

ORIGINAL INVESTIGATIONS

Long-Term Evolocumab in Patients With Familial Hypercholesterolemia



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ABSTRACT

BACKGROUND Proprotein convertase subtilisin/kexin type 9 inhibitor therapy is a treatment option for patients with familial hypercholesterolemia (FH) who are unable to reach low-density lipoprotein cholesterol (LDL-C) goals.

OBJECTIVES The aim of this study was to provide long-term safety and efficacy data for evolocumab in patients with homozygous FH (HoFH) and severe heterozygous FH (HeFH).

METHODS In this open-label, single-arm study, patients with HoFH or severe HeFH ≥ 12 years of age and on stable lipid-lowering therapy began subcutaneous evolocumab 420 mg monthly or 420 mg every 2 weeks if on lipoprotein apheresis. After 12 weeks, those not on apheresis could be up-titrated to 420 mg every 2 weeks. The primary endpoint was the incidence of treatment-emergent adverse events; secondary endpoints were changes in LDL-C and other lipids.

RESULTS In total, 300 patients (106 with HoFH, including 14 < 18 years of age at enrollment) received evolocumab for a median of 4.1 years. Adverse events occurred in 89.3% of patients, the most common of which were nasopharyngitis, influenza, upper respiratory tract infection, and headache. Mean change in LDL-C from baseline to week 12 was -21.2% (-59.8 mg/dl) in patients with HoFH and -54.9% (-104.4 mg/dl) in those with severe HeFH and was sustained over time. Of 48 patients with HoFH who were up-titrated, mean change in LDL-C improved from -19.6% at week 12 to -29.7% after 12 weeks of 420 mg every 2 weeks. The adjudicated cardiovascular event rate was 2.7% per year. Of 61 patients receiving apheresis at enrollment, 16 discontinued apheresis.

CONCLUSIONS Evolocumab was well tolerated and effectively reduced plasma LDL-C levels in patients with HoFH and severe HeFH over a median of 4.1 years. (J Am Coll Cardiol 2020;75:565-74) © 2020 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**ApoB** = apolipoprotein B**CV** = cardiovascular**FH** = familial
hypercholesterolemia**HeFH** = heterozygous familial
hypercholesterolemia**HoFH** = homozygous familial
hypercholesterolemia**LDL-C** = low-density
lipoprotein cholesterol**LDLR** = low-density lipoprotein
receptor**MI** = myocardial infarction**PCSK9** = proprotein
convertase subtilisin/kexin
type 9**Q2W** = every 2 weeks**QM** = once monthly

Familial hypercholesterolemia (FH) is a monogenic disorder of lipoprotein metabolism that is characterized by high plasma levels of low-density lipoprotein cholesterol (LDL-C), tendon xanthomas, and an increased risk for premature cardiovascular (CV) disease. Genetic causes of FH include loss-of-function mutations in the low-density lipoprotein receptor (*LDLR*), occurring in >90% of cases; loss of function in the apolipoprotein B gene; gain-of-function in proprotein convertase subtilisin/kexin type 9 (*PCSK9*); and, rarely, loss of function in both alleles of the *LDLR* adaptor protein gene, which leads to autosomal recessive hypercholesterolemia (1-3).

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Classically, FH was defined by clinical criteria into 2 phenotypes: homozygous FH (HoFH), with an estimated prevalence of 1 in 1,000,000 and heterozygous FH (HeFH), with an approximate prevalence of 1 in 500 (4,5). In the past decade, with the advent of genetic analysis combined with cascade screening, the worldwide prevalence of both HoFH and HeFH has been shown to be significantly higher, ranging from 1 in 160,000 to 300,000 for HoFH and 1 in 125 to 250 for HeFH. Broader application of genetic testing has revealed a greater phenotypic spectrum of FH, with lower LDL-C levels and lack of physical characteristics in some patients (4-6).

Most patients with FH do not reach recommended LDL-C goals, despite the combined use of maximal doses of the most efficacious statins and a cholesterol absorption inhibitor (ezetimibe) (6-10). A contemporary registry of patients with HeFH showed that <5% of patients attain LDL-C <70 mg/dl (1.8 mmol/l), despite the majority receiving maximally tolerated statins plus ezetimibe (11). In HoFH, far fewer patients achieve LDL-C <100 mg/dl (2.6 mmol/l), and although some may achieve this goal with the

addition of lomitapide or mipomersen, these agents are costly and have significant tolerability and safety concerns (12,13). Furthermore, these agents have not been approved for a pediatric population, which limits their use in HoFH, a disease that manifests from birth (6). The addition of lipoprotein apheresis, scheduled weekly or every 2 weeks (Q2W), in these patients can reduce LDL-C in the short term by 50% to 75%. These reductions are, however, transient and may fluctuate considerably between treatment cycles, with LDL-C reduced by approximately 30% to 40% when time averaged. In addition, apheresis is time intensive and costly, requires vascular access, and is difficult to obtain in many countries (14,15).

