The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 20, 2020 VOL. 383 NO. 8

Evinacumab for Homozygous Familial Hypercholesterolemia

Frederick J. Raal, M.D., Ph.D., Robert S. Rosenson, M.D., Laurens F. Reeskamp, M.D., G. Kees Hovingh, M.D., Ph.D., John J.P. Kastelein, M.D., Ph.D., Paolo Rubba, M.D., Shazia Ali, Pharm.D., Poulabi Banerjee, Ph.D., Kuo-Chen Chan, Ph.D., Daniel A. Gipe, M.D., Nagwa Khilla, M.S., Robert Pordy, M.D., David M. Weinreich, M.D., George D. Yancopoulos, M.D., Ph.D., Yi Zhang, Ph.D., and Daniel Gaudet, M.D., Ph.D., for the ELIPSE HoFH Investigators*

ABSTRACT

BACKGROUND

Homozygous familial hypercholesterolemia is characterized by premature cardiovascular disease caused by markedly elevated levels of low-density lipoprotein (LDL) cholesterol. This disorder is associated with genetic variants that result in virtually absent (null–null) or impaired (non-null) LDL-receptor activity. Loss-of-function variants in the gene encoding angiopoietin-like 3 (*ANGPTL3*) are associated with hypolipidemia and protection against atherosclerotic cardiovascular disease. Evinacumab, a monoclonal antibody against ANGPTL3, has shown potential benefit in patients with homozygous familial hypercholesterolemia.

METHODS

In this double-blind, placebo-controlled, phase 3 trial, we randomly assigned in a 2:1 ratio 65 patients with homozygous familial hypercholesterolemia who were receiving stable lipid-lowering therapy to receive an intravenous infusion of evinacumab (at a dose of 15 mg per kilogram of body weight) every 4 weeks or placebo. The primary outcome was the percent change from baseline in the LDL cholesterol level at week 24.

RESULTS

The mean baseline LDL cholesterol level in the two groups was 255.1 mg per deciliter, despite the receipt of maximum doses of background lipid-lowering therapy. At week 24, patients in the evinacumab group had a relative reduction from baseline in the LDL cholesterol level of 47.1%, as compared with an increase of 1.9% in the placebo group, for a between-group least-squares mean difference of −49.0 percentage points (95% confidence interval [CI], −65.0 to −33.1; P<0.001); the between-group least-squares mean absolute difference in the LDL cholesterol level was −132.1 mg per deciliter (95% CI, −175.3 to −88.9; P<0.001). The LDL cholesterol level was lower in the evinacumab group than in the placebo group in patients with null–null variants (−43.4% vs. +16.2%) and in those with non-null variants (−49.1% vs. −3.8%). Adverse events were similar in the two groups.

CONCLUSIONS

In patients with homozygous familial hypercholesterolemia receiving maximum doses of lipid-lowering therapy, the reduction from baseline in the LDL cholesterol level in the evinacumab group, as compared with the small increase in the placebo group, resulted in a between-group difference of 49.0 percentage points at 24 weeks. (Funded by Regeneron Pharmaceuticals; ELIPSE HoFH ClinicalTrials.gov number, NCT03399786.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Raal at the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, or at frederick.raal@wits.ac.za; or to Dr. Gaudet at the Department of Medicine, Université de Montréal Community Gene Medicine Center, Chicoutimi, QC, Canada, or at daniel.gaudet@umontreal.ca.

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

N Engl J Med 2020;383:711-20.
DOI: 10.1056/NEJMoa2004215

Homozygous familial hypercholesterolemia is a rare genetic disorder of lipid metabolism affecting approximately 1 in 300,000 persons. The condition is most often caused by the presence of loss-of-function variants in the low-density lipoprotein (LDL) receptor, which leads to low or absent hepatic clearance of LDL cholesterol from the circulation.[1] Genetic alterations that cause a virtually complete absence of LDL-receptor expression (null homozygotes) result in higher LDL cholesterol levels than alterations that partially reduce LDL-receptor activity with either two non-null alleles or one null and one non-null allele (non-null homozygotes).[2]

This disorder is characterized by a markedly elevated plasma LDL cholesterol level from birth, which results in an increased risk of premature atherosclerotic cardiovascular disease.[1] Attempts to lower cholesterol levels often require multiple lipid-lowering drugs and LDL apheresis.[1,3] Despite these therapies, a majority of patients with this disorder do not reach guideline-recommended LDL cholesterol levels.[4] Because traditional lipid-lowering therapies such as statins and proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors act by up-regulating LDL-receptor expression, they have little efficacy in these patients and virtually no activity in those with two null alleles.

