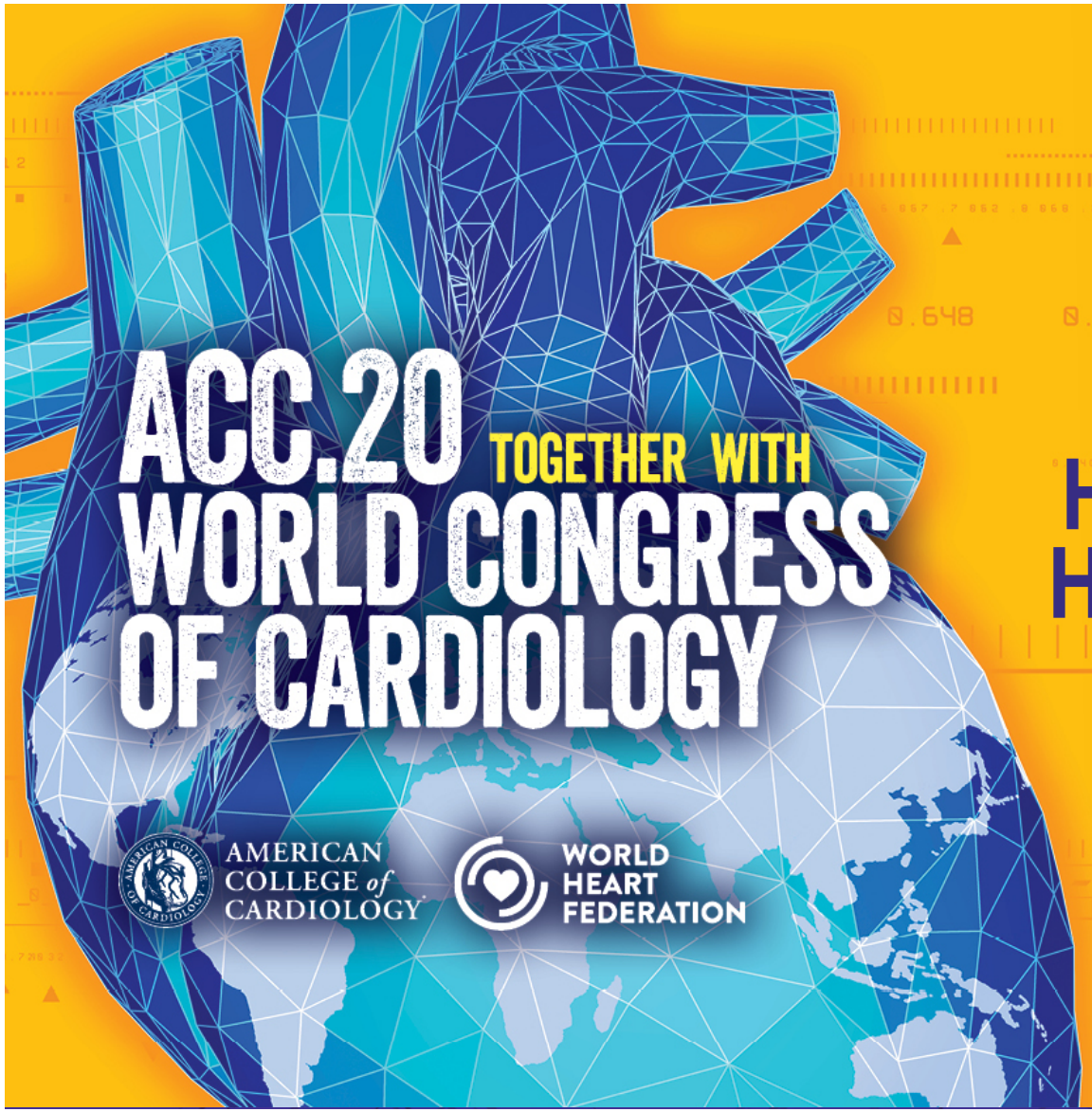

Evinacumab in Patients with Homozygous Familial Hypercholesterolemia

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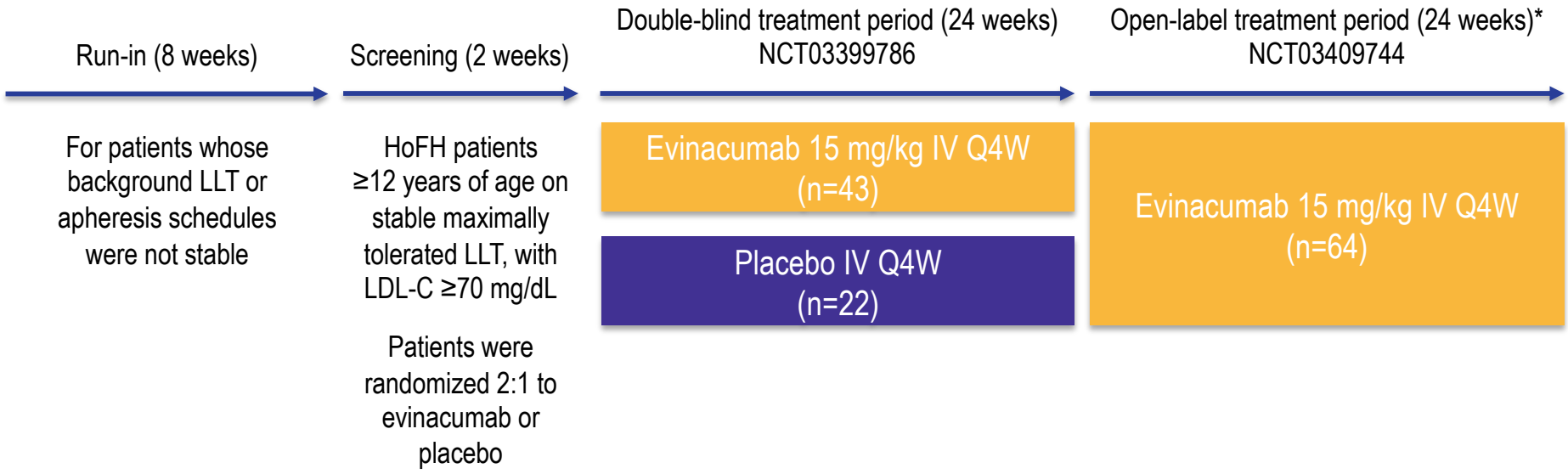
Background

