CLINICAL STUDY PROTOCOL

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

Investigational Product: Obicetrapib

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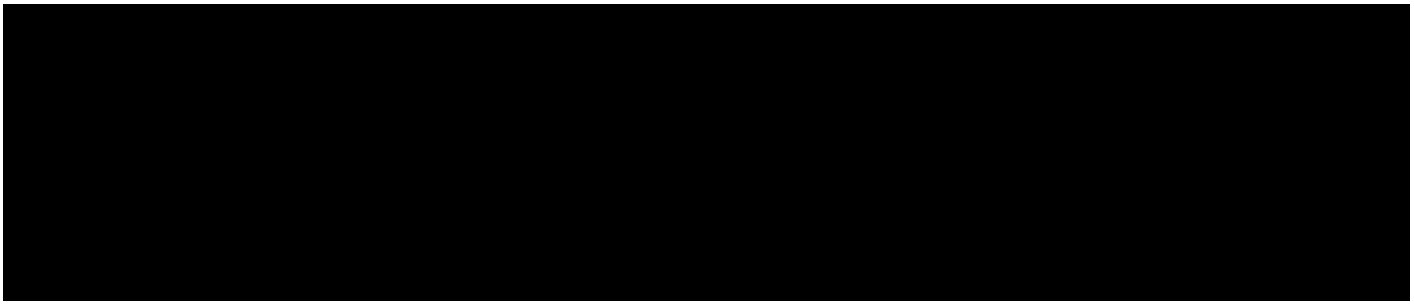
SIGNATURE PAGE

STUDY TITLE: Obicetrapib on Top of Maximum Tolerated Lipid-Modifying Therapies (BROADWAY): A Placebo-Controlled, Double-Blind, Randomized Phase 3 Study to Evaluate the Effect of 10 mg Obicetrapib in Participants With Underlying HeFH and/or Atherosclerotic Cardiovascular Disease (ASCVD) Who are Not Adequately Controlled by Their Lipid-Modifying Therapies



INVESTIGATOR AGREEMENT

By signing below, I agree that:

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

I agree to conduct this study in full accordance with Ethics Committee Regulations and International Council for Harmonisation Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

SYNOPSIS

TITLE: Obicetrapib on Top of Maximum Tolerated Lipid-Modifying Therapies (BROADWAY): A Placebo-Controlled, Double-Blind, Randomized Phase 3 Study to Evaluate the Effect of 10 mg Obicetrapib in Participants With Underlying HeFH and/or Atherosclerotic Cardiovascular Disease (ASCVD) Who are Not Adequately Controlled by Their Lipid-Modifying Therapies

PROTOCOL NUMBER: TA-8995-302

INVESTIGATIONAL PRODUCT: Obicetrapib

PHASE: 3

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

OBJECTIVES:

The primary objective of this study is to evaluate the effect of obicetrapib on LDL-C levels at Day 84.

The secondary objectives of this study include the following:

- To evaluate the effect of obicetrapib on LDL-C levels at Days 180 and 365;
- To evaluate the effect of obicetrapib on apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglycerides (TG) at Days 84, 180, and 365;
- To evaluate the effect of obicetrapib on lipoprotein (a) (Lp[a]) and apolipoprotein A1 (ApoA1) at Day 84; and
- To evaluate the safety and tolerability profile of obicetrapib in a representative population of adult males and females with HeFH and/or ASCVD of all ages, assessed by adverse events (AEs), events of special interest (ESIs), vital signs (including blood pressure), electrocardiogram (ECG) measurements, and clinical laboratory values.

The exploratory objectives of this study include the following:

- To evaluate the effect of obicetrapib on the following:
  - Proportion of participants achieving prespecified LDL-C levels at Days 84, 180, and 365; and
  - Biomarkers, including glycosylated hemoglobin (HbA1c), homeostatic model assessment of insulin resistance (HOMA-IR), and blood glucose at Day 365.
- To evaluate trough levels of obicetrapib from Baseline to Day 365 in the obicetrapib group;

- To evaluate the effect of obicetrapib on CV death, non-fatal myocardial infarction (MI), non-fatal stroke, or non-elective coronary revascularization; and
- To evaluate the effect of obicetrapib on hospitalization for unstable angina and/or chest pain, hospitalization for heart failure (HF), and transient ischemic attack (TIA).

POPULATION:

The population for this study will comprise participants with underlying HeFH and/or a history of ASCVD who are not adequately controlled by their maximally tolerated lipid-modifying therapy. At least 70% of the participants enrolled into this study must be taking high-intensity statins (HIS). HIS include atorvastatin 40 and 80 mg and rosuvastatin 20 and 40 mg. Participants with underlying HeFH but without a history of ASCVD will comprise up to a maximum of 20% of the total participants enrolled into the study. The study aims to enroll adult males and females ≥18 years of age.

STUDY DESIGN AND DURATION:

This study will be a multisite, placebo-controlled, double-blind, randomized Phase 3 study in approximately 2400 participants with underlying HeFH and/or a history of ASCVD who are not adequately controlled by their lipid-modifying therapy to evaluate the efficacy, safety, and tolerability of obicetrapib. Informed consent will be obtained from participants before the initiation of any study-specific procedures.

Approximately 2400 eligible participants will be randomized in a 2:1 ratio, respectively, to the following treatment groups:

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

Treatment allocation will be stratified based on CV risk (HeFH or non-HeFH) and Baseline statin dose (HIS or non-HIS). At least 70% of the participants enrolled into this study must be taking HIS. Participants with underlying HeFH but without a history of ASCVD will comprise up to a maximum of 20% of the total participants enrolled into the study. Starting on Day 1, each participant will self-administer their assigned study drug once daily until Day 365. During the Treatment Period, participants will return to the study site for efficacy and safety assessments. Blood samples for pharmacokinetic (PK) assessment will be collected at specified visits throughout the study. An onsite End of Study Visit will be conducted 35 days after the participant's last dose of study drug, during which an assessment of vital signs, concomitant medications, CV events, and AEs will be completed and documented in the participant's record.

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

The study will be governed by a Steering Committee. A Data and Safety Monitoring Board will provide independent oversight of participant safety. An independent Clinical Events Committee (CEC) will adjudicate all events of death and all potential or suspected CV events.

The responsibilities, procedures, and workflow for these committees will be defined in separate charters outside of the protocol.

INCLUSION AND EXCLUSION CRITERIA:

Inclusion criteria

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

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

     Note: Females are not considered to be of childbearing potential if they meet 1 of the following criteria as documented by the Investigator:

     - They have had a hysterectomy or tubal ligation at a minimum of 1 cycle prior to signing the ICF; or
     - They are postmenopausal, defined as ≥1 year since their last menstrual period for females ≥55 years of age or ≥1 year since their last menstrual period and have a follicle-stimulating hormone level in the postmenopausal range at Screening (Visit 1) for females <55 years of age.
   - Females of childbearing potential must agree to use an effective method of avoiding pregnancy from Screening (Visit 1) until 35 days after the last dose of study drug. Males whose partners are of childbearing potential must agree to use an effective method of avoiding pregnancy from Screening (Visit 1) until 35 days after the last dose of study drug. Effective methods of avoiding pregnancy are contraceptive methods used consistently and correctly (including implantable contraceptives, injectable contraceptives, oral contraceptives, transdermal contraceptives, intrauterine devices, and barrier methods) or a sterile sexual partner.
3. Have underlying HeFH and/or a history of ASCVD;

   Diagnosis of HeFH:

   Diagnosis must be made by either prior historical genotyping or by clinical assessment using either the World Health Organization Criteria/Dutch Lipid Clinic Network Criteria with a score that is ≥3 points or the Simon Broome Register Diagnostic Criteria with an assessment

of "Possible HeFH" or "Definite HeFH." LDL-C values are required to assess the Dutch Lipid Clinic Network Criteria and/or Simon Broome Register Diagnostic Criteria. In some cases, historical lipid values may not be obtainable, as participants may have initiated lipid-modifying therapies years prior. In these instances, the Investigator will need to estimate an "off-treatment" LDL-C value to calculate whether the participant qualifies for the study. For this purpose, the Protocol contains correction factors for a variety of statins and/or ezetimibe. The current LDL-C value obtained most recently and/or through the screening process can be converted using the appropriate correction factor. This value will be used to assess whether the participant meets either the Dutch Lipid Clinic Network Criteria or the Simon Broome Register Diagnostic Criteria. Participants with a diagnosis of HeFH may or may not have a history of ASCVD or ASCVD-risk equivalents;

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

- Coronary artery disease:
  - MI;
  - Prior coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting);
  - Angiographic or computed tomography (CT) imaging (eg, multidetector CT or CT angiography) evidence of coronary atherosclerosis with >70% stenosis in at least 1 major epicardial coronary artery; or
  - Coronary calcium score >100 Agatston units within 6 months prior to Screening (Visit 1).
- Cerebrovascular disease:
  - Prior ischemic stroke confirmed by a brain imaging study (CT or magnetic resonance imaging), considered not to be caused by atrial fibrillation, valvular heart disease, or mural thrombus;
  - Carotid artery stenosis >70% on prior angiography or ultrasound; or
  - History of percutaneous or surgical carotid artery revascularization.
- Peripheral arterial disease:
  - Prior documentation of a resting ankle-brachial index ≤0.85;
  - History of percutaneous or surgical revascularization of an iliac, femoral, or popliteal artery; or
  - Prior non-traumatic amputation of a lower extremity due to peripheral artery disease.

4. Are on maximally tolerated lipid-modifying therapy as an adjunct to a lipid-lowering diet and other lifestyle modifications, defined as follows:
   - A statin at a maximally tolerated stable dose;
     - A participant's maximally tolerated stable statin dose will be determined by the Investigator using his/her medical judgment and available sources, including the

participant's self-reported history of lipid-modifying therapy for at least 8 weeks prior to Screening (Visit 1); and

- For any participant not taking statin therapy due to statin intolerance, including those participants taking bempedoic acid or fibrate monotherapy, written confirmation will be required of both the participant and the Investigator stating that the participant was statin intolerant, aware of the benefit of statins to reduce the risk of a major adverse CV event, and aware that many other patients who are unable to tolerate a statin were actually able to tolerate a different statin or dose.

  Note: Statin intolerance will be defined as intolerance due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued, resulting in an inability to tolerate either 1) two or more statins at any dose, or 2) one statin at any dose and either an unwillingness to attempt a second statin or advice by a physician not to attempt a second statin.

- Ezetimibe for at least 8 weeks with or without maximally tolerated statin prior to Screening (Visit 1);
- Bempedoic acid for at least 8 weeks in combination with a maximally tolerated statin prior to Screening (Visit 1); and/or
- A proprotein convertase subtilisin/kexin type 9-targeted therapy alone or in combination with other lipid-modifying therapy for at least 4 stable doses prior to Screening (Visit 1).

Note: At least 70% of the participants enrolled into this study must be taking HIS. Documentation in the electronic case report form (eCRF) of the reason why a participant is unable to take HIS is required. HIS include the following: atorvastatin 40 and 80 mg and rosuvastatin 20 and 40 mg.

5. Have a fasting serum LDL-C at Screening (Visit 1) as follows:
   - Have a fasting serum LDL-C ≥55 mg/dL (≥1.4 mmol/L) to <100 mg/dL (<2.6 mmol/L) OR non-HDL-C ≥85 mg/dL (≥2.2 mmol/L) to <130 mg/dL (<3.4 mmol/L) with at least 1 of the following risk enhancers:
     - Recent MI (>3 and <12 months prior to Randomization [Visit 2]);
     - Type 2 diabetes mellitus;
     - Current daily cigarette smoking;
     - Age of >60 years;
     - High sensitivity C-reactive protein ≥2.0 mg/L (≥19.0 nmol/L) at Screening (Visit 1) or within 6 months prior to Screening (Visit 1);
     - Fasting TG >150 mg/dL (>1.7 mmol/L);
     - Fasting Lp(a) >30 mg/dL (>70 nmol/L); and/or
     - Fasting HDL-C <40 mg/dL (<1.0 mmol/L).

   OR

- Have a fasting serum LDL-C ≥100 mg/dL (≥2.6 mmol/L) OR non-HDL-C ≥130 mg/dL (≥3.4 mmol/L).

  Note: LDL-C at Screening (Visit 1) will be calculated using the Friedewald equation unless TG ≥400 mg/dL (≥4.5 mmol/L) or LDL-C ≤50 mg/dL (≤1.3 mmol/L). If TG ≥400 mg/dL (≥4.5 mmol/L) or LDL-C ≤50 mg/dL (≤1.3 mmol/L), then LDL-C level will be measured directly by preparative ultracentrifugation, also referred to as beta quantification.

6. Have fasting TG <500 mg/dL (<5.7 mmol/L) at Screening (Visit 1); and
7. Have an estimated glomerular filtration rate ≥30 mL/min/1.73 m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration equation at Screening (Visit 1).

Exclusion criteria

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

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

   Note: An abnormal ALT, AST, or total bilirubin must be confirmed by a repeat abnormal measurement at least 1 week apart.

7. Have HbA1c ≥10.0% (≥0.100 hemoglobin fraction) or a fasting glucose ≥270 mg/dL (≥15.0 mmol/L) at Screening (Visit 1);
8. Have thyroid-stimulating hormone >1.5 × ULN at Screening (Visit 1);
9. Have creatine kinase >3 × ULN at Screening (Visit 1);

10. Have a history of a malignancy that required surgery (excluding local and wide local excision), radiation therapy, and/or systemic therapy during the 3 years prior to Randomization (Visit 2);
11. Have a known history of alcohol and/or drug abuse within 5 years prior to Randomization (Visit 2);
12. Have received treatment with other investigational products or devices within 30 days of Screening (Visit 1) or 5 half-lives of the previous investigational product, whichever is longer;

    Note: Participants who have received treatment for Coronavirus Disease 2019 with standard of care and/or emergency use authorization medications, including vaccinations and boosters, within 30 days of Screening (Visit 1) or 5 half-lives of the previous investigational product **will** be permitted.
13. Are taking gemfibrozil or have taken gemfibrozil within 30 days of Screening (Visit 1);
14. Have planned use of other investigational products or devices during the course of the study;
15. Have participated in any clinical study evaluating obicetrapib;
16. Have a known allergy or hypersensitivity to the study drug, placebo, or any of the excipients in the study drug or placebo; or
17. Have any participant condition that, according to the Investigator, could interfere with the conduct of the study, such as, but not limited to, the following:
    - Are unable to communicate or to cooperate with the Investigator;
    - Are unable to understand the protocol requirements, instructions and study-related restrictions, and the nature, scope, and possible consequences of the study (including participants whose cooperation is doubtful due to drug abuse or alcohol dependency);
    - Are unlikely to comply with the protocol requirements, instructions, and study-related restrictions (eg, uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study);
    - Have any medical or surgical condition which, in the opinion of the Investigator, would put the participant at increased risk from participating in the study; or
    - Are directly involved in the conduct of the study.

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

The study drugs used in this study are as follows:

- 10 mg obicetrapib tablet; or
- Placebo tablet.

All study drugs will be administered by the participant orally, once daily at approximately the same time, from Visit 2 (Day 1) to the End of Treatment Visit (Day 365). Study drug should be administered with water and can be taken with or without food.

EFFICACY ENDPOINTS:

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

The secondary efficacy endpoints include the following:

- Percent change from Baseline to Days 180 and 365 in LDL-C in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Days 84, 180, and 365 in ApoB in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Days 84, 180, and 365 in non-HDL-C in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Days 84, 180, and 365 in HDL-C in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Day 84 in Lp(a) and ApoA1 in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Days 84, 180, and 365 in TC in the obicetrapib group compared to the placebo group; and
- Percent change from Baseline to Days 84, 180, and 365 in TG in the obicetrapib group compared to the placebo group.

The exploratory efficacy endpoints include the following:

- Proportion of participants at Days 84, 180, and 365 who achieve LDL-C <70 mg/dL (<1.8 mmol/L) in the obicetrapib group compared to the placebo group;
- Proportion of participants at Days 84, 180, and 365 who achieve LDL-C <55 mg/dL (<1.4 mmol/L) in the obicetrapib group compared to the placebo group;
- Proportion of participants at Days 84, 180, and 365 who achieve LDL-C <40 mg/dL (<1.0 mmol/L) in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Day 365 in HbA1c in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Day 365 in HOMA-IR in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Day 365 in blood glucose in the obicetrapib group compared to the placebo group;
- Trough levels of obicetrapib from Baseline to Day 365 in the obicetrapib group;
- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, non-fatal stroke, or non-elective coronary revascularization;

- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, or non-fatal stroke; and
- The time from Randomization until the first confirmed occurrence of hospitalization for unstable angina and/or chest pain, hospitalization for HF, and TIA.

SAFETY ENDPOINTS:

The safety endpoints include the following:

- Safety and tolerability profile of obicetrapib assessed by AEs, ESIs, vital signs (including blood pressure as assessed by office blood pressure measurements), ECGs, and clinical laboratory values; and
- Assessment of ABPM measured at Screening (Visit 1) and at Day 270 (Visit 6).