Angiopoietin-like 3 (ANGPTL3) is an inhibitor of lipoprotein and endothelial lipase and plays a key role in lipid metabolism by increasing the levels of triglycerides and other lipids.[5-7] Loss-of-function variants in *ANGPTL3* have been associated with low levels of both LDL cholesterol and triglycerides and with a 41% lower risk of coronary artery disease, despite the presence of low levels of high-density lipoprotein (HDL) cholesterol.[8,9] Both *ANGPLT3* loss-of-function variants and ANGPTL3 pharmacologic inhibition reduce LDL cholesterol levels independently of the LDL receptor.[5,10,11]

Evinacumab is a fully human monoclonal antibody that is an inhibitor of ANGPTL3.[10] (A description of the methods used in the development of evinacumab is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) In a phase 2, open-label, proof-of-concept study involving nine patients with homozygous familial hypercholesterolemia, evinacumab treatment resulted in a mean reduction from baseline of 49% in the LDL cholesterol level.[12] Here, we describe the results of a phase 3, randomized, placebo-controlled, parallel-group trial, the Evinacumab Lipid Studies in Patients with Homozygous Familial Hypercholesterolemia (ELIPSE HoFH) trial, which we conducted to further evaluate the efficacy and safety of evinacumab in patients with nullnull variants and in those with non-null variants.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted the trial at 30 sites in 11 countries. The principal investigators and the sponsor (Regeneron Pharmaceuticals) designed the trial protocol (available at NEJM.org) and selected the participating sites. The protocol was approved by the institutional review board or ethics committee at each site.

The trial was conducted in accordance with the principles of the Declaration of Helsinki, consistent with the Good Clinical Practice guidelines of the International Conference on Harmonisation. Monitoring and site supervision were performed by a contract research organization (ICON) with oversight by the sponsor. The sponsor also participated in the collection, analysis, and interpretation of the data and checked information provided in the manuscript. Editorial support for the writing of the manuscript was provided by Prime Global and financed by the sponsor. All the authors had access to the data, contributed to the drafting of an initial version of the manuscript, participated in revisions, and concurred with the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PATIENTS

Patients with homozygous familial hypercholesterolemia who were 12 years of age or older were eligible for inclusion. Patients were required to be receiving stable lipid-lowering therapy at the maximum dose that did not cause unacceptable side effects and to have an LDL cholesterol level of 70 mg per deciliter (1.8 mmol per liter) or more at screening. The full list of inclusion and exclusion criteria is provided in the Supplementary Appendix. Written informed consent was obtained from each patient.

The diagnosis of homozygous familial hypercholesterolemia was based on either genetic or clinical criteria. The genetic diagnosis was defined as a documented variant in two *LDLR* alleles or the presence of homozygous or compound heterozygous variants in apolipoprotein B (*APOB*) or *PCSK9*. Patients who had compound heterozygosity or homozygosity for variants in the gene encoding LDL receptor adaptor protein 1 (*LDLRAP1*) were also eligible. The clinical diagnosis was defined as an untreated total cholesterol level of more than 500 mg per deciliter (12.9 mmol per liter), with either the presence of cutaneous or tendinous xanthomas before the age of 10 years or documentation of an untreated total cholesterol level of more than 250 mg per deciliter (6.5 mmol per liter) in both parents. A patient was considered to be a null–null variant carrier if the LDL-receptor activity was less than 15% according to in vitro assessments of functionality, as reported in the literature.[11] A post hoc analysis of data from patients who had very little or no LDL-receptor activity (based on a definition of less than 2% functional activity) was also conducted.[13]

PROCEDURES

The trial included a run-in period of up to 8 weeks for patients who did not have a diagnosis of homozygous familial hypercholesterolemia and opted to undergo genotyping for confirmation or whose background lipid-lowering therapy or apheresis schedules were not stable before screening. The run-in period was followed by a 2-week screening period to determine trial eligibility.

Eligible patients were randomly assigned in a 2:1 ratio through an interactive voice- or Web-response system to receive an intravenous infusion of either evinacumab (at a dose of 15 mg per kilogram of body weight) every 4 weeks or matching placebo. The randomization was stratified according to whether the patients had received previous apheresis treatment and whether they lived in Japan (to provide data on pharmacodynamic and safety findings in an Asian population). Double-blind treatment continued for 24 weeks. Concomitant lipid-lowering therapies were to be continued for the duration of the trial. After completion of the double-blind treatment period, patients had the option of entering a 24-week open-label study to receive the same regimen of evinacumab that was used in the randomized trial. Patients who did not choose to enter the open-label study entered a 24-week follow-up period after the last dose of evinacumab or placebo.

OUTCOMES

The primary outcome was the percent change in the calculated LDL cholesterol level from baseline to week 24 during the double-blind treatment period. The baseline LDL cholesterol level was defined as the last calculated LDL cholesterol value obtained before the administration of the first dose of evinacumab or placebo. For the efficacy analysis, the LDL cholesterol level was obtained within the 24-week window, regardless of adherence to treatment and subsequent therapies. Secondary outcomes are listed in the Supplementary Appendix. The mean total serum level of evinacumab over time was also analyzed.

STATISTICAL ANALYSIS

We estimated that a sample size of 57 patients (38 assigned to receive evinacumab and 19 assigned to receive placebo) was required to provide a power of 90% to confirm the primary efficacy hypothesis of a between-group absolute difference in the mean percent change in the LDL cholesterol level of 38 percentage points, according to a two-sample t-test with a two-sided significance level of 0.05. This assumption was based on a common standard deviation of 35% of the percent change from baseline in the two groups, after a 20% adjustment to account for patients who had withdrawn from the trial or could not otherwise be evaluated.

