A Randomized Phase 3 Trial Evaluating Alirocumab Every Four Weeks Dosing as Add-on to Statin or as Monotherapy: ODYSSEY CHOICE I

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Industry Relationships and Institutional Affiliations

Author	Disclosure
Eli M Roth	Employee of a company that has received research funds and has received consulting fees from Regeneron, Sanofi, and Amgen
Daniel Rader	Received consultant/advisory board fees from Sanofi
Patrick M Moriarty	Received research grants from Pfizer, Catabasis, Espirion, B. Braun, Kaneka, Amgen, Kowa, Lilly, Novartis, Sanofi, Regeneron, and Genzyme; received honoraria from Amarin and Kowa; is a consultant for Regeneron, Duke Clinical Research Institute, Lilly, Catabasis, B. Braun, Kaneka, and Genzyme
Jean Bergeron	Received consultant/advisory board fees from Amgen (Canada) and Sanofi (Canada), and gave educational lecture to GPs for Merck (Canada) and Valeant
Gisle Langslet	Received consultant/advisory board fees from Amgen, Sanofi-Aventis, and Janssen Pharmaceuticals
Marie T Baccara-Dinet	Employee of and stockholder in Sanofi
Jian Zhao	Employee of Regeneron (contractor)
Garen Manvelian	Employee of and stockholder in Regeneron

Background

- A high proportion of adult patients with hypercholesterolemia at risk of cardiovascular disease (CVD) fail to reach their individual LDL-C goals despite standard-of-care with statins and other LLTs[1,2]
- Additionally, many patients in need of LLTs are not on statin therapy or receive a sub-optimal dose of statins, mainly due to statin intolerance[3]
- Alirocumab, a fully human monoclonal antibody to PCSK9, has been demonstrated to reduce LDL-C levels by 47–62% using doses of 75 or 150 mg Q2W either on a background of statins, other LLTs, or as monotherapy[4–8]
  - In a prior Phase 2 study, alirocumab 300 mg Q4W reduced LDL-C by 48% when added to statin therapy in a patient population with LDL-C levels ≥100 mg/dL (2.6 mmol/L)[9]
- Q4W dosing may be a convenient, effective option for some patients[8,9]

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

1. Hess G, et al. *Curr Med Res Opin*. 2014;10:1–14.
2. Huijgen R, et al. *PLoS One*. 2010;5:e9220.
3. Rosenson RS, et al. *J Clin Lipodol*. 2014;8:S58–71.
4. Roth EM, et al. *Int J Cardiol*. 2014 Sep;176:55–61.
5. Cannon CP, et al. *Eur Heart J.* 2015;36(19):1186–1194.
6. Robinson JG, et al. *N Eng J Med*. 2015;372:1489–1499 .
7. Kereiakes DJ, et al. *Am Heart J.* 2015 [in press].
8. Rey J, et al. *ACC* 2014 Abstract 1183/131.
9. McKenney JM, et al. *J Am Coll Cardiol.* 2012; 59(25):2344–2353.

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ODYSSEY CHOICE Studies Rationale

- Magnitude and duration of LDL-C reductions with alirocumab are related to dose and its elimination following administration[1-3]
- Alirocumab elimination occurs through binding to its antibody target (PCSK9) in a process known as target-mediated clearance[4]
- Statins are known to increase PCSK9 levels, and when co-administered with alirocumab appear to reduce its duration of effect via enhanced target-mediated elimination[4]
- Fenofibrate and ezetimibe are associated with limited or no impact on alirocumab duration of effect[5]
- CHOICE Studies evaluated potential starting regimens:
  - CHOICE I: Alirocumab 300 mg Q4W, in patients on concomitant statin therapy and patients who are not
  - CHOICE II: Alirocumab 150 mg Q4W, when used as monotherapy or on background of ezetimibe or fenofibrate

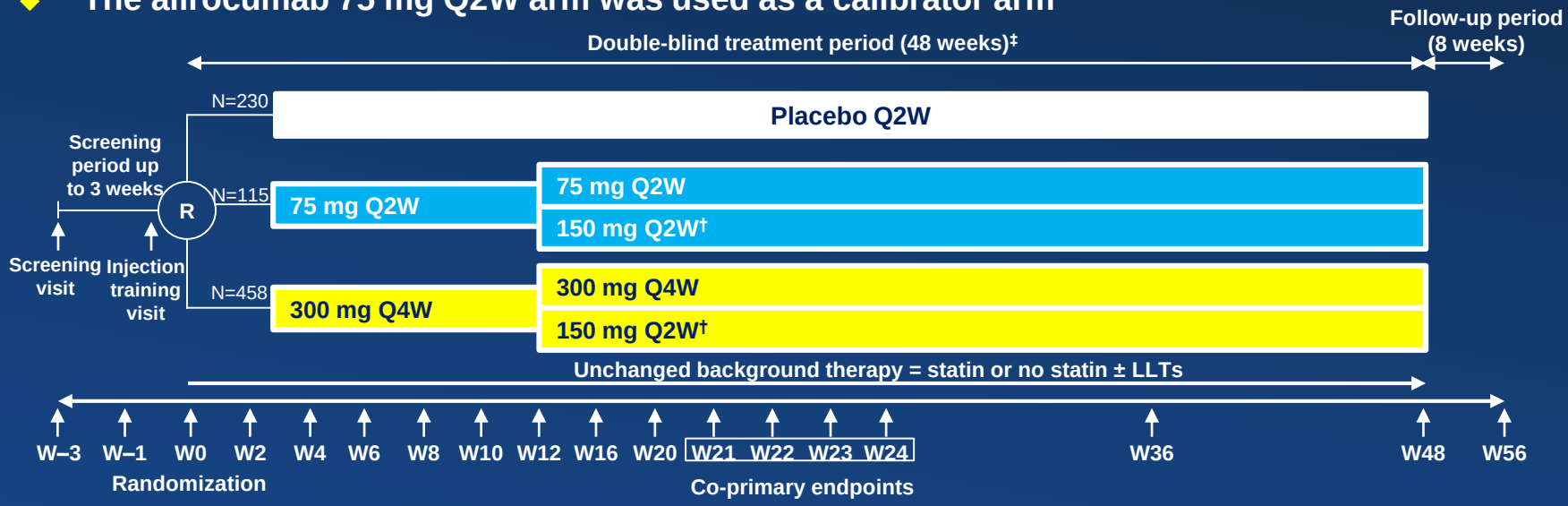
LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; Q4W, every 4 weeks.

