE

STUDY TITLE: A Placebo-Controlled, Double-Blind, Randomized Phase 2 Study to Evaluate the Effect of Obicetrapib in Combination with Ezetimibe in Participants with Mild Dyslipidemia

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

[redacted]

[redacted]

[redacted]

[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 product 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/Ethics Committee 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 Study to Evaluate the Effect of Obicetrapib in Combination with Ezetimibe in Participants with Mild Dyslipidemia

PROTOCOL NUMBER: TA-8995-303

INVESTIGATIONAL PRODUCT: Obicetrapib

PHASE: 2

INDICATION: Mild dyslipidemia

OBJECTIVES:

The primary objective of this study is to evaluate the effect of obicetrapib in combination with ezetimibe compared to placebo on low-density lipoprotein cholesterol (LDL-C) at Day 57.

The secondary objectives of this study include the following:

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

The exploratory objectives of this study include the following:

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

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

POPULATION:

The population for this study includes men and women 18 to 70 years of age, inclusive, with a body mass index <40 kg/m^2 and mild dyslipidemia defined as fasting LDL-C levels >2.5 mmol/L (>100 mg/dL) and <4.5 mmol/L (<175 mg/dL) and TG levels <4.5 mmol/L (<400 mg/dL).

STUDY DESIGN AND DURATION:

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

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. Participants will also receive counselling regarding the Therapeutic Lifestyle Changes diet and will receive instructions on how to follow this diet. Participants will be required to begin the diet starting at the Screening Visit.

Treatment Period

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

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

During the 8-week Treatment Period, the assigned study drugs will be administered by the participant orally and once daily on Days 1 through 57. Participants will return to the site every 4 weeks for efficacy, safety, PK, and CETP mass 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 the PK Visit (Visit 6) for the last participant 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, PK, and CETP mass assessments.

Pharmacokinetic Period

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

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

The study drugs used in this study are as follows:

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

Participants will be randomized to receive 2 of the study drugs listed above for the duration of the study. Both of the assigned study drugs will be administered by the participant orally and once daily on Days 1 through 57.

EFFICACY VARIABLES:

The primary efficacy endpoint is percent change from Day 1 to Day 57 in LDL-C for the combination therapy group compared to the placebo group.

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

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

The exploratory efficacy endpoints include the following:

- Percent change from Day 1 to Day 57 in ApoB for the ezetimibe monotherapy group compared to the placebo group;
- Pairwise comparisons among the various treatment groups for the percent change from Day 1 to Day 57 in non-HDL-C, VLDL-C, HDL-C, TG, ApoE, and HDL-ApoE (with and without ApoC3);
- Pairwise comparisons among the various treatment groups for the proportion of participants at Day 57 that achieve LDL-C <2.6 mmol/L (<100 mg/dL), LDL-C <1.8 mmol/L (<70 mg/dL), and LDL-C <1.3 mmol/L (<50 mg/dL);
- Pairwise comparisons among the various treatment groups for the change from Day 1 to Day 57, Day 1 to Week 12, and Day 1 to Week 16 in the mean trough plasma levels of obicetrapib; and
- Pairwise comparisons among the various treatment groups for the change from Day 1 to Day 57, Day 1 to Week 12, and Day 1 to Week 16 in CETP mass.

SAFETY VARIABLES:

The safety and tolerability profiles of obicetrapib alone, ezetimibe alone, and obicetrapib in combination with ezetimibe will be assessed by clinical laboratory values and the incidence of AEs.

STATISTICAL ANALYSES:

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

The Per-Protocol (PP) Population will include all participants in the mITT Population who have a baseline value for the LDL-C assessment, have a Day 57 value for the LDL-C assessment, and who did not experience a major protocol deviation that potentially impacted the primary efficacy endpoint. 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 57 in LDL-C will be performed using a mixed model for repeated measures (MMRM) approach. The analysis will include fixed effects for treatment, visit, and treatment-by-visit interaction, along with a covariate of the baseline value. The Restricted Maximum Likelihood estimation approach will be used with an unstructured covariance matrix. The least squares means, standard errors, and 2-sided 95% confidence intervals for each treatment group, for the pairwise comparisons of the combination therapy, obicetrapib monotherapy, and ezetimibe monotherapy to placebo, and for the pairwise comparisons of combination therapy and obicetrapib monotherapy versus ezetimibe monotherapy will be provided. The treatment comparison will be performed using a 2-sided test at the $\alpha = 0.05$ level of significance.

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 Statistical Analysis Plan (SAP).

