

Efficacy and Safety of Alirocumab in Patients with Hypercholesterolemia not on Statin Therapy: the ODYSSEY CHOICE II Study

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Industry Relationships and Institutional Affiliations

Author	Disclosure
Erik Stroes	Received consulting/research grant from BMS, Amgen, Merck, and Sanofi.
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Norman Lepor	Received consultant fees/honoraria from Gilead, Quest Diagnostics, and Takeda; has a role in US Medical Innovations; received research/research grants from Amarin, Amgen, Gilead, Novartis, Regeneron, and Sanofi; and is a member of speaker's bureau for Abbott, Arbor, Astellas Pharma US, Boehringer-Ingelheim, Bristol Myers Squibb, Eli Lilly/Diachi Sankyo, Gilead, Pfizer, and Vivus
Fernando Civeira	Received grants, consulting fees, and/or honoraria from Amgen, Merck, and Sanofi
Daniel Gaudet	Received consultant/honoraria fees from Amgen, Catabasis, Chiesi, Novartis, Regeneron, and Sanofi-Aventis; and research/research grants from Aegerion Pharmaceuticals, Amgen, Astra Zeneca, Catabasis, Eli Lilly, Genzyme Corporation, ISIS Pharmaceuticals, Merck, Novartis, Pfizer, Regeneron, and Sanofi-Aventis
Gerald F Watts	Received research grants and advisory board fees from Sanofi, Amgen and MSD Australia
Garen Manvelian	Employee of and a stockholder in Regeneron
Guillaume Lecorps, Marie T Baccara-Dinet	Employees of and stockholders in Sanofi

Background

- ◆ **Alirocumab, a fully human monoclonal antibody to PCSK9, reduces LDL-C by 47–62% when dosed 75 or 150 mg Q2W¹⁻⁴**
- ◆ **Statins increase PCSK9 levels, potentially reducing alirocumab duration of effect⁵, whereas fenofibrate and ezetimibe have no impact on PCSK9 levels⁶**
- ◆ **150mg Q4W alone or on background of non-statin LLTs may be convenient and effective for patients^{6,7}**
 - **Alirocumab 150 mg Q4W in Phase I: LDL-C –57% as monotherapy⁷**
 - **Alirocumab 150 mg Q4W in Phase II: LDL-C –28.9% on background statin⁸**

LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; Q4W, every 4 weeks

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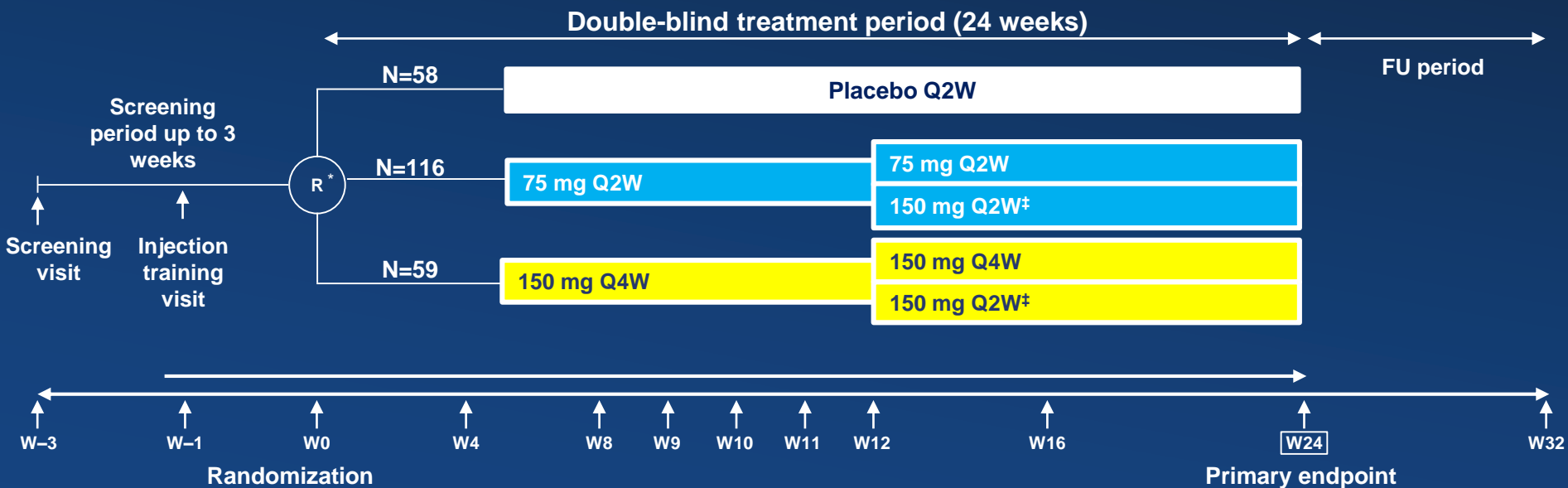
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ODYSSEY CHOICE II

Study Design

LDL-C-lowering effect of
alirocumab 150 mg Q4W (potential dose increase to 150 mg Q2W)
 in patients **not** receiving statins

- ◆ **Hypercholesterolemic patients receiving ezetimibe, fenofibrate, or diet with:**
 - No statin due to statin-associated muscle symptoms with moderate to very high CV risk
 - No statin with moderate CV risk



CV, cardiovascular; SC, subcutaneous.

