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ORIGINAL RESEARCH

CARDIOMETABOLIC

The Long-Term Efficacy and Safety of Evinacumab in Patients With Homozygous Familial Hypercholesterolemia

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ABSTRACT

BACKGROUND Homozygous familial hypercholesterolemia (HoFH) is characterized by early-onset atherosclerotic cardiovascular disease due to the high low-density lipoprotein cholesterol (LDL-C) burden. Patients with null-null low-density lipoprotein receptor (*LDLR*) variants respond poorly, if at all, to statins and proprotein convertase subtilisin/kexin type 9 inhibitors, which act by upregulating *LDLR* expression. The 24-week double-blind treatment period (DBTP) of the phase 3 ELIPSE HoFH (Evinacumab Lipid Studies in Patients with Homozygous Familial hypercholesterolemia; NCT03399786) study demonstrated significant LDL-C reductions in patients with HoFH; LDL-C reductions were also observed in those with null-null *LDLR* mutations.

OBJECTIVES The purpose of this study was to evaluate longer-term efficacy and safety of evinacumab in patients with HoFH from the ELIPSE HoFH study.

METHODS Patients with HoFH on stable lipid-lowering therapies (LLTs) ± lipoprotein apheresis and screening LDL-C ≥70 mg/dL who completed the DBTP entered the 24-week open-label treatment period (OLTP) and received intravenous evinacumab 15 mg/kg every 4 weeks. OLTP results were summarized descriptively.

RESULTS A total of 64 patients completed the DBTP and received open-label evinacumab. Despite multiple LLTs, the mean baseline LDL-C at DBTP entry was 250.5 ± 162.3 mg/dL. From baseline to week 48 (end of OLTP), evinacumab reduced mean LDL-C by 46.3% (mean reduction, 134.3 ± 117.3 mg/dL), with similar mean LDL-C reductions for patients with null-null (47.2%) and non-null variants (45.9%). Adverse events occurred in 47 (73.4%) patients; 4 (6.3%) patients experienced adverse events considered evinacumab-related (drug hypersensitivity, infusion-related reaction and asthenia, generalized pruritis, and muscle spasms).

CONCLUSIONS In patients with HoFH, evinacumab demonstrated substantial and sustained LDL-C reduction regardless of LDLR function, and was generally well tolerated. (JACC Adv 2023;2:100648) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ANGPTL3 = angiopoietin-like 3

ASCVD = atherosclerotic cardiovascular disease

DBTP = double-blind treatment period

HoFH = homozygous familial hypercholesterolemia

LDL-C = low-density lipoprotein cholesterol

LDLR = low-density lipoprotein receptor

LLT = lipid-lowering therapy

OLTP = open-label treatment period

PCSK9 = proprotein convertase subtilisin/kexin type 9

Homozygous familial hypercholesterolemia (HoFH) is a rare genetic disorder of cholesterol metabolism affecting approximately 1 in 250,000 people worldwide.[1-3] This disorder is characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) levels from birth, with the resultant LDL-C burden dramatically increasing the risk of early-onset atherosclerotic cardiovascular disease (ASCVD).[1] HoFH is predominately caused by low-density lipoprotein receptor (*LDLR*) loss-of-function variants, resulting in minimal or absent hepatic clearance of LDL-C from the circulation.[1,4] Genetic alterations that lead to minimal or absent *LDLR* expression (null homozygotes) tend to have higher LDL-C levels than alterations that partially reduce *LDLR* expression with 2 non-null alleles, or 1 null and 1 non-null allele (non-null homozygotes).[5]

Current approaches to reducing LDL-C include the use of multiple standard lipid-lowering therapies (LLTs) such as statins, ezetimibe, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, and lomitapide.[1,6-10] Statins and PCSK9 inhibitors act mainly by upregulating hepatic *LDLR* expression; however, these agents have limited to no efficacy in patients with severe HoFH, particularly those with 2 null *LDLR* alleles.[7,8,11-13] Lomitapide acts independently of LDLR function but is associated with dose-limiting safety issues, including high rates of gastrointestinal side effects and hepatic steatosis.[12,14,15] Patients with HoFH may also be treated with lipoprotein apheresis, an invasive time-consuming therapy that has ramifications for patient quality of life and is not widely accessible but is effective for LDL-C lowering in patients refractory to other interventions.[1,6] Despite these available therapies, guideline-recommended LDL-C treatment goals are rarely achieved in patients with HoFH.[6]

Angiopoietin-like 3 (ANGPTL3) is an important regulator of lipid metabolism, acting mainly by inhibiting lipoprotein lipase and endothelial lipase.[8,16,17] Animal models have shown that ANGPTL3 knock-out, or its pharmacologic inhibition, reduces LDL-C independently of the LDLR.[18-22] In humans, familial combined hypolipidemia due to homozygous loss-of-function polymorphisms in *ANGPTL3* is associated with low LDL-C and reduced ASCVD risk.[23] Mendelian randomization studies also show decreased LDL-C and ASCVD in association with loss-of-function polymorphisms in *ANGPTL3*.[20,21,24]

ANGPTL3 inhibition leads to enhanced lipoprotein clearance upstream of low-density lipoprotein (LDL) production,[25,26] with very low-density lipoprotein (VLDL) being cleared from the circulation by an endothelial lipase-dependent VLDL remodeling and remnant clearance pathway independent of the LDLR (**Figure 1**).[25]

Evinacumab is a recombinant human monoclonal antibody directed against ANGPTL3.[19] During the double-blind treatment period (DBTP) of the pivotal phase 3 ELIPSE HoFH study (NCT03399786), evinacumab significantly reduced LDL-C by approximately 50% when added to maximally tolerated LLTs, with or without lipoprotein apheresis.[10] In the United States, evinacumab is approved as an adjunct to other LDL-C-lowering therapies for the treatment of patients with HoFH aged 5 years and older.[27]

Here, we report results from the open-label treatment period (OLTP) of the ELIPSE HoFH study investigating the longer-term efficacy and safety of evinacumab in patients with HoFH. Moreover, alterations in lipoproteins as assessed by nuclear magnetic resonance (NMR) spectroscopy and results of post hoc subanalyses for both the DBTP and OLTP are presented.

