ORIGINAL ARTICLE

Safety and Efficacy of Obicetrapib in Patients at High Cardiovascular Risk

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ABSTRACT

BACKGROUND

Obicetrapib is a highly selective cholesteryl ester transfer protein inhibitor that reduces low-density lipoprotein (LDL) cholesterol levels. The efficacy and safety of obicetrapib have not been fully characterized among patients at high risk for cardiovascular events.

METHODS

We conducted a multinational, randomized, placebo-controlled trial involving patients with heterozygous familial hypercholesterolemia or a history of atherosclerotic cardiovascular disease who were receiving maximum tolerated doses of lipid-lowering therapy. Patients with an LDL cholesterol level of 100 mg per deciliter or higher or a non–high-density lipoprotein (HDL) cholesterol level of 130 mg per deciliter or higher, as well as those with an LDL cholesterol level of 55 to 100 mg per deciliter or a non-HDL cholesterol level of 85 to 130 mg per deciliter and at least one additional cardiovascular risk factor, were eligible for inclusion. The patients were randomly assigned in a 2:1 ratio to receive either 10 mg of obicetrapib once daily or matching placebo for 365 days. The primary end point was the percent change in the LDL cholesterol level from baseline to day 84.

RESULTS

A total of 2530 patients underwent randomization; 1686 patients were assigned to receive obicetrapib and 844 to receive placebo. The mean age of the patients was 65 years, 34% were women, and the mean baseline LDL cholesterol level was 98 mg per deciliter. The least-squares mean percent change from baseline to day 84 in the LDL cholesterol level was −29.9% (95% confidence interval [CI], −32.1 to −27.8) in the obicetrapib group, as compared with 2.7% (95% CI, −0.4 to 5.8) in the placebo group, for a between-group difference of −32.6 percentage points (95% CI, −35.8 to −29.5; P<0.001). The incidence of adverse events appeared to be similar in the two groups.

CONCLUSIONS

Among patients with atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia who were receiving maximum tolerated doses of lipid-lowering therapy and were at high risk for cardiovascular events, obicetrapib reduced LDL cholesterol levels by 29.9%. (Funded by NewAmsterdam Pharma; BROADWAY ClinicalTrials.gov number, NCT05142722.)

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*A list of the BROADWAY investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Clinical trials have consistently shown that lowering the levels of low-density lipoprotein (LDL) cholesterol reduces the risk of cardiovascular events in the context of primary or secondary prevention.[1,2] More intensive lipid lowering has been associated with greater clinical benefit,[1-3] a finding that has led to the recommendation of lower treatment goals for LDL cholesterol for patients at high risk for cardiovascular events in society guidelines that address management of lipids to reduce cardiovascular risk.[4,5]

Treatment targets for LDL cholesterol will not be reached in most patients at high risk for cardiovascular events, despite treatment with low-intensity[6] or high-intensity statin therapy.[7-9] Dose escalation of statins is often limited because of concerns about the small degree of incremental LDL cholesterol lowering, symptomatic myalgia, and new-onset diabetes.[7-9] In most patients at very high risk for cardiovascular events, combination therapy is needed to achieve an LDL cholesterol level of less than 55 mg per deciliter (1.42 mmol per liter). However, observational studies have shown a low rate of use of combination lipid-lowering therapy.[7,8] Therefore, more patients at high risk will most likely be receiving inadequate treatment and may have adverse cardiovascular outcomes.

Obicetrapib is a highly selective cholesteryl ester transfer protein (CETP) inhibitor with hydrophilicity that accommodates more avid and selective binding to the CETP tunnel.[10] Obicetrapib has been shown in early trials to lower LDL cholesterol levels and increase high-density lipoprotein (HDL) cholesterol levels.[11-14] In addition, when added to a maximum tolerated dose of lipid-lowering therapy, obicetrapib has the potential to help patients at high cardiovascular risk reach LDL cholesterol treatment goals.[11-14] The Randomized Study to Evaluate the Effect of Obicetrapib on Top of Maximum Tolerated Lipid-Modifying Therapies (BROADWAY) aimed to determine the effect of obicetrapib on lipid levels and characterize its safety and side-effect profile in patients at high risk for cardiovascular events.

METHODS

TRIAL ORGANIZATION AND OVERSIGHT

The trial design has been reported previously.[15] The trial protocol, available with the full text of this article at NEJM.org, was approved by the local ethics committee at each participating site. All the patients provided written informed consent before undergoing any trial procedures. The sponsor (NewAmsterdam Pharma) funded the trial and participated in its design and conduct, including data collection, in collaboration with the academic steering committee (additional details provided in the Supplementary Appendix, available at NEJM.org). The primary statistical analysis was performed by statisticians at MedPace, a contract research organization, in collaboration with an academic statistician who represented the steering committee. The first author wrote the first draft of the manuscript, and the final version of the manuscript was reviewed and approved by all the authors. The sponsor reviewed the manuscript; however, the final decision on content was reserved for the first author, who vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol and statistical analysis plan.

