

Obicetrapib in patients with heterozygous familial hypercholesterolemia: the BROOKLYN randomized clinical trial

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Most patients with heterozygous familial hypercholesterolemia fail to achieve adequate low-density lipoprotein (LDL) cholesterol lowering. Here we carried out a randomized trial to test the safety and efficacy of obicetrapib, a highly selective cholesteryl ester transfer protein inhibitor that lowers LDL cholesterol levels in patients with heterozygous familial hypercholesterolemia and an LDL cholesterol level ≥ 70 mg dl⁻¹ on maximally tolerated lipid-lowering therapy. The trial enrolled 354 patients (190 women, 164 men) with a mean LDL cholesterol level of 122 mg dl⁻¹ (87% on statins) who were randomized (2:1) to receive obicetrapib 10 mg or placebo daily for 365 days. For the primary endpoint, the change in LDL cholesterol from baseline to day 84, obicetrapib treatment resulted in a placebo-adjusted change in LDL cholesterol of -36.3% (95% confidence interval -42.2% to -30.4%, $P < 0.0001$). In analyses of secondary endpoints at day 84, treatment with obicetrapib resulted in placebo-adjusted reductions in apolipoprotein B of -24.4%, non-HDL cholesterol of -34.5% and lipoprotein(a) of -45.9%, as well as a placebo-adjusted increase in high-density lipoprotein cholesterol of +138.7%. Obicetrapib was well tolerated. These findings suggest that obicetrapib is an effective therapy for additional lipid lowering in patients with heterozygous familial hypercholesterolemia. ClinicalTrials.gov registration: [NCT05425745](https://clinicaltrials.gov/ct2/show/study/NCT05425745).

Heterozygous familial hypercholesterolemia (HeFH) is a prevalent form of genetic dyslipidemia, occurring in approximately 1 in 300 individuals across all regions of the world¹. Individuals with HeFH demonstrate higher levels of low-density lipoprotein (LDL) cholesterol from birth and an increased risk of premature atherosclerotic cardiovascular events². Clinical guidelines recommend early initiation of lipid-lowering therapies to lower LDL cholesterol levels and reduce the risk of adverse outcomes². However, most patients with HeFH fail to achieve adequate

lipid lowering and remain at a high cardiovascular risk^{3,4}. Several therapeutic agents are available for the treatment of patients with HeFH beyond statins, including ezetimibe and bempedoic acid, which produce modest incremental lipid lowering, and proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors and evinacumab, which are injectable, costly and have barriers to access in the clinic. As a result, adjunctive lipid-lowering therapies, beyond statins, are infrequently used for the treatment of patients with HeFH^{4,5}.

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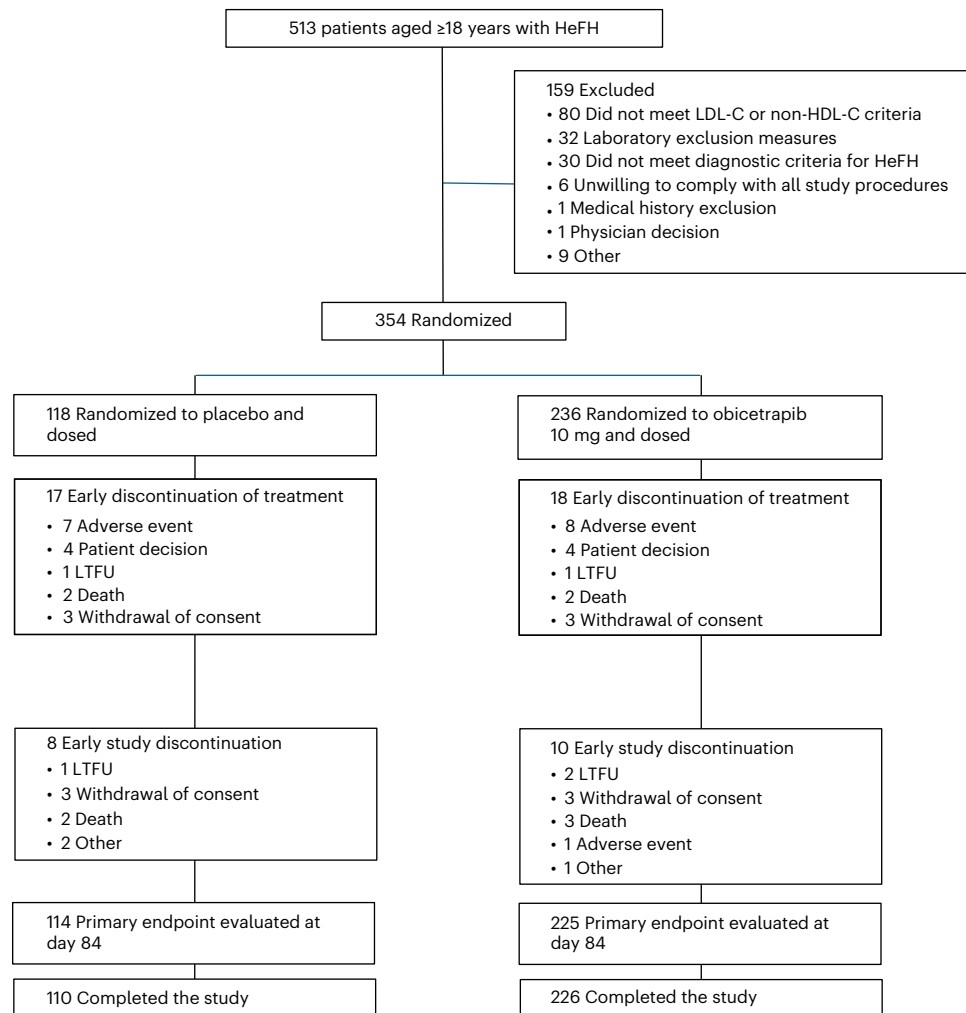


Fig. 1 | Flow of study participants. Participant flow through screening, randomization and early discontinuation in placebo and obicetrapib groups. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LTFU, loss to follow-up.

Cholesteryl ester transfer protein (CETP) plays a pivotal role in lipid metabolism by facilitating the exchange of esterified cholesterol from high-density lipoproteins (HDL) to LDL and very-low-density lipoprotein particles. Initial development of CETP inhibitors based on their ability to raise HDL cholesterol levels proved disappointing in cardiovascular outcome trials^{6–8}. Observations from genomic studies⁹ and analysis of the clinical trial demonstrating a reduction in cardiovascular events over time with anacetrapib^{10,11} suggested that CETP inhibition may reduce cardiovascular risk proportional to its degree of decrease in atherogenic lipids, but not proportional to the degree of increase in HDL cholesterol. Accordingly, any further development of CETP inhibitors was likely to have greater promise if it focused on reductions in LDL cholesterol levels.

Obicetrapib is a potent and selective, orally administered, CETP inhibitor that lowers levels of LDL cholesterol and raises HDL cholesterol in initial studies of patients treated with statin therapy^{12–16}. The use of obicetrapib has the potential to improve lipid lowering in patients with HeFH. The objective of the Evaluate the Effect of Obicetrapib in Patients with HeFH on Top of Maximum Tolerated Lipid-Modifying Therapies (BROOKLYN) study was to determine the degree of LDL cholesterol reduction through addition of obicetrapib in patients with HeFH that were treated with maximally tolerated lipid-lowering therapy.

Results

Patient disposition and clinical characteristics

From 29 July 2022 to 17 April 2023, 354 patients were randomized to treatment with placebo or obicetrapib at 70 sites in Europe, the UK,

South Africa, Canada and the USA. During the trial, 35 patients (9.9%) discontinued study treatment, primarily due to adverse events (4.2%), patient decision (2.3%) or because they were lost to follow-up (0.6%). A total of 18 (5.1%) patients did not complete the study, primarily due to loss to follow-up (0.8%), withdrawal of consent (1.7%) and death (1.4%) (Fig. 1). Evaluable data to investigate changes from baseline in LDL cholesterol were available for 341 patients (96.3%) at day 84 and 330 patients (93.2%) at day 365. A total of 4 patients, 1 (0.8%) in the placebo group and 3 (1.3%) in the obicetrapib group, were randomized, but were then subsequently discovered to not meet the protocol definition of HeFH. Given the intent-to-treat nature of the trial, they were included in the analysis. Clinical characteristics and use of background lipid-lowering medications at baseline are summarized in Table 1. Patients had a mean age of 57 years, 53% were female, 93% white race with a mean body mass index of 29 kg m⁻². A diagnosis of HeFH was made by genotyping, by the presence of a Dutch Lipid Clinic Network score greater than 8, by either a definite Simon Broome criteria classification (as in 72% of participants) or a possible Simon Broome criteria classification (26% of participants). Medical history included diabetes in 20% and atherosclerotic cardiovascular disease in 35.9% of participants. Concomitant use of lipid-lowering medications included statins in 87%, of which 75% were high intensity, ezetimibe in 53% and PCSK9 inhibitors in 16% of participants. Biochemical measures at baseline included a mean LDL cholesterol of 122 mg dl⁻¹, mean HDL cholesterol of 52 mg dl⁻¹, median triglycerides of 122 mg dl⁻¹ and median lipoprotein(a) of 42 nmol l⁻¹.

Table 1 | Clinical characteristics and medication use at baseline

Parameter	Placebo (n = 118)	Obicetrapib (n = 236)
Age—years	56.6 ± 11.1	57.0 ± 12.7
Females—n (%)	65 (55.1)	125 (53.0)
Race		
White—n (%)	110 (93.2)	219 (92.8)
Asian—n (%)	1 (0.8)	6 (2.5)
Black—n (%)	3 (2.5)	3 (1.3)
Body mass index—kg m ⁻²	29.6 ± 6.3	29.3 ± 5.3
Diabetes—n (%)	26 (22.0)	47 (19.9)
HeFH ^a		
Genotype confirmed, DLCN > 8 or Simon Broome definite—n (%)	84 (71.2)	172 (72.9)
Simon Broome possible—n (%)	33 (28.0)	61 (25.8)
Atherosclerotic cardiovascular disease—n (%)	47 (39.8)	80 (33.9)
Medication use		
Statins—(%)	99 (83.9)	209 (88.5)
High-intensity statin—n (%)	80 (67.8)	186 (78.8)
PCSK9 inhibitor—n (%)	26 (22.0)	32 (13.6)
Ezetimibe—n (%)	59 (50.0)	127 (53.8)
Biochemistry		
Total cholesterol—mg dl ⁻¹	197.0 ± 60.7	201.6 ± 53.0
LDL cholesterol—mg dl ⁻¹	119.9 ± 54.5	123.4 ± 49.2
HDL cholesterol—mg dl ⁻¹	50.2 ± 14.0	53.2 ± 15.7
Triglycerides—mg dl ⁻¹	129.0 (88.0, 178.0)	119.0 (77.0, 165.0)
non-HDL cholesterol—mg dl ⁻¹	146.7 ± 60.4	148.4 ± 55.7
Apolipoprotein B—mg dl ⁻¹	105.3 ± 34.2	107.2 ± 31.4
Apolipoprotein A1—mg dl ⁻¹	159.3 ± 27.8	163.0 ± 28.2
Lipoprotein(a)—nmol l ⁻¹	34.9 (13.3, 185.8)	45.8 (12.5, 168.2)
eGFR—ml min ⁻¹ 1.73 m ⁻²	92.4 ± 16.0	91.6 ± 18.7
hsCRP—mg l ⁻¹	1.4 (1.0, 3.0)	1.3 (1.0, 3.0)

Clinical characteristics, background use of lipid-modifying therapies and baseline biochemistry of patients at baseline. Categorical parameters are presented as number (percentage of patients) and continuous parameters as mean ± standard deviation or median (interquartile range) if not normally distributed. ^aFour patients (one in the placebo group and three in the obicetrapib group) were found after randomization not to meet the diagnostic criteria for HeFH and were included in the intention-to-treat analysis. DLCN, Dutch Lipid Clinical Network; eGFR, estimated glomerular filtration rate.