A similar MMRM model will be used for the analysis of the secondary and exploratory efficacy endpoints corresponding to the percent change from baseline. For the binary efficacy endpoints, a logistic regression analysis will be performed with model covariates of treatment group and baseline LDL-C.

In order to maintain the overall Type I error rate, the secondary efficacy endpoints will be tested sequentially at the 0.05 significance level according to the pre-specified order of hierarchy. No adjustment will be made for multiplicity in testing the exploratory efficacy endpoints. Nominal p-values will be provided when applicable. Descriptive and graphical summaries by treatment group will also be presented. 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.

Pharmacokinetic Analysis

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

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

Participants will be stratified according to their Screening Visit (Visit 1) LDL-C value (<3.5 mmol/L [<135 mg/dL] or ≥3.5 mmol/L [≥135 mg/dL]).

SITES: Approximately 10 to 15 sites in North America and Europe as appropriate

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[1] Hovingh GK, Kastelein JJ, van Deventer SJ, et al. Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet*. 2015;386(9992):452-460.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
ApoC3	Apolipoprotein C3
ApoE	Apolipoprotein E
CETP	Cholesteryl ester transfer protein
CRA	Clinical Research Associate
CTA	Clinical trial authorisation
CVD	Cardiovascular disease
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EIU	Exposure In Utero
EU	European Union
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
HMGCR	3-hydroxy-3-methylglutaryl-Coenzyme A reductase
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
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)
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMRM	Mixed model for repeated measures
NODM	New-onset diabetes mellitus
Non-HDL-C	Non-high-density lipoprotein cholesterol
PK	Pharmacokinetic(s)
PP	Per-Protocol

Abbreviation	Definition
SAE	Serious adverse event
SAMS	Statin-associated muscle symptoms
SAP	Statistical Analysis Plan
SD	Standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TG	Triglycerides
TLC	Therapeutic Lifestyle Changes
ULN	Upper limit of normal
VLDL	Very low-density lipoprotein
VLDL-C	Very low-density lipoprotein cholesterol

1 INTRODUCTION AND BACKGROUND INFORMATION

Despite advances in treatment, cardiovascular disease (CVD) is the leading cause of death globally, resulting in over 17 million deaths per year.[1] Elevated low-density lipoprotein (LDL) cholesterol (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, and the clinical risk reduction is linearly proportional to the absolute LDL-C reduction.[4] Approximately 100 million people worldwide are treated with lipid lowering therapies, predominantly statins, to reduce LDL-C and the associated risk of cardiovascular events.

Statins are generally well tolerated, but their use is limited in a substantial number of patients due to various adverse effects, including statin-associated muscle symptoms (SAMS) and new-onset diabetes mellitus (NODM). SAMS comprise myopathy, myalgia, and the most severe manifestation, rhabdomyolysis, which can result in serious complications including renal failure. However, in most cases, patients experience mild to moderate muscle pain and weakness. The risk of NODM increases with intensive statin therapy, particularly in patients with prediabetes.[5] These manifestations, and other adverse events (AEs), may lead to discontinuation of statin therapy. This is commonly referred to as statin intolerance[5] and may occur in 10% to 15% of patients,[6] depriving patients of the cardioprotective benefits of statins. In addition, discontinuation of statin therapy can increase the risk of acute cardiovascular events.[7] Indeed, it is estimated that 9% of all cardiovascular events across the European Union (EU) are the consequence of statin intolerance.

An alternative to statins is the use of proprotein convertase subtilisin/kexin 9 inhibitors. However, there are several limitations with this line of therapy, including very high costs. Based on currently completed, long-term studies, outcomes are not as successful compared to statins, and muscle-related events are still reported.[5]

Accordingly, there remains an unmet need for therapies to reduce elevated LDL-C levels and cardiovascular risk, at an acceptable cost, and with a more favorable safety profile to encourage long-term use and patient compliance.

1.1 Cholesteryl Ester Transfer Protein Inhibition

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein produced in the liver and adipose tissue. It circulates in the blood bound primarily to high-density lipoprotein (HDL) 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 HDL to the apolipoprotein B (ApoB)-containing particles, very low-density lipoprotein (VLDL) 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 levels and ultimately to increased LDL-C levels.

Inhibition of CETP activity reduces LDL-C levels and increases HDL-C levels. These effects are not only caused by inhibition of CETP-mediated cholesterol transfer from HDL to LDL, but also by a decrease in the number of ApoB-containing lipoproteins and an increase in apolipoprotein A1 (ApoA1)-containing lipoproteins. The LDL-C lowering effect, which arises from CETP inhibition and occurs through upregulation of the LDL-receptor, will benefit patients with elevated LDL-C and increased cardiovascular risk.