*Randomization error occurred, changing randomization ratio from 1:1:2 to 1:2:1 (placebo : alicumab 75 Q2W : alicumab 150 Q4W).

‡Dose regimen changed at W12 if LDL-C at W8 ≥ 100 mg/dL or ≥ 70 mg/dL, depending on CV risk, or if LDL-C reduction $< 30\%$ from baseline at W8.

Methods

- ◆ Randomization to alirocumab 150 mg Q4W, 75 mg Q2W or placebo
- ◆ Week 12: dose increase if LDL-C at Week 8 not at goal
 - ≥ 70 mg/dL for patients very high CV risk
 - ≥ 100 mg/dL for those with moderate or high CV risk
 - if $\geq 30\%$ reduction in LDL-C from baseline was not achieved
- ◆ Primary efficacy endpoint:
 - % change in calculated LDL-C from baseline to Week 24 (ITT analysis)
- ◆ Secondary efficacy endpoints included:
 - % change in Lp(a), non-HDL-C and apo B from baseline to Week 24
 - % change in calculated LDL-C from baseline to averaged Weeks 9-12
- ◆ Optional device questionnaire completed by the patient during the study
- ◆ Safety parameters were assessed throughout the study

Baseline characteristics

Randomized population	(N=233)		
Treatment group	Placebo (n=58)	Alirocumab 75mg Q2W* (n=116)	Alirocumab 150mg Q4W* (n=59)
Age, mean (SD), years	63.1 (10.7)	62.5 (9.9)	64.2 (10.0)
Male, %	53.4	59.5	50.8
Race, white, %	96.6	93.1	93.2
BMI \geq 30 kg/m ² , %	35.1	39.7	28.8
HeFH, %	8.6	12.9	15.3
Statin intolerance, %	87.9	91.4	89.8
Diabetes mellitus (type 2), %	27.6	20.7	20.3
Any LLT other than statins, %	70.7	70.7	71.2
Ezetimibe	60.3	60.3	59.3
Fenofibrate	5.2	10.3	8.5
Diet alone	34.5	30.2	33.9
CVD risk, %:			
Very high / High	75.9	76.7	78.0
Moderate	24.1	23.3	22.0

◆ Baseline characteristics were balanced between treatment groups

*With potential W12 increase to 150 mg Q2W.

BMI, body mass index; HeFH, heterozygous familial hypercholesterolemia; SD, standard deviation.

Baseline lipid parameters

Randomized population	(N=233)		
Treatment group	Placebo (n=58)	Alirocumab 75mg Q2W* (n=116)	Alirocumab 150mg Q4W* (n=59)
LDL-C mean (SE), mg/dL	158.5 (47.3)	154.5 (44.6)	163.9 (69.1)
Lp(a), median (Q1:Q3), mg/dL	10.5 (4.0 : 31.0)	16.0 (5.0 : 46.0)	19.0 (5.0 : 41.0)
Apo B, mean (SE), mg/dL	120.3 (27.6)	120.2 (27.1)	126.5 (44.8)
Non-HDL-C, mean (SE), mg/dL	191.9 (51.0)	188.0 (49.9)	195.9 (76.4)
Fasting TG, median (Q1:Q3), mg/dL	154.5 (105.0 : 218.0)	147.5 (107.0 : 225.0)	145.0 (102.0 : 211.0)
HDL-C, mean (SD), mg/dL	52.8 (16.6)	51.1 (15.1)	54.9 (13.4)