METHODS

TRIAL OVERSIGHT. This phase 3 study (NCT03399786) was conducted at 30 sites in 11 countries, and in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study protocol was approved by the appropriate institutional review board or independent ethics

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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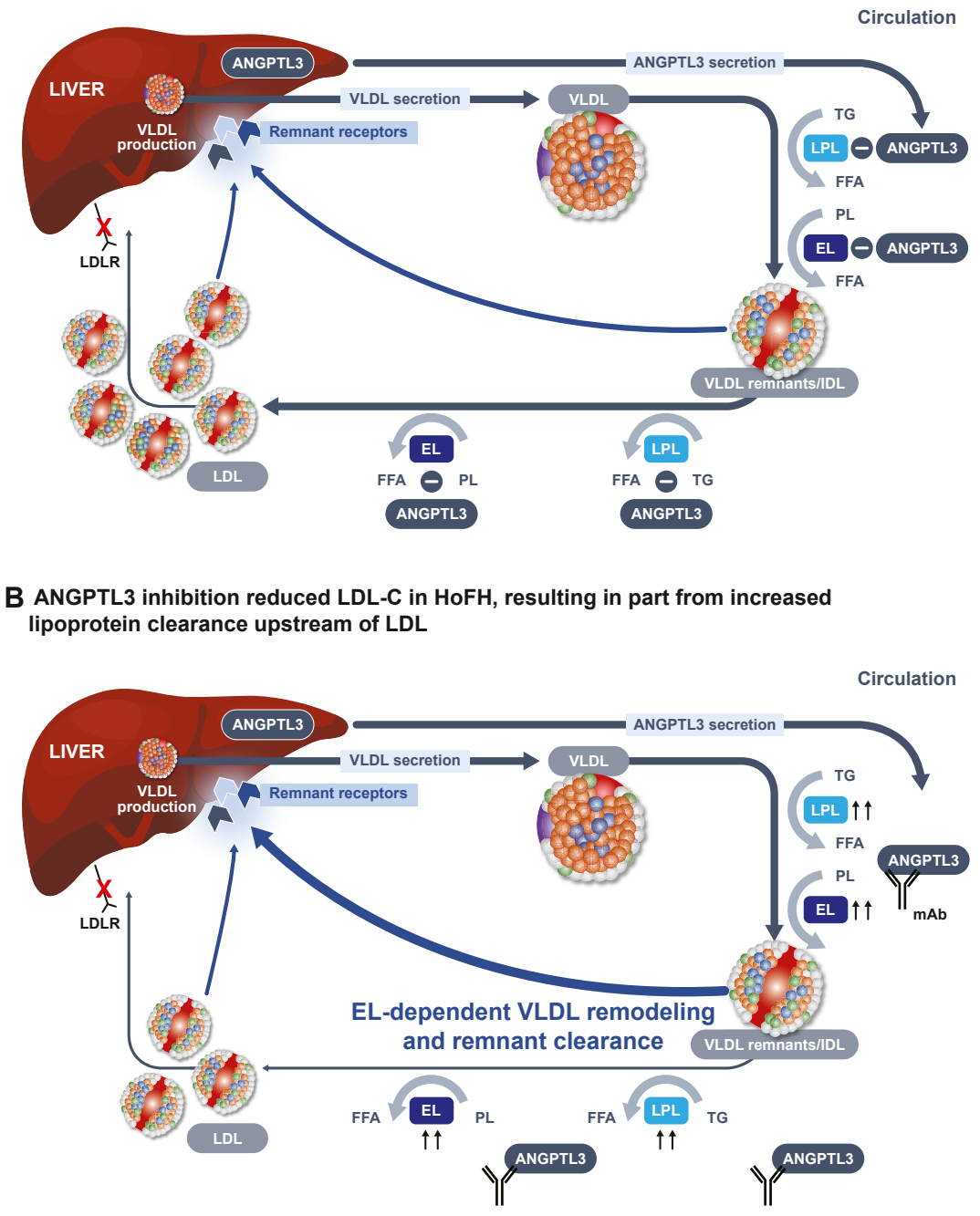
FIGURE 1 LDL Metabolism and Mechanism of ANGPTL3 Inhibition in Patients With HoFH



LDL metabolism in (A) patients with HoFH, and (B) mechanism of ANGPTL3 inhibition in patients with HoFH. ANGPTL3 regulates lipoprotein metabolism via inhibition of LPL and EL. LPL is a key enzyme responsible for the catabolism of TGs, converting VLDL into IDL, and further to LDL. In patients with HoFH, that have near or absent LDLR function, hepatic uptake of LDL is impaired resulting in elevated LDL-C. Inhibition of ANGPTL3 by evinacumab leads to extensive remodeling of VLDL, generating lipid-depleted remnant particles, which accelerates their removal from circulation via remnant receptors. This in turn leads to depletion of the LDL precursor pool, thus reducing LDL-C levels. Endothelial lipase is the key mediator of this LDLR-independent pathway. ANGPTL3 = angiopoietin-like 3; EL = endothelial lipase; FFA = free fatty acid; HoFH = homozygous familial hypercholesterolemia; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LDLR = low-density lipoprotein receptor; LPL = lipoprotein lipase; mAb = monoclonal antibody; PL = phospholipase; TG = triglyceride; VLDL = very low-density lipoprotein.

committee at each study site. All patients provided written informed consent before enrollment.

STUDY DESIGN. The full methodology has been published previously.[10] In brief, following a run-in period to stabilize background LLTs and lipoprotein apheresis and a 2-week screening period, patients with HoFH entered a 24-week randomized, placebo-controlled DBTP and then either a 24-week optional single arm OLTP or a 24-week follow-up after the last dose of study drug (for those patients who decided not to enter the optional OLTP). During the DBTP, all eligible patients were randomized 2:1 to receive intravenous (IV) evinacumab 15 mg/kg every 4 weeks or matching placebo. Randomization was stratified according to prior receipt or nonreceipt of lipoprotein apheresis and by geographic region (Japan vs the rest of the world). All patients who entered the OLTP received IV evinacumab 15 mg/kg every 4 weeks.

PATIENTS. Patients with HoFH who were ≥12 years of age were eligible for inclusion (Supplemental Appendix for a complete list of eligibility criteria). At screening, patients were required to have LDL-C ≥70 mg/dL (1.8 mmol/L), despite receiving stable, maximally tolerated LLTs (with or without lipoprotein apheresis, either weekly or biweekly). Patients were diagnosed with HoFH using genetic or clinical criteria. Genetic diagnosis was defined as the documented presence of pathogenic variants in 2 *LDLR* alleles (either null-null or non-null) or the documented presence of homozygous or compound heterozygous variants in apolipoprotein B (*APOB*) or *PCSK9*. Patients with double heterozygous variants in different genes (eg, *LDLR/PCSK9*) and patients with homozygous variants in LDLR adapter protein 1 (*LDLRAP1*) were also eligible. Clinical diagnosis was defined as an untreated total cholesterol of >500 mg/dL (12.9 mmol/L) with either the presence of cutaneous or tendinous xanthomas before the age of 10 years or documented untreated total cholesterol of >250 mg/dL (6.5 mmol/L) in both parents. A genetic variant in the *LDLR* or *LDLRAP1* gene was considered null-null if the resulting LDLR activity was <15% based on in vitro assessment of function.[28]

