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Effect of alirocumab dose increase on LDL lowering and lipid goal attainment in patients with dyslipidemia

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Objectives **The objective of this study is to report the dose response in ODYSSEY phase 3 clinical trials of proprotein convertase subtilisin kexin type 9 inhibition with alirocumab in patients not at prespecified lipid goals who received a per-protocol dose increase from 75 every 2 weeks (Q2W) to 150 mg Q2W.**

Methods **Patients ($n = 2181$) receiving statins were enrolled in six phase 3 randomized, double-blind, double-dummy trials (24–104 weeks): alirocumab versus placebo or ezetimibe 10 mg/day. The 75 mg subcutaneous Q2W dose was increased to 150 mg at week 12 if week 8 LDL cholesterol (LDL-C) was greater than or equal to 70 mg/dl (>100 mg/dl in OPTIONS studies for patients without previous coronary heart disease, but with other risk factors). LDL-C percentage reductions from baseline (on-treatment data, $n = 1291$) were compared at week 12 versus week 24.**

Results **Most patients ($n = 951$; 73.7%) with 75 mg Q2W dose plus background statin achieved LDL-C less than 70 or less than 100 mg/dl at week 8. In 340 (26.3%) patients, alirocumab dose was increased to 150 mg Q2W at week 12, and 60.9% of these patients achieved LDL-C goals at week 24, with an additional 14.2% reduction in LDL-C from week 12 to week 24. Adverse event rates were comparable in patients with versus without a dose increase (72.4 vs. 71.8% in placebo-controlled trials; 67.0 vs. 67.6% in ezetimibe-controlled trials).**

Conclusion **Most patients achieved LDL-C goals with alirocumab 75 mg Q2W plus statins. Of those (26.3%) receiving a dose increase, 60.9% achieved LDL-C goals at week 24 with an additional 14.2% reduction in LDL-C.** ***Coron Artery Dis*** **28:190–197 Copyright © 2017 The Author(s). Published by Wolters Kluwer Health, Inc.**

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Introduction

Current guidelines for the management of hypercholesterolemia acknowledge that, although most patients achieve sufficient reduction in LDL cholesterol (LDL-C) levels with high-dose statin therapy, a proportion of patients may require the addition of a nonstatin lipid-lowering therapy (LLT) [1–4]. Such patients include those who either have atherosclerotic cardiovascular disease (ASCVD) or are at high risk of developing it, patients with heterozygous familial hypercholesterolemia (HeFH), and those with high baseline LDL-C levels, or those who cannot tolerate the statin doses necessary to achieve treatment goals [1–4].

Alirocumab (Praluent) is a fully human monoclonal antibody administered by subcutaneous injection that binds with high affinity and specificity to proprotein convertase subtilisin kexin type 9 (PCSK9), with a resultant reduction in levels of LDL-C of up to 62% [5–11]. Alirocumab is approved by the European Medicines Agency in adults with primary hypercholesterolemia (heterozygous familial and nonfamilial) or mixed dyslipidemia as an adjunct to diet in combination with a statin with or without other LLTs in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or alone or in combination with other LLTs in patients who are statin-intolerant, or for whom a statin is contraindicated [12]. Alirocumab is also approved by the US Food and Drug Administration as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD who require additional lowering of LDL-C [13]. Alirocumab is available as a single 1 ml injection in two doses (75 and 150 mg) to be administered once every 2 weeks (Q2W). The majority of ODYSSEY phase 3 clinical trials utilized a graduated alirocumab dose strategy designed to individualize LDL-C lowering, whereby the dose could be increased at week 12 based on

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achievement of prespecified LDL-C levels at week 8. In six studies from the ODYSSEY program enrolling patients receiving background statin therapy (at maximally tolerated dose in four of the six studies), the starting dose of 75 mg Q2W was sufficient for the majority of patients (56.6–92.0%) to achieve prespecified LDL-C goals. When required, 150 mg Q2W resulted in further LDL-C reduction [5–9]. The objective of this analysis is to determine the effect on LDL-C in patients treated with alirocumab when the dose was increased from 75 to 150 mg (26.3%) in those patients from the pooled six-trial database for whom a dose increase was required based on protocol stipulation.

Methods

Data were included from the following six ODYSSEY studies: FH I (*http://www.clinicaltrials.gov* identifier NCT01623115), FH II (NCT01709500), COMBO I (NCT01644175), COMBO II (NCT01644188), OPTIONS I (NCT01730040), and OPTIONS II (NCT01730053). Trial methods and results have been reported previously [5–9]. All study protocols were approved by the appropriate institutional review board and all patients provided informed, written consent.