TRIAL DESIGN AND PATIENTS

Eligible patients were at least 18 years of age, had a history of atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia, and were being treated with maximum tolerated doses of statin therapy, with or without ezetimibe, bempedoic acid, or inhibitors of proprotein convertase subtilisin–kexin type 9 (PCSK9). Diagnosis of heterozygous familial hypercholesterolemia was made by means of genotyping or according to clinical criteria. For patients who did not undergo genotyping, the clinical diagnosis was based on the Simon Broome criteria for definite or possible familial hypercholesterolemia or the World Health Organization–Dutch Lipid Clinic Network criteria, with a score of at least 3 points (a score of 3 to 5 points indicates possible familial hypercholesterolemia; 6 to 8 points, probable; and >8 points, definite). Further details on the diagnostic scoring criteria are available in the protocol. Atherosclerotic cardiovascular disease was defined by the presence of coronary artery disease (a history of myocardial infarction, coronary revascularization, angiographic evidence of a coronary artery stenosis >70%, or a calcium score of >100 Agatston units on computed tomography), cerebrovascular disease (carotid artery stenosis >70%, carotid revascularization or ischemic stroke not due to atrial

fibrillation, valvular heart disease, or the presence of a mural thrombus), or peripheral arterial disease (resting ankle–brachial index ≤0.85, peripheral artery revascularization, or nontraumatic lower-limb amputation). Additional details about the qualifying criteria for the diagnosis of atherosclerotic cardiovascular disease are provided in the Supplementary Appendix.

For analysis of biochemical variables, all blood samples were obtained according to standard procedures after overnight fasting. Patients without risk-enhancing factors were eligible for inclusion if they had a serum LDL cholesterol level of at least 100 mg per deciliter (2.59 mmol per liter) or non-HDL cholesterol level of at least 130 mg per deciliter (3.37 mmol per liter). Patients with an LDL cholesterol level of 55 to 100 mg per deciliter or a non-HDL cholesterol level of 85 mg per deciliter (2.20 mmol per liter) to 130 mg per deciliter were also eligible for inclusion if they had at least one cardiovascular risk factor. Cardiovascular risk factors included a myocardial infarction within the previous 3 to 12 months, type 2 diabetes, current smoking, age greater than 60 years, a high-sensitivity C-reactive protein level of at least 2 mg per liter, a triglyceride level greater than 150 mg per deciliter (1.69 mmol per liter), a lipoprotein(a) level greater than 70 nmol per liter, or an HDL cholesterol level of less than 40 mg per deciliter (1.04 mmol per liter).[4,5]

The key exclusion criteria were a cardiovascular event within the previous 3 months, New York Heart Association class III or IV heart failure, uncontrolled severe hypertension, homozygous familial hypercholesterolemia, uncontrolled diabetes (a glycated hemoglobin level of ≥10% or a glucose level of ≥270 mg per deciliter [14.98 mmol per liter]), or active liver disease (current infectious, neoplastic, or metabolic conditions of the liver; unexplained elevations of aminotransferase levels to >3 times the upper limit of the normal range [ULN]; or total bilirubin levels >2 times the ULN). Patients were also excluded from the trial if they had received previous treatment with obicetrapib or if they had a history of cancer that had been treated with surgery, radiation, or systemic therapy.

Eligible patients were randomly assigned in a 2:1 ratio to receive oral obicetrapib at a dose of 10 mg once daily or matching placebo for 365 days. Patients were evaluated at trial visits that took place at screening, at the time of randomization, and at days 30, 84, 180, 270, and 365; an end-of-trial visit was performed 35 days after the last dose was administered. At each visit, trial procedures included measurement of vital signs, physical examination, laboratory studies (including lipid assays), and recording of adherence to the trial regimen and any reported adverse events, including the severity and potential relationship of the events to the trial regimen. All the patients, investigators, members of the academic leadership, the sponsor, and the staff of the contract research organization were unaware of the trial-group assignments and the results of lipid assays. Patients were asked not to start treatment with any new lipid-lowering agent or change the doses of existing treatments during the trial.

END POINTS

The primary efficacy end point was the percent change from baseline in LDL cholesterol at day 84 in the obicetrapib group as compared with the placebo group. For evaluation of the primary end point, we used direct measures of LDL cholesterol levels obtained by preparative ultracentrifugation; we also used the Friedewald and Martin–Hopkins equations to calculate LDL cholesterol levels in prespecified exploratory analyses.[16] Secondary end points included the percent change from baseline in LDL cholesterol levels at days 30, 180, 270, and 365; levels of apolipoprotein B, non-HDL cholesterol, total cholesterol, and triglycerides at days 84, 180, and 365; and levels of lipoprotein(a) and apolipoprotein A1 at day 84. Prespecified exploratory end points included LDL cholesterol levels of less than 40 mg per deciliter, 55 mg per deciliter, and 70 mg per deciliter (1.81 mmol per liter) at days 84, 180, and 365, respectively, and the occurrence of cardiovascular events, which were adjudicated by a committee whose members were unaware of the trial-group assignments.

SAFETY

Adverse events and laboratory findings, such as cardiovascular events, liver-enzyme abnormalities, muscle enzyme abnormalities, new-onset diabetes, worsening of glycemic control, and worsening of kidney function, were monitored. Worsening glycemic control was defined as an increase from baseline of more than 0.5 percentage points in the glycated hemoglobin level or

the use of a new concomitant medication or an increase in the current dose of antidiabetic therapy in a patient with a glycated hemoglobin level of at least 6.5% at baseline (or a combination of these). Worsening kidney function was defined a decrease from baseline of more than 25% in the estimated glomerular filtration rate or an increase from baseline in the serum creatinine level of at least 0.3 mg per deciliter (≥26.5 μmol per liter).