STUDY ENDPOINTS AND ASSESSMENTS. The primary end point was percentage change in calculated LDL-C with evinacumab vs placebo from baseline to week 24 during the DBTP. LDL-C was calculated using the Friedewald formula. The objective of the OLTP was to assess long-term efficacy of evinacumab on lipid and lipoprotein parameters, and to evaluate long-term safety of evinacumab. We report percentage changes from baseline to week 48 (the end of the OLTP) in calculated LDL-C, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, total cholesterol, triglycerides, ApoB, and lipoprotein(a) [Lp(a)]. Among patients undergoing lipoprotein apheresis, only preapheresis laboratory results were assessed. The safety and tolerability of open-label evinacumab 15 mg/kg were assessed by measuring the incidence of treatment-emergent adverse events (TEAEs). Only new TEAEs occurring during the OLTP or worsening TEAEs were captured. Adverse events that occurred during the DBTP and persisted in the OLTP were not recorded as TEAEs during the OLTP. Subgroup analyses were conducted for the DBTP and OLTP, including the effect of evinacumab on LDL-C goal attainment, change in LDL-C according to background LLTs, and the effect of evinacumab on eligibility for lipoprotein apheresis.

LIPOPROTEIN SUBCLASS CHARACTERIZATION. NMR spectroscopy, which provides estimates of particle concentrations and sizes of VLDL, LDL, and HDL subclasses,[29,30] as well as their lipid content,[31] was conducted to characterize lipoprotein subclasses. Lipoprotein subclasses were quantified from the amplitudes of their spectroscopically distinct lipid methyl group NMR signals.[29] The NMR platform used was from LipoScience, Inc (now available through LabCorp).

STATISTICAL ANALYSIS. The efficacy of evinacumab was assessed through laboratory evaluation of lipid/lipoprotein parameters. Efficacy and safety analyses were conducted once all open-label data through week 48 had been collected and validated; the baseline lipid parameter for the OLTP was baseline (day 1) of the DBTP. Efficacy and safety were assessed in all patients who received at least 1 dose of open-label evinacumab and comprised all double-blind evinacumab patients (n = 44) and double-blind placebo patients (n = 20; those who previously received placebo in the DBTP and who then received evinacumab in the OLTP). The open-label period for evaluation of TEAEs was defined as the interval between administration of the first dose of open-label evinacumab to administration of the last dose of open-label evinacumab plus 24 weeks. OLTP safety and efficacy results were summarized descriptively.

RESULTS

PATIENTS. A total of 64 patients completed the DBTP and entered the OLTP to receive evinacumab 15 mg/kg every 4 weeks, 62 of whom (96.9%)

TABLE 1 Demographic and Baseline Characteristics of Patients Who Entered the OLTP[a]

	DB Evinacumab 15 mg/kg IV Q4W (n = 44)	DB Placebo IV Q4W (n = 20)	Total (N = 64)
Age, y	44.5 ± 16.7	35.6 ± 11.3	41.7 ± 15.7
Female	24 (54.5)	10 (50.0)	34 (53.1)
Race			
White	32 (72.7)	15 (75.0)	47 (73.4)
Black or African American	2 (4.5)	0	2 (3.1)
Asian	6 (13.6)	4 (20.0)	10 (15.6)
Other	4 (9.1)	1 (5.0)	5 (7.8)
BMI, kg/m^2	26.1 ± 5.8	24.9 ± 5.9	25.7 ± 5.8
History of CHD	22 (50.0)	11 (55.0)	33 (51.6)
Method of HoFH diagnosis			
Genotyping	29 (65.9)	15 (75.0)	44 (68.8)
Clinical diagnosis	15 (34.1)	5 (25.0)	20 (31.3)
Activity of LDLR variant			
<15%[b]	15 (34.1)	6 (30.0)	21 (32.8)
Concomitant LLT			
Statin	42 (95.5)	18 (90.0)	60 (93.8)
Ezetimibe	33 (75.0)	16 (80.0)	49 (76.6)
PCSK9 inhibitor	35 (79.6)	14 (70.0)	49 (76.6)
Lomitapide	11 (25.0)	3 (15.0)	14 (21.9)
Apheresis	14 (31.8)	8 (40.0)	22 (34.4)
Calculated LDL-C, mg/dL	257.1 ± 171.1	236.1 ± 144.3	250.5 ± 162.3
LDL particle number, nmol/L	2059.5 (1400.5, 2521.8)	1883.5 (1138.8, 2969.5)	2059.5 (1261.6, 2575.2)
Small VLDL particle number, nmol/L	30.7 (17.8, 50.9)	27.9 (14.8, 67.7)	29.2 (16.5, 53.9)
Medium VLDL particle number, nmol/L	6.2 (1.8, 15.6)	3.8 (0.2, 11.8)	5.3 (0.7, 14.7)
Apolipoprotein B, mg/dL	168.3 ± 82.0	164.2 ± 80.2	167.0 ± 80.8
HDL-C, mg/dL	43.9 ± 14.8	46.0 ± 16.7	44.5 ± 15.3
Non-HDL-C, mg/dL	279.6 ± 171.3	259.3 ± 148.9	273.3 ± 163.7
Total cholesterol, mg/dL	323.5 ± 169.3	305.3 ± 141.4	317.8 ± 160.2
Triglycerides, mg/dL	91.0 (66.0, 140.5)	101.0 (57.5, 187.5)	94.0 (65.0, 163.0)
Lipoprotein(a), nmol/L	65.5 (22.5, 174.5)	47.0 (32.0, 125.0)	56.5 (28.5, 166.5)

Values are mean ± SD, n (%), or median (Q1, Q3). [a]Baseline data for the OLTP are from entry to the DBTP study. All results in patients undergoing apheresis are preapheresis. [b]Patients with null-null variants have LDLR activity of <15%.

