Alirocumab Efficacy And Safety In Adults With Homozygous Familial Hypercholesterolemia (ODYSSEY HoFH)

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Background

- HoFH is characterized by extremely high LDL-C levels and early onset atherosclerotic cardiovascular disease despite treatment with conventional lipid lowering treatment[1-3]
- HoFH includes true homozygotes, compound heterozygotes and double heterozygotes[1]
- HoFH results from severely impaired LDLR function, most commonly due to mutations in both copies of the *LDLR* gene[1]
- Mutation in other genes of the LDLR pathway (*APOB*, *PCSK9*, and *LDLRAP1*) may also affect LDLR function[1]

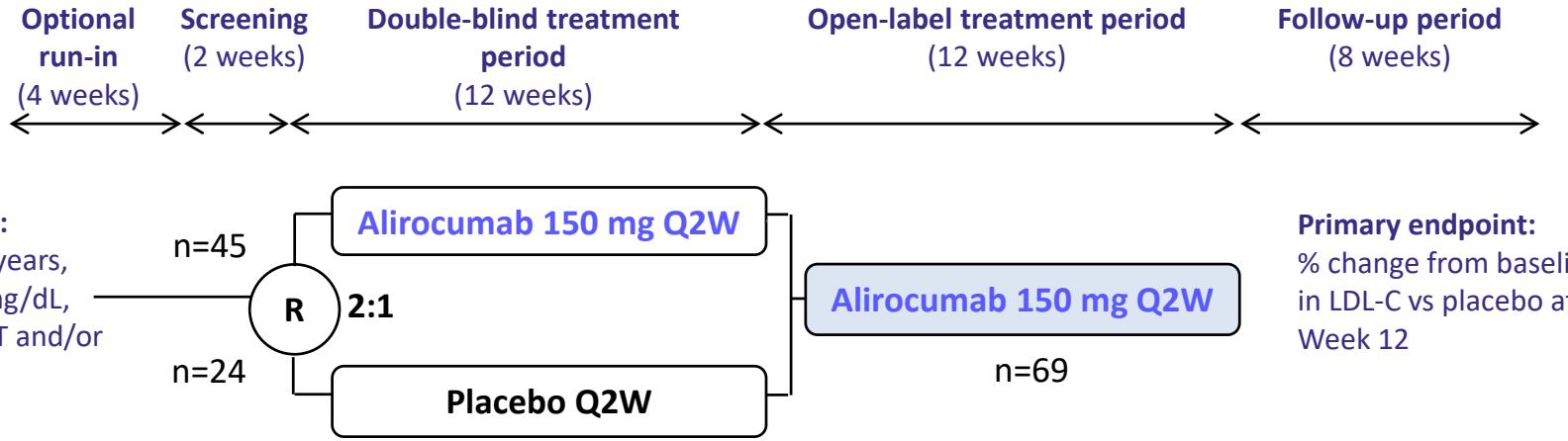
APOB, gene encoding apolipoprotein B100; HoFH, homozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; *LDLR*, gene encoding low-density lipoprotein receptor; *LDLRAP*, gene encoding low-density lipoprotein receptor adaptor protein 1; *PCSK9*, gene encoding proprotein convertase subtilisin/kexin type 9.

1. Cuchel M et al. *Eur Heart J*. 2014;35:2146-2157. 2. Hovingh GK, Goldberg AC, Moriarty PM. *J Clin Lipidol*. 2017;11:602-616. 3. Raal FJ, Hovingh GK, Catapano AL. *Atherosclerosis*. 2018;277:483-492.

Objective

- The objective of this randomized, double-blind, placebo-controlled, parallel-group, phase 3 study was to evaluate LDL-C reduction with the PCSK9 inhibitor alirocumab in adult patients with clinically or genetically diagnosed HoFH

Study Design



ClinicalTrials.gov Identifier: NCT03156621

LLT, lipid-lowering therapy; Q2W, every 2 weeks; R, randomization.