All potential or suspected CV events will be reviewed and adjudicated by an independent CEC and reported in the appropriate clinical endpoint eCRF. In addition, these events are subject to normal AE/serious AE reporting procedures.

CLINICAL EVENTS COMMITTEE:

An independent CEC will adjudicate all events of death and all potential or suspected CV events. A committee charter will be drafted to define the composition, roles, and responsibilities of the CEC.

STATISTICAL ANALYSES:

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

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

Analysis populations

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

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

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

The Per-Protocol (PP) Population will include all participants in the mITT Population who did not experience a major protocol deviation that potentially impacted the primary efficacy endpoint. The PP Population, along with the reason for exclusion, will be finalized prior to study unblinding.

The Safety Population will include all participants who receive at least 1 dose of any study drug. Treatment classification will be based on the actual treatment received. The Safety Population will be the primary population used for the safety analyses.

Efficacy analysis

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

The primary efficacy endpoint is the percent change from Baseline to Day 84 in LDL-C in the obicetrapib group compared to the placebo group. The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model with a fixed effect for the treatment group and covariates of Baseline LDL-C, CV risk (HeFH or non-HeFH), and Baseline statin therapy (HIS or non-HIS). The least squares (LS) mean, standard errors, and 2-sided 95% confidence intervals for each treatment group and for the mean difference compared to placebo will be obtained. The model will be fit assuming unequal variances for each treatment group.

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

Missing data will be imputed for the primary efficacy analysis based on a pattern mixture model that uses a multiple imputation technique analyzed with ANCOVA with pre-specified fixed factors and covariates. If appropriate, based on the number of retrieved dropouts, missing measurements of non-retrieved dropouts will be modeled by known measurements from retrieved dropouts (ie, participants who remain in the study after treatment discontinuation) in the same treatment group. The imputation model will be further clarified in the SAP.

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

In order to control the Type I error rate, a fixed sequential testing procedure will be implemented. In a hierarchical step-down manner, the primary endpoint will be tested first, followed by the secondary efficacy endpoints in a pre-specified order. The pre-specified order of the hypothesis testing for the secondary endpoints will be described in the SAP. No adjustment for multiple comparisons will be made for the exploratory efficacy endpoints.

Continuous secondary efficacy endpoints will be analyzed using similar methods as in the primary efficacy analysis.

Exploratory efficacy endpoints corresponding to continuous variables will be analyzed using a similar ANCOVA model as in the primary efficacy analysis. The 2-sided 95% confidence interval for LS means will be provided for continuous variables. Odds ratio and 95% confidence interval for the odds ratio will be provided for exploratory efficacy endpoints corresponding to binary variables. For time-to-event endpoints, the log-rank test, stratified by CV risk (HeFH or

non-HeFH) and Baseline statin therapy (HIS or non-HIS), will be used to compare differences in the time-to-event between obicetrapib and placebo. The hazard ratio and the associated 95% confidence interval will be estimated using a stratified Cox proportional hazards model with treatment as an explanatory variable, stratified by CV risk (HeFH or non-HeFH) and Baseline statin therapy (HIS or non-HIS). Additionally, Kaplan-Meier estimates of the time-to-event will be determined and displayed graphically. The proportional hazard assumption will be evaluated, such as through the examination of complementary log-log (event times) versus log (time) plots, etc. If the proportional hazard assumption raises concerns, additional analyses will be considered and will be further detailed in the SAP. Nominal p-values will be provided when applicable. Descriptive and graphical summaries by treatment group will also be presented. A population PK analysis will be described in a separate document.

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

Safety analysis

The Safety Population will be the primary population for the safety analysis. All safety endpoints will be summarized descriptively.

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

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

SAMPLE SIZE DETERMINATION:

Enrollment of approximately 2400 participants globally is planned for this study.

Assuming an approximate 5% drop out rate, approximately 2280 participants will be evaluable for efficacy. This sample size of at least 2280 evaluable participants will provide more than 90% power to detect a 30% reduction of LDL-C (standard deviation 15%) levels in the obicetrapib group compared to the placebo group at a 1-sided significance level of 0.025. This sample size will also contribute to sufficient participant exposure and safety data.

ABPM substudy

This substudy is designed for a non-inferiority assessment in systolic blood pressure from Screening (Visit 1) to Day 270 (Visit 6) between obicetrapib and placebo. The non-inferiority margin was selected in accordance with the United States Food and Drug Administration guidelines (Assessment of Pressor Effects of Drugs, Guidance for Industry). The non-inferiority margin was chosen to assess if obicetrapib is not substantially inferior to placebo for elevations in systolic blood pressure. The assumption for the common standard deviation is determined by a literature review and the obicetrapib Phase 2 program. From the reference paper by Vollmer et al, the estimate of the standard deviation for the change in systolic blood pressure (mmHg) for

hypertensive participants based on 24-hour ABPM measurements was 8.0 (95% confidence interval: 6.9, 9.4).[1]

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

SITES: Approximately 180 study sites globally

SPONSOR:

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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
CABG	Coronary artery bypass grafting
CD	Calendar day
CEC	Clinical Events Committee
CETP	Cholesteryl ester transfer protein
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CK	Creatine kinase
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CT	Computed tomography
CTA	Clinical trial authorisation
CV	Cardiovascular
CVD	Cardiovascular disease
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EIU	Exposure In Utero
EOS	End of Study
EOT	End of Treatment
ESI	Event of special interest
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FH	Familial hypercholesterolemia
GCP	Good Clinical Practice
HA	Health Authorities
HbA1c	Glycosylated hemoglobin

Abbreviation	Definition
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HeFH	Heterozygous familial hypercholesterolemia
HF	Heart failure
HIS	High-intensity statin(s)
HOMA-IR	Homeostatic model assessment of insulin resistance
hsCRP	High sensitivity C-reactive protein
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)
LS	Least squares
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
mITT	Modified Intent-to-Treat
NODM	New-onset diabetes mellitus
Non-HDL-C	Non-high-density lipoprotein cholesterol
PCI	Percutaneous coronary intervention
PCSK9	Proprotein convertase subtilisin/kexin type 9
PK	Pharmacokinetic(s)
PP	Per-Protocol
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	Total cholesterol
TG	Triglycerides
TIA	Transient ischemic attack
ULN	Upper limit of normal
VLDL	Very low-density lipoprotein
WHO	World Health Organization

1 INTRODUCTION AND BACKGROUND INFORMATION

1.1 Background Information on the Disease to be Treated

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

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

Lowering LDL-C is the primary therapeutic lipid target in ASCVD and HeFH patients. LDL-C is largely accepted as a valid surrogate endpoint of CV events by clinicians and regulatory authorities.[9] Chronic LDL-C elevations lead to progressive accumulation of atherosclerotic lesions in the arteries that require long-term management. While lifestyle changes are the primary intervention, these measures seldom reduce plasma LDL-C by >15%. Particularly in ASCVD and HeFH patients, pharmacologic treatments are required to adequately treat hyperlipidemia.[10] Evidence supporting LDL-C as a therapeutic target and surrogate for CV outcomes comes from interventional studies with LDL-C-lowering therapies, epidemiological studies, and genetic variants (both gain of function and loss of function). Large randomized clinical studies aimed at lowering LDL-C show a consistent, logarithmic-linear relationship between LDL-C reduction and CV risk reduction, independent of the way LDL-C lowering was achieved based on the mechanism of action.[10] A published patient-level meta-analysis, including 26 studies and more than 160,000 participants, showed a consistent relationship between LDL-C reduction and CV outcomes.[10] This analysis showed that each 1 mmol/L (38.67 mg/dL) reduction in LDL-C is associated with a 22% reduction in the 5-year incidence of major coronary events, revascularizations, and ischemic strokes. Intensive statin therapy relative to low- or moderate-intensity statin treatment confers a greater benefit in patients at high CV risk.[10] Non-statin therapies may provide additional lowering of CV risk as demonstrated in the

IMPROVE-IT study adding ezetimibe to statin therapy.[11,12] Unfortunately, despite being treated with maximally tolerated lipid-modifying therapy, a substantial number of patients still do not reach their target guideline goals.[11]

Patients with ASCVD and HeFH who require additional lipid lowering despite treatment with maximally tolerated lipid-modifying therapy, including maximally tolerated doses of statins, have an unmet medical need. Obicetrapib may offer a useful option for these patients. Obicetrapib has been well tolerated to date and its Phase 2 data demonstrate significant LDL-C lowering, thus prompting further evaluation in Phase 3 clinical studies.

1.2 Background Information on 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 ApoB-containing particles, VLDL, and LDL-C, in exchange for TG.

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, will benefit patients with elevated LDL-C and increased CV risk.

The relative reduction in major adverse CV events (MACEs) 2 years after completion of the REVEAL study was nearly double (approximately 18%) than 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.[13]

1.3 Obicetrapib (TA-8995)

Obicetrapib (TA-8995) has been shown to be a selective CETP inhibitor. Apart from preventing the shuttling of cholesterol esters from HDL-C to LDL-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 also 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.[14] This effect is considered important because it is expected to reduce established atheroma burden.

1.4 Clinical Development of Obicetrapib

Both single ascending dose (TA-8995-01) and multiple ascending dose (TA-8995-02) studies have been conducted in healthy volunteers. A formal thorough QT/heart rate-corrected QT interval study (TA-8995-04) has been completed and obicetrapib was shown to have no effect on the 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

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).

The first patient study conducted was a Phase 2 clinical study (TA-8995-03) in Denmark and The Netherlands where the aim was to evaluate the optimal dose of obicetrapib alone and in combination with statins in patients with mild dyslipidemia. This study concluded that a daily dose of 10 mg of obicetrapib therapy resulted in an LDL-C reduction of 45.4%, an HDL-C increase of 179.0%, an ApoA1 increase of 63.4%, and a significant increase of HDL-C efflux capacity. Furthermore, given on top of atorvastatin 20 mg, obicetrapib 10 mg resulted in an additional 50.3% reduction in LDL-C. A second patient study (TA-8995-06) 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 was not likely to be clinically relevant.

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

This study is a pivotal Phase 3 study to investigate the treatment of elevated LDL-C levels in participants with underlying HeFH and/or a history of ASCVD. This study will include participants on maximally tolerated lipid-modifying therapy, including maximally tolerated doses of statins.

1.4.1 Dose Selection Rationale

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

1.5 Rationale

An alternative to statin use is the use of PCSK9-targeted therapies. However, there are notable limitations with this line of therapy, including very high costs and limited data regarding long-term

success relative to statins. Because PCSK9-targeted therapies are injectable, this poses a less attractive option for patients who prefer oral medications.

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

1.6 Risk/Benefit

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

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

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

1.6.1 Coronavirus Disease 2019 Impacts

In March 2020, the Coronavirus Disease 2019 (COVID-19), caused by infection with severe acute respiratory syndrome coronavirus 2, was characterized as a pandemic by the World Health Organization (WHO). The COVID-19 pandemic has impacted clinical studies worldwide due to quarantines, site closures, travel limitations, diversion of resources, and/or general interruptions in study-related procedures. This study will be initiated during the ongoing COVID-19 pandemic. The Sponsor has reviewed guidance from regulatory authorities and reports from the literature while planning study start-up and conduct (ie, European Medicines Agency 2022, Food and Drug Administration [FDA] 2021).[15,16]

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

This study protocol includes contingency measures to ensure participant safety while enabling sites to generate reliable data and maintain integrity of the study and study data (see Section 3.1.1). The

impacts of these implemented contingency measures on the outcomes of this study, including any protocol deviations that result from COVID-19 illness and/or COVID-19 control measures, will be discussed in the Clinical Study Report.

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

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the effect of obicetrapib on LDL-C levels at Day 84.

2.2 Secondary Objectives

The secondary objectives of this study include the following:

- To evaluate the effect of obicetrapib on LDL-C levels at Days 180 and 365;
- To evaluate the effect of obicetrapib on ApoB, non-high-density lipoprotein cholesterol (non-HDL-C), HDL-C, total cholesterol (TC), and TG at Days 84, 180, and 365;
- To evaluate the effect of obicetrapib on Lp(a) and ApoA1 at Day 84; and
- To evaluate the safety and tolerability profile of obicetrapib in a representative population of adult males and females with HeFH and/or ASCVD of all ages, assessed by AEs, events of special interest (ESIs), vital signs (including blood pressure), ECG measurements, and clinical laboratory values.

2.3 Exploratory Objectives

The exploratory objectives of this study include the following:

- To evaluate the effect of obicetrapib on the following:
  - Proportion of participants achieving prespecified LDL-C levels at Days 84, 180, and 365; and
  - Biomarkers, including glycosylated hemoglobin (HbA1c), homeostatic model assessment of insulin resistance (HOMA-IR), and blood glucose at Day 365.
- To evaluate trough levels of obicetrapib from Baseline to Day 365 in the obicetrapib group;
- To evaluate the effect of obicetrapib on CV death, non-fatal MI, non-fatal stroke, or non-elective coronary revascularization; and
- To evaluate the effect of obicetrapib on hospitalization for unstable angina and/or chest pain, hospitalization for heart failure (HF), and transient ischemic attack (TIA).

3 STUDY DESCRIPTION

3.1 Summary of Study Design

This study will be a multisite, placebo-controlled, double-blind, randomized Phase 3 study in approximately 2400 participants with underlying HeFH and/or a history of ASCVD who are not adequately controlled by their lipid-modifying therapy to evaluate the efficacy, safety, and tolerability of obicetrapib. Informed consent will be obtained from participants before the initiation of any study-specific procedures.

Approximately 2400 eligible participants will be randomized in a 2:1 ratio, respectively, to the following treatment groups:

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

Treatment allocation will be stratified based on CV risk (HeFH or non-HeFH) and Baseline statin dose (HIS or non-HIS). At least 70% of the participants enrolled into this study must be taking HIS. Participants with underlying HeFH but without a history of ASCVD will comprise up to a maximum of 20% of the total participants enrolled into the study. Starting on Day 1, each participant will self-administer their assigned study drug once daily until Day 365. During the Treatment Period, participants will return to the study site for efficacy and safety assessments. Blood samples for pharmacokinetic (PK) assessment will be collected at specified visits throughout the study. An onsite End of Study (EOS) Visit will be conducted 35 days after the participant's last dose of study drug, during which an assessment of vital signs, concomitant medications, CV events, and AEs will be completed and documented in the participant's record.

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

The study will be governed by a Steering Committee. A Data and Safety Monitoring Board (DSMB) will provide independent oversight of participant safety. An independent Clinical Events Committee (CEC) will adjudicate all events of death and all potential or suspected CV events.

The responsibilities, procedures, and workflow for these committees will be defined in separate charters outside of the protocol.

3.1.1 COVID-19 Contingency Measures

In cases of COVID-19 limitations, it is the Investigator's responsibility to assure the safety of participants. If necessary, the Sponsor will implement and document mitigation strategies. It may be necessary to conduct some study visits virtually. At the Investigator's discretion, the study visit(s) can be conducted in-clinic or virtually. If conducted virtually, the visit will include alternative methods for safety, efficacy, and distribution/collection of study drug, including but not limited to phone/video contact, alternative location for biologic sample collection, alternative

secure delivery of study drug, home health care (if available), and a secured way of transferring participant data from and to home health services and the site.

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

3.2 Study Indication

Obicetrapib is being developed as an adjunct to diet and maximally tolerated lipid-modifying therapy for the treatment of adults with HeFH or a history of ASCVD who require additional lowering of LDL-C.

