# Fixed-dose combination of obicetrapib and ezetimibe for LDL cholesterol reduction (TANDEM): a phase 3, randomised, double-blind, placebo-controlled trial

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## Summary

**Background** Reducing LDL cholesterol prevents atherosclerotic cardiovascular disease (ASCVD) events. The aim of this study was to evaluate the LDL cholesterol-lowering efficacy of a fixed-dose combination (FDC) of obicetrapib, a CETP inhibitor, and ezetimibe.

**Methods** This randomised, double-blind trial across 48 US sites including hospitals, private and group practices, and independent research centres included participants at least 18 years old with pre-existing or high risk for ASVCD or heterozygous familial hypercholesterolaemia with LDL cholesterol concentrations of 1·8 mmol/L (70 mg/dL) or greater despite maximally tolerated lipid-lowering therapy excluding ezetimibe, or having statin intolerance. Participants were randomly assigned (1:1:1:1) to obicetrapib 10 mg plus ezetimibe 10 mg FDC, obicetrapib 10 mg monotherapy, ezetimibe 10 mg monotherapy, or placebo administered daily for 84 days. The co-primary endpoints in the intention-to-treat population were the percent LDL cholesterol changes in the FDC group compared with placebo, ezetimibe monotherapy, and obicetrapib monotherapy, and the placebo-adjusted change in the obicetrapib monotherapy group. The trial was prospectively registered (NCT06005597) and is completed.

**Findings** Between March 4 and July 3, 2024, 407 participants were randomly assigned. The median age was 68·0 years (IQR 62·0–73·0) and 177 (43%) were female. Mean baseline LDL cholesterol was 2·4 mmol/L, 2·5 mmol/L, 2·6 mmol/L, and 2·5 mmol/L in the placebo (n=102), ezetimibe monotherapy (n=101), obicetrapib monotherapy (n=102), and FDC groups (n=102), respectively. At day 84, percent differences in LDL cholesterol reduction with the FDC were –48·6% (95% CI –58·3 to –38·9) versus placebo, –27·9% (–37·5 to –18·4) versus ezetimibe, and –16·8% (–26·4 to –7·1) versus obicetrapib. Obicetrapib monotherapy decreased LDL cholesterol by 31·9% (22·1 to 41·6) versus placebo. Adverse event rates were similar in the FDC (52 [51%] of 102), obicetrapib (55 [54%] of 102), and ezetimibe (54 [53%] of 101) groups and lowest with placebo (38 [37%] of 102). Serious adverse event rates were generally similar across FDC (three [3%] of 102), obicetrapib (six [6%] of 102), ezetimibe (seven [7%] of 101), and placebo (four [4%] of 102) groups. Deaths occurred in one [1%] of 102 participants with FDC, one [1%] of 102 with obicetrapib, one [1%] of 101 with ezetimibe, and none with placebo.

**Interpretation** Combination therapy of obicetrapib and ezetimibe significantly reduced LDL cholesterol. This oral, single-pill therapy could improve LDL cholesterol management in patients with pre-existing or high risk for ASCVD.

**Funding** NewAmsterdam Pharma.



Published Online
May 7, 2025
https://doi.org/10.1016/S0140-6736(25)00721-4

See Online/Comment
https://doi.org/10.1016/S0140-6736(25)00827-X

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## Introduction

Treatment of elevated LDL cholesterol concentrations is a primary strategy for risk reduction in individuals with pre-existing or high risk for atherosclerotic cardiovascular disease (ASCVD).[1,2] Clinical trials of several classes of LDL cholesterol-lowering drugs have shown consistent reductions in major adverse cardiovascular events.[3–9] A large meta-analysis of statin drug trials demonstrated a 22% reduction in cardiovascular events for each 1 mmol/L (38·7 mg/dL) reduction in LDL cholesterol concentration.[3] Despite the availability of multiple classes of drugs that lower LDL cholesterol, including treatment with high-intensity statins, many patients with ASCVD do not achieve target concentrations of LDL cholesterol.[10] Barriers to the effective control of LDL cholesterol after the use of maximally tolerated statin therapy include the limited use of non-statin therapies, particularly limited access to injectable medications, and possibly patient fears about injectable medications.[11,12] Accordingly, there is an unmet medical need for effective orally administered LDL cholesterol-lowering therapies.

Pharmacological inhibition of the cholesteryl ester transfer protein (CETP) has been associated with inconsistent reductions in LDL cholesterol in previous trials.[13–16] Obicetrapib is an orally administered, selective CETP inhibitor that significantly reduced LDL cholesterol

## Research in context

### Evidence before this study

A PubMed search for all articles with the keywords "obicetrapib" and "ezetimibe" published from database inception to March 2, 2025 yielded two results of original research manuscripts. Of these, only one study, namely the ROSE2 trial, studied the combination of obicetrapib and ezetimibe. ROSE2 was a randomised phase 2 trial of obicetrapib plus ezetimibe for LDL cholesterol reduction, and provided initial data regarding the LDL cholesterol-lowering efficacy of obicetrapib plus ezetimibe in 97 patients with dyslipidaemia.

### Added value of this study

The TANDEM study provides randomised phase 3 trial evidence, for the first time, regarding the LDL cholesterol-lowering efficacy, safety, and tolerability of an orally administrated, single-pill, fixed-dose combination (FDC) of obicetrapib 10 mg and ezetimibe 10 mg in patients with high risk for or pre-existing atherosclerotic cardiovascular disease (ASCVD). The FDC of obicetrapib and ezetimibe provided nearly 50% LDL cholesterol lowering compared with placebo and was generally well tolerated across 84 days.

### Implications of all the available evidence

Many patients with high risk for or pre-existing ASCVD do not meet LDL cholesterol treatment goals despite the use of intensive statin therapy and the availability of multiple classes of LDL cholesterol-lowering drugs. The FDC of obicetrapib and ezetimibe could offer an orally administrated, tolerable, single-pill therapy to improve LDL cholesterol management in these high-risk patients who can be challenging to treat.

in small phase 2 studies in participants without ASCVD when administered as monotherapy or in combination with ezetimibe.[17,18] We conducted the phase 3 TANDEM trial (Study of Obicetrapib and Ezetimibe Fixed Dose Combination on Top of Maximum Tolerated Lipid-modifying Therapies) to determine the efficacy and safety of the fixed-dose combination (FDC) of obicetrapib with ezetimibe in participants with pre-existing or high risk for ASCVD whose LDL cholesterol concentrations were elevated despite receiving maximally tolerated lipid-lowering therapies at baseline.

## Methods

### Study design

See Online for appendix

This was a randomised, double-blind trial which was performed at 48 sites in the USA (the list of sites is in the appendix pp 2–3). The trial protocol and statistical analysis plan are included in the appendix. The trial protocol was reviewed by the US Food and Drug Administration and designed to support the potential approval of the obicetrapib plus ezetimibe FDC for reduction of LDL cholesterol. The protocol and amendments were approved by a central ethics committee (Advarra) for all sites, with initial approval on Sept 28, 2023 (trial reference number Pro00074209). This study was conducted in accordance with ethical principles derived from the Declaration of Helsinki and international ethical guidelines from the Council for International Organizations of Medical Sciences. The trial is registered with ClinicalTrials.gov (NCT06005597) and is completed.

### Participants

Participants who were at least 18 years old with pre-existing ASCVD, pre-existing heterozygous familial hypercholesterolaemia (HeFH), or multiple risk factors for ASCVD were eligible for inclusion. Participants were required to have a fasting LDL cholesterol concentration of 1·8 mmol/L (70 mg/dL) or greater at baseline while receiving stable doses of maximally tolerated lipid-lowering therapy excluding ezetimibe. Participants were required to be receiving maximally tolerated statin therapy or have documented statin intolerance with written confirmation from the participant and the investigator. Other lipid-lowering regimens were allowed, such as bempedoic acid, and proprotein convertase subtilisin/kexin type 9 (PCSK9)-targeting therapies including monoclonal antibodies or inclisiran. Pre-existing ASCVD was defined by at least one of the following conditions: coronary artery disease, cerebrovascular disease, or peripheral arterial disease. HeFH was defined by either historical genotyping or clinical scoring criteria (Dutch Lipid Clinic Network Criteria with a score of ≥3 points, or the Simon Broome Register Diagnostic Criteria with an assessment of "Possible HeFH" or "Definite HeFH"). Multiple risk factors for ASCVD were defined as either type 2 diabetes plus one additional risk factor, or three non-diabetes risk factors. Full inclusion and exclusion criteria are provided in the trial protocol in the appendix. All participants provided written informed consent before undergoing any study procedures.

### Randomisation and masking

Participants who met all inclusion criteria and none of the exclusion criteria were randomly assigned in a 1:1:1:1 ratio to receive once per day orally administered FDC of obicetrapib 10 mg plus ezetimibe 10 mg, obicetrapib 10 mg monotherapy, ezetimibe 10 mg monotherapy, or matching placebo. Randomisation was computer-generated by a contract research organisation through the ClinTrak Interactive Response Technology system. A permuted block design was used (block size of 8). Every participant received three oral study drugs to take daily, which included one tablet of obicetrapib 10 mg plus ezetimibe 10 mg FDC or a matching placebo, one tablet of obicetrapib 10 mg or a matching placebo, and one capsule of ezetimibe 10 mg or a matching placebo, as

appropriate for their treatment group. For example, participants assigned to the FDC treatment group received one FDC tablet, one obicetrapib-matching placebo tablet, and one ezetimibe-matching placebo capsule. Masking was achieved by the use of identical tablets and capsules such that study investigators and participants could not determine whether they contained active drug or placebo. Further details regarding the formulation, packaging, and dispensing of study drugs are provided in the protocol. Participants, investigators, academic leadership, the contract research organisation, and the sponsor were masked to treatment allocation and all lipid results during the trial until all study-related visits and assessments were completed and the database was locked. Participants were asked not to initiate new lipid-lowering therapies and not to change the dose of background lipid-lowering therapies during the trial. Data were collected by local study staff and managed by contract research organisation staff masked to treatment allocation.

### Procedures

At screening, participants were evaluated for trial eligibility and underwent evaluation of vital signs, a physical examination, a 12-lead electrocardiogram, haematology, fasting chemistry, coagulation, fasting lipids, and urine analysis for the urine albumin–creatinine ratio. Informed consent was obtained at that time. Randomisation was performed at week 0. Study visits were performed at weeks 0 (day 1), 4, 12, and 16 (safety follow-up). Study drug kits were dispensed to participants at week 0 and week 4 with clearly labelled instructions to take two tablets and one capsule orally every day from week 0 (day 1) to week 12 (day 84). Information about adverse events, vital signs, fasting chemistry, haematology, and urine analysis were assessed at every visit. All concomitant medications and changes to concomitant medications, including lipid-modifying therapies, were reviewed with the participant at each study visit. Evaluation of study drug adherence was performed at weeks 4 and 12. Fasting lipid profiles were assessed at weeks 0, 4, and 12. Fasting lipoprotein (a) concentrations were assessed at weeks 0 and 12.

For all participants, blood samples for lipid profiles were obtained after fasting for a minimum of 8 h. LDL cholesterol was measured by preparative ultracentrifugation, also known as beta-quantification, at week 0 (day 1) and week 12 (day 84), or, in cases of early discontinuation of study drug or study, at the end of treatment visit. LDL cholesterol was also calculated using the Martin–Hopkins and Friedewald equations unless triglycerides were more than 4·5 mmol/L (>400 mg/dL) or LDL cholesterol was less than 1·3 mmol/L (<50 mg/dL) in which case LDL cholesterol was measured directly by preparative ultracentrifugation. Lipoprotein (a) was measured by an immunoturbidimetric assay. Apolipoprotein B was measured through an immunonephelometric assay. Lipid profiles were analysed at a central laboratory. Safety data were reviewed by an independent medical monitor (a cardiologist) from the contract research organisation during aggregate data reviews which occurred approximately monthly beginning 1 month after enrolment of the first patient.

### Outcomes

The four co-primary efficacy endpoints of the trial were the percent changes in LDL cholesterol concentrations from baseline to day 84 measured by beta quantification. The obicetrapib–ezetimibe FDC group was compared with each of the other three treatment groups: the placebo group, the ezetimibe 10 mg monotherapy group, and the obicetrapib 10 mg monotherapy group. The percent change in LDL cholesterol concentrations from baseline to day 84 in the obicetrapib 10 mg monotherapy group compared with the placebo group was also a prespecified co-primary endpoint.

Secondary endpoints were tested in a prespecified hierarchical order, including the percent change from day 1 to day 84 in non-HDL cholesterol concentrations for the obicetrapib 10 mg plus ezetimibe 10 mg FDC treatment group compared with the placebo group. Additionally, the percent change from day 1 to day 84 in apolipoprotein B concentrations for the obicetrapib 10 mg plus ezetimibe 10 mg FDC treatment group was compared with the placebo group. The analysis also included the percent change from day 1 to day 84 in non-HDL cholesterol concentrations for the obicetrapib 10 mg monotherapy treatment group compared with the placebo group, as well as the percent change from day 1 to day 84 in apolipoprotein B concentrations for the obicetrapib 10 mg monotherapy treatment group compared with the placebo group. Furthermore, the percent change from day 1 to day 84 in non-HDL cholesterol concentrations for the obicetrapib 10 mg plus ezetimibe 10 mg FDC treatment group was compared with the ezetimibe 10 mg monotherapy treatment group, and the percent change from day 1 to day 84 in apolipoprotein B concentrations for the obicetrapib 10 mg plus ezetimibe 10 mg FDC treatment group was compared with the ezetimibe 10 mg monotherapy treatment group. Lastly, the percent change from day 1 to day 84 in non-HDL cholesterol concentrations for the obicetrapib 10 mg plus ezetimibe 10 mg FDC treatment group was compared with the obicetrapib 10 mg monotherapy treatment group, and the percent change from day 1 to day 84 in apolipoprotein B concentrations for the obicetrapib 10 mg plus ezetimibe 10 mg FDC treatment group was compared with the obicetrapib 10 mg monotherapy treatment group. All prespecified secondary endpoints are reported.

Exploratory endpoints included the percent changes from baseline to day 84 in lipoprotein (a) and HDL cholesterol concentrations, and the proportion of participants who had LDL cholesterol thresholds of less

than 2·6 mmol/L (<100 mg/dL), less than 1·8 mmol/L (<70 mg/dL), and less than 1·4 mmol/L (<55 mg/dL) at day 84.

The safety population included all participants who received at least one dose of any study drug and was the primary population used for safety analyses. Safety endpoints included vital signs, physical examination findings, clinical laboratory assessments, and the incidence of adverse events and events of special interest.