We used a mixed-effects model for repeated measures to analyze the percent change from baseline in the calculated LDL cholesterol level at week 24 in the intention-to-treat population. The model included the fixed categorical effects of trial-group assignment (evinacumab vs. placebo), randomization strata (apheresis [yes vs. no] and geographic region [Japan vs. rest of world]), time point (week 2, 4, 8, 12, 16, 20, or 24), and interactions between strata and time point and between treatment and time point, as well as the continuous fixed covariates of the interaction between baseline levels of calculated LDL cholesterol and time point.

We assessed the continuous secondary outcomes using the same model that was used for the primary outcome, except for variables that

were anticipated to have a non-normal distribution, including triglycerides and lipoprotein(a), which we assessed using a robust regression model[14] after applying a multiple-imputation approach (i.e., a log transformation of data before multiple imputation) for handling missing data. In the model, the outcome of interest was the response variable with trial group, randomization strata, and corresponding baseline values as covariates. Binary outcomes were assessed by logistic regression after the application of a multiple-imputation approach, with the trial group and corresponding baseline values as covariates, stratified according to randomization strata. The overall type I error was controlled for primary and key secondary outcomes with a hierarchical inferential approach, as described in the Supplementary Appendix.

The safety analysis population included all the patients who had undergone randomization and had received at least one dose of evinacumab or placebo. The period for the evaluation of adverse events was defined as the interval from the day of administration of the first dose of evinacumab or placebo until week 24. All safety data were assessed descriptively. The percent change from baseline in the HDL cholesterol level was assessed descriptively as a safety outcome because of reductions in this measure that had been observed after evinacumab treatment in previous studies.[12,15]

RESULTS

PATIENTS

Of the 75 patients who were screened, 65 underwent randomization (43 to receive evinacumab and 22 to receive placebo (Fig. S1 in the Supplementary Appendix). The first patient was enrolled on February 15, 2018, and the last on December 18, 2018. The date of the database lock was July 29, 2019. All the patients who had undergone randomization also received at least one dose of evinacumab or placebo. One patient in the placebo group received evinacumab in error at week 20 during the double-blind treatment period and was therefore included in the evinacumab group for all safety analyses.

The demographic and baseline characteristics of the patients were generally well balanced in the two groups (Table 1). One adolescent patient (12 to <18 years of age) was included in each group. The mean baseline LDL cholesterol level was 260 mg per deciliter (6.7 mmol per liter) in the evinacumab group and 247 mg per deciliter (6.4 mmol per liter) in the placebo group. A total of 53 patients (82%) had a genetically confirmed diagnosis of homozygous familial hypercholesterolemia. Genotype data are provided in Table S1.

Null–null LDL-receptor variants (<15% activity) were identified in 15 of 43 patients (35%) in the evinacumab group and in 6 of 22 patients (27%) in the placebo group. At baseline, the mean (±SD) LDL cholesterol level was 312±158 mg per deciliter (8.1±4.1 mmol per liter) in the 21 patients with null–null variants and 228±164 mg per deciliter (5.9±4.2 mmol per liter) in the 44 patients with non-null variants.

The majority of the trial patients (94%) were receiving a statin (a high-intensity statin in 77%). In addition, a PCSK9 inhibitor was being administered in 77% of the patients, ezetimibe in 75%, and lomitapide in 25%; 34% of the patients were undergoing apheresis (Table S2). A total of 63% of the patients were taking at least three lipid-modifying drugs.

PRIMARY EFFICACY AND SUBGROUP OUTCOME ANALYSES

At week 24, patients in the evinacumab group had a 47.1% reduction from baseline in the LDL cholesterol level, as compared with a 1.9% increase in the placebo group, for a between-group least-squares mean difference of −49.0 percentage points (95% confidence interval [CI], −65.0 to −33.1; P<0.001) (Table 2). The reduction in LDL cholesterol levels with evinacumab was observed at the first post-treatment lipid assessment at week 2 and was maintained throughout the 24-week double-blind treatment period (Fig. 1). The between-group least-squares mean absolute difference in the LDL cholesterol level was −132 mg per deciliter (−3.4 mmol per liter); 95% CI, −175 to −89 mg per deciliter (−4.5 to −2.3 mmol per liter) (P<0.001) (Table 2). Waterfall plots for the percent and absolute changes in LDL cholesterol levels as grouped according to genotype for each patient are provided in Figure S2.