- 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)

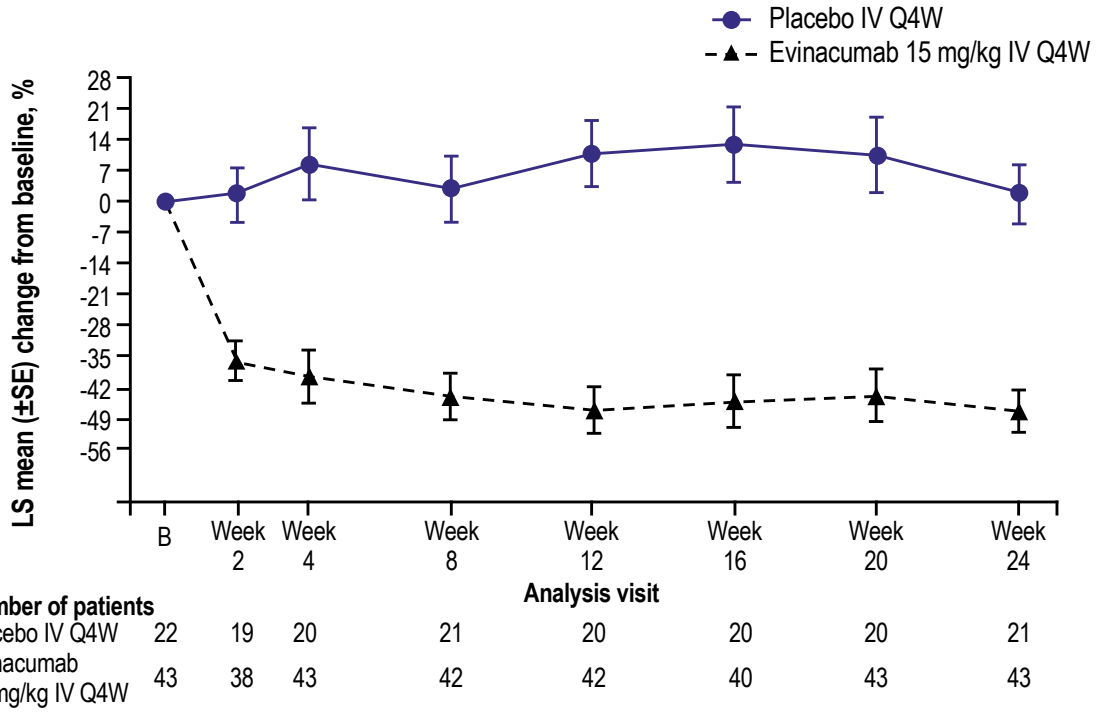
IV, intravenous; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); PCSK9, proprotein convertase subtilisin/kexin type 9; Q4W, every 4 weeks.