1. Stein EA, et al. N Engl J Med. 2012;366:1108–1118.
2. McKenney JM, et al. J Am Coll Cardiol. 2012; 59(25):2344–2353.
3. Stein EA, et al. Lancet. 2012;380:29–36.
4. McKenney JM, et al. EAS 2013, Lyon, France.
5. Rey J, et al. ACC 2014 Abstract 1183/131.

ODYSSEY CHOICE I: Study Design

ODYSSEY CHOICE I (NCT01926782) studied the efficacy and safety of **alirocumab 300 mg Q4W with potential regimen adjustment to 150 mg Q2W** ± concomitant statin and other LLT

- **Patients: inadequately controlled hypercholesterolemia and**
  - **Moderate to very-high CV risk and receiving maximally tolerated statin OR**
  - **Moderate CV risk and not receiving statin OR**
  - **Moderate to very-high CV risk and statin intolerance**
- **Two-thirds of the study population was planned to be on statin**
- **The alirocumab 75 mg Q2W arm was used as a calibrator arm**



†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 was <30% from baseline at W8; ‡The blind was maintained in all patients, including those receiving dose adjustment; the study treatment was two 1 mL subcutaneous injections Q2W.

Methods

- Patients were randomized to alirocumab 300 mg Q4W, alirocumab 75 mg Q2W, or placebo
  - At Week 12, the dose regimen was changed (using a blinded process) in patients who either did not achieve their predetermined treatment goal (<70 mg/dL for patients with very high CV risk or <100 mg/dL for those with moderate or high CV risk) or did not have ≥30% reduction in LDL-C from baseline at Week 8
- Co-primary efficacy endpoints
  - % change in calculated LDL-C from baseline to Week 24 (ITT analysis)
  - % change in calculated LDL-C from baseline to averaged LDL-C over Weeks 21–24 (ITT analysis)
- Secondary efficacy endpoints included assessment of % change in other lipid parameters including Lp(a), non-HDL-C, and Apo B from baseline to Week 24
- Safety parameters were assessed throughout the study
- Results are shown separately for the no statin and statin groups

Patient Characteristics at Baseline (Randomized Population)

	No statin group (N=256)			Statin group (N=547)		
Treatment group	Placebo (n=73)	Alirocumab 75 mg Q2W (n=37)	Alirocumab 300 mg Q4W (n=146)	Placebo (n=157)	Alirocumab 75 mg Q2W (n=78)	Alirocumab 300 mg Q4W (n=312)
Age, mean (SD), years	59.4 (10.2)	59.3 (11.3)	59.2 (10.8)	61.6 (9.7)	60.7 (9.1)	61.6 (10.0)
Male, %	54.8	37.8	45.2	64.3	65.4	60.9
Race, white, %	84.9	86.5	84.2	87.3	87.2	89.4
BMI ≥30 kg/m^2,%	63.0	43.2	50.7	47.8	48.7	51.6
HeFH, %	1.4	0	1.4	7.6	7.7	8.3
Patients on atorvastatin, rosuvastatin or simvastatin, %	0	0	1.4	100	100	99.4
Any LLT other than statins, %	45.2	32.4	45.2	32.5	28.2	40.1
Diabetes mellitus (type 2), %	23.3	10.8	19.2	31.8	28.2	30.8
CVD risk, %: Very high High Moderate	 27.4 20.5 52.1	 18.9 21.6 59.5	 22.6 15.1 62.3	 65.0 19.7 15.3	 70.5 15.4 14.1	 65.4 21.2 13.5

- **Baseline characteristics were generally similar and balanced across the treatment groups within the no statin and statin cohorts**
  - **Of the patients not receiving statin therapy, 42.2% (n=108/256) were not receiving statin due to statin intolerance.**

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

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Lipid Parameters at Baseline (Randomized Population)

	No statin group (N=256)			Statin group (N=547)		
Treatment group	Placebo (n=73)	Alirocumab 75 mg Q2W (n=37)	Alirocumab 300 mg Q4W (n=146)	Placebo (n=157)	Alirocumab 75 mg Q2W (n=78)	Alirocumab 300 mg Q4W (n=312)
LDL-C (calculated), mean (SD), mg/dL [mmol/L]	131.0 (30.4) [3.4 (0.8)]	148.4 (36.8) [3.8 (1.0)]	146.1 (33.5) [3.8 (0.9)]	112.1 (37.3) [2.9 (1.0)]	114.9 (36.0) [3.0 (0.9)]	112.4 (32.8) [2.9 (0.9)]
Lp(a), median (Q1:Q3), mg/dL	12.5 (6.0:39.0)	13.0 (6.0:45.0)	15.0 (7.0:42.0)	25.5 (7.0:73.0)	28.0 (9.5:58.0)	27.0 (7.0:65.0)
Apo B, mean (SD), mg/dL	109.8 (21.6)	115.9 (24.7)	117.3 (22.7)	96.0 (24.3)	99.6 (25.0)	96.6 (21.3)
Non-HDL-C, mean (SD), mg/dL	162.8 (34.7)	175.7 (40.8)	176.5 (38.0)	140.0 (41.9)	146.4 (42.3)	141.3 (35.4)
Fasting TG, median (Q1:Q3), mg/dL	139.0 (101.0:201.0)	120.0 (86.0:172.0)	136.5 (93.0:190.0)	125.0 (93.0:176.0)	132.0 (99.0:171.0)	128.0 (95.0:173.0)
HDL-C, mean (SD), mg/dL	49.8 (15.4)	58.2 (15.0)	52.4 (16.4)	50.5 (15.7)	48.9 (14.1)	50.1 (14.8)