The degree of lowering of cholesterol levels was higher in the evinacumab group than in the placebo group among patients with null–null variants (−43.4% and +16.2%, respectively) and

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

Characteristic	Evinacumab (N=43)	Placebo (N=22)	Total (N=65)
Age			
Mean — yr	44.3±16.8	36.7±11.5	41.7±15.5
Distribution — no. (%)			
12 to <18 yr	1 (2)	1 (5)	2 (3)
18 to <45 yr	23 (53)	16 (73)	39 (60)
45 to <65yr	11 (26)	5 (23)	16 (25)
≥65 yr	8 (19)	0	8 (12)
Female sex — no. (%)	24 (56)	11 (50)	35 (54)
Race — no. (%)†			
White	31 (72)	17 (77)	48 (74)
Black	2 (5)	0	2 (3)
Asian	6 (14)	4 (18)	10 (15)
Other or not reported	4 (9)	1 (5)	5 (8)
Body-mass index‡	26.1±5.9	24.6±5.7	25.6±5.8
History of coronary heart disease — no. (%)	38 (88)	21 (95)	59 (91)
Method of HoFH diagnosis — no. (%)			
Genotyping	29 (67)	15 (68)	44 (68)
Clinical diagnosis	14 (33)	7 (32)	21 (32)
Activity of LDL-receptor variants — no. (%)			
<2%	8 (19)	2 (9)	10 (15)
<15%	15 (35)	6 (27)	21 (32)
Cholesterol — mg/dl			
Calculated LDL	259.5±172.4	246.5±153.7	255.1±165.2
High-density lipoprotein	43.6±14.9	46.0±16.1	44.4±15.2
Non–high-density lipoprotein	281.9±172.6	269.9±157.8	277.8±166.6
Total cholesterol	325.6±170.8	315.9±150.4	322.3±163.1
Median triglycerides (IQR) — mg/dl	91 (65–145)	104 (59–182)	97 (65–162)
Median lipoprotein(a) (IQR) — nmol/liter	59 (22–173)	53 (32–60)	57 (29–166)
Apolipoprotein B — mg/dl	169.1±82.8	175.9±98.8	171.4±87.8

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HoFH denotes homozygous familial hypercholesterolemia, IQR interquartile range, and LDL low-density lipoprotein.
† Race was reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

non-null variants (–49.1% and –3.8%, respectively) (Fig. 2). The percent changes in LDL cholesterol levels from baseline to week 24 were consistent across the range of background therapies, including statins, ezetimibe, lomitapide, PCSK9 inhibitors, and apheresis (Table S3).

SECONDARY AND POST HOC EFFICACY OUTCOME ANALYSES

Patients in the evinacumab group had significantly lower levels of apolipoprotein B, non-HDL cholesterol, and total cholesterol from baseline to week 24 than those in the placebo group

Table 2. Trial Outcomes at 24 Weeks.*

Outcome	Evinacumab (N=43)	Placebo (N=22)	LS Mean (±SE) Difference 95% CI	Odds Ratio 95% CI	P Value
Primary outcome					
Percent change from baseline in LDL cholesterol	−47.1±4.6	1.9±6.5	−49.0±8.0 (−65.0 to −33.1)	—	<0.001
Key secondary outcomes					
Percent change from baseline in apolipoprotein B	−41.4±3.3	−4.5±4.8	−36.9±5.9 (−48.6 to −25.2)	—	<0.001
Percent change from baseline in non-HD lipoprotein cholesterol	−49.7±3.8	2.0±5.4	−51.7±6.6 (−64.8 to −38.5)	—	<0.001
Percent change from baseline in total cholesterol	−47.4±3.0	1.0±4.2	−48.4±5.1 (−58.7 to −38.1)	—	<0.001
Patients with ≥30% reduction from baseline in LDL cholesterol — no. (%)†	36 (84)	4 (18)	—	25.2 (5.7 to 110.5)	<0.001‡
Patients with ≥50% reduction from baseline in LDL cholesterol — no. (%)†	24 (56)	1 (5)	—	24.2 (3.0 to 195.6)	0.003‡
Absolute change from baseline in calculated LDL cholesterol — mg/dl	−134.7±12.4	−2.6±17.6	−132.1±21.5 (−175.3 to −88.9)	—	<0.001
Patients who met U.S. apheresis eligibility criteria — no. (%)†§	3 (7)	5 (23)	—	0.1 (0.0 to 1.3)	0.09‡
Patients with LDL cholesterol <100 mg/dl — no. (%)†	20 (47)	5 (23)	—	5.7 (1.3 to 24.9)	NA¶
Patients who met EU apheresis eligibility criteria — no. (%)‖	14 (33)	17 (77)	—	0.1 (0.0 to 0.3)	NA
Other secondary outcomes					
Percent change from baseline in triglycerides	−55.0±3.1	−4.6±7.0	−50.4±7.7 (−65.6 to −35.2)	—	NA
Percent change from baseline in lipoprotein(a)	−5.5±4.0	−3.6±5.8	−1.9±7.1 (−15.7 to 12.0)	—	NA
Percent change from baseline in apolipoprotein C-III	−84.1±3.9	5.8±5.5	−90.0±6.7 (−103.5 to −76.5)	—	NA
Patients with calculated LDL cholesterol <70 mg/dl — no. (%)†	12 (28)	1 (5)	—	20.9 (1.6 to 276.8)	NA

* Plus–minus values are means ±SD unless otherwise indicated. The outcome categories are listed in the hierarchical-testing order. The between-group differences and odds ratios are for the value in the evinacumab group, as compared with the placebo group. Details regarding the percent and absolute changes in LDL cholesterol levels according to genotype for each patient are provided in Figure S2 in the Supplementary Appendix. HD denotes high density, LS least squares, and NA not applicable.