STATISTICAL ANALYSIS

We estimated that a sample size of at least 2280 patients would provide the trial with more than 90% power to detect a difference in the percent change in the LDL cholesterol level of 30 percentage points with obicetrapib as compared with placebo. Assuming that 5% of the patients would drop out of the trial, we determined that at least 2400 patients should be included. The primary efficacy analysis was performed in the intention-to-treat population, which included all the patients who underwent randomization, regardless of adherence to the trial regimen. The primary efficacy end point was calculated with the use of an analysis of covariance model, with trial group as a fixed effect and baseline LDL cholesterol level, type of cardiovascular risk (familial hypercholesterolemia or atherosclerotic cardiovascular disease), and use of high-intensity statins as covariates. To account for missing data owing to competing terminal events or other reasons, we used multiple imputation with a pattern-mixture model for the primary efficacy analysis. Least-squares means with 95% confidence intervals were determined for each group and for the differences between the groups. A fixed-sequence testing approach, conducted in a prespecified order, was used to control the type I error; no adjustment for multiple comparisons was made for exploratory efficacy end points. Adverse events were reported according to standard terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 28.0. Additional details regarding the statistical methods and analyses are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From December 2021 through August 2023, a total of 2530 patients were randomly assigned to receive obicetrapib (1686 patients) or placebo (844 patients) at 188 sites in China, Europe, Japan, and the United States. A total of 292 patients (11.5%) discontinued the trial regimen prematurely; the primary reasons for discontinuation were adverse events (4.4%), patient decision (3.6%), and loss to follow-up (1.7%). A total of 135 patients (5.3%) did not complete the trial because of loss to follow-up (2.1%), withdrawal of consent (1.5%), or death (1.1%) (Fig. S1). Demographic and clinical characteristics of the patients at baseline, including the use of lipid-lowering therapies, are summarized in Table 1 and Table S1. The mean age of the patients was 65 years, 34% were women, and the mean body-mass index (the weight in kilograms divided by the square of the height in meters) was 29. A total of 38% of the patients had diabetes, 89% had atherosclerotic cardiovascular disease, and 17% had heterozygous familial hypercholesterolemia. Most of the patients (91%) were receiving statin therapy, of whom 70% were receiving high-intensity statins; 27% were receiving ezetimibe, and 4% were receiving PCSK9 inhibitors. The mean LDL cholesterol level at baseline was 98 mg per deciliter (2.54 mmol per liter), the HDL cholesterol level was 49 mg per deciliter (1.27 mmol per liter), and the levels of triglycerides and lipoprotein(a) were 124 mg per deciliter (1.40 mmol per liter) and 39 nmol per liter, respectively.

PRIMARY END POINT

The changes from baseline in LDL cholesterol levels and the differences between the groups (obicetrapib vs. placebo) are summarized in Figure 1 and Table 2, as well as in Figure S2 and Tables S2 and S3. The least-squares mean percent change from baseline to day 84 in the LDL cholesterol level (the primary end point) was –29.9% (95% confidence interval [CI], –32.1 to –27.8) among patients who received obicetrapib and 2.7% (95% CI, –0.4 to 5.8) among those who received placebo (Fig. 1A), for a between-group difference of –32.6 percentage points (95% CI, –35.8 to –29.5; P<0.001). The mean (±SD) LDL cholesterol level at day 84 was 62.8±37.3 mg per deciliter (1.63±0.97 mmol per liter) in the obicetrapib group and 92.3±35.1 mg per deciliter (2.39±0.91 mmol per liter) in the placebo group (Fig. 1B). At day 84, the percentage of patients whose LDL cholesterol levels had reached less than

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Obicetrapib (N=1686)	Placebo (N=844)
Age — yr	65.4±9.9	65.3±9.6
Female sex — no. (%)	573 (34.0)	280 (33.2)
Race — no. (%)†		
White	1241 (73.6)	647 (76.7)
Asian	312 (18.5)	150 (17.8)
Black	112 (6.6)	39 (4.6)
Body-mass index‡	29.4±5.4	29.7±5.7
Diabetes — no. (%)	624 (37.0)	336 (39.8)
Atherosclerotic cardiovascular disease — no. (%)	1505 (89.3)	746 (88.4)
Coronary artery disease	1320 (78.3)	645 (76.4)
Cerebrovascular disease	350 (20.8)	166 (19.7)
Peripheral arterial disease	110 (6.5)	61 (7.2)
Heterozygous familial hypercholesterolemia — no. (%)§	284 (16.8)	143 (16.9)
Definite	166 (9.8)	91 (10.8)
Possible	106 (6.3)	51 (6.0)
Lipid-lowering therapy — no. (%)		
Statin	1533 (90.9)	782 (92.7)
High-intensity statin	1182 (70.1)	592 (70.1)
Ezetimibe	453 (26.9)	220 (26.1)
PCSK9 inhibitor	62 (3.7)	33 (3.9)
Laboratory test results		
Total cholesterol — mg/dl	174.2±44.6	175.3±45.2
LDL cholesterol — mg/dl	98.1±37.1	98.4±37.9
HDL cholesterol — mg/dl	49.5±14.8	49.7±14.9
Median triglycerides (IQR) — mg/dl	122.0 (91.0–170.0)	127.0 (91.0–175.0)
Non-HDL cholesterol — mg/dl	124.7±43.5	125.6±44.4
Apolipoprotein B — mg/dl	91.6±26.2	91.9±27.0
Apolipoprotein A1 — mg/dl	155.2±27.7	156.3±26.6
Median lipoprotein(a) (IQR) — nmol/liter	39.2 (11.2–166.3)	40.7 (11.8–159.1)
Estimated GFR — ml/min/1.73 m^2	84.2±18.0	84.8±17.7
High-sensitivity C-reactive protein (IQR) — mg/liter	1.3 (0.6–3.4)	1.4 (0.6–3.1)