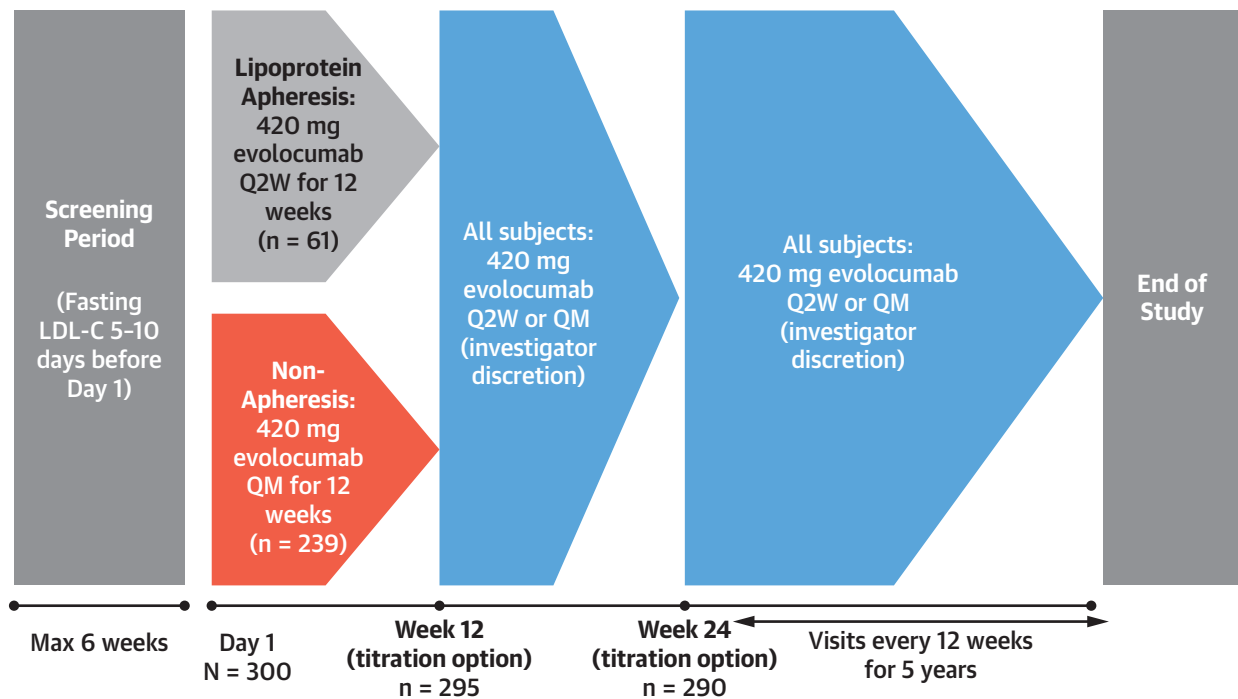
Evolocumab is a monoclonal antibody that lowers plasma LDL-C levels by binding PCSK9, thereby preventing the degradation of the *LDLR* and increasing *LDLR* expression on the cell surface (16). Evolocumab is currently approved as an adjunct to diet and maximally tolerated statin therapy in patients with HoFH and those with HeFH. Approval for the treatment of HoFH was based on the TESLA (Trial Evaluating PCSK9 Antibody in Subjects With LDL Receptor Abnormalities) Part B study (NCT01588496), which enrolled 50 patients, none of whom received apheresis, and reported that evolocumab reduced LDL-C levels by an average of 31% compared with placebo (17). For HeFH, the larger phase 3 study, RUTHERFORD-2 (Reduction of LDL-C With PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study-2), found that evolocumab reduced LDL-C levels by approximately 60% compared with placebo (18).

The present study, TAUSIG (Trial Assessing Long Term Use of PCSK9 Inhibition in Subjects With Genetic LDL Disorders) (NCT01624142), published interim results that examined only the HoFH subgroup at a mean follow-up of 1.7 years (19). In this final report, we present extended (median 4.1 years) safety and efficacy data for a greater number of patients with severe FH receiving open-label evolocumab, with or without apheresis, including a subgroup

has served as principal investigator for clinical trials conducted with a.o. Amgen, Sanofi, Eli Lilly, Novartis, Kowa, Genzyme, Cerenis, Pfizer, Dezima, and AstraZeneca; has received research grants from ZonMW, the European Union, Amgen, Sanofi, AstraZeneca, Aegerion, and Synageva; has received honoraria and investigator fees (to the Department of Vascular Medicine) for sponsor-driven studies and lectures for companies with approved lipid-lowering therapy in the Netherlands; and is partly employed by Novo Nordisk (0.7FTE) and the AMC (0.3FTE). Dr. Blom has received honoraria for consulting, speaking activities, or research from Amgen, Sanofi/Regeneron, Aegerion, Gemphire, AstraZeneca, and Novo Nordisk. Dr. Soran has received research grants from Akcea, Amgen, Amryt, Sanofi-Genzyme, Alexion, Pfizer, and Merck Sharp & Dohme; and has received honoraria from Sanofi, Bristol-Myers Squibb, Eli Lilly, AstraZeneca, Pfizer, Takeda, Amgen, and Merck Sharp & Dohme. Dr. Watts has received honoraria for advisory board membership or research grants from Amgen, Regeneron, Sanofi, Pfizer, Gemphire, Kowa, and Arrowhead. Drs. López, Bray, Kurtz, and Hamer are employees and shareholders of Amgen. Dr. Raal has received research grants, honoraria, or consulting fees for professional input and/or lectures from Sanofi, Regeneron, Amgen, and The Medicines Company.