† In this category, the combined estimate for the number of patients and odds ratio was based on a logistic-regression model that used 100 simulation data sets for imputation of missing data.

‡ P value is based on the odds ratio.

§ In the United States, the criterion for eligibility to undergo apheresis is an LDL cholesterol level of 300 mg per deciliter or more.

¶ Hierarchical testing was terminated with the previous outcome, since it did not meet the cutoff for statistical significance.

‖ In the European Union (EU), the criterion for eligibility to undergo apheresis is either an LDL cholesterol level of more than 160 mg per deciliter if the patient is being treated for primary prevention of cardiovascular disease or an LDL cholesterol level of more than 120 mg per deciliter if the patient is being treated for secondary prevention of cardiovascular disease.

(P<0.001 for all comparisons) (Table 2). Percent and absolute changes for apolipoprotein B are shown in Figure S3. HDL cholesterol levels (which were assessed as a safety outcome) were reduced from baseline by 29.6% in the evinacumab group, as compared with an increase of 0.8% in the placebo group. A reduction in the LDL cholesterol level of at least 30% was ob-

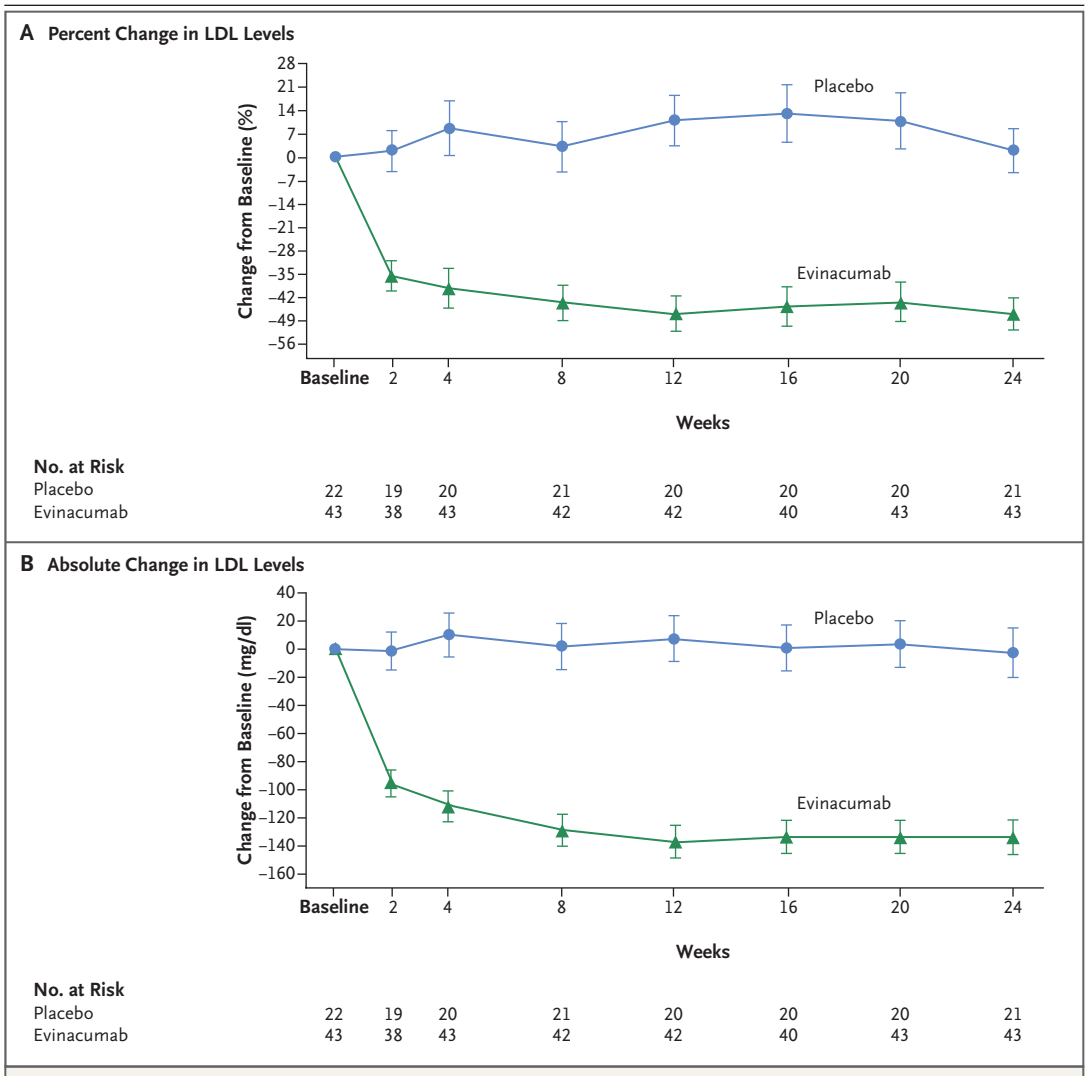


Figure 1. Changes from Baseline in Low-Density Lipoprotein (LDL) Cholesterol Levels at 24 Weeks.