Overview of studies included in this analysis

Study designs

Patients were randomized to alirocumab or placebo in the FH I, FH II, and COMBO I studies, and to alirocumab or ezetimibe in the OPTIONS I, OPTIONS II, and COMBO II studies. The OPTIONS studies also included control arms where the background statin dose was either increased or switched to another statin; data from these arms are not included in the present analysis.

All patients allocated to alirocumab were randomized to receive a dose of 75 mg Q2W up to week 12. The dose was increased automatically in a blinded manner at 12–150 mg Q2W if the LDL-C level at week 8 was greater than or equal to 70 mg/dl [or ≥ 70 and ≥ 100 mg/dl, respectively, for patients with and without prior cardiovascular disease (CVD) in OPTIONS I and II]. The study protocols did not allow for reduction of the 150 mg Q2W dose to 75 mg Q2W.

Patients

These studies included patients (men and women) aged 18 years or older, with either HeFH or high cardiovascular risk and LDL-C greater than or equal to 70 mg/dl (prior CVD) or at least 100 mg/dl (no prior CVD, but with other cardiovascular risk factors). Patients in the COMBO I and II and FH I and II studies received background maximally tolerated statin therapy (atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg/day, or lower doses with an investigator-approved reason, e.g. intolerance or regional practices). In OPTIONS I, patients received background atorvastatin 20 or 40 mg/day and in OPTIONS II, they received rosuvastatin 10 or 20 mg/day.

Table 1 Study entry criteria and baseline statin use

	FH I	FH II	COMBO I	COMBO II	OPTIONS I	OPTIONS II
Patient population	HeFH + inadequate LDL-C control on maximally tolerated LLT		Established CHD or CHD risk equivalents + inadequate LDL-C control on maximally tolerated LLT		Very high CVD risk + LDL-C levels ≥ 70 mg/dl/high CVD risk + LDL-C ≥ 100 mg/dl	
Baseline statin used (stable dose for at least 4 weeks before screening)	Rosuvastatin 20–40 mg, atorvastatin 40–80 mg, or simvastatin 80 mg[a]			Rosuvastatin 20/40 mg, atorvastatin 40/80 mg, or simvastatin 80 mg (if on this dose for > 1 year)[a]	Atorvastatin 20/40 mg/day[b]	Rosuvastatin 10/20 mg/day[b]
Other LLT	± Stable dose of other LLT > 4 weeks before enrollment (fenofibrate > 6 weeks; other fibrates not allowed)			Other LLTs not allowed	± Stable dose of other LLT > 4 weeks before enrollment; ezetimibe not allowed	
Taking high-dose statin [% (*n*)][c]	83.5 (406)	88.0 (218)	63.0 (199)	68.6 (494)	52.4 (186)	52.5 (160)
Taking moderate-dose statin [% (*n*)][d]	10.5 (51)	7.2 (18)	25.9 (82)	21.0 (151)	47.6 (169)	47.5 (145)
Taking low-dose statin [% (*n*)][e]	6.0 (29)	4.4 (11)	10.4 (33)	10.3 (74)	0	0

CHD, coronary heart disease; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; LDL-C, LDL cholesterol; LLT, lipid-lowering treatment.
[a]Lower doses permitted with investigator-documented justification, for example, intolerance to higher statin doses.
[b]Fixed statin dose; no other statins or doses allowed.
[c]High-dose statin: atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg.
[d]Moderate-dose statin: atorvastatin 20 to less than 40 mg, rosuvastatin 10 to less than 20 mg, or simvastatin 40 to less than 80 mg.
[e]Low-dose statin: atorvastatin less than 20 mg, rosuvastatin less than 10 mg, simvastatin less than 40 mg.