Ference and colleagues have recently investigated the association between changes in LDL-C levels (and other lipoproteins) and the risk of cardiovascular 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.[8] The results of these Mendelian randomization analyses demonstrate that treatment with a CETP inhibitor as monotherapy has the potential to effectively reduce the risk of cardiovascular events. Both genetic and therapeutic inhibition of CETP leads to quantitatively concordant changes in LDL-C and ApoB levels when considered in the absence of HMGCR inhibition. A further Mendelian randomization analysis concluded that the clinical benefit of lower TG levels was similar to the clinical benefit of lower LDL-C levels per unit difference in ApoB and may be related to the absolute reduction in ApoB-containing lipoprotein particles.[9] Therefore, treatment with a potent CETP inhibitor without a statin could lead to large absolute reductions in both LDL-C and ApoB, which could in turn lead to large relative reductions in cardiovascular events. Future cardiovascular outcome studies evaluating CETP inhibitor therapy in statin intolerant patients could test this hypothesis directly.[8] This has indeed been confirmed in a recent review where it was concluded that CETP inhibitors could represent a useful addition to drugs currently being used to treat high-risk patients intolerant to or not adequately treated with statins.[10] Recently, the Clinical Trial Service Unit, University of Oxford, also presented that the absolute reduction in major adverse cardiovascular events 2 years after the REVEAL study was completed was nearly double (approximately 18%) compared to that seen at the end of the 4-year treatment period with the CETP inhibitor anacetrapib (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.[11] In conclusion, CETP inhibition as monotherapy robustly lowers LDL-C and reduces CVD risk in those patients who are intolerant to statins, and the REVEAL study has shown no long-term on-target safety issues.

1.2 Obicetrapib (TA-8995)

Obicetrapib (TA-8995) has been shown to be a selective CETP inhibitor. In addition to shuttling cholesterol esters from LDL-C to HDL-C particles, obicetrapib has several additional compound-specific activities that are hypothesized to be beneficial in patients. Obicetrapib treatment has recently been shown to reduce the number of ApoB-containing particles that constitute LDL-C. Obicetrapib increases apolipoprotein E, which leads to removal of cholesterol via the liver and also reduces lipoprotein (a) (Lp(a)). Finally, obicetrapib not only potently increases HDL-C and the number of ApoA1-containing lipoproteins, but has been demonstrated to be a potent inducer of cholesterol efflux, which is the main driver of reverse cholesterol transport.[12] 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 corrected QT interval by Fridericia. 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 in healthy males concluded that obicetrapib is steadily absorbed, and the principal route of excretion was in the feces (TA-8995-07). Finally, bioequivalence between obicetrapib capsule and tablet formulations was investigated (TA-8995-08) and established.

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 participants with mild dyslipidemia. This study concluded that a daily dose of 5 mg obicetrapib resulted in an LDL-C reduction of 45.3%, an ApoB reduction of 33.6%, an HDL-C increase of 157.1%, an ApoA1 increase of 57.5%, and a significant increase in HDL-C efflux capacity.[13] A second patient study (TA-8995-06) was conducted where the effect of obicetrapib on Lp(a) was investigated following 12 weeks of treatment. There was 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 for Obicetrapib and Ezetimibe Combination Therapy

An important therapeutic goal is to maximize LDL-C reduction for patients who cannot tolerate statin 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.[14] 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.[15] Although there is a lack of evidence that ezetimibe monotherapy reduces cardiovascular events, the IMPROVE-IT study,[16] 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 cardiovascular 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.

Accordingly, to evaluate the potential for ezetimibe to further augment LDL-C as well as ApoB reduction achieved by a CETP inhibitor, this study will test the effect of obicetrapib and ezetimibe combination therapy compared to obicetrapib monotherapy and ezetimibe monotherapy in participants with mild dyslipidemia.

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.

Obicetrapib has been shown to be a selective CETP inhibitor. In addition to shuttling cholesterol esters from LDL-C to HDL-C particles, obicetrapib has several additional compound-specific activities that are hypothesized to be beneficial in patients. A dose of 5 mg obicetrapib resulted in an LDL-C reduction of 45.3%, an ApoB reduction of 33.6%, an HDL-C increase of 157.1%, an

ApoA1 increase of 57.5%, and a significant increase in HDL-C efflux capacity.[13] This effect is considered important because it is expected to reduce established atheroma burden.