Baseline Characteristics

	Alirocumab (n=45)	Placebo (n=24)
Age, years, mean (SD)	42.3 (14.1)	45.4 (15.8)
Male, n (%)	21 (46.7)	13 (54.2)
Race, n (%)		
White	36 (80.0)	18 (75.0)
Black or African American	2 (4.4)	0
Asian	7 (15.6)	5 (20.8)
Body mass index, kg/m^2, mean (SD)	25.1 (5.4)	25.1 (5.1)
History of CHD, n (%)	21 (46.7)	9 (37.5)

CHD, coronary heart disease; SD, standard deviation.

Genotyping Results

n (%)	Alirocumab (n=45)	Placebo (n=24)
Homozygous *LDLR*[a]	18 (40.0)	10 (41.7)
Compound heterozygous *LDLR*[b]	11 (24.4)	7 (29.2)
Double heterozygous (*LDLR* + *APOB* or *LDLR* + *PCSK9*)	4 (8.9)	0
Homozygous *LDLRAP1*	1 (2.2)	0
Homozygous *PCSK9*	0	1 (4.2)
Other (heterozygous, undetermined, or no mutation identified)	11 (24.4)	6 (25.0)

[a]Both alleles carrying the same mutation. [b]Each allele carrying a different mutation.

Lipid-Lowering Therapy at Screening[a]

n (%)	Alirocumab (n=45)	Placebo (n=24)
Any statin	44 (97.8)	23 (95.8)
High-intensity statin[b]	38 (84.4)	21 (87.5)
Ezetimibe	31 (68.9)	19 (79.2)
Statin + ezetimibe	30 (66.7)	19 (79.2)
Lomitapide	7 (15.6)	3 (12.5)
Apheresis + other LLT	6 (13.3)	4 (16.7)

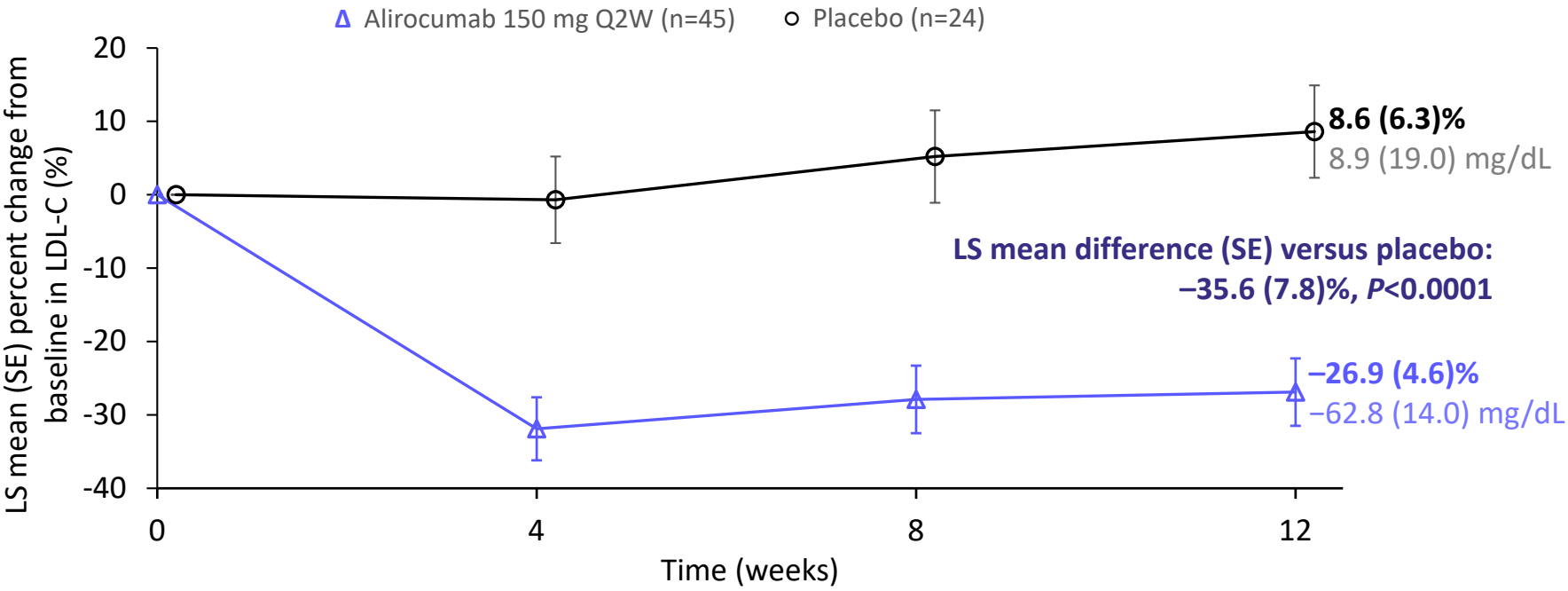
[a]A patient can be counted in several categories. [b]High-intensity statin corresponds to atorvastatin 40–80 mg daily or rosuvastatin 20–40 mg daily.