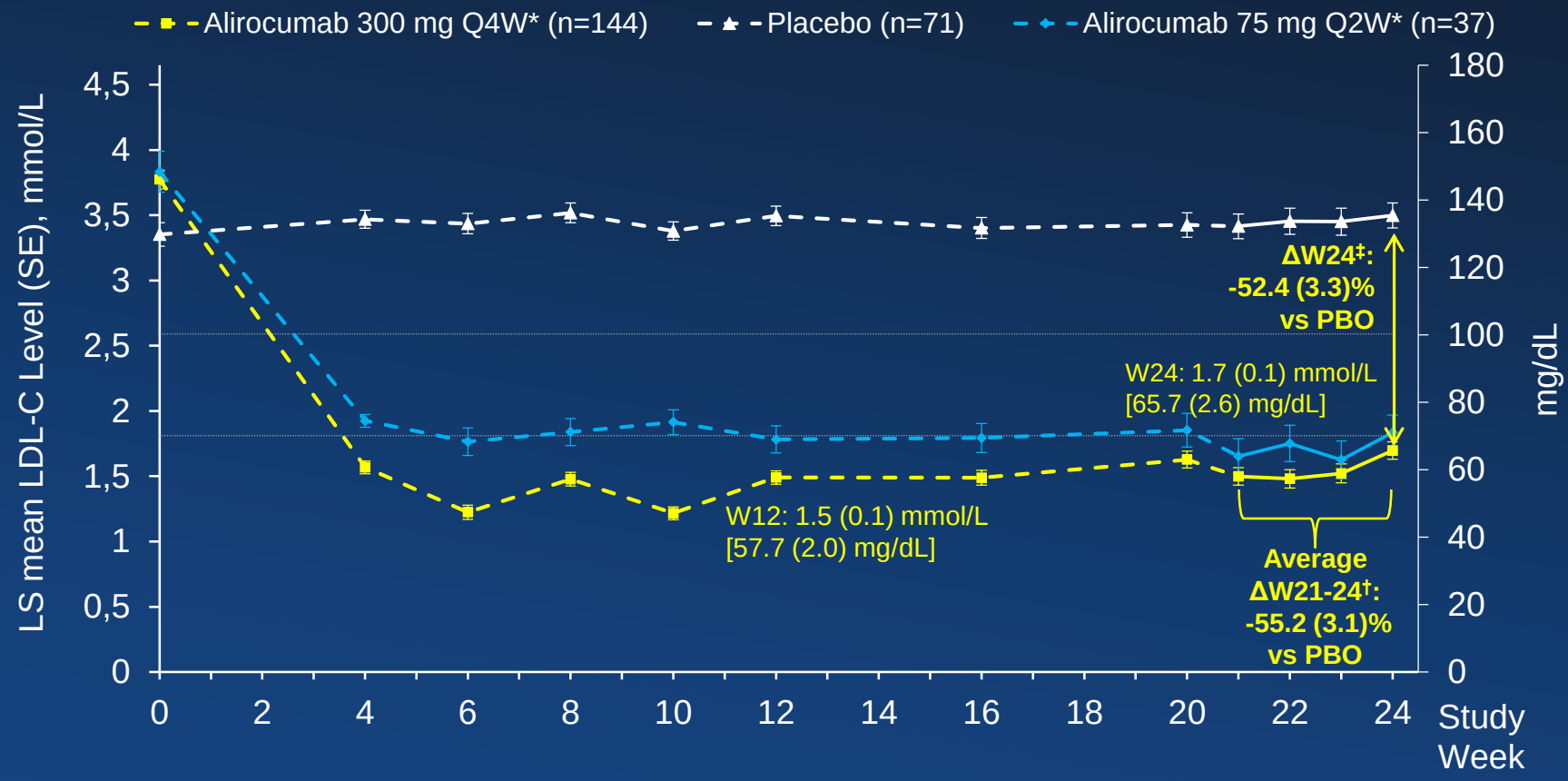
- **Lipid parameters were generally similar and balanced across the treatment groups within the no statin and statin cohorts**

Co-primary Endpoints:

% change in calculated LDL-C from baseline to (a) W24 and (b) averaged W21-24

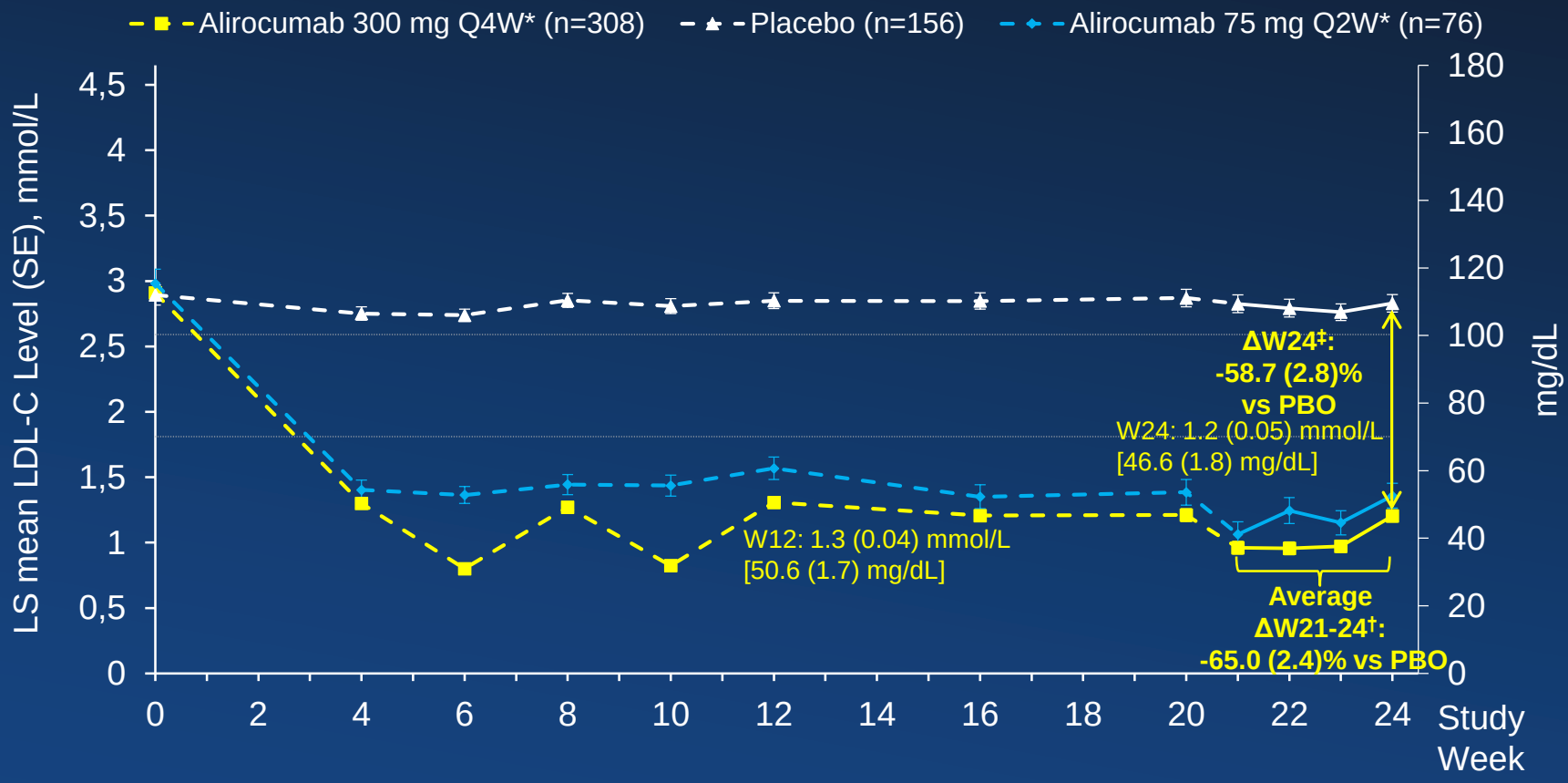
	No statin group			Statin group		
Treatment group	**Placebo (n=71)**	**Alirocumab 75mg Q2W (n=37)**	**Alirocumab 300mg Q4W (n=144)**	**Placebo (n=156)**	**Alirocumab 75mg Q2W (n=76)**	**Alirocumab 300mg Q4W (n=308)**
LS mean (SE) % change in LDL-C baseline to W24	-0.3 (2.7)	-50.2 (3.7)	-52.7 (1.9)	-0.1 (2.3)	-51.6 (3.3)	-58.8 (1.6)
LS mean (SE) difference vs placebo		-49.8 (4.6)	-52.4 (3.3)		-51.5 (4.0)	-58.7 (2.8)
P value vs placebo		<0.0001	<0.0001		<0.0001	<0.0001
LS mean (SE) % change in LDL-C baseline to averaged W21-24	-1.6 (2.6)	-54.0 (3.6)	-56.9 (1.8)	-0.8 (2.0)	-57.9 (2.8)	-65.8 (1.4)