4 SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 Inclusion Criteria

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

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

     Note: Females are not considered to be of childbearing potential if they meet 1 of the following criteria as documented by the Investigator:

     - They have had a hysterectomy or tubal ligation at a minimum of 1 cycle prior to signing the ICF; or
     - They are postmenopausal, defined as ≥1 year since their last menstrual period for females ≥55 years of age or ≥1 year since their last menstrual period and have a follicle-stimulating hormone level in the postmenopausal range at Screening (Visit 1) for females <55 years of age.
   - Females of childbearing potential must agree to use an effective method of avoiding pregnancy from Screening (Visit 1) until 35 days after the last dose of study drug. Males whose partners are of childbearing potential must agree to use an effective method of avoiding pregnancy from Screening (Visit 1) until 35 days after the last dose of study drug. Effective methods of avoiding pregnancy are contraceptive methods used consistently and correctly (including implantable contraceptives, injectable contraceptives, oral contraceptives, transdermal contraceptives, intrauterine devices, and barrier methods) or a sterile sexual partner.
3. Have underlying HeFH and/or a history of ASCVD;

   Diagnosis of HeFH:

   Diagnosis must be made by either prior historical genotyping or by clinical assessment using either the WHO Criteria/Dutch Lipid Clinic Network Criteria with a score that is ≥3 points, as specified in Appendix C, or the Simon Broome Register Diagnostic Criteria with an assessment of "Possible HeFH" or "Definite HeFH," as specified in Appendix D.[17,18] LDL-C values are required to assess the Dutch Lipid Clinic Network Criteria and/or Simon Broome Register Diagnostic Criteria. In some cases, historical lipid values may not be obtainable, as participants may have initiated lipid-modifying therapies years prior. In these instances, the Investigator will need to estimate an "off-treatment" LDL-C value to calculate whether the participant qualifies for the study. For this purpose, Appendix E contains correction factors for a variety

of statins and/or ezetimibe. The current LDL-C value obtained most recently and/or through the screening process can be converted using the appropriate correction factor. This value will be used to assess whether the participant meets either the Dutch Lipid Clinic Network Criteria or the Simon Broome Register Diagnostic Criteria. Participants with a diagnosis of HeFH may or may not have a history of ASCVD or ASCVD-risk equivalents;

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

- Coronary artery disease:
  - MI;
  - Prior coronary revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]);
  - Angiographic or computed tomography (CT) imaging (eg, multidetector CT or CT angiography) evidence of coronary atherosclerosis with >70% stenosis in at least 1 major epicardial coronary artery; or
  - Coronary calcium score >100 Agatston units within 6 months prior to Screening (Visit 1).
- Cerebrovascular disease:
  - Prior ischemic stroke confirmed by a brain imaging study (CT or magnetic resonance imaging), considered not to be caused by atrial fibrillation, valvular heart disease, or mural thrombus;
  - Carotid artery stenosis >70% on prior angiography or ultrasound; or
  - History of percutaneous or surgical carotid artery revascularization.
- Peripheral arterial disease:
  - Prior documentation of a resting ankle-brachial index ≤0.85;
  - History of percutaneous or surgical revascularization of an iliac, femoral, or popliteal artery; or
  - Prior non-traumatic amputation of a lower extremity due to peripheral artery disease.

4. Are on maximally tolerated lipid-modifying therapy as an adjunct to a lipid-lowering diet and other lifestyle modifications, defined as follows:
   - A statin at a maximally tolerated stable dose;
     - A participant's maximally tolerated stable statin dose will be determined by the Investigator using his/her medical judgment and available sources, including the participant's self-reported history of lipid-modifying therapy for at least 8 weeks prior to Screening (Visit 1); and

- For any participant not taking statin therapy due to statin intolerance, including those participants taking bempedoic acid or fibrate monotherapy, written confirmation will be required of both the participant and the Investigator stating that the participant was statin intolerant, aware of the benefit of statins to reduce the risk of a MACE, and aware that many other patients who are unable to tolerate a statin were actually able to tolerate a different statin or dose.

  Note: Statin intolerance will be defined as intolerance due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued, resulting in an inability to tolerate either 1) two or more statins at any dose, or 2) one statin at any dose and either an unwillingness to attempt a second statin or advice by a physician not to attempt a second statin.[19]

- Ezetimibe for at least 8 weeks with or without maximally tolerated statin prior to Screening (Visit 1);
- Bempedoic acid for at least 8 weeks in combination with a maximally tolerated statin prior to Screening (Visit 1); and/or
- A PCSK9-targeted therapy alone or in combination with other lipid-modifying therapy for at least 4 stable doses prior to Screening (Visit 1).

Note: At least 70% of the participants enrolled into this study must be taking HIS. Documentation in the electronic case report form (eCRF) of the reason why a participant is unable to take HIS is required. HIS include the following: atorvastatin 40 and 80 mg and rosuvastatin 20 and 40 mg.

5. Have a fasting serum LDL-C at Screening (Visit 1) as follows:

   - Have a fasting serum LDL-C ≥55 mg/dL (≥1.4 mmol/L) to <100 mg/dL (<2.6 mmol/L) OR non-HDL-C ≥85 mg/dL (≥2.2 mmol/L) to <130 mg/dL (<3.4 mmol/L) with at least 1 of the following risk enhancers:
     - Recent MI (>3 and <12 months prior to Randomization [Visit 2]);
     - Type 2 diabetes mellitus;
     - Current daily cigarette smoking;
     - Age of >60 years;
     - High sensitivity C-reactive protein (hsCRP) ≥2.0 mg/L (≥19.0 nmol/L) at Screening (Visit 1) or within 6 months prior to Screening (Visit 1);
     - Fasting TG >150 mg/dL (>1.7 mmol/L);
     - Fasting Lp(a) >30 mg/dL (>70 nmol/L); and/or
     - Fasting HDL-C <40 mg/dL (<1.0 mmol/L).

   OR

   - Have a fasting serum LDL-C ≥100 mg/dL (≥2.6 mmol/L) OR non-HDL-C ≥130 mg/dL (≥3.4 mmol/L).

Note: LDL-C at Screening (Visit 1) will be calculated using the Friedewald equation unless TG ≥400 mg/dL (≥4.5 mmol/L) or LDL-C ≤50 mg/dL (≤1.3 mmol/L). If TG ≥400 mg/dL (≥4.5 mmol/L) or LDL-C ≤50 mg/dL (≤1.3 mmol/L), then LDL-C level will be measured directly by preparative ultracentrifugation, also referred to as beta quantification.

6. Have fasting TG <500 mg/dL (<5.7 mmol/L) at Screening (Visit 1); and
7. Have an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration equation at Screening (Visit 1).

4.2 Exclusion Criteria

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

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

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

12. Have received treatment with other investigational products or devices within 30 days of Screening (Visit 1) or 5 half-lives of the previous investigational product, whichever is longer;

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

13. Are taking gemfibrozil or have taken gemfibrozil within 30 days of Screening (Visit 1);
14. Have planned use of other investigational products or devices during the course of the study;
15. Have participated in any clinical study evaluating obicetrapib;
16. Have a known allergy or hypersensitivity to the study drug, placebo, or any of the excipients in the study drug or placebo; or
17. Have any participant condition that, according to the Investigator, could interfere with the conduct of the study, such as, but not limited to, the following:
    - Are unable to communicate or to cooperate with the Investigator;
    - Are unable to understand the protocol requirements, instructions and study-related restrictions, and the nature, scope, and possible consequences of the study (including participants whose cooperation is doubtful due to drug abuse or alcohol dependency);
    - Are unlikely to comply with the protocol requirements, instructions, and study-related restrictions (eg, uncooperative attitude, inability to return for follow-up visits, and improbability of completing the study);
    - Have any medical or surgical condition which, in the opinion of the Investigator, would put the participant at increased risk from participating in the study; or
    - Are directly involved in the conduct of the study.

4.3 Withdrawal Criteria

Participation of a participant in this clinical study will be discontinued for any of the following reasons:

- Withdrawal of consent; or
- Termination of the study by the Sponsor or the regulatory authority.

Study drug treatment may be discontinued either permanently or temporarily (although the participant should be encouraged to remain in the study and to follow-up for study visits) for any of the following reasons:

- 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 serious AE (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 (permanent discontinuation of study drug);

- Requirement of prohibited concomitant medication; or
- Participant failure to comply with protocol requirements or study-related procedures.

Participants are free to withdraw consent from the study (which means permanent discontinuation of study drug and all follow-up assessments) at any time without prejudice. Note that discontinuation of study drug in and of itself is **not** considered withdrawal of consent.

An excessive rate of withdrawals (either discontinuation of study drug or study withdrawal) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided, and all efforts should be taken to motivate participants to comply with all of the study-specific procedures and to continue follow-up until the end of the study to detect the occurrence of CV events and assess vital status.

Every attempt should be made to keep participants on study drug throughout the duration of the study. Before permanently discontinuing study drug (either participant- or Investigator-initiated), an interruption should be considered. Participants who temporarily discontinue study drug for any reason should restart as soon as it is medically justified in the opinion of the Investigator. In addition, participants should not be withdrawn from the study drug or from the study after experiencing a potential CV event.

All participants who permanently discontinue study drug should continue scheduled study visits. If the participant declines continued onsite visits but is agreeable to telephone calls, he/she will be contacted by the Investigator periodically to assess occurrence of CV events until death, documented withdrawal of participant informed consent (in writing if allowed by local regulations), or the final closure of the study.

The Investigator should show due diligence and explore all possible options to reach a participant who fails to return for a visit. In the case of participants lost to follow-up, attempts to contact the participant must be made and documented in the participant's medical records and in source documents. Per routine, in order to avoid participants lost to follow-up, the Investigator should ask the participant at the study start for the contact details of a relative or friend who can be contacted for participant contact information in case the participant cannot be reached.

Participants should not be withdrawn from follow-up unless they explicitly withdraw consent to be contacted. All efforts should therefore be made to minimize the number of participants who withdraw consent as, in general, no further information on CV events and survival status may be collected after that point. Participants who do not want regular in-person follow-up after cessation of study drug should be offered alternative methods of follow-up, including periodic telephone follow-up, contact at study closure, or assessment of health status via treating physicians or medical records. Such participants would then not be viewed as withdrawal of consent. The Investigator must explain to the participant all options for continued participation, and document which options were refused by the participant and the reason for refusal. Withdrawal of consent to all follow-up must be ascertained and documented in writing by the Investigator, who must inform the Sponsor and document the withdrawal of consent in the eCRF and medical records.

For participants who permanently discontinue from study treatment **and who decline continued study participation**, an Early Termination (ET) Visit will be scheduled as soon as possible followed by an onsite EOS Visit 35 days later. The ET Visit procedures are identical to the End of Treatment (EOT) Visit procedures. If the discontinuation occurs at a specific onsite visit, this visit will become the ET Visit and EOT Visit procedures should be followed. Participants who

withdraw consent to all follow-up will be asked about the reason(s) and will be assessed for the presence of any AEs.

For participants who completely withdraw consent, life status will be obtained at study end through public record information according to local guidelines and as allowed by local regulations.

If premature withdrawal from the study occurs for any reason, the Investigator must determine the primary reason for a participant's premature withdrawal from the study and record this information in the medical records and on the eCRF.

Withdrawn participants will not be replaced.

4.4 Retesting

If laboratory abnormalities during Screening (Visit 1) are considered by the Investigator to be transient, then the laboratory tests may be repeated once during Screening (Visit 1). Laboratory samples may also be repeated if samples are unable to be tested due to hemolysis, platelet clumping, or other processing errors. Retesting will be performed by the central laboratory. The Investigator's rationale for retesting should be documented. If the retest result is no longer exclusionary, the participant may be randomized.

4.5 Rescreening

Participants who have screen failed are permitted to rescreen, following consultation with the Medical Monitor. Rescreening may be scheduled after at least 5 days have elapsed from the previous study visit. Rescreened participants will be assigned a new participant number.

5 STUDY TREATMENTS

5.1 Treatment Groups

Approximately 2400 eligible participants will be randomized in a 2:1 ratio, respectively, to the following treatment groups:

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

All study drugs will be administered by the participant orally from Visit 2 (Day 1) to the EOT Visit (Day 365).

5.2 Rationale for Dosing

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

5.3 Randomization and Blinding

Participants who meet all inclusion criteria and none of the exclusion criteria will be randomized on Day 1 (Visit 2) via the [redacted] Interactive Response Technology (IRT) system in a 2:1 ratio to receive obicetrapib or placebo.

Treatment allocation will be stratified based on CV risk (HeFH or non-HeFH) and Baseline statin dose (HIS or non-HIS). At least 70% of the participants enrolled into this study must be taking HIS. Participants with underlying HeFH but without a history of ASCVD will comprise up to a maximum of 20% of the total participants enrolled into the study.

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

Active and placebo product will be identical. Medication bottles with a unique code will be assigned to participants at various points in the study by the IRT system.

5.4 Breaking the Blind

Study drug will be managed using the IRT system. Each user will have a unique username and passcode to access the system. Investigators shall not break the study blind during the study, and Investigators should treat all participants as if they had received obicetrapib. However, in situations

in which knowledge of the participant's study drug is necessary for clinical management, the Investigator should proceed with unblinding.

Once a participant's treatment assignment has been unblinded, the Medical Monitor or designee should be notified within 24 hours of unblinding of the treatment. Information relating to unblinding (eg, date and time of the call to the Medical Monitor by the Investigator, reason for unblinding, and date and time of unblinding) shall be clearly recorded in the participant's study file and in the electronic data capture (EDC) system, as part of relevant standard operating procedures. In addition, the Investigator should consider whether the clinical event prompting unblinding should be considered an AE or SAE, according to the regulatory definitions or criteria for AEs or SAEs, and if so, submit an AE/SAE report to the Sponsor or designee (see Section 8.4). The Sponsor or designee will also unblind any SAE reports that are unexpected and considered to be related to the study drug, in accordance with safety reporting guidance and regulations.

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

5.5 Drug Supplies

5.5.1 Formulation and Packaging

Obicetrapib 10 mg tablets are round, 6 mm diameter, white, film-coated tablets with no identifying markings and contain 10 mg of obicetrapib drug substance. [redacted]. Obicetrapib 10 mg tablets are manufactured in accordance with current Good Manufacturing Practices. Matching placebo tablets are identical in qualitative composition except for the absence of obicetrapib drug substance.

The tablets are packaged in high-density polyethylene bottles, using tamper-evident/child-resistant screw caps made of polypropylene. Each bottle will contain 40 tablets, sufficient for a 1-month supply, with an allowance for visit windows.

Active and placebo product will be identical. A unique identifier will be added to each bottle.

5.5.2 Study Drug Preparation and Dispensing

Participants will receive one 40-count bottle of study drug at Visit 2, two 40-count bottles at Visit 3, and three 40-count bottles at Visits 4, 5, and 6. Study drug will be assigned in a double-blind manner via the IRT system at each applicable study visit.

5.5.3 Study Drug Administration

All study drugs will be administered by the participant orally, once daily at approximately the same time, from Visit 2 (Day 1) to the EOT Visit (Day 365). Study drug should be administered with water and can be taken with or without food.

At Visits 2, 5, and 7, participants should take study drug after a trough PK sample has been drawn.

5.5.4 Treatment Compliance

Participants will return used and unused bottles of study drug at Visits 3, 4, 5, 6, and 7. The number of tablets returned should be counted and documented in the source documentation and in the eCRF for compliance. Any discrepancies between the number of days and the number of tablets administered should be clarified and documented in the source.

Compliance with study drug dosing will be assessed using the following formula:

$$Compliance\ (\%) = \frac{(\#\ tablets\ dispensed - \#\ tablets\ returned)}{\#\ expected\ dosing\ days} \times 100$$

5.5.5 Storage and Accountability

All study drug must be stored below 25°C (77°F) in a secure area with access limited to the Investigator and authorized study site personnel. Study drug should not be frozen or refrigerated.

In accordance with regulatory requirements, the Investigator or designated study site personnel must document the amount of study drug dispensed and/or administered to participants, the amount returned by participants, and the amount received from and returned to the Sponsor (or representative), when applicable. Study drug accountability records must be maintained throughout the course of the study. The accountability unit for this study is a tablet. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused study drug will be provided in the appropriate study manual.

5.6 Prior and Concomitant Medications and/or Procedures

5.6.1 Excluded Medications and/or Procedures

Participants who have received treatment with other investigational products or devices within 30 days of Screening (Visit 1) or 5 half-lives of the previous investigational product (whichever is longer) will be excluded from study participation.

Participants with a known history of alcohol and/or drug abuse within 5 years prior to Randomization (Visit 2) will be excluded from study participation.

Participants who plan to use other investigational products or devices during the course of the study will be excluded from study participation.

Participants who are taking gemfibrozil or who have taken gemfibrozil within 30 days of Screening (Visit 1) will be excluded from study participation per Exclusion Criterion 13.

5.6.2 Restricted Medications and/or Procedures

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

Participants are not required to be taking statins. Reasons for not using statin therapy must be documented (eg, the participant is statin intolerant) as described in Section 5.6.3. If the participant is statin intolerant, written confirmation will be required of both the participant and the Investigator stating that the participant was statin intolerant, aware of the benefit of statins to reduce the risk of a MACE, and aware that many other patients who are unable to tolerate a statin were actually able to tolerate a different statin or dose. Statin intolerance, as defined in Inclusion Criterion 4, should be recorded as intolerance to any dose of any statin as historical events attributed to the statin in question, in the source documentation and eCRF as part of the medical history to confirm intolerance to statins.[19]

Participants must agree not to donate blood during study participation.

5.6.3 Documentation of Prior and Concomitant Medication Use

All prior and concomitant medications must be documented in the source documents and applicable eCRFs. Concomitant medications will continue to be assessed and recorded at every study visit from the time of informed consent until study participation is complete.

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

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

No more than 10% of participants in this study will be statin intolerant. For any participant not taking statin therapy due to statin intolerance (as defined in Inclusion Criterion 4), including those participants taking bempedoic acid or fibrate monotherapy, written confirmation will be required of both the participant and the Investigator stating that the participant was statin intolerant, aware of the benefit of statins to reduce the risk of a MACE, and aware that many other patients who are unable to tolerate a statin were actually able to tolerate a different statin or dose.[19]

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

5.6.4 Dietary Guidelines

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

6 STUDY PROCEDURES

Please refer to Appendix A (Schedule of Procedures) for a complete list of procedures to be completed at each study visit.