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



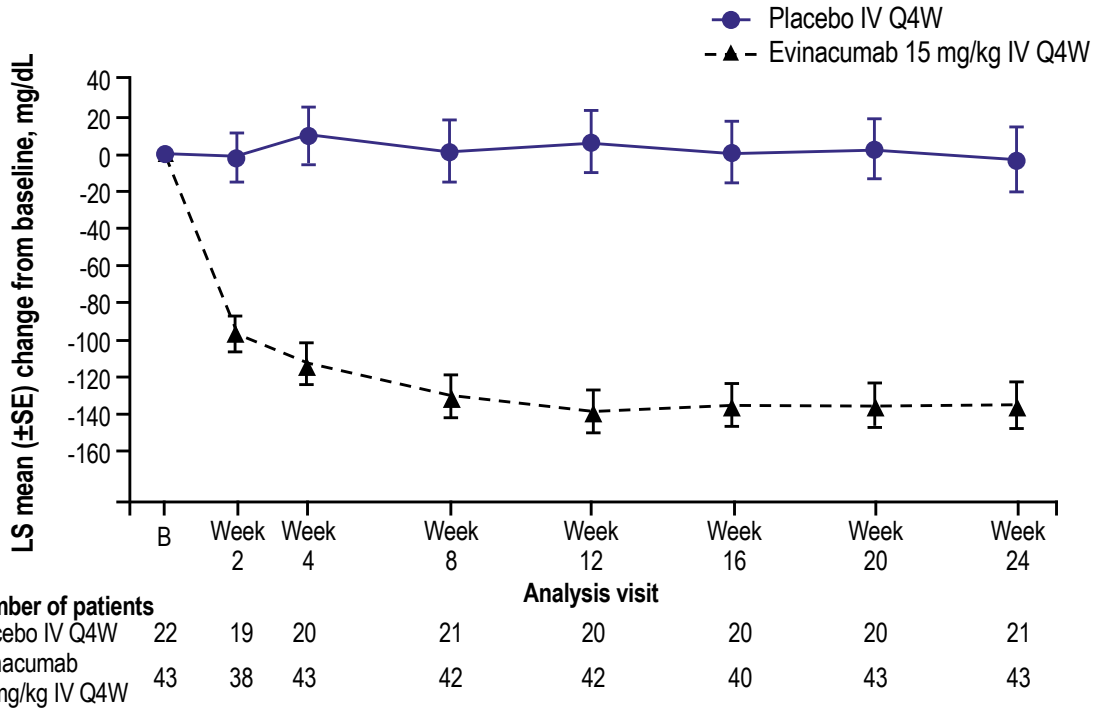
Number of patients	B	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Placebo IV Q4W	22	19	20	21	20	20	20	21
Evinacumab 15 mg/kg IV Q4W	43	38	43	42	42	40	43	43

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	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

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.

