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.
John R Guyton	Received consulting/honoraria fees from Amgen Inc., ARMCO, Novella, and Regeneron, and research/research grants from Amarin, Amgen Inc., Regeneron, and Sanofi-Aventis.
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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 borad 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 Q2W[1-4]**
- **Statins increase PCSK9 levels, potentially reducing alirocumab duration of effect[5], whereas fenofibrate and ezetimibe have no impact on PCSK9 levels[6]**
- **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 monotherapy[7]**
  - **Alirocumab 150 mg Q4W in Phase II: LDL-C –28.9% on background statin[8]**

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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2. Cannon CP et al. *Eur Heart J*. 2015; 36:1186-94
3. Robinson JG et al. *N Eng J Med*. 2015;372:1489–1499
4. Kereiakes DJ et al. *Am Heart J*. 2015 [in press].
5. McKenney JM, et al. EAS 2013, Lyon, France.
6. Rey J, et al. *ACC* 2014 Abstract 1183/131.
7. Stein EA, et al. *N Engl J Med*. 2012;366:1108–1118.
8. Stein EA, et al. Lancet. 2012;380:29–36.

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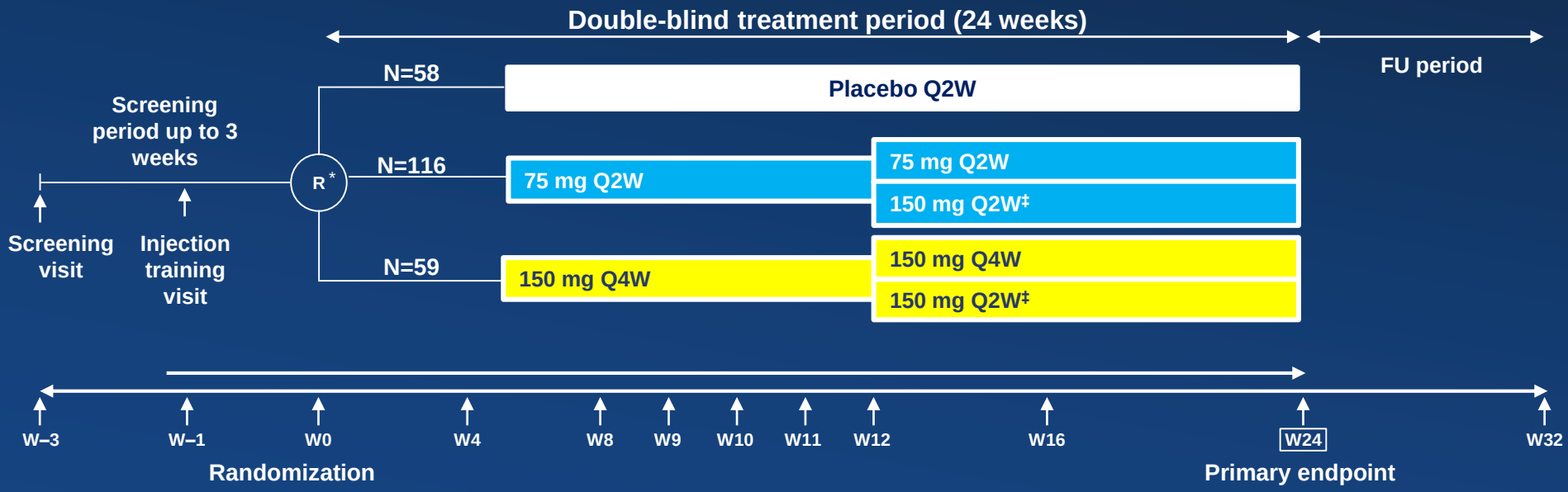
Study Design

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 : alirocumab 75 Q2W : alirocumab 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 ≥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 ≥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