Table 2 Baseline demographics and medical history

	Dose increase	FH I ($n=311$)	FH II ($n=158$)	COMBO I ($n=191$)	COMBO II ($n=446$)	OPTIONS I ($n=93$)	OPTIONS II ($n=92$)	Pool of six studies ($n=1291$)
% (n)	No	56.6 (176)	61.4 (97)	83.2 (159)	81.6 (364)	86.0 (80)	81.5 (75)	73.7 (951)
	Yes	43.4 (135)	38.6 (61)	16.8 (32)	18.4 (82)	14.0 (13)	18.5 (17)	26.3 (340)
Characteristics								
Age [mean (SD)] (years)	No	53.9 (12.5)	54.2 (12.0)	63.3 (9.1)	62.6 (9.1)	63.1 (10.1)	60.5 (10.4)	60.1 (11.0)
	Yes	50.0 (12.9)	50.6 (13.6)	61.6 (10.6)	57.8 (9.8)	64.1 (7.5)	57.8 (11.3)	54.0 (12.7)
Male [% (n)][a]	No	60.8 (107)	56.7 (55)	67.9 (108)	77.2 (281)	68.8 (55)	60.0 (45)	68.5 (651)
	Yes	49.6 (67)	47.5 (29)	43.8 (14)	74.4 (61)	38.5 (5)	52.9 (9)	54.4 (185)
Race (White) [% (n)][a]	No	93.8 (165)	97.9 (95)	84.9 (135)	86.0 (313)	90.0 (72)	86.7 (65)	88.9 (845)
	Yes	91.1 (123)	100.0 (61)	75.0 (24)	81.7 (67)	84.6 (11)	76.5 (13)	87.9 (299)
BMI [mean (SD)] (kg/m^2)	No	28.0 (4.0)	28.2 (4.7)	32.4 (6.3)	29.9 (5.2)	30.6 (6.0)	30.8 (6.9)	29.9 (5.6)
	Yes	30.4 (4.9)	29.5 (4.2)	33.2 (6.5)	30.5 (5.5)	32.3 (7.3)	31.5 (7.5)	30.6 (5.4)
Medical history								
CHD[b] [% (n)][a]	No	48.9 (86)	39.2 (38)	80.5 (128)	93.1 (339)	53.8 (43)	53.3 (40)	70.9 (674)
	Yes	41.5 (56)	24.6 (15)	68.8 (22)	87.8 (72)	69.2 (9)	47.1 (8)	53.5 (182)
HeFH [% (n)][a]	No	100.0 (176)	100.0 (97)	0	0	11.3 (9)	17.3 (13)	31.0 (295)
	Yes	100.0 (135)	100.0 (61)	0	0	15.4 (2)	5.9 (1)	58.5 (199)

CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolemia; MI, myocardial infarction.
[a]Percentages calculated from the total number of patients with and without dose increase in each study.
[b]Acute MI, silent MI, unstable angina, coronary revascularization procedure, other clinically significant CHD.

Patients were allowed to receive other background LLTs in addition to their statin, except in COMBO II, in which other LLTs were not permitted. Ezetimibe was not allowed as background LLT in OPTIONS I and II as it was used as a comparator (Table 1).

Endpoints

The present analysis focuses on percentage changes in LDL-C from baseline to week 12 (i.e. before a possible dose increase) and at week 24 (primary endpoint in all studies). The analysis includes only those patients with at least one study drug injection after week 12 to allow for an assessment of the effect of the dose increase (which would only be apparent from week 16 or beyond). Furthermore, data were analyzed using an on-treatment approach, which included only data collected while the patient was receiving study treatment. Other efficacy endpoints included the proportion of patients achieving risk-based LDL-C goals. Clinic visits occurred at baseline (week 0) and subsequently at weeks 4, 8, 12, 16, and 24 and at weeks 36 and 52 for trials lasting longer than 24 weeks (later time points are not included from the 104-week COMBO II study and the 78-week FH I and II studies). Patient blood samples for lipid and safety laboratory assessments were obtained after a 10-h overnight fast. All lipid measurements and laboratory tests were performed using standard procedures by a central laboratory (Medpace Reference Laboratories, Cincinnati, Ohio, USA, Leuven, Belgium, and Singapore; or Covance Central Laboratory, Indianapolis, Indiana, USA and Geneva, Switzerland). Total and free PCSK9 concentrations in serum were quantified using a validated enzyme-linked immunosorbent assay method (Regeneron Pharmaceuticals Inc., Tarrytown, New York, USA). LDL-C was calculated using the Friedewald formula at all sampling points, reflecting the most commonly used method in clinical practice. LDL-C was also measured by ultracentrifugation and precipitation (β-quantification) in the case of triglycerides more than 400 mg/dl (4.5 mmol/l) and at weeks 0 and 24 in all studies included in the pooled analysis. Investigators remained blinded to laboratory data (except clinical safety tests) throughout the study.

Safety was assessed by reporting of treatment-emergent adverse events (TEAEs), defined as those events occurring after the dose of study treatment administered at week 12 (following potential up-titration to 150 mg Q2W) and up to 70 days after the last dose.

Statistics

This analysis presents baseline, efficacy, and safety data according to whether patients had alirocumab dose increase or not. No formal statistical comparison between these two groups was performed as they were post-randomization subgroups; hence, the statistical analyses presented are descriptive. For assessment of the impact of baseline parameters (LDL-C, BMI, etc.), odds ratios and *P*-values were calculated from a multivariate logistic regression. Factors were selected using a stepwise approach with an entry/stay significance level of 0.05.