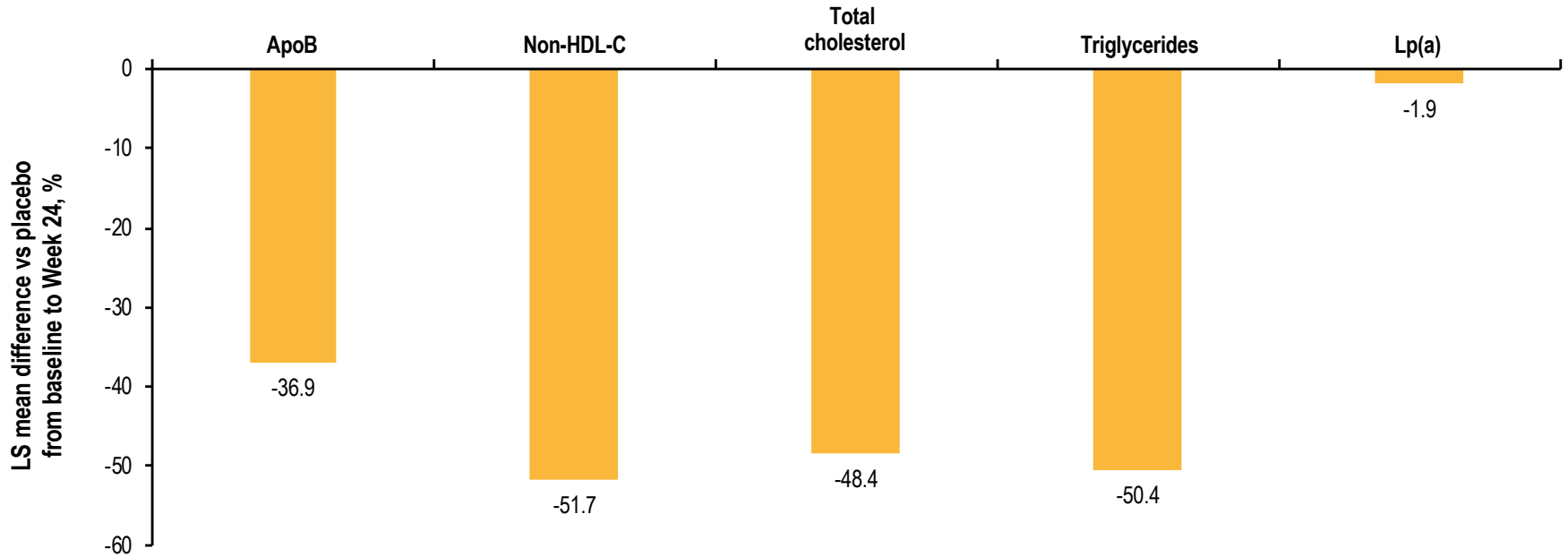
Key Secondary Endpoints: Others

	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

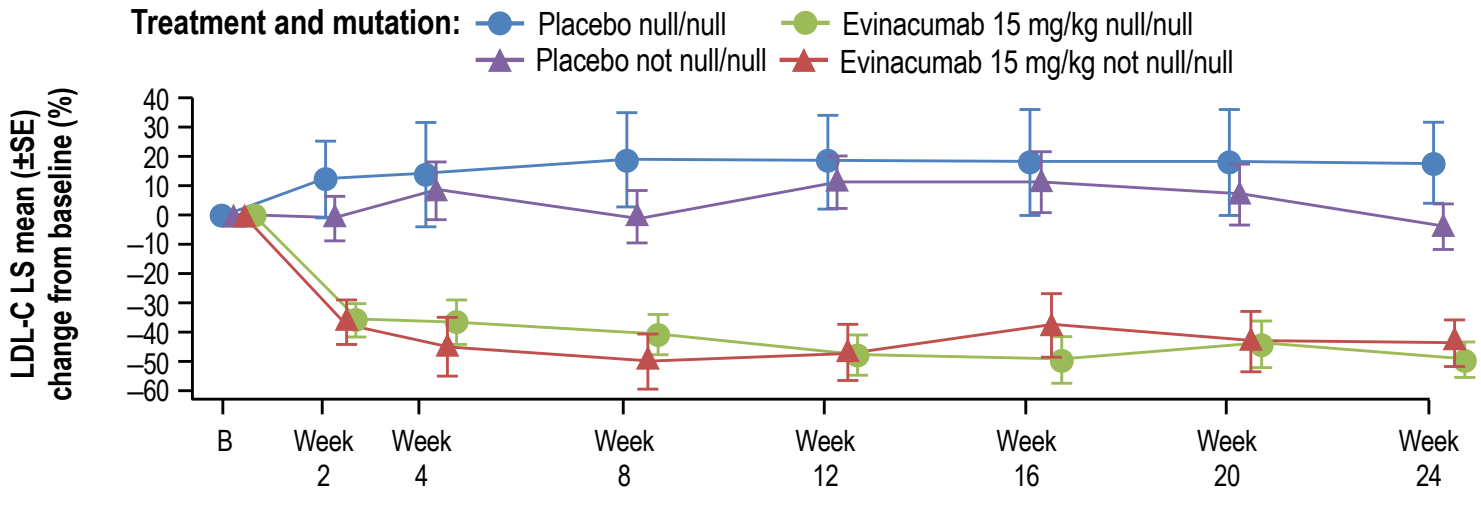
CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; LS, least squares; SE, standard error; US, United States

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