Evinacumab in Patients with Homozygous Familial Hypercholesterolemia

Frederick Raal

Faculty of Health Sciences
University of the Witwatersrand
Johannesburg, South Africa

Robert S. Rosenson, Laurens F. Reeskamp, G. Kees Hovingh, John J.P. Kastelein, Paolo Rubba, Shazia Ali, Poulabi Banerjee, Kuo-Chen Chan, Daniel A. Gipe, Nagwa Khilla, Robert Pordy, David M. Weinreich, George D. Yancopoulos, Yi Zhang, Daniel Gaudet

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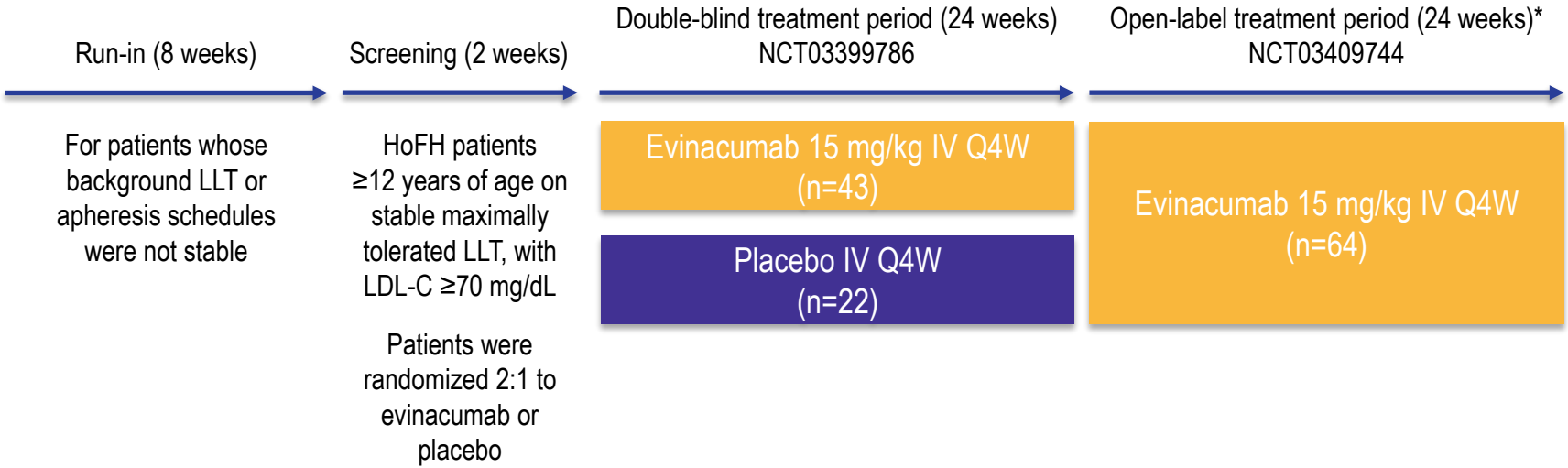
Background

- HoFH is a rare genetic disorder usually caused by LDL receptor loss-of-function mutations that prevent the effective clearance of LDL-C from circulation
- Most affected individuals are less responsive (or unresponsive) to standard lipid-lowering therapies, including statins and PCSK9 inhibitors, which act mainly by upregulation of LDL receptor function
- Evinacumab, a fully human monoclonal antibody inhibitor of ANGPTL3, reduces LDL-C independent of the LDL receptor
- In this study, the safety and efficacy of evinacumab were assessed in HoFH patients who had high LDL-C despite being on multiple lipid-lowering therapies with or without apheresis

ANGPTL3, angiopoietin-like 3; HoFH, homozygous familial hypercholesterolemia; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

Study Design



Primary endpoint: % change in calculated LDL-C from baseline to Week 24 during the double-blind treatment period

*The open-label treatment study was ongoing at the time of database lock for the double-blind treatment period.
IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Q4W, every 4 weeks.

Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Age ≥12 years at screening
- Diagnosis of HoFH by at least one of the following:
  - a) Documented pathogenic mutations in both LDLR alleles
  - b) Presence of homozygous or compound heterozygous mutations in ApoB or PCSK9
  - c) Double heterozygotes or patients with homozygous LDLRAP1 mutations
  - d) Untreated total cholesterol >500 mg/dL and triglycerides <300 mg/dL AND either both parents with documented total cholesterol >250 mg/dL OR cutaneous or tendinous xanthoma before 10 years of age

Exclusion Criteria

- LDL-C <70 mg/dL at screening
- Background lipid-lowering therapy (including lipid apheresis) not stable before screening visit

Apo, apolipoprotein; HoFH, homozygous familial hypercholesterolemia; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

Baseline Characteristics

	Placebo IV Q4W (n=22)	Evinacumab 15 mg/kg IV Q4W (n=43)
Age, years, mean (range)	36.7 (12–55)	44.3 (15–75)
Female, n (%)	11 (50.0)	24 (55.8)
Race, white, n (%)	17 (77.3)	31 (72.1)
BMI, kg/m^2, mean (SD)	24.6 (5.7)	26.1 (5.9)
Any history of CHD, n (%)	21 (95.5)	38 (88.4)
Genotype status, n (%)		
Non-null/null	16 (72.7)	28 (65.1)
Null/null*	6 (27.2)	15 (34.9)
Null/null <2% LDL receptor activity	2 (9.1)	8 (18.6)

*A genetic variant was considered null/null if LDL receptor activity was ≤15%.

BMI, body mass index; CHD, coronary heart disease; IV, intravenous; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); Q4W, every 4 weeks; SD, standard deviation.

Baseline Characteristics

	Placebo IV Q4W (n=22)	Evinacumab 15 mg/kg IV Q4W (n=43)
LLT, n (%)		
Statin	20 (90.9)	41 (95.3)
Ezetimibe	16 (72.7)	33 (76.7)
PCSK9 inhibitor	16 (72.7)	34 (79.1)
Lomitapide	3 (13.6)	11 (25.6)
Apheresis	8 (36.4)	14 (32.6)
LLT combinations, n (%)		
Statin + ezetimibe + PCSK9 inhibitor	8 (36.4)	21 (48.8)
Statin + ezetimibe + PCSK9 inhibitor + lomitapide	3 (13.6)	4 (9.3)
At least three LLTs	11 (50.0)	30 (69.8)

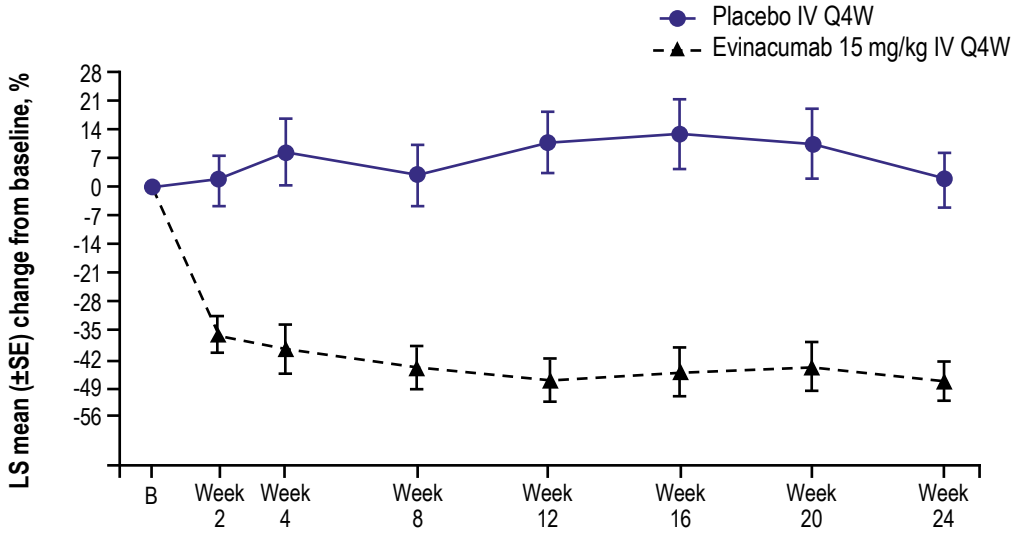
IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); PCSK9, proprotein convertase subtilisin/kexin type 9; Q4W, every 4 weeks.