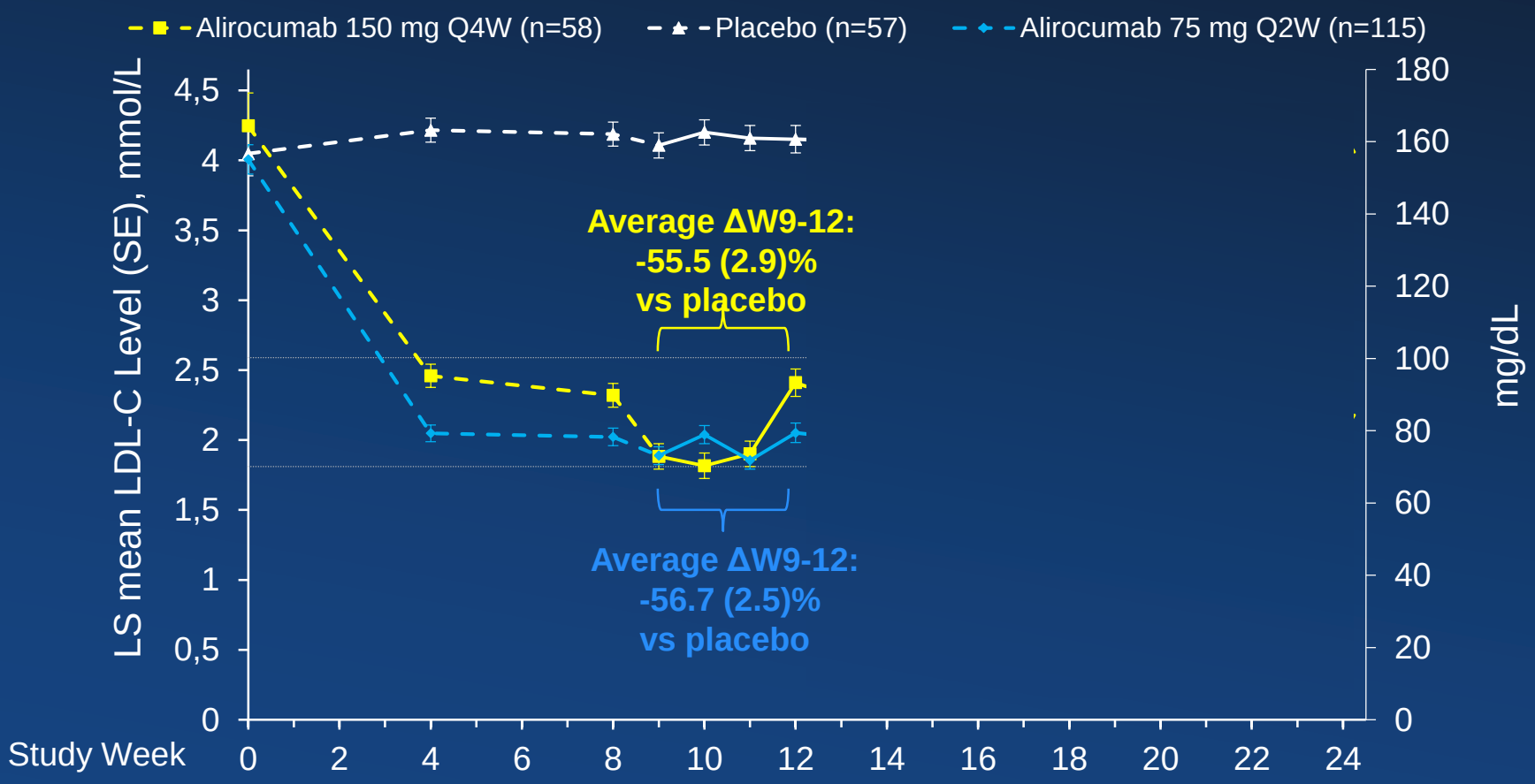
Randomized population	(N=233)		
Treatment group	Placebo (n=58)	Alirocumab 75mg Q2W* (n=116)	Alirocumab 150mg Q4W* (n=59)
LDL-C mean (SE), mg/dL	158.5 (47.3)	154.5 (44.6)	163.9 (69.1)
Lp(a), median (Q1:Q3), mg/dL	10.5 (4.0 : 31.0)	16.0 (5.0 : 46.0)	19.0 (5.0 : 41.0)
Apo B, mean (SE), mg/dL	120.3 (27.6)	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