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FIGURE 1 TAUSSIG Study Schema



TAUSSIG (Trial Assessing Long Term Use of PCSK9 Inhibition in Subjects With Genetic LDL Disorders) was an open-label, single-arm study with a 6-week maximum screening period. Fasting low-density lipoprotein cholesterol (LDL-C) was assessed 5 to 10 days before the study start date. Initial evolocumab dosing was determined by apheresis status at enrollment; patients undergoing apheresis began subcutaneous evolocumab 420 mg every 2 weeks (Q2W), and patients not undergoing apheresis began evolocumab 420 mg once monthly (QM). Dosing could be changed at week 12 or 24 at the clinician's discretion. Visits occurred every 12 weeks until end of study with fasting (≥ 9 h) lipids, adverse events, and anti-evolocumab antibodies assessed at each visit.

with more severe manifestations of HeFH over a much longer follow-up period.

METHODS

TAUSSIG was an open-label, single-arm, multicenter study that examined the long-term safety and efficacy of evolocumab in patients with HoFH and severe HeFH. Patients with HoFH could enroll directly or after completing Part A or B of the TESLA study (17). Patients with HoFH were diagnosed by either genotype or clinical criteria (history of untreated LDL-C >500 mg/dl [13 mmol/l] plus xanthoma before age 10 years or evidence of HeFH in both parents). Severe HeFH was determined at the investigator's discretion on the basis of suboptimal response to lipid-lowering therapy and the presence of CV disease or other CV disease risk factors. The Institutional Review Board at each site approved the study protocol, and all patients provided written informed consent.

The inclusion criteria selected patients age ≥ 12 years receiving stable lipid-lowering therapy

for ≥ 4 weeks with 1 of the following: 1) baseline LDL-C ≥ 130 mg/dl (3.4 mmol/l); 2) baseline LDL-C ≥ 100 mg/dl (2.6 mmol/l) with a diagnosis of coronary heart disease or risk equivalent; or 3) undergoing biweekly apheresis treatment. Patients with fasting triglycerides >400 mg/dl (4.5 mmol/l) or with recent (within 3 months of screening) myocardial infarction (MI), unstable angina, percutaneous coronary intervention, coronary artery bypass graft surgery, or stroke were excluded from the study.

The screening period lasted a maximum of 6 weeks, and fasting LDL-C was assessed 5 to 10 days before the study start date. Visits occurred every 12 weeks until the end of study, and fasting (≥ 9 h) lipids, adverse events, and antievolocumab antibodies were assessed at each visit. Among those receiving apheresis, blood samples were collected immediately prior to the apheresis session for lipid measurement.

Apheresis status at enrollment determined the initial dosing of evolocumab. Patients undergoing apheresis at enrollment began subcutaneous evolocumab 420 mg Q2W to correspond with their biweekly

TABLE 1 Baseline Characteristics

	HoFH (n = 106)	Severe HeFH (n = 194)
Age, yrs	34.3 ± 14.4	54.7 ± 11.9
Male	52 (49.1)	116 (59.8)
Race		
White	85 (80.2)	179 (92.3)
Asian	13 (12.3)	3 (1.5)
Black or African American	0 (0.0)	6 (3.1)
Other*	8 (7.5)	6 (3.1)
Ethnicity		
Hispanic/Latino	5 (4.7)	22 (11.3)
Cardiovascular history		
Coronary artery disease	50 (47.2)	116 (59.8)
Cerebrovascular or peripheral arterial disease	20 (18.9)	40 (20.6)
Aortic valve replacement	17 (16.0)	5 (2.6)
Hypertension	19 (17.9)	101 (52.1)
Type 2 diabetes mellitus	3 (2.8)	20 (10.3)
Current cigarette use	8 (7.5)	19 (9.8)
Lipid-lowering therapy		
Statin	106 (100.0)	167 (86.1)
High intensity†	96 (90.6)	112 (57.7)
Ezetimibe	95 (89.6)	121 (62.4)
Bile acid sequestrants	11 (10.4)	13 (6.7)
Apheresis at enrollment	34 (32.1)	27 (13.9)
Baseline lipids		
LDL-C, mg/dL, calculated	329.0 ± 136.7	192.7 ± 64.6
ApoB, mg/dL	200.7 ± 69.9	139.2 ± 35.6
Lp(a), nmol/L	77.0 (25.5-152.5)	68.5 (20.0-190.5)
HDL-C, mg/dL	39.5 ± 13.3	48.9 ± 15.2
Non-HDL-C, mg/dL	350.5 ± 138.4	222.1 ± 68.3
Total cholesterol, mg/dL	390.0 ± 134.7	271.0 ± 67.4
Triglycerides, mg/dL	107.3 ± 55.7	147.0 ± 72.3
hsCRP, mg/L	0.5 (0.3-1.7)	1.0 (0.5-3.0)
Serum PCSK9, ng/mL	670.3 ± 200.8	637.9 ± 224.7

Values are mean ± SD, n (%), or median (interquartile range). To convert LDL-C, HDL-C, non-HDL-C, and total cholesterol to millimoles per liter, multiply by 38.67. Pre-apheresis LDL-C was calculated in patients undergoing apheresis. *Includes American Indian or Alaskan Native, mixed race, and other. †Defined as daily atorvastatin ≥40 mg or daily rosuvastatin ≥20 mg.

ApoB = apolipoprotein B; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp(a) = lipoprotein(a); PCSK9 = proprotein convertase subtilisin/kexin type 9.

apheresis schedule, with evolocumab administered immediately after apheresis. Patients not on apheresis at enrollment received evolocumab 420 mg once monthly (QM). The dosing regimen could be changed at week 12 or week 24 at the clinician's discretion and was dependent on lipid levels measured at the end of previous dosing intervals (weeks 4 and 8). Patients could be up-titrated to evolocumab 420 mg Q2W if the free PCSK9 level was inadequately lowered (≥100 ng/mL). Patients could be down-titrated to evolocumab 420 mg QM provided there was evidence of some response to evolocumab (LDL-C reduction of 5% or greater). If any patient had a <5% reduction in LDL-C from baseline with maximally suppressed

serum-free PCSK9 concentrations (<100 ng/mL), he or she could be withdrawn from the study at week 12 or 24 at the discretion of the treating physician.