Effects of obicetrapib on LDL cholesterol

Changes in LDL cholesterol levels and placebo-adjusted differences between the treatment groups are summarized in Fig. 2 and Table 2. The primary endpoint, percent change in LDL cholesterol levels from baseline to day 84, showed a nonsignificant change of 0.3% (95% confidence interval (CI) -4.6% to 5.1%) with placebo and a statistically significant change of -36.1% (95% CI -39.5% to -32.6%) with obicetrapib, resulting in a 36.3% placebo-adjusted reduction (95% CI -42.2% to -30.4%, $P < 0.0001$) for obicetrapib. Missing day 84 values were imputed in the primary analysis for seven patients in the obicetrapib group and four patients in the placebo group; as a sensitivity analysis, based on observed data only, the placebo-adjusted reduction with obicetrapib was 36.1% (95% CI -41.8% to -30.4%, $P < 0.0001$). Waterfall plots of individual changes demonstrated a lowering of LDL cholesterol from

baseline of more than 50% in 3% of patients treated with placebo and 38% of patients treated with obicetrapib. A lower LDL cholesterol (77.0 ± 41.3 versus 118.2 ± 53.5 mg dl⁻¹, $P < 0.0001$) was achieved with obicetrapib compared to placebo and a greater percentage of patients achieved an LDL cholesterol of less than 40 mg dl⁻¹ (16.3% versus 0.9%, $P < 0.0001$), less than 55 mg dl⁻¹ (31.3% versus 2.6%, $P < 0.0001$), less than 70 mg dl⁻¹ (51.1% versus 11.4%, $P < 0.0001$) and less than 100 mg dl⁻¹ (77.1% versus 39.5%, $P < 0.0001$) at day 84 on exploratory analysis (Extended Data Fig. 1). A secondary endpoint, placebo-adjusted change in LDL cholesterol with obicetrapib of 41.5% (95% CI -51.1% to -31.8%, $P < 0.0001$) from baseline to day 365, was observed. Subgroup analysis demonstrated no heterogeneity of the effect of obicetrapib on LDL cholesterol levels (Extended Data Fig. 2). Similar effects were observed when LDL cholesterol was determined by Friedewald and Martin-Hopkins methods.

Effects of obicetrapib on other lipid and inflammatory parameters

Secondary endpoints, placebo-adjusted changes in other lipid and lipoprotein parameters, are summarized in Table 3 and Extended Data Fig. 3. The obicetrapib group demonstrated mean percent changes in apolipoprotein B at day 84 of -24.4% (95% CI -28.6% to -20.2%), at day 180 of -24.3% (95% CI -29.4% to -19.3%) and at day 365 of -25.8% (95% CI -31.9% to -19.7%); non-HDL cholesterol at day 84 of -34.5% (95% CI -39.7% to -29.2%), at day 180 of -33.0% (95% CI -39.4% to -26.7%) and at day 365 of -37.5% (95% CI -46.4% to -28.6%); and triglycerides at day 84 of -11.7% (95% CI -21.5% to -2.0%), at day 180 of -7.9% (95% CI -17.9% to -2.0%) and at day 365 of -5.1% (95% CI -17.7% to -7.5%). A greater percentage of patients treated with obicetrapib as opposed to placebo achieved non-HDL cholesterol and apolipoprotein B treatment goals (Extended Data Fig. 1).

The obicetrapib group demonstrated percent changes in HDL cholesterol at day 84 of +138.7% (95% CI 126.4% to 150.9%), at day 180 of +131.2% (95% CI 118.3% to 144.1%) and at day 365 of +121.4% (95% CI 107.0% to 135.8%); total cholesterol at day 84 of +9.8% (95% CI 5.4% to 14.1%) and at day 180 of +10.0% (95% CI 5.1% to 14.9%); and apoA1 at day 84 of +44.5% (95% CI 40.0% to 48.9%) and at day 365 of +39.6% (95% CI 33.8% to 45.4%).

Placebo-adjusted reductions in lipoprotein(a) were observed with obicetrapib at day 84 of -45.9% (95% CI -65.9% to -26.0%). Waterfall plots demonstrated a lowering of lipoprotein(a) levels from baseline of more than 50% in 3% of patients treated with placebo and 38% of patients treated with obicetrapib (Extended Data Fig. 4). No significant changes in high-sensitivity C-reactive protein (hsCRP) were observed. Trough plasma obicetrapib concentrations increased with administration and were demonstrated to decrease within 35 days after the last dose (Extended Data Fig. 5).

Effects of obicetrapib on lipoprotein particles

Nuclear magnetic resonance spectroscopy exploratory analysis of lipoprotein particles at baseline and day 180 and placebo-adjusted changes with obicetrapib are summarized in Extended Data Table 1 and Extended Data Fig. 6. A reduction in the concentration of total LDL (-52.5%, 95% CI -59.7% to -45.3%) and small LDL (-102.4%, 95% CI -122.8% to -82.0%), but not large LDL (+74.0%, 95% CI -36.8% to 184.8%) was observed with obicetrapib. An increase in the concentration of large HDL (+224.7%, 95% CI 198.3% to 251.1%), but not total HDL (4.5%, 95% CI -1.1% to 10.0%) was observed with obicetrapib.

Safety and tolerability of obicetrapib

Adverse events and laboratory-related study findings are summarized in Table 4. There was no difference between the placebo and obicetrapib groups regarding the incidence of treatment-emergent adverse events (70.3% versus 63.7%), their severity, attributed relationship to study drug or rationale to stop treatment. Adverse events leading to death

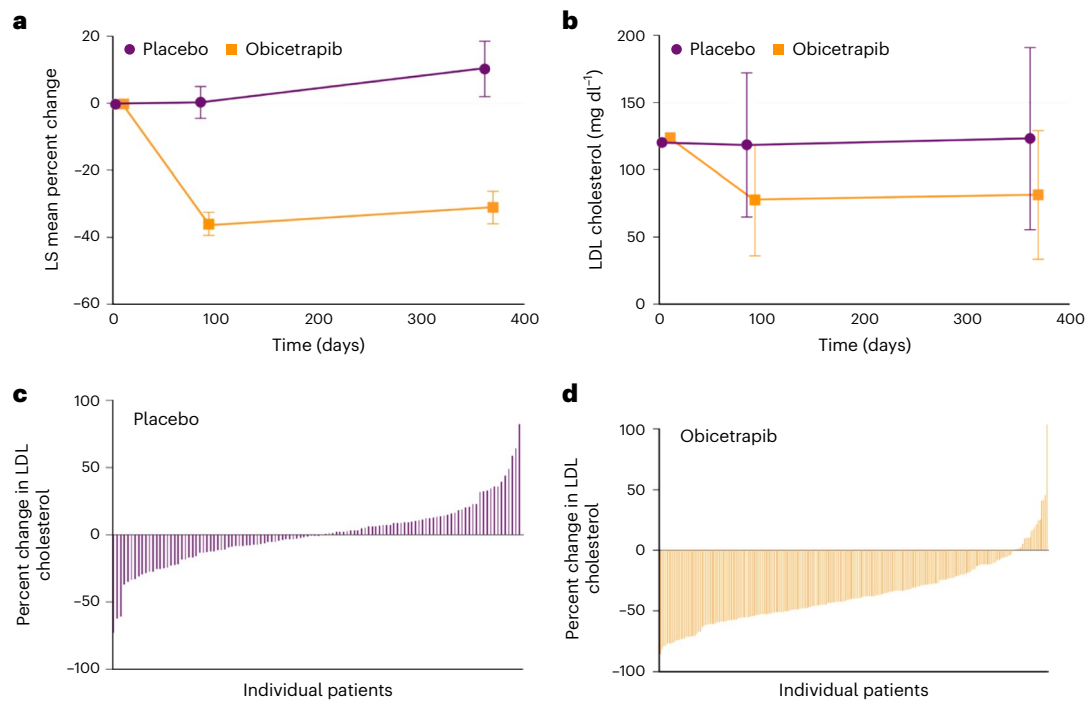


Fig. 2 | Effects on LDL cholesterol. **a**, Least squares (LS) mean percent change from baseline in LDL cholesterol in patients treated with placebo ($n = 118$) or obicetrapib ($n = 236$). Error bars represent 95% CIs calculated using analysis of covariance with baseline LDL cholesterol, cardiovascular risk type and high-intensity statin use as covariates. **b**, Mean absolute levels of LDL cholesterol

in patients treated with placebo ($n = 118$) or obicetrapib ($n = 236$). Error bars represent 95% CIs. **c,d**, Waterfall plots reflecting individual percent change in LDL cholesterol from baseline to day 84 in patients treated with placebo ($n = 118$) (**c**) or obicetrapib ($n = 236$) (**d**). Data represent biological replicates (individual patients with HeFH on maximally tolerated lipid-lowering therapy), $P < 0.0001$.

occurred in two patients (1.7%) in the placebo group and three patients (1.3%) in the obicetrapib group. The incidence of the most common adverse events did not differ between the treatment groups. Safety laboratory studies demonstrated no difference between placebo and obicetrapib groups in liver (0% versus 0%) and muscle (3.4% versus 1.3%) enzyme abnormalities. Several events of special interest were investigated, showing a similar incidence of new-onset diabetes or worsening of glycemic control (19.5% versus 16.7%) and worsening renal function (8.5% versus 3.8%) in the placebo and obicetrapib groups, respectively. While the overall cardiovascular rate was low, a higher rate of events (4.2% versus 2.1%) was observed in the placebo group compared to obicetrapib-treated patients. No significant changes in vital signs were observed in either group.

Discussion

This study evaluated the impact of the addition of the CETP inhibitor obicetrapib on plasma atherogenic lipid parameters to maximally tolerated lipid-lowering therapy in patients with HeFH. Administration of obicetrapib produced placebo-adjusted reductions in LDL cholesterol of 36.3% at day 84 and 41.5% at day 365. Patients treated with obicetrapib achieved lower LDL cholesterol levels (77.0 mg dl⁻¹ versus 118.2 mg dl⁻¹) and were more likely to achieve LDL cholesterol treatment goals. At day 84, treatment with obicetrapib also produced placebo-adjusted changes in apolipoprotein B of -24.4%, in non-HDL cholesterol of -34.5%, in lipoprotein(a) of -45.9% and in HDL cholesterol of +138.7%. Obicetrapib administration was well tolerated by patients with no excess rate of adverse events compared to placebo.