LS mean (SE) difference vs placebo		-52.4 (4.4)	-55.2 (3.1)		-57.1 (3.4)	-65.0 (2.4)
P value vs placebo		<0.0001	<0.0001		<0.0001	<0.0001

Mean Calculated LDL-C Levels (ITT Population)
No Statin Group



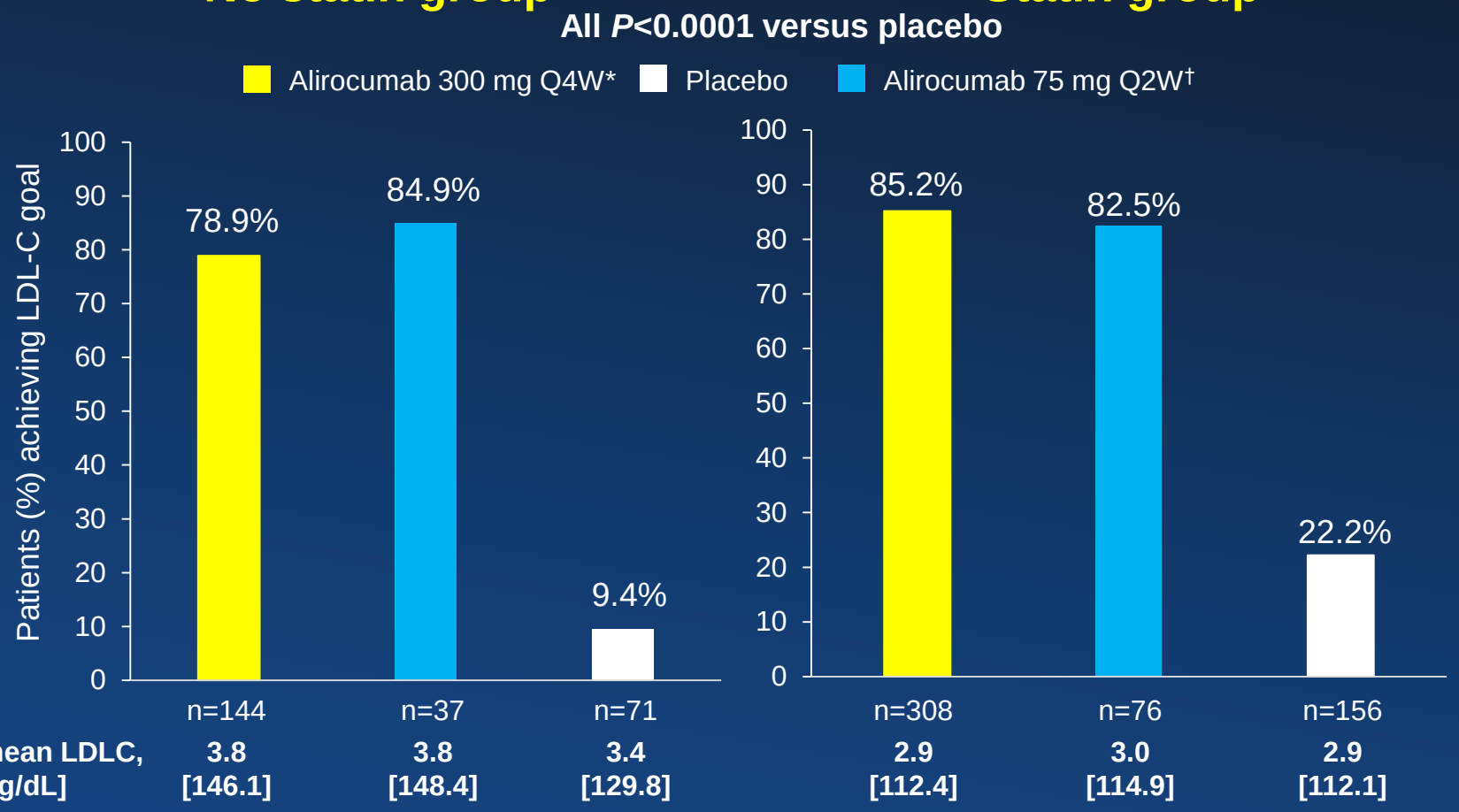
*At Week 12, 14.7% and 21.2% of patients received dose adjustment to 150 mg Q2W, based on Week 8 LDL-C levels, in the alirocumab 300 mg Q4W and 75 mg Q2W groups.
†ΔW 21–24 defined as % change in calculated LDL-C from baseline to averaged values from Week 21–24 versus placebo in the ITT population
‡ΔW 24 defined as % change in calculated LDL-C from baseline to Week 24 versus placebo in the ITT population.