## Statistical analysis

Assuming a standard deviation of 25% at a one-sided significance level of 0·025, a sample size of 95 participants per treatment group (380 total) was estimated to provide more than 90% power to detect a 30% difference in LDL cholesterol reduction for the FDC treatment group compared with the placebo group, a 20% difference in LDL cholesterol reduction for the FDC group compared with the ezetimibe monotherapy group, a 12% difference

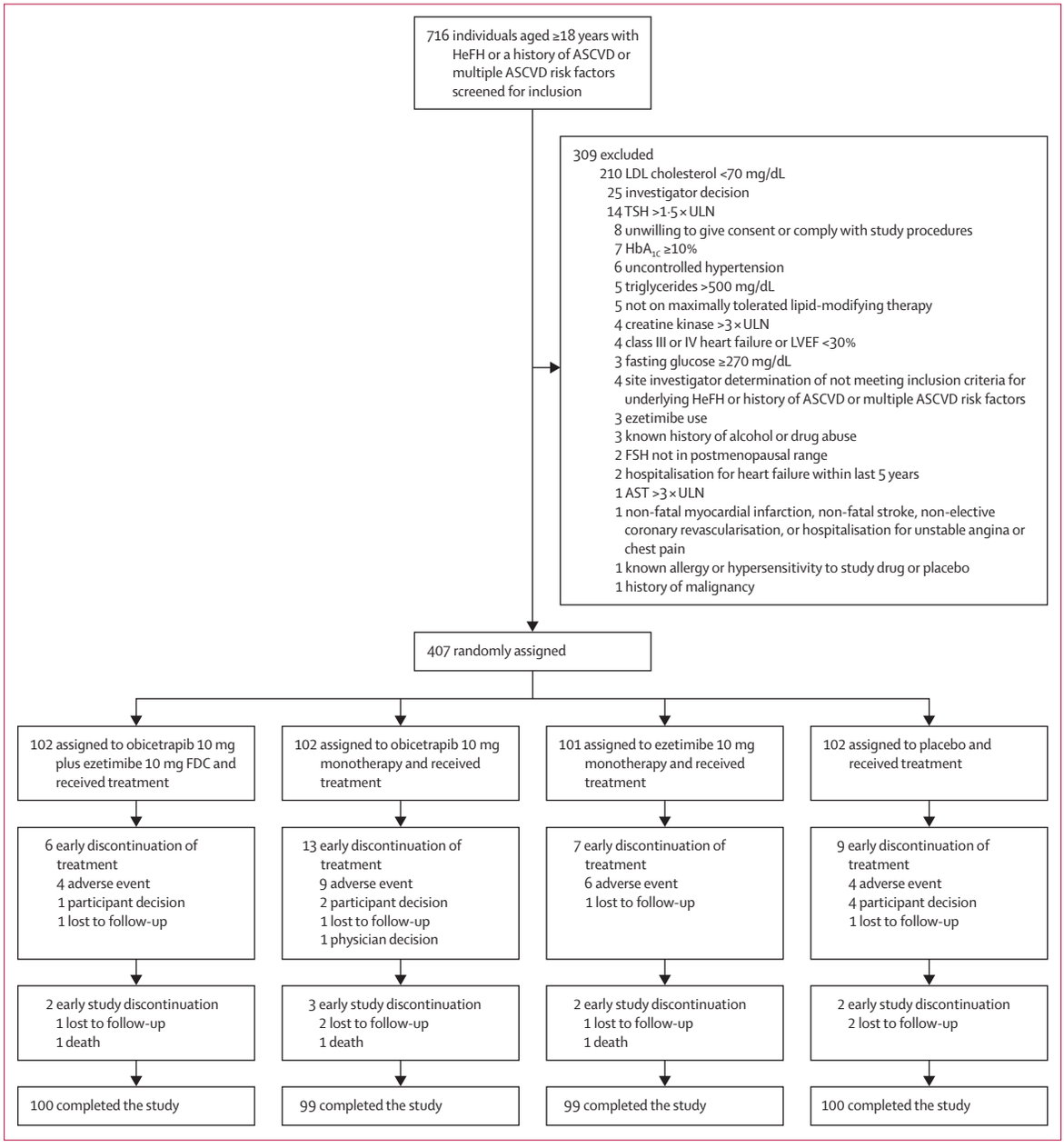


***Figure 1:*** **Trial profile**

ASCVD=atherosclerotic cardiovascular disease. AST=aspartate aminotransferase. FDC=fixed-dose combination. FSH=follicle-stimulating hormone. $HbA_{1c}$=glycated haemoglobin. HeFH=heterozygous familial hypercholesterolaemia. LVEF=left ventricular ejection fraction. TSH=thyroid-stimulating hormone. ULN=upper limit of normal.

in LDL cholesterol reduction for the FDC group compared with the obicetrapib monotherapy group, and a 15% difference in LDL cholesterol reduction for the obicetrapib monotherapy group compared with the placebo group.[5,18,19]

The primary efficacy assessment was performed using the intention-to-treat population which included all randomly assigned participants. An ANCOVA model with a fixed effect for the treatment group and a covariate of baseline LDL cholesterol was used to assess the primary efficacy parameter to obtain the values for the difference expressed as least-squares mean percent change in LDL cholesterol from baseline to day 84 between the treatment and comparator groups. Standard errors and the 95% CIs were calculated. Missing data were imputed for the co-primary efficacy and secondary endpoints analysis based on a pattern mixture model that uses a multiple imputation technique analysed with ANCOVA. Missing follow-up laboratory data were imputed from assigned treatment and baseline laboratory measurements. Each comparison within the co-primary endpoint family was conducted at a two-sided significance level of 0·05. Only if all four co-primary endpoint tests met criteria for statistical significance would the null hypothesis be rejected. If the null hypothesis was rejected for the co-primary endpoints, hypothesis testing was then allowed to proceed to the prespecified secondary endpoints for hierarchical step-down testing through similar ANCOVA analyses at a two-sided significance level of 0·05.

No multiplicity adjustments were applied to exploratory endpoints. Differences in changes in lipoprotein (a) from baseline to day 84 between groups were evaluated using a prespecified ANCOVA model with fixed effects for treatment group and the baseline lipoprotein (a) concentration as a continuous covariate. In a post-hoc analysis of this exploratory endpoint, differences in changes in lipoprotein (a) between groups was also evaluated by the non-parametric Hodges–Lehmann estimator. A post-hoc sensitivity analysis of the co-primary endpoints was performed after excluding participants who were not receiving statin therapy at baseline. Statistical analyses were performed using SAS version 9.4.

## Role of the funding source

The trial was designed by the sponsor, NewAmsterdam Pharma, in collaboration with the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) which is an academic research organisation, and an academic executive committee. A contract research organisation (Medpace) collected the data. At completion of the trial, the database was transferred to C5Research, where statisticians independently conducted the data analyses. The first author wrote the first draft of the manuscript, which was reviewed and approved by all the authors. The sponsor reviewed the manuscript and

| | Obicetrapib plus ezetimibe FDC (n=102) | Obicetrapib monotherapy (n=102) | Ezetimibe monotherapy (n=101) | Placebo (n=102) |
|---|---|---|---|---|
| Median age (IQR), years | 68·0 (63·0–72·0) | 67·0 (61·0–74·0) | 68·0 (64·0–73·0) | 67·5 (62·0–72·0) |
| Sex | | | | |
| Female | 48 (47%) | 33 (32%) | 45 (45%) | 51 (50%) |
| Male | 54 (53%) | 69 (68%) | 56 (55%) | 51 (50%) |
| Race | | | | |
| White | 86 (84%) | 85 (83%) | 82 (81%) | 84 (82%) |
| Black or African American | 14 (14%) | 15 (15%) | 13 (13%) | 17 (17%) |
| Asian | 1 (1%) | 0 | 3 (3%) | 1 (1%) |
| Unspecified or other | 1 (1%) | 0 | 2 (2%) | 0 |
| Ethnicity | | | | |
| Hispanic or Latino | 4 (4%) | 2 (2%) | 1 (1%) | 2 (2%) |
| Not Hispanic or Latino | 98 (96%) | 100 (98%) | 100 (99%) | 100 (98%) |
| Mean LDL cholesterol (SD), mmol/L | 2·5 (0·7) | 2·6 (0·9) | 2·5 (0·8) | 2·4 (0·7) |
| Mean non-HDL cholesterol (SD), mmol/L | 3·2 (1·0) | 3·3 (1·1) | 3·2 (1·1) | 3·0 (0·7) |
| Mean HDL cholesterol (SD), mmol/L | 1·2 (0·3) | 1·2 (0·4) | 1·3 (0·4) | 1·3 (0·4) |
| Mean apolipoprotein B (SD), mg/dL | 88·9 (23·0) | 90·6 (25·6) | 89·2 (24·9) | 85·3 (18·4) |
| Median triglycerides (IQR), mmol/L | 1·6 (1·1–1·9) | 1·4 (1·0–2·0) | 1·3 (0·9–1·9) | 1·3 (1·0–1·9) |
| Median lipoprotein (a) (IQR), nmol/L | 50·9 (13·8–199·8) | 33·7 (14·5–175·7) | 32·8 (8·1–154·8) | 48·3 (7·7–196·4) |
| Median hsCRP (IQR), mg/L | 2·3 (0·9–4·5) | 1·9 (1·1–3·2) | 1·3 (0·7–3·7) | 1·7 (0·8–4·6) |
| Lipid-lowering therapies | | | | |
| Statin | 91 (89%) | 87 (85%) | 93 (92%) | 93 (91%) |
| High-intensity statin | 75 (74%) | 66 (65%) | 71 (70%) | 75 (74%) |
| PCSK9 inhibitor | 6 (6%) | 1 (1%) | 3 (3%) | 6 (6%) |
| Bempedoic acid | 0 | 2 (2%) | 2 (2%) | 2 (2%) |
| No statin therapy due to intolerance | 11 (11%) | 16 (16%) | 7 (7%) | 9 (9%) |
| History of ASCVD | 72 (71%) | 76 (75%) | 67 (66%) | 65 (64%) |
| Coronary artery disease | 62 (61%) | 66 (65%) | 60 (59%) | 60 (59%) |
| Peripheral arterial disease | 4 (4%) | 7 (7%) | 7 (7%) | 4 (4%) |
| Cerebrovascular disease | 22 (22%) | 20 (20%) | 15 (15%) | 19 (19%) |
| HeFH | 7 (7%) | 5 (5%) | 6 (6%) | 12 (12%) |
| Diabetes | 49 (48%) | 52 (51%) | 49 (49%) | 49 (48%) |
| Hypertension | 84 (82%) | 82 (80%) | 86 (85%) | 85 (83%) |
| Current cigarette smoking | 15 (15%) | 13 (13%) | 12 (12%) | 16 (16%) |
| Family history of coronary heart disease* | 26 (25%) | 32 (31%) | 37 (37%) | 28 (27%) |

Data are n (%) unless otherwise indicated. The conversion factors between conventional units and SI units for LDL, HDL, and total cholesterol are 38·67 mg/dL = 1 mmol/L; and for triglycerides, 88·57 mg/dL = 1 mmol/L. ASCVD=atherosclerotic cardiovascular disease. FDC=fixed-dose combination. HeFH=heterozygous familial hypercholesterolaemia. hsCRP=high-sensitivity C-reactive protein. *Family history of coronary heart disease was defined as a first-degree relative with clinical coronary heart disease (males ≤55 years or females ≤65 years of age).

***Table 1:*** **Baseline characteristics**

provided suggested revisions, but the final decision on content was reserved for the academic authors with no restrictions on content or the right to publish.

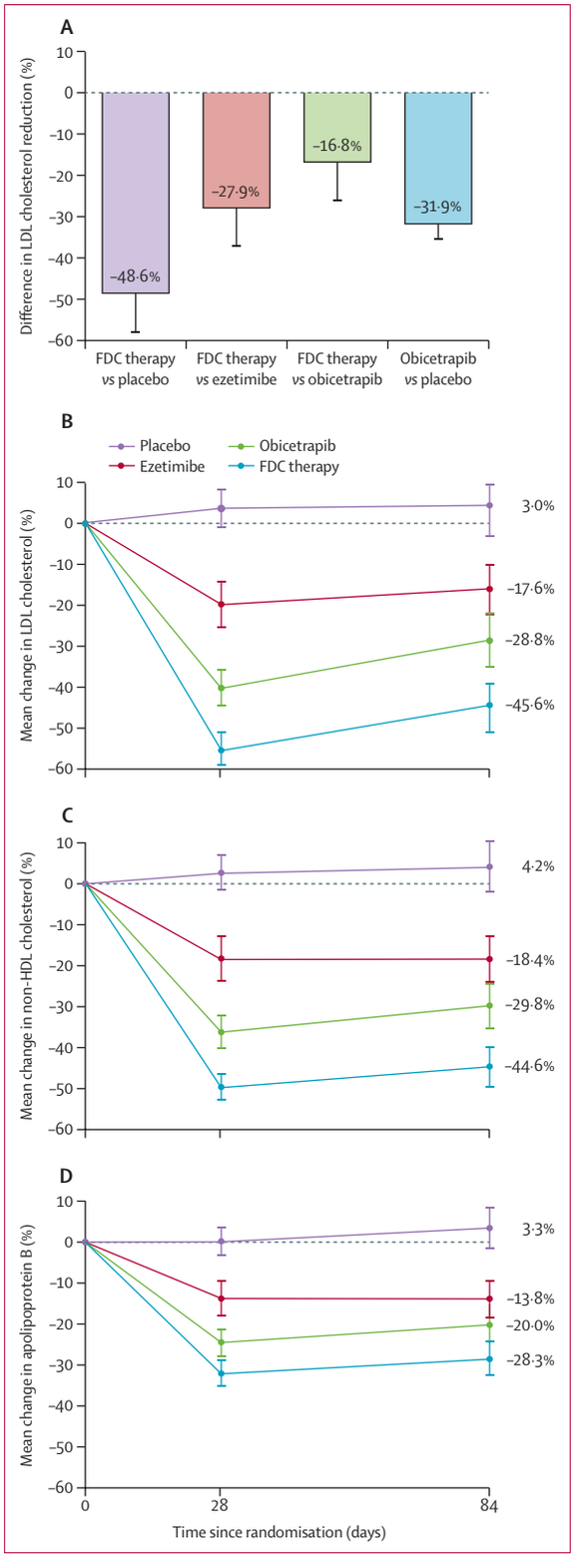


***Figure 2:*** **Co-primary and secondary endpoints**
(A) Co-primary endpoints—percent difference in LDL cholesterol reduction at day 84. Least-squares mean percent differences in the reduction of LDL cholesterol concentrations measured by preparative ultracentrifugation at day 84 following randomisation in the intention-to-treat population. An ANCOVA model with a fixed effect for the treatment group and a covariate of baseline LDL cholesterol was used to assess the primary efficacy parameter to obtain the values for the difference in least-squares mean percent change. The number of missing observations at day 84 were as follows: 3 in the FDC group, 5 in the obicetrapib monotherapy group, 5 in the ezetimibe monotherapy group, and 4 in the placebo group. (B) Change in LDL cholesterol over time. Mean percent change in LDL cholesterol concentrations from baseline during the 84 days following randomisation in the intention-to-treat population. The markers at day 28 represent the mean percent change as measured by the Martin–Hopkins estimation method. The markers at day 84 represent the least-squares mean percent change measured using beta quantification. An ANCOVA model with a fixed effect for the treatment group and a covariate of baseline LDL cholesterol was used to assess the primary efficacy parameter to obtain the values for the least-squares mean percent changes at day 84. The number of missing observations at day 84 were as follows: 3 in the FDC group, 5 in the obicetrapib monotherapy group, 5 in the ezetimibe monotherapy group, and 4 in the placebo group. (C) Change in non-HDL cholesterol over time. Mean percent change in non-HDL cholesterol concentrations from baseline during the 84 days following randomisation in the intention-to-treat population. The markers at day 28 and day 84 represent the mean percent change at each timepoint. The number of missing observations at day 84 were as follows: 3 in the FDC group, 5 in the obicetrapib monotherapy group, 5 in the ezetimibe monotherapy group, and 4 in the placebo group. (D) Change in apolipoprotein B over time. Mean percent change in apolipoprotein B concentrations from baseline during the 84 days following randomisation in the intention-to-treat population. The markers at day 28 and day 84 represent the mean percent change at each timepoint. The number of missing observations at day 84 were as follows: 3 in the FDC group, 6 in the obicetrapib monotherapy group, 5 in the ezetimibe monotherapy group, and 4 in the placebo group. In all panels, the error bars represent the 95% CIs. FDC=fixed-dose combination of obicetrapib and ezetimibe.

## Results

Between March 4 and July 3, 2024, 407 participants were randomly assigned (figure 1). Of 716 individuals who were screened, a total of 309 were excluded (the most common reason was an LDL cholesterol concentration below 1·8 mmol/L at screening). Random assignment and treatment of the 407 participants took place between March 4, 2024 (first participant, first visit) and Oct 16, 2024 (last participant, last visit); 102 were assigned to obicetrapib plus ezetimibe FDC, 102 assigned to obicetrapib monotherapy, 101 assigned to ezetimibe monotherapy, and 102 assigned to placebo. All intention-to-treat and safety analyses were performed on this full set of 407 participants. Among the 407 participants, 398 (98%) completed the study, with 372 (91%) still taking the assigned treatment at trial completion. The mean time on treatment was 75·1 days (SD 22·3), and median was 84 days (IQR 78–86).