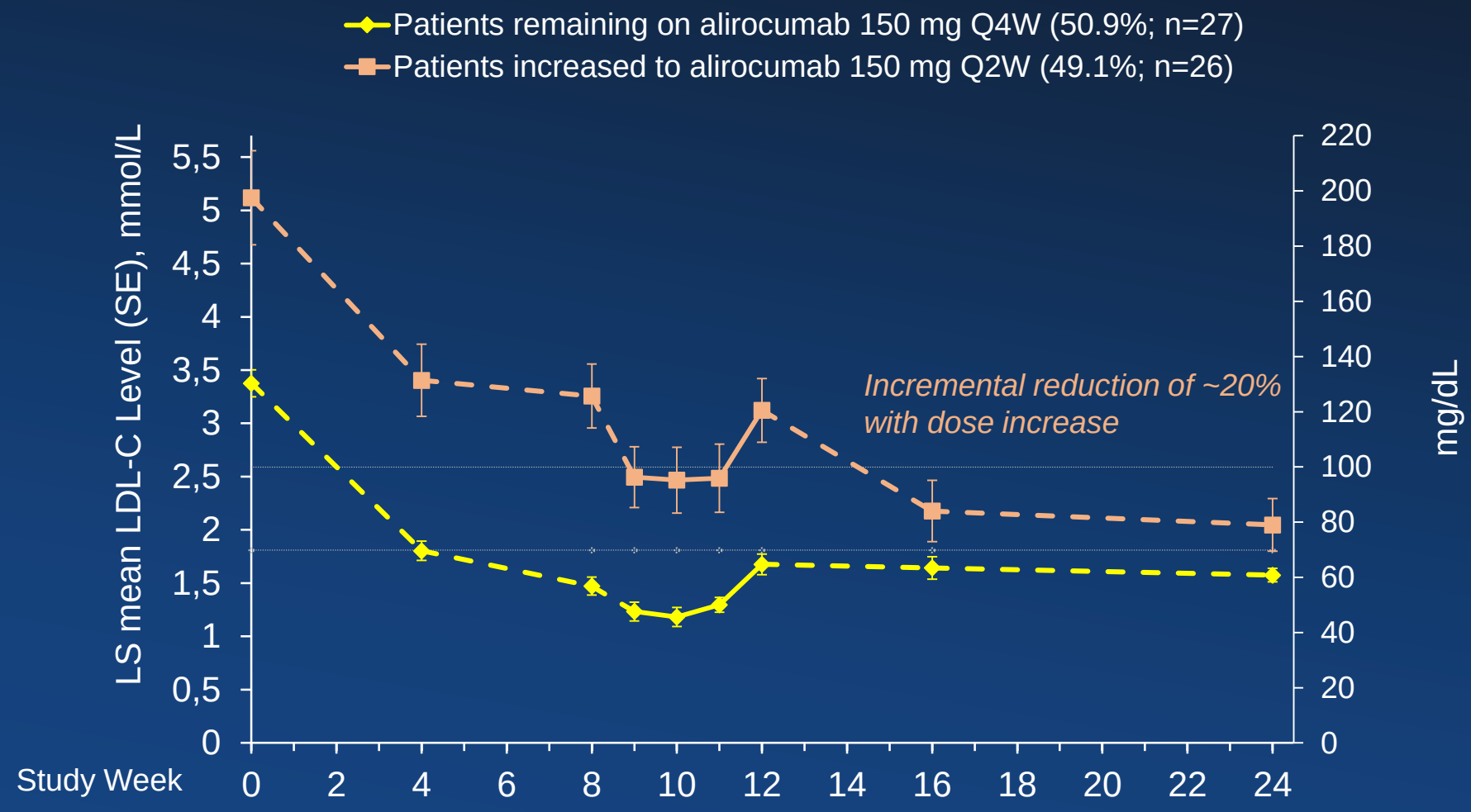
(N=230); ITT analysis



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