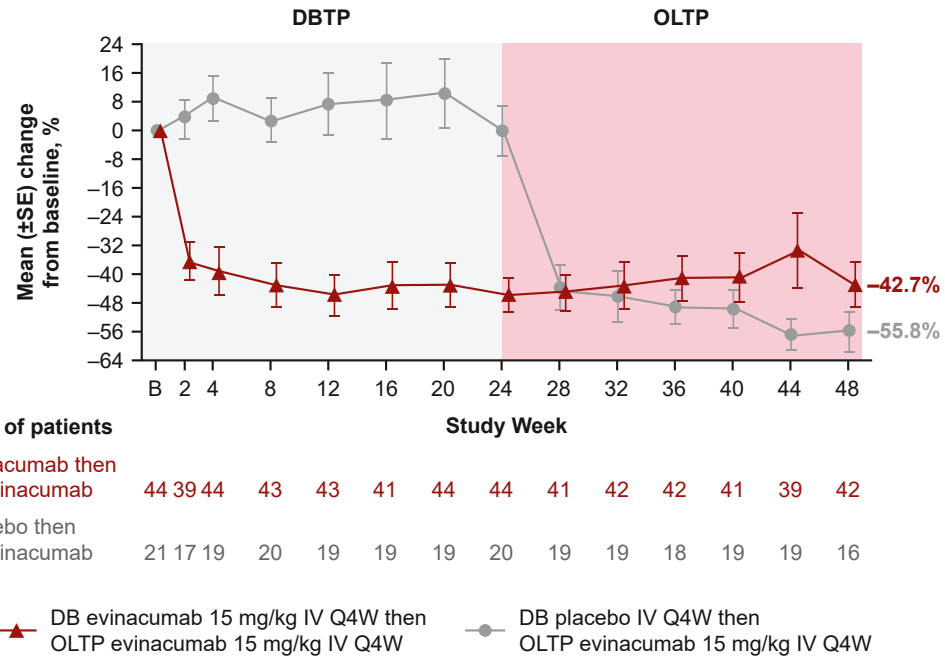
ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; CHD = coronary heart disease; DB = double-blind; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesterolemia; IV = intravenous; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; OLTP = open-label treatment period; PCSK9 = proprotein convertase subtilisin/kexin type 9; Q4W = every 4 weeks; VLDL = very-low density lipoprotein.

completed the 24-week OLTP. One patient from the double-blind evinacumab group discontinued due to pregnancy after 1 dose of evinacumab in the OLTP, and 1 patient from the double-blind placebo group discontinued due to protocol noncompliance (Supplemental Figure 1). During the OLTP, 10 patients (15.6%) were treated at sites in Japan, 22 patients (34.4%) at sites in the EU (Austria [n = 2], France [n = 5], Greece [n = 4], Italy [n = 7], and the Netherlands [n = 4]), and 32 patients (50.0%) were treated in non-EU countries (Australia [n = 4], Canada [n = 3], the USA [n = 10], South Africa [n = 8], and Ukraine [n = 7]). The mean number of infusions during the OLTP was 5.8 ± 0.8, with a mean duration of study drug exposure of 23.5 ± 3.3 weeks.

Baseline characteristics are summarized in Table 1. Overall, the mean baseline LDL-C level was 250.5 ± 162.3 mg/dL (6.7 ± 4.4 mmol/L). In-study genotyping confirmed that 21 patients (32.8%) had null-null variants in either *LDLR* (n = 20, 31.3%) or *LDLRAP1* (n = 1, 1.6%); 43 (67.2%) patients had non-null variants in either *LDLR* (n = 41, 64.1%) or *LDLRAP1* (n = 2, 3.1%). Three patients (4.7%) had mutations in both *LDLR* and *APOB*. During the OLTP, 22 patients (34.4%) received lipoprotein apheresis, and almost all patients (n = 63/64; 98.4%) were receiving at least one concomitant LLT (Table 1).

EFFICACY DURING THE OLTP. At week 48 (the end of the OLTP), LDL-C data were available for 58 of the 62 patients who completed the OLTP (double-blind

FIGURE 2 Mean Percent Change in Calculated LDL-C From Baseline Over Time



B = baseline; DB = double-blind; DBTP = double-blind treatment period; IV = intravenous; LDL-C = low-density lipoprotein cholesterol; OLTP = open-label treatment period; Q4W = every 4 weeks; SE = standard error.

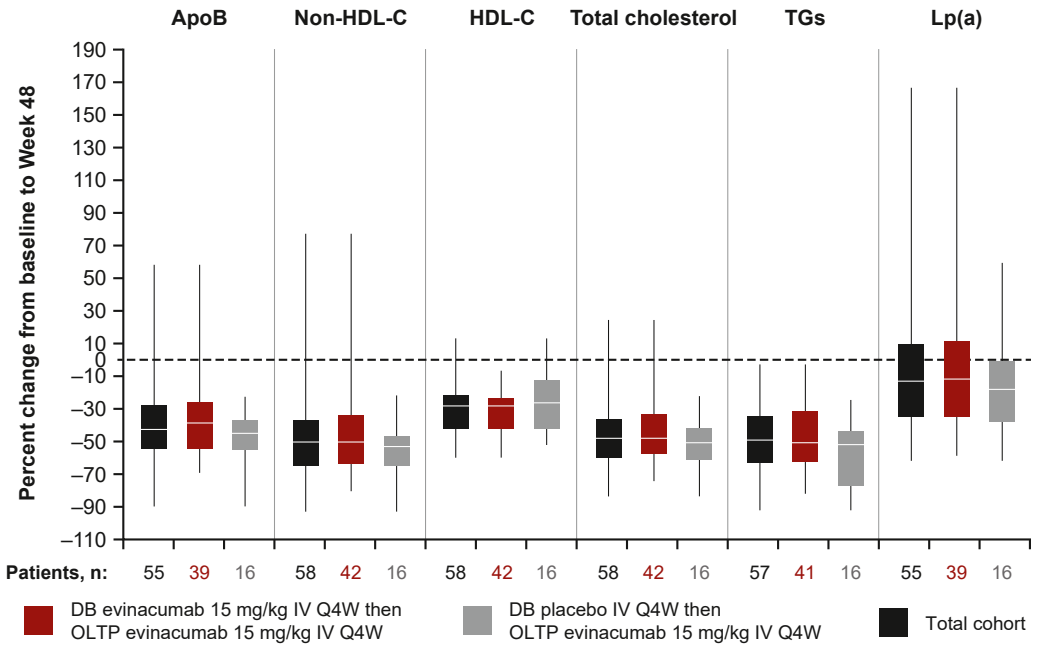
evinacumab group [n = 42]; double-blind placebo group [n = 16]; completion of the OLTP did not require a week 48 LDL-C value). Mean (median; Q1, Q3) LDL-C reduction from baseline (week 0) to week 48 with open-label evinacumab was 46.3% (53.6%, 64.8%, 34.3%) for all patients (n = 58), with mean (median; Q1, Q3) reductions of 42.7% (52.5%; 63.6%, 33.5%) and 55.8% (55.1%; 65.4%, 41.1%) for the double-blind evinacumab (n = 42) and placebo (n = 16) groups, respectively (Figure 2). Corresponding mean absolute LDL-C reductions from baseline were 134.3 ± 117.3, 130.3 ± 124.2, and 145.0 ± 99.8 mg/dL for the overall, double-blind evinacumab, and double-blind placebo groups, respectively. At week 48, LDL-C data were available for 19 patients with null-null variants and 39 patients with non-null variants. Mean percent reduction in LDL-C at week 48 from baseline with open-label evinacumab was similar for patients with null-null (47.2%) vs non-null (45.9%) variants (median [Q1, Q3] percent reduction of 52.6% [63.1%, 27.0%] and 54.4% [65.9%, 38.6%], respectively). Individual percentage change in LDL-C from baseline to week 48 per genotype status is shown in Supplemental Figure 2. In the overall population, reductions at week 48 from baseline with open-label evinacumab were observed for HDL-C (mean, 30.4%; median, 30.8%), non-HDL-C (mean, 48.9%; median, 52.8%), total cholesterol (mean, 47.0%; median, 50.0%), ApoB (mean, 40.8%; median, 44.7%), triglycerides (median, 51.9%), and Lp(a) (median, 16.3%) (Figure 3).