The baseline characteristics were generally similar across the four groups (table 1). The median age of participants was 68·0 years (IQR 62·0–73·0), 79 (19%) were at least 75 years of age, 177 (43%) were female, 337 (83%) were White, and 59 (14%) were Black or African American. At baseline, 364 (89%) participants were receiving statin therapy, with 287 (71%) receiving

high-intensity statin therapy, and 16 (4%) were receiving PCSK9 inhibition. A total of 280 (69%) participants had a history of ASCVD and 30 (7%) had HeFH. No participants had a genetically confirmed diagnosis of HeFH. A total of 11 (3%) participants had Dutch Lipid Clinic Network scores of 3 or higher.

For all participants at baseline, the mean LDL cholesterol was 2·5 mmol/L (96·4 mg/dL; SD 0·8 mmol/L), the mean non-HDL cholesterol was 3·2 mmol/L (122·2 mg/dL; SD 1·0 mmol/L), the mean apolipoprotein B was 88·5 mg/dL (SD 23·2 mg/dL), the mean HDL cholesterol was 1·3 mmol/L (49 mg/dL; SD 0·4 mmol/L), the median triglyceride was 1·6 mmol/L (123·0 mg/dL, IQR 1·0–1·9 mmol/L), and the median lipoprotein (a) was 38·6 nmol/L (IQR 10·0–187·2).

Data regarding the co-primary efficacy endpoints are shown in figure 2 and table 2. At day 84, the difference in the reduction of LDL cholesterol concentrations in the obicetrapib–ezetimibe FDC group was –48·6% (95% CI –58·3 to –38·9, p<0·0001) compared with the placebo treatment group, –27·9% (–37·5 to –18·4, p<0·0001) compared with the ezetimibe monotherapy group, and –16·8% (–26·4 to –7·1, p=0·0007) compared with the obicetrapib monotherapy group. The placebo-adjusted LDL cholesterol reduction in the obicetrapib monotherapy group was –31·9% (–41·6 to –22·1, p<0·0001). The null hypothesis was rejected for the co-primary endpoints. A post-hoc sensitivity analysis of the co-primary endpoints after excluding participants who were not on statin therapy at baseline showed similar treatment effect sizes (appendix p 8).

Absolute changes in LDL cholesterol from baseline to day 84 are outlined in table 2. From baseline to day 84, there was an observed change of –1·2 mmol/L (95% CI –1·3 to –1·0) in the obicetrapib–ezetimibe FDC group, –0·9 mmol/L (–1·0 to –0·7) in the obicetrapib monotherapy group, –0·5 mmol/L (–0·7 to –0·3) in the ezetimibe monotherapy group, and 0·05 mmol/L (–0·1 to 0·2) in the placebo group. The percent changes in LDL cholesterol over time from baseline to day 84 among the four treatment groups are displayed graphically in figure 2, with maximal LDL cholesterol reduction observed by day 28. Figure 3 shows the waterfall plots demonstrating the percent changes in LDL cholesterol in individual participants from baseline to day 84.

Prespecified hierarchical secondary endpoints are reported in table 2. At day 84, in the FDC group compared with the placebo group, the difference in the reduction of non-HDL cholesterol concentrations was –45·1% (95% CI –53·4 to –36·8) and the difference in the reduction of apolipoprotein B concentrations was –29·2% (–36·0 to –22·4). In the obicetrapib monotherapy group compared with the placebo group, the difference in the reduction of non-HDL cholesterol concentrations was –29·9% (–38·3 to –21·5), and the difference in the reduction of apolipoprotein B concentrations was –19·8% (–26·7 to –12·8). In the FDC group compared with the ezetimibe monotherapy group, the difference in the reduction of non-HDL cholesterol concentrations was –25·4% (–33·7 to –17·2), and the difference in the reduction of apolipoprotein B concentrations was –14·2% (–21·1 to –7·4). In the FDC group compared with the obicetrapib monotherapy group, the difference in the reduction of non-HDL cholesterol concentrations was –15·2% (–23·5 to –6·9), and the difference in the reduction

| | Obicetrapib plus ezetimibe FDC (n=102) | Obicetrapib monotherapy (n=102) | Ezetimibe monotherapy (n=101) | Placebo (n=102) |
|---|---|---|---|---|
| **Primary endpoint: least-squares mean percent difference in LDL cholesterol reduction (95% CI)** | | | | |
| Obicetrapib plus ezetimibe FDC | NA | –16·8 (–26·4 to –7·1) | –27·9 (–37·5 to –18·4) | –48·6 (–58·3 to –38·9) |
| Obicetrapib monotherapy | NA | NA | NA | –31·9 (–41·6 to –22·1) |
| **Secondary endpoints** | | | | |
| Least-squares mean percent difference in non-HDL cholesterol reduction (95% CI) | | | | |
| Obicetrapib plus ezetimibe FDC | NA | –15·2 (–23·5 to –6·9) | –25·4 (–33·7 to –17·2) | –45·1 (–53·4 to –36·8) |
| Obicetrapib monotherapy | NA | NA | NA | –29·9 (–38·3 to –21·5) |
| Least-squares mean percent difference in apolipoprotein B reduction (95% CI) | | | | |
| Obicetrapib plus ezetimibe FDC | NA | –9·4 (–16·3 to –2·6) | –14·2 (–21·1 to –7·4) | –29·2 (–36·0 to –22·4) |
| Obicetrapib monotherapy | NA | NA | NA | –19·8 (–26·7 to –12·8) |
| Observed values for LDL cholesterol, mean (95% CI), mmol/L | | | | |
| Baseline | 2·5 (2·3 to 2·6) | 2·6 (2·4 to 2·8) | 2·5 (2·4 to 2·7) | 2·4 (2·2 to 2·5) |
| Day 84* | 1·3 (1·1 to 1·5) | 1·7 (1·5 to 1·9) | 2·0 (1·8 to 2·2) | 2·5 (2·3 to 2·6) |
| Observed difference at day 84* | –1·2 (–1·3 to –1·0) | –0·9 (–1·0 to –0·7) | –0·5 (–0·7 to –0·3) | 0·05 (–0·1 to 0·2) |

FDC=fixed-dose combination. NA=not applicable. The conversion factor between conventional units and SI units for LDL is 38·67 mg/dL = 1 mmol/L. *Day 84 values and observed differences were calculated among patients with non-missing LDL cholesterol data at baseline and day 84, namely 99 patients in the obicetrapib plus ezetimibe FDC group, 97 patients in the obicetrapib monotherapy group, 96 patients in the ezetimibe monotherapy group, and 96 patients in the placebo group.

***Table 2:*** **Efficacy endpoints in the intention-to-treat population**

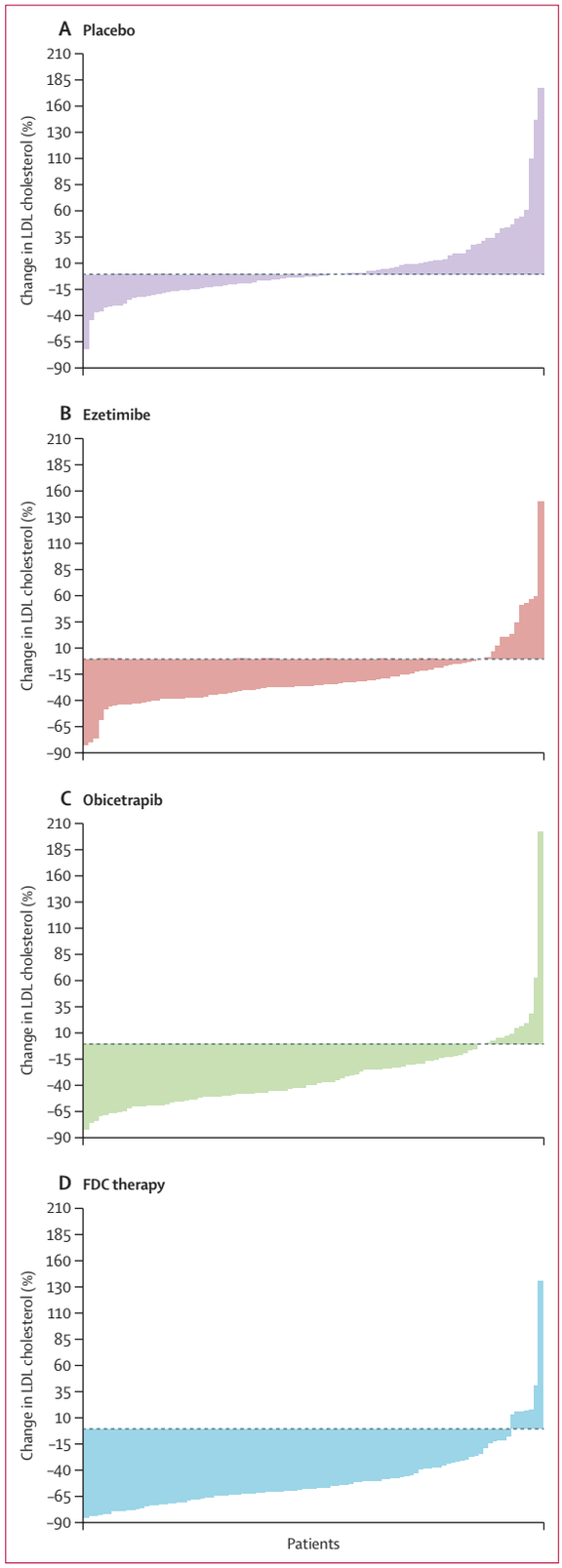


***Figure 3*: Waterfall plots showing the distribution of individual LDL cholesterol responses in the treatment groups**

Each vertical bar represents the percent change in LDL cholesterol measured by preparative ultracentrifugation for an individual patient in the treatment group from baseline to day 84 following randomisation in the intention-to-treat population. FDC=fixed-dose combination of obicetrapib and ezetimibe.

of apolipoprotein B concentrations was –9·4% (–16·3 to –2·6). Percent changes in non-HDL cholesterol and apolipoprotein B concentrations over time are depicted in figure 2, with maximal reductions from baseline at day 84 observed in the obicetrapib–ezetimibe FDC group.

At the end of the follow-up period, among participants with non-missing LDL cholesterol data at day 84, 70 (71%) of 99 participants in the FDC group had an LDL cholesterol concentration below 1·4 mmol/L, compared with 40 (41%) of 97 in the obicetrapib monotherapy group, 24 (25%) of 96 in the ezetimibe monotherapy group, and seven (7%) of 98 in the placebo group (appendix p 7).

Effects on lipoprotein (a), an exploratory endpoint, are reported in the appendix (pp 4–5). Compared with placebo, treatment with obicetrapib–ezetimibe FDC for 84 days resulted in a least-squares mean percent change of –62·9% (95% CI –140·6 to 14·8), and treatment with obicetrapib monotherapy resulted in a least-squares mean percent change of –56·2% (–133·8 to 21·5) at day 84.

From baseline to day 84, HDL cholesterol, an exploratory endpoint, changed by 127·6% (95% CI 115·5 to 139·6) in the obicetrapib–ezetimibe FDC group, 137·5% (123·1 to 151·9) in the obicetrapib monotherapy group, 1·1% (95% CI –2·1 to 4·3) in the ezetimibe group, and –0·9% (–3·8 to 2·1) in the placebo group (appendix p 6).

Adverse events are reported in table 3. The incidence of any adverse event was lowest in the placebo group (38 [37%] of 102) and generally similar between the obicetrapib–ezetimibe FDC (52 [51%] of 102), obicetrapib monotherapy (55 [54%] of 102), and ezetimibe monotherapy (54 [53%] of 101) groups. The incidences of serious adverse events, trial agent-related adverse events, and adverse events leading to discontinuation of the trial agent were broadly similar between the FDC group and the other three groups. The incidences of investigator-reported prespecified events or laboratory findings of special interest, including elevations in hepatic enzyme concentrations, elevation in creatine kinase concentrations, new-onset diabetes or worsening glycaemic control, changes in dosing of or initiation of antihypertensive medications due to changes in blood pressure, and decrease in renal function from baseline were also broadly similar in the FDC group versus the other three groups. From baseline to day 84, in the obicetrapib–ezetimibe FDC treatment group, systolic blood pressure changed by a mean of –0·8 mm Hg (SD 13·2) and diastolic blood pressure changed by –1·4 mm Hg (7·6). In the placebo group, systolic blood pressure changed by 0 mm Hg (13·6) and diastolic blood pressure changed by 0·2 mm Hg (7·5).

## Discussion

Among participants with pre-existing or high risk for ASCVD or HeFH whose LDL cholesterol concentration was 1·8 mmol/L or higher while receiving maximally

| | Obicetrapib plus ezetimibe FDC (n=102) | Obicetrapib monotherapy (n=102) | Ezetimibe monotherapy (n=101) | Placebo (n=102) |
|---|---|---|---|---|
| Any adverse event | 52 (51%) | 55 (54%) | 54 (53%) | 38 (37%) |
| Trial agent-related adverse event | 3 (3%) | 7 (7%) | 3 (3%) | 4 (4%) |
| Adverse event leading to discontinuation of trial agent | 5 (5%) | 9 (9%) | 7 (7%) | 4 (4%) |
| Death | 1 (1%) | 1 (1%) | 1 (1%) | 0 |
| Cardiogenic and septic shock | 0 | 0 | 1 (1%) | 0 |
| Metastatic cancer | 0 | 1 (1%) | 0 | 0 |
| Shock | 1 (1%) | 0 | 0 | 0 |
| Serious adverse event | 3 (3%) | 6 (6%) | 7 (7%) | 4 (4%) |
| Cardiac disorders* | 1 (1%) | 1 (1%) | 3 (3%) | 1 (1%) |
| Infections† | 0 | 2 (2%) | 2 (2%) | 0 |
| Nervous system disorders‡ | 0 | 3 (3%) | 1 (1%) | 0 |
| Respiratory, thoracic, and mediastinal disorders§ | 1 (1%) | 1 (1%) | 2 (2%) | 0 |
| Gastrointestinal disorders | 0 | 0 | 3 (3%) | 0 |
| Hepatobiliary disorders | 0 | 1 (1%) | 1 (1%) | 0 |
| Neoplasms | 0 | 1 (1%) | 0 | 1 (1%) |
| Vascular disorders¶ | 1 (1%) | 0 | 0 | 1 (1%) |
| Thrombocytopenia | 0 | 1 (1%) | 0 | 0 |
| Chest pain | 1 (1%) | 0 | 0 | 0 |
| Dehydration | 0 | 1 (1%) | 0 | 0 |
| Accidents | 0 | 0 | 0 | 1 (1%) |
| Osteoarthritis | 1 (1%) | 0 | 0 | 0 |
| Acute kidney injury | 1 (1%) | 0 | 0 | 0 |
| Prespecified events or laboratory findings of special interest | | | | |
| AST or ALT >3 × ULN | 0 | 2 (2%) | 1 (1%) | 0 |
| Total bilirubin >2 × ULN | 0 | 0 | 0 | 0 |
| Creatine kinase >5 × ULN | 1 (1%) | 1 (1%) | 0 | 0 |
| New-onset diabetes or worsening of glycaemic control‖ | 31 (30%) | 28 (27%) | 42 (42%) | 31 (30%) |
| Changes to or initiation of antihypertensive medications due to changes in blood pressure** | 5 (5%) | 4 (4%) | 0 | 2 (2%) |
| Decrease of renal function from baseline†† | 7 (7%) | 5 (5%) | 6 (6%) | 5 (5%) |
| Macular degeneration | 0 | 0 | 0 | 0 |
| Other adverse events and changes in vital signs | | | | |
| Arthralgia | 2 (2%) | 7 (7%) | 5 (5%) | 3 (3%) |
| Upper respiratory tract infection | 4 (4%) | 4 (4%) | 3 (3%) | 3 (3%) |
| Diarrhoea | 5 (5%) | 3 (3%) | 2 (2%) | 0 |
| Fatigue | 4 (4%) | 5 (5%) | 0 | 1 (1%) |
| Headache | 1 (1%) | 6 (6%) | 1 (1%) | 2 (2%) |
| Hypokalaemia | 0 | 0 | 4 (4%) | 1 (1%) |
| Change in systolic blood pressure from baseline to day 84, mm Hg | –0·8 (13·2) | 1·8 (12·7) | 0·7 (12·6) | 0 (13·6) |
| Change in diastolic blood pressure from baseline to day 84, mm Hg | –1·4 (7·6) | 0·2 (7·2) | –0·9 (6·9) | 0·2 (7·5) |
| Increase in blood pressure‡‡ | 2 (2%) | 0 | 1 (1%) | 0 |