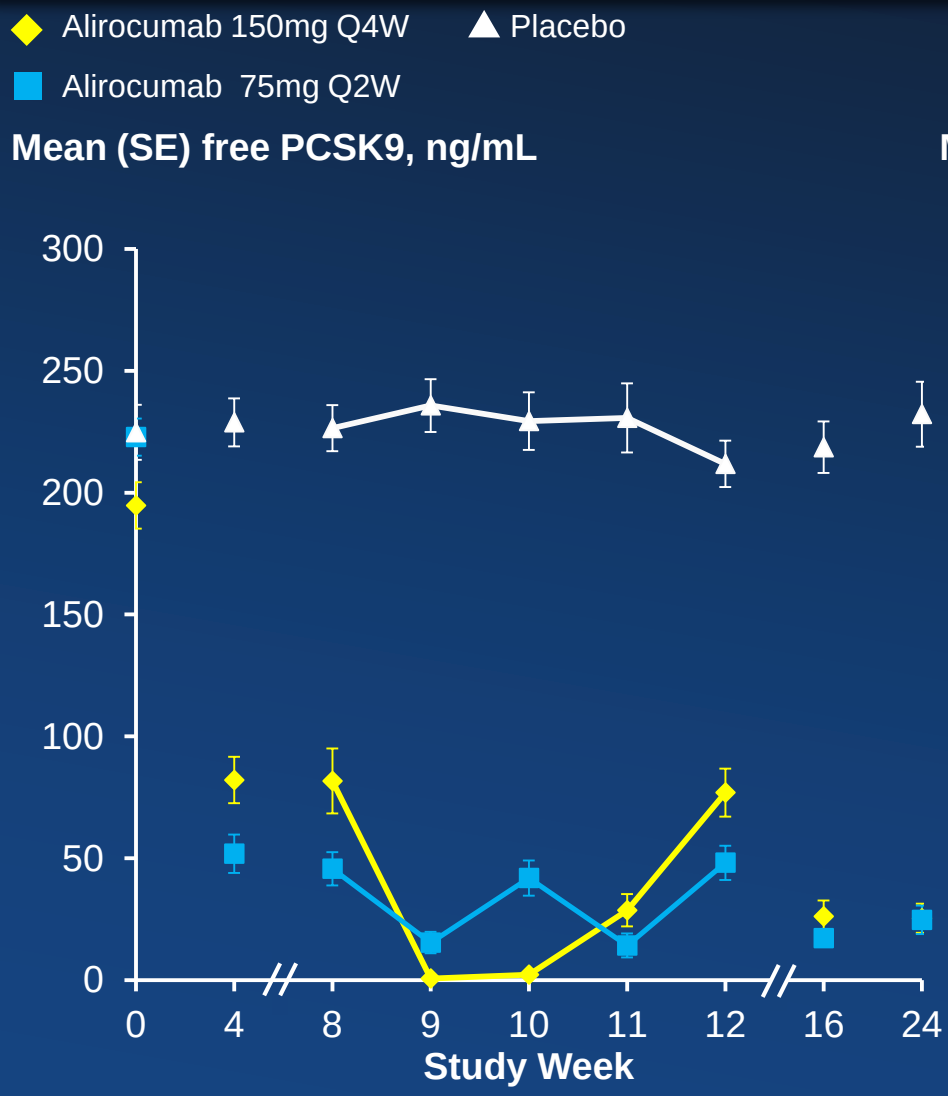
Alirocumab 150mg Q4W: **49.1%** increased to 150mg Q2W