7 EFFICACY ASSESSMENTS

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

The secondary efficacy endpoints include the following:

- Percent change from Baseline to Days 180 and 365 in LDL-C in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Days 84, 180, and 365 in ApoB in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Days 84, 180, and 365 in non-HDL-C in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Days 84, 180, and 365 in HDL-C in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Day 84 in Lp(a) and ApoA1 in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Days 84, 180, and 365 in TC in the obicetrapib group compared to the placebo group; and
- Percent change from Baseline to Days 84, 180, and 365 in TG in the obicetrapib group compared to the placebo group.

The exploratory efficacy endpoints include the following:

- Proportion of participants at Days 84, 180, and 365 who achieve LDL-C <70 mg/dL (<1.8 mmol/L) in the obicetrapib group compared to the placebo group;
- Proportion of participants at Days 84, 180, and 365 who achieve LDL-C <55 mg/dL (<1.4 mmol/L) in the obicetrapib group compared to the placebo group;
- Proportion of participants at Days 84, 180, and 365 who achieve LDL-C <40 mg/dL (<1.0 mmol/L) in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Day 365 in HbA1c in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Day 365 in HOMA-IR in the obicetrapib group compared to the placebo group;
- Percent change from Baseline to Day 365 in blood glucose in the obicetrapib group compared to the placebo group;
- Trough levels of obicetrapib from Baseline to Day 365 in the obicetrapib group;
- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, non-fatal stroke, or non-elective coronary revascularization;

- The time from Randomization until the first confirmed occurrence of a composite of CV death, non-fatal MI, or non-fatal stroke; and
- The time from Randomization until the first confirmed occurrence of hospitalization for unstable angina and/or chest pain, hospitalization for HF, and TIA.

7.1 Lipid Profile/Biomarkers

Samples will be collected for the lipid profile/biomarkers at visits specified in the Schedule of Procedures (Appendix A). The lipid profile/biomarker samples will be analyzed for ApoB, HDL-C, LDL-C, non-HDL-C, TC, and TG. Samples should be collected while the participant is fasting (a minimum of 8 hours).

At Baseline (Visit 2), Day 84 (Visit 4), and Day 365 (Visit 7)/EOT/ET, LDL-C will be measured for all participants by preparative ultracentrifugation, also referred to as beta quantification. At all other scheduled visits, LDL-C will be calculated using the Friedewald equation unless TG ≥400 mg/dL (≥4.5 mmol/L) or LDL-C ≤50 mg/dL (≤1.3 mmol/L). If TG ≥400 mg/dL (≥4.5 mmol/L) or LDL-C ≤50 mg/dL (≤1.3 mmol/L), then LDL-C level will be measured directly by preparative ultracentrifugation.

All lipid profile/biomarker values will be blinded during the study through the EOS Visit (Visit 8). Participants, the Sponsor, Investigators, and all study site personnel involved in the study, including personnel carrying out study procedures, evaluating participants, entering study data, and/or evaluating study data, will remain blinded to lipid profile/biomarker values until all participants have completed the EOS Visit and the database has been locked for analysis.

7.2 CV Event Endpoint Definitions

CV death, stroke, TIA, non-elective coronary revascularization, hospitalization for unstable angina, and hospitalization for HF will be defined based on the 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials described in Appendix F.[20] MI will be defined based on the Fourth Universal Definition of Myocardial Infarction described in Appendix G.[21]

An independent CEC will adjudicate all events of death and all potential or suspected CV events.

Additional details will be provided in the CEC Charter.

7.2.1 CV Death

CV death is defined as death resulting from an acute MI, sudden cardiac death, death due to HF, death due to stroke, death due to CV procedures, death due to CV hemorrhage, or death due to other CV causes.[20]

Death due to acute MI refers to death by any CV mechanism (eg, arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤30 days after an MI, related to the immediate consequences of the MI (eg, progressive HF or recalcitrant arrhythmia). Death resulting from a procedure to treat an MI (eg, PCI, CABG surgery), or to treat a complication resulting from an MI, should also be considered a death due to an acute MI.

Sudden cardiac death refers to death that occurs unexpectedly and not within 30 days of an acute MI. Death due to HF refers to death in association with clinically worsening symptoms and/or signs of HF regardless of HF etiology. Death due to stroke refers to death after a stroke that is

either a direct consequence of the stroke or a complication of the stroke. Death due to CV procedures refers to death caused by the immediate complications of a cardiac procedure. Death resulting from an elective coronary procedure to treat myocardial ischemia or death due to an MI that occurs as a direct consequence of a CV investigation, procedure, or operation should be considered as a death due to CV procedure. Death due to CV hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage (eg, subdural hematoma), non-procedural or non-traumatic vascular rupture (eg, aortic aneurysm), or hemorrhage causing cardiac tamponade.

Death due to other CV causes refers to CV death not included in the above categories but with a specific, known cause (eg, pulmonary embolism or peripheral arterial disease).[20]

7.2.2 Myocardial Infarction

The term acute MI should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cardiac troponin values with at least 1 value above the 99th percentile upper reference limit and at least 1 of the following:[21]

- Symptoms of myocardial ischemia;
- New ischemic ECG changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; or
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MI).

More details regarding the diagnosis of MI are provided in Appendix G.

7.2.3 Stroke and TIA

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.[20] A TIA, defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia without acute infarction, should not be classified as a stroke.[20]

More details regarding the diagnosis of stroke and TIA are provided in Appendix F.

7.2.4 Non-Elective Coronary Revascularization

Coronary revascularization includes any coronary arterial vascular intervention done to treat clinical or functional ischemia and/or prevent major ischemic events, including PCI or surgical intervention of the coronary arteries.

A non-elective coronary revascularization includes “emergent” or “urgent” classification, as defined by the following:[20]

- Emergency: The procedure should be performed as soon as possible because of substantial concerns that ongoing myocardial ischemia and/or MI could lead to death. “As soon as possible” refers to a participant who is of sufficient acuity that one would cancel a scheduled case to perform this procedure immediately in the next available room during business hours, or one would activate the on-call team were this to occur during off-hours; and

- Urgent: The procedure should be performed on an inpatient basis and prior to discharge because of significant concerns that there is risk of myocardial ischemia, MI, and/or death. Participants who are outpatients or in the emergency department at the time that the cardiac catheterization is requested would warrant hospital admission based on their clinical presentation.

More details regarding the classification of coronary revascularization procedures are provided in Appendix F.

7.2.5 Hospitalization for Unstable Angina

Unstable angina requiring hospitalization is defined as all of the following:[20]

- Ischemic discomfort (angina or symptoms thought to be equivalent) ≥10 minutes in duration occurring either at rest or in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity;
- Prompting an unscheduled hospitalization within 24 hours of the most recent symptoms, with hospitalization being defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24-hour stay (or a change in calendar date if the hospital admission or discharge times are not available);
- At least 1 of the following:
  - New or worsening ST or T wave changes on resting ECG (in the absence of confounders, such as left bundle branch block or left ventricular hypertrophy) (see Appendix F);
  - Definite evidence of inducible myocardial ischemia (see Appendix F);
  - Angiographic evidence of new or worse ≥70% lesion (≥50% for left main lesion) and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs; or
  - Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s), as defined in the bullet above. This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge.
- Negative cardiac biomarkers and no evidence of acute MI.

More details regarding the diagnosis of unstable angina are provided in Appendix F.

7.2.6 Hospitalization for HF

A HF hospitalization must meet all of the following criteria:[20]

- The participant is admitted to the hospital with a primary diagnosis of HF;
- The participant's length of stay in hospital extends for at least 24 hours (or a change in calendar date if the hospital admission and discharge times are unavailable);
- The participant exhibits documented new or worsening symptoms due to HF on presentation, including at least 1 of the following symptoms: dyspnea, decreased exercise tolerance, fatigue, or other symptoms of compromised or worsened end-organ perfusion (see Appendix F);

- The participant has objective evidence of new or worsening HF, including physical examination findings and/or laboratory abnormalities (see Appendix F); and
- The participant receives at least 1 of the following treatments specifically for HF: significant augmentation in oral diuretic therapy, initiation of intravenous diuretic or vasoactive agent, or mechanical or surgical intervention.

More details regarding the diagnosis of HF are provided in Appendix F.

7.3 HOMA-IR

Samples will be collected for HOMA-IR at visits specified in the Schedule of Procedures (Appendix A). Samples should be collected while the participant is fasting (a minimum of 8 hours).

7.4 PK Sampling

A Baseline PK sample will be collected prior to study drug administration for trough measurement of obicetrapib in plasma at visits specified in the Schedule of Procedures (Appendix A).

7.5 Lp(a) and ApoA1

A plasma sample for Lp(a) and ApoA1 will be collected at visits specified in the Schedule of Procedures (Appendix A). Samples should be collected prior to study drug administration and while the participant is fasting (a minimum of 8 hours).

7.6 Serum Archive Samples for Future Assessment

Serum archive samples will be collected at Baseline (prior to the first dose at Visit 2) and at Visit 7 (EOT) for potential future assessment of dyslipidemia and/or CV risk. Samples should be collected prior to study drug administration and while the participant is fasting (a minimum of 8 hours). Serum archive sample is not collected in China.

8 SAFETY ASSESSMENTS

The safety endpoints include the following:

- Safety and tolerability profile of obicetrapib assessed by AEs, ESIs, vital signs (including blood pressure as assessed by office blood pressure measurements), ECGs, and clinical laboratory values; and
- Assessment of ABPM measured at Screening (Visit 1) and at Day 270 (Visit 6).

8.1 Handling of CV Events

All potential or suspected CV events will be reviewed and adjudicated by an independent CEC and reported in the appropriate clinical endpoint eCRF. In addition, these events are subject to normal AE/SAE reporting procedures.

Timelines for CV event reporting will be identical to timelines for SAE reporting (Section 8.4). All CV events occurring from the time of informed consent until the end of study participation (up to 35 days post last dose) will be reported to [redacted] within 24 hours of knowledge of the occurrence.

8.2 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 signing of informed consent at Screening (Visit 1) until the EOS Visit (35 days after the EOT Visit). 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 treatment. Beginning at the time of signing of informed consent, 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 AE 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 Screening (Visit 1) should be recorded as medical history and not be reported as an AE unless the medical condition or signs or symptoms present at Baseline changes in severity, frequency, or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at Screening (Visit 1) and significantly worsen during the

study should be reported as AEs, as described below. The Investigator will exercise his/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 (eg, ECG abnormalities) should be reported as an AE if any of the following are applicable:

- If an intervention is required as a result of the abnormality;
- If action taken with the study drug is required as a result of the abnormality; or
- Based on the clinical judgment of the Investigator.

8.2.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. "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.

8.2.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information.

8.2.3 Assessment of AEs 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 (not related or unlikely to be related) – The time course between the administration of study drug and the occurrence or worsening of the AE is not consistent with a causal relationship and another cause (concomitant drugs, therapies, complications, etc) is suspected.

Yes (possibly, probably, or definitely related) – The time course between the administration of study 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.

8.2.4 CV Events

By the design of this study, CV events will be captured as exploratory endpoints (see Section 7); these events will be reviewed and adjudicated by an independent CEC and reported in the appropriate clinical endpoint eCRF. In addition, these events are subject to normal AE/SAE reporting procedures.

8.2.5 Events of Special Interest

ESIs will be monitored over time by the independent DSMB on a bi-annual basis (ie, approximately every 6 months), regardless of whether these events were reported as AEs. Any events that qualify as an AE or SAE will be reported accordingly (see Sections 8.2, 8.3, and 8.4).

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

- AST or ALT >3 × ULN;
- Total bilirubin >2 × ULN;

- CK >5 × ULN;
- NODM or worsening of glycemic control;

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

  - AE indicating new type 1 or type 2 diabetes;
  - Initiation of anti-diabetes medication with confirmation of the diagnosis of diabetes by blinded external review by experts in diabetology;
  - HbA1c ≥6.5% (≥0.065 hemoglobin fraction); and/or
  - Two consecutive values of fasting plasma glucose that are ≥126 mg/dL (≥7.0 mmol/L).

  Note: Worsening of glycemic control will be defined as an HbA1c increase from Baseline >0.5% (>0.005 hemoglobin fraction) and/or a new concomitant medication or increase in current antidiabetic therapy in a participant with a Baseline HbA1c ≥6.5% (≥0.065 hemoglobin fraction).
- A >25% decrease in eGFR from Baseline or an eGFR <30 mL/min/1.73 m^2, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, and/or an increase in serum creatinine of ≥0.3 mg/dL (≥26.5 μmol/L) from Baseline;
- Changes to antihypertensive medication(s) due to changes in blood pressure in those participants receiving antihypertensive medication(s) treatment at Baseline; and
- Macular degeneration.

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

8.2.5.1 Guidelines for management of elevated liver enzymes

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

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

If the above abnormalities are confirmed:

- Repeat liver enzyme and serum bilirubin tests 2 or 3 times weekly. The frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the participant is asymptomatic;
- Obtain a more detailed history of symptoms and prior or concurrent diseases;
- Obtain a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diet;

- Rule out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease;
- Obtain a history of exposure to environmental chemical agents;
- Obtain additional tests to evaluate liver function, as appropriate (eg, international normalized ratio, direct bilirubin); and
- Consider gastroenterology or hepatology consultations.

Study drug discontinuation should occur if:

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

8.2.5.2 Guidelines for monitoring and management of CK

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

A repeat CK assessment will include query for related symptoms.

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

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

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

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

If no alternative explanation exists, consideration should be given to withdrawing the participant from study drug treatment.

If the repeat CK assessment confirms an unexplained (ie, not associated with recent trauma or physically strenuous activity) CK >10 × ULN, the participant should be withdrawn and given no further doses of study drug, even in the absence of symptoms. The signs and symptoms and laboratory assessments as outlined above should also be evaluated. The participant should continue being followed in the study for safety.

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

8.2.5.3 Guidelines for monitoring and management of NODM

Diabetes mellitus may be newly diagnosed during the study as described in Section 8.2.5. If a participant is newly diagnosed with diabetes mellitus during the course of the study, the Investigator will recommend referral for initial diabetes education and management by an appropriate healthcare provider (eg, diabetologist, endocrinologist, or primary care provider). Interventions for management may include diet and lifestyle counseling, self-monitoring of blood glucose, oral glucose-lowering medications, injectable medications, or insulin as deemed necessary by the treating physician based on the level of hyperglycemia and relevant symptoms.

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

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

- A >25% decrease in eGFR from Baseline, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation;
- An eGFR <30 mL/min/1.73 m^2, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation; and/or
- An increase in serum creatinine of ≥0.3 mg/dL (≥26.5 µmol/L) from Baseline.

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

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

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

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

8.2.5.6 Guidelines for management of macular degeneration

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

8.3 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, respite care) will not be considered inpatient hospitalizations.

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

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

SAEs that meet the definition of CV outcome events should also be captured in the CV events eCRF.

The plan for exemption from expedited SAE reporting for disease-related events will be described in the Statistical Analysis Plan (SAP), Data Management Plan, and CEC Charter documents.

8.4 SAE Reporting − Procedures for Investigators

Initial reports

All SAEs occurring from the time of informed consent until the end of study participation (up to 35 days post last dose) will be reported, regardless of the Investigator's determination as to relatedness, 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 ([redacted]).

To report the SAE, complete the SAE form electronically in the EDC system for the study. If the event meets serious criteria and it is not possible to access the EDC system, send an email to [redacted] at [redacted] or call the [redacted] SAE reporting line (telephone number listed in Section 8.7), and fax/email the completed back-up paper SAE form to [redacted] (contact information listed in Section 8.7) 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.

8.5 Pregnancy Reporting

If a participant becomes pregnant during the study, the Investigator is to stop dosing with the study drug immediately and permanently. However, the participant should be encouraged to remain in the study and to follow-up for study visits. See Section 4.3 for more details regarding withdrawal criteria and discontinuation of study drug.

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 (Part 1) for completion. The Investigator/site must complete the EIU form (Part 1) and fax/email it back to [redacted]

If the female partner of a male participant becomes pregnant while the participant is receiving study drug, the Investigator should notify [redacted] as described above.

The pregnancy should be followed until the outcome of the pregnancy is known, whenever possible. Once the outcome of the pregnancy is known, the EIU form (Part 2) 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.

8.6 Expedited Reporting

The Sponsor/designee [redacted]) will report all relevant information about Suspected Unexpected Serious Adverse Reactions (SUSARs) that are fatal or life-threatening to the FDA, applicable Competent Authorities in all Member States (including all Institutional Review Boards [IRBs]/Independent Ethics Committees [IECs]), and to the Central Ethics Committees no later than 7 calendar days (CDs) after knowledge by the Sponsor/designee of such a case. Relevant follow-up information will subsequently be communicated within an additional 8 CDs.

All other SUSARs will be reported to the FDA, applicable Competent Authorities in all Member States (including all IRBs/IECs), and to the Central Ethics Committees within a maximum of 15 CDs of first knowledge by the Sponsor/designee.

