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Lerodalcibep and evolocumab for the treatment of homozygous familial hypercholesterolaemia with *PCSK9* inhibition (LIBerate-HoFH): a phase 3, randomised, open-label, crossover, non-inferiority trial

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Summary

Background Lerodalcibep, a small binding anti-PCSK9 protein (adnectin), showed effective LDL cholesterol reduction in heterozygous familial hypercholesterolaemia. We aimed to assess the safety and efficacy of lerodalcibep and evolocumab in a globally diverse homozygous familial hypercholesterolaemia population.

Methods This phase 3, randomised, open-label, crossover, non-inferiority study consisted of two 24-week treatment periods separated by an 8-week washout. The study was conducted in 12 lipid clinics in six countries (India, Israel, Norway, South Africa, Türkiye, and the USA). Patients aged 10 years or older with genetically confirmed homozygous familial hypercholesterolaemia were randomly assigned by computer-generated randomisation scheme performed centrally via interactive response technology to either monthly lerodalcibep 300 mg (1·2 mL subcutaneous injection) or monthly evolocumab 420 mg (subcutaneous 9 min infusion of 3·5 mL) for 24 weeks (period A) followed by an 8-week washout and then crossed over to the alternate therapy for the next 24 weeks (period B). The trial was open label, but all efficacy parameters were masked to patients, study staff, and the sponsor from randomisation. The primary efficacy endpoint was the percent change from baseline (day 1 of period A) in LDL cholesterol concentration to week 24 for period A and B. The intention-to-treat (ITT) population, defined as all randomly assigned patients, was used for the primary analysis. The safety population included all patients who received any study medication. The margin used to establish non-inferiority was 6%. The trial is registered with ClinicalTrials.gov (NCT04034485) and EudraCT (2019–003611–62), and has now finished.

Findings Patients were enrolled from Nov 11, 2019, to July 2, 2021, and the final study visit took place on Aug 8, 2022. Of 82 patients screened, 66 entered period A (ITT population). The mean age was 28·7 years (SD 15·2); 20 (30%) of 66 were paediatric patients; 36 (55%) of 66 were female and 30 (45%) of 66 were male; and the mean baseline LDL cholesterol was 10·59 mmol/L (SD 4·37). Mean LDL cholesterol reduction by ITT analysis at week 24 was –4·9% (SE 3·5) on lerodalcibep compared with –10·3% (3·5) on evolocumab; the mean difference between treatments was 5·4% (95% CI –0·2 to 11·1), which did not show non-inferiority at the prespecified 6% margin. LDL cholesterol response varied considerably across the patient population but was generally similar in the same patients with both lerodalcibep and evolocumab. When averaged across all monthly visits, LDL cholesterol response was –9·1% (SE 3·2) on lerodalcibep and –10·8% (3·2) on evolocumab. Importantly, genotyping and free PCSK9 suppression were not predictive of response. Both drugs were well tolerated, with no treatment-related serious adverse events. Injection site reactions were reported in one (2%) of 65 patients on lerodalcibep and 15 (24%) of 62 patients on evolocumab.

Interpretation The LDL cholesterol response was highly variable, but generally similar in patients treated with both lerodalcibep and evolocumab. Importantly, the study showed the inability to predict response based on genotyping, reinforcing the rationale for PCSK9 inhibition in all patients with homozygous familial hypercholesterolemia and continuing its use in responders.

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Introduction

Homozygous familial hypercholesterolaemia is a rare but serious genetic disorder characterised by reduced hepatic clearance of, and resultant markedly elevated, LDL cholesterol from conception, leading to premature atherosclerotic cardiovascular disease as early as the first decade of life.[1] The condition affects approximately 1 in 300 000 people worldwide, but prevalence is higher in populations with founder variants, such as French Canadians and South African Afrikaners.[2]

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Research in context

Evidence before this study

Despite initial scepticism, studies conducted a decade ago with monoclonal antibody (mAb) therapy inhibiting circulating PCSK9 were shown to significantly reduce LDL cholesterol in patients with homozygous familial hypercholesterolaemia, resulting in regulatory approval and acceptance as add-on therapy to statins and ezetimibe for homozygous familial hypercholesterolaemia. The patients with homozygous familial hypercholesterolaemia in these early studies were predominantly of European lineage, with most exhibiting some residual LDL receptor activity that could be upregulated by PCSK9 inhibition. Subsequent trials in both children and adults with homozygous familial hypercholesterolaemia, with either mAbs directed against PCSK9 or with a short interfering RNA, inclisiran (which markedly inhibits hepatic PCSK9 synthesis) in more diverse homozygous familial hypercholesterolaemia populations produced mixed results, with minimal overall LDL cholesterol reductions and large numbers of non-responders.

Added value of this study

This study had a diverse population with homozygous familial hypercholesterolaemia, including patients from Türkiye and India and paediatric patients, confirmed by genotyping at time of screening to have pathogenic variants. The trial compared the efficacy of an approved mAb (evolocumab) with lerodalcibep, a novel, third generation PCSK9 inhibitor, in a randomised crossover design with all participants receiving both PCSK9 inhibitors for 24 weeks separated by an 8-week washout.

Implications of all the available evidence

Although there were minimal differences in mean averaged LDL cholesterol response over the 24 weeks of treatment with both drugs, the primary analysis at week 24 the ITT population did not achieve non-inferiority of least squares mean percent changes from baseline of LDL cholesterol with lerodalcibep compared with evolocumab. The study provides new evidence that despite maximal PCSK9 suppression and LDL cholesterol responses being highly variable between patients, reductions were similar in the same patients treated with two different PCSK9 inhibitors. The study also shows that genotype, even when presumed to result in minimal or no residual functional LDL receptor activity, is not predictive of response, suggesting that other factors affect LDL cholesterol response. The study supports that LDL cholesterol response can therefore only be determined by treatment with a PCSK9 inhibitor, validating recommendations of a trial of PCSK9 inhibitor therapy in all patients with homozygous familial hypercholesterolaemia, with continued therapy in responders.