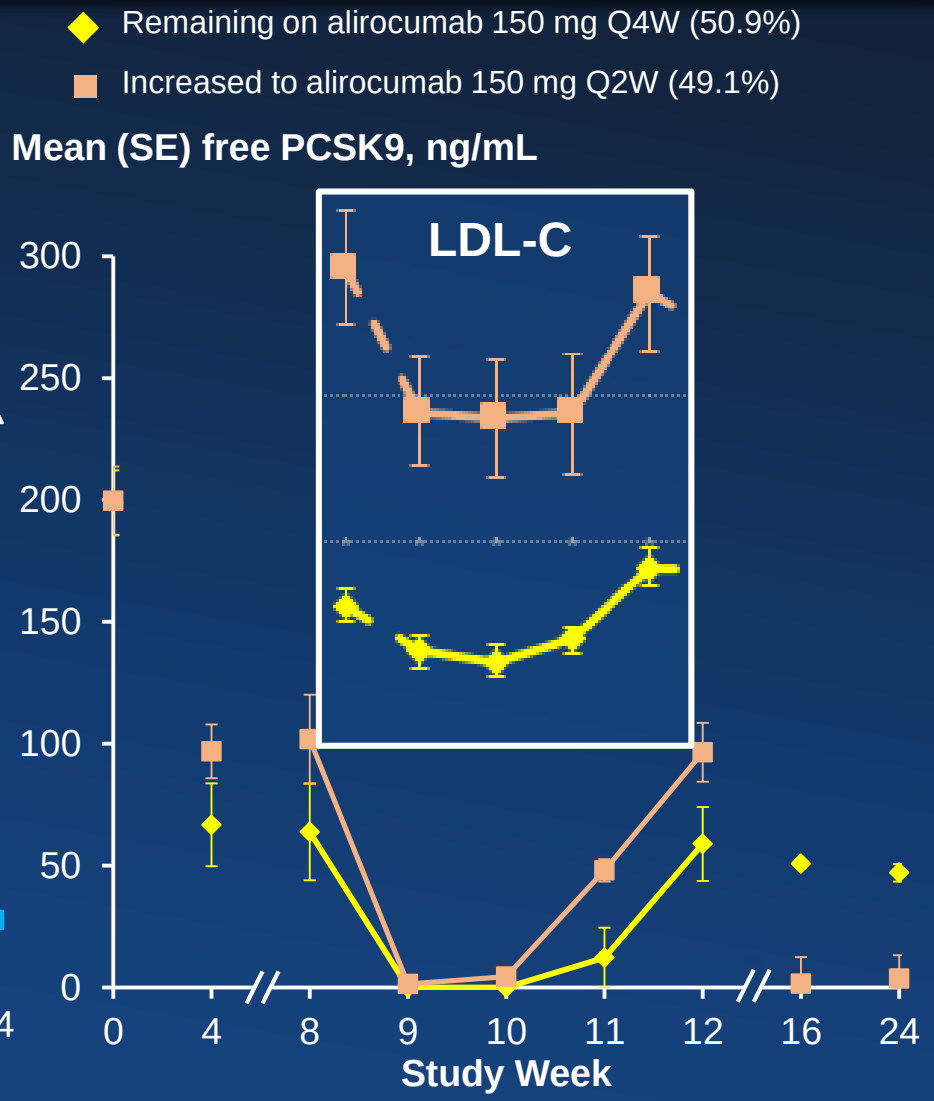
Impact of Dose Increase



Patients with dose increase at Week 12 and had at least one subsequent injection.