Baseline Lipid Parameters

	Placebo IV Q4W (n=22)	Evinacumab 15 mg/kg IV Q4W (n=43)
Calculated LDL-C, mg/dL, mean (SD)	246.5 (153.7)	259.5 (172.4)
ApoB, mg/dL, mean (SD)	175.9 (98.8)	169.1 (82.8)
HDL-C, mg/dL, mean (SD)	46.0 (16.1)	43.6 (14.9)
Non-HDL-C, mg/dL, mean (SD)	269.9 (157.8)	281.9 (172.6)
Total cholesterol, mg/dL, mean (SD)	315.9 (150.4)	325.6 (170.8)
Triglycerides, mg/dL, median (IQR)	103.5 (123)	91 (80)
Lp(a), nmol/L, median (IQR)	53 (102)	59 (151)

IQR, interquartile range; IV, intravenous; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); Q4W, every 4 weeks; SD, standard deviation.

Primary Endpoint: Percent Change in LDL-C



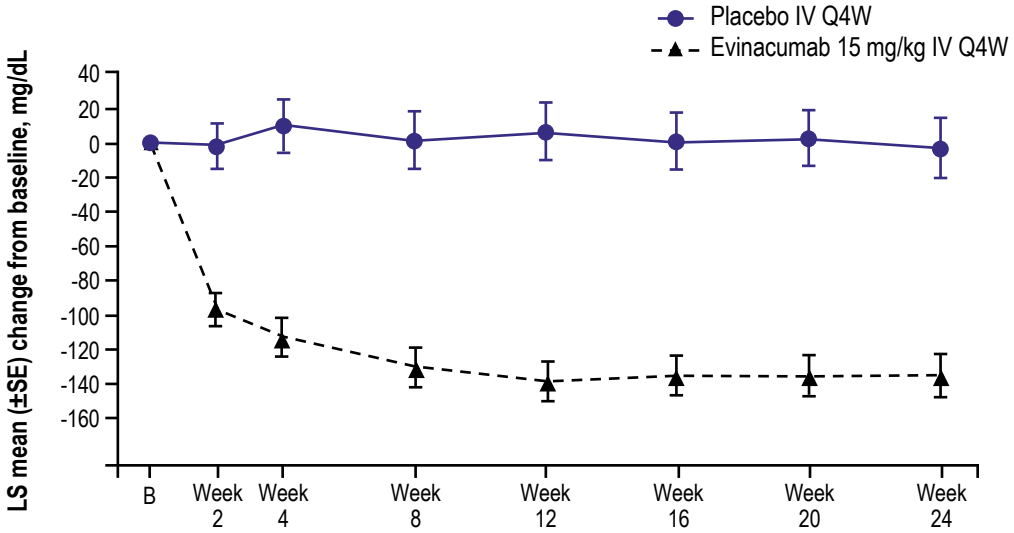
Number of patients	B	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Placebo IV Q4W	22	19	20	21	20	20	20	21
Evinacumab 15 mg/kg IV Q4W	43	38	43	42	42	40	43	43

Primary endpoint
Percent change in LDL-C at Week 24 (LS mean [SE]):

Evinacumab –47.1% (4.6)
Placebo +1.9% (6.5)
Difference –49.0% (8.0)
P<0.0001

B, baseline; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LS, least squares; Q4W, every 4 weeks; SE, standard error.

Key Secondary Endpoints: Absolute Change in LDL-C



Number of patients								
Placebo IV Q4W	22	19	20	21	20	20	20	21
Evinacumab 15 mg/kg IV Q4W	43	38	43	42	42	40	43	43

Key secondary endpoint
Absolute change in LDL-C at Week 24 (LS mean [SE]):

Evinacumab –134.7 mg/dL (12.4)
Placebo –2.6 mg/dL (17.6)
Difference –132.1 mg/dL (21.5)
P<0.0001

B, baseline; IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LS, least squares; Q4W, every 4 weeks; SE, standard error.