More than 90% of patients with homozygous familial hypercholesterolaemia of European ancestry have pathogenic variants in both *LDLR* alleles. Variants in *APOB*, *PCSK9*, or *LDLRAP1* can also be causal, but are less frequent.[3] Variants in *LDLR* can be identical (biallelic monogenic identical variants) but the majority of patients have two different pathogenic *LDLR* variants (biallelic monogenic different variants). More rarely, the clinical features result from the combination of *LDLR*, *APOB*, or *PCSK9* gain-of-function variants (biallelic digenic variants).

The residual *LDLR* functional activity generally determines the severity of LDL cholesterol elevation, propensity for early atherosclerotic cardiovascular disease and response to therapies that upregulate *LDLR* function, such as statins and PCSK9 inhibitors.[4–6] Variants causing a virtually complete absence of *LDLR* function (null–null homozygotes) result in higher LDL cholesterol concentrations than variants that partially reduce *LDLR* function (non-null homozygotes) and, as shown in trials with both statins and PCSK9 inhibitors, minimal or no LDL cholesterol response.[4–6]

In addition, in individuals with homozygous familial hypercholesterolaemia with identical pathogenic *LDLR* variants, the *LDLR* function varies considerably at baseline and after treatment with a PCSK9 monoclonal antibody, as exemplified by widely varying LDL cholesterol reductions.[7,8] This variability implies that other factors unrelated to the underlying genetic *LDLR* variants present affect response.

However few, if any, functional *LDLR* activity studies have been carried out in patients with homozygous familial hypercholesterolaemia from countries with large populations of people with homozygous familial hypercholesterolaemia, such as India and Türkiye.[9,10] Although genotyping of variants in homozygous familial hypercholesterolaemia have been reported in the Indian population, showing marked differences from those in other countries, with only 32% having *LDLR* variants, 4% *APOB* variants, 2% *PCSK9* variants, and 37% unknown, there is little information regarding residual *LDLR* function in those with identified pathogenic variants. In addition, the spectrum of *LDLR* variants in India is more heterogeneous than in other countries and includes novel variants not previously reported.[9] In Türkiye, where the prevalence of consanguinity is estimated to be 23%, and more than 100 patients with clinically diagnosed homozygous familial hypercholesterolaemia have been reported, few have been genotyped and the pathogenic variants and residual *LDLR* activity is largely unknown.[10]

Unfortunately, despite the routine use of statins and ezetimibe, the vast majority of patients with homozygous familial hypercholesterolaemia still have markedly elevated LDL cholesterol concentrations, as these therapies only reduce LDL cholesterol concentration

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modestly in homozygous familial hypercholesterolaemia. Therefore, these patients have the highest unmet medical need for additional LDL cholesterol lowering therapies.[1] These therapies include PCSK9 inhibitors, lomitapide, and evinacumab, as well as lipoprotein apheresis and hepatic transplantation.[1,2] Of these therapies, PCSK9 inhibitors are the most widely available, least expensive, and best tolerated and, for this reason, are recommended in guidelines for additional LDL cholesterol lowering in homozygous familial hypercholesterolaemia.[1]

See Online for appendix 1

Initial and phase 3 registration studies with the PCSK9 inhibitor evolocumab in patients with homozygous familial hypercholesterolaemia from west Europe, north and south America, South Africa, Australia, and New Zealand showed promise with LDL cholesterol reductions of approximately 20–30% on top of statins and ezetimibe.[6,11] However, even in these early trials, patients with identical *LDLR* pathogenic variants, showed marked interindividual variability in LDL cholesterol lowering response.[7] In the past 3 years, trials with evolocumab, as well as with alirocumab and inclisiran, in patients with homozygous familial hypercholesterolaemia and novel *LDLR* variants in India, Türkiye, the Middle East, east Europe, and Asia–Pacific have yielded confounding results with minimal overall reductions in LDL cholesterol compared with placebo or baseline.[12–14] Furthermore, re-examination of responses in children with homozygous familial hypercholesterolaemia, with both evolocumab or alirocumab, have also reported less efficacy than in adults with the same pathogenic variants.[13,15]

Lerodalcibep is a third generation PCSK9 inhibitor consisting of a recombinant fusion small binding protein, with an anti-PCSK9 domain (adnectin) linked to human serum albumin, which, similar to monoclonal antibodies, binds to and inactivates PCSK9 in the circulation. Previous studies with 300 mg (1·2 mL) of lerodalcibep dosed subcutaneously monthly, showed highly effective PCSK9 suppression and LDL cholesterol reduction in patients with heterozygous familial hypercholesterolaemia.[16] The LIBerate-HoFH trial aimed to assess safety and efficacy in a global diverse and genetically confirmed paediatric and adult homozygous familial hypercholesterolaemia population treated with both lerodalcibep and evolocumab.

See Online for appendix 2

Methods

Study design

This phase 3, randomised, open-label, crossover, non-inferiority study consisted of two 24-week treatment periods separated by an 8-week washout. This study design was deemed optimal to compare the efficacy, tolerability, and safety of both lerodacibep and evolocumab, a previously approved and marketed PCSK9 monoclonal antibody, in the same patients from a rare homozygous familial hypercholesterolaemia population aged 10 years or older known to have markedly varied responses to PCSK9 inhibitors. The study was conducted in 12 lipid clinics in six countries (India, Israel, Norway, South Africa, Türkiye, and the USA). The protocol was reviewed and approved by statutory regulatory authorities in each country and the appropriate ethics committee at each institution. The trial is registered with ClinicalTrials.gov (NCT04034485) and EudraCT (2019–003611–62). The protocol is available in appendix 1.