Data are n (%) or mean (SD). ALT=alanine aminotransferase. AST=aspartate aminotransferase. FDC=fixed-dose combination. ULN=upper limit of normal. *Includes reported events of angina, acute myocardial infarction, atrial fibrillation, cardiomyopathy, congestive heart failure, and cardiogenic shock. †Includes reported events of appendicitis, pneumonia, urinary tract infection, and septic shock. ‡Includes reported events of stroke, cerebrovascular accident, transient ischaemic attack, and metabolic encephalopathy. §Includes reported events of acute respiratory failure, chronic obstructive pulmonary disease, and hypoxia. ¶Includes reported events of arterial haemorrhage, hypertension, and shock. ||Defined as one or more of the following criteria: adverse events indicating new type 1 or type 2 diabetes, initiation of anti-diabetes medication with confirmation of the diagnosis of diabetes by blinded external review, $HbA_{1c}$ ≥6·5%, or two consecutive values of fasting plasma glucose ≥7·0 mmol/L (≥126 mg/dL). **Defined as changes in antihypertensive medications due to changes in blood pressure in participants receiving antihypertensive medication(s) at baseline, and new antihypertensive medication prescriptions in participants not previously treated for hypertension. ††Defined as a >25% decrease in estimated glomerular filtration rate (eGFR) from baseline, or an eGFR <30 mL/min/1·73 $m^2$ calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, or an increase in serum creatinine of ≥0·3 mg/dL (≥26·5 µmol/L) from baseline. ‡‡Investigator-reported.

***Table 3:*** **Adverse events and safety-related laboratory findings in the safety population**

tolerated lipid-lowering therapies (excluding ezetimibe) at baseline, an orally administered FDC of obicetrapib and ezetimibe reduced LDL cholesterol concentrations by 48·6% compared with placebo. Approximately 70% of participants were receiving high-intensity statin therapy at baseline. The effects of the obicetrapib–ezetimibe FDC were rapid, reaching a maximal effect within 28 days which was maintained to 84 days following initiation of treatment, with an absolute LDL cholesterol reduction of 1·2 mmol/L from baseline. Hierarchical testing of prespecified secondary endpoints demonstrated significant placebo-adjusted reduction of non-HDL cholesterol and apolipoprotein B concentrations with administration of obicetrapib with ezetimibe. The FDC was not associated with increased adverse effects as compared with ezetimibe monotherapy or obicetrapib monotherapy. Serious adverse events, adverse events leading to discontinuation of the trial agent, and prespecified events or laboratory findings of special interest were not meaningfully different between the FDC, obicetrapib monotherapy, and ezetimibe monotherapy treatment groups.

There is a major unmet medical need for additional oral therapies to reduce atherogenic lipoproteins in patients at high risk for ASCVD events. Attainment of LDL cholesterol goals remains low in many patients globally despite the availability of low-cost statins and multiple non-statin therapies, including injectable PCSK9 inhibitors.[10,20–22] Perceived adverse effects with statins, limited LDL cholesterol-lowering efficacy of oral therapies beyond statins, patient hesitation regarding injectable lipid-lowering therapies, and variable insurance coverage for parenteral medications contribute to low use of lipid-lowering therapies and suboptimal LDL cholesterol reduction.[11,12,23] The nearly 50% additive LDL cholesterol lowering with once-daily administration of the FDC of obicetrapib and ezetimibe over 84 days could provide a useful option as an addition to statin therapy for patients with pre-existing or high risk for ASCVD with a suboptimal response or intolerance to existing therapies. The FDC achieved significant LDL cholesterol reduction compared with obicetrapib or ezetimibe monotherapy without additional safety concerns, which supports the approach of using initial combination therapy for LDL cholesterol lowering rather than the traditional approach of initiating and intensifying monotherapy over time.

Four previous attempts have sought to develop CETP inhibitors to treat ASCVD, but none have been successful in achieving regulatory approval.[13–16] The mechanism of action of CETP inhibitors and genetic observations resulted in considerable interest in developing this class of drugs.[24,25] CETP facilitates the transfer of cholesteryl esters from HDL particles to non-HDL lipoproteins including VLDL and LDL particles.[24] Genetic deficiency of CETP has been associated with lower LDL cholesterol and a lower risk of coronary heart disease, suggesting potential impact on the metabolism of apolipoprotein B-containing lipoproteins, leading to a less atherogenic lipid profile.[25] The initial efforts to develop CETP inhibitors focused on the ability of this class of drugs to raise concentrations of HDL cholesterol, although varying reductions in LDL cholesterol were observed across different drugs.

In the first phase 3 cardiovascular outcome trial of a CETP inhibitor, treatment with torcetrapib increased morbidity and mortality, most likely as a consequence of off-target toxicity attributed to an aldosterone-like effect with an increase in systolic blood pressure of 5·4 mm Hg.[15] In the present trial, an increase in blood pressure was not observed. The mean change from baseline in systolic blood pressure in the obicetrapib–ezetimibe FDC treatment group was –0·8 mm Hg, and the mean change in diastolic blood pressure was –1·4 mm Hg. A large cardiovascular outcome trial studying dalcetrapib, a relatively weak CETP inhibitor, did not reduce cardiovascular events but the effect on HDL cholesterol was moderate (31–40% increase from baseline) and there was minimal effect on LDL cholesterol concentrations.[16] A trial of evacetrapib reported an LDL cholesterol reduction of 31·1% but a smaller reduction in apolipoprotein B (15·5%) and no reduction in cardiovascular events.[14] A trial of anacetrapib showed a mean LDL cholesterol reduction of only 17% measured by beta quantification after ultracentrifugation (the primary measurement method used in the present trial) and a small, but significant, reduction in cardiovascular events compared with placebo (rate ratio 0·91, 95% CI 0·85 to 0·97).[13]

In the present trial, the magnitude of percent LDL cholesterol reduction with obicetrapib–ezetimibe FDC was comparable to the effects of a high-intensity statin. More than 70% of participants receiving the FDC had an LDL cholesterol concentration below 1·4 mmol/L at day 84, with a mean absolute reduction in LDL cholesterol concentration of approximately 1·2 mmol/L. However, the observed reduction of 29% in apolipoprotein B with the FDC as compared with placebo is less than typically observed with a high-intensity statin and is more comparable to a moderate-intensity statin. The observed percent reduction in non-HDL cholesterol was comparable to that of high-intensity statin therapy.[26,27] The placebo-adjusted LDL cholesterol reduction observed with obicetrapib monotherapy (31·9%) in the present trial was greater than observed in phase 3 data of other contemporary oral non-statin therapies, including ezetimibe monotherapy (around 20%) and bempedoic acid monotherapy (around 22%).[5,8] The nearly 50% placebo-adjusted LDL cholesterol reduction observed with obicetrapib–ezetimibe FDC is slightly lower than that observed with PCSK9 inhibitors.[6,7] Compared with the phase 2 ROSE2 study, the present phase 3 TANDEM trial is larger, includes patients with pre-existing or high risk for ASCVD including HeFH,

and used a primary intention-to-treat analysis, which might explain the observed differences in LDL cholesterol reduction between TANDEM and previous studies including ROSE2 and a recently published meta-analysis evaluating obicetrapib.[18,28]

Clinical trials of intensive LDL cholesterol reduction to low absolute concentrations have shown consistent associations with reduction in adverse ASCVD outcomes. In the IMPROVE-IT trial of patients with recent acute coronary syndrome, the addition of ezetimibe (an oral lipid-lowering medication with generally modest efficacy) to statin therapy incrementally lowered LDL cholesterol concentrations to a median of 1·4 mmol/L (53·7 mg/dL) and led to an improvement in cardiovascular outcomes.[5] Long-term follow-up data from placebo-controlled randomised trials of PCSK9 inhibitors demonstrated the consistent association between the achievement of very low absolute LDL cholesterol concentrations and reduction in adverse ASCVD events.[29,30] In a clinical trial using intravascular ultrasound to evaluate atherosclerotic plaque burden, intensive reduction of LDL cholesterol concentrations (to an average of 1·6 mmol/L [60·8 mg/dL]) using high-intensity statin therapy led to significant regression of atherosclerosis.[31] The 2019 European Society of Cardiology/European Atherosclerosis Society dyslipidaemia guidelines recommend an LDL cholesterol treatment goal of less than 1·4 mmol/L for primary and secondary prevention in patients at very high cardiovascular risk.[2] Therefore, the magnitude of LDL cholesterol reduction observed with the FDC of obicetrapib and ezetimibe, with more than 70% of participants achieving absolute LDL cholesterol concentrations below 1·4 mmol/L at day 84, might allow this medication to contribute to cardiovascular prevention. While LDL cholesterol remains the primary target of lipid-lowering therapies to reduce cardiovascular risk, data indicate the totality of apolipoprotein B-containing particles is a better predictor of risk as compared with LDL cholesterol.[32] A large cardiovascular outcome trial is currently fully enrolled and will ultimately answer the critical question of whether the favourable changes in LDL cholesterol and apolipoprotein B concentrations with obicetrapib treatment will translate into a reduction of major adverse cardiovascular events.[33]

Effect on lipoprotein (a) concentrations was an exploratory endpoint and is reported in this study. However, the relatively low levels and skewed distribution of lipoprotein (a) concentrations might impact the interpretation of the results. To fully evaluate the effects of obicetrapib on lipoprotein (a) concentrations, participants with high baseline concentrations will need to be evaluated in future studies.

The trial has several limitations. First, most participants were White; however, the trial enrolled 14% Black or African American participants as well as 43% women, who have traditionally been under-represented in clinical trials. Second, the follow-up period was only 84 days, which potentially limits the study's ability to detect long-term efficacy, tolerability, or safety events. However, ezetimibe has been previously studied in a long-term cardiovascular outcome trial without evidence of additional safety or tolerability issues, and a long-term, large cardiovascular outcome trial of obicetrapib is already underway.[5,33] There was a small observed diminishing of LDL cholesterol reduction from 28 days to 84 days in the obicetrapib–ezetimibe and obicetrapib monotherapy groups, and to a lesser degree in the ezetimibe monotherapy group. LDL cholesterol reduction remained statistically significant at both timepoints. Difficulty with sustained adherence to the trial regimen (three pills daily) might have contributed to these trends. Long-term efficacy data from the ongoing cardiovascular outcome study of obicetrapib should clarify this issue.[33]

In this randomised, double-blind, phase 3 trial involving participants with pre-existing or high risk for ASCVD whose LDL cholesterol was 1·8 mmol/L or greater despite receiving maximally tolerated lipid-lowering therapies at baseline (excluding ezetimibe), treatment with oral FDC therapy of obicetrapib and ezetimibe for 84 days was well tolerated and reduced LDL cholesterol by nearly 50%, with achievement of LDL cholesterol concentrations below 1·4 mmol/L in more than 70% of participants. Combination therapy with obicetrapib and ezetimibe offers the potential to substantially reduce LDL cholesterol in this high-risk population.

#### Contributors

NewAmsterdam Pharma (ASt, DK, ALN, JK, MDa, MDi) helped design the study in collaboration with the academic investigators. DB was the trial statistician. ASa, DB, and SEN had access to the full set of raw data and accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors contributed to the interpretation of results. ASa wrote the first draft of the manuscript. The manuscript was critically reviewed, revised, and approved by all authors.

#### Declaration of interests

ASt, DK, ALN, JK, MDa, and MDi are employees of NewAmsterdam Pharma. ASt, DK, ALN, MDa, and MDi report stock ownership in NewAmsterdam Pharma. ASa and DB report funding paid to their institution from NewAmsterdam Pharma. DM, KH, and GT report funding and travel support paid to their institution from NewAmsterdam Pharma. SEN reports funding paid to his institution from NewAmsterdam Pharma, AstraZeneca, and Crispr Therapeutics. ACG reports support from NewAmsterdam Pharma; funding to her institution from Novartis, Arrowhead, Roegeneron, Ionis, Esperion, Sanofi, and 89bio; consulting fees from Piper; honoraria from Medscape, National Lipid Association (NLA), Preventive Cardiology Nurses Association, and Ionis; travel support from NLA, 89bio, and the Global CardioVascular Clinical Trialists Forum; and other financial or non-financial interests from Novartis, Amgen, Arrowhead, Esperion, NewAmsterdam Pharma, and NLA. EDM reports consulting fees from Amgen, Arrowhead, Boehringer Ingelheim, Bayer, Esperion, Edwards Lifesciences, Ionis, Merck, Medtronic, NewAmsterdam Pharma, Novartis, Novo Nordisk, Eli Lilly, Pfizer, and Zoll. SJN reports grants from AstraZeneca, NewAmsterdam Pharma, Amgen, Anthera, Cyclarity, Eli Lilly, Esperion, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraReDx, Roche, Sanofi-Regeneron, and LipoScience; and consulting fees from Abcentra, AstraZeneca, Amarin, Akcea, Eli Lilly, Anthera, Omthera, Merck, Takeda, Resverlogix, Sanofi-Regeneron, CSL Behring, Esperion, Boehringer Ingelheim, Daiichi Sankyo, Silence Therapeutics, CSL Seqirus, and Vaxxinity. DKM reports consulting fees

from Novo Nordisk, AstraZeneca, Pfizer, Bayer, Lexicon, Lilly USA, Boehringer Ingelheim, NewAmsterdam Pharma, Amgen, Neurotronics, Metsera Pharma, Kailera, Zealand, and Alveus Pharma.

### Data sharing

There is no plan to share individual participant data due to limitations of patient consent.

### Acknowledgments

Study funding was provided by NewAmsterdam Pharma.