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

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

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

8.6.1 Project Specific Exemption From SAE Immediate Reporting to Health Authorities and IRBs

The guidance document of the Committee for Medicinal Products for Human Use (CHMP), "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use," states that for trials in high morbidity and/or high mortality disease, where efficacy endpoints could also be adverse reactions reported as SUSARs, these serious events could be treated as disease-related events and not be subject to systematic unblinding and expedited reporting.[22]

Moreover, the FDA guidance documents titled "Guidance for clinical investigators, sponsors, and IRBs. Adverse event reporting to IRBs – improving human subject protection" and "Guidances for industry and investigators on safety reporting requirements for investigational new drug applications and bioavailability/bioequivalence studies" state that only AEs which are unexpected, serious, and would have implications for the conduct of the study should be reported in an expedited manner.[23,24]

Aggregate unblinded analysis by the independent DSMB will be conducted in order to identify safety concerns, such as potential imbalances in event rates between the drug treatment and control groups. Should the DSMB identify any potential safety concerns, they will be able to recommend reporting of these findings to the Health Authorities (HA), Investigators, Ethics Committees, and IRBs. Additionally, the DSMB will have the freedom to determine, based on their ongoing review of the safety data, if any of the exempted AEs should be changed to become subject to expedited reporting from that point on. A safety report will be submitted if an aggregate analysis indicates the anticipated SAEs are occurring more frequently in the treatment group compared to the placebo group.

8.7 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 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 situation report form and faxed/emailed to [redacted] (contact information listed below) within 24 hours of knowledge of the event. In addition, all special situation events must be entered into the EDC system 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]
Telephone: [redacted]
Fax: [redacted]
Email: [redacted]

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

8.8 Clinical Laboratory Evaluations

Clinical laboratory evaluations (including a full serum chemistry panel, hematology, coagulation, and urine dipstick analysis) will be collected at visits specified in the Schedule of Procedures (Appendix A). A limited serum chemistry panel will also be collected per the Schedule of Procedures (Appendix A). All safety laboratory samples should be collected while the participant is fasting (a minimum of 8 hours) and prior to the next dose of study drug (at applicable visits). Assessment of laboratory eligibility criteria will be based on central laboratory values obtained within timeframes defined in the inclusion and exclusion criteria.

Urine dipstick analysis will be performed locally from a sample of mid-stream urine. In case of abnormal results, microscopy and other assessments will be performed at the local laboratory and the abnormality recorded as an AE.

Please see Appendix B for a complete list of laboratory analytes.

8.8.1 Urine Albumin-Creatinine Ratio and Urine Protein-Creatinine Ratio

A urine sample for urine albumin-creatinine ratio and urine protein-creatinine ratio will be collected at visits specified in the Schedule of Procedures (Appendix A). Samples should be collected while the participant is fasting (a minimum of 8 hours).

8.8.2 Aldosterone and hsCRP

A plasma sample for aldosterone and hsCRP will be collected at visits specified in the Schedule of Procedures (Appendix A). Samples should be collected while the participant is fasting (a minimum of 8 hours).

8.8.3 Efficacy Endpoint Laboratory Assessments

Although laboratory values that are part of the efficacy endpoints will not be provided to the sites, the Investigator will be notified of critical high LDL-C values as follows:

- If **before Day 84**, when the LDL-C values of a participant are >200 mg/dL (>5.2 mmol/L) **AND** exhibit a >50% increase compared to Baseline; or
- If **after Day 84**, when the LDL-C values of a participant are >200 mg/dL (>5.2 mmol/L) **OR** exhibit a >50% increase compared to Baseline.

These critical high values will need to be confirmed by a repeat measurement (new fasting blood sample). The Investigator should be encouraged to consult with the Medical Monitor. Investigators and the blinded study team will be informed that random sham alerts will also be sent to sites, in order to maintain the study blind.

8.8.4 Managing Abnormal and Critical Laboratory Values

Any laboratory test result abnormality that fulfills the criteria for an SAE will be reported as such on the appropriate AE and SAE eCRF. Any treatment-emergent abnormal laboratory result that is clinically significant, ie, meets 1 or more of the following criteria, will be recorded as a single diagnosis on the AE eCRF:

- Is accompanied by clinical symptoms;
- Leads to a change in study drug (eg, study drug interruption or permanent discontinuation); and/or
- Requires a change in concomitant therapy or a medical intervention (eg, the addition of, interruption of, or discontinuation of, or any other change in a concomitant medication, therapy, or treatment).

These criteria apply to any protocol and non-protocol-specified safety and/or efficacy laboratory results from tests performed after the first dose of study drug that meet clinical significance criteria. These criteria do not apply to any abnormal laboratory test results which fall outside the laboratory reference range, but which do not meet clinical significance criteria (these will be analyzed and reported as laboratory abnormalities) or those which are a result of an AE or an endpoint which has already been reported.

The Investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual participant represents a clinically significant change from the participant's Baseline values. In general, laboratory abnormalities without clinical significance should not be recorded as AEs. Where applicable, the clinical sequelae, not the laboratory abnormality, should be recorded as the AE.

Critical laboratory values are values that may warrant medical intervention to avoid possible harm to a participant. Critical laboratory values will be defined in the Laboratory Manual for the study, and the Medical Monitor and Investigator will be notified of the occurrence of a critical laboratory value (critical high or critical low) by a special annotation (flag) in the laboratory reports provided to the sites.

If LDL-C values are confirmed critically high (see Section 8.8.3), OR if TG levels exceed 500 mg/dL (5.7 mmol/L), the Investigator may need to take appropriate medical action, which could include the following: reinforce/intensify therapeutic lifestyle changes (including diet and physical activity), increase the dose of the present statin therapy, add ezetimibe, or prescribe a more potent lipid-modifying therapy to lower LDL-C. The Investigator should use the best clinical judgment for each participant.

8.9 Vital Signs

Vital signs (consisting of heart rate and blood pressure) will be measured in triplicate prior to study drug administration at applicable visits (see Appendix A). On Day 1 (Visit 2), blood pressure will be measured prior to Randomization. When available, an automated blood pressure device is recommended for collection of blood pressure and the result should be recorded to the nearest mmHg.

Vital signs will be measured using the following standardized procedures:

- Participants should not exercise, smoke, or consume caffeinated beverages or food 30 minutes prior to assessment of vital signs; and
- Vital signs should be obtained prior to ECG recordings.

8.9.1 Blood Pressure Monitoring

Blood pressure specifically will be measured using the following standardized procedures:

- Participants should be seated for at least 5 minutes in the examination room with the back supported, feet flat on the floor, and the measurement arm supported so that the midpoint of the manometer cuff is at heart level;
- An appropriately sized cuff should be used with the bladder centered over the brachial artery;
- The cuff size and arm used for the measurement should be recorded; the same arm should be used for all readings;
- Three seated blood pressure measurements (each measurement 1 to 2 minutes apart) should be obtained using the same arm at each site visit. Mean seated blood pressure is defined as the average of 3 seated blood pressure measurements at a single site visit; and
- If the lowest and highest blood pressure measurements are >15 mmHg apart, additional readings should be performed.

Blood pressure readings, both systolic and diastolic, will be evaluated over time by the independent DSMB, who will monitor unblinded safety data during the study on a bi-annual basis (ie, approximately every 6 months). Changes in blood pressure, as well as heart rate, will be compared between treatment groups with respect to mean and median values over time using both actual values and absolute changes from Baseline. In addition, treatment groups will be compared with respect to the incidence of hypertensive status and other vital sign abnormalities as defined in the SAP.

8.9.1.1 24-hour ABPM

Participants from selected study sites who consent to participate in the ABPM substudy will have a 24-hour ABPM assessment conducted at applicable visits (see Appendix A). The 24-hour ABPM assessment at Screening (Visit 1) should be completed after the participant's eligibility has been confirmed at that visit. It should be ensured that sufficient time is allotted during Screening (Visit 1) to allow for a repeat 24-hour ABPM assessment, if the first is not successful, prior to Randomization (Visit 2). For the 24-hour ABPM assessment at Visit 6 (Day 270), it should be ensured that a repeat assessment (if necessary) is completed within the respective visit window and that the assessment is not done concurrently with other study procedures.

Please refer to the separate study manual for additional details surrounding the 24-hour ABPM assessment for the substudy.

8.10 Electrocardiograms

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

8.11 Physical Examinations

Physical examinations will be completed at visits specified in Appendix A. The physical examination should comprise a focused examination, which includes general, respiratory, CV, abdominal, and extremities evaluations; ophthalmological examination; and recording of weight and height. Height will be measured at Screening (Visit 1) only and used to calculate body mass index.

9 STATISTICS

9.1 Analysis Populations

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

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

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

The Per-Protocol (PP) Population will include all participants in the mITT Population who did not experience a major protocol deviation that potentially impacted the primary efficacy endpoint. The PP Population, along with the reason for exclusion, will be finalized prior to study unblinding.

The Safety Population will include all participants who receive at least 1 dose of any study drug. Treatment classification will be based on the actual treatment received. The Safety Population will be the primary population used for the safety analyses.

9.2 Statistical Methods

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

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

9.2.1 Analysis of Efficacy

9.2.1.1 Primary efficacy analysis

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

The primary efficacy endpoint is the percent change from Baseline to Day 84 in LDL-C in the obicetrapib group compared to the placebo group. The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model with a fixed effect for the treatment group and covariates of Baseline LDL-C, CV risk (HeFH or non-HeFH), and Baseline statin therapy (HIS or non-HIS). The least squares (LS) mean, standard errors, and 2-sided 95% confidence intervals for each treatment group and for the mean difference compared to placebo will be obtained. The model will be fit assuming unequal variances for each treatment group.

The primary estimand will correspond to a treatment policy estimand. The target population will comprise participants who are randomized into the study. The primary summary measure to assess the treatment effect will be the LS mean difference for the primary endpoint between obicetrapib

and placebo based on the ANCOVA methodology. The primary estimand will be addressed using the in-study observation period (ie, including data collected post-treatment discontinuation or post-prohibited medication use).

Missing data will be imputed for the primary efficacy analysis based on a pattern mixture model that uses a multiple imputation technique analyzed with ANCOVA with pre-specified fixed factors and covariates. If appropriate, based on the number of retrieved dropouts, missing measurements of non-retrieved dropouts will be modeled by known measurements from retrieved dropouts (ie, participants who remain in the study after treatment discontinuation) in the same treatment group. The imputation model will be further clarified in the SAP.

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

9.2.1.2 Secondary and exploratory efficacy analysis

In order to control the Type I error rate, a fixed sequential testing procedure will be implemented. In a hierarchical step-down manner, the primary endpoint will be tested first, followed by the secondary efficacy endpoints in a pre-specified order. The pre-specified order of the hypothesis testing for the secondary endpoints will be described in the SAP. No adjustment for multiple comparisons will be made for the exploratory efficacy endpoints.

Continuous secondary efficacy endpoints will be analyzed using similar methods as in the primary efficacy analysis.

Exploratory efficacy endpoints corresponding to continuous variables will be analyzed using a similar ANCOVA model as in the primary efficacy analysis. The 2-sided 95% confidence interval for LS means will be provided for continuous variables. Odds ratio and 95% confidence interval for the odds ratio will be provided for exploratory efficacy endpoints corresponding to binary variables. For time-to-event endpoints, the log-rank test, stratified by CV risk (HeFH or non-HeFH) and Baseline statin therapy (HIS or non-HIS), will be used to compare differences in the time-to-event between obicetrapib and placebo. The hazard ratio and the associated 95% confidence interval will be estimated using a stratified Cox proportional hazards model with treatment as an explanatory variable, stratified by CV risk (HeFH or non-HeFH) and Baseline statin therapy (HIS or non-HIS). Additionally, Kaplan-Meier estimates of the time-to-event will be determined and displayed graphically. The proportional hazard assumption will be evaluated, such as through the examination of complementary log-log (event times) versus log (time) plots, etc. If the proportional hazard assumption raises concerns, additional analyses will be considered and will be further detailed in the SAP. Nominal p-values will be provided when applicable. Descriptive and graphical summaries by treatment group will also be presented. A population PK analysis will be described in a separate document.

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

9.2.2 Analysis of Safety

The Safety Population will be the primary population for the safety analysis. All safety endpoints will be summarized descriptively.

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

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

9.2.2.1 Analysis of ESIs

Liver-associated enzymes and total bilirubin will be summarized by the value and change from Baseline in the value, by treatment group and visit. In addition, the number and percent of participants with abnormal values for ALT, AST, and total bilirubin will be summarized. These summaries of participants with abnormal values will be performed overall; by normal Baseline; and by abnormal Baseline for ALT, AST, and total bilirubin individually. Hy's Law criteria (>3 × ULN for either ALT or AST, with accompanying total bilirubin >2 × ULN) will also be applied to the data. Any potential Hy's Law cases will be listed separately.

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

CK levels will be summarized by the value and change from Baseline in value, by treatment group and visit. In addition, the number and percent of participants with abnormal CK values will be summarized. These summaries of participants with abnormal CK values will be performed overall, by normal Baseline CK, and by abnormal Baseline CK. Values of CK from Baseline to EOT will be summarized by treatment group and by Baseline eGFR category.

Cases of NODM will be recorded and summarized using the appropriate system organ class. These events will be summarized by severity and relationship to study drug for each treatment group. Fasting plasma glucose and HbA1c will be monitored as specified in Appendix A.

Baseline eGFR will be summarized by treatment group for actual value and for Baseline eGFR categories. Shift tables of eGFR category from Baseline to EOT will be provided by treatment group. Shift tables of urine albumin-creatinine ratio and urine protein-creatinine ratio from Baseline to EOT will be provided by treatment group.

The number and percentage of participants receiving antihypertensive medication(s) treatment at Baseline with changes to antihypertensive medication(s) due to changes in blood pressure will be summarized by treatment group.

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

9.2.3 Interim Analysis

No interim analysis is planned for the study. The study will be governed by a Steering Committee.

9.2.4 Clinical Events Committee

An independent CEC will adjudicate all events of death and all potential or suspected CV events. A committee charter will be drafted to define the composition, roles, and responsibilities of the CEC.

9.2.5 Data and Safety Monitoring Board

An independent DSMB will monitor unblinded safety data, including blood pressure changes over time and the occurrence of ESIs, during the study on a bi-annual basis (ie, approximately every 6 months).

Additional information is provided in the DSMB Charter.

9.2.6 Sample Size Determination

Enrollment of approximately 2400 participants globally is planned for this study.

Assuming an approximate 5% drop out rate, approximately 2280 participants will be evaluable for efficacy. This sample size of at least 2280 evaluable participants will provide more than 90% power to detect a 30% reduction of LDL-C (standard deviation 15%) levels in the obicetrapib group compared to the placebo group at a 1-sided significance level of 0.025. This sample size will also contribute to sufficient participant exposure and safety data.

9.2.6.1 ABPM substudy

This substudy is designed for a non-inferiority assessment in systolic blood pressure from Screening (Visit 1) to Day 270 (Visit 6) between obicetrapib and placebo. The non-inferiority margin was selected in accordance with the United States FDA guidelines (Assessment of Pressor Effects of Drugs, Guidance for Industry).[25] The non-inferiority margin was chosen to assess if obicetrapib is not substantially inferior to placebo for elevations in systolic blood pressure. The assumption for the common standard deviation is determined by a literature review and the obicetrapib Phase 2 program. From the reference paper by Vollmer et al, the estimate of the standard deviation for the change in systolic blood pressure (mmHg) for hypertensive participants based on 24-hour ABPM measurements was 8.0 (95% confidence interval: 6.9, 9.4).[26]

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

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 Data Management

10.1.1 Data Handling

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

10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

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

10.1.5 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the downloaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the study 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 drug, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the study site. Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10.3 End of Study

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

11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

11.1 Ethical Conduct of the Study

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

11.2 IRB/IEC

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and wellbeing of participants. The study will only be conducted at sites where 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 in countries where submission is carried out by the site to the IRB/IEC. In countries where the Sponsor is responsible for submission to regulatory authorities/IRB/IEC, the documents will be submitted by the Sponsor or by designee based on Letter of Authorization.

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

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

It is the responsibility of the Sponsor or their designee (ie, [redacted]) to obtain the approval of the responsible ethics committees according to the national regulations.

The study will only start at the respective study sites once the respective committee's written approval has been given.

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.

In order to participate in the ABPM substudy, participants must provide written informed consent in a substudy-specific ICF.

11.4 Subject Card

On enrollment in the study, the participant will receive a subject card to be carried at all times. The subject card will state that the participant is participating in a clinical research study, type of treatment, 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; Declaration of Helsinki; ICH GCP E6; 21 CFR Parts 11, 50 A and B, 54, and 56; and applicable legal and regulatory requirements according to the country of conduct, and that valid data are entered into the eCRFs.

To achieve this objective, the CRA's duties are to aid the Investigator and, at the same time, the Sponsor, in the maintenance of complete, legible, well-organized, and easily retrievable data. Before the enrollment of any participant in this study, the Sponsor or their designee will review with the Investigator and study 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 are entered by the study 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 CRA and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the study 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 FDA, the Sponsor or their designee, applicable HA, 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 participating 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 or another institution. In countries where the local law permits, the acceptable designee may also be the Sponsor (eg, outside of European Union countries).