The primary objective of this study was to investigate the safety and tolerability, assessed by the incidence of treatment-emergent adverse events, of long-term administration of evolocumab among patients with HoFH and severe HeFH; the secondary objective was to quantify the lipid-lowering efficacy of evolocumab in patients with severe FH, defined as the percentage changes from baseline in LDL-C, non-high-density lipoprotein cholesterol, apolipoprotein B (ApoB), lipoprotein(a), total cholesterol/high-density lipoprotein cholesterol ratio, and ApoB/apolipoprotein A1 ratio at each scheduled visit, as well as the response rate of patients with 15% or greater reductions in LDL-C.

An independent clinical events committee adjudicated all-cause mortality, MI, hospitalization for unstable angina, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure.

The final assessment was projected at week 260 (approximately 5 years); however, the study was terminated early, before all patients reached 260 weeks of treatment, on the basis of a decision by the sponsor that sufficient information had been gathered to address long-term safety and efficacy in this population.

Qualified researchers may request data from Amgen clinical studies.

RESULTS

Of 300 patients enrolled, 106 (35%) were diagnosed with HoFH (of whom 14 were age <18 years at enrollment). The remaining 194 (65%) were diagnosed with severe HeFH. A total of 54 patients with HoFH enrolled in this study after completing Part A or B of the TESLA study. Patients received evolocumab for a median duration of 4.1 years (range: 0.2 to 5.0 years) (Figure 1, Online Figure 1).

Patients with HoFH had higher baseline LDL-C, non-high-density lipoprotein cholesterol, and ApoB and received more intensive lipid-lowering treatment, including apheresis, than those with severe HeFH (Table 1). All patients with HoFH were receiving statins (90.6% high-intensity statins), compared with 86.1% of patients with HeFH (57.7% high-intensity statins). Ezetimibe therapy was used in 89.6% and 62.4% of patients with HoFH and severe HeFH, respectively. At enrollment, apheresis treatment was used by 32.1% of the HoFH group, including 4 of 14 adolescents, and 13.9% of the severe HeFH group.

CV disease was prominent and similar between the groups, but the severe HeFH group was significantly older at enrollment than the HoFH group.

Mutation status and lipid-lowering efficacy by mutation status were previously reported in a published interim analysis of the 104 patients with HoFH (19). All patients with HoFH met clinical criteria for HoFH; 105 of 106 were confirmed by genotyping (Online Table 1).

Baseline LDL-C concentration did not predict the magnitude of LDL-C lowering during treatment with evolocumab (Online Figure 2).

Evolocumab appeared to have greater LDL-C-lowering effects in the 4 patients with PCSK9 gain-of-function mutations than in those with other causative mutations, while a lesser effect was observed in those with 2 negative LDLR mutations (Online Figure 3).

The incidence of treatment-emergent adverse events was similar for both groups (HoFH and severe HeFH) (Table 2). There was no notable difference in the safety profile of evolocumab compared with previous studies (14,20). The most common adverse events ($\geq 10\%$ frequency overall) were nasopharyngitis, influenza, upper respiratory tract infection, headache, myalgia, and diarrhea.

A total of 11 patients (3.7%) discontinued evolocumab because of treatment-emergent adverse events. Injection-site reactions were mostly minor and did not lead to evolocumab discontinuation. Absolute mean $\pm$ SD changes from baseline in fasting plasma glucose and hemoglobin A_{1c} at week 216 were, respectively, 2.0 ± 8.3 mg/dl and $0.04 \pm 0.30\%$ for HoFH and 4.5 ± 12.6 mg/dl and $0.09 \pm 0.30\%$ for severe HeFH.

No neutralizing antievolocumab antibodies were detected. Binding antibodies developed in 8 patients; these were present at or before baseline ($n = 3$) or were transient with a negative result at the last time point tested ($n = 5$).

Safety findings between groups receiving and not receiving apheresis, detailed in the interim analysis (19), were similar with the exception of injection-site reactions, which occurred more commonly in patients undergoing apheresis at enrollment than those not receiving apheresis at enrollment (respectively, 29.4% vs. 5.6% for HoFH and 18.5% vs. 10.2% for severe HeFH). These patients undergoing apheresis at enrollment also began treatment with more frequent dosing of subcutaneous evolocumab (Q2W vs. QM). Safety results were similar overall for the adolescent group; none of these patients developed antibodies (binding or neutralizing) or had neurocognitive events or adjudicated CV events.