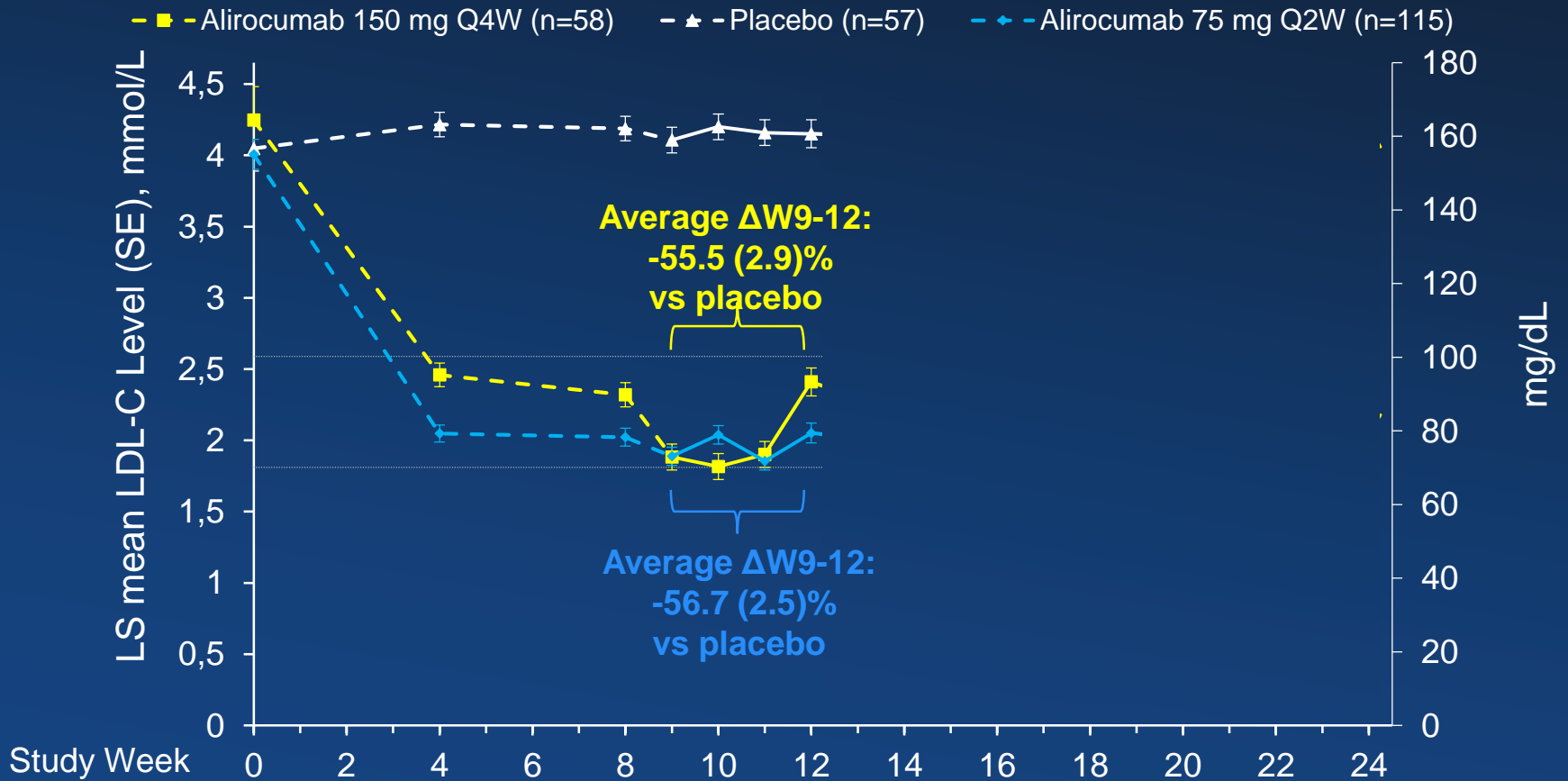
- ◆ Lipid parameters were balanced between treatment groups

*With potential W12 increase to 150 mg Q2W.

Apo B, apolipoprotein B; Lp(a), lipoprotein (a); HDL, high-density lipoprotein.