Baseline Lipids

	Alirocumab (n=45)	Placebo (n=24)
LDL-C, mg/dL, mean (SD)	295.0 (154.6)	259.6 (175.8)
Non-HDL-C, mg/dL, mean (SD)	320.5 (160.4)	282.0 (177.4)
Apolipoprotein B, mg/dL, mean (SD)	193.3 (87.6)	175.0 (95.1)
HDL-C, mg/dL, mean (SD)	43.8 (14.8)	43.2 (12.0)
Triglycerides, mg/dL, median (Q1:Q3)	110.0 (79.0:160.0)	80.5 (61.0:128.5)
Lp(a), mg/dL, median (Q1:Q3)	36.0 (10.0:68.0)	32.5 (12.0:52.5)

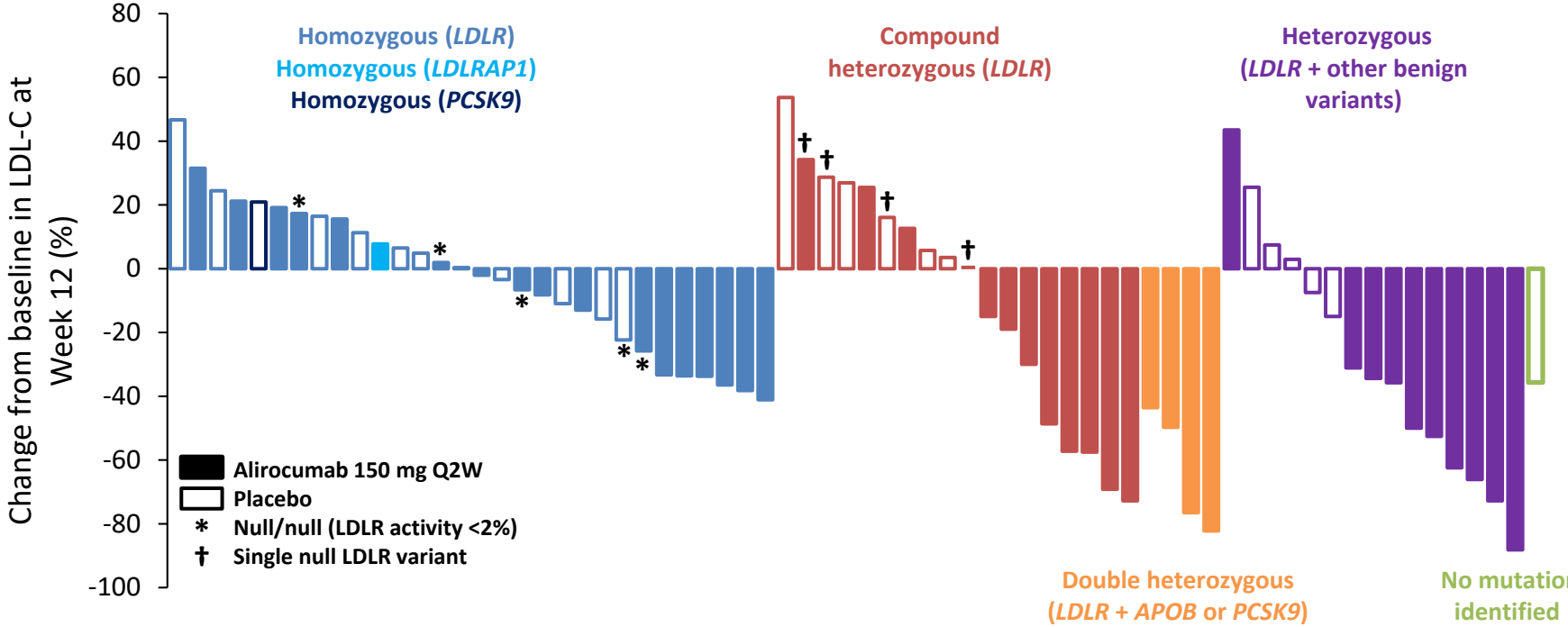
Lp(a), lipoprotein (a); non-HDL-C, non-high-density lipoprotein cholesterol.