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 Financial Disclosure

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

11.10 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.

11.11 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 Investigator by [redacted] or the Sponsor. All protocol amendments will undergo the same review [redacted]nd 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.

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APPENDIX A: SCHEDULE OF PROCEDURES

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

Footnotes are at the end of the table.

	Screening	Treatment Period						EOS[1]
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7/EOT/ET[2]**	**V8**
Study Day	**-28 to -1**	**1**	**30**	**84**	**180**	**270**	**365**	**35 days after last dose**
Window (±days)			**±3**	**±7**	**±7**	**±7**	**±7**	**±7**
Study drug return/compliance calculations			X	X	X	X	X	
CV events assessment[19]	X	X	X	X	X	X	X	X
AEs assessment	X	X	X	X	X	X	X	X

1. The onsite EOS Visit will include an assessment of vital signs, concomitant medications, CV events, and AEs will be completed and documented in the participant's record.
2. For participants who permanently discontinue from study treatment **and who decline continued study participation**, an ET Visit will be scheduled as soon as possible followed by an onsite EOS Visit 35 days later. If the discontinuation occurs at a specific onsite visit, this visit will become the ET Visit and EOT Visit procedures should be followed. Participants who withdraw consent to all follow-up will be asked about the reason(s) and will be assessed for the presence of any AEs. For participants who completely withdraw consent, life status will be obtained at study end through public record information according to local guidelines and as allowed by local regulations.
3. Informed consent will be obtained from participants before the initiation of any study-specific procedures. In order to participate in the ABPM substudy, participants must provide written informed consent in a substudy-specific ICF.
4. Assessment of laboratory eligibility criteria will be based on central laboratory values obtained within timeframes defined in the inclusion and exclusion criteria.
5. Urine pregnancy tests will be performed for females of childbearing potential only (performed locally using central laboratory kit supplies). FSH will only be performed at Screening (Visit 1) in females <55 years of age and postmenopausal, defined as ≥1 year since their last menstrual period.
6. The physical examination should comprise a focused examination, which includes general, respiratory, CV, abdominal, and extremities evaluations; ophthalmological examination; and recording of weight and height.
7. Height will be measured at Screening (Visit 1) only and used to calculate BMI.
8. Vital signs (consisting of heart rate and blood pressure) will be measured as described in Section 8.9.
9. Only participants who consent to participate in the ABPM substudy will have this assessment performed.
10. The 24-hour ABPM assessment at Screening (Visit 1) should be completed after the participant's eligibility has been confirmed at that visit. It should be ensured that sufficient time is allotted during Screening (Visit 1) to allow for a repeat 24-hour ABPM assessment, if the first is not successful, prior to Randomization (Visit 2). Additional details surrounding this substudy are included in a separate study manual.
11. It should be ensured that a repeat assessment (if necessary) is completed within the respective visit window and that the assessment is not done concurrently with other study procedures.
12. A single l2-lead ECG will be performed in the supine position after 10 minutes of rest.
13. Participants must fast for a minimum of 8 hours prior to samples being collected.
14. Samples should be collected prior to study drug administration.
15. Serum archive sample is not collected in China.
16. Only hsCRP will be assessed at Screening (Visit 1).
17. Urine dipstick analysis will be performed locally from a sample of mid-stream urine. In case of abnormal results, microscopy and other assessments will be performed at the local laboratory and the abnormality recorded as an AE.
18. A PK sample will be collected prior to study drug administration for trough measurement of obicetrapib in plasma. At Visits 2, 5, and 7, participants should take study drug after a trough PK sample has been drawn.
19. CV events include CV death, non-fatal myocardial infarction, non-fatal stroke, non-elective coronary revascularization, hospitalization for unstable angina and/or chest pain, hospitalization for heart failure, and transient ischemic attack.

ABPM = ambulatory blood pressure monitoring; AE = adverse event; ApoA1 = apolipoprotein A1; BMI = body mass index; CV = cardiovascular; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; ET = Early Termination; FSH = follicle-stimulating hormone; HOMA-IR = homeostatic model assessment of insulin resistance;

hsCRP = high sensitivity C-reactive protein; ICF = informed consent form; Lp(a) = lipoprotein (a); PK = pharmacokinetic(s); TSH = thyroid-stimulating hormone; UACR = urine albumin-creatinine ratio; UPCR = urine protein-creatinine ratio; V = Visit.

APPENDIX B: CLINICAL LABORATORY ANALYTES

Full Serum Chemistry Panel

Alanine aminotransferase	Albumin
Alkaline phosphatase	Aspartate aminotransferase
Bicarbonate	Bilirubin (direct, indirect, and total)
Blood urea nitrogen	Calcium
Chloride	Creatine kinase
Creatinine	Estimated glomerular filtration rate [1]
Gamma-glutamyl transferase	Glucose (fasting)
Glycosylated hemoglobin (HbA1c)	Inorganic phosphorus
Potassium	Sodium
Total protein	Uric acid

1. Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Limited Serum Chemistry Panel

Alanine aminotransferase	Alkaline phosphatase
Aspartate aminotransferase	Bilirubin (total)
Creatine kinase	Creatinine
Estimated glomerular filtration rate [1]	Gamma-glutamyl transferase
Glucose (fasting)	HbA1c

1. Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

Lipid Profile/Biomarkers

Apolipoprotein B	High-density lipoprotein cholesterol
Low-density lipoprotein cholesterol (LDL-C) [1]	Non-high-density lipoprotein cholesterol
Total cholesterol	Triglycerides (TG)

1. At Baseline (Visit 2), Day 84 (Visit 4), and Day 365 (Visit 7)/End of Treatment/Early Termination, LDL-C will be measured for all participants by preparative ultracentrifugation, also referred to as beta quantification. At all other scheduled visits, LDL-C will be calculated using the Friedewald equation unless TG ≥400 mg/dL (≥4.5 mmol/L) or LDL-C ≤50 mg/dL (≤1.3 mmol/L). If TG ≥400 mg/dL (≥4.5 mmol/L) or LDL-C ≤50 mg/dL (≤1.3 mmol/L), then LDL-C level will be measured directly by preparative ultracentrifugation.

Endocrinology

Homeostatic model assessment of insulin resistance	Insulin
Follicle-stimulating hormone [1]	Human chorionic gonadotrophin [2]
Thyroid-stimulating hormone	

1. Follicle-stimulating hormone will only be performed in females <55 years of age and postmenopausal, defined as ≥1 year since their last menstrual period.
2. Human chorionic gonadotrophin will be performed for females of childbearing potential.

Hematology

Hematocrit	Hemoglobin
Mean corpuscular hemoglobin	Mean corpuscular hemoglobin concentration
Mean corpuscular volume	Platelets
Red blood cell count	Reticulocyte count
White blood cell count and differential [1]	

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

Coagulation

Activated partial thromboplastin	International normalized ratio
Prothrombin time	

Urine Dipstick Analysis

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

1. Urine dipstick analysis will be performed locally from a sample of mid-stream urine. In case of abnormal results, microscopy and other assessments will be performed at the local laboratory and the abnormality recorded as an adverse event.

Other Laboratory Analytes

Aldosterone	Apolipoprotein A1
High sensitivity C-reactive protein	Lipoprotein (a)
Urine albumin-creatinine ratio	Urine protein-creatinine ratio

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

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

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

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

Sources:

World Health Organization. Familial hypercholesterolaemia (FH): report of a second WHO consultation. 04 September 1998. http://whqlibdoc.who.int/hq/1999/WHO_HGN_FH_CONS_99.2.pdf. Accessed 21 April 2022

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

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

APPENDIX D: SIMON BROOME REGISTER DIAGNOSTIC CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA

Definite Familial Hypercholesterolemia:

Required laboratory = high cholesterol levels:

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

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

Plus at least 1 of the 2:

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

  OR

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

Possible Familial Hypercholesterolemia:

Laboratory = high cholesterol levels:

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

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

Plus at least 1 of the 2:

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

OR

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

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

APPENDIX E: CORRECTION FACTORS FOR LIPID-MODIFYING DRUGS

Lipid-Modifying Drug Dose	Reduction in Percentage	Correction Factor[1]
Atorvastatin		
10 mg	37	1.59
20 mg	43	1.75
40 mg	49	1.96
80 mg	55	2.22
Fluvastatin		
20 mg	21	1.27
40 mg	27	1.37
80 mg	33	1.49
Pravastatin		
10 mg	20	1.25
20 mg	24	1.32
40 mg	39	1.64
Rosuvastatin		
5 mg	38	1.61
10 mg	43	1.75
20 mg	48	1.92
40 mg	53	2.13
Simvastatin		
5 mg	23	1.30
10 mg	27	1.37
20 mg	32	1.47
40 mg	37	1.59
Statin/Ezetimibe		
Low-dose/10 mg	44	1.79
Mid-dose/10 mg	45	1.81
High-dose/10 mg	53	2.13
Ezetimibe		
10 mg	19	1.23

Correction factor = 100/(100 – reduction in percentage).

1. The correction factor should be multiplied by a historical or Screening LDL-C value. For example, a patient taking atorvastatin 80 mg, with an LDL-C of 93 mg/dL, has the equivalent of an "off-treatment" LDL-C value of 206.46 mg/dL (93 mg/dL × 2.22 = 206.46 mg/dL).

LDL-C = low-density lipoprotein cholesterol.

Sources:

Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003;326(7404):1423. doi:10.1136/bmj.326.7404.1423

Davidson MH, Ballantyne CM, Kerzner B, et al. Efficacy and safety of ezetimibe coadministered with statins: randomised, placebo-controlled, blinded experience in 2382 patients with primary hypercholesterolemia. *Int J Clin Pract*. 2004;58(8):746-755

Source: Besseling J, Kindt I, Hof M, et al. Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. *Atherosclerosis*. 2014;233(1):219-223

APPENDIX F: ENDPOINT DEFINITIONS PER THE 2017 CARDIOVASCULAR AND STROKE ENDPOINT DEFINITIONS FOR CLINICAL TRIALS[20]

CARDIOVASCULAR DEATH

Cardiovascular (CV) death includes death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to CV procedures, death due to CV hemorrhage, and death due to other CV causes.

Classifying CV mortality more specifically (MI, sudden death, etc) is usually not needed for outcome trials. Moreover, such classification is difficult because the classifications refer both to underlying cause (eg, acute MI, which can cause fatal arrhythmias or HF) and to mode of death (sudden/arrhythmic; HF, which can result from an MI or worsening HF), and they overlap substantially. The following definitions can, however, be used if desired:

1. Death due to acute MI refers to death by any CV mechanism (eg, arrhythmia, sudden death, HF, stroke, pulmonary embolus, peripheral arterial disease) ≤30 days[2] after an MI, related to the immediate consequences of the MI, such as progressive HF or recalcitrant arrhythmia. We note that there may be assessable mechanisms of CV death during this time period, but for simplicity, if the CV death occurs ≤30 days after the MI, it will be considered a death due to MI.

   Acute MI should be verified to the extent possible by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombosis.

   Death resulting from a procedure to treat an MI (percutaneous coronary intervention [PCI], coronary artery bypass graft [CABG] surgery), or to treat a complication resulting from MI, should also be considered a death due to acute MI.

   Death resulting from an elective coronary procedure to treat myocardial ischemia (ie, chronic stable angina) or death due to an MI that occurs as a direct consequence of a CV investigation/procedure/operation should be considered a death due to a CV procedure.

2. Sudden cardiac death refers to death that occurs unexpectedly and not within 30 days of an acute MI. Sudden cardiac death includes the following scenarios:
   a. Death witnessed and occurring without new or worsening symptoms;
   b. Death witnessed within 60 minutes of the onset of new or worsening cardiac symptoms, unless the symptoms suggest acute MI;
   c. Death witnessed and attributed to an identified arrhythmia (eg, captured on an electrocardiogram [ECG], witnessed on a monitor, or unwitnessed but found on implantable cardioverter-defibrillator [ICD] review);

[2] The 30 day cut-off is arbitrary.

d. Death after unsuccessful resuscitation from cardiac arrest (eg, ICD unresponsive sudden cardiac death, pulseless electrical activity arrest);

e. Death after successful resuscitation from cardiac arrest and without identification of a specific cardiac or non-cardiac etiology; and

f. Unwitnessed death in a participant seen alive and clinically stable ≤24 hours prior to being found dead without any evidence supporting a specific non-CV cause of death (information regarding the participant's clinical status preceding death should be provided, if available).

General considerations:

Unless additional information suggests an alternate specific cause of death (eg, death due to other CV causes), if a participant is seen alive within ≤24 hours of being found dead, sudden cardiac death (Criterion 2f) should be recorded. For participants who were not observed alive within 24 hours of death, undetermined cause of death should be recorded (eg, a participant found dead in bed, but who had not been seen by family for >24 hours).

3. Death due to HF refers to death in association with clinically worsening symptoms and/or signs of HF regardless of HF etiology. Deaths due to HF can have various etiologies, including single or recurrent MIs, ischemic or non-ischemic cardiomyopathy, hypertension, or valvular disease.
4. Death due to stroke refers to death after a stroke that is either a direct consequence of the stroke or a complication of the stroke. Acute stroke should be verified to the extent possible by the diagnostic criteria outlined for stroke.
5. Death due to CV procedures refers to death caused by the immediate complications of a cardiac procedure.
6. Death due to CV hemorrhage refers to death related to hemorrhage such as a non-stroke intracranial hemorrhage (eg, subdural hematoma), non-procedural or non-traumatic vascular rupture (eg, aortic aneurysm), or hemorrhage causing cardiac tamponade.
7. Death due to other CV causes refers to CV death not included in the above categories but with a specific, known cause (eg, pulmonary embolism or peripheral arterial disease).

NON-CARDIOVASCULAR DEATH

Non-CV death is defined as any death with a specific cause that is not thought to be CV in nature. Detailed recommendations on the classification of non-CV causes of death are beyond the scope of this appendix. The level of detail required and the optimum classification will depend on the nature of the study population and the anticipated number and type of non-CV deaths. Any specific anticipated safety concern should be included as a separate cause of death. The following is a suggested list of non-CV causes of death:

- Pulmonary;
- Renal;
- Gastrointestinal;
- Hepatobiliary;
- Pancreatic;
- Infection (includes sepsis);
- Inflammatory (eg, Systemic Inflammatory Response Syndrome, other immune conditions [including autoimmune]; may include anaphylaxis from environmental factors [eg, food allergies]);
- Hemorrhage that is neither CV bleeding nor a stroke;
- Non-CV procedure or surgery;
- Trauma (includes homicide);
- Suicide;
- Non-prescription drug reaction or overdose;
- Prescription drug reaction or overdose (may include anaphylaxis);
- Neurological (non-CV) (excludes CV death from ischemic stroke, hemorrhagic stroke, or undetermined cause of stroke or CV hemorrhage of central nervous system);
- Malignancy (eg, leukemia, lymphoma, or other malignancy); and
- Other non-CV.

UNDETERMINED CAUSE OF DEATH

Undetermined cause of death refers to death not attributable to 1 of the above categories of CV death or to a non-CV cause. Inability to classify the cause of death may be due to lack of information (eg, the only available information is “participant died”) or when there is insufficient supporting information or detail to assign the cause of death. In general, most deaths should be classifiable as CV or non-CV, and the use of this category of death, therefore, should be discouraged and should apply to few participants in well-run clinical studies.

A common analytic approach for cause of death analyses is to assume that all undetermined cases are included in the CV category (eg, presumed CV death, specifically “death due to other CV causes”). Nevertheless, the appropriate classification and analysis of undetermined causes of death depends on the population, the intervention under investigation, the duration of follow-up, and the disease process (presuming CV death does not seem appropriate, for example, for people with late stage cancer, advanced pulmonary disease, long-standing infections, etc). The approach should be prespecified and described in the protocol and other study documentation such as the endpoint adjudication procedures and/or the Statistical Analysis Plan.

UNSTABLE ANGINA

Unstable angina requiring hospitalization is defined as all of the following:

1. Ischemic discomfort (angina or symptoms thought to be equivalent) ≥10 minutes in duration occurring:
   - At rest; or
   - In an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity.
2. Prompting an unscheduled hospitalization **within 24 hours** of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24-hour stay (or a change in calendar date if the hospital admission or discharge times are not available).
3. At least 1 of the following:
   a. New or worsening ST or T wave changes on resting ECG (in the absence of confounders, such as left bundle branch block or left ventricular hypertrophy) as follows:
      - Transient ST elevation (duration <20 minutes), defined as a new ST elevation at the J point in 2 contiguous leads with the following cut-points: ≥0.1 mV in all leads other than leads V2 to V3 where the following cut-points apply: ≥0.2 mV in men ≥40 years (≥0.25 mV in men <40 years) or ≥0.15 mV in women; or
      - ST depression and T-wave changes, defined as new horizontal or down-sloping ST depression ≥0.05 mV in 2 contiguous leads and/or new T-wave inversion ≥0.3 mV in 2 contiguous leads with prominent R wave or R/S ratio >1.

   b. Definite evidence of inducible myocardial ischemia as demonstrated by:
      - An early positive exercise stress test, defined as an ST elevation or ≥2 mm ST depression prior to 5 metabolic equivalents;

        OR
      - Stress echocardiography (reversible wall motion abnormality); **or**
      - Myocardial scintigraphy (reversible perfusion defect); **or**
      - Magnetic resonance imaging (myocardial perfusion deficit under pharmacologic stress); **and**
      - Believed to be responsible for the myocardial ischemic symptoms/signs.

   c. Angiographic evidence of new or worse ≥70% lesion (≥50% for left main lesion) and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs; or

   d. Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s), as defined in 3c. This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge.