Participants

The study population included male and female patients aged 10 years or older with homozygous familial hypercholesterolaemia with final entry eligibility requiring genetic confirmation in the central laboratory (Medpace Reference Laboratories, Cincinnati, OH, USA) of pathogenic variants in both *LDLR* alleles or a combination of a *LDLR* pathogenic variant with pathogenic variants in *PCSK9* (dominant-gain of function), receptor binding defective variants in *APOB*, or patients with autosomal recessive hypercholesterolaemia due to biallelic defects in *LDLRAP1*. The study required all patients to have a confirmed genetic diagnosis before randomisation and included patients with homozygous familial hypercholesterolaemia in India and Türkiye with novel variants of unknown or unreported residual *LDLR* function. Patients on and able to maintain stable maximal tolerable statin, ezetimibe, lomitapide, or other approved oral lipid lowering therapies were eligible. Those on lipoprotein apheresis were not eligible. Patients recently given (in the past 6 weeks) or currently on evolocumab or alirocumab underwent an 8-week or longer post last-dose washout period before randomisation and a second 8-week washout after the last dose in period A. Detailed inclusion and exclusion criteria are provided in appendix 2 (pp 4–5). All participants reviewed and signed an approved informed consent form before any procedures including paediatric patients and their parent or legal guardian.

Randomisation and masking

Eligible patients were randomly assigned by computer-generated randomisation scheme performed centrally via interactive response technology in period A to receive lerodalcibep or evolocumab as their first study treatment. There was no stratification or restricted criteria. The trial was open label but all efficacy parameters, including plasma lipids and PCSK9 protein concentrations, were masked to patients, study staff, and the sponsor from randomisation. Masking was effective as efficacy parameters were measured in a central laboratory and no results were returned to the clinical sites, the contract research organisation monitoring the sites, or the sponsors until after the trial was completed and the data locked.

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Procedures

Eligible patients were randomly assigned in period A to lerodalcibep 300 mg monthly, as a 1·2 mL subcutaneous injection, or evolocumab 420 mg monthly, delivered as a subcutaneous 9 min infusion of 3·5 mL or three 140 mg 1 mL subcutaneous injections, for 24 weeks. This regimen was followed by an 8 week or longer washout period after the last dose of study drug, more than 4 half-lives of both drugs, after which time patients entered period B, when they were crossed over from evolocumab to lerodalcibep or vice versa for the next 24 weeks (appendix 2 p 10). The randomised crossover design, with adequate washout between treatment periods, was determined to be the most optimal for this rare population in which response varies considerably across both adult and paediatric patients, even in those with identical genetic variants.[17] As recommended for crossover trials in rare patient populations to further reduce potential effect of variability of percent and absolute reductions in LDL cholesterol during treatment, the baseline LDL cholesterol at initial randomisation of period A was used for both treatment periods and each treatment period was of a prolonged 24 weeks duration with monthly efficacy assessments.[17]

Patients were categorised according to assumed residual *LDLR* activity as either null–null (two null *LDLR* variants) or non-null with at least one defective *LDLR* variant (null–defective or defective–defective).[18] *LDLR* activity assumptions were derived from the Global Variome Shared Leiden Open-source Variation Database and ClinVar databases at the time of study screening.[19] A null qualifier was given if the reported *LDLR* activity was 15% or lower.[20] More detailed methods of genetic testing is provided in appendix 2 (p 7).

Outcomes

The primary efficacy endpoint was the percent change from baseline (day 1 of period A) in LDL cholesterol concentration to week 24 (by Friedewald formula) for period A and B. The primary outcome was centrally assessed by indepent statistician JV. Secondary efficacy endpoints were percent change from baseline in LDL cholesterol concentration at week 24, assessed with the Hopkins formula and by preparative ultracentrifugation; LDL cholesterol concentration at the mean of weeks 22 and 24 assessed by Friedewald formula and by Hopkins formula; serum total and unbound (free) PCSK9 concentrations in those on lerodalcibep, with evolocumab samples stored; absolute and percent reductions for lerodalcibep and evolocumab in serum lipids, including total, HDL, non-HDL, and VLDL cholesterol and triglycerides; and absolute and percent reductions for lerodalcibep and evolocumab in apolipoprotein B and lipoprotein(a) serum concentrations. The secondary endpoints were also analysed for LDL cholesterol with a general linear model for the change from baseline for the observed values at the endpoint of weeks 16, 20 22, and 24, and the mean of weeks 22 and 24.

Adverse events were coded with the Medical Dictionary for Regulatory Activities version 22.0. Treatment-emergent adverse events and serious adverse events were summarised by overall number of patient adverse events, severity, and relationship to study drug per treatment group of all participants randomly assigned. Adverse events leading to withdrawal and serious adverse events leading to death were recorded. Injection site reactions were graded and reported at all study visits. The safety laboratory data were summarised by visit and by treatment group, along with changes from baseline. Laboratory abnormalities of special interest, such as liver function tests, creatine kinase elevations, and anti-drug antibodies were collected. Participants confirmed positive for lerodalcibep antibodies were also tested for neutralising antibodies.

Statistical analysis

Determination of the sample size for this study is described in appendix 2 (p 9). As prespecified in the protocol and statistical analysis plan, the intention-to-treat (ITT) population, defined as all randomly assigned patients, was used for the primary analysis. Results were analysed with a general linear model, accounting for variation in factors such as sequence, period and treatment, and patients nested within sequences as a random effect. The baseline LDL cholesterol was included as a covariate. The difference between treatment group means was compared with a non-inferiority margin of 6%, based on the average reduction of 5% to 7% in LDL cholesterol reported with doubling the dose of statins in a non-homozygous familial hypercholesterolaemia population.[21,22] A two-sided 95% CI was estimated from the model for treatment comparison. If the upper bound of the 95% CI was less than 6%, non-inferiority could be concluded. Multiple imputation was used to impute missing LDL cholesterol results at week 24. The imputation model used the patient's baseline LDL cholesterol value plus a random error term, including patients randomly assigned but not completing the baseline visit at which screening LDL cholesterol values were used.