Primary Endpoint: LDL-C % Change vs. Placebo at Week 12[a]

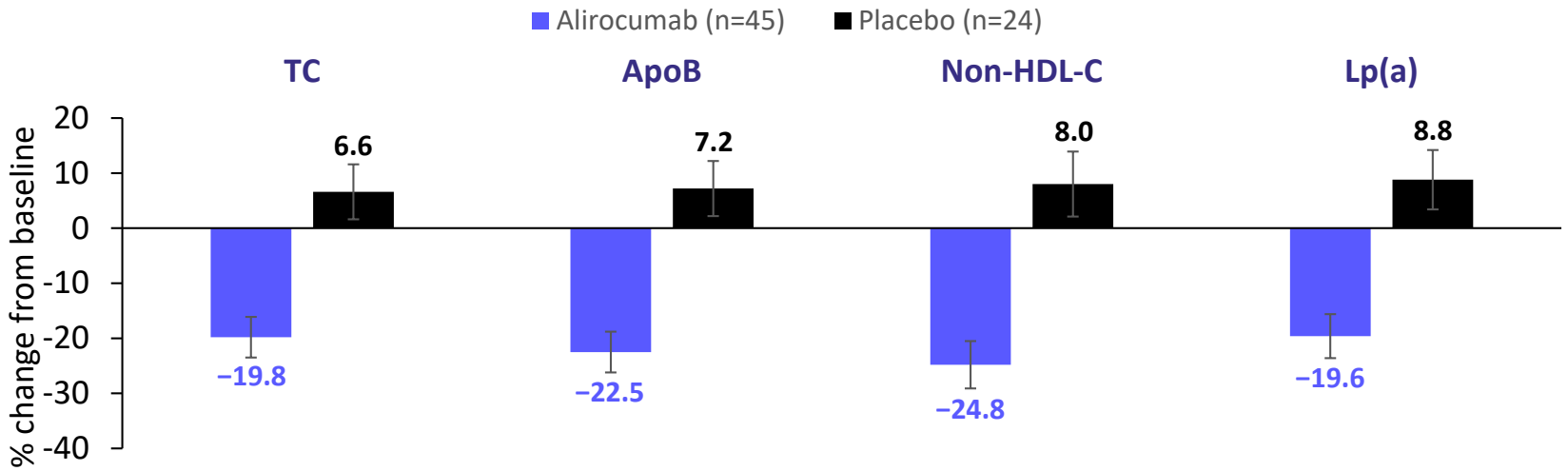


[a]Mixed effect model with repeated measures approach (intention-to-treat analysis).
LS, least squares; SE, standard error.