At week 48, LDL-C data were available for 10 patients from Japan and 48 patients from the rest of the world. Mean absolute reductions in LDL-C of 97.9 ± 63.7 mg/dL and 141.9 ± 124.8 mg/dL were observed from baseline to week 48 for patients from Japan and the rest of the world, respectively, corresponding to mean (median) percent reductions of 41.4% (47.2%) and 47.3% (55.4%).

For patients either receiving apheresis (n = 20) or not receiving apheresis (n = 38), mean reductions in LDL-C of 112.1 ± 76.6 mg/dL and 146.1 ± 133.4 mg/dL were observed from baseline to week 48, respectively, corresponding to mean (median) percent reductions of 43.8% (47.2%) and 47.6% (57.0%).

CHARACTERIZATION OF LIPOPROTEINS BY NMR DURING THE DBTP. At week 24, absolute median change in total LDL particle concentration (LDL-P) from baseline was −1,008.0 nmol/L (Q1, Q3: -1,350.0,

FIGURE 3 Percent Change in Lipid Parameters From Baseline to Week 48



Box indicates interquartile range; horizontal line indicates median; vertical line indicates minimum and maximum values.
ApoB = apolipoprotein B; DB = double-blind; HDL-C = high-density lipoprotein cholesterol; IV = intravenous; Lp(a) = lipoprotein(a); OLTP = open-label treatment period; Q4W = every 4 weeks; TG = triglyceride.

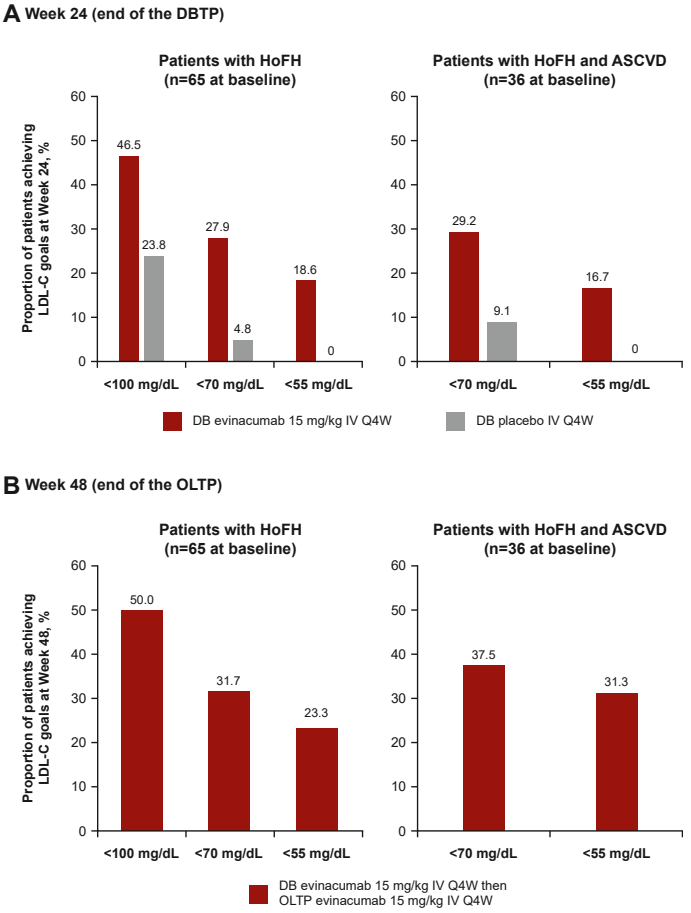
-383.2) with evinacumab vs −75.0 nmol/L (Q1, Q3: -480.0, 164.5) with placebo; the median percent change in total LDL-P was −49.6% (Q1, Q3: -64.9, -26.1) with evinacumab vs −5.1% (Q1, Q3: -19.5, 11.6) with placebo (nominal $P < 0.0001$) (Supplemental Figure 3A). At week 24, absolute median change in total HDL particle concentration (HDL-P) from baseline was −5.2 μmol/L (Q1, Q3: -9.5, -2.6) with evinacumab vs +1.0 μmol/L (Q1, Q3: -1.8, 4.3) with placebo; the median percent change in total HDL-P at week 24 with evinacumab was −25.0% (Q1, Q3: -38.0, -11.5) vs +4.4% (Q1, Q3: -5.1, 22.4) with placebo (nominal $P < 0.0001$) (Supplemental Figure 3B).

A reduction in small and medium VLDL particle concentration (VLDL-P) was observed with evinacumab from baseline through to week 24. Absolute median change in small VLDL-P was −13.8 nmol/L (Q1, Q3: -36.9, 1.9) with evinacumab vs −0.9 nmol/L (Q1, Q3: -10.5, 9.9) with placebo; the median percent change in small VLDL-P was −41.0% (Q1, Q3: −73.8, 11.0) with evinacumab vs −1.9% (Q1, Q3: −33.7, 36.8) with placebo (nominal $P = 0.0028$) (Supplemental Figure 3C). Absolute median change in medium VLDL-P was −4.0 nmol/L (Q1, Q3: -14.9, -0.3) with evinacumab vs 0.0 nmol/L (Q1, Q3: -3.4, 5.7) with placebo; the median percent change in medium VLDL-P was −87.1% (Q1, Q3: −96.2, -34.8) with evinacumab vs −25.0% (Q1, Q3: −52.3, 220.2) with placebo (nominal $P = 0.0005$) (Supplemental Figure 3D).