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## Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Sarraju A, Brennan D, Hayden K, et al. Fixed-dose combination of obicetrapib and ezetimibe for LDL cholesterol reduction (TANDEM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2025; published online May 7. https://doi.org/10.1016/S0140-6736(25)00721-4

**Appendix**

**Table of contents.**

**Table 1. List of study investigators and sites**

| Investigator | Institution | Location | Number of Participants Recruited |
|---|---|---|---|
| Keung Lee | Triad Internal Medicine | Asheboro, NC, USA | 37 |
| Kathryn Jean Lucas | Lucas Research, Inc. | Morehead City, NC, USA | 35 |
| Angela Ritter | Center for Advanced Research and Education | Gainesville, GA, USA | 34 |
| Scott Rigby | Summit Research Group, LLC | Stow, OH, USA | 30 |
| Earl Martin | DM Clinical Research | Houston, TX, USA | 27 |
| Venkatesh Nadar | Capital Area Research | Newport, PA, USA | 17 |
| Traci Turner | Metabolic and Atherosclerosis Research Center | Cincinnati, OH, USA | 16 |
| Alexander White | Progressive Medical Research | Port Orange, FL, USA | 15 |
| Zahid Zafar | Wellness Clinical Research Associates | McKinney, TX, USA | 14 |
| Bram Wieskopf | North Georgia Clinical Research | Woodstock, GA, USA | 11 |
| Joshua Macomber | Cary Research Group, LLC | Cary, NC, USA | 11 |
| Stephan Jannach | Spectrum Medical, Inc. | Danville, VA, USA | 11 |
| George Kichura | St. Louis Heart and Vascular Cardiology | Sanit Louis, MO, USA | 10 |
| Rajesh Pradhan | Monument Health Clinical Research, a department of Monument Health Rapid City Hospital, Inc | Rapid City, SD, USA | 9 |
| Sharath Subramanian | CentraCare Heart & Vascular Center | Saint Cloud, MN, USA | 8 |
| James Roberts | Novant Health Heart and Vascular Institute | Charlotte, NC, USA | 8 |
| Jay Sandberg | Oakland Medical Research Center | Troy, MI, USA | 8 |
| Joaquin Martinez-Arraras | Amarillo Heart Clinical Research Institute, Inc. | Amarillo, TX, USA | 7 |
| Randall Miller | Horizon Research Group of Opelousas | Eunice, LA, USA | 6 |
| Raymond Plack, Jr. | Maryland Cardiovascular Specialists | Baltimore, MD, USA | 6 |
| Mitzie Hewitt | Northern Pines Health Center | Buckley, MI, USA | 6 |
| Eugene Ryan | Chattanooga Research & Medicine, PLLC | Chattanooga, TN, USA | 6 |
| Michael Koren | Jacksonville Center for Clinical Research | Jacksonville, FL, USA | 6 |
| Jeffrey Geohas | Evanston Premier Healthcare Research LLC | Skokie, IL, USA | 5 |
| David Brabham | PharmaTex Research, LLC | Amarillo, TX, USA | 5 |
| Charles Treasure II | Cardiovascular Research of Knoxville | Powell, TN, USA | 5 |
| Christie Ballantyne | Baylor College of Medicine | Houston, TX, USA | 4 |
| Shamaila Aslam | Northwest Houston Heart Center | Tomball, TX, USA | 4 |

| | | | |
|---|---|---|---|
| Anjanette Tan | Diabetes and Thyroid Center of Fort Worth | Fort Worth, TX, USA | 4 |
| Siddharth Gandhi | McClaren Bay Heart and Vascular | Bay City, MI, USA | 4 |
| Barry Bertolet | North Mississippi Medical Center | Tupelo, MS, USA | 4 |
| Vinod Namana | Cardiovascular Research of Northwest Indiana, LLC | Munster, IN, USA | 4 |
| Brian Webster | Wilmington Health Associates | Wilmington, NC, USA | 4 |
| Steven Leichter | Centricity Research - Columbus | Columbus, GA, USA | 3 |
| Rocio Harbison | Juno Research, LLC – Medical Center Office | Houston, TX, USA | 3 |
| Steven Hearne | TidalHealth Peninsula Regional, Inc. | Salisbury, MD, USA | 3 |
| William Cromwell | Novant Health Clinical Research, LLC | Charlotte, NC, USA | 3 |
| Narendra Singh | NSC Research | Johns Creek, GA, USA | 3 |
| Travis Taylor | South Texas Clinical Research | Corpus Christi, TX, USA | 3 |
| Justin Mansfield | Alpine Research Organization, Inc. | Clinton, UT, USA | 2 |
| William Eaves | Grace Research, LLC – Bossier City, LA | Bossier City, LA, USA | 2 |
| David Strobl | Sparrow Clinical Research Institute | Lansing, MI, USA | 1 |
| Jeremiah Stitham | Washington University in St. Louis | Saint Louis, MO, USA | 1 |
| Samir Abdelshaheed | Hampton Roads Center for Clinical Research | Suffolk, VA, USA | 1 |
| Devendra Wadwekar | East Valley Diabetes & Endocrinology | Gilbert, AZ, USA | 1 |
| Damaris Vega | Juno Research, LLC | Houston, TX, USA | 0 |
| Glenn Gould | Burke Primary Care | Morganton, NC, USA | 0 |
| Phillip Toth | Midwest Institute for Clinical Research | Indianapolis, IN, USA | 0 |

**Table 2. Effects on lipoprotein (a) levels (intention-to-treat population).**

| Outcome | Obicetrapib Plus Ezetimibe (N=102) | Obicetrapib (N=102) | Ezetimibe (N=101) | Placebo (N=102) |
|---|---|---|---|---|
| Mean lipoprotein (a) level at baseline (95% CI) – nmol/L | 108·3 (84·3 to 132·2) | 115·7 (86·6 to 144·8) | 94·3 (69·5 to 119·0) | 102·5 (102·5 to 115·9) |
| Median lipoprotein (a) level at baseline (IQR) – nmol/L | 50·9 (13·8 to 199·8) | 33·7 (14·5, 175·7) | 32·8 (8·1, 154·8) | 48·3 (7·7, 196·4) |
| **Day 84[a]** | **N=99** | **N=96** | **N=96** | **N=96** |
| Mean lipoprotein (a) at Day 84 (95% CI) – nmol/L | 91·2 (68·2 to 114·2) | 95·0 (64·5 to 135·5) | 91·3 (66·6 to 115·9) | 104·4 (80·4 to 128·5) |
| Median lipoprotein (a) at Day 84 (IQR) – nmol/L | 20·6 (5·6 to 191·4) | 15·0 (5·5 to 155·9) | 34·8 (6·8 to 136·5) | 49·3 (8·2 to 182·7) |
| Mean change in lipoprotein (a) from baseline to Day 84 (95% CI) – nmol/L | -17·3 (-24·9 to -9·7) | -18·0 (-27·1 to -8·9) | 2·3 (-3·4 to 8·0) | 2·7 (-1·1 to 6·5) |
| Mean percent change in lipoprotein (a) from baseline to Day 84 (95% CI) | -28·8 (-35·6 to -22·1) | -34.3 (-41·9 to -26·7) | 7.1 (-0·2 to 14·4) | 5.3 (-1·7 to 12·3) |
| Median change in lipoprotein (a) levels from baseline to Day 84 (IQR) – nmol/L | -7·6 (-26·9 to -1·2) | -7·8 (-28·3 to -0·5) | 1·2 (-2·2 to 7·6) | 0·1 (-4·7 to 7·0) |
| Median percent change in lipoprotein (a) levels from baseline to Day 84 – (IQR) | -22·4 (-59·3 to -0·8) | -37·2 (-70·0, -2·8) | 3·8 (-14·9 to 21·7) | 0·6 (-11·6 to 21·3) |
| **Differences in percent change in lipoprotein (a) from baseline to day 84** | **N=102** | **N=102** | **N=101** | **N=102** |
| Least squares mean percent difference at Day 84 with obicetrapib-ezetimibe FDC (95% CI)[b] | NA | -6·8 (-67·5 to 53·9) | -46·7 (-106·1 to 12·6) | -62·9 (-140·6 to 14·8) |

| | | | | |
|---|---|---|---|---|
| Least squares mean percent difference at Day 84 with obicetrapib monotherapy (95% CI)[b] | NA | NA | NA | -56·2 (-133·8 to 21·5) |
| Least squares median percent difference at Day 84 with obicetrapib-ezetimibe FDC (95% CI)[c] | NA | 5·9 (-4·1 to 17·1) | -32·1 (-42·1 to -22·5) | -28·6 (-40·7 to -20·3) |
| Least squares median percent difference at Day 84 with obicetrapib monotherapy (95% CI)[c] | NA | NA | NA | -38·6 (-50·0 to -27·9) |

FDC = fixed dose combination. nmol/L = nanomoles per liter. CI = confidence interval

[a]Three participants in the obicetrapib-ezetimibe FDC group, six participants in the obicetrapib monotherapy group, five participants in the ezetimibe monotherapy group, and four participants in the placebo group had missing lipoprotein (a) data at day 84.

[b]Missing lipoprotein (a) values at day 84 were imputed using a multiple imputation model assuming that the data are not missing at random. Missing measurements of non-retrieved dropouts were modeled by known measurements from retrieved dropouts in the same treatment group. 100 datasets were imputed. For each imputation dataset, the percent change from baseline to Day 84 was analyzed using an analysis of covariance model with fixed effects for treatment group and the baseline lipoprotein (a) level as a continuous covariate. The results from the 100 analyses were combined using Rubin's method.

[c] Differences between groups were also estimated using the non-parametric Hodges-Lehmann estimator in a post-hoc analysis.

**Table 3. Effects on high-density lipoprotein cholesterol.**

| Outcome | Obicetrapib Plus Ezetimibe FDC (N=102) | Obicetrapib (N=102) | Ezetimibe (N=101) | Placebo (N=102) |
|---|---|---|---|---|
| Mean HDL cholesterol level at baseline (95% CI) – mmol/L | 1·2 (1·2 to 1·3) | 1·2 (1·1 to 1·3) | 1·3 (1·2 to 1·4) | 1·3 (1·2 to 1·4) |
| **Day 84[a]** | **N=99** | **N=97** | **N=96** | **N=98** |
| Mean HDL cholesterol level at day 84 (95% CI) – mmol/L | 2·8 (2·6 to 2·9) | 2·8 (2·6 to 3·0) | 1·3 (1·2 to 1·4) | 1·3 (1·2 to 1·3) |
| Mean change in HDL cholesterol level from baseline to day 84 (95% CI) – mmol/L | 1·5 (1·4 to 1·6) | 1·6 (1·4 to 1·7) | -0·01 (-0·06 to 0·03) | -0·02 (-0·07 to 0·1) |
| Percent change in HDL cholesterol from baseline to day 84 (95% CI) | 127·6 (115·5 to 139·6) | 137·5 (123·1 to 151·9) | 1·1 (-2·1 to 4·3) | -0·9 (-3·8 to 2·1) |

FDC = fixed dose combination. mmol/L = millimoles per liter, CI = confidence interval

[a]Three participants in the obicetrapib-ezetimibe FDC group, five participants in the obicetrapib monotherapy group, five participants in the ezetimibe monotherapy group, and four participants in the placebo group had missing HDL cholesterol values at day 84.

**Figure 1. Proportion with low-density lipoprotein cholesterol level <2·6 mmol/L (<100 mg/dL), <1·8 mmol/L (<70 mg/dL) and <1·4 mmol/L (<55 mg/dL) at day 84**

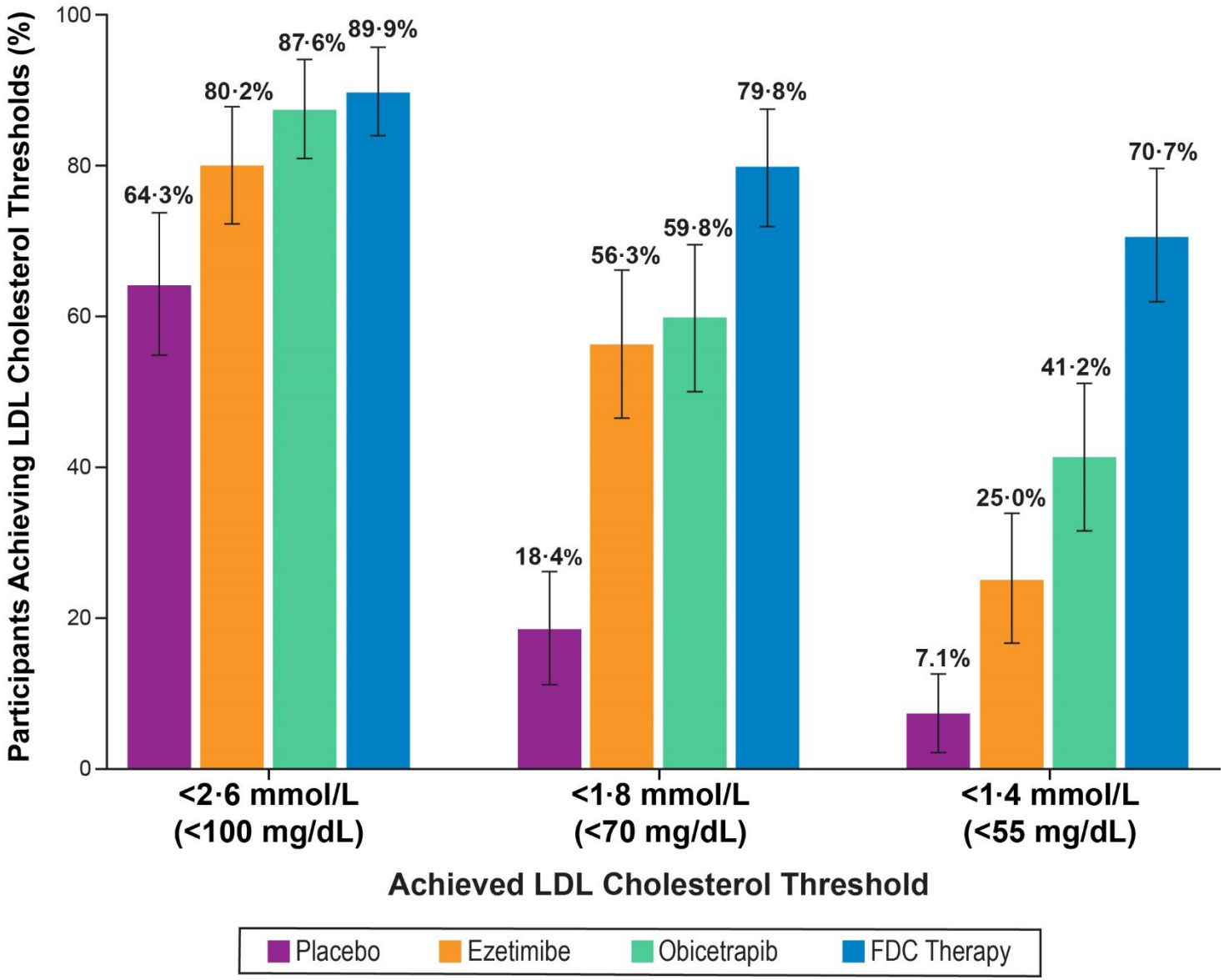

**Table 4. Post-hoc sensitivity analysis of co-primary endpoints after excluding participants who were not on statin therapy at baseline.**

| Comparator | Obicetrapib Plus Ezetimibe FDC (N=91) | Obicetrapib (N=87) | Ezetimibe (N=93) | Placebo (N=93) |
|---|---|---|---|---|
| **Primary end point: Percent difference in LDL cholesterol (95% CI)** | | | | |
| Obicetrapib plus ezetimibe FDC | NA | -17.6 (-28·4 to -6.8) | -29.1 (-39.8 to -18·4) | -49.4 (-60.5 to -38·4) |
| Obicetrapib monotherapy | NA | NA | NA | -31·8 (-42.7 to -20.9) |

FDC = fixed dose combination. CI = confidence interval

# CLINICAL STUDY PROTOCOL

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

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

**Sponsor:**
NewAmsterdam Pharma B.V.
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1411 DC
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The Netherlands
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**Version Number:** 4.0
**Original Protocol:** 14 December 2022
**Amendment 1:** 10 August 2023
**Amendment 2:** 08 November 2023
**Amendment 3:** 09 October 2024

| | |
|---|---|
| Sponsor's Medical Expert: | Marc Ditmarsch, MD<br>Chief Development Officer, NewAmsterdam Pharma B.V.<br>Gooimeer 2-35<br>1411 DC<br>Naarden<br>The Netherlands<br>+31 (0) 35 206 2971<br>marc.ditmarsch@newamsterdampharma.com |

# SIGNATURE PAGE

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

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

| Signature | Date |
|---|---|
| *Electronically signed by: Marc Ditmarsch*<br>*Reason: Approved*<br>*Date: Oct 9, 2024 23:30 GMT+2* | 09-Oct-2024 |

Marc Ditmarsch, MD
Chief Development Officer
NewAmsterdam Pharma B.V.