Results

Effect of dose increase on LDL-C reductions

These six trials included a total of 2181 patients; 1291 were randomized to receive alirocumab. The majority of patients (73.7%) achieved LDL-C less than 70 or less than 100 mg/dl (depending on cardiovascular risk) with alirocumab 75 mg Q2W (plus background statin) by week 8 and did not require a dose increase (Table 2). Across the six studies, alirocumab dose was increased as per protocol in 340 of 1291 (26.3%) patients at week 12 as they were not at the predetermined LDL-C risk-based

Table 3 Baseline calculated LDL cholesterol levels, change in LDL cholesterol after dose increase, and achievement of LDL cholesterol goals in patients receiving alirocumab

	FH I ($n=311$)	FH II ($n=158$)	COMBO I ($n=191$)	COMBO II ($n=446$)	OPTIONS I ($n=93$)	OPTIONS II ($n=92$)	Pool of six studies ($n=1291$)
Patients not requiring a dose increase [% (n)]	56.6 (176)	61.4 (97)	83.2 (159)	81.6 (364)	86.0 (80)	81.5 (75)	73.7 (951)
Baseline LDL-C [mean (SD)] (mg/dl)	130.1 (42.5)	118.0 (30.3)	93.9 (23.2)	101.1 (29.7)	104.4 (33.8)	112.4 (29.6)	108.2 (34.2)
Patients with a dose increase [% (n)][a]	43.4 (135)	38.6 (61)	16.8 (32)	18.4 (82)	14.0 (13)	18.5 (17)	26.3 (340)
Baseline LDL-C [mean (SD)] (mg/dl)	164.9 (55.1)	160.4 (43.3)	124.6 (39.8)	140.4 (47.4)	138.0 (46.8)	122.1 (34.5)	151.2 (50.8)
Additional change in LDL-C from weeks 12 to 24 in patients with a dose increase[a]							
LDL-C available at weeks 12 and 24 (n)	124	54	29	72	11	15	305
Percentage change [mean (SD)]	−15.1 (23.8)	−16.9 (26.1)	−22.8 (27.1)	−10.5 (32.6)	4.0 (64.2)	−11.9 (48.1)	−14.2 (30.5)
Absolute change [mean (SD)] (mg/dl)	−25.4 (37.8)	−26.6 (38.0)	−29.3 (35.1)	−15.7 (46.6)	−8.2 (58.9)	−12.3 (52.6)	−22.4 (41.6)
Percentage of patients achieving risk-specific LDL-C goals of less than 70 or less than 100 mg/dl at week 24[b]							
Dose not increased achieving LDL-C goal (%)	81.8	86.6	83.0	87.9	96.3	81.3	86.0
Dose increased achieving LDL-C goal (%)	63.7	77.0	56.3	43.9	69.2	64.7	60.9

CVD, cardiovascular disease; LDL-C, LDL cholesterol; Q2W, every 2 weeks.
[a]Alirocumab dose was increased from 75 to 150 mg Q2W at week 12 if the patient's week 8 LDL-C level was at least 70 mg/dl (or ≥ 70 and ≥ 100 mg/dl for patients with and without previous CVD, respectively, in the OPTIONS studies).
[b]LDL-C goals at week 24 of less than 70 mg/dl (in patients with previous CVD) or less than 100 mg/dl (in patients with no previous CVD, but with other cardiovascular risk factors).

Fig. 1

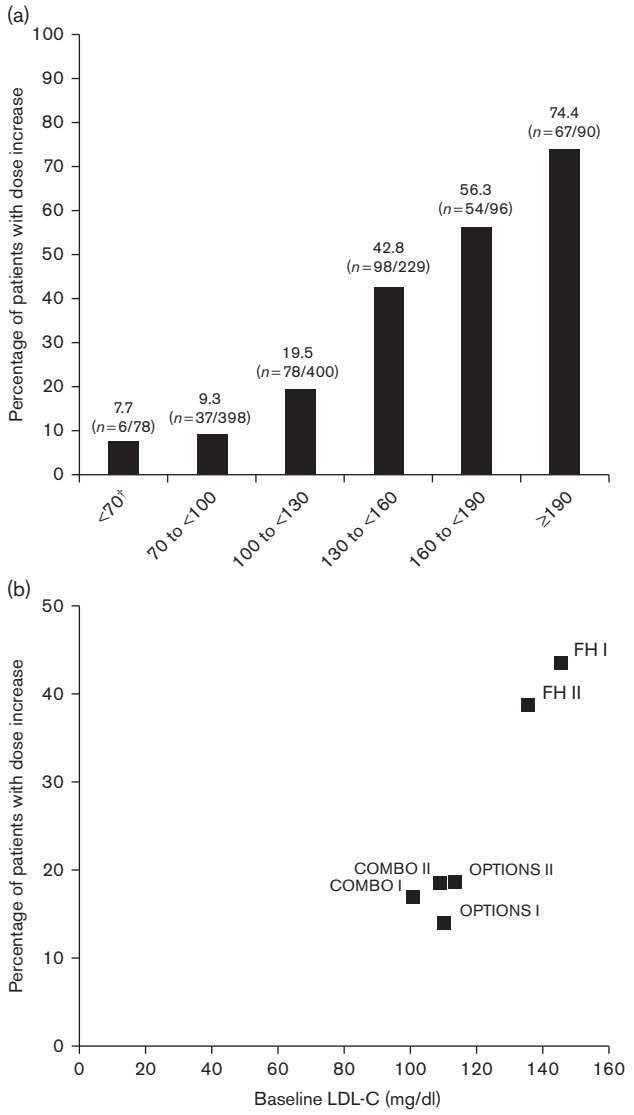
Magnitude of LDL-C reduction in patients on background statins with or without a dose increase. 95% CIs are presented as descriptive because of postrandomization stratification. CI, confidence interval; LDL-C, LDL cholesterol.