ACHIEVEMENT OF LDL-C GOALS DURING THE DBTP AND OLTP. At week 24 (the end of the DBTP), the proportion of patients achieving LDL-C <100 mg/dL was 46.5% with evinacumab vs 23.8% with placebo; the proportion of patients achieving LDL-C <70 mg/dL was 27.9% with evinacumab vs 4.8% with placebo (**Figure 4**). At week 48 (the end of the OLTP), the proportions of patients achieving LDL-C goals of <100 mg/dL and <70 mg/dL were 50.0% and 31.7% with open-label evinacumab, respectively (**Figure 4**).

Overall, 53.8% of patients had ASCVD at baseline of the DBTP. At week 24, the proportion of patients with

FIGURE 4 Proportion of Patients With HoFH Achieving LDL-C Goals



Proportion of patients with HoFH achieving LDL-C goals at (A) week 24 (the end of the DBTP) and (B) week 48 (the end of the OLTP). ASCVD = atherosclerotic cardiovascular disease; DB = double-blind; HoFH = homozygous familial hypercholesterolemia; IV = intravenous; LDL-C = low-density lipoprotein cholesterol; OLTP = open-label treatment period; Q4W = every 4 weeks.

ASCVD achieving LDL-C <70 mg/dL was 29.2% with evinacumab vs 9.1% with placebo; the proportion of patients achieving LDL-C <55 mg/dL was 16.7% with evinacumab vs 0% with placebo. At week 48, the proportions of patients with ASCVD achieving LDL-C <70 mg/dL and <55 mg/dL were 37.5% and 31.3% with open-label evinacumab, respectively (Figure 4).

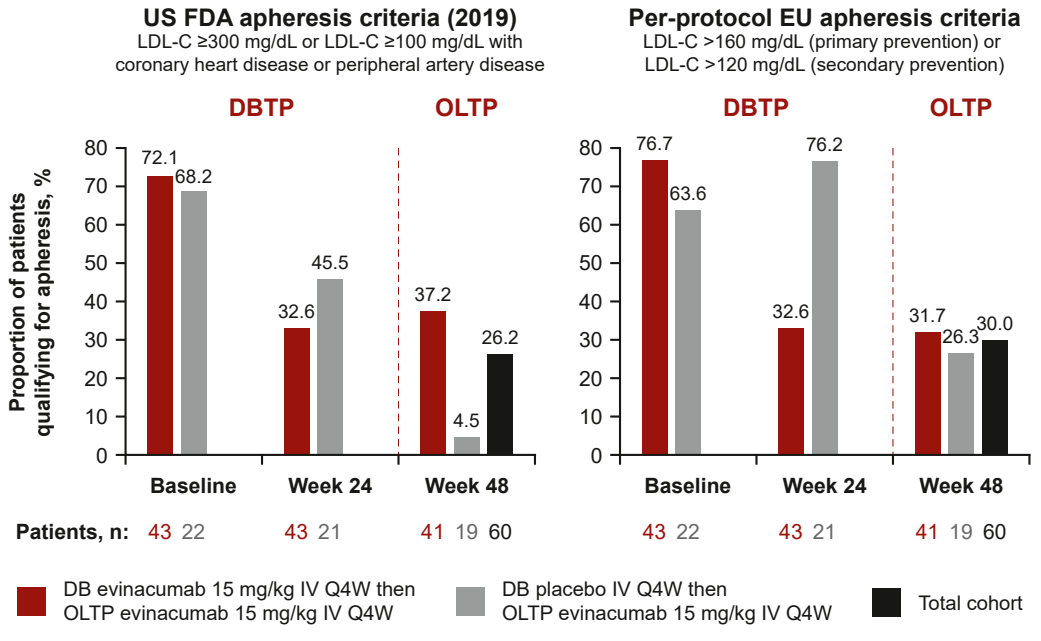
EFFICACY ACCORDING TO BACKGROUND LLT SUBGROUP DURING THE DBTP AND OLTP. Greater mean reductions in LDL-C from baseline to week 24 were observed in all LLT subgroups with evinacumab vs placebo: high-intensity statins, −48.6% vs +2.7%; moderate/low-intensity statins, −41.0% vs +0.1%; lomitapide, −49.6% vs −17.2%; triple therapy (ezetimibe plus PCSK9 inhibitor plus statin), −56.0% vs −4.0%; quadruple therapy (triple therapy plus lomitapide), −66.8% vs −17.2%; and lipoprotein apheresis, −46.2% vs −7.3% (Supplemental Figure 4). At week 48, mean reductions in LDL-C with open-label evinacumab were 46.7% (high-intensity statins), 43.2% (moderate/low-intensity statins), 55.5% (lomitapide), 58.3% (triple therapy), 69.9% (quadruple therapy), and 43.8% (lipoprotein apheresis) (Supplemental Figure 5).

EFFECT ON APHERESIS ELIGIBILITY DURING THE DBTP AND OLTP. Per protocol, patients receiving lipoprotein apheresis at study entry were instructed to remain on this treatment for the duration of the DBTP and OLTP. Patients who were not receiving lipoprotein apheresis at study entry were not allowed to initiate lipoprotein apheresis without breaking study protocol. The proportion of patients who met LDL-C and clinical criteria for lipoprotein apheresis at baseline, week 24, and week 48 was dependent on the application of 2019 U.S. Food and Drug Administration threshold criteria (LDL-C ≥300 mg/dL without or LDL-C ≥100 mg/dL with coronary heart disease or peripheral artery disease)[32] or per-protocol EU threshold criteria (LDL-C >160 mg/dL [primary prevention] or LDL-C >120 mg/dL [secondary prevention]). More than 70% of the total cohort met US and EU criteria for apheresis at baseline. The proportions of patients at week 24 qualifying for apheresis in the evinacumab vs placebo groups were 32.6% vs 45.5% (per 2019 Food and Drug Administration criteria) and 32.6% vs 76.2% (per protocol EU criteria) (Figure 5). The proportion of patients qualifying for lipoprotein apheresis at week 48 of open-label evinacumab was comparable to week 24 (Figure 5).

SAFETY DURING THE OLTP. Overall, TEAEs occurred in 47 patients (73.4%) during the OLTP (Table 2). Four patients (6.3%) experienced at least 1 TEAE classified as related to the study treatment (n = 1, nonserious event of drug hypersensitivity of moderate severity; n = 1, 2 nonserious events of infusion related reaction [pruritus on abdomen and rash of abdomen]; 3 separate nonserious events of asthenia; n = 1, 2 nonserious events of generalized pruritus; and n = 1, mild TEAE of muscle spasms). The most common TEAEs, regardless of attribution were nasopharyngitis (9.4%) and headache (9.4%).