Single doses of obicetrapib up to 150 mg and multiple doses up to 25 mg administered over 28 days were generally well tolerated and safe in these studies. No clinically significant effects on vital sign measurements (systolic and diastolic blood pressure, heart rate, and body temperature), 12-lead electrocardiogram (ECG) findings, or results of safety laboratory tests or physical examinations were observed with obicetrapib treatment. In particular, no clinically significant changes in aldosterone, sodium, potassium, or bicarbonate concentrations were observed.

In addition, no dose-related effects have been observed on the type, frequency, or intensity of treatment-emergent AEs (TEAEs) in clinical studies of obicetrapib to date. In patient studies, most TEAEs were mild or moderate in severity. Of the patients with severe TEAEs, 2 were suspected to be related to both obicetrapib and statin treatment. 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 randomized patients with a treatment-emergent serious AE (SAE), none of which were suspected to be study drug related. One patient had treatment-emergent SAEs that resulted in study discontinuation. No deaths occurred during these studies.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the effect of obicetrapib in combination with ezetimibe compared to placebo on LDL-C at Day 57.

2.2 Secondary Objectives

The secondary objectives of this study include the following:

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

2.3 Exploratory Objectives

The exploratory objectives of this study include the following:

- To evaluate the effect of ezetimibe monotherapy compared to placebo on ApoB at Day 57;
- To evaluate the effect of obicetrapib alone, ezetimibe alone, and obicetrapib in combination with ezetimibe on non-HDL-C, VLDL cholesterol (VLDL-C), HDL-C, TG, apolipoprotein E (ApoE), and HDL-ApoE (with and without apolipoprotein C3 [ApoC3]) at Day 57;
- To evaluate the effect of obicetrapib alone, ezetimibe alone, and obicetrapib in combination with ezetimibe on the proportion of participants achieving predefined LDL-C targets at Day 57;
- To assess the mean trough plasma levels of obicetrapib alone, ezetimibe alone, and obicetrapib in combination with ezetimibe at steady state on Day 57, Week 12, and Week 16;
- To evaluate the effect of obicetrapib alone, ezetimibe alone, and obicetrapib in combination with ezetimibe on CETP mass at Day 57, Week 12, and Week 16; and
- To evaluate the safety and tolerability profiles of obicetrapib alone, ezetimibe alone, and obicetrapib in combination with ezetimibe assessed by clinical laboratory values and incidence of AEs.

3 STUDY DESCRIPTION

3.1 Summary of Study Design

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

The population for this study includes men and women 18 to 70 years of age, inclusive, with a body mass index <40 kg/m^2 and mild dyslipidemia defined as fasting LDL-C levels >2.5 mmol/L (>100 mg/dL) and <4.5 mmol/L (<175 mg/dL) and TG levels <4.5 mmol/L (<400 mg/dL).

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. Participants will also receive counselling regarding the Therapeutic Lifestyle Changes (TLC) diet and will receive instructions on how to follow this diet (see Appendix C). Participants will be required to begin the diet starting at the Screening Visit.

3.1.2 Treatment Period

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

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

During the 8-week Treatment Period, the assigned study drugs will be administered by the participant orally and once daily on Days 1 through 57. Participants will return to the site every 4 weeks for efficacy, safety, PK, and CETP mass 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 the PK Visit (Visit 6) for the last participant 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, PK, and CETP mass assessments.

3.1.4 Pharmacokinetic Period

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

3.2 Study Indication

The indication for this study is mild 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 diet, and agreement to participate in the study by giving written informed consent prior to Screening procedures;
2. Men or women 18 to 70 years of age, inclusive;
    - 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 post-menopausal, 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 menopausal range for women <55 years of age;
    - Women of childbearing potential must agree to use an effective method of avoiding pregnancy from the Screening Visit 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 the Screening Visit 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 >2.5 mmol/L (>100 mg/dL) and <4.5 mmol/L (<175 mg/dL) and TG levels <4.5 mmol/L (<400 mg/dL) (Visit 1); and
4. Willingness to maintain a stable diet and physical activity level throughout the study.