The findings extend reports from previous trials^{12–15} and suggest that obicetrapib may provide a useful adjunctive therapy for the treatment of patients with HeFH. More recently, obicetrapib produced similar lipid lowering in patients with clinically manifest atherosclerotic cardiovascular disease¹⁶. Increasing evidence highlights that a large percentage of patients at high risk of cardiovascular events fail to achieve guideline-recommended LDL cholesterol treatment goals^{17–19}. The

inability to achieve optimal lipid control early in the life of patients with HeFH confers an ongoing increased risk of premature cardiovascular events observed in these individuals. Combination lipid-lowering therapy in the setting of high cardiovascular risk is used less frequently than it should be^{17–19}, exposing patients with HeFH to persistently elevated LDL cholesterol levels when treated with statins, with or without other lipid-lowering agents^{3,4}. To be eligible for study participation, investigators were required to recruit patients with suboptimal LDL cholesterol control, acknowledging its relationship to residual cardiovascular risk, despite a high rate of use of maximally tolerated therapy, as patients randomized to the placebo group would not receive additional lipid lowering during the next 12 months. Accordingly, this study included the highest rate of use of additional, non-statin, lipid-lowering agents observed in trials of patients with HeFH. In this setting, administration of obicetrapib produced effective lipid lowering and enabled a greater number of patients to achieve LDL cholesterol targets.

The current study reflects a paradigm shift from the initial stages of development of CETP inhibitors, which focused on their ability to raise HDL cholesterol. Development of four previous CETP inhibitors proved to be disappointing, with one agent (torcetrapib) associated with cardiovascular and non-cardiovascular adverse events due to off-target effects⁶, two agents (dalcetrapib and evacetrapib) terminated due to the finding of futility in clinical outcomes trials^{7,8} and one agent (anacetrapib) with modest cardiovascular benefit but prolonged adipose tissue accumulation^{10,11}. Subsequent analysis of the benefit with anacetrapib¹⁰ and Mendelian randomization studies⁹ demonstrated that the potential cardiovascular benefit of having less CETP was likely to be associated with lower levels of LDL cholesterol and apolipoprotein B, rather than higher levels of HDL cholesterol. This prompted a change in the development paradigm for CETP inhibitors, which now focuses on LDL cholesterol lowering in patients at high cardiovascular risk with suboptimal LDL cholesterol control.

A potentially relevant observation is the exploratory finding that obicetrapib also reduced levels of lipoprotein(a) at day 84, although this

Table 2 | LDL cholesterol results at different time points

	Preparative ultracentrifugation method			Friedewald method			Martin-Hopkins method		
	Placebo (n=844)	Obicetrapib (n=1686)	P value	Placebo (n=844)	Obicetrapib (n=1686)	Placebo-adjusted change	Placebo (n=844)	Obicetrapib (n=1686)	Placebo-adjusted change
Baseline	119.9 ± 54.5	123.4 ± 49.2		119.1 ± 56.9	121.8 ± 50.7	121.8 ± 56.4	121.8 ± 56.4	123.8 ± 50.2	123.8 ± 50.2
Day 30				117.6 ± 48.4	71.3 ± 38.3	120.4 ± 47.8	120.4 ± 47.8	72.6 ± 38.4	72.6 ± 38.4
Median change				0 (-11.3, 13.6)	-44.8 (-54.0, -28.7)	0.9 (-10.9, 13.5)	0.9 (-10.9, 13.5)	-44.9 (-55.3, -27.7)	-44.9 (-55.3, -27.7)
LS mean change				1.9 (-0.5, 4.3)	-34.8 (-36.5, -33.0)	3.9 (-1.4, 9.2)	3.9 (-1.4, 9.2)	-39.4 (-43.2, -35.7)	-39.4 (-43.2, -35.7)
Day 84				118.2 ± 53.5	77.0 ± 41.3	119.2 ± 56.0	119.2 ± 56.0	77.3 ± 41.7	77.3 ± 41.7
Median change				-0.8 (-12.1, 10.8)	-40.0 (-53.0, -23.1)	2.2 (-8.5, 13.9)	1.1 (-6.9, 12.8)	-39.6 (-53.4, -24.2)	-39.6 (-53.4, -24.2)
LS mean change				0.3 (-4.6, 5.1)	-36.1 (-39.5, -32.6)	-36.3 (-42.2, -30.4)	2.3 (-2.6, 7.2)	-35.8 (-39.3, -32.3)	-35.9 (-39.3, -32.4)
Day 180				121.4 ± 57.7	81.8 ± 48.8	123.9 ± 57.4	123.9 ± 57.4	83.2 ± 48.8	83.2 ± 48.8
Median change				3.6 (-10.6, 15.0)	-37.1 (-51.5, -17.7)	4.3 (-9.9, 16.1)	4.3 (-9.9, 16.1)	-35.5 (-52.4, -16.5)	-35.5 (-52.4, -16.5)
LS mean change				4.2 (1.0, 7.5)	-28.5 (-30.7, -26.3)	-32.7 (-36.0, -29.4)	6.0 (0.3, 11.7)	-31.8 (-35.8, -27.8)	-31.8 (-35.8, -27.8)
Day 270				122.2 ± 60.2	78.7 ± 45.5	125.8 ± 59.3	125.8 ± 59.3	80.5 ± 45.3	80.5 ± 45.3
Median change				1.5 (-13.0, 20.5)	-40.6 (-54.5, -20.4)	2.2 (-13.4, 22.0)	2.2 (-13.4, 22.0)	-39.4 (-52.5, -21.0)	-39.4 (-52.5, -21.0)
LS mean change				3.6 (0.4, 6.8)	-26.6 (-28.9, -24.3)	-30.2 (-33.6, -26.8)	4.6 (-1.2, 10.3)	-32.9 (-37.0, -28.9)	-32.9 (-37.0, -28.9)
Day 365				122.9 ± 67.7	81.1 ± 47.6	127.5 ± 71.6	127.5 ± 71.6	83.0 ± 48.6	83.0 ± 48.6
Median change				-2.7 (-14.8, 13.6)	-36.6 (-54.1, -17.1)	-0.5 (-13.4, 14.1)	-0.5 (-13.4, 14.1)	-34.1 (-52.6, -14.1)	-34.1 (-52.6, -14.1)
LS mean change				10.3 (2.0, 18.6)	-31.1 (-36.1, -26.2)	-41.5 (-51.1, -31.8)	13.5 (4.6, 22.5)	-29.6 (-34.7, -24.5)	-29.6 (-34.7, -24.5)

Data are shown as mean ± standard deviation levels of LDL cholesterol, as determined by preparative ultracentrifugation, Friedewald and Martin-Hopkins methods. Changes and placebo-adjusted changes from baseline are expressed as median (interquartile range) and LS mean (95% CI).

was no longer evident at day 365. Increasing evidence has implicated lipoprotein(a) in the causality of atherosclerosis and calcific aortic valve disease²⁰. Elevated lipoprotein(a) levels identify patients at high residual risk of cardiovascular events, independent of LDL cholesterol, and play an important role as a risk enhancer, including in those with HeFH^{21–25}. While there are currently no effective pharmacological lipoprotein(a) lowering agents in clinical practice, there is considerable interest in developing agents that can produce robust reductions in its levels. This has led to the development of specific agents that lower lipoprotein(a), which are currently being evaluated in clinical trials^{26–31}. Obicetrapib has the potential to independently lower levels of both LDL cholesterol and lipoprotein(a), similar to other CETP inhibitors³², which may result in reduction in cardiovascular risk. It is important to note that patients were not required to have elevated lipoprotein(a) levels for inclusion in this study, and accordingly the effects of obicetrapib need to be further investigated in patients with high lipoprotein(a) levels. Lowering levels of lipoprotein(a) may be particularly important in patients with HeFH because of the high prevalence of elevated lipoprotein(a) in this population and the amplification of cardiovascular risk in such patients^{24,33}.

Consistent with the function of CETP inhibition, we observed significant increases in levels of HDL cholesterol with obicetrapib. The findings from development of other CETP inhibitors failed to demonstrate a favorable effect of raising HDL cholesterol on cardiovascular risk^{6–8,10}. This included the study of dalcetrapib, an agent that elevated HDL cholesterol and had no impact on LDL cholesterol⁸. This observation complemented findings from Mendelian randomization that identify no association between polymorphisms influencing HDL cholesterol levels and cardiovascular risk³⁴. Furthermore, some population studies have suggested that extremely high HDL cholesterol levels may be associated with an increase in risk³⁵. While the development of CETP inhibitors, such as obicetrapib, is focusing on their ability to modulate levels of atherogenic lipid parameters, it currently remains unknown if changes in HDL cholesterol or HDL particles will have any beneficial or detrimental clinical consequences.

We also evaluated the impact of treatment with obicetrapib on lipoprotein particle concentration, size and subspecies using nuclear magnetic resonance spectroscopy, characterizing the effect of a CETP inhibitor on lipid subclasses in a large trial of patients with HeFH. The finding that obicetrapib treatment resulted in reductions in the circulating concentration of total and small LDL particles supports the findings of its effects on apolipoprotein B levels. Given the established role of atherogenic lipoprotein particles in atherosclerosis, these effects have the potential to exert a favorable impact on disease progression. The increase in HDL particle size and concentration of large, but not total, HDL particles is consistent with the inhibition of transfer of esterified cholesterol from HDL with obicetrapib.

The study also demonstrated that obicetrapib was well tolerated by patients, although larger and longer studies will provide an important opportunity to characterize this more comprehensively. This included analysis of overall tolerability and several prespecified events of special interest for the development of lipid-modifying therapies. This is of particular interest given the adverse effects of torcetrapib that led to termination of its clinical development. We observed no adverse effect on biochemical liver, muscle and kidney biomarkers, nor an increase in blood pressure. There was no early evidence of the development of new-onset diabetes or worsening of glycemic control, similar to observations in a larger trial of obicetrapib-treated patients at high cardiovascular risk, which have been observed with the use of high-intensity statins. In fact, post hoc analyses of cardiovascular outcomes trials of other CETP inhibitors have suggested a potentially protective effect against the development of diabetes and improved glycemic control in patients with diabetes at baseline³⁶. Larger and longer studies of obicetrapib will further permit investigation of this effect. This small study observed no excess rate of cardiovascular events in the obicetrapib group.