Mean calculated LDL-C

(N=230); ITT analysis

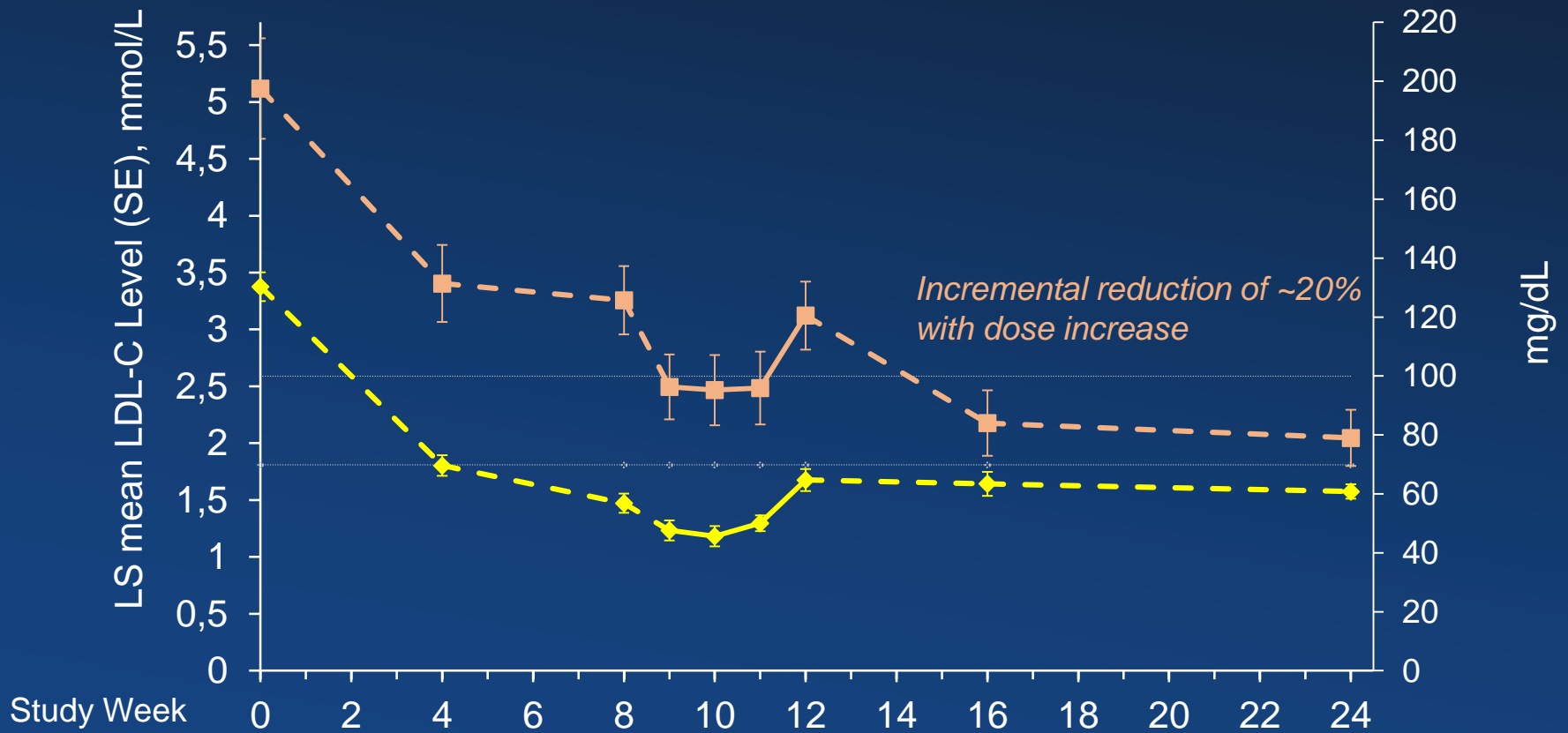


Alirocumab 75 mg Q2W:
 Alirocumab 150mg Q4W:

36.0% increased to 150mg Q2W
 49.1% increased to 150mg Q2W

Impact of Dose Increase

- ◆ Patients remaining on alirocumab 150 mg Q4W (50.9%; n=27)
- Patients increased to alirocumab 150 mg Q2W (49.1%; n=26)