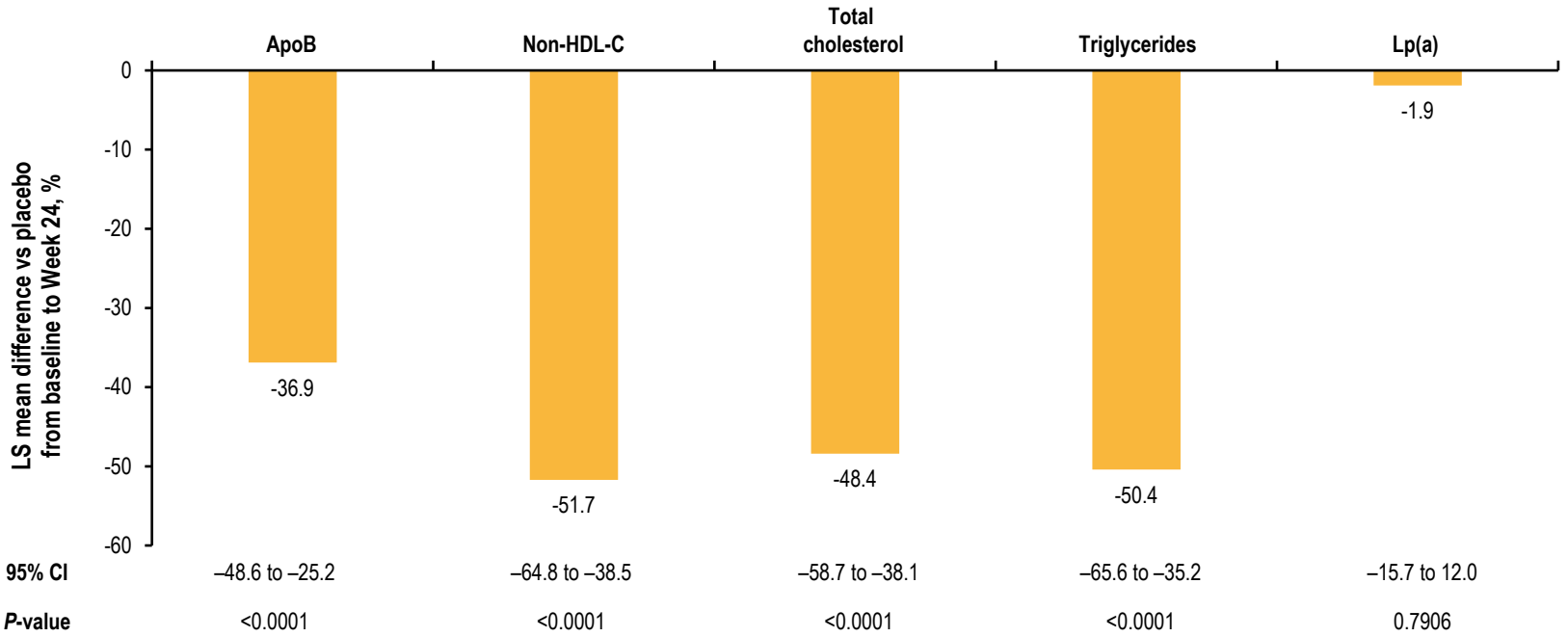
Key Secondary Endpoints: Others

	Placebo IV Q4W (n=22)	Evinacumab 15 mg/kg IV Q4W (n=43)	Combined estimate for odds ratio	95% CI	P-value
Patients with ≥30% reduction in LDL-C	18.2%	83.7%	25.2	5.7 to 110.5	<0.0001
Patients with ≥50% reduction in LDL-C	4.5%	55.8%	24.2	3.0 to 195.6	0.003
Proportion of patients who met US apheresis eligibility criteria‡	22.7%	7.0%	0.1	0.0 to 1.3	0.085
Proportion of patients with LDL-C <100 mg/dL	22.7%	46.5%	5.7	1.3 to 24.9	0.020§

‡A patient is considered as meeting US apheresis eligibility criteria if LDL-C ≥300 mg per deciliter.
§Hierarchical testing terminated for the previous endpoint therefore P-value is nominal