The rationale for using the ITT population for the primary analysis was due to anticipated regulatory requirements at the time the protocol was initiated.[23] However, as per International Council for Harmonisation E9 guidance (Statistical Principles for Clinical Trials) and CONSORT 2010 statement, a modified ITT population (all patients who attended for week 24 during both treatment periods) or per-protocol population (those completing both periods as per protocol) are more appropriate analysis populations for this crossover non-inferiority trial.[24] Use of the ITT analysis in this rare population could be inappropriate and potentially flawed, even if stratified by genotyping, as outlined previously, and could lead to

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biased results.[17] Therefore, analyses for the ITT, modified ITT, and per-protocol populations are reported.

The secondary endpoints were to be tested in a hierarchical manner with the same methods as the primary endpoint, such that inferential conclusions required statistical significance of the previous endpoint. The secondary endpoints were evaluated in the ITT population. Safety was assessed in all patients who received study medication. For adverse events and serious adverse events of special interest, a risk difference, along with the 95% CI, was used to compare the treatment groups.

In addition to the LDL cholesterol week 24 ITT change from baseline, a supplementary exploratory analysis of the modified ITT population was performed on the basis of data published in the past 3 years from homozygous familial hypercholesterolaemia trials with PCSK9 inhibitors that reported markedly divergent and poor efficacy responses in populations included in this trial, such as people from India and children.[12–15] These analyses included the percent change from baseline in LDL cholesterol over entire treatment periods (weeks 4, 8, 12, 16, 20, and 24) as the response variable, with the same general linear model as for the primary endpoint.

Changes at week 24 in lipoprotein(a), apolipoprotein B, and other lipid parameters and at week 12 in LDL cholesterol were analysed in the ITT population with similar methods as for the primary analysis, as these time periods have been the standard used in previous homozygous familial hypercholesterolaemia trials to assess efficacy in trials with evolocumab.[6,11–15] Unbound (free) PCSK9 was measured at week 0 of periods A and B and at all timepoints during the treatment period with lerodalcibep.

The data safety monitoring board is summarised in appendix 2 (p 4). Statistical analysis was performed in SAS version 9.4.

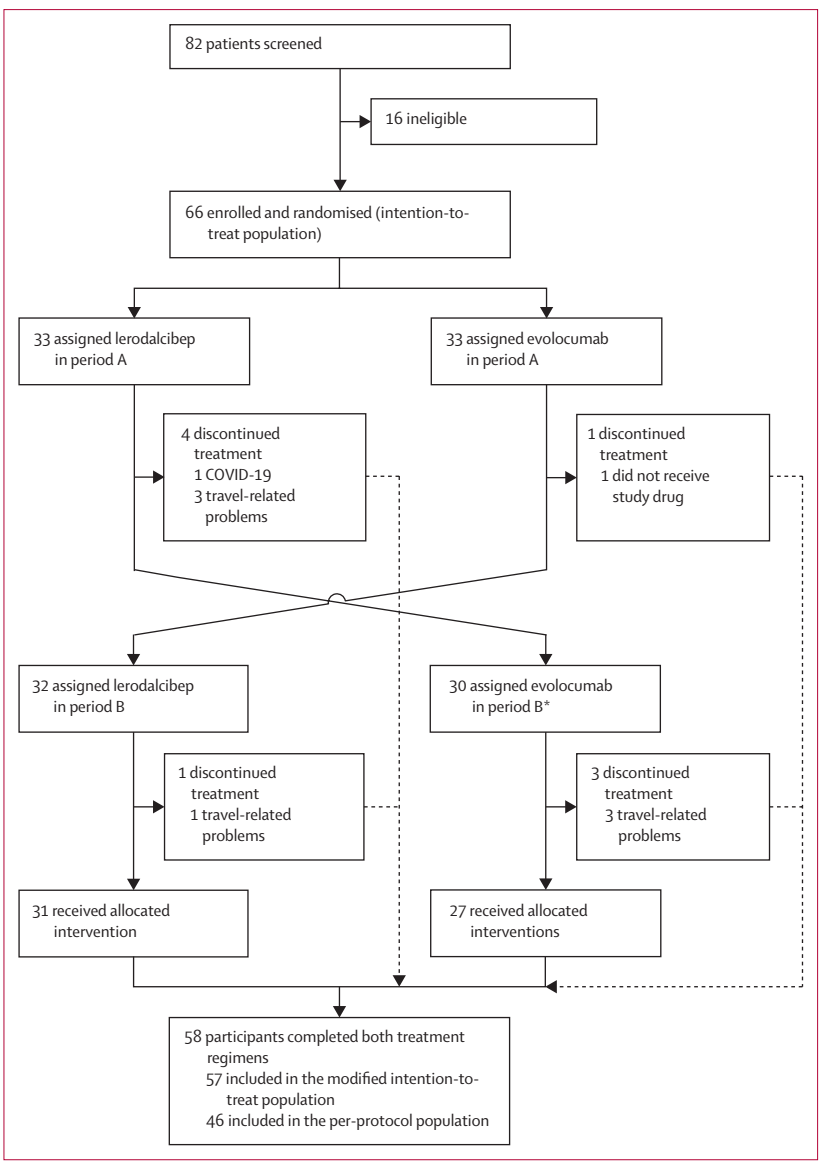


Figure 1: **Trial profile**
*One patient who discontinued lerodalcibep without completing period A went on to enter period B.

Role of the funding source

The sponsors were involved in the study design, and collection, analysis, interpretation of data and writing, as well as data checking of information provided in the manuscript.

Results

Patients were enrolled from Nov 11, 2019, to July 2, 2021, and the final study visit took place on Aug 8, 2022. Despite encompassing the COVID-19 pandemic, 82 patients were screened, 66 met eligibility and were randomly assigned, with 65 completing the baseline week 0 visit and being dosed in period A, and 62 patients were dosed in period B. 58 patients completed both treatment periods, 57 were included in the modified ITT population, and 46 in the per-protocol populations due to missing assessments (figure 1).