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;
2. Participation in another clinical study involving an investigational or marketed drug within 30 days prior to the Screening Visit;
3. Currently taking any lipid-altering therapy;

4. Any clinical manifestation of atherosclerotic CVD or any evidence of ischemic coronary disease present on the 12-lead ECG at the Screening Visit;
5. Diagnosis of type 1 or type 2 diabetes mellitus; or glycosylated hemoglobin (HbA1c) ≥6.5% at the Screening Visit if no prior diagnosis of diabetes mellitus;
6. Uncontrolled hypertension, ie, sitting systolic blood pressure >160 mmHg and/or sitting diastolic blood pressure >90 mmHg taken as the average of triplicate measurements. One retest will be allowed, at which point if the retest result is no longer exclusionary, the participant may be randomized;
7. 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;
8. History of torsades de pointes;
9. Estimated glomerular filtration rate <60 mL/min calculated using the Chronic Kidney Disease Epidemiology Collaboration equation;
10. 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;
11. Anemia, defined as hemoglobin concentration <11 g/dL for males and hemoglobin concentration <9 g/dL for females;
12. History of malignancy within the past 5 years, with the exception of non-melanoma skin cancers;
13. Evidence of any other clinically significant non-cardiac disease or condition that, in the opinion of the Investigator, would preclude participation in the study; or
14. Known ezetimibe or 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

Participants who have screen-failed are permitted to rescreen once, following consultation with the Medical Monitor. Rescreening may be scheduled after at least 5 days have elapsed from the previous study visit.

4.5 Withdrawal Criteria

Participation in this clinical 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.

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. The reason for participant withdrawal must be documented in the electronic case report form (eCRF).

In the case of participants lost to follow-up, at least 3 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 1:1:1:1 ratio to 1 of the following treatment groups:

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

5.2 Rationale for Dosing

In previous multiple-dose clinical studies of obicetrapib in healthy subjects and patients, near maximal effects were observed with the 5 mg obicetrapib dose. At this dose level, CETP activity and concentrations were effectively reduced, and HDL-C levels were increased while LDL-C levels decreased. According to the Summary of Product Characteristics, the recommended daily dose of ezetimibe is 10 mg. Therefore, the present study will utilize a dose of 5 mg obicetrapib, administered with or without 10 mg ezetimibe, in participants with mild dyslipidemia following the TLC diet.

5.3 Randomization and Blinding

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

Participants, Investigators, the Clinical Research Organization, and the Sponsor will be blinded to all lipid results from Day 1 (Visit 2) for the first participant through the PK Visit (Visit 6) for the last participant in order to protect blinding to treatment assignment.

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, the Early Termination Visit should be completed.

5.5 Drug Supplies

5.5.1 Formulation and Packaging

The study drugs will consist of 5 mg obicetrapib tablets or matching placebo tablets, and over-encapsulated 10 mg ezetimibe tablets or matching placebo capsules. All products are manufactured in accordance with ICH current Good Manufacturing Practice.

Obicetrapib tablets are round, white film-coated tablets, with no identifying markings, containing 5 mg of obicetrapib calcium drug substance. [redacted]

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

Ezetimibe capsules are 10 mg ezetimibe tablets filled into capsule shells, 1 tablet per capsule. Each capsule also contains an excipient material, common to the tablets, as a filler to prevent the tablet from rattling in the capsule shell. Placebo capsules to match the ezetimibe capsules are the identical capsule shells filled with the excipient filler material only (no tablets).

Obicetrapib and placebo tablets and ezetimibe and placebo capsules will be packaged into foil blisters and assembled into blister cards providing the 2 study drugs for each treatment group. The blister cards will be clearly labelled to indicate which blisters to use on each day. Blister cards will be assembled into kits, and each kit will provide a sufficient supply for 1 month of dosing. The shelf-life will be assigned based on the stability of the individual products and will not be greater than the expiry date of the input ezetimibe tablets. The kits should be stored below 25°C.

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

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

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

5.5.3 Study Drug Administration

Study drugs will be administered by the participant orally and once daily on Days 1 through 57. Study drugs should be administered at approximately the same time each morning, with food. On days with visits scheduled, study drugs should be administered with food following all fasted blood samples. 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 and capsules. During the Treatment Period, if compliance is not between 80% and 120%, inclusive, the participant will be counselled about the importance of compliance to the regimen. 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 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 or capsule. 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

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

5.6.2 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

A study visit schedule in tabular format is provided in Appendix A.

6.1 Informed Consent

Signed informed consent must be obtained before any study-related procedures are performed. See Section 11.3 for details on informed consent.