% Change in LDL-C at Week 12 by Genotype



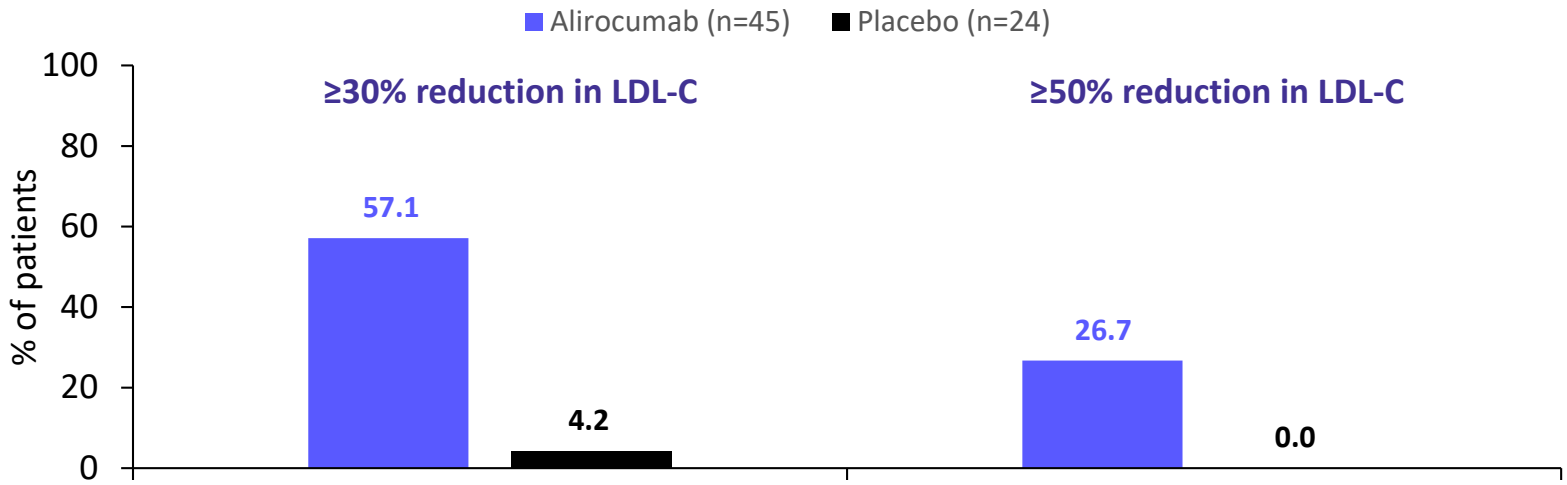
Change In Other Atherogenic Lipids at Week 12



	TC	ApoB	Non-HDL-C	Lp(a)
LS mean (SE)	**−26.5 (6.2)**	**−29.8 (6.3)**	**−32.9 (7.4)**	**−28.4[a] (6.7)**
difference vs placebo	*P*<0.0001	*P*<0.0001	*P*<0.0001	*P*<0.0001

LS means, SEs and *P*-values for lipid parameters were calculated using a mixed-effect model with repeated measures approach, except for Lp(a), which were calculated using multiple imputation followed by robust regression analysis (intention-to-treat analysis). [a]Combined estimate for adjusted mean difference. ApoB, apolipoprotein B; TC, total cholesterol.

% of Patients Who Achieved LDL-C Reductions of ≥30% and ≥50% at Week 12



	≥30% reduction in LDL-C	≥50% reduction in LDL-C
Odds ratio (95% CI) difference vs placebo	**36.5[a] (4.3 to 308.9)** *P*=0.0010	**17.7[b] (3.3 to I)** *P*=0.0017

[a]Combined estimate for odds ratio. [b]Exact odds ratio estimate. CI, confidence interval; I, infinity.

Safety: double-blind treatment period

n (%) of patients	Alirocumab (n=45)	Placebo (n=24)
Any TEAE	20 (44.4)	12 (50.0)
TEAEs of special interest		
Local injection site reaction	1 (2.2)	0
General allergic events	1 (2.2)	0
TEAEs in ≥5% of patients		
Upper respiratory tract infection	2 (4.4)	2 (8.3)
Headache	2 (4.4)	2 (8.3)
Diarrhea	3 (6.7)	0

No serious adverse events, deaths or discontinuations due to TEAEs

TEAE, treatment-emergent adverse event.

Conclusions

- This is the largest randomized controlled interventional trial in HoFH patients to date
- Treatment with alirocumab resulted in a statistically significant and clinically meaningful reduction in LDL-C at Week 12 versus placebo
- Consistent reductions in LDL-C were observed from baseline to Week 12 for all subgroups, including patients on apheresis
- Alirocumab also significantly reduced ApoB, non-HDL-C, TC and Lp(a)
- LDL-C response more variable in patients with HoFH than in other forms of hypercholesterolemia
- Alirocumab was generally well tolerated with no distinct safety differences versus placebo