The mean age of all randomly assigned participants (ITT population; n=66) was 28·7 years (SD 15·2; range 10–58 years) with 20 (30%) being paediatric or adolescent participants aged between 10 years and 17 years. Of 66 participants enrolled, 36 (55%) were female and 30 (45%) were male, and the majority were White (n=42 [64%]) or Asian (n=21 [32%]), with three Black or multiracial participants (5%; table 1). All participants were confirmed as having homozygous familial hypercholesterolaemia on genotyping (appendix 2 pp 12–14). Despite the young mean age of the randomly assigned participants, 25 (38%) of 66 had established atherosclerotic cardiovascular disease and 11 (17%) of 66 had aortic stenosis or had undergone aortic valve replacement. Mean LDL cholesterol was 10·59 mmol/L (range 1·45–19·53 mmol/L), even with 61 (92%) of 66 participants being treated with high-intensity statins,

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63 (95%) of 66 with ezetimibe, and two (3%) of 66 with lomitapide at baseline. 62 (94%) of 66 participants received all six doses of lerodalcibep, and 58 (94%) of 62 participants received all six doses of evolocumab. The demographic and baseline information for the modified ITT and per-protocol populations are shown in appendix 2 (p 15). Of the 57 patients included in the mITT, 18 (32%) were adolescents aged between 10 and 17 years; 31 (54%) were from the USA, Norway, Israel, or South Africa, 16 (28%) were from India, and ten (18%) were from Türkiye.

In the ITT population, the primary endpoint of least-squares mean change in LDL cholesterol at week 24 on lerodalcibep was –4·9% (SE 3·5) and an absolute reduction of 0·38 mmol/L (0·31) compared with –10·3% (3·5) on evolocumab and an absolute reduction of 0·80 mmol/L (0·30). The model-adjusted (least-squares) mean difference between treatments was 5·4% (95% CI –0·2 to 11·1) and therefore did not show non-inferiority at the prespecified 6% margin (table 2). The mean reduction in LDL cholesterol at week 24, measured by ultracentrifugation, on lerodalcibep was 6·6% (3·5), with an absolute reduction of 0·64 mmol/L (SE 0·28), compared with 10·1% (3·5) on evolocumab, with an absolute reduction of 0·82 mmol/L (0·28). The least-squares mean difference between treatments was 3·5 (95% CI –2·1 to 9·1). During the 24 week treatment period, mean LDL cholesterol on lerodalcibep ranged from 9·66 to 10·29 mmol/L and from 9·44 to 10·00 mmol/L on evolocumab, with the mean reduction in LDL cholesterol at week 12 of 12·0% (2·8) on lerodalcibep compared with 11·5% (2·9) on evolocumab. The model-adjusted (least-squares) mean difference between treatments was –0·5 (95% CI –8·5 to 7·5; appendix 2 p 10). Results for primary and key secondary efficacy endpoints in the ITT population, including apolipoprotein B, lipoprotein(a), and other lipid parameters with model-adjusted changes from baseline to week 24 are shown in table 2.

Model adjusted changes from baseline to week 24 of LDL cholesterol and other lipid parameters for the modified ITT and per-protocol populations are shown in appendix 2 (p 16). The mean LDL cholesterol in both treatment groups for weeks 4, 8, 12, 16, 20, and 24 are shown in appendix 2 (p 10), and if averaged across all monthly study visits, the mean changes were –9·1% (SE 3·2) on lerodalcibep and –10·8% (3·2) on evolocumab, with a model-adjusted mean difference between treatments of 1·7% (SE 2·2; 95% CI –2·7 to 6·1). Although LDL cholesterol responses were highly variable between patients, the percent change from baseline for average LDL cholesterol was similar in individual patients for both drugs (r=0·79; figure 2).

Reductions in exploratory selected LDL cholesterol cutoff points of at least 15% were seen in 15 (27%) of 56 patients who completed both periods of analysis participants with lerodalcibep and in 21 (38%) of 56 participants with evolocumab, with a reduction of at least 30% in eight (14%) of 56 participants with lerodalcibep and 12 (21%) of 56 participants with evolocumab (appendix 2 p 16). The changes in averaged LDL cholesterol over the 24-week treatment periods in subgroups of interest were; adolescent participants –0·4% (SE 4·7) and 2·4% (6·2); participants from India –3·1% (5·6) on lerodalcibep and –3·0% (6·1) on evolocumab and participants from Türkiye –4·5% (5·1) on lerodalcibep and –2·1% (8·1) on evolocumab; compared with reductions of 14·3% (4·9) on lerodalcibep and 19·1% (5·0) on evolocumab in patients from USA, Norway, South Africa, and Israel. There was a mean reduction at trough (4 weeks post doses) in free PCSK9 of at least 80% with lerodalcibep (appendix 2 p 17) and there was no difference in free PCSK9 suppression in those with an LDL cholesterol reductions of at least 15% (ie, responders), 5–15% (ie, poor responders), or no reductions (ie, non-responders; appendix 2 p 17).

Among all patients who received study medication, a higher percentage reported at least one treatment-emergent adverse event while on evolocumab (38 [61%]

	All participants (n=66)	Participants assigned lerodalcibep in period A (n=33)	Participants assigned evolocumab in period A (n=33)
Age, years	28·7 (15·2)	29·8 (14·8)	27·6 (15·8)
Range	10–58	10–58	11–58
Paediatric and adolescent patients (aged 10–17 years)	20 (30%)	8 (24%)	12 (36%)
Sex			
Female	36 (55%)	16 (48%)	20 (61%)
Male	30 (45%)	17 (52%)	13 (39%)
Race			
White	42 (64%)	23 (70%)	19 (58%)
Asian	21 (32%)	9 (27%)	12 (36%)
Black or multiracial	3 (5%)	1 (3%)	2 (6%)
BMI, kg/m²	24·9 (5·7)	25·5 (4·9)	24·4 (6·5)
Range	14·7–41·1	15·1–37·4	14·7–41·1
Established atherosclerotic cardiovascular disease	25 (38%)	14 (42%)	11 (33%)
Aortic valve stenosis	11 (17%)	6 (18%)	5 (15%)
High-intensity statin	61 (92%)	29 (88%)	32 (97%)
Ezetimibe	63 (95%)	31 (94%)	32 (97%)
Baseline lipids			
Total cholesterol, mmol/L	12·17 (4·34)	11·70 (4·36)	12·68 (4·34)
Triglycerides, mmol/L	1·36 (0·85)	1·32 (0·66)	1·39 (1·00)
LDL cholesterol (Friedewald formula), mmol/L	10·59 (4·37)	10·15 (4·43)	11·05 (4·32)
HDL cholesterol, mmol/L	0·98 (0·36)	0·95 (0·39)	1·00 (0·33)
Apolipoprotein B, g/L	2·47 (0·87)	2·39 (0·88)	2·54 (0·87)
Lipoprotein(a), nmol/L	113 (38–191)	100 (36–202)	142 (41–190)
Free PCSK9, ng/mL	543 (281)	412 (264)	678 (233)

