Original Article

Evinacumab for Homozygous Familial Hypercholesterolemia

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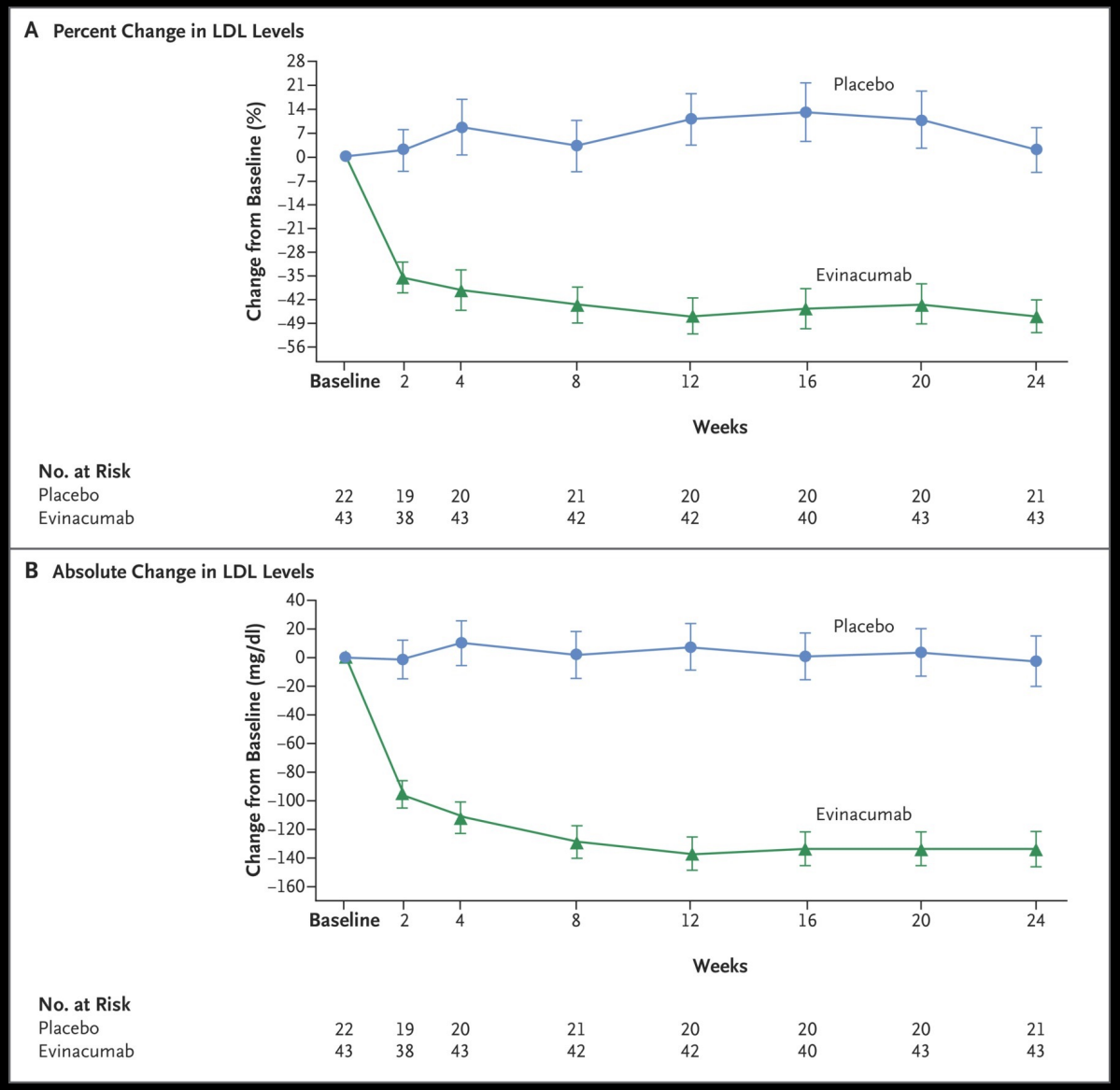
Study Overview

- Among 65 patients with homozygous familial hypercholesterolemia, the use of evinacumab, a monoclonal antibody against ANGPTL3, resulted in a reduction from baseline in the LDL cholesterol level, as compared with a small increase with placebo, for a between-group difference of 49.0 percentage points at 24 weeks.