* Plus–minus values are means ±SD. Categorical measures are expressed as percentages, and continuous measures as means or as medians and interquartile ranges (IQR) if not normally distributed. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. GFR denotes glomerular filtration rate, HDL high-density lipoprotein, LDL low-density lipoprotein, and PCSK9 proprotein convertase subtilisin–kexin type 9.
† Race was reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ Definite and possible heterozygous familial hypercholesterolemia (FH) were diagnosed by genotyping or according to Dutch Lipid Clinic Network criteria or applicable criteria outlined by the Simon Broome Register Group. A Dutch Lipid Clinic Network score of 3 to 5 points indicates possible FH; 6 to 8 points, probable FH; and greater than 8 points, definite FH.

40 mg per deciliter was 27.9% in the obicetrapib group and 1.1% in the placebo group; the percentage of patients with levels of less than 55 mg per deciliter was 51.0% in the obicetrapib group and 8.0% in the placebo group; and the percentage of patients with levels of less than 70 mg per

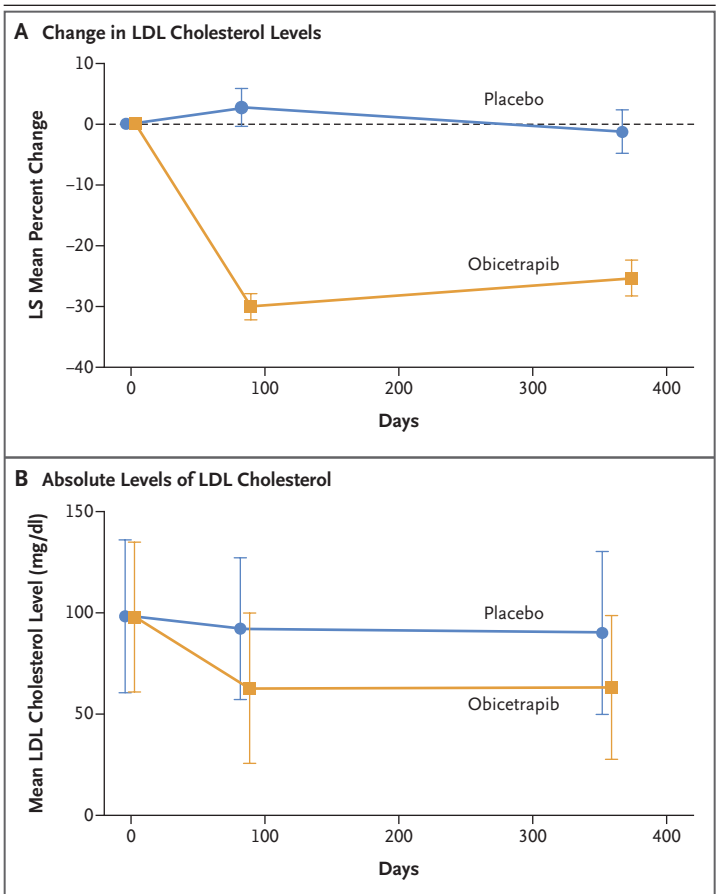

Figure 1. Relative and Absolute Changes in LDL Cholesterol Levels.

Panel A shows the least-squares (LS) mean percent changes from baseline in low-density lipoprotein (LDL) cholesterol levels. The I bars indicate 95% confidence intervals. Panel B shows the mean absolute levels of LDL cholesterol among patients who received placebo and those who received obicetrapib. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

deciliter was 68.4% in the obicetrapib group and 27.5% in the placebo group (Figure S2).

OTHER END POINTS

The least-squares mean percent change from baseline in the LDL cholesterol level (a secondary end point) favored obicetrapib over placebo, with a between-group difference of −36.6 percentage points (95% CI, −39.1 to −34.2) at day 30, −32.7 percentage points (95% CI, −36.0 to −29.4) at day 180, −30.2 percentage points (95% CI, −33.6 to −26.8) at day 270, and −24.0 percentage points (95% CI, −27.9 to −20.1) at day 365 (Table 2). Results of the subgroup analysis of the primary end point are shown in Figure S3. Similar effects were observed when the LDL cholesterol level was calculated with the use of the Friedewald and Martin–Hopkins equations (Table S2).