Serious adverse events (SAEs) occurred in 7 patients (10.9%) including angina pectoris (n = 1), carotid artery restenosis (n = 1), congestive cardiac failure (n = 1), unstable angina (n = 1), coronary artery disease (n = 1), pyelonephritis and nephrocalcinosis

FIGURE 5 Proportion of Patients Who Met Criteria for Lipoprotein Apheresis at Baseline, Week 24, and Week 48 According to US FDA (2019) and Per-Protocol EU Apheresis Criteria



DB = double-blind; DBTP = double-blind treatment period; FDA = Food and Drug Administration; IV = intravenous; LDL-C = low-density lipoprotein cholesterol; OLTP = open-label treatment period; Q4W = every 4 weeks.

(both in a single patient), cardiac procedure complication, aortic stenosis, and acute myocardial infarction (all in a single patient). No SAEs were considered related to the study treatment. Only 1 patient, who had a pregnancy, discontinued study treatment. While not considered a TEAE, information was collected as an adverse event and reported in the summary. No deaths occurred during the OLTP.

Supplemental Table 2 summarizes the change from baseline to week 24 (the end of the DBTP) and week 48 (the end of the OLTP) in liver function parameters for patients according to baseline use of lomitapide, a drug known to provoke hepatic steatosis. No clinically relevant change in alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, or bilirubin was observed with evinacumab treatment, irrespective of lomitapide use.

DISCUSSION

Although several LLTs are available for reducing LDL-C, many patients with HoFH respond poorly, and guideline-recommended LDL-C goals are seldom achieved.[8,9,33] The results of this open-label extension study show that evinacumab 15 mg/kg every 4 weeks reduced mean calculated LDL-C by 46.3% in patients with HoFH, with reductions maintained throughout the 48-week OLTP (**Central Illustration**), supporting results from the previously published 24-week DBTP.[10] The observed reductions in LDL-C from baseline to week 48 were achieved with evinacumab across an extensive range of standard-of-care background LLTs, with the greatest LDL-C reduction observed in the subgroup of patients on background quadruple therapy (ezetimibe plus PCSK9 inhibitor plus statin plus lomitapide). Marked reductions in LDL-C from baseline to week 48 were observed in patients with both null-null and non-null *LDLR* mutations in the context of aggressive multimodality baseline LLTs. This finding is of clinical significance, as null-null patients respond poorly, if at all, to therapies requiring LDLR activity and therefore remain at very high risk for cardiovascular events.[34] The present study suggests that the LDL-C reductions achieved with evinacumab are highly relevant for patients with HoFH who need additional lipid lowering beyond their existing treatment, the vast majority of whom have exhausted all other available LDL-C-lowering treatment options.

TABLE 2 Safety Overview: TEAEs During the OLTP

	DB Evinacumab Then OLTP Evinacumab 15 mg/kg/IV Q4W (n = 44)	DB Placebo Then OLTP Evinacumab IV Q4W (n = 20)	Total Cohort (N = 64)
Any TEAE	35 (79.5)	12 (60.0)	47 (73.4)
Treatment-emergent SAEs	7 (15.9)	0	7 (10.9)
TEAEs leading to treatment discontinuation	1 (2.3)	0	1 (1.6)
TEAEs leading to death	0	0	0
TEAEs occurring in ≥2 patients of the total cohort			
Headache	5 (11.4)	1 (5.0)	6 (9.4)
Nasopharyngitis	5 (11.4)	1 (5.0)	6 (9.4)
Back pain	3 (6.8)	0	3 (4.7)
Nausea	3 (6.8)	0	3 (4.7)
Asthenia	2 (4.5)	0	2 (3.1)
Influenza-like illness	2 (4.5)	0	2 (3.1)
Muscle spasms	2 (4.5)	0	2 (3.1)
Toothache	1 (2.3)	1 (5.0)	2 (3.1)
Upper respiratory tract infection	2 (4.5)	0	2 (3.1)

Values are n (%).

DB = double-blind; IV = intravenous; OLTP = open-label treatment period; Q4W = every 4 weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

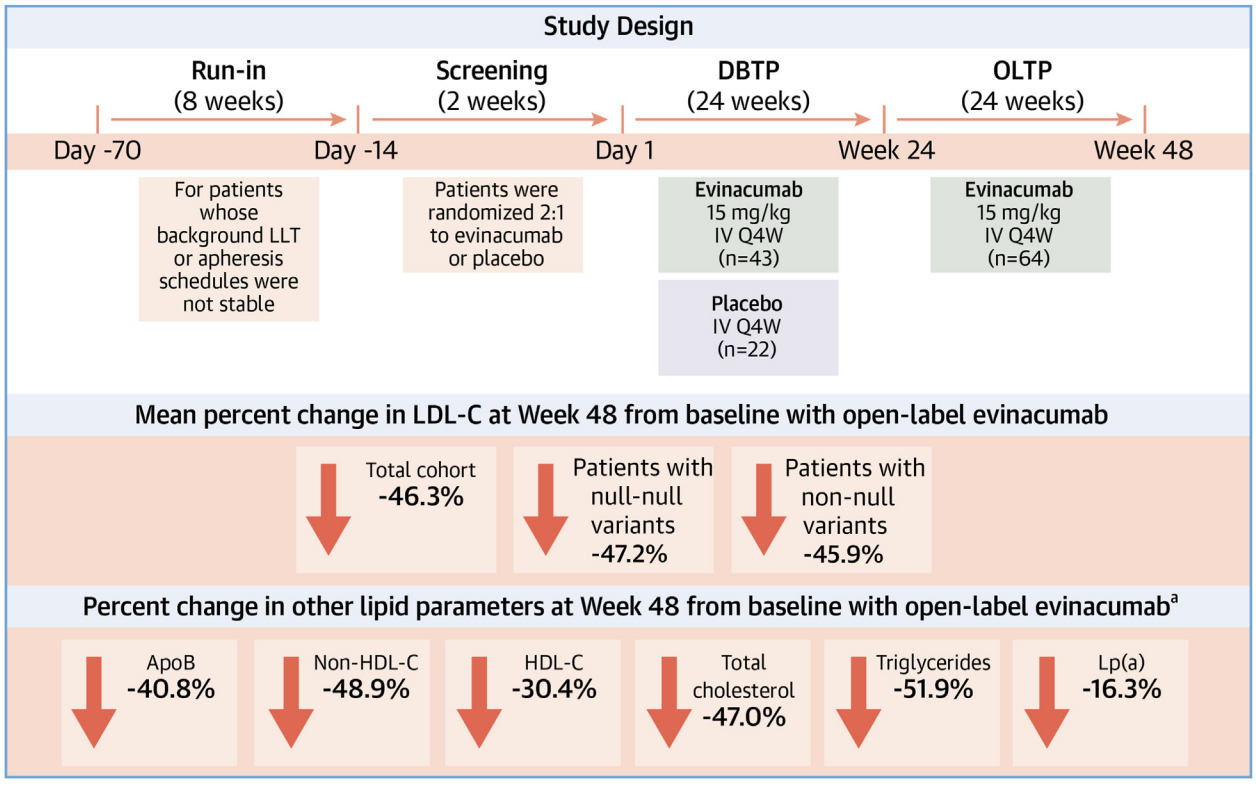
Lipoprotein apheresis is widely used as part of the treatment strategy for patients with HoFH. Although LDL-C levels are reduced rapidly, the major drawback of apheresis is that it must be performed frequently (weekly or biweekly), as LDL-C levels tend to rebound to near-baseline levels within 2 weeks of previous apheresis.[35,36] There are also many barriers to the use of lipoprotein apheresis, including lack of access in many parts of the world and the time-consuming, invasive nature of the procedure that greatly impacts patients' quality of life.[37,38] Although more than 70% of patients met US and EU criteria for apheresis at baseline, only 34.4% were undergoing treatment with apheresis, which reflects barriers to access. In this study, evinacumab reduced the proportion of patients who met criteria for lipoprotein apheresis by more than 50% in the total cohort at 24 and 48 weeks. Although, per protocol, no patients were allowed to discontinue apheresis treatment, this subanalysis indicates that evinacumab lowers LDL-C sufficiently to allow some patients with HoFH to reduce the frequency of, or requirement for, lipoprotein apheresis. Further studies are needed to assess these possibilities.