6.2 Screening Visit (Visit 1, Day -14 to Day -1)

The following procedures will be performed at the Screening Visit:

- Obtain signed informed consent;
- Confirm the participant meets the inclusion and exclusion criteria;
- Record demographic information;
- Record medical and surgical history;
- Record prior and concomitant medications;
- Record weight and height;
- Perform physical examination;
- Obtain vital signs;
- Perform 12-lead ECG;
- Perform urine pregnancy test for women of childbearing potential only;
- Collect blood sample for FSH test for peri-menopausal women, defined as women <55 years of age for whom it has been ≥1 year since their last menstrual period;
- Collect fasting (≥10 hours) blood samples for chemistry and hematology panels;

  Note: At Screening Visit only, hematology panel will include HbA1c.
- Collect urine sample for urinalysis;
- Collect fasting (≥10 hours) blood sample for lipid profile;
- Counsel participant on TLC diet and instruct them to begin diet; and
- Register visit in IRT.

6.3 Treatment Period – Visits 2 Through 4

6.3.1 Visit 2 (Day 1)

The following procedures will be performed at Visit 2 (Day 1):

- Confirm the participant continues to meet the inclusion and exclusion criteria and assess any updates since the Screening Visit;
- Record concomitant medications;

- Obtain vital signs;
- Collect fasting (≥10 hours) blood samples for chemistry and hematology panels;
- Collect urine sample for urinalysis;
- Collect fasting (≥10 hours) blood sample for lipid profile;
- Collect blood samples for PK and CETP mass and store for future analysis;
- Randomize the participant;
- Dispense randomized study drugs, as appropriate;
- Instruct the participant to self-administer the study drugs with food following all fasted blood samples;
- Counsel participant on TLC diet;
- Register visit in IRT; and
- Assess AEs.

6.3.2 Visit 3 (Day 29 ±3 Days)

The following procedures will be performed at Visit 3 (Day 29 ±3 days):

- Record concomitant medications;
- Obtain vital signs;
- Collect fasting (≥10 hours) blood samples for chemistry and hematology panels;
- Collect urine sample for urinalysis;
- Collect fasting (≥10 hours) blood sample for lipid profile;
- Perform study drug compliance check;
- Dispense randomized study drugs, as appropriate;
- Instruct the participant to self-administer the study drugs with food following all fasted blood samples;
- Counsel participant on TLC diet;
- Register visit in IRT; and
- Assess AEs.

6.3.3 Visit 4 (Day 57 ±3 Days)

The following procedures will be performed at Visit 4 (Day 57 ±3 days):

- Record concomitant medications;
- Record weight;
- Perform physical examination;

- Obtain vital signs;
- Collect fasting (≥10 hours) blood samples for chemistry and hematology panels;
- Collect urine sample for urinalysis;
- Collect fasting (≥10 hours) blood sample for lipid profile;
- Collect blood samples for PK and CETP mass and store for future analysis;
- Instruct the participant to self-administer the study drugs with food following all fasted blood samples;
- Perform study drug compliance check;
- Register visit in IRT; and
- Assess AEs.

6.4 Safety Follow-up Visit (Visit 5, Day 85 ±3 Days)

The following procedures will be performed at the Safety Follow-up Visit (Visit 5):

- Record concomitant medications;
- Obtain vital signs;
- Collect fasting (≥10 hours) blood samples for chemistry and hematology panels;
- Collect urine sample for urinalysis;
- Collect blood samples for PK and CETP mass and store for future analysis; and
- Assess AEs.

6.5 Pharmacokinetic Visit (Visit 6, Day 113 ±7 Days)

The following procedures will be performed at the PK Visit (Visit 6):

- Collect blood samples for PK and CETP mass and store for future analysis; and
- Assess AEs.

6.6 Early Termination Visit and Withdrawal Procedures

The end of the study for participants completing the study is Visit 6. For participants who are withdrawn from the study prior to completion, all of the following procedures will be performed at an Early Termination Visit:

- Record concomitant medications;
- Record weight;
- Perform physical examination;
- Obtain vital signs;
- Collect fasting (≥10 hours) blood samples for chemistry and hematology panels;
- Collect urine sample for urinalysis;

- Collect fasting (≥10 hours) blood sample for lipid profile;
- Perform study drug compliance check;
- Register visit in IRT; and
- Assess AEs.

7 EFFICACY ASSESSMENTS

The primary efficacy endpoint is percent change from Day 1 to Day 57 in LDL-C for the combination therapy group compared to the placebo group.