Table 3 | Other lipid and lipoprotein parameters

	Placebo (n=118)	Obicetrapib (n=236)	Placebo-adjusted changes
Apolipoprotein B			
Baseline	105.3 ± 34.2	107.2 ± 31.4	
Day 30	106.6 ± 30.6	78.6 ± 21.0	
Median change	3.0 (-9.1, 11.6)	-25.1 (-37.0, -12.8)	
Day 84	107.1 ± 34.2	81.4 ± 23.5	
Median change	1.3 (-7.0, 12.5)	-24.3 (-34.8, -10.6)	
LS mean change	2.9 (-0.5, 6.4)	-21.5 (-23.8, -19.1)	-24.4 (-28.6, -20.2)
Day 180	108.9 ± 35.1	85.1 ± 27.5	
Median change	5.1 (-7.3, 16.3)	-20.1 (-33.8, -5.9)	
LS mean change	6.0 (1.9, 10.2)	-18.3 (-21.2, -15.4)	-24.3 (-29.4, -19.3)
Day 270	108.1 ± 35.3	82.4 ± 25.1	
Median change	3.0 (-10.8, 16.4)	-22.5 (-36.6, -7.9)	
Day 365	107.9 ± 41.5	84.1 ± 26.0	
Median change	0.1 (-12.4, 10.1)	-20.7 (-34.8, -5.3)	
LS mean change	8.2 (3.0, 13.3)	-17.6 (-20.9, -14.4)	-25.8 (-31.9, -19.7)
Non-HDL cholesterol			
Baseline	146.7 ± 60.4	148.4 ± 55.7	
Day 30	145.8 ± 52.5	93.1 ± 41.6	
Median change	-0.8 (-10.0, 13.5)	-39.8 (-49.0, -23.8)	
Day 84	148.4 ± 61.0	98.0 ± 44.2	
Median change	2.5 (-5.2, 12.5)	-34.5 (-47.8, -20.0)	
LS mean change	2.8 (-1.5, 7.1)	-31.6 (-34.6, -28.6)	-34.5 (-39.7, -29.2)
Day 180	150.3 ± 62.7	105.6 ± 52.6	
Median change	4.9 (-9.4, 15.7)	-31.2 (-45.6, -11.9)	
LS mean change	5.9 (0.7, 11.1)	-27.1 (-30.7, -23.4)	-33.0 (-39.4, -26.7)
Day 270	153.2 ± 66.2	102.6 ± 49.0	
Median change	2.9 (-11.1, 19.3)	-32.4 (-47.2, -16.6)	
Day 365	152.4 ± 76.8	104.6 ± 52.0	
Median change	0.9 (-13.0, 12.5)	-31.0 (-47.0, -12.3)	
LS mean change	11.6 (4.0, 19.3)	-25.8 (-30.4, -21.3)	-37.5 (-46.4, -28.6)
HDL cholesterol			
Baseline	50.2 ± 14.0	53.2 ± 15.7	
Day 30	50.2 ± 14.7	121.1 ± 31.0	
Median change	0 (-9.8, 10.8)	134.7 (98.5, 164.8)	
Day 84	51.4 ± 16.8	122.0 ± 33.7	
Median change	0 (-8.0, 11.1)	135.8 (98.1, 172.5)	
LS mean change	1.3 (-8.7, 11.2)	139.9 (132.8, 147.0)	138.7 (126.4, 150.9)
Day 180	52.2 ± 17.3	120.2 ± 35.2	
Median change	2.9 (-9.3, 13.2)	134.1 (98.6, 167.7)	
LS mean change	2.6 (-8.1, 13.4)	133.8 (126.5, 141.1)	131.2 (118.3, 144.1)
Day 270	52.6 ± 18.9	118.9 ± 36.9	
Median change	1.5 (-8.1, 13.6)	131.8 (96.0, 166.1)	
Day 365	54.2 ± 20.0	118.8 ± 37.5	
Median change	5.7 (-7.4, 16.1)	133.0 (91.9, 172.2)	
LS mean change	6.3 (-5.5, 18.0)	127.7 (119.4, 136.0)	121.4 (107.0, 135.8)
Total cholesterol			
Baseline	197.0 ± 60.7	201.6 ± 53.0	
Day 30	196.0 ± 53.5	214.2 ± 49.9	
Median change	0 (-7.3, 8.9)	9.1 (-5.8, 22.6)	

Table 3 (continued) | Other lipid and lipoprotein parameters

	Placebo (n=118)	Obicetrapib (n=236)	Placebo-adjusted changes
Day 84	199.9 ± 61.0	220.0 ± 52.5	
Median change	1.6 (−5.3, 9.5)	9.6 (−3.2, 27.7)	
LS mean change	2.3 (−1.2, 5.9)	12.1 (9.6, 14.6)	9.8 (5.4, 14.1)
Day 180	202.5 ± 62.4	225.7 ± 59.0	
Median change	4.9 (−3.7, 11.0)	11.3 (−4.2, 32.0)	
LS mean change	4.4 (0.4, 8.5)	14.4 (11.6, 17.3)	10.0 (5.1, 14.9)
Day 270	205.8 ± 66.2	221.5 ± 56.8	
Median change	3.1 (−7.3, 15.9)	11.1 (−4.6, 27.6)	
Day 365	206.6 ± 77.2	223.4 ± 56.7	
Median change	2.2 (−7.7, 11.1)	10.6 (−2.7, 27.5)	
LS mean change	9.3 (3.8, 14.8)	13.9 (10.6, 17.2)	4.6 (−1.8, 11.0)
Triglycerides			
Baseline	129.0 (88.0, 178.0)	119.0 (77.0, 165.0)	
Day 30	134.0 (88.0, 176.0)	102.0 (81.5, 134.5)	
Median change	−0.7 (−17.7, 25.0)	−6.4 (−25.7, 17.7)	
Day 84	126.0 (96.0, 172.0)	104.0 (83.0, 135.0)	
Median change	3.4 (−15.9, 21.8)	−4.4 (−25.6, 18.5)	
LS mean change	10.2 (1.9, 18.4)	−1.6 (−6.6, 3.5)	−11.7 (−21.5, −2.0)
Day 180	124.0 (89.0, 182.0)	103.0 (83.0, 145.0)	
Median change	5.1 (−17.5, 28.6)	−3.7 (−24.7, 25.2)	
LS mean change	12.4 (4.2, 20.6)	4.5 (−1.2, 10.1)	−7.9 (−17.9, 2.0)
Day 270	132.0 (84.0, 202.0)	111.0 (84.0, 147.0)	
Median change	7.3 (−18.8, 28.6)	−4.7 (−25.6, 29.2)	
Day 365	120.5 (79.0, 169.0)	107.5 (83.5, 144.5)	
Median change	−6.3 (−26.3, 18.0)	−2.2 (−25.5, 22.4)	
LS mean change	7.4 (−3.7, 18.5)	2.3 (−4.0, 8.6)	−5.1 (−17.7, 7.5)
Lipoprotein(a)			
Baseline	34.9 (13.3, 185.8)	45.8 (12.5, 168.2)	
Day 84	39.9 (12.5, 191.8)	18.8 (5.3, 104.0)	
Median change	3.7 (−9.3, 22.2)	−34.5 (−65.7, −8.2)	
LS mean change	10.5 (−8.0, 29.1)	−35.4 (−44.3, −26.5)	−45.9 (−65.9, −26.0)
Day 365	49.2 (13.5, 231.8)	20.4 (5.6, 103.4)	
Median change	0 (−17.8, 20.0)	−29.7 (−59.5, −5.4)	
LS mean change	24.4 (−49.0, 97.7)	−29.9 (−51.9, −7.9)	−54.3 (−131.1, 22.5)
Apolipoprotein A1			
Baseline	159.3 ± 27.8	163.0 ± 28.2	
Day 84	154.6 ± 27.4	229.5 ± 45.3	
Median change	−2.8 (−9.2, 3.2)	42.0 (27.7, 56.3)	
LS mean change	−2.3 (−5.9, 1.4)	42.2 (39.6, 44.8)	44.5 (40.0, 48.9)
Day 365	163.7 ± 31.7	233.7 ± 50.3	
Median change	2.6 (−6.7, 10.0)	41.9 (29.1, 60.8)	
LS mean change	3.0 (−1.9, 7.8)	42.6 (39.2, 45.9)	39.6 (33.8, 45.4)

Data shown as mean ± standard deviation or median (interquartile range) if not normally distributed. Changes and placebo-adjusted changes from baseline are expressed as median (interquartile range) and LS mean (95% CI).

Several limitations should be noted. Patients with HeFH have been treated with obicetrapib in earlier studies; however, the BROOKLYN study represents the first trial, to our knowledge, exclusively conducted to determine the effect of obicetrapib on lipid and lipoprotein parameters

in the setting of HeFH. While the sample size was sufficiently powered to demonstrate differences in LDL cholesterol lowering with obicetrapib, the study was small and only evaluated treatment of patients for 365 days. Therefore, the longer-term efficacy and safety of obicetrapib will require

Table 4 | Adverse events, laboratory-related study findings and events of special interest

Parameter	Placebo (n=118)	Obicetrapib (n=234)
Any TEAE—n (%)	83 (70.3)	149 (63.7)
Study drug-related TEAEs—n (%)	8 (6.8)	10 (4.3)
Mild—n (%)	5 (4.2)	5 (2.1)
Moderate—n (%)	3 (2.5)	5 (2.1)
Severe—n (%)	0 (0)	0 (0)
TEAEs leading to withdrawal from treatment—n (%)	8 (6.8)	10 (4.3)
Serious adverse events—n (%)	8 (6.8)	13 (5.6)
Most common TEAEs		
Influenza—n (%)	7 (5.9)	22 (9.4)
COVID-19—n (%)	8 (6.8)	15 (6.4)
Hypertension—n (%)	8 (6.8)	14 (6.0)
Nasopharyngitis—n (%)	5 (4.2)	15 (6.4)
Diarrhea—n (%)	8 (6.8)	9 (3.8)
Upper respiratory tract infection—n (%)	4 (3.4)	12 (5.1)
Headache—n (%)	6 (5.1)	7 (3.0)
Back pain—n (%)	6 (5.1)	7 (3.0)
Arthralgia—n (%)	3 (2.5)	9 (3.8)
Urinary tract infection—n (%)	5 (4.2)	7 (3.0)
Myalgia—n (%)	1 (0.8)	10 (4.3)
Fatigue—n (%)	7 (5.9)	2 (0.9)
Cough—n (%)	3 (2.5)	5 (2.1)
Gastroenteritis—n (%)	0 (0)	7 (3.0)
Cardiovascular events		
Cardiovascular death—n (%)	2 (1.7)	1 (0.4)
Nonfatal myocardial infarction—n (%)	0 (0)	1 (0.4)
Nonfatal stroke—n (%)	0 (0)	1 (0.4)
Coronary revascularization—n (%)	3 (2.5)	2 (0.8)
Musculoskeletal adverse events—n (%)		
Neurocognitive adverse events—n (%)		
Events of special interest		
Alanine or aspartate aminotransferase >3 × ULN—n (%)	0 (0)	0 (0)
Bilirubin >2 × ULN—n (%)	2 (1.7)	0 (0)
CK >5 × ULN—n (%)	4 (3.4)	3 (1.3)
New diabetes or worsening glycemic control—n (%)	23 (19.5)	39 (16.7)
HbA1c absolute increase >0.5% from baseline—n (%)	8 (6.8)	23 (9.8)
eGFR <30—n (%)	0 (0)	1 (0.4)
>25% decrease eGFR—n (%)	10 (8.5)	9 (3.8)
≥0.3 mg dl ⁻¹ serum creatinine—n (%)	9 (7.6)	5 (2.1)
Macular degeneration—n (%)	0 (0)	0 (0)
Vital signs		
Change in heart rate from baseline to day 84 (beats min ⁻¹)	+0.9 ± 8.6	0 ± 7.2
Change in systolic blood pressure from baseline to day 84 (mm Hg)	-1.7 ± 12.0	-0.6 ± 10.8
Change in diastolic blood pressure from baseline to day 84 (mm Hg)	-0.7 ± 7.7	-0.5 ± 7.0

Data shown as number (percentage of patients). CK, creatine kinase; HbA1c, glycated hemoglobin; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

further evaluation. In fact, there was attenuation of the placebo-adjusted effects of obicetrapib over the course of the study. Whether this reflects discontinuation of the study drug is uncertain, but additional longer studies will provide the opportunity to characterize the long-term effects of obicetrapib on lipid and lipoprotein parameters to a greater degree. While more than half of patients were female, the study lacked diversity in race and ethnicity. As prespecified, no adjustment was performed for multiple comparisons of the exploratory efficacy endpoints. The study was not powered to evaluate the effect of obicetrapib on clinical outcomes; a large cardiovascular outcomes trial of high-risk patients with elevated LDL cholesterol levels is underway.