The differences between the obicetrapib and placebo groups in the changes from baseline in other lipid and lipoprotein levels are summarized in Table 2 and in Table S4 and Figure S4. The between-group difference in the apolipoprotein B level was −18.9 percentage points (95% CI, −20.8 to −17.1) at day 84, −18.3 percentage points (95% CI, −20.4 to −16.2) at day 180, and −13.8 percentage points (95% CI, −16.2 to −11.4) at day 365. The between-group difference in the non-HDL cholesterol level was −29.4 percentage points (95% CI, −31.9 to −27.0) at day 84, −28.3 percentage points (95% CI, −30.9 to −25.7) at day 180, and −23.0 percentage points (95% CI, −26.1 to −20.0) at day 365. The between-group difference in the lipoprotein(a) level was −33.5 percentage points (interquartile range, −36.9 to −30.2) at day 84. The between-group difference in the triglyceride level was −7.8 percentage points (95% CI, −11.6 to −4.1) at day 84, −8.0 percentage points (95% CI, −12.1 to −3.8) at day 180, and −5.7 percentage points (95% CI, −10.3 to −1.2) at day 365.

The between-group difference in the HDL cholesterol level was 136.3 percentage points (95% CI, 132.5 to 140.1) at day 84, 139.9 percentage points (95% CI, 135.6 to 144.2) at day 180, and 122.0 percentage points (95% CI, 117.5 to 126.6) at day 365. The between-group difference in the total cholesterol level was 17.7 percentage points (95% CI, 16.1 to 19.3) at day 84, 17.8 percentage points (95% CI, 16.0 to 19.7) at day 180, and 18.5 percentage points (95% CI, 16.4 to 20.7) at day 365. At day 84, the between-group difference in the apolipoprotein A1 level was 43.2 percentage points (95% CI, 41.7 to 44.6).

SAFETY

Adverse events and laboratory findings are summarized in Table 3 and in Tables S5, S6, and S7. An adverse event emerged during the trial period in 59.7% of the patients in the obicetrapib group and in 60.8% of those in the placebo group; no apparent differences were observed between the groups with respect to severity, relationship to the trial regimen, or the rationale for stopping treatment. The incidence of the most common adverse events also appeared to be similar in the

Table 2. Percent Changes from Baseline in Lipid and Lipoprotein Levels.*

End Point	Obicetrapib (N = 1686)	Placebo (N = 844)	Between-Group Difference	P Value
Primary end point				
Least-squares mean percent change in LDL cholesterol at day 84 (95% CI)	−29.9 (−32.1 to −27.8)	2.7 (−0.4 to 5.8)	−32.6 (−35.8 to −29.5)	<0.001
Secondary end points				
Least-squares mean percent change in LDL cholesterol (95% CI)				
Day 30	−34.8 (−36.5 to −33.0)	1.9 (−0.5 to 4.3)	−36.6 (−39.1 to −34.2)	<0.001
Day 180	−28.5 (−30.7 to −26.3)	4.2 (1.0 to 7.5)	−32.7 (−36.0 to −29.4)	<0.001
Day 270	−26.6 (−28.9 to −24.3)	3.6 (0.4 to 6.8)	−30.2 (−33.6 to −26.8)	<0.001
Day 365	−25.3 (−28.2 to −22.3)	−1.3 (-4.8 to 2.3)	−24.0 (−27.9 to −20.1)	<0.001
Least-squares mean percent change in apolipoprotein B (95% CI)				
Day 84	−17.8 (−19.2 to −16.5)	1.1 (−0.7 to 2.9)	−18.9 (−20.8 to −17.1)	<0.001
Day 180	−16.1 (−17.5 to −14.6)	2.2 (0.2 to 4.3)	−18.3 (−20.4 to −16.2)	<0.001
Day 365	−15.6 (−17.4 to −13.8)	−1.8 (−4.1 to 0.5)	−13.8 (−16.2 to −11.4)	<0.001
Least-squares mean percent change in non-HDL cholesterol (95% CI)				
Day 84	−26.6 (−28.4 to −24.9)	2.8 (0.4 to 5.2)	−29.4 (−31.9 to −27.0)	<0.001
Day 180	−24.6 (−26.5 to −22.7)	3.7 (1.1 to 6.2)	−28.3 (−30.9 to −25.7)	<0.001
Day 365	−22.4 (−24.7 to −20.1)	0.6 (−2.3 to 3.5)	−23.0 (−26.1 to −20.0)	<0.001
Least-squares mean percent change in HDL cholesterol (95% CI)				
Day 84	136.9 (133.2 to 140.5)	0.6 (−2.1 to 3.3)	136.3 (132.5 to 140.1)	<0.001
Day 180	141.8 (137.7 to 146.0)	1.9 (−1.1 to 5.0)	139.9 (135.6 to 144.2)	<0.001
Day 365	125.4 (121.1 to 129.7)	3.4 (0.1 to 6.6)	122.0 (117.5 to 126.6)	<0.001
Median percent change in lipoprotein(a) at day 84 (IQR)†	−32.3 (−62.8 to −4.7)	−0.9 (−15.7 to 13.0)	−33.5 (−36.9 to −30.2)	—
Least-squares mean percent change in apolipoprotein A1 at day 84 (95% CI)	43.4 (41.7 to 44.6)	0.3 (−0.9 to 1.4)	43.2 (41.7 to 44.6)	—
Least-squares mean percent change in total cholesterol (95% CI)				
Day 84	17.7 (16.3 to 19.0)	0 (−1.5 to 1.5)	17.7 (16.1 to 19.3)	—
Day 180	18.7 (17.2 to 20.2)	0.9 (−0.9 to 2.6)	17.8 (16.0 to 19.7)	—
Day 365	18.0 (16.2 to 19.7)	−0.6 (−2.6 to 1.4)	18.5 (16.4 to 20.7)	—
Least-squares mean percent change in triglycerides (95% CI)				
Day 84	−0.2 (−3.0 to 2.7)	7.7 (4.1 to 11.2)	−7.8 (−11.6 to −4.1)	—
Day 180	0.3 (−2.9 to 3.4)	8.2 (4.2 to 12.3)	−8.0 (−12.1 to −3.8)	—
Day 365	0.6 (−2.9 to 4.1)	6.3 (2.1 to 10.5)	−5.7 (−10.3 to −1.2)	—