4. Negative cardiac biomarkers and no evidence of acute MI.

General considerations

1. Escalation of pharmacotherapy for ischemia, such as intravenous nitrates or increasing dosages of β-blockers, should be considered supportive but not diagnostic of unstable angina. However, a typical presentation and admission to the hospital with escalation of pharmacotherapy, without any of the additional findings listed under category 3, would be insufficient to support classification as hospitalization for unstable angina.
2. If participants are admitted with suspected unstable angina, and subsequent testing reveals a non-cardiac or non-ischemic etiology, this event should not be recorded as hospitalization for unstable angina. Potential ischemic events meeting the criteria for MI should not be adjudicated as unstable angina.
3. Planned hospitalization or rehospitalization for performance of an elective revascularization in participants who do not fulfill the criteria for unstable angina should not be considered a hospitalization for unstable angina. For example:
    - Hospitalization of a participant with stable exertional angina for coronary angiography and PCI that is prompted by a positive outpatient stress test should not be considered hospitalization for unstable angina; and
    - Rehospitalization of a participant meeting the criteria for unstable angina who was stabilized, discharged, and subsequently readmitted for revascularization, does not constitute a second hospitalization for unstable angina.
4. A participant who undergoes an elective catheterization where incidental coronary artery disease is found and who subsequently undergoes coronary revascularization will not be considered as meeting the hospitalization for unstable angina endpoint.

STROKE AND TRANSIENT ISCHEMIC ATTACK

These definitions of stroke and transient ischemic attack (TIA) apply to a wide range of clinical trials. They are general, overarching, and widely applicable definitions combined with a specific clinical measurement of disability. They are flexible in their application and consistent with contemporary understanding of the pathophysiology of stroke. This approach enables clinical trials to assess the clinically relevant consequences of vascular brain injury for determining the safety or effectiveness of an intervention.

The distinction between an ischemic stroke and a TIA is the presence of cerebral infarction. Persistence of symptoms is an acceptable indicator of acute infarction. Thus, duration of symptom persistence that will be used to distinguish between transient ischemia and acute infarction should be defined for any clinical trial in which it is used.

In trials involving participants with stroke, evidence of vascular central nervous system injury without recognized neurological dysfunction may be observed. Examples include microhemorrhage, asymptomatic infarction, and asymptomatic hemorrhage. When encountered, the clinical relevance of these findings may be unclear. If appropriate for a given clinical trial, however, they should be precisely defined and categorized.

Subdural hematomas are intracranial hemorrhagic events and not strokes.

TIA

TIA is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, ***without*** acute infarction.

Stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Classification of stroke is as follows:

a. Ischemic stroke:

   Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue.

   Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

b. Hemorrhagic stroke:

   Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

c. Undetermined stroke:

   Undetermined stroke is defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as either ischemic or hemorrhagic.

Stroke disability

Disability should be measured by a reliable and valid scale in all cases, typically at each visit and 90 days after the event. For example, the modified Rankin Scale may be used to address this requirement (see Table A1).

Table A1. Modified Rankin Scale for Stroke Disability

Scale	Disability
0	No symptoms at all.
1	No significant disability despite symptoms; able to carry out all usual duties and activities.
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance.
3	Moderate disability; requiring some help, but able to walk without assistance.
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance.
5	Severe disability; bedridden, incontinent, and requiring constant nursing care and attention.
6	Dead.

HEART FAILURE EVENT

A HF event includes hospitalization for HF and may include urgent outpatient visits. HF hospitalizations should remain delineated from urgent visits. If urgent visits are included in the HF event endpoint, the number of urgent visits needs to be explicitly presented separately from the hospitalizations.

A HF hospitalization is defined as an event that meets **ALL** of the following criteria:

1. The participant is admitted to the hospital with a ***primary diagnosis*** of HF;
2. The participant's length of stay in hospital extends for **at least 24 hours** (or a change in calendar date if the hospital admission and discharge times are unavailable);
3. The participant exhibits documented new or worsening symptoms due to HF on presentation, including **at least 1** of the following:
   a. Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, or paroxysmal nocturnal dyspnea);
   b. Decreased exercise tolerance;
   c. Fatigue; or
   d. Other symptoms of compromised or worsened end-organ perfusion or volume overload (must be specified and described by the protocol).
4. The participant has objective evidence of new or worsening HF, consisting of **at least 2** physical examination findings **OR 1** physical examination finding and **at least 1** laboratory criterion, including:
   a. Physical examination findings considered to be due to HF, including new or worsened:
      - Peripheral edema;
      - Increasing abdominal distention or ascites (in the absence of primary hepatic disease);
      - Pulmonary rales/crackles/crepitations;
      - Increased jugular venous pressure and/or hepatojugular reflux;
      - S3 gallop; or
      - Clinically significant or rapid weight gain thought to be related to fluid retention.
   b. Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
      - Increased B-type natriuretic peptide (BNP)/N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of HF (such as BNP >500 pg/mL or NT-proBNP >2000 pg/mL). In participants with chronically elevated natriuretic peptides, a significant increase should be noted above Baseline;
      - Radiological evidence of pulmonary congestion;
      - Non-invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. For example, echocardiographic

criteria could include septal or lateral E/e' >15 or >12, respectively; a D dominant pulmonary venous inflow pattern; a plethoric inferior vena cava with minimal collapse on inspiration; or a decreased left ventricular outflow tract minute stroke distance (time velocity integral); **OR**

- Invasive diagnostic evidence with right heart catheterization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mmHg, a central venous pressure ≥12 mmHg, or a cardiac index <2.2 L/min/m^2.

Note: All results from diagnostic tests should be reported, if available, even if they do not meet the above criteria, because they provide important information for the adjudication of these events.

5. The participant receives **at least 1** of the following treatments specifically for HF:
   a. Significant augmentation in oral diuretic therapy (eg, doubling of loop diuretic dose, initiation of maintenance loop diuretic therapy, initiation of combination diuretic therapy);
   b. Initiation of intravenous diuretic (even a single dose) or vasoactive agent (eg, inotrope, vasopressor, or vasodilator); or
   c. Mechanical or surgical intervention, including the following:
      - Mechanical circulatory support (eg, intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart); or
      - Mechanical fluid removal (eg, ultrafiltration, hemofiltration, dialysis).

General considerations (HF hospitalization)

Combination diuretic therapy could include 1) a thiazide-type diuretic (eg, hydrochlorothiazide, metolazone, chlorothiazide) plus a loop diuretic; or 2) a mineralocorticoid receptor antagonist (eg, spironolactone or eplerenone) plus a loop diuretic.

An urgent HF visit is defined as an event that meets all of the following:

1. The participant has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF, but not meeting the criteria for a HF hospitalization;
2. The participant meets all signs and symptoms for HF hospitalization as indicated above; and
3. The participant receives **at least 1** of the following treatments specifically for HF:
   a. Initiation of intravenous diuretic or vasoactive agent (eg, inotrope, vasopressor, or vasodilator);[3]
   b. Mechanical or surgical intervention, including:
      - Mechanical circulatory support (eg, intra-aortic balloon pump, ventricular assist device, extracorporeal membrane oxygenation, total artificial heart); or
      - Mechanical fluid removal (eg, ultrafiltration, hemofiltration, dialysis).

[3] Note that significant augmentation of oral diuretic therapy will NOT be sufficient to fulfill the urgent HF visit criteria.

General considerations (urgent HF visit)

Clinic visits for *scheduled* administration of HF therapies or procedures (eg, intravenous diuretics, intravenous vasoactive agents, or mechanical fluid removal) **do NOT** qualify as non-hospitalized HF events.

INTERVENTIONAL CARDIOLOGY

Clinical definitions

1. Clinically driven target lesion revascularization: Revascularization is clinically driven if the target lesion diameter stenosis is >50% by quantitative coronary angiography (QCA) and the participant has clinical or functional ischemia which cannot be explained by another native coronary or bypass graft lesion. Clinical or functional ischemia includes any of the following:
   a. A history of angina pectoris, presumably related to the target vessel;
   b. Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel; or
   c. Abnormal results of any invasive functional diagnostic test (eg, coronary flow reserve or fractional flow reserve).

   Note: Target lesion revascularization of a >70% diameter stenosis by QCA in the absence of the above signs or symptoms may be considered clinically driven.

   Note: In the absence of QCA data or if a <50% stenosis is present, target lesion revascularization may be considered clinically driven by the Clinical Events Committee (CEC) if severe ischemic signs and symptoms attributed to the target lesion are present.
2. Non-target lesion and non-target lesion revascularization: A lesion for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.
3. Non-target vessel and non-target vessel revascularization: A vessel for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.
4. PCI status:
   a. Elective: The procedure can be performed on an outpatient basis or during a subsequent hospitalization without significant risk of MI or death. For stable inpatients, the procedure is being performed during this hospitalization for convenience and ease of scheduling and **NOT** because the participant's clinical situation demands the procedure prior to discharge.
   b. Urgent: The procedure should be performed on an inpatient basis and prior to discharge because of significant concerns that there is risk of myocardial ischemia, MI, and/or death. Participants who are outpatients or in the emergency department at the time that the cardiac catheterization is requested would warrant hospital admission based on their clinical presentation.
   c. Emergency: The procedure should be performed as soon as possible because of substantial concerns that ongoing myocardial ischemia and/or MI could lead to death. "As soon as possible" refers to a participant who is of sufficient acuity that one would cancel a scheduled case to perform this procedure immediately in the next available room during business hours, or one would activate the on-call team were this to occur during off-hours.
   d. Salvage: The procedure is a last resort. The participant is in cardiogenic shock when the PCI begins (ie, the time at which the first guide wire or intracoronary device is introduced

into a coronary artery or bypass graft for the purpose of mechanical revascularization) **OR** within the last 10 minutes prior to the start of the case or during the diagnostic portion of the case, the participant has also received chest compressions or has been on unanticipated circulatory support (eg, intra-aortic balloon pump, extracorporeal membrane oxygenation, or cardiopulmonary support).

5. PCI: Placement of an angioplasty guide wire, balloon, or other device (eg, stent, atherectomy catheter, brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or CABG for the purpose of mechanical coronary revascularization. In the assessment of the severity of coronary lesions with the use of intravascular ultrasound, coronary flow reserve, or fractional flow reserve, insertion of a guide wire will **NOT** be considered PCI.
6. Procedural success: Achievement of <30% residual diameter stenosis of the target lesion assessed by visual inspection or QCA and no in-hospital major adverse cardiac events, a composite of death, MI, or repeat coronary revascularization of the target lesion. Ideally, the assessment of the residual stenosis at the end of the procedure should be performed by an angiographic core laboratory.

   Note: For some device interventions (eg, balloon angioplasty), achievement of <50% diameter stenosis by visual inspection or QCA is an acceptable definition for procedural success.
7. Target lesion: Any lesion treated or attempted to be treated during the PCI with the study device. The target lesion includes the arterial segment treated with the study device (stent, in most cases) plus 5 mm proximal and 5 mm distal to the treatment site.
8. Target lesion failure: The composite of ischemia-driven revascularization of the target lesion, MI related to the target vessel, or cardiac death related to the target vessel. If it cannot be determined with certainty whether the MI or death was related to the target vessel, it is considered a target lesion failure.
9. Target lesion revascularization: Any repeat percutaneous intervention of the target lesion (including 5 mm proximal and 5 mm distal to the target lesion) or surgical bypass of the target vessel performed for restenosis or other complication involving the target lesion. In the assessment of target lesion revascularization, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the CEC for review upon request.
10. Target vessel: A major native coronary artery (eg, left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, or right coronary artery) or bypass graft containing the target lesion. A native coronary artery target vessel includes the arterial segments upstream and downstream to the target lesion plus major side branches.
11. Target vessel failure: The composite of ischemia-driven revascularization of the target vessel, MI related to the target vessel, or cardiac death related to the target vessel. If it cannot be determined with certainty whether the MI or death was related to the target vessel, it is considered a target vessel failure.
12. Target vessel, non-target lesion, and target vessel, non-target lesion revascularization: Any lesion or revascularization of a lesion in the target vessel other than the target lesion, respectively.

13. Target vessel revascularization: Any repeat percutaneous intervention or surgical bypass of any segment of the target vessel. In the assessment of target vessel revascularization, angiograms should be assessed by an angiographic core laboratory (if designated) and made available to the CEC for review upon request.
14. Vascular complications include the following:
    - Access site hematoma: Development of a new, localized collection of blood at a vascular access site sufficient to produce a palpable mass within 72 hours of a procedure;
    - Arteriovenous fistula: Development of a new, unintended communication between an artery and a vein occurring at a vascular access site within 72 hours of a procedure;
    - Peripheral ischemia: Development of new arterial insufficiency sufficient to produce clinical signs or symptoms of ischemia (pallor, pain, paresthesia) distal to a vascular access site within 72 hours of a procedure;
    - Peripheral nerve injury: Development of new sensory or motor loss of peripheral nerve function from external nerve compression (eg, as a result of positioning during a procedure), or internal compression or direct nerve damage from the procedure, occurring within 72 hours of a procedure;
    - Pseudoaneurysm: Development of a new localized collection of blood with a persistent communication (neck) originating at a vascular access site and occurring within 72 hours of a procedure; or
    - Retroperitoneal hemorrhage: Development of new bleeding into the retroperitoneal space originating at a vascular access site and occurring within 72 hours of a procedure.

Angiographic definitions

1. Abrupt closure is defined as a new intra-procedural severely reduced flow (Thrombolysis in Myocardial Infarction [TIMI] Grade 0 to 1) within the target vessel that persists and requires intervention by stenting or other treatment, or results in MI or death. Abrupt closure requires an association with a vascular dissection, thrombus, or severe spasm at the treatment site or within the instrumented vessel.
2. Coronary lesions treated are defined as shown in Table A2:

Table A2. Coronary Lesions Treated and Definitions

Coronary Artery Segments	Definition
Right coronary artery ostium	Origin of the right coronary artery, including the first 3 mm of the artery.
Proximal right coronary artery	Proximal portion of the right coronary artery, from the ostium of the right coronary artery to the origin of the first right ventricular branch (pRCA).
Mid right coronary artery	Middle portion of the right coronary artery, from the origin of the first right ventricular branch to the acute margin (mRCA).
Distal right coronary artery	Distal portion of the right coronary artery, from the acute margin to the origin of the posterior descending artery (dRCA).
Right posterior descending artery	In right dominant and mixed circulations, the vessel that runs in the posterior interventricular groove and supplies septal perforator branches (PDA).

Coronary Artery Segments	Definition
Posterolateral segmental artery	In right dominant circulations, the distal continuation of the right coronary artery in the posterior atrioventricular groove after the origin of the right posterior descending artery (PLSA).
First right posterolateral branch	In right dominant circulations, the first posterolateral branch originating from the right posterior atrioventricular artery (RPL1).
Second right posterolateral branch	In right dominant circulations, the second posterolateral branch originating from the right posterior atrioventricular artery (RPL2).
Third right posterolateral branch	In right dominant circulations, the third posterolateral branch originating from the right posterior atrioventricular artery (RPL3).
Posterior descending septal perforator	Septal perforator vessel originating from the posterior descending artery.
Right ventricular branch	Branch arising from the right coronary artery to supply the right ventricular wall (RV).
Left main coronary artery ostium	Origin of the left coronary artery, including the first 3 mm of the artery.
Left main coronary artery body	Body of the left main coronary artery, from the ostium to the bifurcation (LM).
Left main coronary artery bifurcation	Distal end of the left main, including the terminal 3 mm through the bifurcation of the left main into the left anterior descending and left circumflex arteries.
Left anterior descending artery ostium	Origin of the left anterior descending coronary artery, including the first 3 mm of the artery.
Proximal left anterior descending artery	Proximal portion of the left anterior descending coronary artery, from the ostium to the origin of the first septal (pLAD).
Mid left anterior descending artery	Middle portion of the left anterior descending coronary artery, from the origin of the first septal artery to the origin of the third septal artery (mLAD).
Distal left anterior descending artery	Distal portion of the left anterior descending coronary artery, from the origin of the third septal artery to the terminus (dLAD).
First diagonal branch	First of the 3 longest branches originating from the left anterior descending artery to supply the anterolateral wall of the left ventricle (D1).
First diagonal lateral branch	Branch of the first diagonal branch.
Second diagonal branch	Second of the 3 longest branches originating from the left anterior descending artery to supply the anterolateral wall of the left ventricle (D2).
Second diagonal lateral branch	Branch of the second diagonal branch.
Third diagonal branch	Third of the 3 longest branches originating from the left anterior descending artery to supply the anterolateral wall of the left ventricle (D3).
Third diagonal lateral branch	Branch of the third diagonal branch.
Anterior descending septal perforator	Septal perforator vessel originating from the left anterior descending artery to supply the interventricular septum.
Left circumflex artery ostium	Origin of the left circumflex coronary artery, including the first 3 mm of the artery.
Proximal left circumflex artery	Proximal portion of the left circumflex coronary artery, from the ostium to the origin (or the nominal location of) the first marginal branch (pLCX).