TABLE 2 Safety Data

	HoFH (n = 106)	Severe HeFH (n = 194)	Overall (n = 300)
TEAEs*	94 (88.7)	174 (89.7)	268 (89.3)
SAEs†	29 (27.4)	57 (29.4)	86 (28.7)
Leading to evolocumab discontinuation	3 (2.8)	8 (4.1)	11 (3.7)
Most common TEAEs ($\geq 10\%$ overall)			
Nasopharyngitis	17 (16.0)	36 (18.6)	53 (17.7)
Influenza	17 (16.0)	21 (10.8)	38 (12.7)
Upper respiratory tract infection	18 (17.0)	17 (8.8)	35 (11.7)
Headache	18 (17.0)	16 (8.2)	34 (11.3)
Myalgia	6 (5.7)	24 (12.4)	30 (10.0)
Diarrhea	8 (7.5)	22 (11.3)	30 (10.0)
Any post-baseline visit			
ALT or AST $>3 \times$ ULN	12 (11.3)	12 (6.2)	24 (8.0)
CK $>5 \times$ ULN	13 (12.3)	9 (4.6)	22 (7.3)
CK $>10 \times$ ULN	8 (7.5)	7 (3.6)	15 (5.0)
Binding antibodies	1 (0.9)	7 (3.6)	8 (2.7)
Neutralizing antibodies	0 (0.0)	0 (0.0)	0 (0.0)
Normalized vitamin E (μ mol/mmol), change from baseline to week 96‡	0.8 ± 1.6	1.6 ± 1.7	1.3 ± 1.7
Absolute change from baseline to week 216			
HbA _{1c} , %	0.04 ± 0.30	0.09 ± 0.30	0.07 ± 0.30
Glucose, mg/dl	2.0 ± 8.3	4.5 ± 12.6	3.4 ± 11.2
Potential neurocognitive events§	2 (1.9)	7 (3.6)	9 (3.0)
Potential muscle-related events	9 (8.5)	33 (17.0)	42 (14.0)
Potential injection site reactions	14 (13.2)	22 (11.3)	36 (12.0)

Values are n (%) or mean $\pm$ SD. *Occurred on or after the first dose and up to 30 days after the earliest of end of study or end of evolocumab. Adjudicated cardiovascular events are reported in Table 4. †Of the 160 treatment-emergent SAEs, 50 were in patients with HoFH and 110 in patients with HeFH. ‡Vitamin E was normalized by dividing serum vitamin E by total cholesterol. Week 96 was the last time point measured per protocol. §Neurocognitive events were defined using Medical Dictionary for Regulatory Activities high-level group terms of delirium, cognitive and attentive disorders and disturbances, dementia and amnesic conditions, disturbances in thinking and perception, and mental impairment disorders.

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; CK = creatine kinase; HbA_{1c} = hemoglobin A_{1c}; SAE = serious adverse event; TEAE = treatment-emergent adverse event; ULN = upper limit of normal; other abbreviations as in Table 1.

Patient retention was high overall. In total, there were 10 patients, all with HoFH, who had LDL-C reductions $<5\%$ at weeks 12 and 24. One patient, who had a percentage reduction in LDL-C of $<5\%$, discontinued the study between weeks 12 and 24. Analysis of laboratory data is focused on results through week 216, as <20 patients in either group were analyzed beyond this time point.

LDL-C levels were persistently reduced at weeks 12 through 216 compared with baseline in patients with HoFH and severe HeFH, with or without apheresis (Table 3, Figure 2). Mean $\pm$ SD percentage changes in LDL-C were $-21.2 \pm 25.0\%$ at week 12 and $-24.0 \pm 41.3\%$ at week 216 for patients with HoFH. Mean absolute LDL-C changes in the HoFH group were -59.8 ± 75.3 mg/dl at week 12 and -74.9 ± 124.5 mg/dl at week 216. The corresponding percentage changes in LDL-C

TABLE 3 Absolute and Percentage Changes at Weeks 12, 48, and 216 in LDL-C, Apolipoprotein B, and Lipoprotein(a)

Efficacy	HoFH (n = 106)	Severe HeFH (n = 194)
LDL-C, calculated		
Change at week 12		
%	-21.2 ± 25.0	-54.9 ± 17.4
Absolute, mg/dl	-59.8 ± 75.3, n = 104	-104.4 ± 42.4, n = 191
Change at week 48		
%	-24.8 ± 31.7	-56.9 ± 19.2
Absolute, mg/dl	-79.7 ± 97.2, n = 93	-108.3 ± 51.0, n = 187
Change at week 216		
%	-24.0 ± 41.3	-47.2 ± 27.9
Absolute, mg/dl	-74.9 ± 124.5, n = 68	-90.6 ± 61.9, n = 96
Apolipoprotein B		
Change at week 12		
%	-15.0 ± 22.7	-43.7 ± 16.1
Absolute, mg/dl	-26.4 ± 42.2, n = 105	-60.5 ± 26.4, n = 192
Change at week 48		
%	-17.9 ± 27.6	-43.0 ± 18.4
Absolute, mg/dl	-37.2 ± 50.6, n = 94	-60.0 ± 31.9, n = 190
Change at week 216		
%	-16.6 ± 36.2	-35.5 ± 24.3
Absolute, mg/dl	-32.9 ± 68.1, n = 68	-49.3 ± 38.7, n = 98
Lipoprotein(a)		
Change at week 12		
%	-7.69 (-21.6 to 6.8)	-24.4 (-40.3 to -9.1)
Absolute, nmol/l	-3.0 (-21.5 to 2.5), n = 105	-12.5 (-34.8 to -2.0), n = 192
Change at week 48		
%	-13.2 (-30.5 to 0.0)	-26.3 (-41.9 to -10.5)
Absolute, nmol/l	-9.3 (-30.0 to 0.0), n = 94	-13.5 (-40.0 to -2.5), n = 189
Change at week 216		
%	-14.1 (-36.1 to 4.1)	-0.7 (-23.6 to 23.8)
Absolute, nmol/l	-8.5 (-38.0 to 1.3), n = 68	-0.3 (-11.5 to 4.5), n = 98

Values are mean ± SD, median (interquartile range), or n. LDL-C was measured using ultracentrifugation through week 48 and was calculated thereafter.
Abbreviations as in Table 1.

in the severe HeFH group were $-54.9 \pm 17.4\%$ at week 12 and $-47.2 \pm 27.9\%$ at week 216; absolute changes were -104.4 ± 42.4 mg/dl at week 12 and -90.6 ± 61.9 mg/dl at week 216. Persistent and substantial mean changes in ApoB were also observed (from -15% to -21% for HoFH and from -35% to -44% for severe HeFH). Median changes in lipoprotein(a) from weeks 12 through 216 ranged from -7.0% to -23.6% for HoFH and from -0.7% to -32.4% for HeFH (Table 3).

