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.

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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

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.

See Online for appendix

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

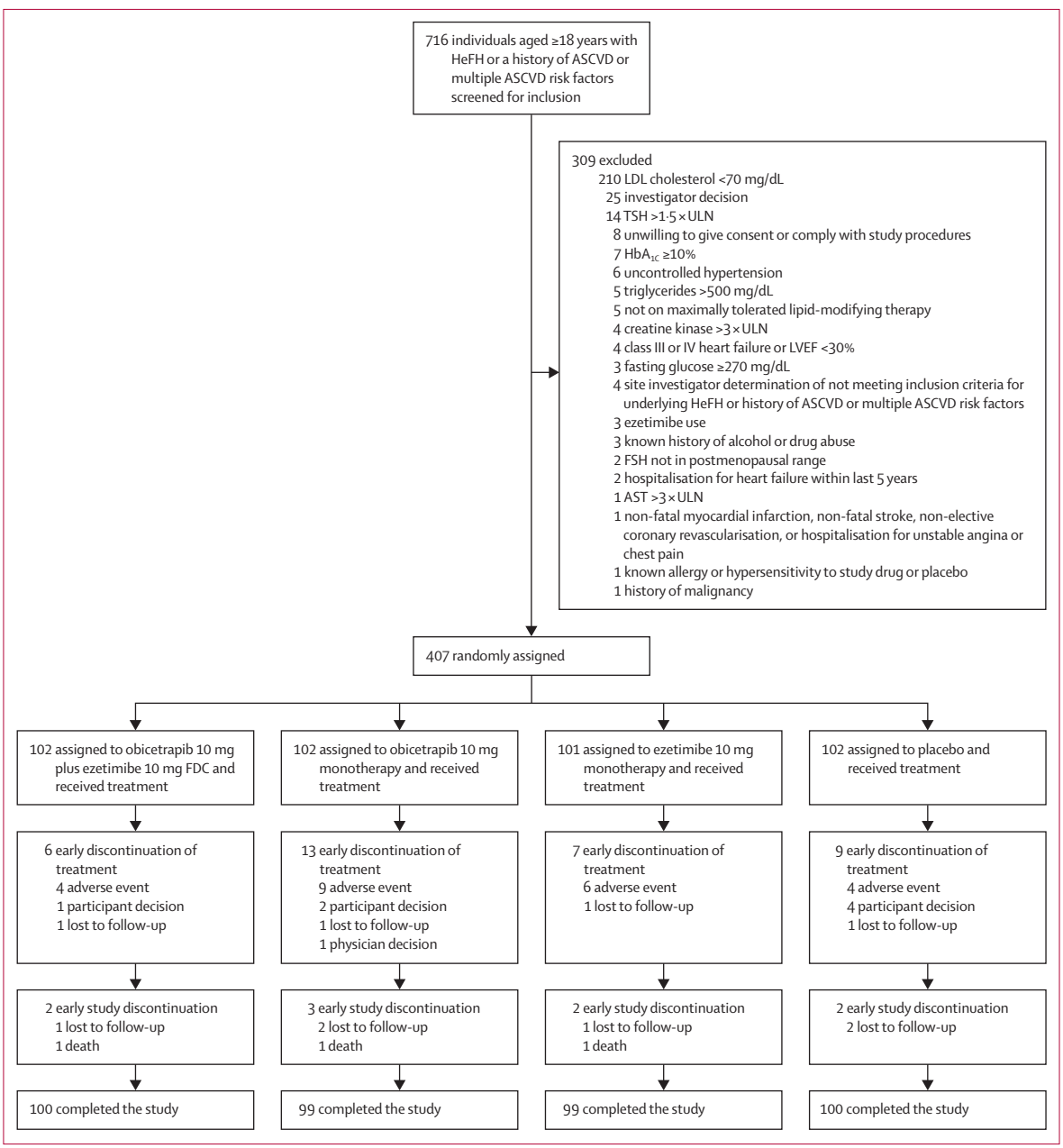

Figure 1: **Trial profile**

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.