Coronary Artery Segments	Definition
Mid left circumflex artery	Middle portion of the left circumflex coronary artery, from the origins of (or nominal locations of) the first marginal to the second marginal (mLCX).
Distal left circumflex artery	Distal portion of the left circumflex coronary artery, from the origin of (or the nominal location of) the second marginal to the terminus (in right dominant systems), or to the origin of the first left posterolateral in all other dominance systems (dLCX).
First obtuse marginal branch	First of the 3 longest branches originating from the left circumflex artery to supply the lateral wall of the left ventricle (OM1).
First obtuse marginal lateral branch	Branch of the first marginal branch.
Second obtuse marginal branch	Second of the 3 longest branches originating from the left circumflex artery to supply the lateral wall of the left ventricle (OM2).
Second obtuse marginal lateral branch	Branch of the second marginal branch.
Third obtuse marginal branch	Third of the 3 longest branches originating from the left circumflex artery to supply the lateral wall of the left ventricle (OM3).
Third obtuse marginal lateral branch	Branch of the third marginal branch.
Left atrioventricular artery	In left dominant and mixed circulations, the distal continuation of the left circumflex coronary artery in the posterior atrioventricular groove.
Left posterior descending artery	In left dominant circulations, the vessel that arises from the distal continuation of the left atrioventricular artery, travels in the posterior interventricular groove, and supplies septal perforator branches (LPDA).
First left posterolateral branch	In left dominant and mixed circulations, the first posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL1).
Second left posterolateral branch	In left dominant and mixed circulations, the second posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL2).
Third left posterolateral branch	In left dominant and mixed circulations, the third posterolateral branch originating from the posterior atrioventricular left circumflex artery (LPL3).
Ramus intermedius branch	Branch vessel whose origin bisects the origins of the left anterior descending and circumflex arteries (RI).
Ramus intermedius lateral branch	Branch of the ramus intermedius branch.

3. Dissection is defined based on the National Heart, Lung, and Blood Institute Dissection Classification System as follows:
   - Grade A: Minor radiolucencies within the lumen during contrast injection with no persistence after dye clearance;
   - Grade B: Parallel tracts or double lumen separated by a radiolucent area during contrast injection with no persistence after dye clearance;
   - Grade C: Extraluminal cap with persistence of contrast after dye clearance from the lumen;
   - Grade D: Spiral luminal filling defect with delayed but complete distal flow;

- Grade E: New persistent filling defect with delayed antegrade flow; and
- Grade F: Non-A through E types with total coronary occlusion and no distal antegrade flow.

Note: Grade E and F dissections may represent thrombus.

4. Late loss is defined as the minimum lumen diameter (MLD) assessed at follow-up angiography minus the MLD assessed immediately after the index procedure. MLDs are measured by QCA.
5. MLD is the mean minimum lumen diameter (typically measured in-lesion, in-stent, and in segment) derived from 2 orthogonal views by QCA.
6. No reflow is defined as an acute reduction in coronary flow (TIMI Grade 0 to 1) in the absence of dissection, thrombus, spasm, or high-grade residual stenosis at the original target lesion.
7. Percent diameter stenosis is the value calculated as 100 × (1 – MLD/reference vessel diameter [RVD]) using the mean values determined by QCA from 2 orthogonal views (when possible).
8. RVD is defined as the average of normal segments within 10 mm proximal and 10 mm distal to the target lesion from 2 orthogonal views using QCA.
9. Restenosis is defined as re-narrowing of the vessel following the treatment of a prior stenosis and is classified further as follows:
   - Binary restenosis is defined as a diameter stenosis of >50% at the previously treated lesion site, including the originally treated site plus the adjacent vascular segments 5 mm proximal and 5 mm distal to the site; and
   - In-stent restenosis is defined as a previously stented lesion with a >50% diameter stenosis.
10. Thrombus (angiographic) is defined as a discrete, mobile, intraluminal filling defect with defined borders with or without associated contrast staining.
11. TIMI flow grades are defined as follows:
    - Grade 0 (no perfusion): There is no antegrade flow beyond the point of occlusion;
    - Grade 1 (penetration without perfusion): The contrast material passes beyond the area of obstruction but “hangs up” and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cineangiographic filming sequence;
    - Grade 2 (partial perfusion): The contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast material into the vessel distal to the obstruction or its rate of clearance from the distal bed (or both) is perceptibly slower than its entry into or clearance from comparable areas not perfused by the previously occluded vessel (eg, the opposite coronary artery or the coronary bed proximal to the obstruction); and
    - Grade 3 (complete perfusion): Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into the bed proximal to the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved bed in the same vessel or the opposite artery.
12. Vessels are defined as follows:
    - Left main coronary artery;

- Left anterior descending artery with septal and diagonal branches;
- Left circumflex artery with obtuse marginal branches;
- Ramus intermedius artery;
- Right coronary artery and any of its branches;
- Posterior descending artery;
- Saphenous vein bypass graft(s); and
- Arterial bypass graft(s): Right internal mammary graft, left internal mammary graft, radial artery graft, and gastroepiploic artery graft.

PERIPHERAL VASCULAR INTERVENTION

1. Peripheral vascular intervention (PVI): PVI[4] is a catheter-based or open surgical procedure designed to improve arterial or venous blood flow or otherwise modify or revise vascular conduits. Procedures may include, but are not limited to, percutaneous transluminal balloon angioplasty, stent placement, thrombectomy, embolectomy, atherectomy, dissection repair, aneurysm exclusion, treatment of dialysis conduits, placement of various devices, intravascular thrombolysis or other pharmacotherapies, and open surgical bypass or revision.

   In general, the intention to perform ***percutaneous*** PVI is denoted by the insertion of a guide wire into a peripheral artery or vein.

   The target vessel(s) and the type of revascularization procedure (eg, surgical bypass, thrombectomy, endarterectomy, percutaneous transluminal angioplasty, stent placement, thromboembolectomy, and thrombolysis) should be specified and recorded. For the sake of simplicity, this definition applies to the extracranial carotid artery and other non-cardiac arteries and veins and excludes the intracranial vessels and lymphatics.

2. Procedural success: In the case of percutaneous intervention for obstructive lesions, procedural success is defined as the achievement of a satisfactory final residual diameter stenosis by angiography at the end of the procedure (and without flow limiting dissection or hemodynamically significant translesional pressure gradient). The specific parameter for final percent residual stenosis is typically between <30% and <50%; selection of the appropriate percentage may vary depending upon the specific intervention applied, the vascular territory, and anticipated or desired therapeutic response. Procedural success also implies absence of in-hospital major adverse events (AEs) (eg, death, stroke, MI, acute onset of limb ischemia, need for urgent/emergent vascular surgery, and other procedure-specific major AEs). The balloon inflation, stent placement, or other therapeutic intervention may be preceded by use of adjunctive devices (eg, percutaneous mechanical thrombectomy, directional or rotational atherectomy, laser, and chronic total occlusion crossing device), as predefined in the protocol.

3. Procedural status: non-elective and elective:

   a. Non-elective: Non-elective procedures include emergent and urgent procedures. A non-elective procedure is a procedure that is performed without delay, because there is clinical consensus that the procedure should occur imminently. Non-elective procedures imply a degree of instability of the participant, urgency of the medical condition, or instability of the threatening lesion. Emergent and urgent are defined as follows:

      - Emergent: A procedure that is performed immediately because of the acute nature of the medical condition (eg, acute limb ischemia, acute aortic dissection) and the increased morbidity or mortality associated with a temporal delay in treatment; or
      - Urgent: An urgent procedure is one that is not an emergency but is required to be performed on a timely basis (≤24 hours) (eg, a participant who has been stabilized

[4] We note that peripheral vascular disease includes veins, arteries, and lymphatics. However, for simplicity, this definition will focus on peripheral artery and venous interventions.

following initial treatment of acute limb ischemia, and there is clinical consensus that a definitive procedure should occur within the next 24 hours).

b. Elective: An elective procedure is one that is scheduled and is performed on a participant with stable disease, or in whom there is no urgency and/or increased morbidity or mortality associated with a planned procedure.

4. Target lesion: A target lesion is any vascular segment treated or attempted to be treated during the study procedure with the index device. The target lesion is the treated segment starting 10 mm proximal and ending 10 mm distal to the index device or therapy (stent, balloon, atherectomy catheter, or aortic stent-graft).
5. Target vessel: A target vessel is any vessel (eg, non-cardiac or non-intracranial) that contains the target lesion treated with the study device. The target vessel includes the target lesion as well as the entire length of native vessel upstream and downstream from the target lesion, including side branches. For the arteries of the leg, the vasculature is divided into 3 vessel "levels:" aorto-iliac, femoral-popliteal, and tibial-crural.
6. Non-target lesion and non-target lesion revascularization: A lesion for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.
7. Non-target vessel and non-target vessel revascularization: A vessel for which revascularization is not attempted or one in which revascularization is performed using a non-study device, respectively.
8. Target vessel, non-target lesion and target vessel, non-target lesion revascularization: Any lesion or revascularization of a lesion in the target vessel other than the target lesion, respectively.
9. Target lesion revascularization: Target lesion revascularization is any repeat intervention of the target lesion (including 10 mm proximal and 10 mm distal to the index device, as target lesion is defined above) or surgical intervention/bypass of the target vessel performed for restenosis or other complication involving the target lesion. In the assessment of target lesion revascularization, angiograms should be assessed by an angiographic core laboratory (if designated). Angiograms (and core laboratory assessment thereof) and other source documentation should be made available to the CEC for review upon request.
10. Target vessel revascularization: Target vessel revascularization is any repeat intervention or surgical bypass of any segment of the target vessel. In the assessment of target vessel revascularization, angiograms should be assessed by an angiographic core laboratory (if designated). Angiograms (and core laboratory assessment thereof) and other source documentation should be made available to the CEC for review upon request.
11. Clinically driven target lesion revascularization: Clinically driven target lesion revascularization is defined as target lesion revascularization performed due to target lesion diameter stenosis >50% **AND** either evidence of clinical or functional ischemia (eg, recurrent/progressive intermittent claudication, critical limb ischemia) **OR** recurrence of the clinical syndrome for which the initial procedure was performed. Clinically driven target lesion revascularization occurs in the absence of protocol-directed surveillance ultrasound or angiography.

12. Vessel patency: Vessel patency at a given time point will be determined by the absence of clinically driven target lesion revascularization and/or absence of recurrent target lesion diameter stenosis >50% by imaging (eg, invasive angiography or most commonly, duplex ultrasonography). If patency data are incorporated within the primary endpoint of a clinical study, the angiographic images or duplex ultrasonographic images should be assessed by appropriate core laboratories and made available to the CEC for review upon request.
13. Restenosis: Re-narrowing of the artery following the treatment of a prior stenosis, defined further as follows:
    - Binary restenosis: A diameter stenosis of >50% at the previously treated lesion site, including the originally treated site plus the adjacent vascular segments 10 mm proximal and 10 mm distal to the site (or as otherwise defined by the Protocol, as noted above); or
    - In-stent restenosis: A previously stented lesion that has >50% diameter stenosis.

STENT THROMBOSIS

Stent thrombosis: timing

Stent thrombosis should be reported as a cumulative value over time and at the various individual time points as specified below. Time 0 is defined as the time point after the guiding catheter has been removed and the participant has left the cardiac catheterization laboratory. Stent thrombosis timing is described in Table A3.

Table A3. Stent Thrombosis: Timing

Type of Stent Thrombosis	Timing
Acute stent thrombosis[1]	0 to 24 hours post stent implantation
Subacute stent thrombosis[1]	>24 hours to 30 days post stent implantation
Late stent thrombosis[2]	>30 days to 1 year post stent implantation
Very late stent thrombosis[2]	>1 year post stent implantation

1. Acute or subacute stent thrombosis can also be replaced by the term early stent thrombosis. Early stent thrombosis (0 to 30 days) will be used herein.
2. Includes "primary" as well as "secondary" late stent thrombosis; "secondary" late stent thrombosis is a stent thrombosis after a target lesion revascularization.

Stent thrombosis: categories

We propose 3 categories of evidence to define stent thrombosis, as follows:

1. Definite stent thrombosis is defined as follows:

   Definite stent thrombosis is considered to have occurred by ***either*** angiographic or pathological confirmation:

   a. Angiographic confirmation of stent thrombosis[5] is defined as:

      - The presence of a thrombus[6] that originates in the stent or in the segment 5 mm proximal or distal to the stent and presence of at least 1 of the following criteria within a 48-hour time window:
        - Acute onset of ischemic symptoms at rest;
        - New ischemic ECG changes that suggest acute ischemia;
        - Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI);
        - Nonocclusive thrombus; or

          Note: Intracoronary thrombus is defined as a (spherical, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.

[5] The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).
[6] Intracoronary thrombus.

- Occlusive thrombus.

  Note: TIMI 0 or TIMI 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originates from the side branch).

b. Pathological confirmation of stent thrombosis is defined as evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy.

2. Probable stent thrombosis is defined as follows:

   Clinical definition of probable stent thrombosis is considered to have occurred after intracoronary stenting in the following cases:

   a. Any unexplained death within the first 30 days;[7] or

   b. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause.

3. Possible stent thrombosis is defined as follows:

   Clinical definition of possible stent thrombosis is considered to have occurred with any unexplained death from 30 days after intracoronary stenting until end of study follow-up.

[7] For studies with an ST-elevation MI population, one may consider the exclusion of unexplained death within 30 days as evidence of probable stent thrombosis.

APPENDIX G: UNIVERSAL DEFINITIONS OF MYOCARDIAL INJURY AND MYOCARDIAL INFARCTION: SUMMARY FROM THE FOURTH UNIVERSAL DEFINITION OF MYOCARDIAL INFARCTION (2018)[21]

CRITERIA FOR MYOCARDIAL INJURY

The term myocardial injury should be used when there is evidence of elevated cardiac troponin (cTn) values with at least 1 value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values.

CRITERIA FOR ACUTE MYOCARDIAL INFARCTION (TYPES 1, 2, AND 3 MI)

The term acute myocardial infarction (MI) should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia and with detection of a rise and/or fall of cTn values with at least 1 value above the 99th percentile URL and at least 1 of the following:

- Symptoms of myocardial ischemia;
- New ischemic electrocardiogram (ECG) changes;
- Development of pathological Q waves;
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology; or
- Identification of a coronary thrombus by angiography or autopsy (not for types 2 or 3 MI).

Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for type 1 MI.

Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for type 2 MI.

Cardiac death in participants with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes before cTn values become available or abnormal meets criteria for type 3 MI.

CRITERIA FOR CORONARY PROCEDURE-RELATED MYOCARDIAL INFARCTION (TYPES 4 AND 5 MI)

Percutaneous coronary intervention (PCI)-related MI is termed type 4a MI.

Coronary artery bypass grafting (CABG)-related MI is termed type 5 MI.

Coronary procedure-related MI ≤48 hours after the index procedure is arbitrarily defined by an elevation of cTn values >5 × for type 4a MI and >10 × for type 5 MI of the 99th percentile URL in participants with normal Baseline values. Participants with elevated pre-procedural cTn values, in whom the pre-procedural cTn levels are stable (≤20% variation) or falling, must meet the criteria for a >5- or >10-fold increase and manifest a change from the Baseline value of >20%, in addition to at least 1 of the following:

- New ischemic ECG changes (this criterion is related to type 4a MI only);
- Development of new pathological Q waves;
- Imaging evidence of loss of viable myocardium that is presumed to be new and in a pattern consistent with an ischemic etiology; or
- Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow, or distal embolization.

Isolated development of new pathological Q waves meets the type 4a MI or type 5 MI criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.

Other types of 4 MI include type 4b MI stent thrombosis and type 4c MI restenosis that both meet type 1 MI criteria.

Post-mortem demonstration of a procedure-related thrombus meets the type 4a MI criteria or type 4b MI criteria if associated with a stent.

CRITERIA FOR PRIOR OR SILENT/UNRECOGNIZED MYOCARDIAL INFARCTION

Any 1 of the following criteria meets the diagnosis for prior or silent/unrecognized MI:

- Abnormal Q waves with or without symptoms in the absence of non-ischemic causes;
- Imaging evidence of loss of viable myocardium in a pattern consistent with ischemic etiology; or
- Patho-anatomical findings of a prior MI.