From weeks 12 through 216, LDL-C reductions of $\geq 15\%$ were observed in 56.7% to 72.2% of patients with HoFH and 88.5% to 99.0% of patients with severe HeFH.

LDL-C reductions for patients receiving apheresis at enrollment were similar to those in patients not receiving apheresis at enrollment for both the HoFH and severe HeFH groups (Online Table 2).

In total, 32 patients had positively adjudicated CV events, resulting in an annualized event rate of 2.7% per year (2.8% in the HoFH group, 2.6% in the severe HeFH group) (Table 4). In the HoFH cohort, a total of 12 patients (11.3%) had positively adjudicated CV events, with a similar percentage in the severe HeFH cohort of 10.3% (20 patients). Twenty-two of 32 patients underwent coronary revascularization (8 with HoFH and 14 with severe HeFH), the majority of which were percutaneous coronary interventions. A total of 7 patients experienced MIs, 2 (1.9%) in the HoFH cohort and 5 (2.6%) in the severe HeFH cohort. Of the 9 deaths that occurred, 2 were CV related and considered treatment emergent, occurring within 30 days of the end of treatment or study: 1 due to MI in the HoFH group and the other due to hemorrhagic stroke in the severe HeFH group.

Of the 61 patients undergoing apheresis at enrollment, 3 of 34 (9%) with HoFH were able to discontinue apheresis, and 13 of 27 (48%) with severe HeFH were able to discontinue apheresis, sparing on average 36 months of apheresis treatment over the course of the study. Of the 16 patients who stopped apheresis overall, 10 patients were able to do so within 90 days of starting evolocumab treatment. Three patients, all with HoFH and 1 of whom was an adolescent, were initiated on apheresis during the study. The decision to discontinue apheresis was made after week 12 at the discretion of the patient and treating physician and was not protocol driven on the basis of the achieved LDL-C concentration. Ten of 16 patients achieved LDL-C <50 mg/dl after stopping apheresis.

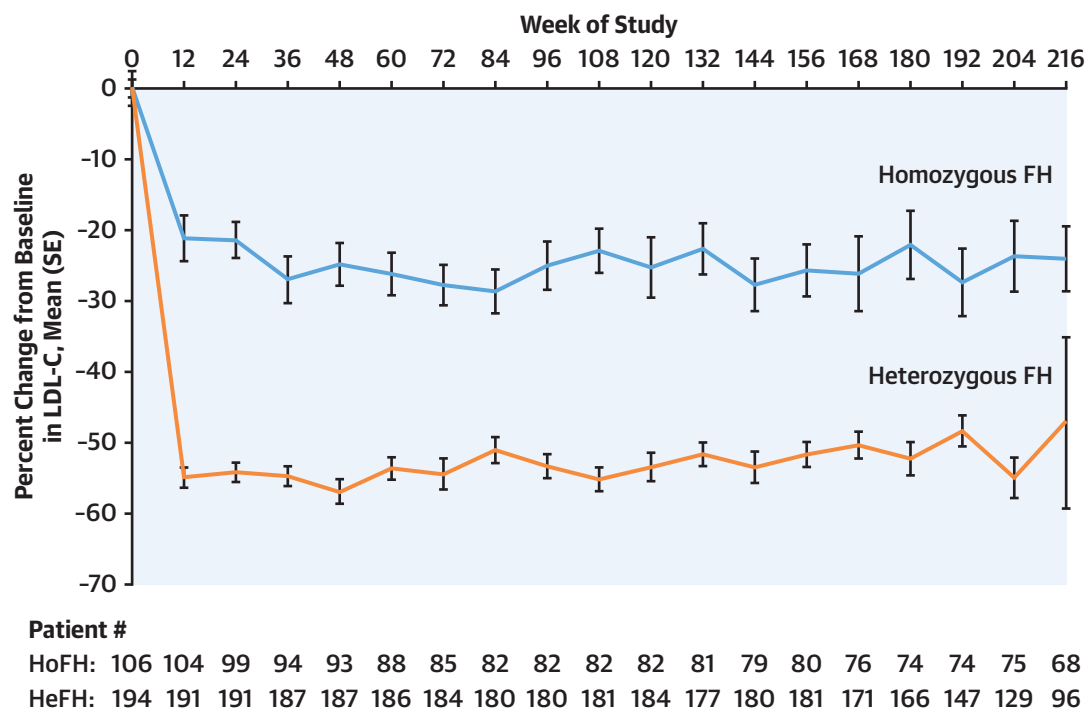
Among the nonapheresis patients, evolocumab 420 mg QM was up-titrated to 420 mg Q2W in 48 patients, and this resulted in a subsequent LDL-C mean change from baseline of -19.6% at week 12 (pre-titration) to -29.7% at week 24 (post-titration).