Mean Calculated LDL-C Levels (ITT Population)
Statin Group



*At Week 12, 19.3% and 19.7% of patients received dose adjustment to 150 mg Q2W, based on Week 8 LDL-C levels, in the alirocumab 300 mg Q4W and 75 mg Q2W groups.
†ΔW 21–24 defined as % change in calculated LDL-C from baseline to averaged values from Week 21–24 versus placebo in the ITT population
‡ΔW 24 defined as % change in calculated LDL-C from baseline to Week 24 versus placebo in the ITT population.

A Majority of Alirocumab-Treated Patients Achieved LDL-C Goals at Week 24 (ITT population)



LDL-C goals <1.81 mmol/L (<70 mg/dL, very high CV risk) or <2.59 mmol/L (<100 mg/dL, moderate or high CV risk) (ITT) secondary endpoint

*At Week 12, 14.7% and 19.3% of patients in the 300 mg Q4W group received dose adjustment to 150 mg Q2W, based on Week 8 LDL-C levels, in the no statin and statin groups, respectively; †in the 75 mg Q2W groups, 21.2% and 19.7% received dose increase to 150 mg Q2W, respectively.
LDL-C goals analyzed using multiple imputation followed by logistic regression.

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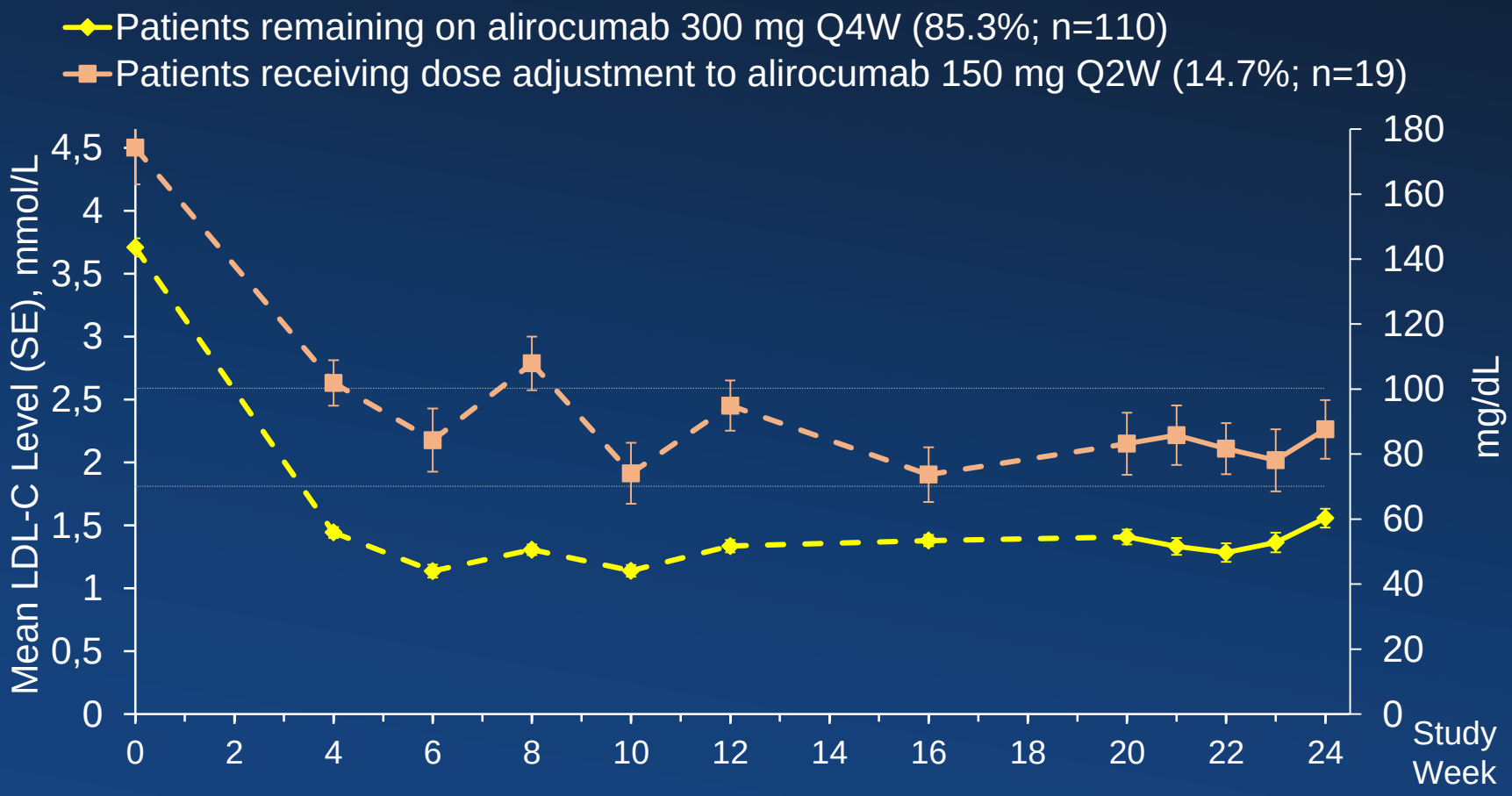
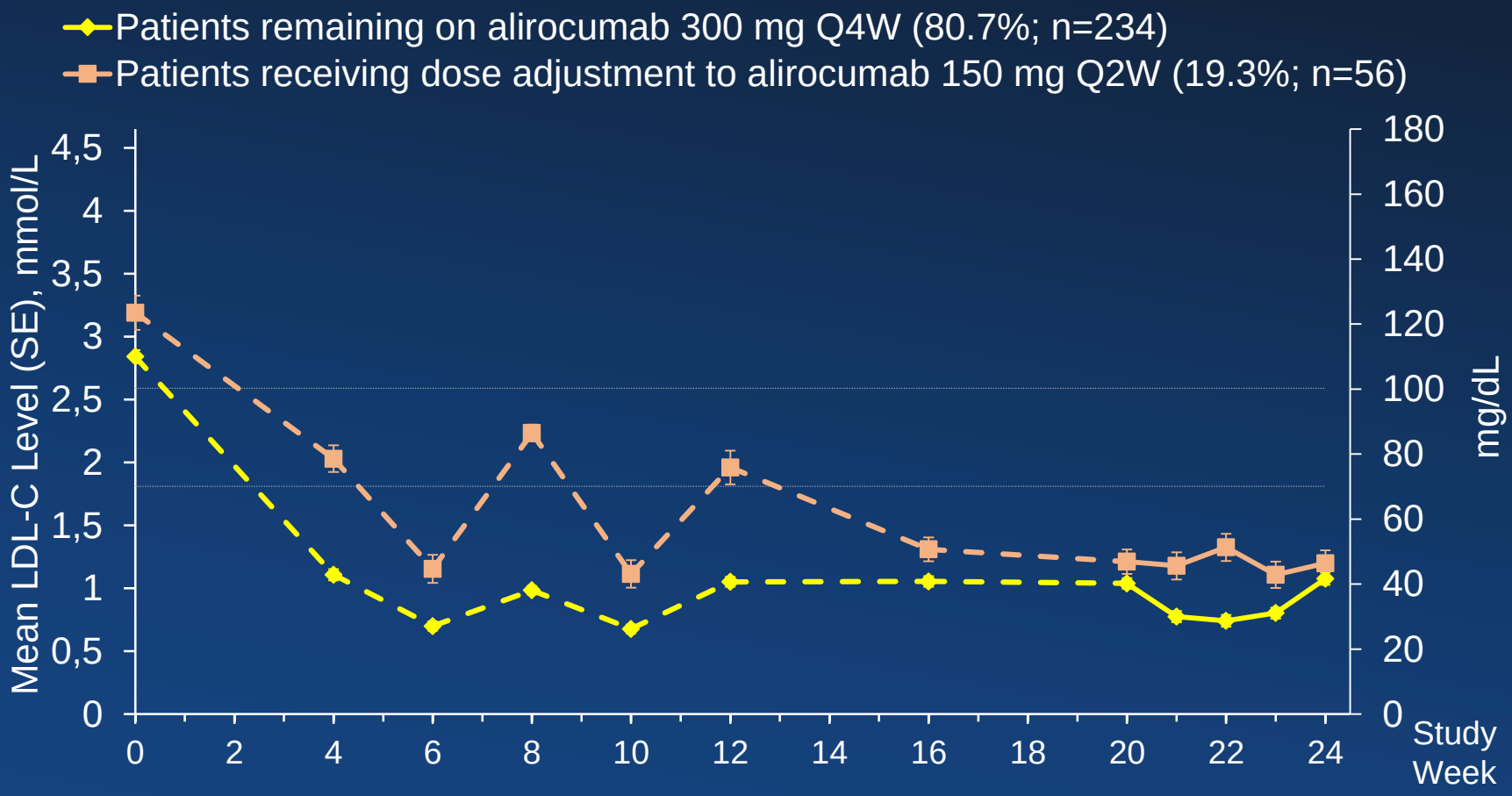
Impact of Dosing/Frequency Adjustment (ITT Population)
No Statin Group



Patients who received dose adjustment at Week 12 and had at least one subsequent injection.