# INVESTIGATOR AGREEMENT

By signing below I agree that:

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

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

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name

# SYNOPSIS

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

**PROTOCOL NUMBER:** OBEZ-301

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

**PHASE:** 3

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

**OBJECTIVES:**

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

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

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

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

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

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

The exploratory objectives of this study include the following:

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

**POPULATION:**

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

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

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

**STUDY DESIGN AND DURATION:**

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

Screening Period

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

Treatment Period

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

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

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

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

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

Safety Follow-Up Period

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

**DOSAGE FORMS AND ROUTE OF ADMINISTRATION:**

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

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

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

**EFFICACY ASSESSMENTS:**

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

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

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

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

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

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

The exploratory efficacy endpoints include the following:

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

**PHARMACOKINETIC ASSESSMENTS:**

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

**SAFETY ASSESSMENTS:**

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

**STATISTICAL ANALYSES:**

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

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

Analysis Populations

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

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

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

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

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

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

Analysis of Efficacy

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

The primary efficacy endpoint is the percent change from Day 1 to Day 84 in LDL-C. Co-primary endpoints include the percent change from Day 1 to Day 84 in LDL-C for the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with each of the following: placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy, and for the obicetrapib 10 mg monotherapy treatment group compared with placebo. The primary endpoint will be analyzed using an analysis of covariance (ANCOVA) model with a fixed effect for the treatment group and a covariate of baseline LDL-C. The least squares (LS) mean, standard errors, and 2-sided 95% confidence intervals for each treatment group and for the mean difference compared to placebo will be obtained.

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

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

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

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

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

Analysis of Safety

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

**SAMPLE SIZE DETERMINATION:**

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

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

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

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

**SITES:** Approximately 60 sites

**SPONSOR:**

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# TABLE OF CONTENTS

# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

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

# 1 INTRODUCTION AND BACKGROUND INFORMATION

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

## 1.1 Background on Cardiovascular Disease

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

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

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

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

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

### 1.2 Cholesteryl Ester Transfer Protein Inhibitors

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

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

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

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

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

### 1.3 Obicetrapib (TA-8995)

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

### 1.4 Clinical Development of Obicetrapib

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

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

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

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

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

## 1.5 Rationale

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

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

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

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

### 1.5.1 Rationale for Obicetrapib and Ezetimibe Fixed Dose Combination Therapy

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

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

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

### 1.5.2 Dose Selection Rationale

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

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

## 1.6 Risk/Benefit

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

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

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

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

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

### 1.6.1 Coronavirus Disease 2019 Impacts

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

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

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

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

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

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

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

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

## 2.2 Secondary Objectives

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

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

## 2.3 Exploratory Objectives

The exploratory objectives of this study include the following:

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

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

# 3 STUDY DESCRIPTION

## 3.1 Summary of Study Design

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

### 3.1.1 Screening Period

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

### 3.1.2 Treatment Period

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

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

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

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

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

### 3.1.3 Safety Follow-Up Period

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

### 3.1.4 Coronavirus Disease 2019 Contingency Measures

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

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

## 3.2 Study Indication

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

# 4 SELECTION AND WITHDRAWAL OF PARTICIPANTS

## 4.1 Inclusion Criteria

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

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

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

   Diagnosis of HeFH:

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

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

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

Multiple risk factors for ASCVD, defined as follows:

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

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

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

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

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

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

### 4.2 Exclusion Criteria

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

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

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

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

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

### 4.3 Retesting

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

### 4.4 Rescreening

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

### 4.5 Withdrawal Criteria

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

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

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

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

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

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

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

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

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

# 5 STUDY TREATMENTS

## 5.1 Treatment Groups

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

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

## 5.2 Rationale for Dosing

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

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

## 5.3 Randomization and Blinding

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

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

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

Participants, the Sponsor, Investigators, and all study site personnel involved in the study, including personnel carrying out study procedures, evaluating participants, entering study data,

and/or evaluating study data, will remain blinded to treatment allocations until all participants have completed all study-related visits and assessments and the database has been locked for analysis.

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

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

## 5.4 Breaking the Blind

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

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

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

## 5.5 Drug Supplies

### 5.5.1 Formulation and Packaging

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

Obicetrapib 10 mg + ezetimibe 10 mg FDC tablets are white to off-white, round, film-coated tablets with no identifying markings, containing 10 mg of obicetrapib (as obicetrapib calcium drug substance) and 10 mg of ezetimibe drug substance. The excipients present in the tablet cores are microcrystalline cellulose, lactose monohydrate, povidone, sodium starch glycolate, sodium lauryl sulfate, mannitol, colloidal silicon dioxide, and magnesium stearate. A commercially available film-coating formula (Opadry AMB II white, ex Colorcon) is applied to the cores.

Obicetrapib tablets are round, white film-coated tablets, with no identifying markings, containing 10 mg of obicetrapib (as obicetrapib calcium drug substance). The excipients present in the tablet cores are microcrystalline cellulose, mannitol, sodium starch glycolate, colloidal silicon dioxide,

and magnesium stearate. A commercially available film-coating formula (Opadry II white, ex Colorcon) is applied to the cores.

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

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

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

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

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

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

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

### 5.5.2 Study Drug Preparation and Dispensing

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

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

### 5.5.3 Study Drug Administration

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

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

### 5.5.4 Treatment Compliance

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

### 5.5.5 Storage and Accountability

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

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

## 5.6 Prior and Concomitant Medications and/or Procedures

### 5.6.1 Excluded Medications and/or Procedures

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

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

### 5.6.2 Restricted Medications and/or Procedures

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

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

### 5.6.3 Documentation of Prior and Concomitant Medication Use

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

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

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

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

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

### 5.6.4 Dietary Guidelines

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

# 6 STUDY PROCEDURES

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

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

# 7 EFFICACY AND PHARMACOKINETIC ASSESSMENTS

## 7.1 Efficacy Assessments

### 7.1.1 Efficacy Endpoints

#### 7.1.1.1 Primary efficacy endpoint

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

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

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

#### 7.1.1.2 Secondary efficacy endpoints

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

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

#### 7.1.1.3 Exploratory efficacy endpoints

The exploratory efficacy endpoints include the following:

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

### 7.1.2 Lipid Profile/Biomarkers

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

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

### 7.1.3 Lipoprotein (a)

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

#### 7.1.4 Nuclear Magnetic Resonance Analysis of Lipids

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

#### 7.1.5 Urine Albumin-Creatinine Ratio

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

#### 7.1.6 Serum Archive Samples for Future Assessment

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

### 7.2 Pharmacokinetic Assessments

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

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

# 8 SAFETY ASSESSMENTS

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

## 8.1 Adverse Events

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

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

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

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

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

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

- Based on the clinical judgment of the Investigator.

### 8.1.1 Adverse Reaction

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

### 8.1.2 Unexpected Adverse Drug Reaction

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

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

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

### 8.1.3 Assessment of Adverse Events by the Investigator

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

Assessment of severity

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

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

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

Causality assessment

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

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

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

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

The following factors should also be considered:

- The temporal sequence from a study drug administration-

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

- Underlying, concomitant, intercurrent diseases-

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

- Concomitant drug-

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

- Known response pattern for this class of study drug-

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

- Exposure to physical and/or mental stresses-

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

- The pharmacology and PK of the study drugs-

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

### 8.1.4 Events of Special Interest

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

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

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

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

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

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

Note: Worsening of glycemic control will be defined as an HbA1c increase from baseline >0.5% (>0.005 hemoglobin fraction) and/or a new concomitant medication or increase in current antidiabetic therapy in a participant with a baseline HbA1c ≥6.5% (≥0.065 hemoglobin fraction).

- A >25% decrease in eGFR from baseline or an eGFR <15 mL/min/1.73 $m^2$, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, and/or an increase in serum creatinine of ≥0.3 mg/dL (≥26.5 μmol/L) from baseline;
- Changes to antihypertensive medication(s) due to changes in blood pressure in those participants receiving antihypertensive medication(s) treatment at baseline, and new antihypertensive medication prescriptions for participants not previously treated for hypertension; and
- Macular degeneration.

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

#### 8.1.4.1 Guidelines for management of elevated liver enzymes

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

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

If the above abnormalities are confirmed:

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

Study drug discontinuation should occur if:

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

8.1.4.2 Guidelines for monitoring and management of creatine kinase

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

A repeat CK assessment will include query for related symptoms.

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

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

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

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

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

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

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

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

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

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

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

- A >25% decrease in eGFR from baseline, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation;
- An eGFR <15 mL/min/1.73 $m^2$, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation; and/or
- An increase in serum creatinine of ≥0.3 mg/dL (≥26.5 µmol/L) from baseline.

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

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

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

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

#### 8.1.4.6 Guidelines for management of macular degeneration

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

## 8.2 Serious Adverse Events

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

- Death;
- A life-threatening AE;

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

- Requires hospitalization or prolongation of existing hospitalizations;

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

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

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

## 8.3 Serious Adverse Event Reporting − Procedures for Investigators

Initial reports

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

To report the SAE, complete the SAE form electronically in the EDC system for the study. When the form is completed, Medpace Safety and Pharmacovigilance personnel will be notified electronically by the EDC system and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety and Pharmacovigilance at medpace-safetynotification@medpace.com or call the Medpace SAE

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

Follow-up reports

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

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

## 8.4 Pregnancy Reporting

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

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

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

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

## 8.5 Expedited Reporting

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

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

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

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

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

### 8.6 Special Situation Reports

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

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

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

Medpace Safety and Pharmacovigilance Contact Information
Medpace SAE reporting line (office location: Cincinnati, Ohio, United States):
Telephone: +1-513-579-9911, dial 3
Fax: +1-513-570-5196
Email: medpace-safetynotification@medpace.com

## 8.7 Clinical Laboratory Evaluations

### 8.7.1 Chemistry, Hematology, and Coagulation Assessments

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

### 8.7.2 Endocrinology Assessments

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

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

## 8.8 Vital Signs

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

## 8.9 Weight and Height

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

## 8.10 Demographics

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

## 8.11 Electrocardiograms

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

## 8.12 Physical Examinations

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

# 9 STATISTICS

## 9.1 Analysis Populations

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

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

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

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

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

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

## 9.2 Statistical Methods

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

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

### 9.2.1 Analysis of Efficacy

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

#### 9.2.1.1 Primary efficacy analysis

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

will be analyzed using an analysis of covariance (ANCOVA) model with a fixed effect for the treatment group and a covariate of baseline LDL-C. The least squares (LS) mean, standard errors, and 2-sided 95% confidence intervals for each treatment group and for the mean difference compared to placebo will be obtained.

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

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

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

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

#### 9.2.1.2 Secondary efficacy analyses

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

#### 9.2.1.3 Exploratory analyses

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

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

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

### 9.2.2 Analysis of Safety

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

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

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

### 9.2.3 Interim Analysis

No interim analysis is planned for this study.

### 9.2.4 Sample Size Determination

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

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

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

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

# 10 DATA MANAGEMENT AND RECORD KEEPING

## 10.1 Data Management

### 10.1.1 Data Handling

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

### 10.1.2 Computer Systems

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

### 10.1.3 Data Entry

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

### 10.1.4 Medical Information Coding

For medical information, the following thesauri will be used:

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

### 10.1.5 Data Validation

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

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

## 10.2 Record Keeping

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

## 10.3 End of Study

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

# 11 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

## 11.1 Ethical Conduct of the Study

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

## 11.2 Institutional Review Board

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

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

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

## 11.3 Informed Consent Procedures

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

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

## 11.4 Study Monitoring Requirements

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

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

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

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

All monitoring activities will be reported and archived.

### 11.5 Disclosure of Data

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

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

### 11.6 Retention of Records

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

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

### 11.7 Publication Policy

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

## 11.8 Financial Disclosure

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

# 12 STUDY ADMINISTRATIVE INFORMATION

## 12.1 Protocol Amendments

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

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# APPENDIX A: SCHEDULE OF PROCEDURES

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

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

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

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

# APPENDIX B: CLINICAL LABORATORY ANALYTES

### Standard Safety Chemistry Panel

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

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

### Coagulation Parameters

| | |
|---|---|
| International normalized ratio | Prothrombin time |

### Endocrinology

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

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

### Hematology

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

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

**Lipid Profile**

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

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

**Other Laboratory Analytes**

- Lipoprotein (a)
- Urine albumin-creatinine ratio

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

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

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

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

Sources:

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

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

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

# APPENDIX D: SIMON BROOME REGISTER DIAGNOSTIC CRITERIA FOR FAMILIAL HYPERCHOLESTEROLEMIA

**Definite Familial Hypercholesterolemia:**

Required laboratory = high cholesterol levels:

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

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

*Plus at least 1 of the 2:*

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

  OR

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

**Possible Familial Hypercholesterolemia:**

Laboratory = high cholesterol levels:

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

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

*Plus at least 1 of the 2:*

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

  OR

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

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

# STATISTICAL ANALYSIS PLAN

| | |
|---|---|
| **Protocol Title:** | A Placebo-Controlled, Double-Blind Randomized, Phase 3 Study to Evaluate the Effect of Obicetrapib 10 mg and Ezetimibe 10 mg Fixed Dose Combination Daily on Top of Maximally Tolerated Lipid-Modifying Therapy in Participants With Heterozygous Familial Hypercholesterolemia (HeFH) and/or Atherosclerotic Cardiovascular Disease (ASCVD) or Multiple ASCVD Risk Factors |
| **Protocol Number:** | OBEZ-301 |
| **Protocol Version/Date:** | 4.0/09 OCT 2024 |
| **Investigational Product:** | Obicetrapib 10 mg + ezetimibe 10 mg fixed dose combination (FDC) |
| **Sponsor:** | NewAmsterdam Pharma B.V.<br>Gooimeer 2-35<br>1411 DC<br>Naarden<br>The Netherlands |
| **SAP Version/Date:** | 2.0/22-OCT-2024 |

**CONFIDENTIAL**

# SIGNATURE PAGE

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

**Protocol Number:** OBEZ-301

**SAP Version/Date:** 2.0/22-OCT-2024

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

| Signature | Date |
|---|---|
| Violeta Balinskaite *Electronically signed by: Violeta Balinskaite Reason: Approved Date: Oct 22. 2024 11:50 GMT+1* | |
| ***Violeta Balinskaite, PhD*** ***Project Statistician*** ***Medpace, Inc.*** | |
| Richard Lee *Electronically signed by: Richard Lee Reason: Approved Date: Oct 22, 2024 07:26 EDT* | |
| ***Richard Lee MD*** ***Vice President, Medical Department*** ***Medpace, Inc.*** | |
|  *Electronically signed by: Marc Ditmarsch Reason: Approved Date: Oct 22, 2024 08:00 EDT* | |
| ***Marc Ditmarsch, MD*** ***Chief Development Officer*** ***NewAmsterdam Pharma B.V.*** | |

# VERSION HISTORY

| Version | Version Date | Description |
|---|---|---|
| 1.0 | 13 May 2024 | First Version |
| 2.0 | 22 October 2024 | Updates following protocol amendment, minor clarifications, and corrections of typing errors |

Version 2.0 (22-OCT-2024): Summary of changes from SAP Version 1.0 (13-MAY-2024)

| Section | Change* | Rationale |
|---|---|---|
| 2.1 and 2.3 | Adding an additional co-primary endpoint and additional secondary and exploratory endpoints | Following the protocol amendment |
| 3.4.1 | A third sensitivity analysis added for the primary efficacy endpoint | A sensitivity analysis using the last observation carried forward was added to better assess the robustness of the results of primary analysis |

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

# TABLE OF CONTENTS

# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| ADaM | Analysis Data Model |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| ANCOVA | Analysis of covariance |
| ApoA1 | Apolipoprotein A1 |
| ApoB | Apolipoprotein B |
| AST | Aspartate aminotransferase |
| ATC | Anatomical therapeutic chemical |
| BMI | Body mass index |
| CDISC | Clinical Data Interchange Standards Consortium |
| CRF | Case report form |
| CSR | Clinical Study Report |
| CV | Cardiovascular |
| CK | Creatine kinase |
| ECG | Electrocardiogram |
| eGFR | Estimated glomerular filtration rate |
| EOS | End of Study |
| EOT | End of Treatment |
| ESI | Event of special interest |
| ET | Early Termination |
| FAS | Full Analysis Set |
| FDC | Fixed dose combination |
| HbA1c | Glycated hemoglobin |
| HDL-C | High-density lipoprotein cholesterol |
| HeFH | Heterozygous familial hypercholesterolemia |
| HIS | High intensity statin |
| ICF | Informed consent form |
| ITT | Intent-to-Treat |
| LDL | Low-density lipoprotein |
| LDL-C | Low-density lipoprotein cholesterol |
| Lp(a) | Lipoprotein (a) |
| LS | Least squares |
| MAR | Missing at random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | Modified Intent-to-Treat |
| MMRM | Mixed model for repeated measures |
| MNAR | Missing not at random |
| NMR | Nuclear magnetic resonance |
| NODM | New-onset diabetes mellitus |
| Non-HDL-C | Non-high-density lipoprotein cholesterol |
| PK | Pharmacokinetics |
| PP | Per-Protocol |
| PT | Preferred term |
| PUC | Preparative ultracentrifugation |

| Abbreviation | Definition |
|---|---|
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SDTM | Study Data Tabulation Model |
| SOC | System organ class |
| TC | Total cholesterol |
| TFL | Tables, figures, and listings |
| TG | Triglycerides |
| TEAE | Treatment-emergent adverse event |
| TESAE | Treatment-emergent serious adverse event |
| VLDL-C | Very low-density lipoprotein cholesterol |
| WHO | World Health Organization |

# 1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number OBEZ-301. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

# 2 STUDY OVERVIEW

## 2.1 Study Objectives

### *2.1.1 Primary Objective*

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

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

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

### *2.1.2 Secondary Objectives*

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

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

### *2.1.3 Exploratory Objectives*

The exploratory objectives of this study include the following:

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

## 2.2 Study Design

### *2.2.1 Overview*

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

Screening Period

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

Treatment Period

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

- FDC therapy: Obicetrapib 10 mg + ezetimibe 10 mg;
- Obicetrapib monotherapy: Obicetrapib 10 mg;

- Ezetimibe monotherapy: Ezetimibe 10 mg; or
- Placebo.