DISCUSSION

The TAUSIG trial examined the safety and efficacy of evolocumab treatment in 300 patients with either HoFH or severe HeFH with previous atherosclerotic CV disease and/or persistently elevated LDL-C despite standard lipid-lowering therapy. The present study generated the longest follow-up of any study of a PCSK9 inhibitor in this patient population and the largest in patients with HoFH.

In this study, evolocumab was well tolerated and effectively reduced LDL-C, with results sustained over a median of 4.1 years (Central Illustration). The adverse event profile was similar to that observed in previous evolocumab trials, including the FOURIER

FIGURE 2 Mean Percentage Change From Baseline in LDL-C (Calculated) for HoFH and Severe HeFH Cohorts



Low-density lipoprotein cholesterol (LDL-C) levels were persistently reduced with evolocumab at weeks 12 through 216 compared with baseline in patients with homozygous familial hypercholesterolemia (HoFH) and severe heterozygous familial hypercholesterolemia (HeFH). Mean percentage changes in LDL-C were -21.2% at week 12 and -24.0% at week 216 for patients with HoFH. Mean percentage changes in LDL-C in the severe HeFH group were -54.9% at week 12 and -47.2% at week 216. After week 216, the number of patients assessed in either the HoFH or severe HeFH group fell below 20 and is therefore not depicted. SE = standard error.

(Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) trial, in which evolocumab was studied in patients with clinically evident atherosclerotic CV disease (20). No neutralizing antibodies to evolocumab were detected during the extended follow-up period. Also, no clinically significant changes were encountered in fasting blood glucose and hemoglobin A_{1c}.

Effects by genotype among patients with HoFH have been reported (19); however, longer term results confirm that evolocumab has similar efficacy in FH as in non-FH populations if patients have at least 1 normal *LDLR* allele. Although efficacy may be reduced in homozygous or compound heterozygous double *LDLR* mutant carriers, whatever level of LDL-C reduction is achieved seems to be sustained. It is also apparent that evolocumab may be particularly effective in *PCSK9* gain-of-function mutations, as suggested by the present study ($n = 4$) and previously reported with the PCSK9 inhibitor alirocumab (21).

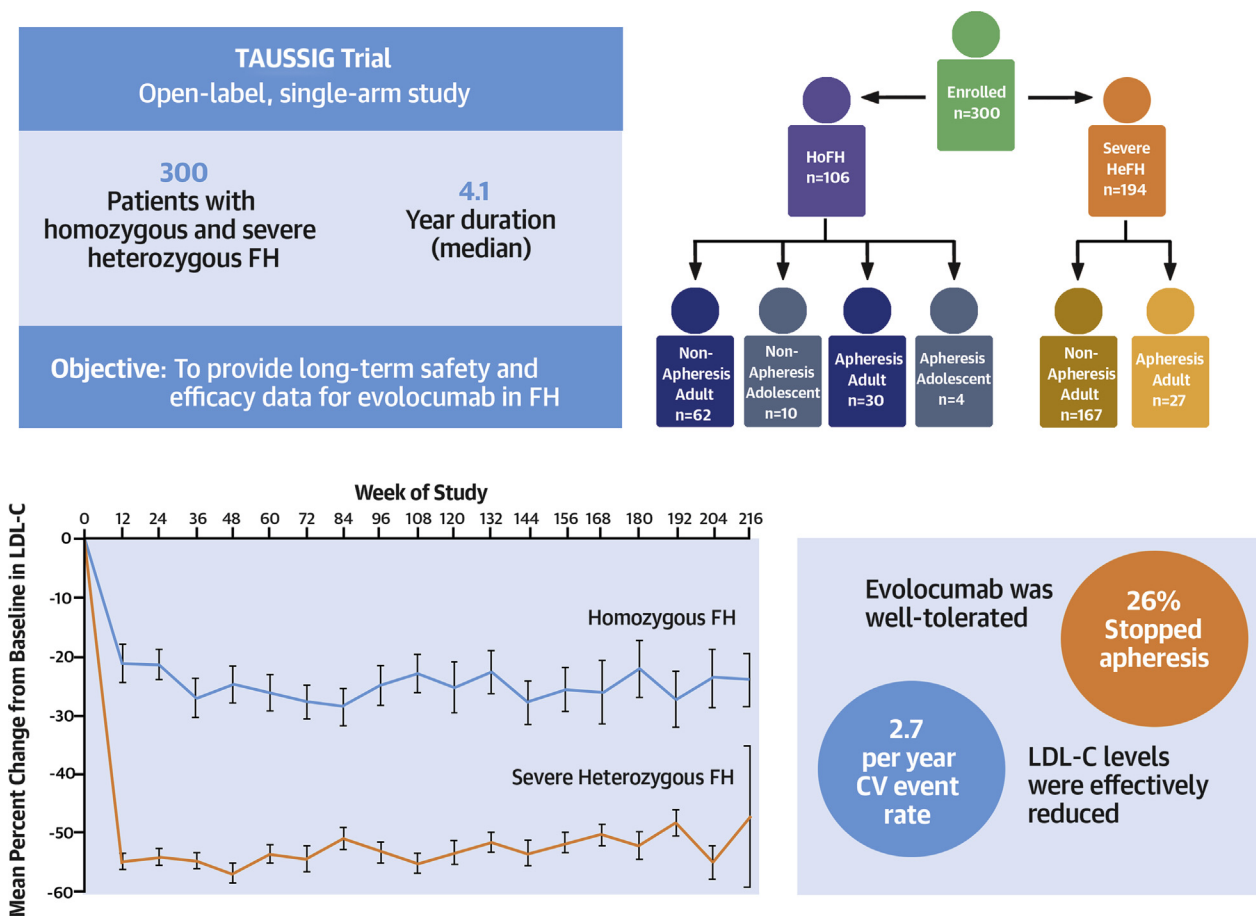
The CV event rate of 2.7% per year was markedly lower than expected given the high risk of these

patients and the event rates observed in other studies (22). About one-half of the patients enrolled in TAUSSIG had established coronary artery disease at baseline along with multiple CV risk factors. In the