HeFH represents a preventable cause of premature cardiovascular disease; however, many patients remain at risk due to late diagnosis and suboptimal control of LDL cholesterol levels, despite use of maximally tolerated statin therapy and the most common add-on therapy ezetimibe. Although PCSK9 inhibitors are effective adjunctive therapies for greater lowering of LDL cholesterol than obicetrapib, their cost, parenteral formulation and availability have limited their use globally. This study demonstrated that administration of obicetrapib, an oral therapeutic, was well tolerated and produced effective lowering of atherogenic lipid parameters, including LDL cholesterol and lipoprotein(a). These favorable effects across the spectrum of atherogenic lipid parameters, in combination with absence of adverse effects on glycemic control, suggest that obicetrapib may be useful as adjunctive therapy to achieve more effective lipid lowering. Whether this translates to improved cardiovascular outcomes will be determined by larger and longer trials that are ongoing. The potential for favorable effects on both lipid lowering and a lack of adverse impact on glycemic control³⁷ suggests that obicetrapib is a promising agent for treatment of patients with HeFH.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at <https://doi.org/10.1038/s41591-025-04179-4>.

References

- Hu, P. et al. Prevalence of familial hypercholesterolemia among the general population and patients with atherosclerotic cardiovascular disease: a systematic review and meta-analysis. *Circulation* **141**, 1742–1759 (2020).
- Nordestgaard, B. G. et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur. Heart J.* **34**, 3478–3490 (2013).
- Perez de Isla, L. et al. Attainment of LDL-cholesterol treatment goals in patients with familial hypercholesterolemia: 5-Year SAFEHEART registry follow-up. *J. Am. Coll. Cardiol.* **67**, 1278–1285 (2016).
- EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). *Lancet* **398**, 1713–1725 (2021).
- Lewek, J. et al. Clinical reality and challenges with familial hypercholesterolemia patients' management. 2024 results from the Regional Center for Rare Diseases (RCRD) Registry in Poland. *Int. J. Cardiol.* **419**, 132667 (2025).
- Barter, P. J. et al. Effects of torcetrapib in patients at high risk for coronary events. *N. Engl. J. Med.* **357**, 2109–2122 (2007).
- Schwartz, G. G. et al. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N. Engl. J. Med.* **367**, 2089–2099 (2012).

8. Lincoff, A. M. et al. Evacetrapib and cardiovascular outcomes in high-risk vascular disease. *N. Engl. J. Med.* **376**, 1933–1942 (2017).
9. Ference, B. A. et al. Association of genetic variants related to CETP inhibitors and statins with lipoprotein levels and cardiovascular risk. *JAMA* **318**, 947–956 (2017).
10. HPS3/TIMI55-REVEAL Collaborative Group et al. Effects of anacetrapib in patients with atherosclerotic vascular disease. *N. Engl. J. Med.* **377**, 1217–1227 (2017).
11. HPS3/TIMI55-REVEAL Collaborative Group et al. Long-term safety and efficacy of anacetrapib in patients with atherosclerotic vascular disease. *Eur. Heart J.* **43**, 1416–1424 (2022).
12. Ford, J. et al. Tolerability, pharmacokinetics and pharmacodynamics of TA-8995, a selective cholesteryl ester transfer protein (CETP) inhibitor, in healthy subjects. *Br. J. Clin. Pharmacol.* **78**, 498–508 (2014).
13. Hovingh, G. K. 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* **386**, 452–460 (2015).
14. Nicholls, S. J. et al. Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial. *Nat. Med.* **28**, 1672–1678 (2022).
15. Ballantyne, C. M. et al. Obicetrapib plus ezetimibe as an adjunct to high-intensity statin therapy: a randomized phase 2 trial. *J. Clin. Lipidol.* **17**, 491–503 (2023).
16. Nicholls, S. J. et al. Safety and efficacy of obicetrapib in patients at high cardiovascular risk. *N. Engl. J. Med.* **393**, 51–61 (2025).
17. Ray, K. K. 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.* **28**, 1279–1289 (2021).
18. Ray, K. K. 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.* **29**, 100624 (2023).
19. Cannon, C. P. 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.* **6**, 1–9 (2021).
20. Kronenberg, F. et al. Lipoprotein(a) in atherosclerotic cardiovascular disease and aortic stenosis: a European Atherosclerosis Society consensus statement. *Eur. Heart J.* **43**, 3925–3946 (2022).
21. The Emerging Risk Factors Collaboration Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. *JAMA* **302**, 412–423 (2009).
22. Bostom, A. G. et al. Elevated plasma lipoprotein(a) and coronary heart disease in men aged 55 years and younger: a prospective study. *JAMA* **276**, 544–548 (1996).
23. Raitakari, O. et al. Long-term tracking and population characteristics of lipoprotein (a) in the Cardiovascular Risk in Young Finns Study. *Atherosclerosis* **356**, 18–27 (2022).
24. Alonso, R. et al. Lipoprotein(a) levels in familial hypercholesterolemia: an important predictor of cardiovascular disease independent of the type of LDL receptor mutation. *J. Am. Coll. Cardiol.* **63**, 1982–1989 (2014).
25. Seed, M. et al. Relation of serum lipoprotein(a) concentration and apolipoprotein(a) phenotype to coronary heart disease in patients with familial hypercholesterolemia. *N. Engl. J. Med.* **322**, 1494–1499 (1990).
26. Tsimikas, S. et al. Lipoprotein(a) reduction in persons with cardiovascular disease. *N. Engl. J. Med.* **382**, 244–255 (2020).
27. O'Donoghue, M. L. et al. Small interfering RNA to reduce lipoprotein(a) in cardiovascular disease. *N. Engl. J. Med.* **387**, 1855–1864 (2022).
28. Nissen, S. E. et al. Single ascending dose study of a short interfering RNA targeting lipoprotein(a) production in individuals with elevated plasma lipoprotein(a) levels. *JAMA* **327**, 1679–1687 (2022).
29. Nissen, S. E. et al. Lepodisiran, an extended-duration short interfering RNA targeting lipoprotein(a): A randomized dose-ascending clinical trial. *JAMA* **330**, 2075–2083 (2023).
30. Nissen, S. E. et al. Single ascending and multiple-dose trial of zerlasiran, a short interfering RNA targeting lipoprotein(a): A randomized clinical trial. *JAMA* **331**, 1534–1543 (2024).
31. Nicholls, S. J. et al. Oral muvalaplin for lowering of lipoprotein(a): A randomized clinical trial. *JAMA* **333**, 222–231 (2025).
32. Thomas, T. et al. CETP (cholesteryl ester transfer protein) inhibition with anacetrapib decreases production of lipoprotein(a) in mildly hypercholesterolemic subjects. *Arterioscler. Thromb. Vasc. Biol.* **37**, 1770–1775 (2017).
33. Langsted, A., Kamstrup, P. R., Benn, M., Tybjaerg-Hansen, A. & Nordestgaard, B. G. High lipoprotein(a) as a possible cause of clinical familial hypercholesterolaemia: a prospective cohort study. *Lancet Diabetes Endo.* **4**, 577–587 (2016).
34. Voight, B. F. et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet* **380**, 572–580 (2012).
35. Madsen, C. M., Varbo, A. & Nordestgaard, B. G. Extreme high high-density lipoprotein cholesterol is paradoxically associated with high mortality in men and women: two prospective cohort studies. *Eur. Heart J.* **38**, 2478–2486 (2017).
36. Dangas, K., Navar, A. M. & Kastelein, J. J. P. The effect of CETP inhibitors on new-onset diabetes: a systematic review and meta-analysis. *EHJ-CVP* **8**, 632 (2022).
37. Banach, M. et al. Personalized management of dyslipidemias in patients with diabetes-it is time for a new approach (2022). *Cardiovasc. Diabetol.* **21**, 263 (2022).

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Methods

Trial organization and oversight

The trial design has been previously reported³⁸ and the protocol was approved by ethics committees at participating sites. All participating patients provided written informed consent before undertaking any study procedures. The study protocol and statistical analysis plan are provided in Supplementary Note 1. A complete list of site investigators and trial leadership is provided in Supplementary Note 2. In collaboration with the academic steering committee, the study sponsor (NewAmsterdam Pharma) participated in its design, conduct and data collection. The primary statistical analysis was performed by statisticians at Medpace, in collaboration with an academic statistician representing the steering committee (M.S.). S.J.N. wrote the first draft of the paper, and the final version was approved by all authors. While the sponsor reviewed the paper, S.J.N. made the final decision on content and vouches for the accuracy and completeness of the data and fidelity of the trial to the protocol and statistical analysis plan (Supplementary Information).

Trial design and patients

Eligible patients were at least 18 years of age with a history of HeFH, defined by genotyping, a Dutch Lipid Clinical Network score greater than 8 points or a Simon Broome Register Diagnostic Criteria categorization of definite or possible FH, and were treated with maximally tolerated lipid-lowering therapy, including ezetimibe, bempedoic or a PCSK9 inhibitor. The protocol prespecified that at least 70% of patients must be taking a high-intensity statin, defined as atorvastatin 40 mg or 80 mg or rosuvastatin 20 mg or 40 mg. Patients were required to have a fasting serum LDL cholesterol of at least 70 mg dl⁻¹ (1.81 mmol l⁻¹), triglyceride less than 400 mg dl⁻¹ (4.52 mmol l⁻¹) and an estimated glomerular filtration rate of at least 30 ml min⁻¹ 1.73 m⁻². Exclusion criteria included a history of a cardiovascular event in the preceding three months, class III or IV heart failure, homozygous FH, uncontrolled hypertension or diabetes, active liver disease, malignancy requiring surgery, radiation or systemic therapy, or previous treatment with obicetrapib.

Eligible patients who met all inclusion and no exclusion criteria were randomized in a 2:1 fashion to treatment with daily oral doses of 10 mg of obicetrapib or placebo for 365 days. Patients were evaluated at study visits at screening, randomization and days 30, 84, 180, 270 and 365, with an end of study visit 35 days after the last dose was administered. At each visit, procedures included measurement of vital signs, physical examination, laboratory studies including lipid assays, and recording of study drug compliance and any reported adverse events, including their severity and potential relationship to study drug. Gender was identified by self-report. All patients, investigators, academic leadership, the sponsor and the contract research organization were blinded to treatment allocation and results of lipid assays. Patients were asked to not initiate any new lipid-lowering agent or change doses of existing therapy during the trial.

Trial endpoints

The primary efficacy endpoint was the percent change from baseline to day 84 in fasting LDL cholesterol in the obicetrapib compared to the placebo group. Secondary endpoints included the percent change from baseline in (1) LDL cholesterol at days 180 and 365, (2) apolipoprotein B, non-HDL cholesterol, HDL cholesterol, total cholesterol and triglycerides at days 84, 180 and 365 and (3) lipoprotein(a) at days 84 and 365. Prespecified exploratory endpoints included the (1) percentage of patients achieving an LDL cholesterol level less than 40 mg dl⁻¹, 55 mg dl⁻¹, 70 mg dl⁻¹ and 100 mg dl⁻¹ at days 84 and 365; (2) percentage of patients achieving a non-HDL cholesterol level less than 85 mg dl⁻¹, 100 mg dl⁻¹ and 130 mg dl⁻¹ at days 84 and 365; (3) percentage of patients achieving an apolipoprotein B level less than 65 mg dl⁻¹, 80 mg dl⁻¹ and 130 mg dl⁻¹ at days 84 and 365; (4) percent change from baseline

in apolipoprotein A1 level at days 84 and 365; (5) percent change from baseline in lipoprotein size and composition at day 180; and (6) trough levels of obicetrapib from baseline to day 365.