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

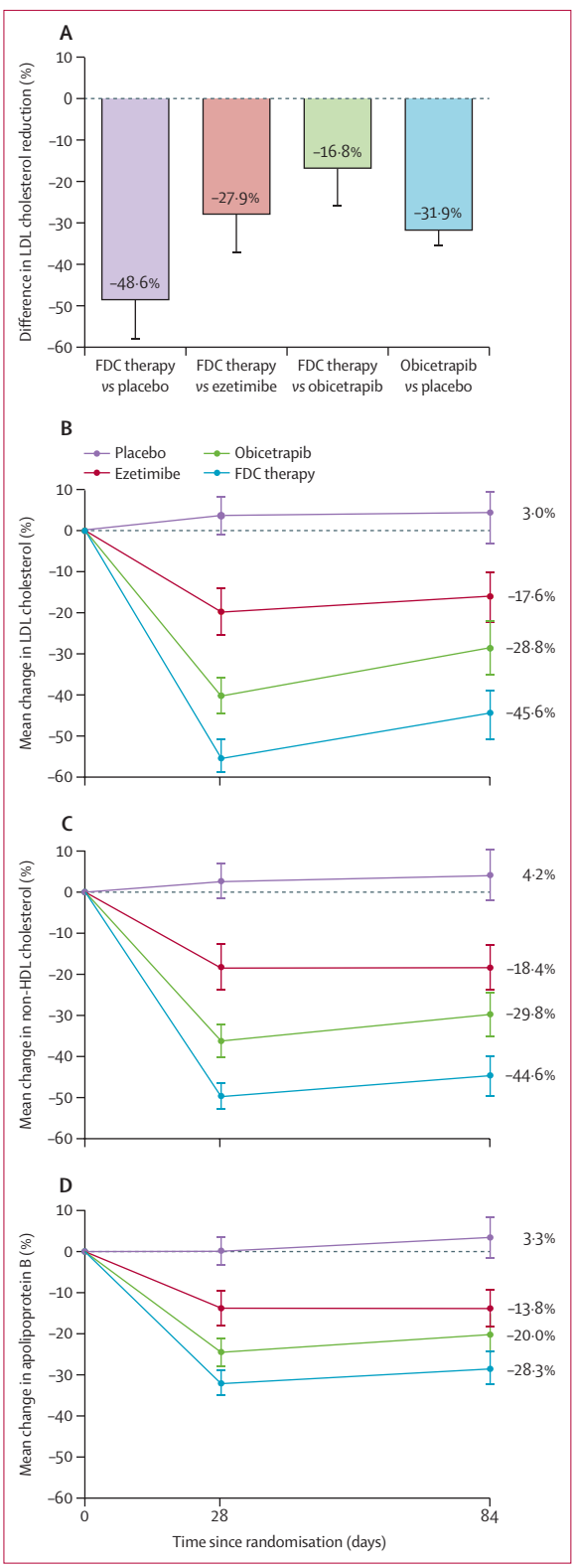

Figure 2: **Co-primary and secondary endpoints**

(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.

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**

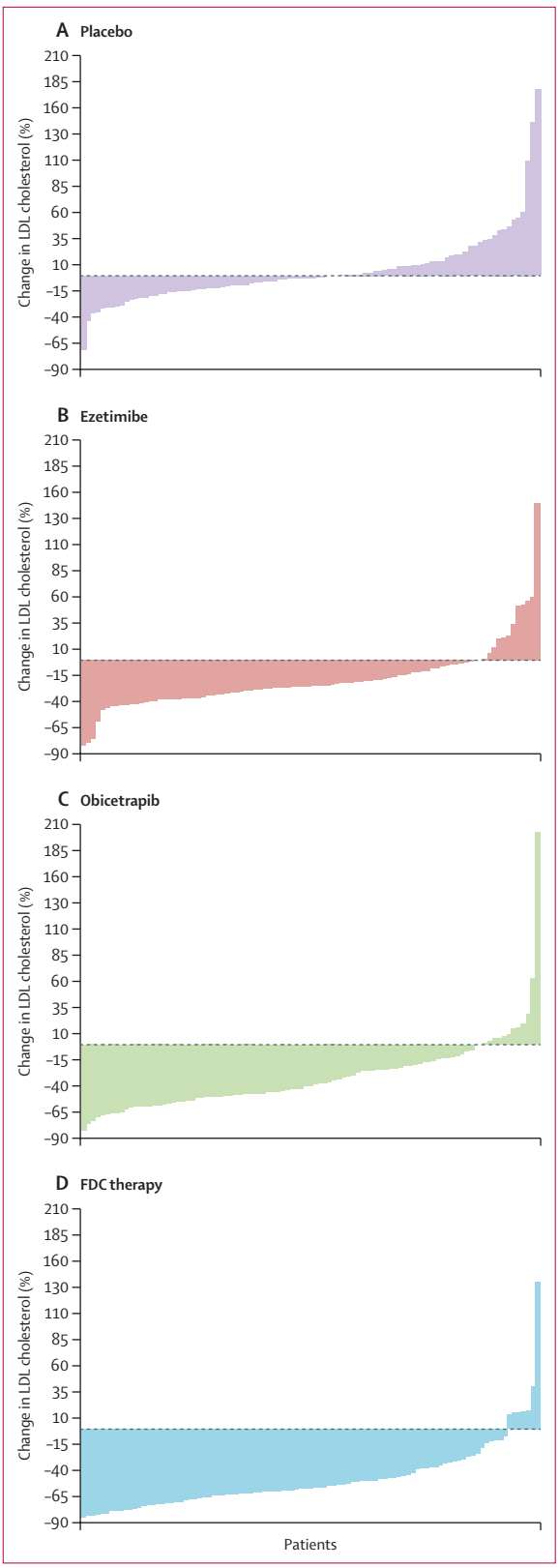

Figure 3: **Waterfall plots showing the distribution of individual LDL cholesterol responses in the treatment groups**
Each vertical bar represents the percent change in LDL cholesterol measured by preparative ultracentrifugation for an individual patient in the treatment group from baseline to day 84 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

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Data sharing

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

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