* Between-group differences may not calculate precisely because of rounding. CI denotes confidence interval.
† The percent change in lipoprotein(a) levels and the between-group difference were analyzed with the use of a nonparametric distribution at baseline with Hodges–Lehmann estimates. The changes in lipoprotein(a) levels were evaluated in a post hoc analysis; no further formal significance testing was performed in accordance with the statistical hierarchy.

Table 3. Adverse Events, Adverse Events of Special Interest, and Changes in Vital Signs.*

Variable	Obicetrapib (N=1686)	Placebo (N=844)
Any adverse event that emerged during treatment period — no. (%)	1007 (59.7)	513 (60.8)
Adverse event related to obicetrapib or placebo that emerged during treatment period — no. (%)	76 (4.5)	39 (4.6)
Mild	51 (3.0)	25 (3.0)
Moderate	23 (1.4)	14 (1.7)
Severe	2 (0.1)	0
Adverse event leading to discontinuation of obicetrapib or placebo that emerged during treatment period — no. (%)	68 (4.0)	43 (5.1)
Serious adverse event that emerged during treatment period — no. (%)	211 (12.5)	117 (13.9)
Most common adverse events that emerged during treatment period — no. (%)		
Covid-19	81 (4.8)	48 (5.7)
Hypertension	82 (4.9)	33 (3.9)
Upper respiratory tract infection	49 (2.9)	33 (3.9)
Nasopharyngitis	43 (2.6)	22 (2.6)
Arthralgia	38 (2.3)	24 (2.8)
Urinary tract infection	39 (2.3)	21 (2.5)
Headache	43 (2.6)	17 (2.0)
Dizziness	40 (2.4)	15 (1.8)
Cardiovascular events — no. (%)		
Death from coronary heart disease, nonfatal MI, stroke, or coronary revascularization	70 (4.2)	44 (5.2)
Death from coronary heart disease	5 (0.3)	4 (0.5)
Nonfatal MI	20 (1.2)	11 (1.3)
Stroke	14 (0.8)	5 (0.6)
Coronary revascularization	31 (1.8)	24 (2.8)
Death from any cause — no. (%)	19 (1.1)	12 (1.4)
Adverse events of special interest — no. (%)		
ALT or AST level of >3×ULN	10 (0.6)	8 (0.9)
Bilirubin level of >2×ULN	2 (0.1)	4 (0.5)
Creatine kinase level of >5×ULN	5 (0.3)	3 (0.4)
New-onset diabetes or worsening glycemic control†	592 (35.1)	338 (40.0)
Increase in glycated hemoglobin level of >0.5 percentage points from baseline	234 (13.9)	133 (15.8)
Estimated GFR of <30 ml/min/1.73 m^2	13 (0.8)	13 (1.5)
Decrease in estimated GFR of >25% from baseline	115 (6.8)	70 (8.3)
Serum creatinine level of ≥0.3 mg/dl	91 (5.4)	61 (7.2)
Macular degeneration	1 (0.1)	0
Changes in vital signs from baseline to day 84		
Heart rate — beats/min	−0.3±7.8	0.3±8.0
Systolic blood pressure — mm Hg	0±12.5	−0.3±12.5
Diastolic blood pressure — mm Hg	−0.2±7.6	−0.1±8.1

* ALT denotes alanine aminotransferase, AST aspartate aminotransferase, Covid-19 coronavirus disease 2019, MI myocardial infarction, and ULN upper limit of the normal range.

† Worsening glycemic control was defined as an increase from baseline of more than 0.5 percentage points in the glycated hemoglobin level or the use of a new concomitant medication or an increase in the current dose of antidiabetic therapy in a patient with a glycated hemoglobin level of at least 6.5% at baseline (or a combination of these).

two groups. Liver-enzyme abnormalities occurred in 0.6% of the patients in the obicetrapib group and in 0.9% of those in the placebo group; muscle enzyme abnormalities occurred in 0.3% and 0.4% of the patients, respectively. New-onset diabetes or worsening of glycemic control occurred in 35.1% of the patients in the obicetrapib group and in 40.0% in the placebo group; worsening kidney function occurred in 6.8% and 8.3%, respectively. Cardiovascular events, including death from coronary heart disease, nonfatal myocardial infarction, stroke, or coronary revascularization, occurred in 4.2% of the patients in the obicetrapib group and in 5.2% in the placebo group (hazard ratio, 0.79; 95% CI, 0.54 to 1.15). There were no apparent differences in vital signs between the trial groups. A total of 229 patients had 24-hour ambulatory blood-pressure measurements at baseline and at day 270; no apparent changes from baseline in blood pressure were observed. There was also no apparent difference between the groups with respect to changes in aldosterone levels (Tables S8 and S9).