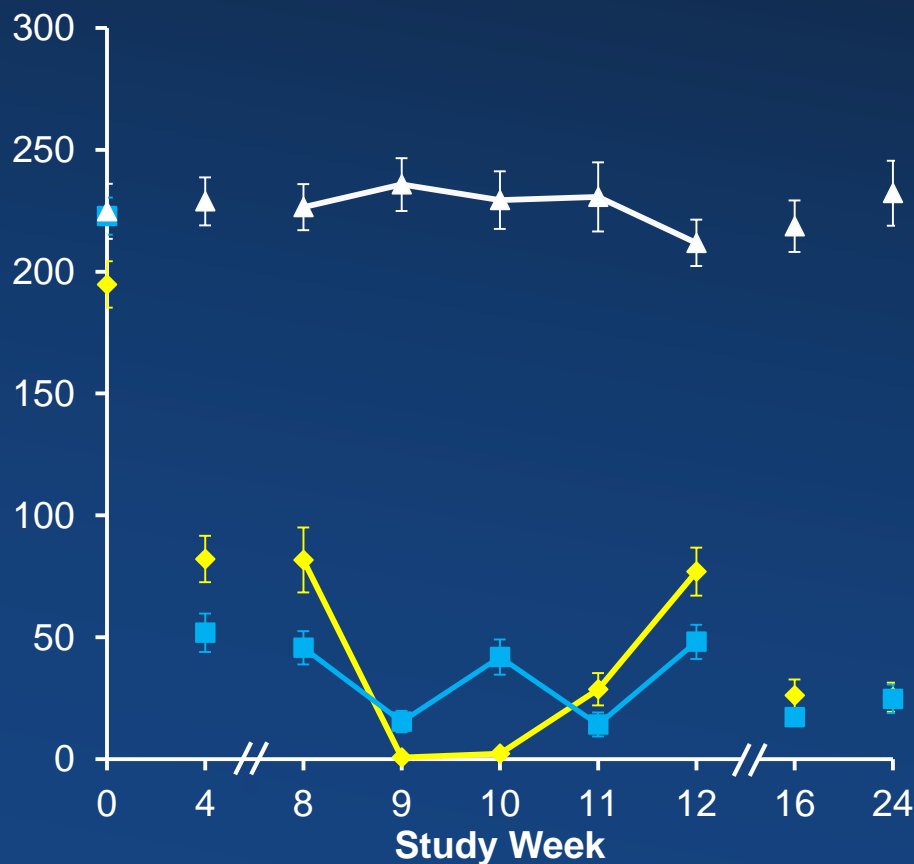


Free PCSK9 Levels in Alirocumab-Treated Patients

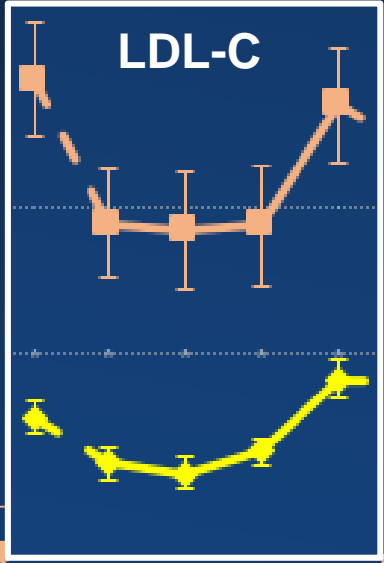
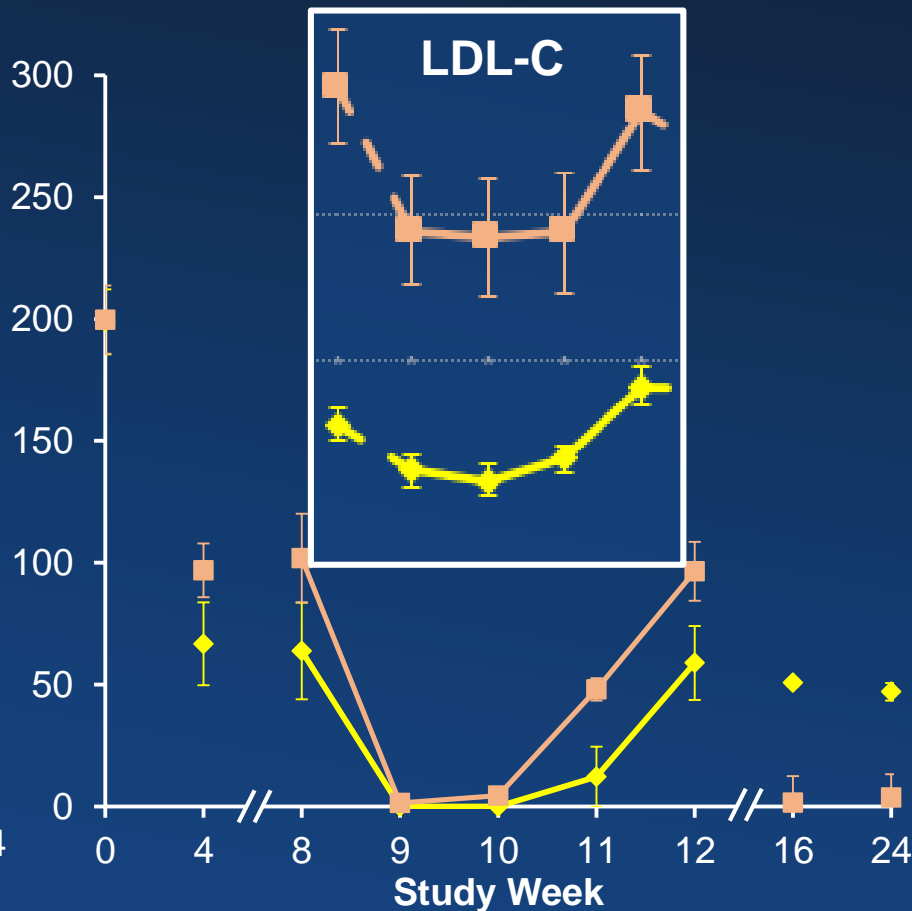
- ◆ Alirocumab 150mg Q4W ▲ Placebo
- Alirocumab 75mg Q2W

- ◆ Remaining on alirocumab 150 mg Q4W (50.9%)
- Increased to alirocumab 150 mg Q2W (49.1%)