The primary analysis was performed using direct measures of LDL cholesterol by preparative ultracentrifugation. Additional analyses were performed using measurements of LDL cholesterol by the Friedewald and Martin–Hopkins equations³⁹. Measurements of cholesterol and triglycerides were performed using enzymatic assay (Beckman Coulter), of lipoprotein(a) by immunoturbidometric assay (Roche), of apolipoproteins by immunonephelometry (Siemens) and of lipoprotein size and composition by nuclear magnetic resonance spectroscopy (Labcorp). Non-HDL cholesterol was calculated as the subtraction of HDL cholesterol from total cholesterol. hsCRP was measured by immunonephelometry.

Statistical analysis

The primary efficacy assessment was performed for the intention-to-treat population, including all patients randomized to either treatment group. The primary and secondary efficacy endpoints were calculated using analysis of covariance with the treatment group as a fixed effect and baseline LDL cholesterol as a covariate. The least squares mean and 95% CI for each group and placebo-adjusted mean differences with obicetrapib were estimated. Missing data were imputed, based on a pattern mixture model assuming the data are missing and not at random. Missing measurements of non-retrieved dropouts were modeled using known measurements from retrieved dropouts (that is, participants who remained in the study after treatment discontinuation) in the same treatment group. One hundred datasets were imputed. For each imputation dataset, the analysis of covariance model described earlier was used and results were combined using Rubin's method⁴⁰. The treatment group difference in percent changes from baseline in hsCRP was analyzed using a Hodges–Lehmann estimate, as the observed distribution of hsCRP values did not conform to parametric assumptions. Safety was reported using standard Medical Dictionary for Regulatory Activities terms as counts and percentages. Sample size calculations determined that at least 285 evaluable patients would provide more than 90% power to detect a 30% reduction in LDL cholesterol with obicetrapib, with a standard deviation of 15%, compared to placebo. Assuming a 5% dropout rate, it was determined to randomize at least 300 patients in the study.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The authors declare that all data supporting the findings of this analysis are available within the article and its Supplementary Information. NewAmsterdam Pharma is committed to sharing, with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. Data requests should be submitted to stephen.nicholls@monash.edu. These requests are reviewed and approved by an independent review and panel on the basis of scientific merit. Researchers can expect a response within 30 business days. Access is subject to approval of a research proposal, execution of a data sharing agreement and compliance with patient privacy regulations. All data provided are anonymized to respect the privacy of patients in accordance with GDPR and in line with applicable laws and regulations.

References

38. Nicholls, S. J. 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.* **274**, 32–45 (2024).

39. Martin, S. S. 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.* **3**, 749–753 (2018).
40. Rubin, D. B. *Multiple Imputation for Nonresponse in Surveys* (Wiley, 1987).

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Author contributions

S.J.N. wrote the first draft of the paper. S.J.N., M.D., J.J.P.K. and M.H.D. designed the study. M.D., E.W., A.L.N., D.K. and A.H. coordinated trial operations and data collection. V.B. and M.S. performed the statistical analyses, with M.S. providing statistical oversight. S.J.N., A.J.N. and J.B. supervised site activities and data collection. S.J.N., A.J.N., C.M.B., K.K.R., A.M.N., S.E.N., A.C.G., L.R.B., B.A.F., U.L., M.B., R.M., A.L.C. and M.H.D. enrolled patients and collected data. All authors contributed to data interpretation, critically reviewed and revised the paper and approved the final version for submission. S.J.N. had full access to all trial data and takes responsibility for the integrity of the data and accuracy of the data analysis.

Competing interests

S.J.N. received grant and/or research support from AstraZeneca, NewAmsterdam Pharma, Amgen, Anthera, Cyclarity, Eli Lilly, Esperion, Novartis, Cerenis, The Medicines Company, Resverlogix, InfraRex, Roche, Sanofi-Regeneron and LipoScience; and was a consultant for 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. A.J.N. has received research support from AstraZeneca, Amgen, Eli Lilly and Novartis; and is a consultant for Amgen, AstraZeneca, Boehringer Ingelheim, CSL Seqirus, Eli Lilly, GSK, Novartis, Novo Nordisk, Sanofi Pasteur and Vaxxinity. C.M.B. has received grants or research support from Abbott Diagnostic, Akcea, Amgen, Arrowhead, Ionis, Merck, NewAmsterdam Pharma, Novartis, Novo Nordisk, Roche Diagnostic, NIH, AHA and ADA; and is a consultant for 89Bio, Abbott Diagnostics, Amarin, Amgen, Arrowhead, AstraZeneca, Denka Seiken, Esperion, Genentech, Illumina, Ionis, Eli Lilly, Merck, NewAmsterdam Pharma, Novartis, Novo Nordisk and Roche Diagnostic. K.K.R. reports research grants from Amgen, Amarin, Sanofi, Daiichi Sankyo and Ultragenyx to Imperial College London; consultancy to Novartis, Daiichi Sankyo, Kowa, Esperion, Novo Nordisk, MSD, Eli Lilly, Silence Therapeutics, AZ, New Amsterdam Pharma, Bayer, Beren Therapeutics, Cleerly, EmendoBio, Scribe, NodThera, CRISPR, Vaxxinity and Sanofi; fees for lectures from Novartis, BI, AZ, Novo Nordisk, Viatrix, Amarin, Sanofi, Amgen, Esperion, Daiichi Sankyo, Dr Reddy's, Mankind and Macleods Pharma for symposia at international meetings; and holding stock options from NewAmsterdam Pharma, Scribe Therapeutics and Pemi31. A.M.N. has received research support to her institution from Amgen and Esperion; and personal fees for consulting from Amgen, Arrowhead, AstraZeneca, Bayer, Eli Lilly, Esperion, Janssen, Merck, NewAmsterdam, Novartis, Novo Nordisk, Pfizer, Roche and Silence Therapeutics. S.E.N. has received research funding to perform clinical trials from AbbVie,

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D.K., A.H. and M.H.D. are employees of NewAmsterdam Pharma and hold stocks or options. J.B. declares no competing interests.

Additional information

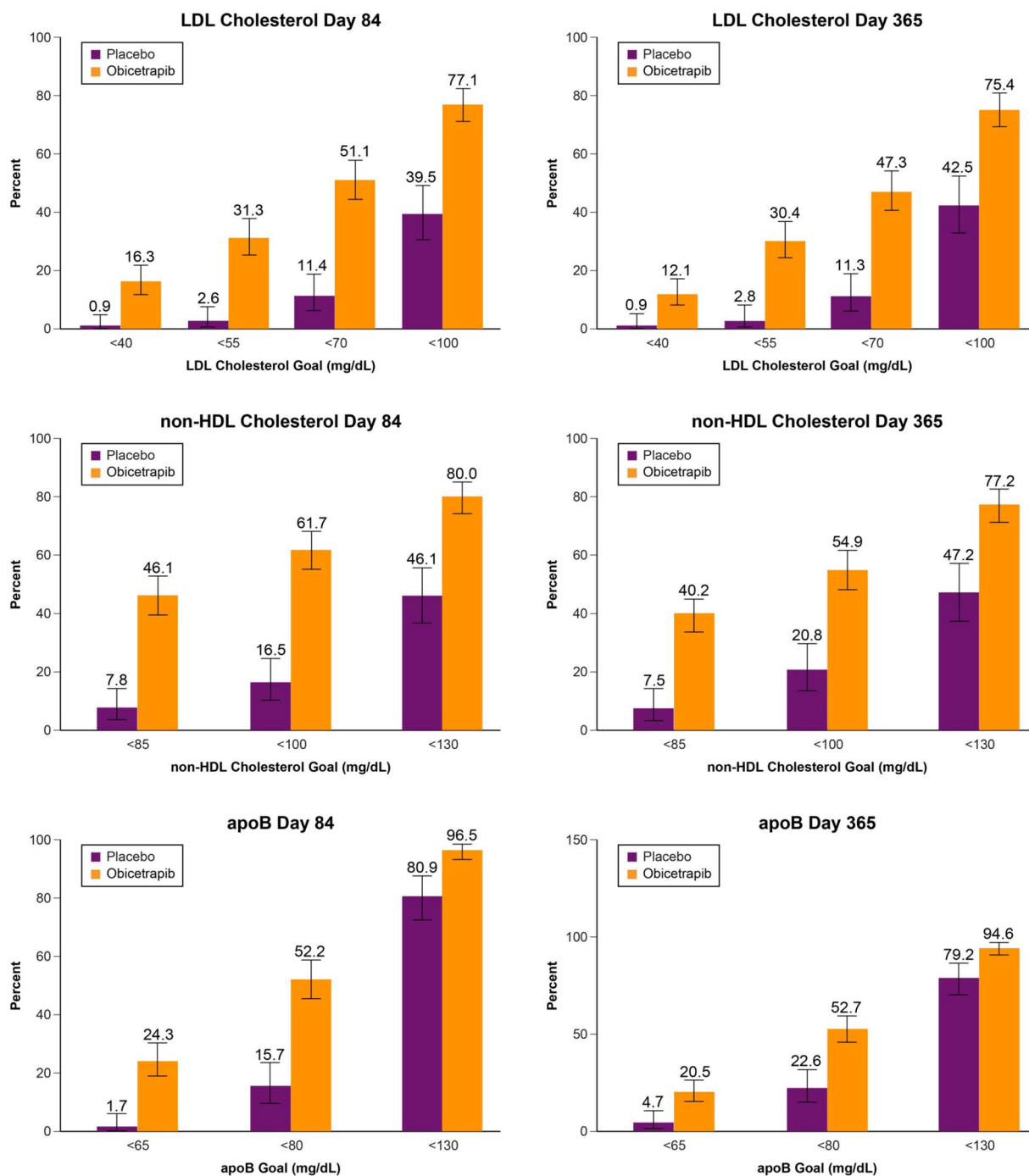
Extended data is available for this paper at <https://doi.org/10.1038/s41591-025-04179-4>.