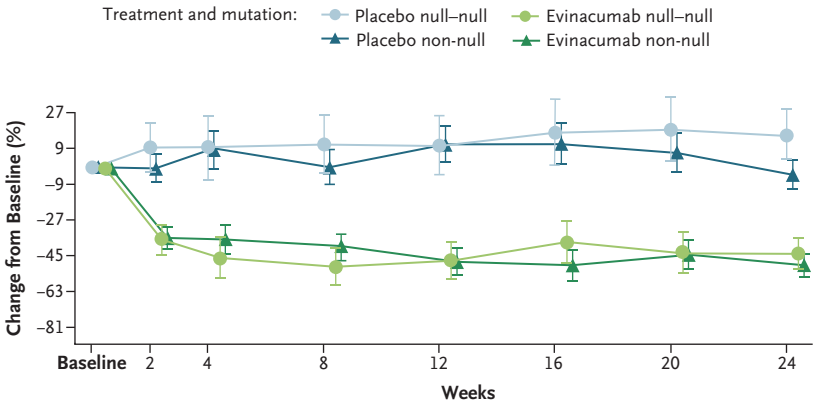
Shown is the least-squares mean percent change (Panel A) and absolute change (Panel B) in calculated LDL cholesterol levels from baseline to week 24 in the evinacumab group and the placebo group. The I bars indicate standard errors.

served in 84% of patients in the evinacumab group and in 18% of those in the placebo group (P<0.001). Results for all other secondary outcomes are provided in Table 2.

Variants with less than 2% functional LDL-receptor activity were identified in 8 patients in the evinacumab group and in 2 patients in the placebo group.[13] In a post hoc analysis investigating the effects of evinacumab in these 8 patients, the baseline mean LDL cholesterol level was 261 mg per deciliter (6.7 mmol per liter). At week 24, the change from baseline in the LDL cholesterol level was a decrease of 53.5% in the evinacumab group and an increase of 18.8% in the placebo group (least-squares mean difference, −72.3 percentage points; 95% CI, −121.8 to −22.8; P=0.005), with an absolute difference in the LDL cholesterol of 245 mg per deciliter (6.3 mmol per liter).

PHARMACOKINETICS

The mean total levels of evinacumab in serum over time are shown in Figure S4. Overall, serum levels of evinacumab were similar in patients receiving apheresis and in those not receiving apheresis.



No. at Risk								
Placebo null–null	6	4	6	6	6	6	6	6
Placebo non-null	16	15	14	15	14	14	14	15
Evinacumab null–null	15	14	15	15	14	15	15	15
Evinacumab non-null	28	24	28	27	28	25	28	28

Figure 2. Percent Change in LDL Cholesterol Levels, According to Type of LDL-Receptor Variants.

Shown is the least-squares mean percent change from baseline in LDL cholesterol levels in the evinacumab group and the placebo group, according to the type of loss-of-function variant in the LDL receptor. Genetic variants that cause a virtually complete absence of LDL-receptor expression (null–null variants) result in higher LDL cholesterol levels than variants that partially reduce LDL-receptor activity (non-null variants). Patients with null–null variants have LDL-receptor activity of less than 15%.

SAFETY

Adverse events during the treatment period occurred in 66% of the patients in the evinacumab group and in 81% of those in the placebo group (Table 3). No patients discontinued either evinacumab or placebo because of an adverse event; there were no deaths. Antidrug antibodies did not develop during the treatment period in any of the patients. Low titers of preexisting antibodies to evinacumab at baseline were reported in 4 patients (3 in the evinacumab group and 1 in the placebo group); the pharmacokinetics of evinacumab were not altered in these patients.

Serious adverse events during the treatment period occurred in 2 patients (5%) in the evinacumab group and were reported as urosepsis and a suicide attempt. Both patients recovered. No cardiovascular events were reported in either group during the double-blind treatment period. An influenza-like illness was reported in 5 of 44 patients (11%) in the evinacumab group and in no patients in the placebo group.

An increase in the level of either alanine or aspartate aminotransferase was reported in 2 of 44 patients (5%) in the evinacumab group and in 2 of 21 patients (10%) in the placebo group, increases that were less than 3 times and 5 times the upper limit of the normal range, respectively. Only elevations in the aspartate aminotransferase level in the placebo group were reported as adverse events during the treatment period. In all cases, elevations were not associated with any symptoms and returned to a normal range while the patients continued to receive either evinacumab or placebo. None of the patients in either trial group met the criteria for drug-induced liver injury, according to Hy's law.[16]

DISCUSSION

In this multicenter trial of ANGPTL3 inhibition involving patients with homozygous familial hypercholesterolemia,[12] the reduction from baseline in the LDL cholesterol level in the evinacumab group, as compared with the small increase in the placebo group, resulted in a between-group difference of 49.0 percentage points at 24 weeks; the corresponding between-group difference in apolipoprotein B levels was 36.9 percentage points. These reductions were achieved regardless of the use of extensive background lipid-lowering therapies with or without apheresis.