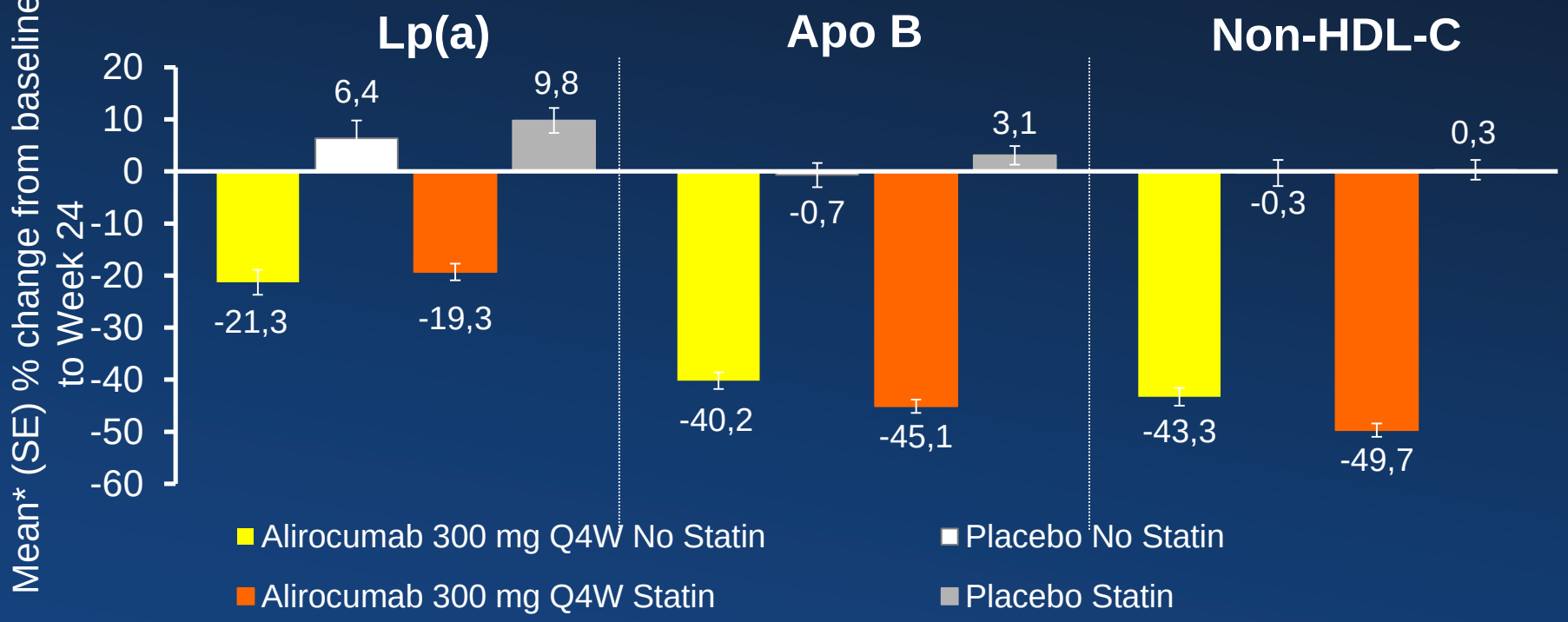
Impact of Dosing/Frequency Adjustment (ITT Population)
Statin Group



Patients who received dose adjustment at Week 12 and had at least one subsequent injection.

Secondary Efficacy Endpoints at Week 24 (ITT Population)

Alirocumab 300 mg Q4W vs Placebo; Statin and No Statin



All *P*<0.0001 versus placebo*

*LS 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.
LS, least squares

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Safety Summary (Safety Population)

	No statin group (N=255)			Statin group (N=547)		
n (%)	Placebo (n=72)	Alirocumab 75 mg Q2W (n=37)	Alirocumab 300 mg Q4W (n=146)	Placebo (n=157)	Alirocumab 75 mg Q2W (n=78)	Alirocumab 300 mg Q4W (n=312)
TEAEs	54 (75.0)	30 (81.1)	114 (78.1)	96 (61.1)	50 (64.1)	223 (71.5)
Treatment-emergent SAE	7 (9.7)	3 (8.1)	14 (9.6)	16 (10.2)	6 (7.7)	25 (8.0)
TEAEs leading to discontinuation	4 (5.6)	2 (5.4)	10 (6.8)	10 (6.4)	3 (3.8)	15 (4.8)
TEAEs leading to death	0	0	0	0	0	0
Safety terms of interest						
General allergic TEAE (CMQ)	8 (11.1)	8 (21.6)	15 (10.3)	9 (5.7)	7 (9.0)	25 (8.0)
Pruritus (PT)	1 (1.4)	1 (2.7)	0	2 (1.3)	0	3 (1.0)
General allergic serious TEAE (CMQ)	0	0	1 (0.7)	1 (0.6)	1 (1.3)	0
Neurocognitive disorders (CMQ)	0	1 (2.7)	0	2 (1.3)	2 (2.6)	2 (0.6)
ALT >3 x ULN (PCSA)	0/71	0/37	1/143 (0.7)	0/154	0/74	1/307 (0.3)

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

Most Frequent TEAEs in No Statin Group (Safety Population)

TEAEs recorded in ≥5% of patients in any group are similar except for injection site reactions

	No statin group (N=255)		
n (%)	Placebo (n=72)	Alirocumab 75 mg Q2W (n=37)	Alirocumab 300 mg Q4W (n=146)
Infections and infestations	**25 (34.7)**	**14 (37.8)**	**60 (41.1)**
Upper respiratory tract infection	4 (5.6)	2 (5.4)	13 (8.9)
Sinusitis	6 (8.3)	3 (8.1)	9 (6.2)
Nasopharyngitis	3 (4.2)	2 (5.4)	7 (4.8)
Urinary tract infection	2 (2.8)	1 (2.7)	7 (4.8)
Bronchitis	4 (5.6)	2 (5.4)	3 (2.1)
Immune system disorders	**1 (1.4)**	**2 (5.4)**	**3 (2.1)**
Hypersensitivity	0	2 (5.4)	1 (0.7)
Nervous system disorders	**11 (15.3)**	**8 (21.6)**	**24 (16.4)**
Headache	4 (5.6)	3 (8.1)	16 (11.0)
Vascular disorders	**8 (11.1)**	**1 (2.7)**	**7 (4.8)**
Hypertension	6 (8.3)	1 (2.7)	5 (3.4)
Gastrointestinal disorders	**19 (26.4)**	**8 (21.6)**	**37 (25.3)**
Diarrhea	5 (6.9)	0	9 (6.2)
Nausea	3 (4.2)	2 (5.4)	9 (6.2)
Skin and subcutaneous tissue disorders	**7 (9.7)**	**6 (16.2)**	**15 (10.3)**
Erythema	0	3 (8.1)	1 (0.7)
Musculoskeletal and connective tissue disorders	**18 (25.0)**	**9 (24.3)**	**35 (24.0)**
Back pain	5 (6.9)	1 (2.7)	3 (2.1)
Arthralgia	3 (4.2)	1 (2.7)	10 (6.8)
Pain in extremity	1 (1.4)	1 (2.7)	10 (6.8)
Muscle spasm	3 (4.2)	1 (2.7)	4 (2.7)
Myalgia	4 (5.6)	1 (2.7)	4 (2.7)
Osteoarthritis	0	2 (5.4)	5 (3.4)
General disorders and administration site conditions	**13 (18.1)**	**6 (16.2)**	**39 (26.7)**
Injection site reaction	6 (8.3)	2 (5.4)	27 (18.5)
Fatigue	2 (2.8)	3 (8.1)	7 (4.8)
Injury, poisoning and procedural complications	**11 (15.3)**	**4 (10.8)**	**30 (20.5)**
Contusion	2 (2.8)	0	3 (2.1)
Arthropod bite	0	2 (5.4)	3 (2.1)