goal at week 8. LDL-C data were available at both weeks 12 and 24 for 305 (89.7%) patients in the dose increase group and 857 (90.1%) patients in the nondose increase group. Data were unavailable for 35 (10.3%) patients in the dose increase group and 94 (9.9%) patients in the nondose increase group who had either discontinued alirocumab treatment before week 24 or had week 24 blood samples taken outside the prespecified time window.

Following a dose increase at week 12, an additional 14.2% LDL-C reduction was observed from week 12 to week 24 in these patients (Table 3 and Fig. 1), corresponding to an absolute LDL-C reduction of 22.4 mg/dl (Table 3). Of those patients who required a dose increase, 60.9% achieved risk-based LDL-C goals at week 24 (Table 3).

Patients with higher baseline LDL-C levels were more likely to require a dose increase (Fig. 2). Baseline LDL-C levels were relatively higher in patients in the FH I and II studies compared with the other studies and the proportion of patients requiring a dose increase was also higher (43.4% in FH I and 38.6% in FH II compared with 14.0–18.5% in the other studies) (Table 3). In a multivariate analysis, the difference between baseline LDL-C level and treatment goal was the best predictor of requiring a dose increase ($P<0.0001$) (Table 4). Other predictors included higher BMI (≥30 kg/m^2; $P<0.0001$), female sex ($P=0.0002$), younger age (<50 years; $P=0.0020$), and higher baseline PCSK9 levels (free PCSK9 > 400 ng/ml) ($P=0.0021$) (Table 4). A summary

Fig. 2



(a) Percentage of patients with a dose increase by baseline LDL-C levels (pool of six studies); (b) Percentage of patients with a dose increase by baseline LDL-C levels (per study). †Patients were included on the basis of LDL-C more than 70 mg/dl at the screening visit, but because of fluctuations in LDL-C levels in the 3 weeks between screening and randomization, these patients had LDL-C less than 70 mg/dl at baseline. LDL-C, LDL cholesterol.

of the baseline characteristics of patients treated with alirocumab who required a dose increase compared with those who did not is shown in Table 2.

Of those patients who were continued on 75 mg Q2W throughout, LDL-C less than 25 mg/dl was reported on two or more consecutive occasions in 174 (13.5%) patients compared with 23 (1.8%) patients who required a dose increase. Two or more consecutive LDL-C values less than 15 mg/dl were reported in 11 (0.9%) patients with a dose increase and 42 (3.3%) of those without.

Safety following a dose increase

Comparable TEAE rates were observed in patients who received a dose increase versus those who did not: 72.4 versus 71.8% in placebo-controlled trials and 67.0 versus 67.6% in ezetimibe-controlled trials, with similar rates of TEAEs in the placebo (71.7%) and ezetimibe (62.3%) groups (Table 5). TEAEs leading to death were also similar in those who received a dose increase compared with those who did not, and compared with control groups, with the highest rate occurring in the ezetimibe group (1.7%) (Table 5). Injection-site reactions were reported by 4.4% of those with a dose increase versus 5.3% of those without in placebo-controlled trials (placebo group: 5.1%) and 0.9% with a dose increase versus 0.8% without in ezetimibe-controlled trials (ezetimibe group: 0.7%).

TEAEs reported in at least 5% of patients are shown in Table 5. TEAEs reported at a higher frequency (≥5%) among patients who received a dose increase compared with those who did not were arthralgia (5.4 vs. 3.1%), headache (7.1 vs. 2.7%), hypertension (8.0 vs. 4.2%), and accidental overdose (15.2 vs. 5.4%), all in ezetimibe-controlled trials.