Mean (SE) free PCSK9, ng/mL

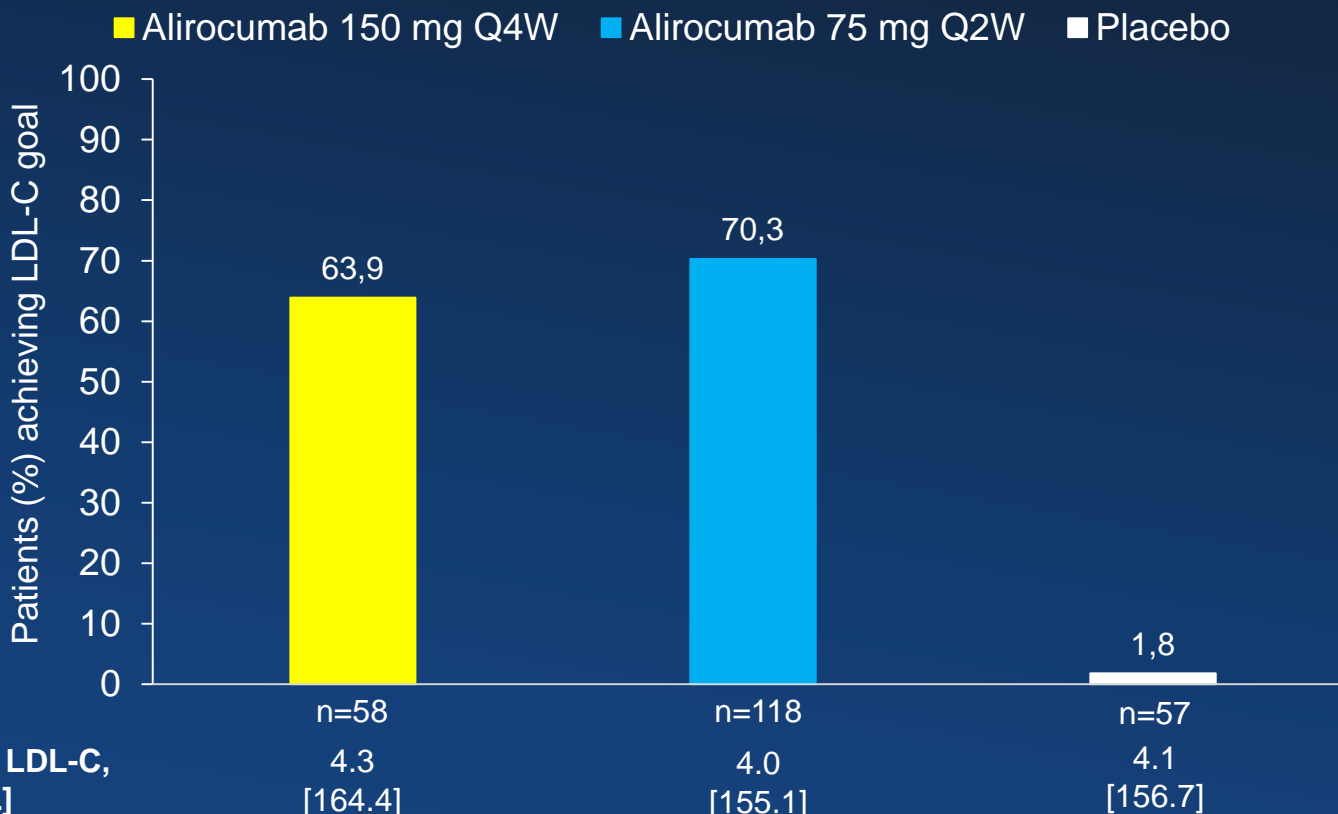


Mean (SE) free PCSK9, ng/mL



Goal achievement of Alirocumab-Treated Patients at Week 24

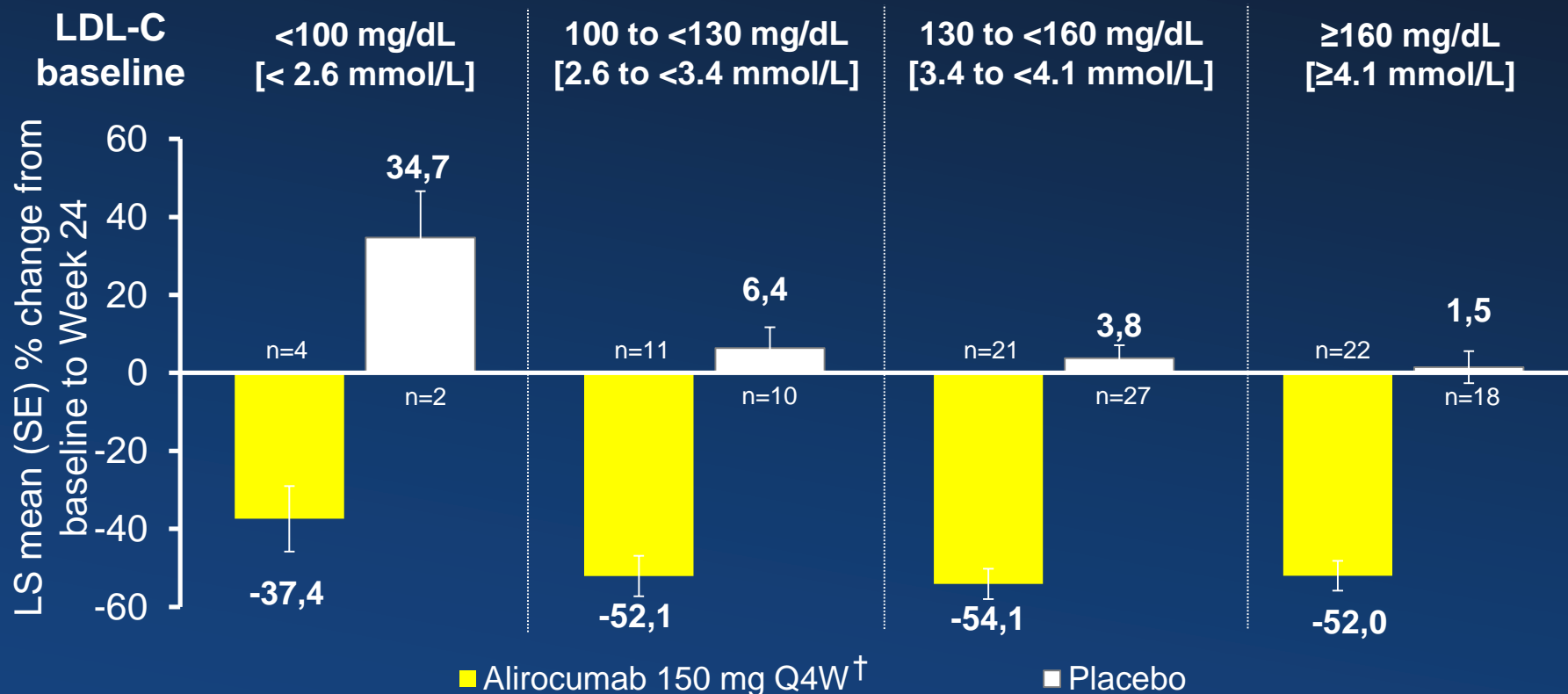
LDL-C goals <70 mg/dL for very high CV risk or <100 mg/dL for moderate/high CV risk
ITT analysis