DISCUSSION

Among patients at high risk for cardiovascular events, the addition of the CETP inhibitor obicetrapib to background lipid-lowering therapy decreased LDL cholesterol levels by 29.9% at day 84, whereas LDL cholesterol levels increased by 2.7% with placebo. The achieved LDL cholesterol levels were numerically lower in the obicetrapib group than in the placebo group (62.8 vs. 92.3 mg per deciliter). Administration of obicetrapib also resulted in between-group differences in the change from baseline to day 84 in the levels of apolipoprotein B (–18.9 percentage points), non-HDL cholesterol (–29.4 percentage points), triglycerides (–7.8 percentage points), HDL cholesterol (136.3 percentage points), and apolipoprotein A1 (43.2 percentage points).

These findings suggest that obicetrapib may be a useful adjunct to lipid lowering in patients at high risk for cardiovascular events. Because treatment goals are not reached in many high-risk patients, despite the use of maximum tolerated doses of statins,[7-9] and there has been a progressive lowering of the treatment goals,[4,5] more effective lipid-lowering approaches, such as combination therapies, are increasingly required. Several oral lipid-lowering agents, such as ezetimibe and bempedoic acid, can be used in combination with statins, an approach that has shown evidence of cardiovascular benefit[17,18]; however, the incremental lipid-lowering effect of these agents is modest. Treatment with injectable PCSK9 inhibitors results in robust lipid lowering and reductions in cardiovascular risk,[19,20] although there are barriers to their access and uptake has been slow, even among adults with atherosclerotic cardiovascular disease.[21] The current findings with obicetrapib monotherapy and previous observations regarding obicetrapib in combination with ezetimibe[11-14] suggest that the addition of obicetrapib to statin therapy can result in more effective treatment of dyslipidemia for many patients.

The CETP inhibitors have been investigated extensively as a potential approach to reducing cardiovascular risk. Although this class of drugs was originally formulated to increase HDL cholesterol levels, their development has proved challenging. The first CETP inhibitor to advance to large clinical trials, torcetrapib, was associated with increased cardiovascular morbidity and mortality.[22] The associated off-target adverse effects of torcetrapib guided the development of subsequent agents.[23] The development of dalcetrapib, a modest CETP inhibitor that does not lower LDL cholesterol levels, and of evacetrapib, a more potent agent with a relatively short duration of treatment, was terminated because no effect was observed on cardiovascular outcomes.[24,25] Administration of anacetrapib, a more potent CETP inhibitor, for a median duration of 4.1 years produced a 9% lower rate of major coronary events than placebo.[26,27] The reduction in cardiovascular risk was associated with reductions in non-HDL cholesterol levels and was considered by investigators to be unrelated to increases in HDL cholesterol levels.[26] These findings complemented observations from genomic analyses, which showed that the association between low levels of CETP and cardiovascular risk correlated with reductions in the levels of LDL cholesterol and apolipoprotein B.[28]

Previous studies of CETP inhibitors have highlighted the challenges in assessing their LDL cholesterol–lowering effects, which have led to challenges with sample size estimation. It is possible that a clinical trial of evacetrapib, for example, may have recruited too few patients and may have had an inadequate treatment duration

to show a benefit with regard to cardiovascular outcomes.[25] A more accurate estimation of the LDL cholesterol–lowering effect of anacetrapib allowed for the design of a trial that could show a reduction in cardiovascular events, proportional to the modest reduction in LDL cholesterol levels.[26] In our trial, the reductions in LDL cholesterol levels in patients treated with obicetrapib were similar when assessed with three different analytic approaches.[16] However, the lowering effect on LDL cholesterol levels diminished by day 365, possibly owing to discontinuation of obicetrapib. The reduction in apolipoprotein B levels that occurred in patients treated with obicetrapib may provide additional cardiovascular benefits beyond decreasing LDL cholesterol levels.[29] The number of adverse effects in the obicetrapib group appeared to similar to those in the placebo group, with no apparent adverse effects related to the incidence of new-onset diabetes and worsening glycemic control or biochemical adverse effects on the kidneys. Owing to its hydrophilic design, obicetrapib has not been shown to accumulate within adipose tissue, an effect that has been observed with some CETP inhibitors.[30] Although fewer cardiovascular events occurred in patients who received obicetrapib than in those who received placebo, the trial was not powered to evaluate this effect; however, it is currently being evaluated in a large long-term cardiovascular outcomes trial (ClinicalTrials.gov number, NCT05202509).

Our trial has limitations that should be considered. First, obicetrapib was evaluated for a total of 365 days, so the efficacy and safety of longer-term administration require further investigation. The trial lacked the demographic diversity (e.g., with respect to gender and ethnic group) of the patients with high cardiovascular risk who are seen in clinical practice, which limits the generalizability of the trial results. Additional trials should evaluate the effects of obicetrapib on lipid levels in a broader range of patients. Treatment with CETP inhibitors, including obicetrapib, lowers lipoprotein(a) levels,[12,13,23] in contrast to treatment with statins, which may raise levels of lipoprotein(a); however, this trial did not require patients to have elevated levels of lipoprotein(a) to enroll. The effect of obicetrapib on lipoprotein(a) levels will need to be evaluated in groups with high baseline levels. In addition, although treatment with CETP inhibitors, including obicetrapib, increases HDL cholesterol levels, any clinical effect has yet to be proved.