Free PCSK9 Levels in Alirocumab-Treated Patients

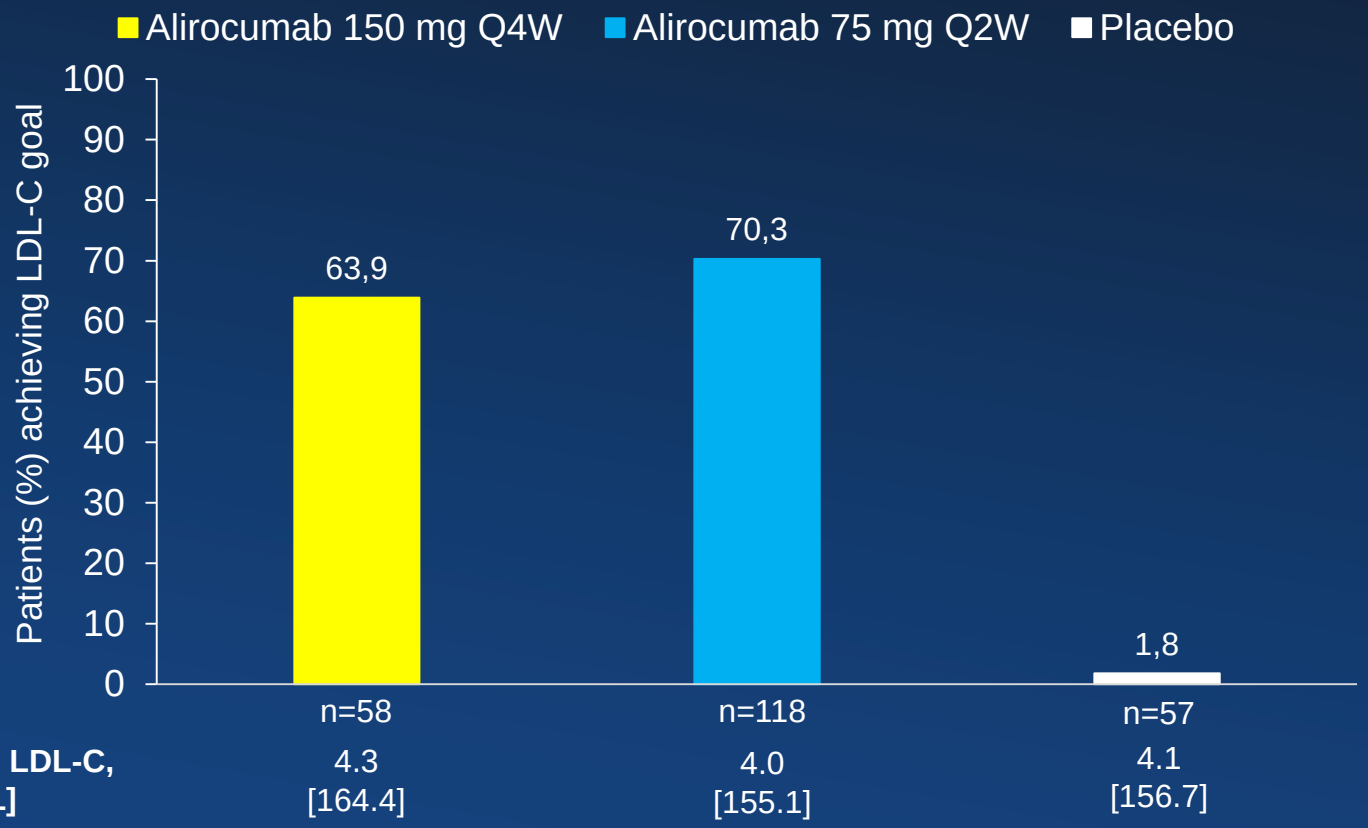




Patients of the safety population who had at least one non-missing sample during double-blind treatment period.

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**

LDL-C goals analyzed using multiple imputation followed by logistical regression.