***P*<0.0001 vs placebo**

***Alirocumab 75 mg Q2W:* 36.0% increased to 150mg Q2W**
***Alirocumab 150mg Q4W:* 49.1% increased to 150mg Q2W**

Impact of LDL-C Baseline Level on Mean Percent LDL-C Change

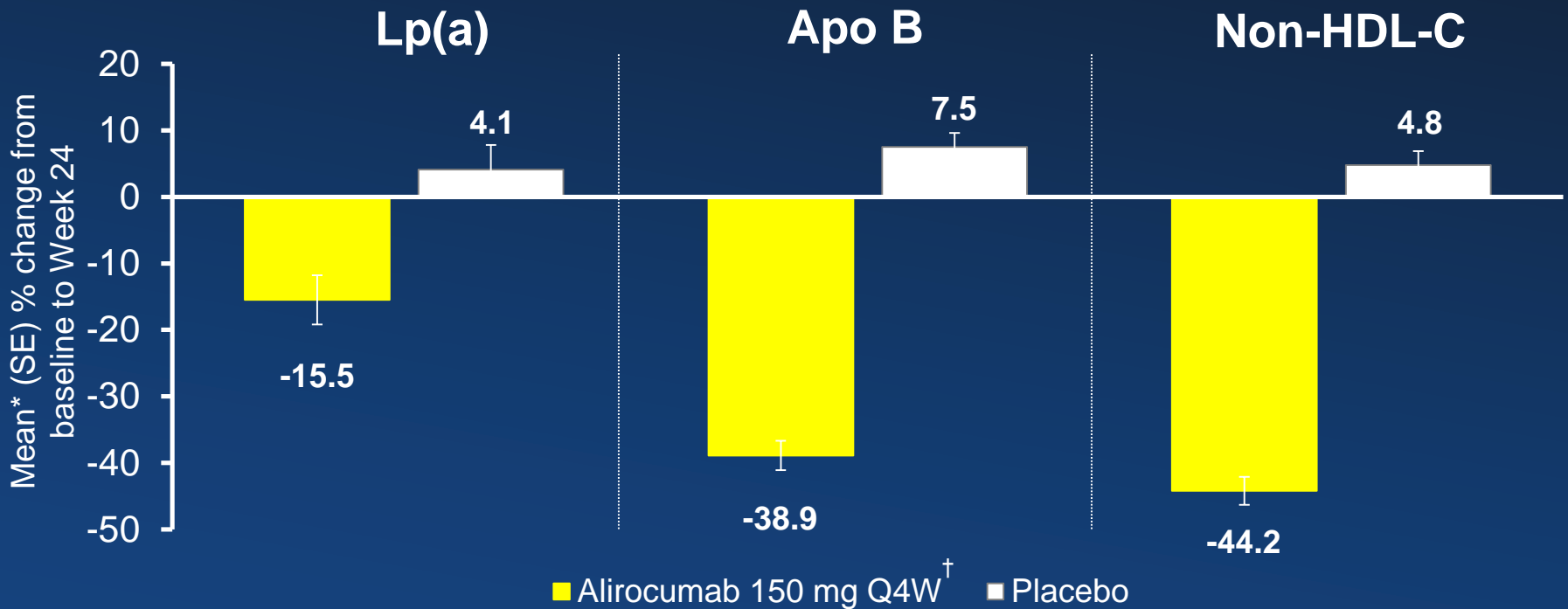


ITT analysis; all $P < 0.0001$ versus placebo

[†]With potential W12 increase to 150 mg Q2W, based on W8 LDL-C levels.

LS, least squares.

Secondary Efficacy Endpoints at Week 24



ITT analysis; all $P < 0.0001$ versus placebo

*Least-square means for Apo B and non-HDL-C from mixed effects model with repeated measures; combined estimate for mean for Lp(a) analyzed with multiple imputation followed by robust regression.