In this patient population, currently available therapies do not typically reduce LDL cholesterol levels to guideline-recommended levels, so new therapies are needed.[17] In such patients, statins and PCSK9 inhibitors, which have a mechanism of action that largely depends on the up-regulation of LDL-receptor function,[17,18] have been shown to reduce LDL cholesterol levels by approximately 20 to 30%, with minimal to no effect among those with null–null homozygosity.[19,20] Although lomitapide and mipomersen act independently of LDL-receptor function, adverse effects limit their wide use.[17,21,22]

It is well established that LDL cholesterol levels predict cardiovascular risk and that cardiovascular benefit from lipid-lowering therapies is proportional to the absolute reduction in the LDL cholesterol level.[17] In a large study of PCSK9 inhibitors (the ODYSSEY OUTCOMES trial), patients who had a baseline LDL cholesterol level of 100 mg per deciliter (2.6 mmol per liter) or more had the greatest benefit with alirocumab, with a relative 24% lower incidence of major adverse cardiovascular events and a 29% lower incidence of overall mortality than with placebo.[23,24] Our trial was not designed to assess the effect of treatment on a reduction in clinical events, but the absolute reduction in LDL cholesterol levels was substantial. Furthermore, genetic studies of *ANGPTL3* loss-of-function variants support the concept that ANGPTL3 inhibition should reduce both LDL cholesterol levels and cardiovascular events, despite a concurrent reduction in HDL cholesterol levels.[8] Studies of *PCSK9* loss-of-function variants provide an important precedent by showing that genetic studies can faithfully predict lipid changes as well as cardiovascular outcomes resulting from pharmacologic intervention in the pathway of interest.[8,10,23,25]

Some patients with homozygous familial hypercholesterolemia are treated with apheresis, an invasive therapy that has a considerable effect on health care costs and quality of life. In our trial, evinacumab provided a similar reduction in LDL cholesterol levels regardless of whether patients were being treated with apheresis, and the receipt of apheresis did not meaningfully affect plasma evinacumab levels. With evinacumab treatment, very few patients (7%) met the criteria for undergoing apheresis in the United States. Also, reductions in the levels of LDL cholesterol and apolipoprotein B from baseline to week 24 were observed with evinacumab both in patients with null–null variants and in those with non-null variants. This finding is important because patients with null–null variants have a higher cardiovascular risk and are less responsive to therapies that depend on LDL-receptor activity than those with non-null variants.[2]

Limitations of this trial include the relatively short duration of treatment and the small number of patients studied. As a consequence, the ability to assess safety, especially long-term safety, is limited. Also, the size and duration of the trial are not sufficient to assess the effect of evinacumab on cardiovascular outcomes in these high-risk patients.

In conclusion, in this phase 3 trial, evinacumab substantially lowered LDL cholesterol levels in patients with homozygous familial hypercholesterolemia, regardless of the degree of their LDL-receptor function.

Table 3. Adverse Events during the Treatment Period.*

Adverse Events	Evinacumab (N=44)	Placebo (N=21)
	no. (%)	
Any adverse event	29 (66)	17 (81)
Nasopharyngitis	7 (16)	5 (24)
Influenza-like illness	5 (11)	0
Headache	4 (9)	5 (24)
Rhinorrhea	3 (7)	0
Gastroenteritis	2 (5)	0
Infusion-site pruritus	2 (5)	0
Pyrexia	2 (5)	1 (5)
Cough	2 (5)	0
Dental caries	2 (5)	0
Diarrhea	2 (5)	1 (5)
Dyspepsia	2 (5)	0
Toothache	2 (5)	2 (10)
Dizziness	2 (5)	0
Urinary tract infection	0	2 (10)
Increased aspartate aminotransferase	0	2 (10)
Myalgia	0	2 (10)
Any serious adverse event	2 (5)	0
Urosepsis	1 (2)	0
Suicide attempt	1 (2)	0

* No adverse event was associated with a discontinuation of evinacumab or placebo. There were no deaths in either group.

Supported by Regeneron Pharmaceuticals.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients, their families, and all the investigators who were involved in trial; Rinal Patel, Pharm.D., who contributed to the data acquisition; and Michele Damo, Pharm.D., of Prime Global, for medical-writing assistance with a previous version of the manuscript.

We dedicate this article to the memory of Daniel A. Gipe, M.D., for his major contributions and commitment to patients with homozygous familial hypercholesterolemia and other dyslipidemias.