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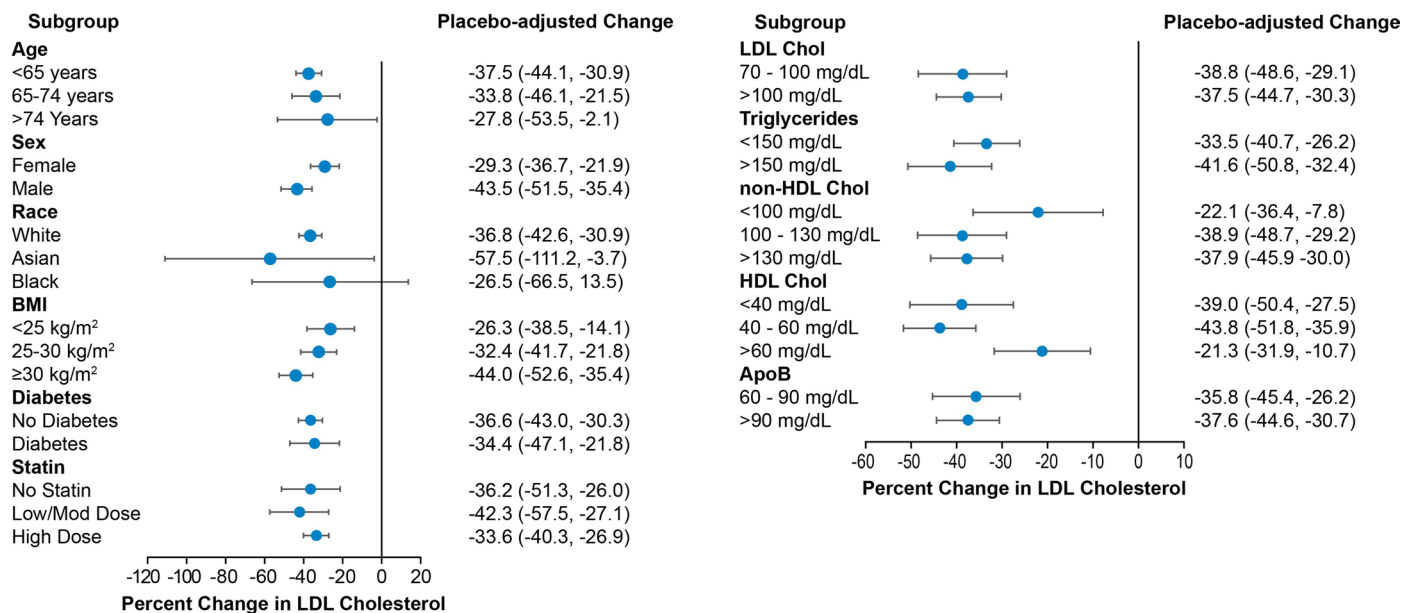
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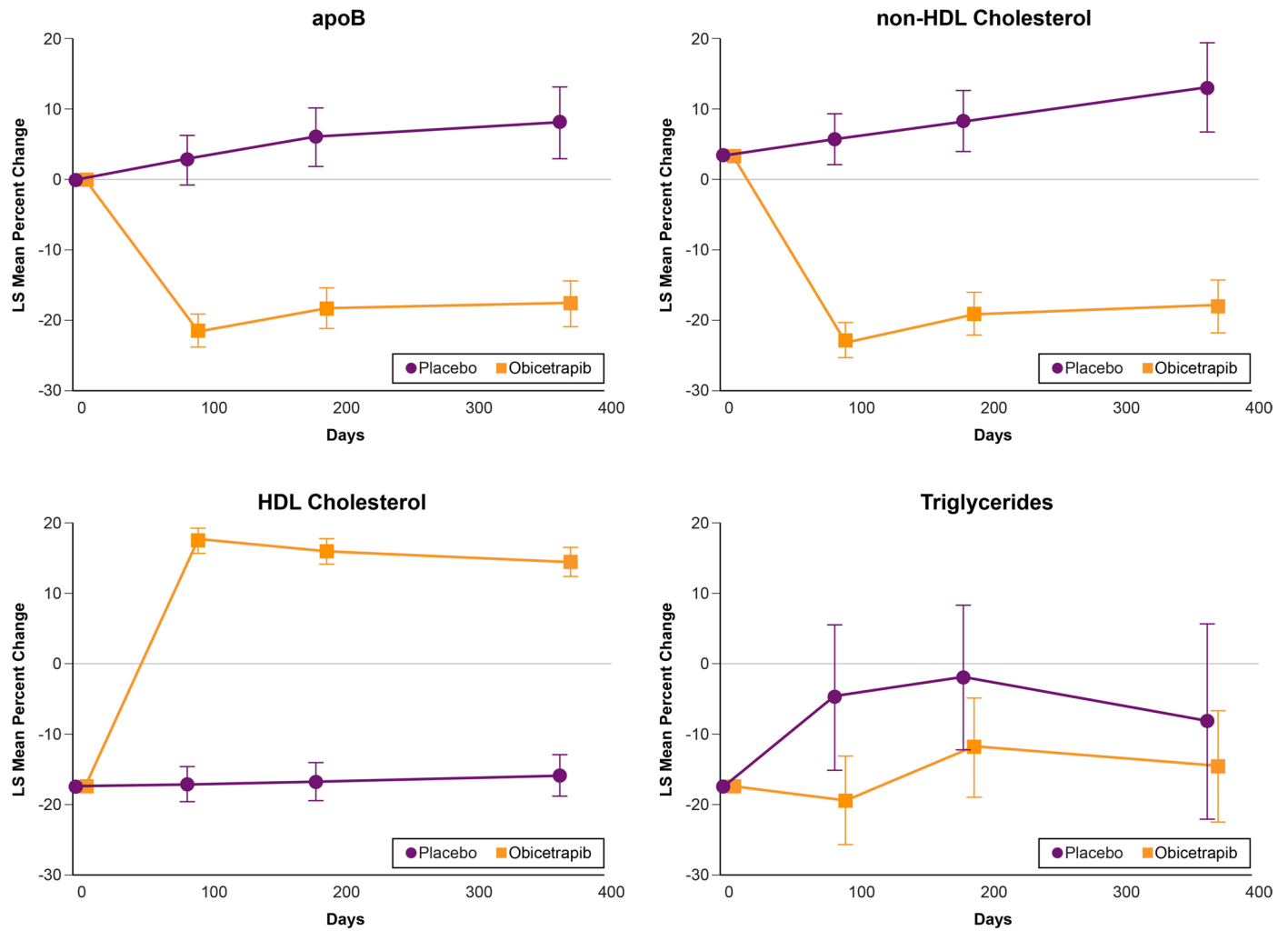
Extended Data Fig. 1 | Atherogenic Lipid Goal Achievement. Achievement of treatment goals for LDL cholesterol, non-HDL cholesterol and apoB in patients treated with placebo or obicetrapib at days 84 and 365. The primary endpoint of the study was the percentage change in LDL cholesterol from baseline to day 84.

Error bars represent 95% confidence intervals. Sample size: n = 118 (placebo), n = 236 (obicetrapib) representing biological replicates (individual patients). apoB, apolipoprotein B; HDL, high-density lipoprotein; LDL, low-density lipoprotein.



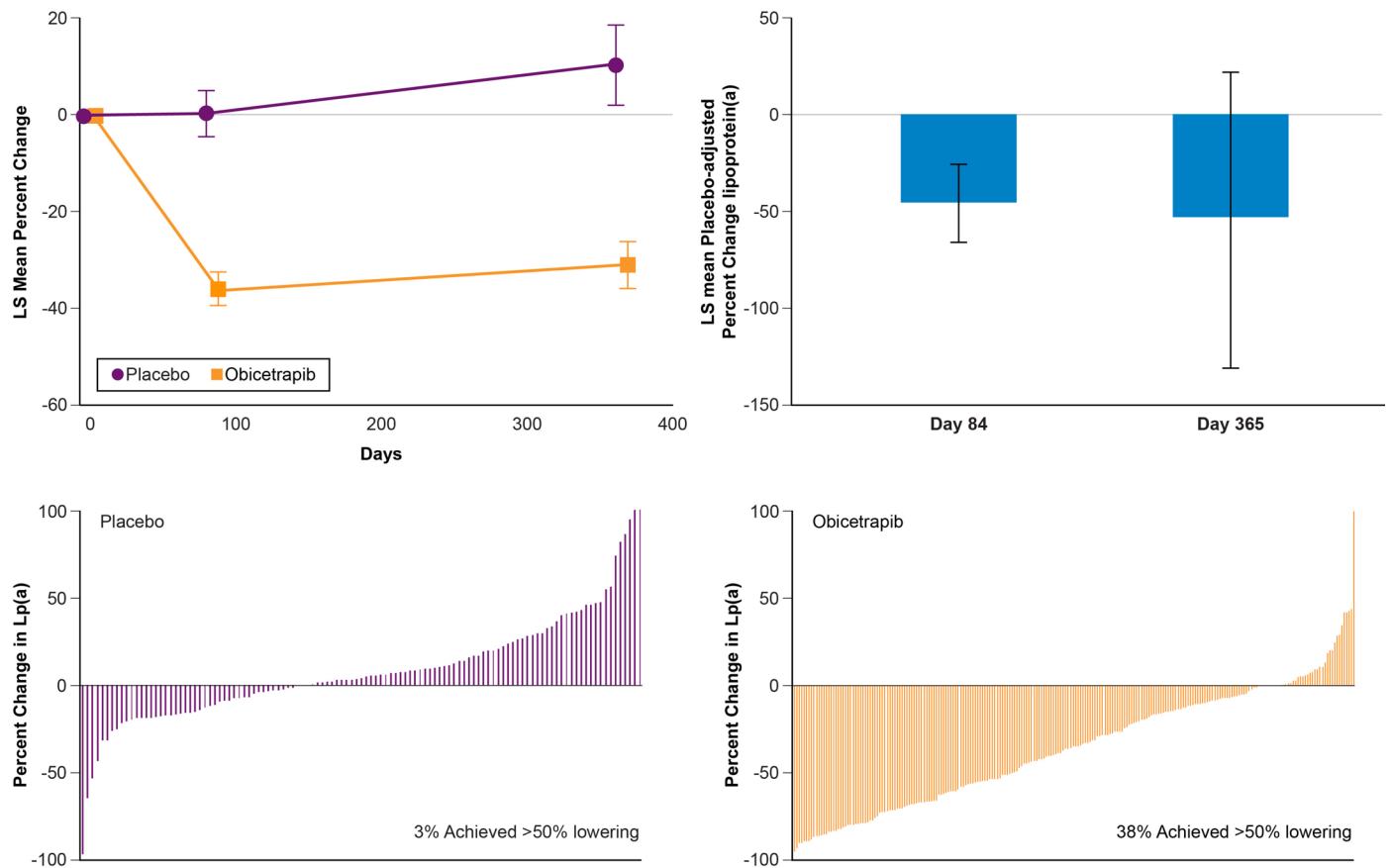
Extended Data Fig. 2 | Median LDL cholesterol percent changes in subgroups (demographics). Least squares mean (95% confidence intervals) treatment group differences in percent changes in LDL cholesterol with obicetrapib at day 84 in patient subgroups of demographics, medical history and statin use.

Apo, apolipoprotein; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein. Sample sizes vary by subgroup. All data represent biological replicates (individual patients with heterozygous familial hypercholesterolemia on maximally tolerated lipid-lowering therapy).



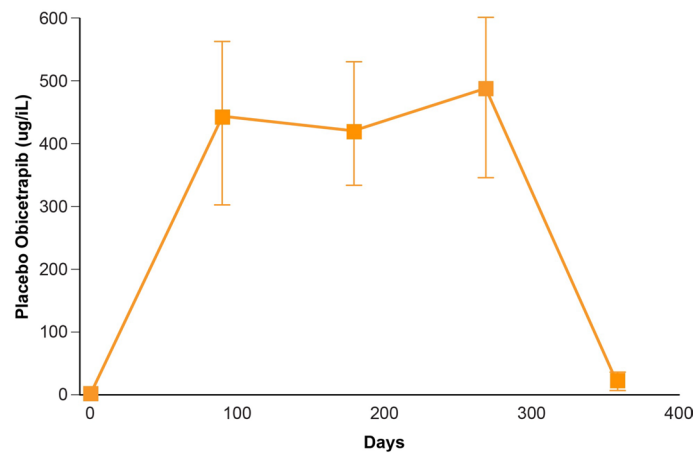
Extended Data Fig. 3 | Change in lipid and lipoprotein parameters. Least squares (LS) mean (95% confidence interval) percent change from baseline in apolipoprotein B (apoB, upper left panel), non-high-density lipoprotein (HDL) cholesterol (upper right panel), HDL cholesterol (lower left panel) and

triglycerides (lower right panel) in patients treated with placebo or obicetrapib. Sample size: n = 118 (placebo), n = 236 (obicetrapib) representing biological replicates (individual patients with heterozygous familial hypercholesterolemia on maximally tolerated lipid-lowering therapy).