Data are mean (SD), n (%), median (IQR), unless otherwise stated.

Table 1: **Demographics and baseline characteristics of the intention-to-treat population, total and by treatment in period A**

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	Percent change		Least-squares mean difference	95% CI
	Lerodalcibep	Evolocumab		
Primary endpoint				
LDL cholesterol at week 24 (Friedewald)	−4·9% (3·5)	−10·3% (3·5)	5·4% (2·9)	−0·2 to 11·1*
Key secondary endpoints				
LDL cholesterol at week 24 (Hopkins)	−4·8% (3·5)	−10·2% (3·5)	5·4% (2·8)	−0·2 to 11·0
LDL cholesterol at week 24 (ultracentrifugation)	−6·6% (3·5)	−10·1% (3·5)	3·5% (2·9)	−2·1 to 9·1
LDL cholesterol at mean of weeks 22 and 24 (Friedewald)	−8·0% (3·4)	−12·2% (3·3)	4·2% (2·2)	−0·2 to 8·6
LDL cholesterol at mean of weeks 22 and 24 (Hopkins)	−7·8% (3·4)	−12·1% (3·3)	4·3% (2·3)	−0·2 to 8·8
Other secondary endpoints				
LDL cholesterol at week 24 (Friedewald)—non-parametric†	−6·3% (−15·1 to 8·3)	−7·9% (−26·7 to 4·2)	6,7	−1·9 to 15·5
LDL cholesterol at week 12 (Friedewald)	−12·0% (2·8)	−11·5% (2·9)	−0·5% (4·0)	−8·5 to 7·5
Total cholesterol at week 24	−4·0% (2·9)	−8·4% (2·9)	4·4% (2·3)	−0·0 to 8·8
Triglycerides at week 24	2·0% (5·7)	2·1% (5·6)	−0·2% (6·9)	−13·6 to 13·3
HDL cholesterol at week 24	−0·2% (2·3)	−1·4% (2·2)	1·2% (2·3)	−3·2 to 5·7
Apolipoprotein B at week 24	−4·7% (6·5)	−16·2% (6·3)	11·5% (5·2)	1·3 to 21·7
Lipoprotein(a) at week 24	−7·3% (5·7)	−6·5% (5·5)	−0·8% (7·1)	−14·7 to 13·2
Lipoprotein(a) at week 24—non-parametric†	−9·4% (−22·5 to 10·6)	−8·0% (−25·0 to 5·6)	0,54	−8·2 to 10·5

Data are mean (SE), unless otherwise specified. *p=0·058. †Treatment results are median (IQR), treatment difference uses the Hodges-Lehmann estimate, and 95% CI is for the location shift.

Table 2: **Primary and key secondary endpoints—intention-to-treat population (n=66)**

of 62 participants) compared with lerodalcibep (31 [48%] of 65 participants). This higher percentage was largely driven by a higher incidence of injection site reactions reported with evolocumab (15 [24%] of 62 participants) compared with lerodalcibep (1 [2%] of 65 participants). However, none of the injection site reactions were severe or persistent. Apart from injection site reactions, the most frequently reported adverse events were COVID-19 infection, headache, and toothache (table 3). Measurement of anti-drug antibodies was only done in those treated with lerodalcibep if low concentrations of sporadic and transient anti-drug antibodies and neutralising antibodies were detected. None of the neutralising antibodies (detected in seven participants) were associated with in-vivo effects (eg, injection site reactions or any impairment in PCSK9 suppression), lerodalcibep concentrations, or the degree of LDL cholesterol reduction over the 24-week period or at the final two visits at weeks 22 and 24. In these participants, the LDL cholesterol changes with lerodalcibep were also similar to the changes seen with evolocumab (appendix 2 p 17). There were no other adverse events of special interest, such as elevations in hepatic aminotransferases or creatine kinase.

Discussion

Although the ITT analysis of last squares mean percent change from baseline in LDL cholesterol did not achieve non-inferiority with lerodalcibep compared with evolocumab, both treatments resulted in similar reductions in calculated or ultracentrifugation-measured LDL cholesterol at weeks 24 and 12 and averaged over the 24-week treatment periods in both the ITT and modified ITT populations. The mean percent reduction in LDL cholesterol with both therapies was less than that previously reported with evolocumab in the homozygous familial hypercholesterolaemia phase 3 trials.[6,11,24,25] To further evaluate the responses in the context of trials published in the past decade in more diverse and paediatric homozygous familial hypercholesterolaemia populations, an exploratory analysis was conducted. Although the responses in the populations from the USA, Norway, Israel, and South Africa were more consistent, with previous trials in these countries, the lower overall reductions in this diverse population were driven predominantly by the large number, nearly 40%, of patients in India and Türkiye and the 32% of paediatric patients, who had minimal response (appendix 2 p 16). This reduced LDL cholesterol response in genetic variants in India and Türkiye is consistent with the mean reductions in LDL cholesterol of only 6·4% in the 12 week open-label RAMAN homozygous familial hypercholesterolaemia trial in India with evolocumab reported in 2021.[12] The variants in the homozygous familial hypercholesterolaemia populations from India and Türkiye is probably related to greater *LDLR* activity impairment than seen in previous trials, and is also consistent with the roughly 50% higher baseline LDL cholesterol concentrations, despite similar statin and other oral therapies, as used in patients with homozygous familial hypercholesterolaemia in the USA, South Africa, Norway, and Israel.