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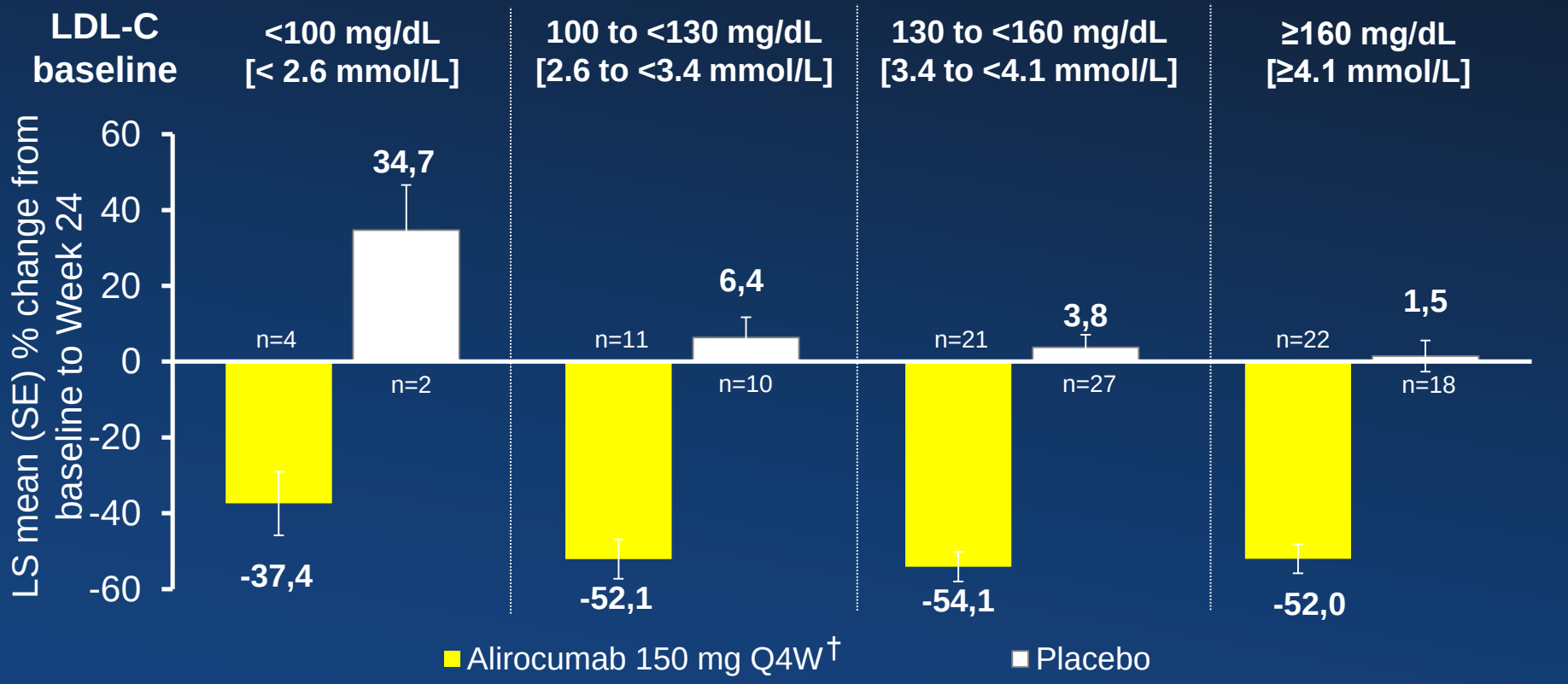
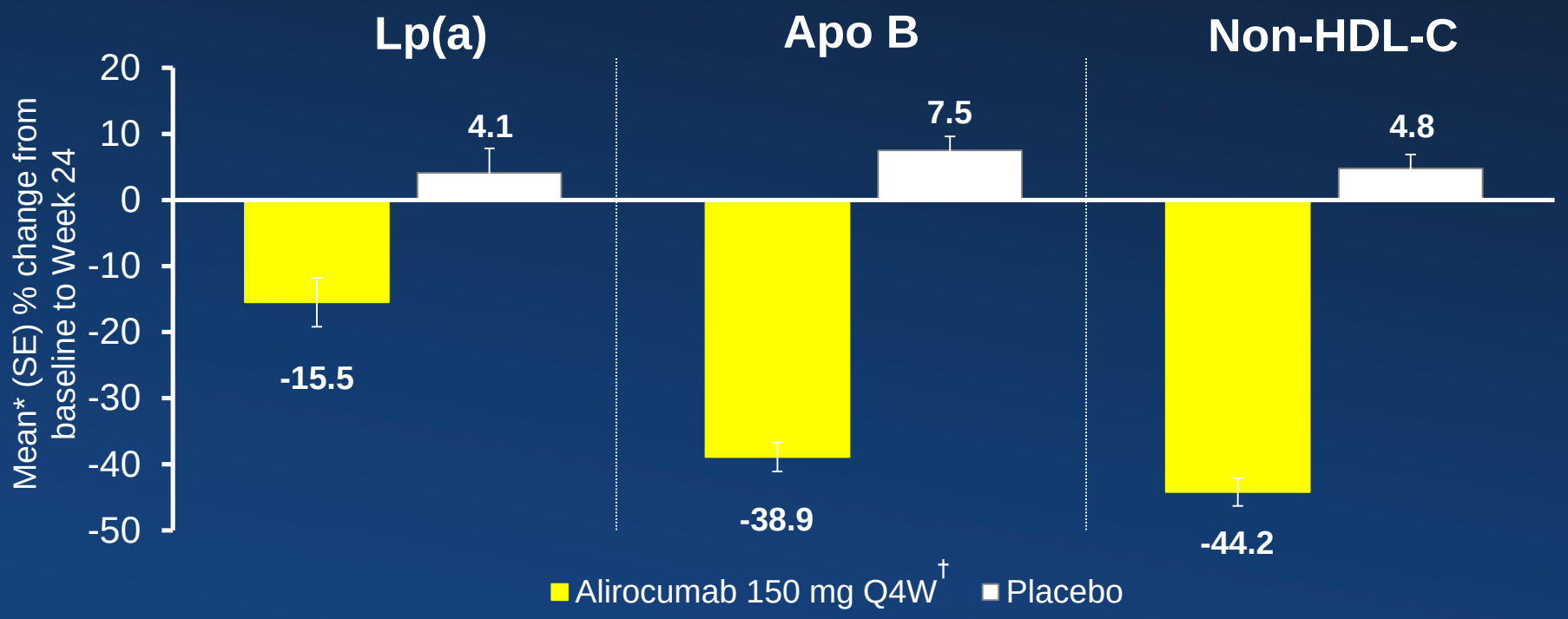
Impact of LDL-C Baseline Level on Mean Percent LDL-C Change



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

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Safety Summary

Safety population	No statin (N=231)		
n, %	Placebo (n=58)	Alirocumab 75mg Q2W* (n=115)	Alirocumab 150mg Q4W* (n=58)
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

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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

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