Discussion

This analysis of pooled data from six randomized controlled trials of alirocumab, which used protocol-driven algorithms for a dose increase (from 75 to 150 mg Q2W) after 12 weeks on the basis of prespecified LDL-C levels, provides the following observations: (a) alirocumab 75 mg Q2W allowed the vast majority of patients with ASCVD and/or HeFH (73.7%) to achieve their predefined LDL-C goal; (b) alirocumab dose increase to 150 mg Q2W was associated with an additional 14.2% reduction in LDL-C, which resulted in 60.9% of patients who had a dose increase achieving LDL-C goals by week 24, with no difference in the overall rates of adverse events (including injection-site reactions) versus patients with no dose increase; (c) the impact of alirocumab dose titration appears to exceed the magnitude of additional LDL-C reduction usually achieved by doubling a statin dose (~5–7%) [14]; (d) patients who required an increase in alirocumab dose tended to have higher baseline LDL-C levels compared with those who did not. In this respect, a baseline LDL-C level further from goal was the single best predictor for requiring a dose increase, which suggests that alirocumab 150 mg Q2W may be the most appropriate starting dose in these patients. The European Medicines Agency allows a starting dose of 150 mg Q2W for patients who require reductions in LDL-C more than 60% [12]. (e) In addition to having higher baseline LDL-C, patients who required alirocumab dose increase were younger (< 50 years), more often women, and were more likely to have BMI more than 30 kg/m^2, as well as higher baseline free PCSK9 levels (>400 ng/ml). These observations add considerably toward our understanding of alirocumab clinical responsiveness.

Table 4 Predictive factors of alirocumab dose increase to 150 mg every 2 weeks: multivariate analysis

Factor	Category	*n*	Dose increase [% (*n*)]	Odds ratio (95% CI)	*P*-value
Distance between baseline LDL-C and treatment goal[a] (mg/dl)	< 30 (ref)	478	9.0 (43)	–	< 0.0001
	≥ 30 to < 60	398	19.6 (78)	2.29 (1.52–3.46)	
	≥ 60 to < 90	229	42.8 (98)	6.42 (4.16–9.89)	
	≥ 90	186	65.1 (121)	18.12 (11.31–29.04)	
BMI (kg/m^2)	< 30 (ref)	727	23.0 (167)	–	< 0.0001
	≥ 30	563	30.6 (172)	1.81 (1.34–2.43)	
Sex	Male (ref)	836	22.1 (185)	–	0.0002
	Female	455	34.1 (155)	1.78 (1.32–2.41)	
Age (years)	< 50 (ref)	270	43.3 (117)	–	0.0020
	≥ 50 to < 65	599	25.4 (152)	0.56 (0.40–0.80)	
	≥ 65 to < 75	335	18.2 (61)	0.53 (0.35–0.82)	
	≥ 75	87	11.5 (10)	0.34 (0.16–0.74)	
Baseline free PCSK9 (ng/ml)	< 200 (ref)	146	28.1 (41)	–	0.0021
	≥ 200 to < 300	291	25.1 (73)	1.34 (0.79–2.27)	
	≥ 300 to < 400	175	24.0 (42)	1.29 (0.72–2.33)	
	≥ 400	117	41.9 (49)	3.29 (1.76–6.14)	
Ethnicity	Not Hispanic/Latino (ref)	1201	27.1 (325)	–	0.0082
	Hispanic or Latino	83	15.7 (13)	0.39 (0.20–0.79)	

Odds ratios and *P*-values calculated from a multivariate logistic regression. Factors selected using a stepwise approach with entry/stay level = 0.05.
CI, confidence interval; LDL-C, LDL cholesterol; PCSK9, proprotein convertase subtilisin kexin type 9; ref, referent group.
[a]Calculated as baseline LDL-C minus risk-based LDL-C goal.

Table 5 Safety analysis in alirocumab-treated patients with and without a dose increase compared with placebo-treated and ezetimibe-treated patients