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

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

The exploratory efficacy endpoints include the following:

- Percent change from Day 1 to Day 57 in ApoB for the ezetimibe monotherapy group compared to the placebo group;
- Pairwise comparisons among the various treatment groups for the percent change from Day 1 to Day 57 in non-HDL-C, VLDL-C, HDL-C, TG, ApoE, and HDL-ApoE (with and without ApoC3);
- Pairwise comparisons among the various treatment groups for the proportion of participants at Day 57 that achieve LDL-C <2.6 mmol/L (<100 mg/dL), LDL-C <1.8 mmol/L (<70 mg/dL), and LDL-C <1.3 mmol/L (<50 mg/dL);
- Pairwise comparisons among the various treatment groups for the change from Day 1 to Day 57, Day 1 to Week 12, and Day 1 to Week 16 in the mean trough plasma levels of obicetrapib; and
- Pairwise comparisons among the various treatment groups for the change from Day 1 to Day 57, Day 1 to Week 12, and Day 1 to Week 16 in CETP mass.

Blood samples for lipid profile must be obtained under fasting conditions (ie, after the participant has fasted for ≥10 hours). For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications. If a participant is not fasting, the Investigator will reschedule the visit as soon as possible.

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 test variables, will be monitored and documented from the time of first dose of study drug until Visit 6. 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 drug, 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 drug should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at baseline change 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 that are detected during the study or are present at the date of the first dose of study drug 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 clinical 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 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. For obicetrapib, the reference safety information is included in the Investigator's Brochure currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

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, or 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 an 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, or 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 one 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 drug 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 [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] reporting line (telephone 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 applicable competent authorities in all the EU Member States concerned, to the Food and Drug Administration (FDA), and to the Central Ethics Committee/Institutional Review Board (IRB), 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 judgment 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 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 errors.
- **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 report 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.

Safety Contact Information: [redacted]
[redacted] SAE reporting line – Europe:
Telephone: [redacted]
Fax: [redacted]
Email: [redacted]

Safety Contact Information: [redacted]
[redacted] SAE reporting line – USA:
Telephone: [redacted]
Fax: [redacted]
Email: [redacted]

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 ≥10 hours). For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications. If a participant is not fasting, the Investigator will reschedule the visit as soon as possible. Estimated glomerular filtration rate will be calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (see Appendix B). At the Screening Visit only, the hematology panel will include HbA1c.

Urine will be obtained as indicated in Appendix A and sent to a central laboratory for complete urinalysis. See Appendix B for a complete list of analytes.

A urine pregnancy test will be performed for women of childbearing potential only prior to their participation in the study at the Screening Visit.

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

Blood samples for PK and CETP mass assessments will be collected as indicated in Appendix A.

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.

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

8.9 Demographics

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

8.10 Electrocardiograms

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

8.11 Physical Examinations

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

The Per-Protocol (PP) Population will include all participants in the mITT Population who have a baseline value for the LDL-C assessment, have a Day 57 value for the LDL-C assessment, and who did not experience a major protocol deviation that potentially impacted the primary efficacy endpoint. 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

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 57 in LDL-C will be performed using a mixed model for repeated measures (MMRM) approach. The analysis will include fixed effects for treatment, visit, and treatment-by-visit interaction, along with a covariate of the baseline value. The Restricted Maximum Likelihood estimation approach will be used with an unstructured covariance matrix. The least squares means, standard errors, and 2-sided 95% confidence intervals for each treatment group, for the pairwise comparisons of the combination therapy, obicetrapib monotherapy, and ezetimibe monotherapy to placebo, and for the pairwise comparisons of combination therapy and obicetrapib monotherapy versus ezetimibe monotherapy will be provided. The treatment comparison will be performed using a 2-sided test at the $\alpha = 0.05$ level of significance.

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 Statistical Analysis Plan (SAP).

9.2.1.2 Secondary and exploratory efficacy analysis

A similar MMRM model will be used for the analysis of the secondary and exploratory efficacy endpoints corresponding to the percent change from baseline. For the binary efficacy endpoints, a logistic regression analysis will be performed with model covariates of treatment group and baseline LDL-C.

In order to maintain the overall Type I error rate, the secondary efficacy endpoints will be tested sequentially at the 0.05 significance level according to the pre-specified order of hierarchy. No adjustment will be made for multiplicity in testing the exploratory efficacy endpoints. Nominal p-values will be provided when applicable. Descriptive and graphical summaries by treatment group will also be presented. 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 (MedDRA) 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 Pharmacokinetic Analysis

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

The sample size for this study was determined in order to provide sufficient power (>80%) for the analyses of the primary efficacy endpoint and secondary efficacy endpoints described in Section 7. The sample size calculations used values reported from a previous clinical trial involving obicetrapib (TA-8995) as a starting point for the assumptions of the treatment difference and

standard deviation.[13] 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 value (<3.5 mmol/L [<135 mg/dL] or ≥3.5 mmol/L [≥135 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 have 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 login to the system using their secure user name 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:

- MedDRA (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 is 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/Independent Ethics Committee

It is the responsibility of the Sponsor or their designee (ie, [redacted]) to ensure the IRB/Independent Ethics Committee (IEC) 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 written IRB/IEC 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/IEC by the Investigator.