Our results in participants younger than 18 years are also consistent with the alirocumab trial in a paediatric homozygous familial hypercholesterolaemia population reported in 2022, in which mean LDL cholesterol was reduced by only 4·1%,[13] and with the 2023 analysis of paediatric patients with homozygous familial hypercholesterolaemia in an open-label extension trial with evolocumab, which reported a median percentage change from baseline in LDL cholesterol of only −2·9% after 12 weeks of treatment with monthly 420 mg of evolocumab.[15] The unpredictability and poor response in patients with homozygous familial hypercholesterolaemia is also highlighted by the trials in homozygous familial hypercholesterolaemia with inclisiran reported in 2024, a small interfering RNA.[14] A pilot open-label study, ORION-2, of inclisiran in four patients with homozygous familial hypercholesterolaemia of European lineage showed robust LDL cholesterol reductions[26] but minimal reductions in the large global phase 3 ORION-5 trial, with 70% of patients having post-randomisation genetically confirmed homozygous familial hypercholesterolaemia.[14]

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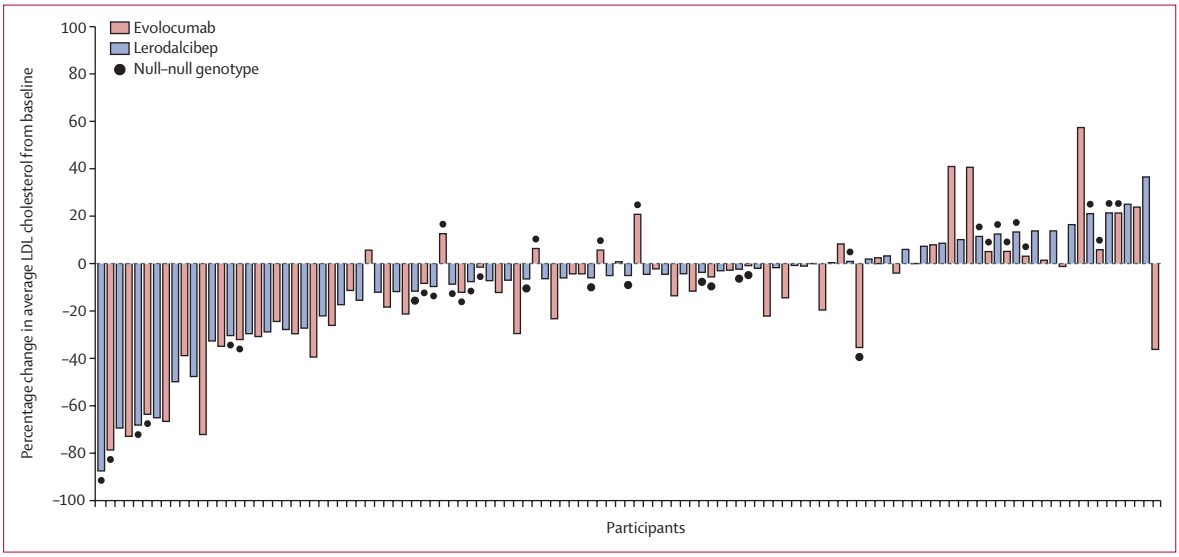


Figure 2: **Waterfall plot showing individual patient's percentage change in average LDL cholesterol from baseline to 24 weeks on lerodalcibep and evolocumab (r=0·79)—modified intention-to-treat population**

Participants sorted by percentage change in LDL cholesterol for the lerodalcibep group. Adjacent boxes in the plot represent percentage change in LDL cholesterol with lerodalcibep and evolocumab for the same patient.

Although a trial of alirocumab in patients with homozygous familial hypercholesterolaemia, selected by clinical criteria, showed a reduction from baseline in LDL cholesterol of 27% and an increase of 9% with placebo, 25% of patients in the study had either a heterozygous familial hypercholesterolaemia or no pathogenic variant. The response in those with genetically confirmed homozygous familial hypercholesterolaemia was substantially less, with approximately 50% of participants showing no reduction in LDL cholesterol.[27] The mean reduction in LDL cholesterol in this homozygous familial hypercholesterolaemia trial, with both lerodalcibep and evolocumab, was less than previously reported in the initial trials with evolocumab. 30% of the participants, including some with substantially higher baseline LDL cholesterol concentrations, had clinically meaningful reductions (≥15%) in average LDL cholesterol, 20% of participants had a 30% or greater reduction, and 10% of participants had robust reductions between 60% and 90% in LDL cholesterol. Good responders included participants with null–null *LDLR* variants based on genotyping. As LDL cholesterol concentrations predict cardiovascular risk and as the benefit from lipid-lowering therapies is proportional to the absolute reduction in LDL cholesterol, even small percentage reductions (eg, 10–15%) in patients with homozygous familial hypercholesterolaemia and a LDL cholesterol baseline of 10 mmol/L or higher, as in this study, translate into large absolute reductions of more than 1 mmol/L.[28–30]

From a clinical standpoint this study showed that, despite LDL cholesterol reductions being highly variable across the patient population, in the same patients LDL cholesterol reductions were similar and not clinically different between lerodalcibep and evolocumab. Although only able to be measured in patients given lerodalcibep the nearly 90% suppression of free PCSK9 measured at every 4-week trough clearly showed no difference between good responders, poor responders, and non-responders. This result is consistent with and provides confirmation that there is a limitation to the degree of LDLR upregulation and increased LDL clearance that can be achieved in individual patients even with non-null *LDLR* variants, suggesting that there must be other factors influencing response.[7,8] The study