[†]With potential W12 increase to 150 mg Q2W, based on W8 LDL-C levels

Safety Summary

Safety population	No statin (N=231)		
	Placebo (n=58)	Alirocumab 75mg Q2W* (n=115)	Alirocumab 150mg Q4W* (n=58)
n, %			
Subjects with any TEAEs	37 (63.8)	84 (73.0)	45 (77.6)
Subject with any treatment-emergent SAE	4 (6.9)	6 (5.2)	7 (12.1)
Patients with any TEAE leading to discontinuation	2 (3.4)	2 (1.7)	4 (6.9)
TEAEs leading to death	0	0	0
Safety terms of interest			
General allergic reactions (CMQ)	4 (6.9)	5 (4.3)	6 (10.3)
Pruritus (PT)	2 (3.4)	1 (0.9)	1 (1.7)
General allergic serious TEAE (CMQ)	0	0	0
Neurocognitive disorders (CMQ)	0	1 (0.9)	1 (1.7)
ALT >3 x ULN (PCSA)	0/58	1/115 (0.9)	0/58

*With potential W12 increase to 150 mg Q2W

CMQ, Custom MedDRA Query; PCSA, Potentially Clinically Significant Abnormalities; PT, preferred term; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Most Frequent TEAEs

TEAEs similar except for injection site reactions

Safety population	No statin (N=231)		
n (%)	Placebo (n=58)	Alirocumab 75mg Q2W* (n=115)	Alirocumab 150mg Q4W* (n=58)
Infections and infestations	13 (22.4)	32 (27.8)	22 (37.9)
Nasopharyngitis	3 (5.2)	10 (8.7)	5 (8.6)
Urinary tract infection	1 (1.7)	4 (3.5)	4 (6.9)
Upper respiratory tract infection	4 (6.9)	4 (3.5)	3 (5.2)
Nervous system disorders	8 (13.8)	17 (14.8)	12 (20.7)
Headache	3 (5.2)	10 (8.7)	5 (8.6)
Dizziness	4 (6.9)	1 (0.9)	4 (6.9)
Gastrointestinal disorders	8 (13.8)	20 (17.4)	10 (17.2)
Nausea	2 (3.4)	6 (5.2)	3 (5.2)
Diarrhea	3 (5.2)	5 (4.3)	1 (1.7)
Skin and subcutaneous tissue disorders	6 (10.3)	9 (7.8)	8 (13.8)
Rash	0	1 (0.9)	3 (5.2)
Musculoskeletal and connective tissue disorders	12 (20.7)	33 (28.7)	14 (24.1)
Arthralgia	2 (3.4)	7 (6.1)	7 (12.1)
Muscle spasm	0	8 (7.0)	3 (5.2)
Myalgia	3 (5.2)	7 (6.1)	3 (5.2)
Pain in extremity	1 (1.7)	4 (3.5)	3 (5.2)
Back pain	0	6 (5.2)	2 (3.4)
General disorders and administration site conditions	8 (13.8)	20 (17.4)	12 (20.7)
Injection site reaction	0	4 (3.5)	8 (13.8)
Fatigue	0	5 (4.3)	4 (6.9)
Injury, poisoning and procedural complications	6 (10.3)	12 (10.4)	5 (8.6)
Fall	2 (3.4)	6 (5.2)	0

*With potential W12 increase to 150 mg Q2W

Injection Site Reactions

Safety population	No statin (N=231)		
n	Placebo (n=58)	Alirocumab 75mg Q2W* (n=115)	Alirocumab 150mg Q4W* (n=58)
Injection site reaction	0	4	8
Mild intensity	0	3	8
Moderate intensity	0	1	0
Severe intensity	0	0	0
Discontinuation due to injection site reaction	0	0	0

On the basis of the rate of ISR per double-blind injection, the ISR rate in this study is not different from those observed in other ODYSSEY studies

Overall experience in performing self-injection at home has been rated with 6 or 7 (7 = extremely satisfied) by 93% of the patients

*With potential W12 increase to 150 mg Q2W.

ISR, injection site reaction.

Summary

- ◆ **Alirocumab 150 mg Q4W (potential increase to 150 mg Q2W) in patients with hypercholesterolemia unable to use/not using a statin**
 - Demonstrated a mean LDL-C reduction of 56.4% versus placebo
 - Achieved target LDL-C in 63.9% of patients
- ◆ **50% of patients required dose increase to achieve target LDL-C,**
 - Providing an incremental 20% reduction of mean LDL-C
 - Patients requiring increase had higher baseline LDL-C levels (>160mg/dl)
- ◆ **Adverse events were generally similar across the study groups, except for injection site reactions**
- ◆ **Easy to use in home setting**
- ◆ **Individualized dosing of Alirocumab allows for robust and safe lowering of LDL-C, with increase dependent primarily on**
 - Baseline LDL-C
 - Baseline CV-risk



Q&A