At baseline, patients with HoFH were receiving aggressive standard-of-care LLTs, with 93.8% on statins, 76.6% on ezetimibe, 76.6% on PCSK9 inhibitors, and 21.9% on lomitapide. In addition, 34.4% of patients were undergoing lipoprotein apheresis. Prior to the addition of evinacumab to aggressive standard-of-care LLTs, few patients with HoFH were achieving LDL-C treatment goals. During the DBTP, evinacumab enabled a higher proportion of patients with HoFH to achieve guideline-recommended LDL-C treatment goals compared with placebo. Although the present study does not evaluate the effect of evinacumab on ASCVD outcomes, increased attainment of LDL-C goals in response to LLTs has been associated with decreased occurrence of ASCVD events.[39]

The risk of ASCVD is not only associated with the plasma LDL-C level but also total LDL-P.[40] LDL-C estimates the amount of cholesterol contained within the LDL particle; however, there can be a discordance between plasma LDL-C and LDL-P, although this occurs predominantly in patients with hypertriglyceridemia, insulin resistance, or type 2 diabetes mellitus who have concomitant elevations in large VLDL as well as remnants.[41] Some studies suggest that the risk of ASCVD is best predicted via measurement of LDL-P,[40,42,43] but this has not been adopted by most lipid treatment guidelines. In our study, results from the NMR analysis demonstrate that evinacumab also substantially reduced total LDL-P by 49.6% at week 24, concordant with changes in LDL-C. In addition to reducing LDL-P, evinacumab reduced small VLDL-P by 41.0% and medium VLDL-P by 87.1% at week 24. These findings align with an NMR-based metabolomics study in which homozygous *ANGPTL3* loss-of-function variant carriers had markedly lower postprandial concentrations of cholesterol in VLDL-P and LDL-P after an oral fat challenge vs *ANGPTL3* loss-of-function heterozygotes and noncarriers.[44]

The additional 24-week safety data from the OLTP demonstrated that the safety profile of evinacumab remained consistent with that observed during the DBTP, with no significant safety signals.[10] As only one patient, who had a pregnancy, discontinued evinacumab across both the DBTP and OLTP, and considering the absence of treatment-related SAEs, most patients could be treated with evinacumab for 48 weeks, which is of particular importance for a drug intended for life-long treatment. Furthermore, no clinically relevant changes in alanine aminotransferase or aspartate aminotransferase were observed with evinacumab treatment after 24 or 48 weeks. This is of particular significance given the recent discontinuation of the vupanorsen program (antisense oligonucleotide targeting intrahepatic *ANGPTL3* as opposed to inhibition of circulating *ANGPT3* in plasma by evinacumab), due in part to marked

CENTRAL ILLUSTRATION **ELIPSE HoFH Study: Efficacy and Safety of Evinacumab in Patients With Homozygous Familial Hypercholesterolemia**



Raal FJ, et al. JACC Adv. 2023;2(9):100648.

[a]Mean percent change reported for ApoB, non-HDL-C, HDL-C, and total cholesterol. Median percent change reported for triglycerides and Lp(a). ApoB = apolipoprotein B; B = baseline; DB = double-blind; DBTP = double-blind treatment period; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesteremia; IV = intravenous; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); LLT = lipid-lowering therapy; OLTP = open-label treatment period; Q4W = every 4 weeks.

elevations in aminotransferases as well as hepatic steatosis in up to 44% of patients receiving higher dosages of vupanorsen, particularly in patients with obesity and elevated triglycerides.[45]

STUDY LIMITATIONS. Limitations of this open-label extension trial included the relatively short duration of treatment and the modest number of patients.

CONCLUSIONS

The results of this study have demonstrated sustained safety and marked LDL-C and LDL-P lowering and LDL-C goal achievement by evinacumab in this high-risk cohort of patients with HoFH, regardless of LDLR function.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with HoFH are difficult to treat, with standard-of-care LLTs providing limited LDL-C-lowering efficacy, especially in patients with absent or severely impaired LDLR activity. In this open-label extension of the phase 3 ELIPSE HoFH study, evinacumab, an ANGPTL3 inhibitor, demonstrated sustained LDL-C reduction in patients with HoFH regardless of LDLR function and irrespective of background LLTs.

TRANSLATIONAL OUTLOOK: Although randomized clinical trials are the gold standard for determining the efficacy and safety of a treatment, the strict application of inclusion and exclusion criteria and monitoring of participants means that trial populations and observed treatment effects are often not representative of patient populations in a real-world clinical setting. Thus, real-world evidence studies are needed to determine whether the observed LDL-C-lowering effect with evinacumab in the clinical trial setting is replicated in real-world patients with HoFH and whether long-term therapy with evinacumab in HoFH patients will reduce cardiovascular events and prolong their lives.

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KEY WORDS angiopoietin-like protein 3, clinical trial, evinacumab, homozygous familial hypercholesterolemia, lipids, lipoprotein

APPENDIX For inclusion and exclusion criteria as well as supplemental tables and figures, please see the online version of this paper.