Federal regulations and ICH guidelines require that approval be obtained from an IRB/IEC prior to participation of patients 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/IEC.

No drug will be released to the site for dosing until written IRB/IEC 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/IEC 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-specific 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/IEC, and/or regulatory agencies. A copy of the signed ICF will be given to the participant.

11.4 Participant Card

On enrollment in the study, the participant will receive a participant card to be carried at all times. The participant card will state that the participant is taking part in a clinical research study, type of treatment, number of treatment packs received, and contact details in case of an SAE.

11.5 Study Monitoring Requirements

It is the responsibility of the Investigator to ensure that the study is conducted in accordance with the protocol, ICH GCP, Directive 2001/20/EC, applicable regulatory requirements, and the Declaration of Helsinki 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-specific monitoring log.

11.6 Disclosure of Data

Data generated by this study must be available for inspection by the Sponsor or their designee, applicable foreign health authorities, and the IRB/IEC 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.

11.7 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.

11.8 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.

11.9 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out participant liability insurance for all participants who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

11.10 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorisation (CTA).

The study will commence (ie, initiation of study centers) when the CTA and favorable Ethics opinion have been received.

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/IEC, unless immediate implementation of the change is necessary for participant safety. In this case, the situation must be documented and reported to the IRB/IEC within 5 working days.

13 REFERENCES

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APPENDIX A: SCHEDULE OF PROCEDURES

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

a. Signed informed consent must be obtained before any study-related procedures are performed.
b. Any updates since the Screening Visit will be assessed.
c. Height and weight will be measured at the Screening Visit and will be used to calculate body mass index. Weight only will be measured at all other visits as indicated. Measurement of weight should be performed with the participant dressed in indoor clothing, with shoes removed, and bladder empty.
d. Vital signs will include body temperature, heart rate, and triplicate blood pressure (systolic and diastolic) measurements.
e. A single, standard 12-lead ECG will be performed by the Investigator or trained site personnel at the Screening Visit and centrally read by [redacted]
f. For women of childbearing potential only.
g. FSH test will be performed in peri-menopausal women, defined as women <55 years of age for whom it has been ≥1 year since their last menstrual period.
h. At Screening Visit only, hematology panel will include HbA1c.
i. At all visits, LDL-C will be calculated using the Friedewald formula. In addition, at Visit 2 and Visit 4, LDL-C will also be measured by preparative ultracentrifugation, also referred to as beta quantification.
j. Samples will be stored for future analysis.
k. Study drugs will be administered by the participant orally and once daily on Days 1 through 57. Study drugs should be administered at approximately the same time each morning, with food. On days with visits scheduled, study drugs should be administered with food following all fasted blood samples.
l. Participants will be instructed to begin the TLC diet at the Screening Visit.

CETP = cholesteryl ester transfer protein; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HbA1c = glycosylated hemoglobin; IRT = interactive response technology; PK = pharmacokinetic; TLC = Therapeutic Lifestyle Changes.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Standard Safety Chemistry Panel

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

[1] Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation: https://www.mdcalc.com/ckd-epi-equations-glomerular-filtration-rate-gfr.

Endocrinology

Follicle-stimulating hormone [1]

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

Hematology

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

[1] Screening Visit only.

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

Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocyte esterase	Microscopy [1]
Nitrite	pH
Protein	Specific gravity
Urobilinogen	

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

Pregnancy Test

Urine

Lipid Profile

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

[1] With and without apolipoprotein C3.

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

APPENDIX C: DIET GUIDELINES

The table below describes guidelines for the Therapeutic Lifestyle Changes diet:

Component	Recommendation
Saturated fats	<7% of total calories
Total fat	25% to 35% of total calories
Dietary cholesterol	<200 mg/day
Sodium	<2400 mg/day
Total calories	Adjust total caloric intake to maintain desirable body weight and/or prevent weight gain

Adapted from the United States National Institutes of Health Therapeutic Lifestyle Changes [TLC] diet.