APPENDIX

The authors' affiliations are as follows: the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg (F.J.R.); the Cardiometabolics Unit, Zena and Michael A. Wiener Cardiovascular Institute, Marie-Josee and Henry R. Kravis Center for Cardiovascular Health, Icahn School of Medicine at Mount Sinai, New York (R.S.R.), and Regeneron Pharmaceuticals, Tarrytown (S.A., P.B, K.-C.C., D.A.G., N.K., R.P., D.M.W. G.D.Y., Y.Z.) — both in New York; the Department of Vascular Medicine, University of Amsterdam, Amsterdam (L.F.R., G.K.H., J.J.P.K.); the Department of Internal Medicine and Surgery, Federico II University, Naples, Italy (P.R.); and the Clinical Lipidology and Rare Lipid Disorders Unit, Department of Medicine, Université de Montréal Community Gene Medicine Center, Lipid Clinic Chicoutimi Hospital and ECOGENE-21 Clinical and Translational Research Center, Chicoutimi, QC, Canada (D.G.).

REFERENCES

1. Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management — a position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J 2014; 35:2146-57.
2. Moorjani S, Roy M, Torres A, et al. Mutations of low-density-lipoprotein-receptor gene, variation in plasma cholesterol, and expression of coronary heart disease in homozygous familial hypercholesterolaemia. Lancet 1993;341:1303-6.
3. Raal FJ, Hovingh GK, Catapano AL. Familial hypercholesterolemia treatments: guidelines and new therapies. Atherosclerosis 2018;277:483-92.
4. Blom DJ, Cuchel M, Ager M, Phillips H. Target achievement and cardiovascular event rates with lomitapide in homozygous familial hypercholesterolaemia. Orphanet J Rare Dis 2018;13:96.
5. Köster A, Chao YB, Mosior M, et al. Transgenic angiopoietin-like (angptl)4 overexpression and targeted disruption of angptl4 and angptl3: regulation of triglyceride metabolism. Endocrinology 2005; 146:4943-50.
6. Fujimoto K, Koishi R, Shimizugawa T, Ando Y. Angptl3-null mice show low plasma lipid concentrations by enhanced lipoprotein lipase activity. Exp Anim 2006; 55:27-34.
7. Shimamura M, Matsuda M, Yasumo H, et al. Angiopoietin-like protein3 regulates plasma HDL cholesterol through suppression of endothelial lipase. Arterioscler Thromb Vasc Biol 2007;27:366-72.
8. Dewey FE, Gusarova V, Dunbar RL, et al. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. N Engl J Med 2017;377:211-21.
9. Athyros VG, Katsiki N, Dimakopoulou A, Patoulias D, Alataki S, Doumas M. Drugs that mimic the effect of gene mutations for the prevention or the treatment of atherosclerotic disease: from PCSK9 inhibition to ANGPTL3 inactivation. Curr Pharm Des 2018;24:3638-46.
10. Gusarova V, Alexa CA, Wang Y, et al. ANGPTL3 blockade with a human monoclonal antibody reduces plasma lipids in dyslipidemic mice and monkeys. J Lipid Res 2015;56:1308-17.
11. Banerjee P, Chan K-C, Tarabocchia M, et al. Functional analysis of LDLR (low-density lipoprotein receptor) variants in patient lymphocytes to assess the effect of evinacumab in homozygous familial hypercholesterolemia patients with a spectrum of LDLR activity. Arterioscler Thromb Vasc Biol 2019;39:2248-60.
12. Gaudet D, Gipe DA, Pordy R, et al. ANGPTL3 inhibition in homozygous familial hypercholesterolemia. N Engl J Med 2017;377:296-7.
13. Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. Hum Mutat 1992;1:445-66.
14. Mehrotra DV, Li X, Liu J, Lu K. Analysis of longitudinal clinical trials with missing data using multiple imputation in conjunction with robust regression. Biometrics 2012;68:1250-9.
15. Ahmad Z, Banerjee P, Hamon S, et al. Inhibition of angiopoietin-like protein 3 with a monoclonal antibody reduces triglycerides in hypertriglyceridemia. Circulation 2019;140:470-86.
16. Reuben A. Hy's law. Hepatology 2004; 39:574-8.
17. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;139(25):e1082-e1143.
18. Gupta S. LDL cholesterol, statins and PCSK 9 inhibitors. Indian Heart J 2015;67: 419-24.
19. Thedrez A, Blom DJ, Ramin-Mangata S, et al. Homozygous familial hypercholesterolemia patients with identical mutations variably express the LDLR (low-density lipoprotein receptor): implications for the efficacy of evolocumab. Arterioscler Thromb Vasc Biol 2018;38:592-8.
20. Raal FJ, Honarpour N, Blom DJ, et al. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B): a randomised, double-blind, placebo-controlled trial. Lancet 2015;385:341-50.
21. Reeskamp LF, Kastelein JJP, Moriarty PM, et al. Safety and efficacy of mipomersen in patients with heterozygous familial hypercholesterolemia. Atherosclerosis 2019; 280:109-17.
22. Kastle Therapeutics. KYNAMRO (mipomersen sodium) injection: solution for subcutaneous injection (prescribing information). 2016 (http://www.kynamro.com/media/pdfs/Kynamro_Prescribing_information.pdf).
23. Steg PG, Szarek M, Bhatt DL, et al. Effect of alirocumab on mortality after acute coronary syndromes. Circulation 2019;140:103-12.
24. Schwartz GG, Steg PG, Szarek M, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018;379:2097-107.
25. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017;376:1713-22.