This trial showed that among patients with atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia who were receiving maximum tolerated doses of lipid-lowering therapy and were at high risk for cardiovascular events, obicetrapib resulted in a reduction in LDL cholesterol levels of 32.6 percentage points after accounting for placebo. Further clinical studies are needed to determine whether this agent will be a useful therapy for the prevention of atherosclerotic cardiovascular disease.

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REFERENCES

1. Wang N, Woodward M, Huffman MD, Rodgers A. Compounding benefits of cholesterol-lowering therapy for the reduction of major cardiovascular events: systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 2022;15(6):e008552.

2. Ference BA, Ginsberg HN, Graham I, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies: a consensus statement

from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017;38:2459-72.
3. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.
4. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73(24):e285-e350.
5. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111-88.
6. Nelson AJ, Haynes K, Shambhu S, et al. High-intensity statin use among patients with atherosclerosis in the U.S. J Am Coll Cardiol 2022;79:1802-13.
7. Ray KK, Molemans B, Schoonen WM, et al. EU-wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: the DA VINCI study. Eur J Prev Cardiol 2021;28:1279-89.
8. Ray KK, Haq I, Bilitou A, et al. Treatment gaps in the implementation of LDL cholesterol control among high- and very high-risk patients in Europe between 2020 and 2021: the multinational observational SANTORINI study. Lancet Reg Health Eur 2023;29:100624.
9. Cannon CP, de Lemos JA, Rosenson RS, et al. Use of lipid-lowering therapies over 2 years in GOULD, a registry of patients with atherosclerotic cardiovascular disease in the US. JAMA Cardiol 2021;6:1060-8.
10. Ford J, Lawson M, Fowler D, et al. Tolerability, pharmacokinetics and pharmacodynamics of TA-8995, a selective cholesteryl ester transfer protein (CETP) inhibitor, in healthy subjects. Br J Clin Pharmacol 2014;78:498-508.
11. Hovingh GK, Kastelein JJ, van Deventer SJ, et al. Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet 2015;386:452-60.
12. Nicholls SJ, Ditmarsch M, Kastelein JJ, et al. Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial. Nat Med 2022;28:1672-8.
13. Ballantyne CM, Ditmarsch M, Kastelein JJ, et al. Obicetrapib plus ezetimibe as an adjunct to high-intensity statin therapy: a randomized phase 2 trial. J Clin Lipidol 2023;17:491-503.
14. Harada-Shiba M, Davidison MH, Ditmarsch M, et al. Obicetrapib as an adjunct to stable statin therapy in Japanese subjects: results from a randomized phase 2 trial. J Atheroscler Thromb 2024;31:1386-97.
15. Nicholls SJ, Nelson AJ, Ditmarsch M, et al. Obicetrapib on top of maximally tolerated lipid-modifying therapies in participants with or at high risk for atherosclerotic cardiovascular disease: rationale and designs of BROADWAY and BROOKLYN. Am Heart J 2024;274:32-45.
16. Martin SS, Giugliano RP, Murphy SA, et al. Comparison of low-density lipoprotein cholesterol assessment by Martin/Hopkins estimation, Friedewald estimation, and preparative ultracentrifugation: insights from the FOURIER trial. JAMA Cardiol 2018;3:749-53.
17. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372:2387-97.
18. Nissen SE, Lincoff AM, Brennan D, et al. Bempedoic acid and cardiovascular outcomes in statin-intolerant patients. N Engl J Med 2023;388:1353-64.
19. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097-107.
20. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-22.
21. Bradley CK, Kolkailah AA, Shah NP, Page CB, Peterson ED, Navar AM. Uptake of non-statin lipid-lowering therapies for secondary prevention in community practice. J Clin Lipidol 2023;17:412-4.
22. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007;357:2109-22.
23. Nicholls SJ, Nelson AJ. CETP inhibitors: should we continue to pursue this pathway? Curr Atheroscler Rep 2022;24:915-23.
24. Schwartz GG, Olsson AG, Abt M, et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. N Engl J Med 2012;367:2089-99.
25. Lincoff AM, Nicholls SJ, Riesmeyer JS, et al. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. N Engl J Med 2017;376:1933-42.
26. The HPS3/TIMI55–REVEAL Collaborative Group. Effects of anacetrapib in patients with atherosclerotic vascular disease. N Engl J Med 2017;377:1217-27.
27. Sammons E, Hopewell JC, Chen F, et al. Long-term safety and efficacy of anacetrapib in patients with atherosclerotic vascular disease. Eur Heart J 2022;43:1416-24.
28. Ference BA, Kastelein JJP, Ginsberg HN, et al. Association of genetic variants related to CETP inhibitors and statins with lipoprotein levels and cardiovascular risk. JAMA 2017;318:947-56.
29. Soffer DE, Marston NA, Maki KC, et al. Role of apolipoprotein B in the clinical management of cardiovascular risk in adults: an expert clinical consensus from the National Lipid Association. J Clin Lipidol 2024;18(5):e647-e663.
30. Nurmohamed NS, Ditmarsch M, Kastelein JJP. Cholesteryl ester transfer protein inhibitors: from high-density lipoprotein cholesterol to low-density lipoprotein cholesterol lowering agents? Cardiovasc Res 2022;118:2919-31.