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

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

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

Safety Follow-Up Period

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

Refer to Table 1 Schedule of Procedures for a complete list of procedures to be completed at each study visit.

### *2.2.2 Sample Size Determination*

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

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

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

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

*Table 1 Schedule of Procedures*

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

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

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

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

## 2.3 Study Endpoints

### *2.3.1 Primary Efficacy Endpoints*

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

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

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

### *2.3.2 Secondary Efficacy Endpoints*

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

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

### *2.3.3 Exploratory Efficacy Endpoints*

The exploratory efficacy endpoints include the following:

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

#### *2.3.4 Safety Endpoints*

The safety endpoints include the following:

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

# 3 STATISTICAL METHODOLOGY

## 3.1 General Considerations

### *3.1.1 Analysis Day*

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

### *3.1.2 Analysis Visits*

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

For each analysis visit, if a scheduled visit occurs within the analysis day window, then the measurement from this scheduled visit will be used. If no scheduled visit occurs or laboratory results of the scheduled visit were unreportable, the unscheduled measurement closest to the target day will be used. If measurements are equidistant to the target day, the later measurement will be used. If laboratory measurements during the scheduled visit were taken while a participant was not in a fasting state and laboratory measurements are available from an unscheduled visit

during which the participant was in a fasting state (and the visit was done within seven days of the scheduled visit), those fasted labs will be utilized in place of the unfasted labs. Otherwise, unscheduled visits will not be re-assigned and will remain labelled as unscheduled.

Early termination (ET) visits will be assigned to analysis visits according to the following visit windows:

| Analysis Visit | Target Analysis Day | Low Analysis Day | High Analysis Day |
|---|---|---|---|
| Day 1 (Visit 2) | 1 | NA | NA |
| Day 28 (Visit 3) | 28 | 2 | 56 |
| Day 84 (Visit 4) | 84 | 57 | 98 |
| Day 112 (Visit 5) | 112 | 99 | NA |

### *3.1.3 Definition of Baseline*

Baseline is defined as the last measurement prior to the first dose of study drug, unless otherwise stated.

### *3.1.4 Summary Statistics*

Categorical data will generally be summarized with counts and percentages of subjects. The denominator used for the percentage calculation will be clearly defined. Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, median, standard deviation, 1st and 3rd quartiles, minimum, and maximum.

### *3.1.5 Hypothesis Testing*

The percentage change in LDL-C from Baseline to Day 84 for each treatment group is defined mathematically as $\mu_j$, where j stands for the $j^{th}$ treatment (j=0,1,2,3) and the subscript 0 refers to the placebo, 1 refers to obicetrapib 10 mg monotherapy, 2 refers to ezetimibe 10 mg monotherapy, and 3 refers to the FDC treatment group. The hypothesis testing to the percent change in LDL-C from Baseline to Day 84 is then defined statistically as following:

$$H_0: \mu_3-\mu_j = 0 \text{ (where j=0,1,2) and } \mu_1-\mu_0 = 0$$

$$H_1: \mu_3-\mu_j \neq 0 \text{ (where j=0,1,2) and } \mu_1-\mu_0 \neq 0.$$

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

### *3.1.6 Evaluation of Site Effect*

This is a multi-center study. Sites will not be pooled for any planned inferential analysis but may be pooled for subgroup analysis to assess the heterogeneity of treatment effects among pooled sites. The final pooling algorithm, if needed, will be specified before treatment unblinding and will be provided as an addendum to the SAP. Additionally, a review of by-site effects will be performed in the context of data listing review.

### *3.1.7 Handling of Dropouts and Missing Data*

The objective is for missing data to be kept to a minimum. Continued efforts will be made to measure endpoints on all subjects, including those who may have discontinued study drug. Accordingly, site investigators have been robustly trained about the importance of participant retention and multiple approaches will be implemented to retain participants who fail to actively maintain contact with the investigator.

*Date Values*

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

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

*Non-Date Values*

For the primary efficacy endpoint, missing values will be imputed using multiple imputation methods (see Section 3.4.1). For the analyses of secondary and exploratory efficacy endpoints, no imputation will be made for missing values. Safety data will be used according to availability, with no imputation for missing data.

### *3.1.8 Laboratory Values Above or Below Limits of Quantification*

For laboratory values less than the lower limit of quantification (LLQ), half of the lower limit value (i.e. LLQ/2) will be used in the analysis. For values greater than the upper limit of quantification (ULQ), the upper limit value (i.e., ULQ) will be used in the analysis.

## 3.2 Analysis Populations

### *3.2.1 Intent-to-Treat (ITT) Population*

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

### *3.2.2 The Full Analysis Set (FAS)*

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

### *3.2.3 Modified Intent-to-Treat (mITT) Population*

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

### *3.2.4 The mITT On-Treatment Population*

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

Rationale: <100 ng/mL is more than three standard deviations from the mean obicetrapib concentration observed in both the ROSE (protocol number TA-8995-201) and TULIP (protocol number TA-8995-03) studies (with a very similar participant population compared to TANDEM (protocol number OBEZ-301) at respectively Week 4 and Week 12 [1-3]. In addition, in none of the previous conducted studies (3 clinical studies and 2 Phase 1) PK / PD studies the minimal observed obicetrapib concentration for Cmax was below 100 µg/mL.

### *3.2.5 Per-Protocol (PP) Population*

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

### *3.2.6 Safety Population*

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

## 3.3 Subject Data and Study Conduct

### *3.3.1 Subject Disposition*

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

For each scheduled visit, counts and percentages of subjects who did not complete the visit, completed in-clinic, completed in-clinic and remote, or completed will be summarized by treatment group and overall. The denominator for calculating percentages will be based on the number of randomized participants.

### *3.3.2 Protocol Deviations*

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

### *3.3.3 Analysis Populations*

Counts and percentages of subjects in each analysis population will be summarized by treatment group and in total based on all randomized subjects. Reasons for exclusion from PP Population will also be summarized.

### *3.3.4 Demographic and Baseline Characteristics*

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

- Age and age categories (<65 years, 65 to 74 years, and 75+ years)
- Sex
- Race
- Ethnicity
- Height
- Weight
- Body Mass Index (BMI)
- HIS, non-HIS. HIS include atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg. Participants will be defined as having HIS therapy based on the data collected in the eCRF and if any following were used at baseline: average daily dose of atorvastatin ≥40 mg or average daily dose of rosuvastatin of ≥20 mg. Participants having any other doses of statin or another statin or no statin will be defined as having non-HIS therapy.
- The history of ASCVD (Yes, No).

If they differ from the ITT Population, summaries will also be provided for the FAS, the mITT Population, the mITT On-Treatment Population, the PP Population, and the Safety Population. Demographic characteristics data will be provided in participant listings.

### *3.3.5 Medical History*

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

A listing of all medical history data will be provided.

### *3.3.6 Concomitant Medications*

The Prior & Concomitant Medications case report form where medication start and stop dates are recorded, will be used to determine whether the medications are prior or concomitant to the study treatment. Concomitant medications are defined as those used on or after the first dose of the study drug. Prior medications are defined as those used prior to and stopped before the first dose of study drug. All prior and concomitant medications will be coded using the current World Health Organization (WHO) Drug Dictionary. Counts and percentages of subjects taking prior and concomitant medications will be summarized by anatomical therapeutic chemical (ATC) class and preferred term by treatment group and overall, for the Safety Population.

Concomitant medications will be listed.

### *3.3.7 Study Drug Exposure and Compliance*

Participant' exposure to randomized study drug will be summarized with descriptive statistics for the Safety Population and mITT On-Treatment Population. Days of exposure to study drug will be calculated as

*date of last dose of study drug – date of first dose of study drug + 1,*

For participants whose date of first dose from the initial kit dispensed was not available, the date of randomization will be used to assign the date of first dose. For subjects who failed to provide the date of last dose of study drug, the earliest date between the end of treatment date and the date of the end of study/early termination will be used.

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

- <3 weeks
- 3 – <5 weeks
- 5 – <7 weeks
- 7 – <9 weeks
- 9 – <11 weeks
- >=11 weeks

Summary statistics will be presented for overall compliance to study drug by treatment group and in total. Counts and percentages of participants will also be tabulated by groups with overall compliance <80%, 80% to 120%, and >120%.

The percentage overall compliance to obicetrapib tablets will be calculated as:

$$\frac{actual\ tablets\ taken}{expected\ study\ drug\ taken} \times 100$$

The percentage overall compliance to ezetimibe capsules will be calculated as:

$$\frac{actual\ capsules\ taken}{expected\ study\ drug\ taken} \times 100$$

The percentage overall compliance to FDC tablet will be calculated as:

$$\frac{actual\ tablet\ taken}{expected\ study\ drug\ taken} \times 100$$

The percentage overall compliance to study drug will be calculated as:

$$\frac{actual\ study\ drug\ taken}{expected\ study\ drug\ taken * 3} \times 100$$

The expected study drug taken will be calculated as the earliest date between the end of treatment date and the date of early termination – the date of randomization- missed doses +1 (missed

doses defined as number of doses missed during IP interruptions due to AE or IP interruptions that are longer than 14 days).

The actual study drug taken is reported on the electronic case report form (eCRF). If no kits are returned, it will be assumed that all study drug from that kit were used.

Study drug interruptions due to AE or IP interruptions longer than 14 days will be listed.

## 3.4 Efficacy Assessment

The ITT Population will be the primary population for the efficacy analysis. Efficacy will also be analyzed using the FAS, the mITT Population, mITT On-Treatment Population, and PP Population as supportive analyses. Primary and secondary efficacy endpoints will be presented in listings.

### *3.4.1 Primary Efficacy Endpoints*

Primary Analysis

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

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

The LDL-C values measured by preparative ultracentrifugation (PUC) will be used. If the later measurement is not available, the LDL-C values will be assumed missing.

All the analysis for primary efficacy endpoint will be repeated with LDL-C values calculated as follows:

1. LDL-C will be calculated using the Friedewald equation unless triglycerides ≥400 mg/dL or LDL-C ≤50 mg/dL; where, LDL-C level will be measured directly by PUC.
2. LDL-C will be calculated using the Martin-Hopkins equation unless triglycerides ≥400 mg/dL or LDL-C ≤50 mg/dL; where, LDL-C level will be measured directly by PUC.

Primary Estimand

To assess the primary efficacy endpoint, the primary estimand is defined by the following key attributes:

- **Treatment**: obicetrapib 10 mg + ezetimibe 10 mg FDC treatment versus placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy, and obicetrapib 10 mg monotherapy versus placebo
- **Target Population**: participants who are randomized into the study
- **Analysis Population**: The ITT Population
- **Intercurrent events**: treatment discontinuation, prohibited medication use

- **Analysis set and handling of intercurrent events**: Treatment policy strategy will be used. All available values of LDL-C at Baseline and Day 84 will be included in the calculation of the percentage change from Baseline to Day 84.
- **Population level summary**: The difference in LS mean percentage change in LDL-C from Baseline to Day 84 between obicetrapib 10 mg + ezetimibe 10 mg FDC treatment versus placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy, and obicetrapic 10 mg monotherapy versus placebo

The analysis of covariance (ANCOVA) model with a fixed effect for the treatment group and covariates of Baseline LDL-C will be used to analyze the primary efficacy endpoint. The least squares (LS) mean, standard errors, and 2-sided 95% confidence intervals for each treatment group and for the treatment comparison (FDC treatment – placebo, FDC treatment – ezetimibe 10 mg, and FDC treatment- obicetrapib 10 mg, and obicetrapib 10 mg - placebo) will be provided. Model diagnostics for the ANCOVA model will be computed that include assessment for homogeneity of variance, normality of the residual, and residual outliers. If substantial deviations from the model assumptions are observed, then supportive analyses, such non-parametric assessments, will be considered.

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 (i.e., participants who remain in the study after treatment discontinuation) in the same treatment group. If the number of retrieved dropouts is such that the model convergence is questionable and the given parameter estimates cannot be obtained, then missing data at the Day 84 assessment will be estimated based on the placebo treatment group as described in subsequent sections of the SAP corresponding to the first sensitivity analysis.

Missing data at Day 84 will be imputed using a retrieved dropout imputation model assuming the data are missing not at random (MNAR). At Day 84, the data will be split into two groups as follows: (1) all participants that did not discontinue treatment and had a non-missing value at Day 84; and (2) either participants that had a missing value at Day 84, or participants that had discontinued treatment and had a non-missing value at Day 84. For the second group, 100 data sets will be imputed. The imputation model will include LDL-C Baseline and Day 84 values, treatment group. Each data set will be combined with the first group to obtain 100 imputed data sets with no missing values at Day 84. For each imputation data set, the percent change from baseline to Day 84 will be analyzed using the ANCOVA model described above. The results of these 100 analyses will be combined to construct the treatment estimates using the parameter estimates and associated standard errors. Similarly, the difference of the adjusted treatment means will be presented with the associated standard error and two-sided 95% confidence interval. Randomly chosen seed numbers will be selected for the analysis and will be retained.