	Lerodalcibep (n=65)	Evolocumab (n=62)	Treatment difference (95% CI)
Patients with any treatment-emergent adverse event	31 (48%)	38 (61%)	−13·6% (−30·8 to 4·0)
Discontinued due to an adverse event	2 (3%)	0	3·1% (−14·3 to 20·4)
Moderate or severe adverse event	21 (32%)	20 (32%)	0·2% (−16·2 to 16·3)
Serious adverse event	5 (8%)	2 (3%)	4·5% (−3·3 to 12·3)
Deaths	0	0	..
Most common adverse events (incidence of >2 patients within a treatment group)			
Injection site reactions	1 (2%)	15 (24%)	−22·7% (−39·0 to −5·0)
Injection site erythema	0	5 (8%)	−8·1% (−25·0 to 9·6)
Coronavirus infection	4 (6%)	4 (6%)	−0·3% (−17·4 to 17·3)
Headache	6 (9%)	3 (5%)	4·4% (−12·7 to 21·9)
Toothache	3 (5%)	1 (2%)	3·0% (−11·4 to 23·3)
Alanine aminotransferase >3 times upper limit of normal	0	1 (2%)	−1·6% (−18·9 to 15·8)
Aspartate aminotransferase >3 times upper limit of normal	1 (2%)	0	1·5% (−15·8 to 18·9)

Data are n (%), unless otherwise specified.

Table 3: **Treatment-emergent adverse events—safety population**

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also highlights that the potential for LDL cholesterol reduction with potent PCSK9-directed therapy in homozygous familial hypercholesterolaemia is unpredictable when based on genetic data.[31] Assigning functional status to *LDLR* pathogenic variants in the absence of molecular or cellular experimental data is an imprecise task. Since the vast majority of *LDLR* variants have not been directly functionally evaluated, most of the variants were assigned status based on the best approximation and data available at the time of the study. Although some variants in this trial are likely to have subsequently been misassigned based on updated data since this trial began, altering the assignments neither changes the overall interpretation of response variability nor the advice from treatment guidelines that response can only be determined by treatment with a PCSK9 inhibitor, supporting the recommendation for an empirical trial of preferably 12 weeks in patients with homozygous familial hypercholesterolaemia.[1]

Thereafter, PCSK9 inhibitor therapy should be continued only if there is a clinically meaningful reduction in LDL cholesterol. Only once the response to PCSK9 inhibition has been determined should the addition of expensive life-long orphan therapies that work independently of LDLR function, such as lomitapide and evinacumab, or lipoprotein apheresis be considered. This recommendation is in keeping with the latest recommendation from the 2023 European Atherosclerosis Society consensus statement for the treatment of homozygous familial hypercholesterolaemia.[1]

The strengths of this study include the randomisation of patients with genetically confirmed homozygous familial hypercholesterolaemia, the great diversity of patients (from countries not previously included in global trials and those with novel and severe variants), a large number of paediatric participants, and treatment with two different PCSK9 inhibitors, both of which bind and inactivate circulating PCSK9. It is also a novel crossover design following the 2010 consort recommendations for such trials, including randomisation to the first treatment period, inclusion of a wash out period sufficient to eliminate carryover effects before crossover for the second treatment period, use of the same baseline to assess efficacy, a long 24-week exposure to each treatment, and multiple robust statistical analyses recommended for crossover trials in rare populations, including a supplementary exploratory analysis to assess differences from trials published in the past 3 years not showing efficacy in paediatric patients and patients with homozygous familial hypercholesterolaemia from the countries included in this trial.[17] Limitations include the open-label nature of the trial and inability to mask each treatment for safety assessment; the absence of direct ex-vivo assessment of residual LDLR function in novel variants from India, Türkiye, and other countries, which rely on databases with extrapolation of LDLR activity related to the structural impairment of pathogenic variants; and other potential but unknown factors that could affect LDL cholesterol response including apolipoproteins (eg, apolipoprotein E) or as yet undiscovered intracellular pathways.[32]

In conclusion, this study is the first study to compare two different inhibitors of plasma PCSK9 in a crossover trial with a washout and treatment periods of sufficient duration to eliminate carry-over effects in a large and diverse genotyped homozygous familial hypercholesterolaemia population. It included countries with novel pathogenic variants, had 30% paediatric patients, and adds new evidence regarding PCSK9 inhibitors, which supports their use as potential adjunct treatment for patients with homozygous familial hypercholesterolaemia, even in those whose benefit was predicted to be limited based on previous knowledge of *LDLR* genotyping.

Contributors

FJR and EAS designed the trial and interpreted the data. JV analysed the data. FJR, DK, JV and EAS had full access to, reviewed, and verified the data and wrote the original manuscript. All authors provided critical revision of drafts and approved the final manuscript. The authors had unrestricted access to study data, were responsible for all content and editorial decisions, and received no honoraria related to the development of this publication. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

FJR reports grants from LIB Therapeutics during the conduct of the study; and personal fees from LIB Therapeutics, Amgen, Sanofi, Regeneron Pharmaceuticals, and Novartis outside the submitted work. VM reports institutional research grants from LIB Therapeutics, Amgen, AstraZeneca, Novo Nordisk, Eli Lilly, Torrent, and Boehringer Ingelheim. MK reports honoraria (for lectures or consultancy) from Abbott, Abdi Ibrahim, LIB Therapeutics, Novartis, NovoNordisk, and Pfizer and research funding from Amgen, Ionis, LIB Therapeutics, MSD, and Novartis for the past 3 years. DB reports clinical trial fees from LIB Therapeutics during the conduct of the study; and personal fees from Amgen, Amryt, MSD, Novartis, Sanofi, and Servier and outside the submitted work. TM, KC, and DK are employees of and own shares in LIB Therapeutics. EAS is the founder of and a partner in LIB Therapeutics. All other authors declare no competing interests.

Data sharing

Qualified researchers can request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymised participant data will be made available once the indication has been approved by a regulatory body, if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification.

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