Most Frequent TEAEs in Statin Group (Safety Population)

TEAEs recorded in ≥5% of patients in any group are similar except for injection site reactions

n (%)	Statin group (N=547)		
	Placebo (n=157)	Alirocumab 75 mg Q2W (n=78)	Alirocumab 300 mg Q4W (n=312)
Infections and infestations	**35 (22.3)**	**26 (33.3)**	**105 (33.7)**
Upper respiratory tract infection	5 (3.2)	5 (6.4)	18 (5.8)
Sinusitis	2 (1.3)	0	10 (3.2)
Nasopharyngitis	10 (6.4)	3 (3.8)	23 (7.4)
Urinary tract infection	4 (2.5)	5 (6.4)	15 (4.8)
Bronchitis	2 (1.3)	2 (2.6)	10 (3.2)
Immune system disorders	**2 (1.3)**	**3 (3.8)**	**6 (1.9)**
Hypersensitivity	2 (1.3)	1 (1.3)	2 (0.6)
Nervous system disorders	**22 (14.0)**	**9 (11.5)**	**38 (12.2)**
Headache	6 (3.8)	3 (3.8)	10 (3.2)
Vascular disorders	**15 (9.6)**	**5 (6.4)**	**19 (6.1)**
Hypertension	5 (3.2)	2 (2.6)	6 (1.9)
Gastrointestinal disorders	**31 (19.7)**	**16 (20.5)**	**48 (15.4)**
Diarrhea	9 (5.7)	4 (5.1)	12 (3.8)
Nausea	10 (6.4)	5 (6.4)	9 (2.9)
Skin and subcutaneous tissue disorders	**12 (7.6)**	**6 (7.7)**	**26 (8.3)**
Erythema	1 (0.6)	0	1 (0.3)
Musculoskeletal and connective tissue disorders	**40 (25.5)**	**13 (16.7)**	**80 (25.6)**
Back pain	6 (3.8)	3 (3.8)	23 (7.4)
Arthralgia	9 (5.7)	4 (5.1)	14 (4.5)
Pain in extremity	2 (1.3)	2 (2.6)	8 (2.6)
Muscle spasm	10 (6.4)	2 (2.6)	4 (1.3)
Myalgia	3 (1.9)	1 (1.3)	10 (3.2)
Osteoarthritis	3 (1.9)	0	8 (2.6)
General disorders and administration site conditions	**27 (17.2)**	**17 (21.8)**	**65 (20.8)**
Injection site reaction	9 (5.7)	7 (9.0)	48 (15.4)
Fatigue	7 (4.5)	0	6 (1.9)
Injury, poisoning and procedural complications	**24 (15.3)**	**5 (6.4)**	**38 (12.2)**
Contusion	8 (5.1)	1 (1.3)	6 (1.9)
Arthropod bite	1 (0.6)	1 (1.3)	2 (0.6)

Injection Site Reaction (Safety Population)

n (%)	No statin group (N=255)			Statin group (N=547)		
	Placebo (n=72)	Alirocumab 75 mg Q2W (n=37)	Alirocumab 300 mg Q4W (n=146)	Placebo (n=157)	Alirocumab 75 mg Q2W (n=78)	Alirocumab 300 mg Q4W (n=312)
Injection site reaction	6 (8.3)	2 (5.4)	27 (18.5)	9 (5.7)	7 (9.0)	48 (15.4)
Mild intensity	6 (8.3)	1 (2.7)	24 (16.4)	8 (5.1)	7 (9.0)	45 (14.4)
Moderate intensity	0	1 (2.7)	2 (1.4)	1 (0.6)	0	2 (0.6)
Severe intensity	0	0	1 (0.7)	0	0	1 (0.3)
Discontinuations due to injection site reactions	0	0	0	0	0	2 (0.6)

- **When examined on the basis of the rate of injection site reactions per double-blind injection, the rate of injection site reactions in this study is not dramatically different than the rates observed in other ODYSSEY studies[1–3]**

1. Cannon CP, et al. *Eur Heart J.* 2015 [Epub ahead of print]
2. Robinson JG, et al. *N Eng J Med*. 2015;372:1489–1499
3. Kereiakes DJ, et al. *Am Heart J.* 2015 [in press].

Summary

- In patients with inadequately controlled baseline LDL-C levels, alirocumab 300 mg Q4W, with possible dose regimen adjustment to alirocumab 150 mg Q2W at W12 if goals were not reached at W8, demonstrated significant reductions in LDL-C levels versus placebo, irrespective of background statin therapy:
  - W24 reduction of 52.4% vs placebo (no statin group)
  - W24 reduction of 58.7% vs placebo (statin group)
- Furthermore, significant average reductions vs placebo were seen over W21-W24 with alirocumab 300 mg Q4W dosing
  - Average W21-24 reduction of 55.2% (no statin group)
  - Average W21-24 reduction of 65.0% (statin group)
- Adverse events were generally similar across the study groups, except for injection site reactions
- An alirocumab 300 mg Q4W dosing regimen may provide an additional treatment option for patients in need of LDL-C-lowering irrespective of statin use, with the possibility to adjust dosing to 150 mg Q2W as required

Q&A

ODYSSEY