	Pool of six trials using a dose increase strategy in addition to background statin[a]					
	Placebo-controlled pool (*n* = 996)			Ezetimibe-controlled pool (*n* = 1037)		
Patients [% (*n*)]	Alirocumab: no dose increase (*n* = 432)	Alirocumab: dose increase (*n* = 228)	Placebo (*n* = 336)	Alirocumab: no dose increase (*n* = 519)	Alirocumab: dose increase (*n* = 112)	Ezetimibe (*n* = 406)
Any TEAE	71.8 (310)	72.4 (165)	71.7 (241)	67.6 (351)	67.0 (75)	62.3 (253)
Treatment-emergent SAE	11.3 (49)	9.2 (21)	11.0 (37)	18.1 (94)	15.2 (17)	15.0 (61)
TEAE leading to death	1.2 (5)	0.4 (1)	0.3 (1)	1.0 (5)	0.9 (1)	1.7 (7)
TEAE leading to discontinuation	2.5 (11)	3.1 (7)	3.3 (11)	4.0 (21)	3.6 (4)	3.2 (13)
TEAE by preferred term in ≥ 5% patients						
Nasopharyngitis	7.9 (34)	7.9 (18)	7.1 (24)	3.5 (18)	3.6 (4)	3.2 (13)
Injection-site reaction	5.3 (23)	4.4 (10)	4.4 (10)	0.8 (4)	0.9 (1)	0.7 (3)
Influenza	5.1 (22)	4.4 (10)	4.4 (10)	3.5 (18)	0	3.2 (13)
Upper respiratory tract infection	5.1 (22)	4.4 (10)	6.3 (21)	6.0 (31)	2.7 (3)	5.7 (23)
Arthralgia	4.2 (18)	3.5 (8)	6.0 (20)	3.1 (16)	5.4 (6)	2.7 (11)
Headache	3.5 (15)	3.9 (9)	2.7 (9)	2.7 (14)	7.1 (8)	3.0 (12)
Hypertension	3.5 (15)	1.3 (3)	1.3 (3)	4.2 (22)	8.0 (9)	3.7 (15)
Accidental overdose	0.9 (4)	0.9 (2)	1.2 (4)	5.4 (28)	15.2 (17)	4.2 (17)

TEAE from first injection after week 12. TEAEs include all adverse events reported, irrespective of relationship with treatment as judged by the investigator.
Database updated for studies FH I, FH II, and COMBO II.
SAE, serious adverse event; TEAE, treatment-emergent adverse event.
[a]All studies on top of statins. Placebo-controlled pools = FH I, FH II, and COMBO I; ezetimibe-controlled pool = COMBO II, OPTIONS I, and OPTIONS II.

Previous subgroup analyses from individual trials have lacked power to define factors associated with differences in LDL-C lowering following alirocumab according to BMI, age, or baseline PCSK9 levels, although a weak heterogeneity between men and women has been reported [8,11]. The absolute differences between groups on the basis of requirement for dose titration were small. For example, 30.6% of patients with BMI more than 30 kg/m^2 required a dose increase compared with 23.0% of those with BMI less than or equal to 30 kg/m^2 (a difference of only 7.6%), yet BMI was a significant determinant of dose response. In addition, because there is an established link between BMI and increased levels of LDL-C [15], this link may be explained by higher baseline levels of LDL-C in patients with higher BMI. These findings should therefore be treated with caution; further evidence would be required to support changes in starting dose based solely on these patient demographics, and the underlying biological mechanisms would require further investigation. In addition, the differences due to age may be linked to a higher proportion of HeFH patients in the less than 50 years age group. The mean age of alirocumab-treated patients in the ODYSSEY FH I and II studies, which exclusively recruited HeFH patients, ranged from 52 to 53 years [8] compared with 59–64 years across the other four studies [5–7,9]. HeFH is

associated with higher baseline LDL-C levels and therefore a higher likelihood of a dose increase, as with BMI.

The additional 14.2% reduction in LDL-C achieved by increasing alirocumab dose from 75 to 150 mg Q2W is consistent with the LDL-C reductions observed across the alirocumab phase 3 program with 75 and 150 mg doses (44.1–54.0 and 61.0% LDL-C lowering, respectively) [5–11]. However, data from the ODYSSEY LONG TERM study of alirocumab 150 mg Q2W versus placebo in 2341 patients with high cardiovascular risk suggest that a longer duration of 150 mg dose treatment results in additional LDL-C reduction. In the LONG TERM study, 80.7% of patients had reached risk-based LDL-C goals of less than 70 or less than 100 mg/dl at week 24, and 79.3% were below 70 mg/dl at week 24, irrespective of initial risk. These patients had received 150 mg alirocumab Q2W for 24 weeks rather than 12 as in the current analysis [11].

The ongoing ODYSSEY OUTCOMES study (NCT01 663402) also uses a dose-titration strategy. In this study, the starting dose of 75 mg Q2W can be increased to 150 mg Q2W after 8 weeks if the patient's LDL-C level is greater than or equal to 50 mg/dl at week 4. Unlike the other clinical studies of Q2W dosing, this study design allows for downward dose titration from 150 to 75 mg Q2W in the event that a patient's LDL-C falls below 25 mg/dl. This design is intended to allow as many patients as possible to reach LDL-C levels of less than 50 mg/dl, while minimizing the number with LDL-C less than 15 mg/dl. The design of ODYSSEY OUTCOMES will allow individualized treatment by selecting the most appropriate dose for each patient, and will further inform understanding of alirocumab dose response and its relationship with clinical outcomes.