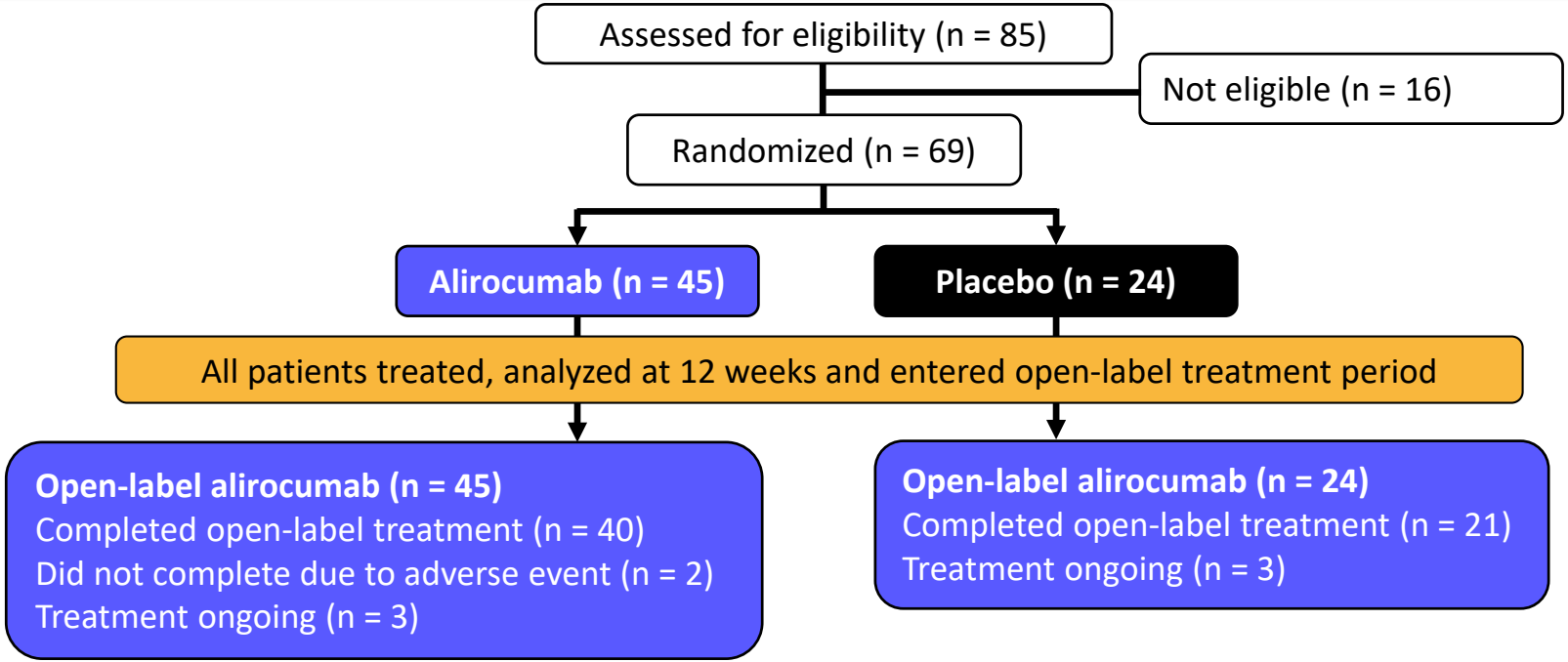
Clinical Perspective

- The degree of LDL-C reduction observed with alirocumab in patients with HoFH was consistent with that observed in previous HoFH studies with high-intensity statins and other PCSK9 inhibitors
- Substantial and significant absolute reductions in LDL-C were observed with alirocumab
- LDL-C % reduction with alirocumab is less pronounced in patients with HoFH than in other forms of hypercholesterolemia as HoFH is characterized by severely impaired LDLR function
- The addition of alirocumab on top of maximally tolerated LLT helps patients get closer to their LDL-C goal
- LDLR-independent therapies include lomitapide, and ANGPTL3 inhibitors are also in development