Sample SAS code is shown below:

```
1.1
**********************************************************************************************************
```

Note: Missing value imputation only using participant group (2): participants that had a missing value at Day 84, or participants that had discontinued treatment and had a non-missing value at Day 84
TREATMENT = 0 (Placebo), 1 (Obicetrapib), 3(Ezetimibe), 4 (FDC Treatment)
LDLC_BASE = Baseline LDL_C value
LDLC_Day84 = LDL_C value at Day 84

```
**********************************************************************************************************
proc mi data=LDL_C seed=382794 nimpute=100 out= LDL_C_IMP;
 class TREATMENT;
 monotone method=reg;
 var TREATMENT LDLC_BASE LDLC_DAY84;
run;
**********************************************************************************************************
```

1.2

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

Note: LDL_C_IMP dataset must be merged with dataset containing participants from group (1): participants that did not discontinue treatment and had a non-missing value at Day 84.
Note: For each imputation dataset, the percentage change from Baseline to Day 84 will be analyzed using an ANCOVA approach with a fixed effect for the treatment group and covariates of Baseline LDL-C.
TREATMENT = 0 (Placebo), 1 (Obicetrapib) , 3(Ezetimibe), 4 (FDC Treatment)
BASE = Baseline LDL_C value
PCHG = Percent change from Baseline to Day 84

```
**********************************************************************************************************
proc mixed data= TEMP;
 by _imputation_;
 class TREATMENT ;
 model PCHG = TREATMENT BASE / solution cl;
 lsmeans TREATMENT / cl diffs;
run;
**********************************************************************************************************
```

1.3

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

Note: MI Analyze to combine imputations.

```
**********************************************************************************************************
proc mianalyze parms(classvar=full)=mixLSM;
 class TREATMENT;
 modeleffects TREATMENT;
 ods output parameterestimates=mi_LSM;
run;
proc mianalyze parms(classvar=full)=mixDIFF;
 class TREATMENT;
 modeleffects TREATMENT;
 ods output parameterestimates=minus_mi_DIFF;
run;
**********************************************************************************************************
```

## Sensitivity Analyses

The first sensitivity analysis will be performed imputing missing LDL-C values at Day 84 based on the assumption the data are MNAR using a control-based pattern mixture method. At Day 84, the data will be split into two groups as follows: (1) all participants randomized to the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy treatment groups that had a non-missing value at Day 84; and (2) either participants randomized to the placebo treatment group, or participants that had a missing value at Day 84. For the second group, 100 data sets will be imputed. The variables for the imputation model will consist of the LDL-C values from Baseline and Day 84. In this manner, missing data at the Day 84 assessment will be estimated from the placebo treatment group. Each data set will be combined with the first group to obtain 100 imputed data sets with no missing values at Day 84. For each imputation data set, the percent change from baseline to Day 84 will be analyzed using the ANCOVA model described above. The results of these 100 analyses will be combined to construct the treatment estimates using the parameter estimates and associated standard errors. Similarly, the difference of the adjusted treatment means will be presented with the associated standard error and two-sided 95% confidence interval. Randomly chosen seed numbers will be selected for the analysis and will be retained.

The second sensitivity analysis will be performed using the ANCOVA model from the primary analysis for the ITT Population using only observed cases with no imputation for missing data.

The third sensitivity analysis will be performed using ANCOVA model from the primary analysis for the ITT Population using the last observation carried forward (LOCF), i.e. if the Day 84 measurement is missing, then the last on-treatment measurement will be used.

Supplemental Analyses

Supplemental analyses will be performed for the primary efficacy endpoint in order to assess any differences with the results from the primary analysis and investigate what effect, if any, protocol violations have on the trial results. In the first supplemental analysis, a mixed model for repeated measures (MMRM) approach will be utilized. The analysis will include fixed effects for treatment group, visit, and treatment-by-visit interaction, along with covariates of the Baseline LDL-C value as a continuous covariate. The restricted maximum likelihood estimation approach will be used with an unstructured covariance matrix. The LS mean, standard errors, and 2-sided 95% confidence intervals for the treatment group and for the comparison of the treatment groups (FDC treatment vs. placebo, FDC treatment vs. ezetimibe 10 mg, and FDC treatment vs. obicetrapib 10 mg, and obicetrapib 10 mg vs. placebo) will be provided. The MMRM approach will include all available assessments of percent change in LDLC from Day 1, Day 28, and Day 84. The model assumes that the data are missing at random (MAR). If any data are missing, the model will use all information from the other time points to estimate the mean treatment difference at the given time point. No imputation of missing data will be performed. The analysis will be conducted for ITT Population.

Additional supplementary analysis will be performed using the ANCOVA model from the primary analysis based on the FAS, mITT, mITT On-Treatment, and PP populations. No imputation for missing data will be performed for the analysis.

Secondary Estimand

A secondary estimand will be assessed for the primary efficacy endpoint. The secondary estimand is defined by the following key attributes:

- **Treatment**:

- obicetrapib 10 mg + ezetimibe 10 mg FDC treatment versus placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy, and obicetrapib 10 mg monotherapy versus placebo
- **Target Population**: participants who are randomized into the study
- **Analysis Population**: The ITT Population
- **Intercurrent events**: treatment discontinuation, prohibited medication use
- **Analysis set and handling of intercurrent events**: A hypothetical strategy will be used. All available values of LDL-C at Baseline and Day 84 will be included in the calculation of the percentage change from Baseline to Day 84.
- **Population level summary**: The difference in LS mean percentage change in LDL-C from Baseline to Day 84 between obicetrapib 10 mg + ezetimibe 10 mg FDC treatment versus placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy, and obicetrapic 10 mg monotherapy versus placebo.

This hypothetical estimand represents the treatment effect of FDC treatment relative to placebo, ezetimibe 10 mg monotherapy, and obicetrapib 10 mg monotherapy, and the treatment effect of obicetrapib 10 mg monotherapy relative to placebo at Day 84 in the randomized participants had they remained on their randomized treatment for the entire planned treatment period. This estimand uses a hypothetical strategy to handle intercurrent events and is intended to provide an estimation of the achievable study treatment effect if participants take the treatment as planned. The resulting missing values (corresponding to unobserved values or excluded values following study drug discontinuation or the use of prohibited medication) will be implicitly handled by using a MMRM approach under the assumption of missing at random. The model will be similar to the MMRM approach described previously for the supplemental analysis of the primary efficacy endpoint. The supplementary analysis for the primary efficacy endpoint assessed by secondary estimand will be performed using the mITT On-Treatment populations.

### *3.4.2 Secondary Efficacy Endpoints*

Similar ANCOVA models as described for the primary analyses will be used to analyze the secondary efficacy endpoints and will be tested sequentially at the 0.05 significant level according to the order specified below, if all 3 co-primary endpoints achieved statistical significance. Otherwise, all statistical comparisons for secondary endpoints are considered descriptive only:

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

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

### *3.4.3 Exploratory Efficacy Endpoints*

Similar ANCOVA models as described for the primary analyses will be used to assess in obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with the placebo treatment group, ezetimibe 10 mg monotherapy treatment group, and obicetrapib 10 mg monotherapy treatment group, and obocetrapib 10 mg monotherapy treatment group compared with the placebo treatment group for the following:

- Percent change from Day 1 to Day 84 in VLDL-C, HDL-C, TG, Lp(a), and sdLDL-C
- Percent change from Day 1 to Day 84 in particle numbers and size, as measured by NMR analysis, of LDL-C, HDL-C, and VLDL-C
- Percent change from Day 1 to Day 28 in LDL-C.

For the percentage change from Day 1 to Day 28 in LDL-C, the LDL-C will be calculated using the Martin-Hopkins equation unless the Triglyceride value is ≥400 mg/dL or the LDL-C value is ≤50 mg/dL; in which case, the LDL-C level measured directly by PUC will be used in the analysis. The latter approach will be used because PUC assessments are not performed at Day 28 as per the protocol, unless the conditions for Triglycerides or LDL-C described above are met at the Day 28 assessment. The analysis will be repeated using the Friedewald equation as described in the Section **Error! Reference source not found.** above.

The proportion of participants at Days 84 who achieved

- LDL-C levels of <55 mg/dL (<1.4 mmol/L), <70 mg/dL (1.8 mmol/L), and <100 mg/dL (<2.6 mmol/L)

in the obicetrapib 10 mg + ezetimibe 10 mg FDC treatment group compared with the placebo treatment group, ezetimibe 10 mg monotherapy treatment group, and the obicetrapib 10 mg monotherapy treatment group, and obicetrapib 10 mg monotherapy compared with the placebo treatment group will be examined using logistic regression models with covariates of treatment group and respective baseline values as covariates. Odds ratio with 95% confidence intervals will be estimated.

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

```
Note:
 TREATMENT =  0 (Placebo),  1 (Obicetrapib), 3(Ezetimibe), 4 (FDC Treatment)
 BASE          = Baseline LDL_C value
 LDLC55       = LDL_C value less than 55mg/dL at DAY84 (YES/NO) for example
*************************************************************************************************************
proc logistic data= LDL_C;
    Class TREATMENT;
    Model LDLC55= TREATMENT BASE / alpha=0.05 expb plcl plrl orpvalue lackfit;
   Ods output
        ParameterEstimates= Log_LDLC55_ParameterEstimates
        CLoddsPL= Log_ LDLC55_OddsRatios
        ;
Run;
*************************************************************************************************************
```

### *3.4.4 Subgroup Analysis*

The primary efficacy endpoint also may be analyzed by the following subgroups:

- Sex (male, female)
- HIS, non-HIS. HIS include atorvastatin 40 or 80 mg, rosuvastatin 20 or 40 mg. Participants will be defined as having HIS therapy based on the data collected in the eCRF and if any following were used at baseline: average daily dose of atorvastatin ≥40 mg or average daily dose of rosuvastatin of ≥20 mg. Participants having any other doses of statin or another statin or no statin will be defined as having non-HIS therapy;
- The history of ASCVD (Yes, No).

The ANCOVA model with a fixed effects for the treatment group, subgroup variable, treatment-by-subgroup variable and covariates of Baseline LDL-C will be used. The least squares (LS) mean, standard errors, and 2-sided 95% confidence intervals for each treatment group and for the mean difference compared to placebo, within each level of the subgroup, will be estimated. No imputation of missing data will be performed; therefore, the subgroup analysis will perform using only observed data. For the primary efficacy endpoint, the LDL-C values measured by preparative ultracentrifugation will be used. However, if the analysis for the primary efficacy endpoint specified above will show a difference between the 3 LDL-C approaches, then Friedewald and Martin-Hopkins equations may be considered for subgroup analysis.

## 3.5 Safety Assessment

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

### *3.5.1 Adverse Events (AEs)*

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

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

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

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

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

### *3.5.2 Event of Special Interest*

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

- AST or ALT > 3×ULN;
- Total bilirubin > 2×ULN;
- Creatine kinase (CK) > 5 × ULN;
- NODM or worsening of glycemic control;
  Note: NODM is defined by 1 or more of the following criteria, based upon information from AE, medication, and laboratory data:
  - AE indicating new type 1 or type 2 diabetes;
  - Initiation of anti-diabetes medication with confirmation of the diagnosis of diabetes by blinded external review by experts in diabetology;
  - HbA1c ≥6.5% (≥0.065 hemoglobin fraction); and/or
  - Two consecutive values of fasting plasma glucose that are ≥126 mg/dL (≥7.0 mmol/L).

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

antihypertensive medication prescriptions for participants not previously treated for hypertension; and
- Macular degeneration.

Values and changes from baseline will be summarized for ALT, AST, and total bilirubin by visit and treatment group. The number and percent of participants with abnormal values for ALT, AST, and total bilirubin will be summarized. These summaries of participants with abnormal values will be performed overall; by normal Baseline; and by abnormal Baseline for ALT, AST, and total bilirubin individually.

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

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

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 from baseline to EOT will be provided by treatment group.

Participants will be identified as those who have a diagnosis of hypertension in their medical history and received antihypertensive medication(s) at Baseline. If a participant has an adverse event related to hypertension after Baseline (see Appendix B for preferred terms) and has any change in antihypertension medication within 30 days of the start date of the adverse event, that change in antihypertension medication will be considered due to a change in blood pressure.
Participants will be identified as those who did not have a prior diagnosis of hypertension in their medical history but had an adverse event of hypertension (see Appendix B) after Baseline. If participants had an adverse event of hypertension and had initiation of antihypertension medication within 30 days of the start date of the adverse event, that initiation of an antihypertension medication will be considered due to a change in blood pressure.
The number and percentage of participants receiving/not receiving antihypertensive medication(s) at Baseline with changes to or initiation of new antihypertensive medication(s) due to changes in blood pressure will be summarized by treatment group.

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

### *3.5.3 Clinical Laboratory Tests*

Blood samples for clinical laboratory evaluations (chemistry, hematology, and coagulation) will be collected at visits specified in Table 1. Blood samples for chemistry and hematology must be obtained under fasting conditions (ie, after the participant has fasted for a minimum of 8 hours) and before study drug administration. For the purposes of this study, fasting will be defined as nothing by mouth except water and any essential medications. See Appendix B of the protocol for a complete list of analytes.

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

Chemistry and hematology laboratory parameters will be listed.

#### *3.5.4 Vital Signs*

Vital signs (body temperature, heart rate and triplicate blood pressure) will be measured at applicable visits as indicated in Table 1. Values will be summarized with descriptive statistics, including the change from baseline at each visit by treatment group and overall.

Vital signs will be listed.

#### *3.5.5 Physical Examinations*

Physical examinations (with focused examination on general, respiratory, CV, abdominal, and extremities evaluations) and recording of weight and height will be performed at Screening Visit and Visit 4/EOT. Height will be measured at Screening Visit only and used to calculate body mass index. BMI will be calculated as weight/(height/100)$^2$ (kg/m$^2$); rounded and displayed to 1 decimal place.

Physical examination parameters will be recorded as normal, abnormal or not done. Abnormal values will be assessed as clinically significant or not clinically significant. Count and percentages for physical parameters will be summarized by treatment group and in total.

# 4 ANALYSIS TIMING

## 4.1 Interim Analysis

No interim analysis is planned.

## 4.2 Pre-Final Analysis

After the database is locked and exclusions from analysis populations have been finalized, the randomized treatment assignments will be unblinded and the pre-final analysis will be generated. Pre-final tables, figures, and listings (TFLs) will be provided approximately 3 weeks after database lock.

## 4.3 Final Analysis

After all comments on the pre-final analysis have been resolved and the study database is declared final, the final analysis will be generated. If there were no changes to the pre-final analysis or the study database, the pre-final TFLs may be considered final. In addition to TFLs, SDTM data and ADaM data along with associated files will be provided. Associated files may include annotated case report forms (CRFs), SDTM specifications, SDTM programs, ADaM specifications, ADaM programs, TFL programs, and CDISC Define packages for both SDTM and ADaM data.

# 5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

There has been one change from the protocol v3.0:

- The inclusion of subgroup analysis.

# 6 PROGRAMMING SPECIFICATIONS

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

# APPENDIX A: REFERENCES

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

2.Nicholls SJ, Ditmarsch M, Kastelein JJ et el. Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial. Nature Medicine 2022; 28 (8): 1672-1678.

3. Ballantyne CM, Ditmarsch M, Kastelein JJ et al. Obicetrapib plus ezetimibe as an adjunct to high-intensity statin therapy: a randomized phase 2 trial. *Journal of Clinical Lipidology*; 2023 June 3.

4.Martin SS, Blaha MJ, Elshazly MB, et al. LDL calculator. John Hopkins Medicine. https://ldlcalculator.com. Accessed 27 October 2023.

# APPENDIX B: PREFFERED TERMS FOR HYPERTENSION

| **Preferred Term** |
|---|
| Accelerated hypertension |
| Blood pressure ambulatory increased |
| Blood pressure diastolic increased |
| Blood pressure inadequately controlled |
| Blood pressure increased |
| Blood pressure orthostatic increased |
| Blood pressure systolic increased |
| Diastolic hypertension |
| Essential hypertension |
| Hypertension |
| Malignant hypertension |
| Mean arterial pressure increased |
| Systolic hypertension |
| Blood pressure abnormal |
| Blood pressure ambulatory abnormal |
| Blood pressure diastolic abnormal |
| Blood pressure orthostatic abnormal |
| Blood pressure systolic abnormal |
| Labile blood pressure<br>Hypertensive crisis |
| Hypertensive emergency |
| Hypertensive urgency<br>Orthostatic hypertension |

**Statistical Analysis Plan Summary of Changes**

Statistical Analysis Plan Version 2.0 dated 22 October 2024 (Final SAP) contains updates to mirror the final protocol amendment. The additional co-primary endpoint and additional secondary and exploratory endpoints, as described in the Protocol Summary of Changes, were added. A third sensitivity analysis was added for the primary efficacy endpoint to use the last observation carried forward to assess the robustness of the results of the primary analysis.