One limitation of the current analysis is that only 26.3% of all patients included required alirocumab dose increase. Therefore, the potential effect of alirocumab dose increase on 73.7% of the study population was not evaluated. On the basis of the results discussed above, those patients who did not have a dose increase might be expected to have additional reductions in LDL-C with a dose increase to 150 mg Q2W.

Conclusion

This analysis shows that when alirocumab dose was increased from 75 to 150 mg Q2W among statin-treated patients not achieving treatment goals, an additional 14.2% LDL-C reduction was observed. Furthermore, 60.9% of patients who required a dose increase to 150 mg/dl subsequently achieved the protocol-specified LDL-C goals at week 24.

Patients most likely to require dose titration usually had higher baseline LDL-C levels, were younger (age <50 years), were more often women, with BMI more than 30 kg/m^2, and had elevated baseline PCSK9 levels. This flexible alirocumab dosing strategy provided comparable safety profiles for both doses used. The benefits of a two-dose treatment option and the impact of treatment on clinical outcomes and safety are being further examined in the ODYSSEY OUTCOMES trial.

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Conflicts of interest

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References

1 Jacobson TA, Ito MK, Maki KC, Orringer CE, Bays HE, Jones PH, *et al.* National lipid association recommendations for patient-centered management of dyslipidemia: part 1 – full report. *J Clin Lipidol* 2015; **9**:129–169.

2 Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, *et al.* Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* 2013; **34**:3478–3390a.

3 Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, *et al.* ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* 2011; **32**:1769–1818.

4 Stone NJ, Robinson J, Lichtenstein AH, Bairey Merz CN, Lloyd-Jones DM, Blum CB, *et al.* 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *J Am Coll Cardiol* 2014; **63**:2889–2934.

5 Bays H, Gaudet D, Weiss R, Ruiz JL, Watts GF, Gouni-Berthold I, *et al.* Alirocumab as add-on to atorvastatin versus other lipid treatment strategies: ODYSSEY OPTIONS I randomized trial. *J Clin Endocrinol Metab* 2015; **100**:3140–3148.

6 Cannon CP, Cariou B, Blom D, McKenney JM, Lorenzato C, Pordy R, *et al.* Efficacy and safety of alirocumab in high cardiovascular risk patients with inadequately controlled hypercholesterolaemia on maximally tolerated doses of statins: the ODYSSEY COMBO II randomized controlled trial. *Eur Heart J* 2015; **36**:1186–1194.

7 Farnier M, Jones P, Severance R, Averna M, Steinhagen-Thiessen E, Colhoun HM, *et al.* Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: the ODYSSEY OPTIONS II randomized trial. *Atherosclerosis* 2016; **244**:138–146.

8 Kastelein JJ, Ginsberg HN, Langslet G, Hovingh GK, Ceska R, Dufour R, *et al.* ODYSSEY FH I and FH II: 78 week results with alirocumab treatment in 735 patients with heterozygous familial hypercholesterolaemia. *Eur Heart J* 2015; **11**:2996–3003.

9 Kereiakes DJ, Robinson JG, Cannon CP, Lorenzato C, Pordy R, Chaudhari U, *et al.* Efficacy and safety of the PCSK9 inhibitor alirocumab among high cardiovascular risk patients on maximally tolerated statin therapy: the ODYSSEY COMBO I study. *Am Heart J* 2015; **169**:906–915.e913.

10 Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve F, *et al.* ODYSSEY ALTERNATIVE Investigators. Efficacy and safety of alirocumab versus ezetimibe in statin-intolerant patients, with a statin re-challenge arm: the ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol* 2015; **9**:758–769.

11 Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, *et al.* Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015; **372**:1489–1499.

12 Sanofi/Regeneron Pharmaceuticals. Summary of product characteristics (Praluent). Available at: *http://ec.europa.eu/health/documents/community-register/2015/20150923132812/anx_132812_en.pdf*. [Accessed 6 September 2016].

13 Sanofi/Regeneron Pharmaceuticals. Praluent prescribing information. Available at: *http://products.sanofi.us/praluent/praluent.pdf*. [Accessed 6 September 2016].

14 Nicholls SJ, Brandrup-Wognsen G, Palmer M, Barter PJ. Meta-analysis of comparative efficacy of increasing dose of atorvastatin versus rosuvastatin versus simvastatin on lowering levels of atherogenic lipids (from VOYAGER). *Am J Cardiol* 2010; **105**:69–76.

15 Klop B, Elte JW, Cabezas MC. Dyslipidemia in obesity: mechanisms and potential targets. *Nutrients* 2013; **5**:1218–1240.