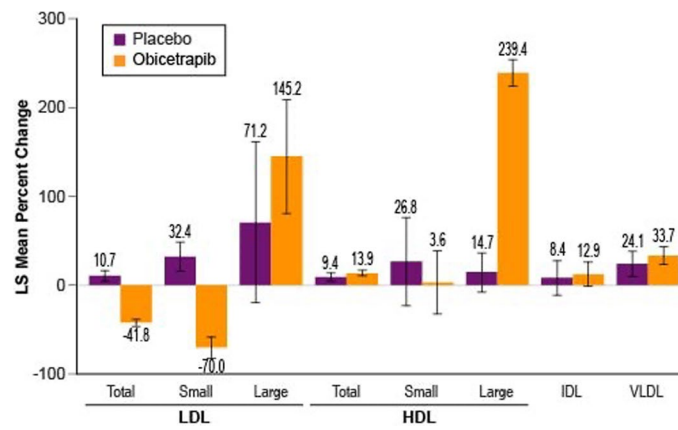
Extended Data Fig. 4 | Change in lipoprotein(a). Least square (LS) mean (95% confidence interval) percent change in lipoprotein(a) in patients treated with obicetrapib or placebo (upper left panel) and LS mean placebo-adjusted changes in lipoprotein(a) with obicetrapib at days 84 and 365 (upper right panel). Waterfall plots demonstrating individual percentage change in lipoprotein(a)

from baseline in patients treated with placebo or obicetrapib (lower panels). Sample size: n = 118 (placebo), n = 236 (obicetrapib) representing biological replicates (individual patients with heterozygous familial hypercholesterolemia on maximally tolerated lipid-lowering therapy).



Extended Data Fig. 5 | Trough plasma obicetrapib levels. Median (interquartile range) trough plasma obicetrapib levels in patients treated with obicetrapib at baseline, days 84, 180 and 365 and at 35 days following the last administration

of study drug. Sample size: $n = 236$ (obicetrapib group only). Each data point represents median trough plasma concentration from biological replicates (individual patients) at specified timepoints.



Extended Data Fig. 6 | Percent change in NMR lipoprotein measures. Least squares (LS) mean percent change in concentration of lipoprotein subclasses in patients treated with placebo or obicetrapib. HDL, high-density lipoproteins; IDL, intermediate density lipoproteins; LDL, low-density lipoproteins; VLDL,

very low-density lipoproteins. Error bars represent 95% confidence intervals. Sample size: n = 118 (placebo), n = 236 (obicetrapib) representing biological replicates (individual patients with heterozygous familial hypercholesterolemia on maximally tolerated lipid-lowering therapy).

Extended Data Table 1 | NMR lipoprotein parameters

	Placebo (N=118)	Obicetrapib (N=236)	Placebo Adjusted Changes
Total LDL particles (nmol/L)			
Baseline	1121.0 (936.0, 1418.0)	1121.5 (916.0, 1402.5)	
Day 180	1183.0 (996.0, 1516.0)	575.0 (404.0, 868.0)	
Median change	9.5 (-2.6, 24.2)	-48.7 (-65.7, -24.6)	
LS mean change	10.7 (4.8, 16.7)	-41.8 (-45.8, -37.7)	-52.5 (-59.7, -45.3)
Small LDL particles (nmol/L)			
Baseline	666.0 (522.0, 833.0)	674.5 (512.0, 842.0)	
Day 180	757.5 (567.5, 946.0)	53.0 (41.0, 76.0)	
Median change	16.1 (-10.5, 41.7)	-92.2 (-94.5, -84.7)	
LS mean change	32.4 (15.9, 48.9)	-70.0 (-82.1, -57.9)	-102.4 (-122.8, -82.0)
Large LDL particles (nmol/L)			
Baseline	226.0 (102.0, 375.0)	285.5 (105.0, 458.0)	
Day 180	281.0 (93.0, 490.0)	318.0 (203.0, 446.0)	
Median change	6.2 (-54.5, 62.5)	7.2 (-38.0, 93.2)	
LS mean change	71.2 (-19.2, 161.7)	145.2 (81.2, 209.3)	74.0 (-36.8, 184.8)
LDL particle size (nm)			
Baseline	20.6±0.7	20.7±0.7	
Day 180	20.6±0.7	21.0±0.4	
Median change	-0.5 (-2.0, 1.4)	1.0 (-0.9, 3.4)	
LS mean change	-0.3 (-0.8, 0.2)	1.2 (0.4, 1.9)	1.5 (0.5, 2.4)
Total HDL particles (µmol/L)			
Baseline	33.7 (29.5, 37.1)	34.4 (29.6, 39.4)	
Day 180	35.4 (30.6, 41.9)	37.4 (32.5, 42.7)	
Median change	7.5 (-1.1, 20.8)	7.2 (-4.8, 25.4)	
LS mean change	9.4 (4.8, 14.0)	13.9 (10.7, 17.1)	4.5 (-1.1, 10.0)
Small HDL particles (µmol/L)			
Baseline	17.5 (13.2, 22.1)	17.7 (13.1, 22.3)	
Day 180	19.4 (12.9, 23.4)	10.1 (4.7, 15.0)	
Median change	7.4 (-16.0, 34.9)	-39.7 (-71.3, -10.7)	
LS mean change	26.8 (-23.1, 76.6)	3.6 (-31.7, 38.9)	-23.1 (-84.2, 38.0)
Medium HDL particles (µmol/L)			
Baseline	8.3 (4.7, 12.3)	8.5 (5.4, 12.9)	
Day 180	8.2 (4.7, 14.2)	5.4 (2.3, 9.2)	
Median change	3.7 (-34.4, 73.6)	-40.0 (-76.0, 9.5)	
LS mean change	59.9 (-36.3, 156.1)	58.0 (-10.8, 126.8)	-1.9 (-120.1, 116.4)
Large HDL particles (µmol/L)			
Baseline	6.3 (4.3, 8.6)	6.9 (4.9, 9.0)	
Day 180	7.1 (5.1, 9.3)	21.8 (18.8, 23.9)	
Median change	12.2 (-7.4, 30.2)	202.2 (126.2, 326.8)	
LS mean change	14.7 (-7.3, 36.6)	239.4 (224.5, 254.3)	224.7 (198.3, 251.1)
HDL particle size (nm)			
Baseline	9.3±0.5	9.4±0.5	
Day 180	9.4±0.5	11.1±0.6	
Median change	0 (-1.1, 2.4)	18.5 (14.9, 22.1)	
LS mean change	0.4 (-0.8, 1.6)	17.7 (16.9, 18.5)	17.3 (15.9, 18.8)
IDL particles (nmol/L)			
Baseline	176.0 (109.0, 313.0)	184.0 (113.5, 304.5)	
Day 180	152.0 (90.5, 252.0)	144.0 (92.0, 247.0)	
Median change	-1.8 (-39.9, 30.7)	-15.9 (-51.0, 35.8)	
LS mean change	8.4 (-11.0, 27.8)	12.9 (-0.9, 26.6)	4.4 (-19.4, 28.2)
VLDL/chylomicron particles (nmol/L)			
Baseline	49.1 (35.4, 61.7)	48.0 (26.8, 63.3)	
Day 180	53.5 (34.0, 73.8)	47.2 (36.7, 61.0)	
Median change	9.6 (-16.6, 42.8)	8.9 (-18.1, 48.2)	
LS mean change	24.1 (9.7, 38.5)	33.7 (23.7, 43.7)	9.6 (-8.0, 27.2)
Small VLDL particles (nmol/L)			
Baseline	28.0 (19.5, 40.6)	28.4 (16.7, 38.5)	
Day 180	28.1 (16.8, 42.5)	22.6 (16.4, 29.5)	
Median change	4.2 (-33.7, 49.7)	-14.7 (-41.7, 36.2)	
LS mean change	34.1 (-1.2, 69.3)	36.7 (11.8, 61.5)	2.6 (-40.6, 45.8)
Medium VLDL particles (nmol/L)			
Baseline	13.5 (7.8, 22.7)	13.3 (7.6, 20.7)	
Day 180	15.4 (8.3, 27.8)	19.8 (12.8, 28.1)	
Median change	11.9 (-31.6, 86.5)	46.7 (1.2, 145.0)	
LS mean change	57.9 (-17.2, 133.0)	179.4 (124.5, 234.2)	121.5 (28.5, 214.5)
Large VLDL/chylomicron particles (nmol/L)			
Baseline	4.1 (1.6, 6.3)	3.6 (1.8, 5.8)	
Day 180	4.2 (2.3, 7.6)	3.4 (1.7, 5.8)	
Median change	28.6 (-11.1, 76.9)	-0.8 (-39.1, 67.3)	
LS mean change	42.4 (20.5, 64.3)	25.7 (10.6, 40.8)	-16.7 (-43.5, 10.2)
VLDL particle size (nm)			
Baseline	51.0±7.1	50.8±6.5	
Day 180	52.5±7.7	52.4±7.4	
Median change	2.3 (-5.9, 13.9)	3.4 (-4.7, 12.8)	
LS mean change	3.7 (1.2, 6.2)	3.8 (2.0, 5.5)	0 (-3.0, 3.1)

Concentration of lipoprotein subclasses, determined by nuclear magnetic resonance (NMR) spectroscopy, in patients treated with placebo or obicetrapib, expressed as mean ± standard deviation or median (interquartile range) if not normally distributed. Change from baseline expressed as median (interquartile range) and least squares (LS) mean (95% confidence interval). HDL, high-density lipoproteins; IDL, intermediate-density lipoproteins; LDL, low-density lipoproteins; VLDL, very low-density lipoproteins. Sample size: n = 118 (placebo), n = 236 (obicetrapib) representing biological replicates (individual patients with heterozygous familial hypercholesterolemia on maximally tolerated lipid-lowering therapy). All measurements performed at day 180.

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Study protocol	Submitted
Data collection	From July 29, 2022, to April 17, 2023, 354 patients were randomized to treatment with placebo or obicetrapib at 70 sites in Europe, United Kingdom, South Africa, Canada and the United States.
Outcomes	The primary efficacy endpoint was the percent change from baseline to day 84 in fasting LDL cholesterol in the obicetrapib compared to the placebo group. Secondary endpoints included the percent change from baseline in (i) LDL cholesterol at days 180 and 365, (ii) apolipoprotein B (apoB), non-HDL cholesterol, HDL cholesterol, total cholesterol and triglycerides at days 84, 180 and 365 and (iii) lipoprotein(a) at days 84 and 365. Prespecified exploratory endpoints included the (i) percentage of patients achieving a LDL cholesterol level less than 40, 55, 70 and 100 mg/dL at days 84 and 365, (ii) percentage of patients achieving a non-HDL cholesterol less than 85, 100 and 130 mg/dL at days 84 and 365, (iii) percentage of patients achieving an apoB less than 65, 80 and 130 mg/dL at days 84 and 365, (iv) percent change from baseline in apolipoprotein A1 (apoA1) at days 84 and 365, (v) percent change from baseline in lipoprotein size and composition at day 180 and (vi) trough levels of obicetrapib from baseline to day 365.

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Seed stocks	<i>Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.</i>
Novel plant genotypes	<i>Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.</i>
Authentication	<i>Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosaicism, off-target gene editing) were examined.</i>