TABLE 4 Annualized Event Rates for Adjudicated Cardiovascular Events

	HoFH (n = 106)	Severe HeFH (n = 194)	Overall (N = 300)
Positively adjudicated cardiovascular events	2.8	2.6	2.7
Death	0.7	0.8	0.8
Cardiovascular deaths	0.7	0.3	0.4
Myocardial infarction	0.5	0.7	0.6
Hospitalization for unstable angina	0.2	0.3	0.3
Coronary revascularization	1.9	1.9	1.9
Percutaneous coronary intervention	1.4	1.6	1.5
Surgical	0.5	0.3	0.3
Cerebrovascular event	0.7	0.1	0.3
Transient ischemic attack	0.2	0.0	0.1
Stroke	0.5	0.1	0.3
Hospitalization for heart failure	0.0	0.1	0.1

Values are %. Patients may have had >1 event.
Abbreviations as in Table 1.

CENTRAL ILLUSTRATION Long-Term Evolocumab Treatment in Patients With Familial HypercholesterolemiaSantos, R.D. et al. *J Am Coll Cardiol.* 2020;75(6):565-74.

Evolocumab was well tolerated and effectively reduced plasma LDL-C levels in patients with HoFH and severe HeFH in the TAUSSIG study. CV = cardiovascular; FH = familial hypercholesterolemia; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; TAUSSIG = Trial Assessing Long Term Use of PCSK9 Inhibition in Subjects With Genetic LDL Disorders.

FOURIER study, which included CV death, MI, stroke, hospitalization for unstable angina, and coronary revascularization in its primary composite endpoint, the annualized event rate was 4.4% in the evolocumab-treated group (vs. 5.1% in the placebo group) (20). Historical cohorts that might have included patients with severe FH appeared to have greater annual CV event rates than in this study; 4S (Scandinavian Simvastatin Survival Study), for instance, had a CV death or MI event rate of 4.6% per year in patients with mean baseline LDL-C of 188 mg/dl (5 mmol/l) (22). In addition, patients with FH who experience acute coronary syndromes have a >2-fold risk for coronary events within the first year (23,24). Major adverse CV events and CV deaths in patients

with HoFH have been closely associated with on-treatment total cholesterol levels, 90% of which is LDL-C (25). This study found that on-treatment mean LDL-C decreased by 90.6 mg/dl (baseline of 192.7 mg/dl) in the severe HeFH group and by 74.9 mg/dl (baseline of 329.0 mg/dl) in the HoFH group at week 216.

During the study, 26% of patients receiving apheresis at enrollment for LDL-C lowering, most with HeFH, stopped this procedure. This may be due in part to the additional LDL-C reduction by evolocumab treatment and is consistent with findings for evolocumab (26) and alirocumab (27) in patients with HeFH. During the present study, apheresis was started in 3 patients with HoFH, and because only 3

patients with HoFH discontinued apheresis, it highlights the difficulty in achieving optimal LDL-C control, and remaining unmet need in many patients with HoFH, particularly those with negative variants in 2 *LDLR* alleles, in which PCSK9 inhibition is not effective in up-regulating *LDLR* expression. Additional candidates under development include antibodies to ANGPTL3 (28).

This study also provides longer term information in 14 adolescent patients with HoFH receiving evolocumab and will be supplemented by a specific pediatric trial in patients 10 to 17 years of age with HeFH in the HAUSER-RCT (Trial Assessing Efficacy, Safety and Tolerability of PCSK9 Inhibition in Paediatric Subjects With Genetic LDL Disorders) study (NCT02392559) (29).

STUDY LIMITATIONS. The limitations of this study include the lack of a control arm, the lack of blinding, and the earlier than planned termination of the trial and hence small number of patients who could be assessed beyond 4 years. After the 4-year time point, the smaller patient numbers in both the HoFH and severe HeFH cohorts resulted in more variability in response. Although for some patients the 420-mg Q2W dosing regimen was more efficacious than the 420-mg QM dosing regimen, the former is not approved in the United States and some other countries.

CONCLUSIONS

We showed in a long-term, open-label study that evolocumab has sustained efficacy, safety, and tolerability in patients with HoFH and severe HeFH.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL

SKILLS: Evolocumab reduces LDL-C and the need for low-density lipoprotein apheresis in patients with severe FH that has been incompletely responsive to lipid-lowering standard therapy.

TRANSLATIONAL OUTLOOK: Further studies in larger cohorts are needed to establish the incremental efficacy of sustained LDL-C lowering with evolocumab for prevention of CV events in patients with severe FH.

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KEY WORDS evolocumab, familial hypercholesterolemia, LDL-C, lipid-lowering therapy, PCSK9 inhibitor, safety

APPENDIX For a list of principal investigators and a summary of serious adverse events as well as supplemental tables and figures, please see the online version of this paper.