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



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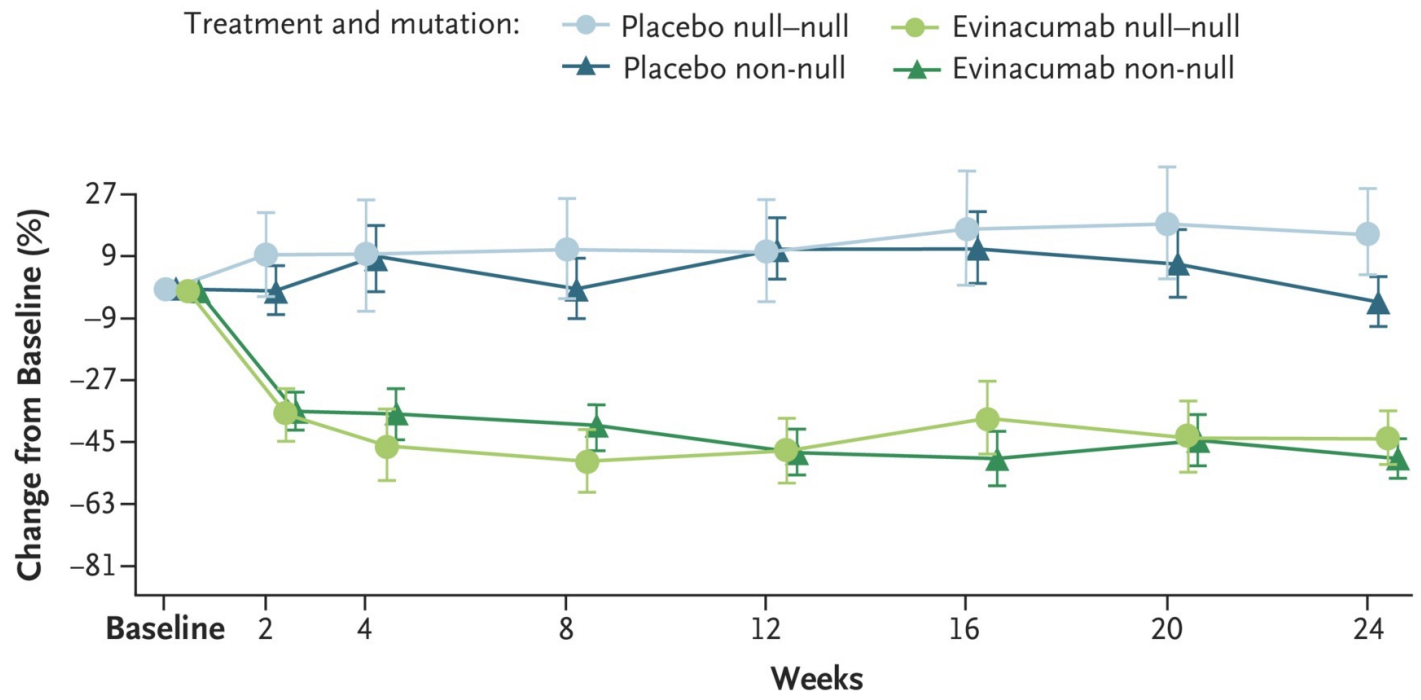
Percent Change in LDL Cholesterol Levels, According to Type of LDL-Receptor Variants.



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

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Demographic and Clinical Characteristics of the Patients at Baseline.

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.

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Trial Outcomes at 24 Weeks.

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.

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Adverse Events during the Treatment Period.

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.

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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.