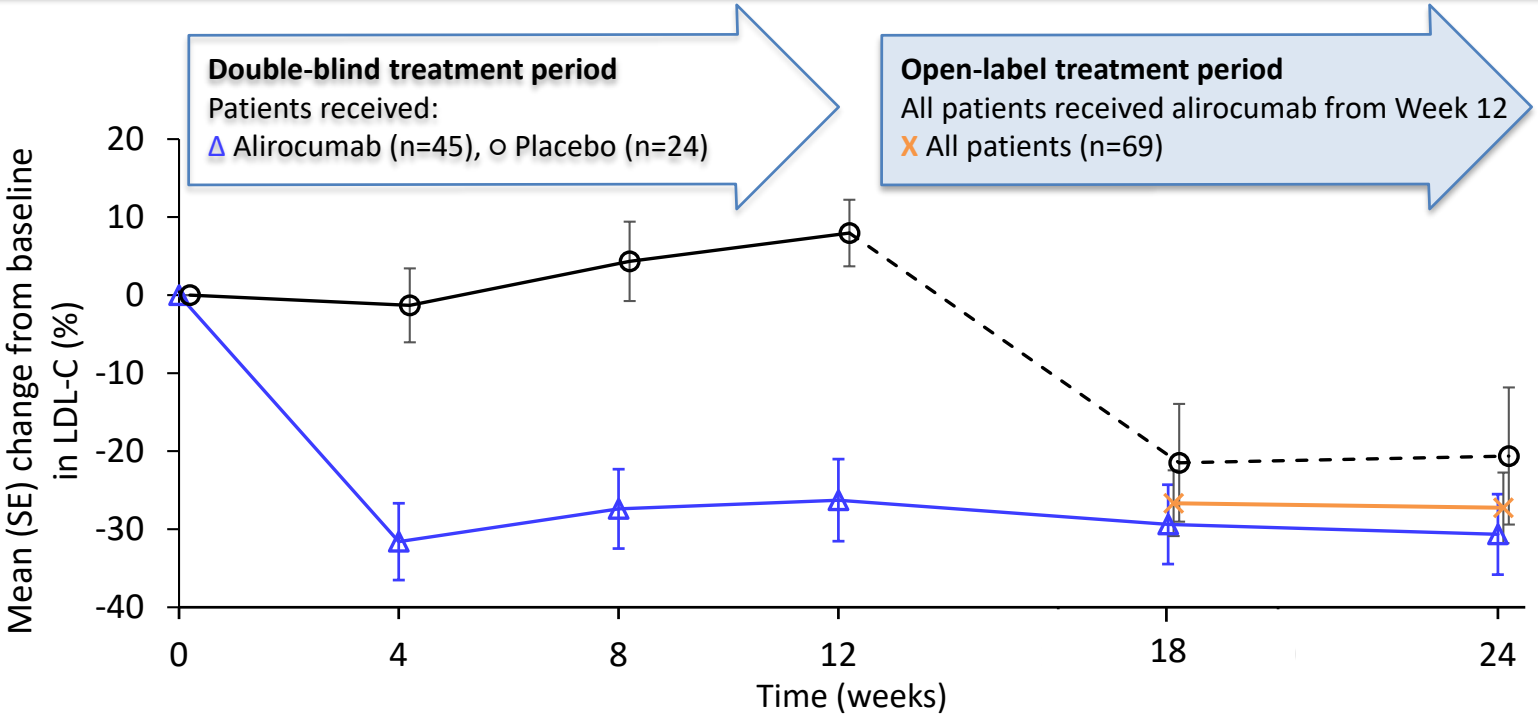
ANGPTL3, Angiopoietin-like protein 3; FH, familial hypercholetesterolemia.

Backup

Patient disposition



Percent change in LDL-C over time (interim analysis of ongoing open-label period)



Safety: open-label treatment period (interim results from ongoing open-label period)

n (%) of patients	All patients received open-label alirocumab (n=69)
Any TEAE	22 (31.9)
Treatment-emergent SAE[a]	1 (1.4)
TEAEs leading to treatment discontinuation[b]	2 (2.9)
TEAEs of special interest	
Local injection site reaction	1 (1.4)
Hepatic disorders	1 (1.4)
TEAEs in ≥5% of patients	
Nasopharyngitis	4 (5.8)

No deaths due to TEAEs

[a]SAE of arthralgia, not considered related to study treatment (patient received alirocumab during the double-blind treatment period). [b]Includes one event each of abnormal hepatic function and injection-site hypersensitivity (both patients received alirocumab during the double-blind treatment period). SAE, serious adverse event; TEAEs, treatment-emergent adverse event.