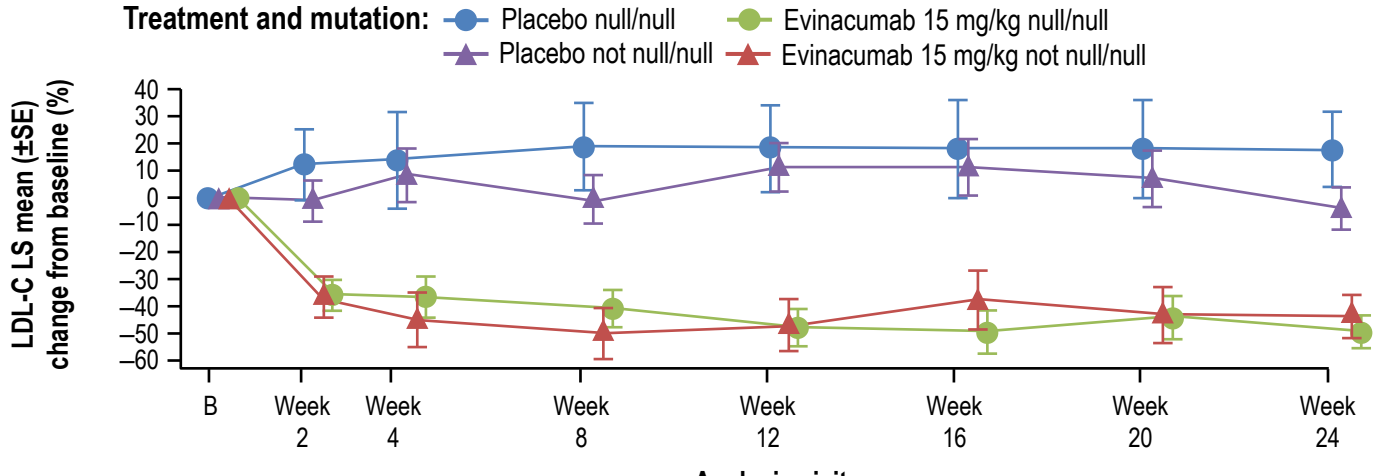
CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; LS, least squares; SE, standard error; US, United States

Change in other key lipid parameters



ApoB, apolipoprotein B; CI, confidence interval; non-HDL-C, non-high-density lipoprotein cholesterol, Lp(a), lipoprotein(a); LS, least squares.

Calculated LDL-C % Change by Null/Null Mutation



Number of patients								
Placebo null/null (n=6)	5	4	5	5	5	5	5	5
Placebo not null/null (n=16)	16	15	14	15	14	14	14	15
Evinacumab 15 mg/kg null/null (n=15)	15	14	15	15	14	15	15	15
Evinacumab 15 mg/kg not null/null (n=28)	28	24	28	27	28	25	28	28

LDL-C, low-density lipoprotein cholesterol; LS, least squares; SE, standard error.

Safety

	Placebo IV Q4W (n=21)	Evinacumab 15 mg/kg IV Q4W (n=44)
Patients with any TEAE, n (%)	17 (81.0)	29 (65.9)
TEAEs with >5% incidence, n (%)		
Nasopharyngitis	5 (23.8)	7 (15.9)
Influenza-like illness	0	5 (11.4)
Headache	5 (23.8)	4 (9.1)
Rhinorrhea	0	3 (6.8)
Toothache	2 (9.5)	2 (4.5)
UTI	2 (9.5)	0
Aspartate aminotransferase	2 (9.5)	0
Myalgia	2 (9.5)	0
Patients with at least one SAE, n (%)	0	2 (4.5)
Urosepsis	0	1 (2.3)
Suicide attempt	0	1 (2.3)

- No AEs resulted in death or discontinuation

AE, adverse event; IV, intravenous; Q4W, every 4 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Conclusions

- This pivotal Phase 3 trial demonstrated that evinacumab substantially lowers LDL-C in HoFH patients, regardless of LDL receptor function, and is generally well tolerated
- Evinacumab may provide an effective treatment option for patients with HoFH who are unable to reach target LDL-C despite multiple conventional lipid-lowering therapies with or without apheresis
- Limitations of this study include the duration, particularly for conclusions regarding long-term safety of evinacumab. Evinacumab safety is being further assessed in the open-label treatment period of the trial

HoFH, homozygous familial hypercholesterolemia; LDL, low-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol