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Pharmacodynamic relationship between PCSK9, alirocumab, and LDL-C lowering in the ODYSSEY CHOICE I trial

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BACKGROUND: The ODYSSEY CHOICE I study (NCT01926782) evaluated alirocumab 300 mg every 4 weeks (Q4W) in patients with hypercholesterolemia receiving maximally tolerated statin or no statin.

OBJECTIVE: The objective of the study was to assess the relationship between alirocumab, proprotein convertase subtilisin/kexin type 9 (PCSK9), and low-density lipoprotein cholesterol (LDL-C) concentrations with the CHOICE I alirocumab dosing regimen.

METHODS: This analysis included 803 patients (547 statin-treated, 256 without statin) who were randomized to alirocumab 300 mg Q4W, alirocumab 75 mg every 2 weeks (Q2W), or placebo. 300 mg Q4W and 75 mg Q2W doses were adjusted to 150 mg Q2W at Week 12 if Week 8 LDL-C was >70 or >100 mg/dL, depending on cardiovascular risk, or if LDL-C reduction was <30% from baseline.

RESULTS: Most patients remained on 300 mg Q4W without dose adjustment as they achieved study-defined LDL-C goals at Week 8 (statin-treated: 80.7%; no statin: 85.3%). LDL-C was reduced by 60.5%–71.9% over Weeks 20–24 in patients on 300 mg Q4W and 57.2%–63.0% in patients with dose adjustment from 300 mg Q4W to 150 mg Q2W. Statin-treated patients had higher cardiovascular risk as well as higher free PCSK9 and lower alirocumab concentrations (vs no statin), suggesting increased target-mediated clearance. Regardless of statin status, the most common adverse events in alirocumab-treated patients were injection-site reaction and headache.

CONCLUSIONS: Data provide further insight on alirocumab's mode of action in terms of relationship between alirocumab, PCSK9, and LDL-C, and disease severity, and support the use of alirocumab 300 mg Q4W as an efficacious dosing regimen for clinically meaningful LDL-C reductions.

Introduction

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a key negative regulator of the low-density lipoprotein (LDL) receptor; the LDL receptor plays a major role in the clearance of LDL particles.[1,2] Alirocumab is a fully human monoclonal antibody that binds to and inhibits PCSK9, thereby preventing PCSK9-mediated degradation of the LDL receptor, increasing the number of LDL receptors on the liver cell, and ultimately increasing the clearance of LDL particles from the circulation.[2] Alirocumab 75 mg every 2 weeks (Q2W) and 300 mg every 4 weeks (Q4W; both doses with possible dose adjustment to 150 mg Q2W if the low-density lipoprotein cholesterol (LDL-C) response is inadequate) have been approved for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease (CVD) who require additional lowering of LDL-C as an adjunct to diet on maximally tolerated statin therapy[3,4] in the United States and the European Union as well as other regions.

Monoclonal antibodies, such as alirocumab, are subject to target-mediated clearance, whereby clearance of the antibody is influenced by the concentration of the target. The elimination of alirocumab from the circulation is affected by PCSK9 concentrations; a Q4W dosing regimen is impacted by factors that affect target production, for example, statin-induced increases in PCSK9 concentrations. Other lipid-lowering therapies such as ezetimibe and fenofibrate appear to have a more modest effect on increasing PCSK9 concentrations and hence alirocumab clearance.[5,6] In addition to statin use, other factors relating to disease background may influence PCSK9 concentrations. PCSK9 concentrations have been shown to be higher in individuals with familial hypercholesterolemia, which may be related to reduced LDL receptor expression and increased PCSK9 half-life.[7] Other factors that have been reported to increase PCSK9 concentrations include chronic kidney disease,[8] insulin resistance,[9] and bacterial infection.[10] However, LDL-C concentration is the most frequently used metric to adjust the alirocumab dose to achieve sufficient LDL-C reduction.[11]

The placebo-controlled ODYSSEY CHOICE I study evaluated alirocumab 300 mg Q4W (with possible dose adjustment to 150 mg Q2W at Week 12) vs placebo, as well as a calibrator arm (alirocumab 75 mg Q2W with possible dose adjustment to 150 mg Q2W).[12] Patients had hypercholesterolemia with moderate–to–very high CVD risk and were receiving either maximally tolerated statin or no statin because of statin intolerance. Alirocumab 300 mg Q4W significantly reduced LDL-C from baseline to Week 24 vs placebo; average LDL-C reductions from baseline to Weeks 21–24 were also significant vs placebo.

A detailed assessment of the indirect pharmacokinetic/pharmacodynamic relationship between alirocumab and LDL-C, and how this is mediated through free/total PCSK9 and influenced by statin use, has not been presented for alirocumab 300 mg Q4W dosing as used in CHOICE I. A feature of CHOICE I that distinguishes it from previous assessment of alirocumab pharmacokinetics and pharmacodynamics in phase 3 studies was that samples were taken weekly between Weeks 20 and 24, allowing for a more detailed assessment over time. The current analysis assessed concentrations of PCSK9 and alirocumab in relation to LDL-

C from CHOICE I over the first 24 weeks of the study, focusing on patients in the 300 mg Q4W dose group and including an analysis in accordance with use of statin.

Methods

Patients and study designs

CHOICE I[12] (Study to evaluate the efficacy and safety of an every four weeks treatment regimen of alirocumab [REGN727/SAR236553] in patients with primary hypercholesterolemia [ODYSSEY CHOICE I]; NCT01926782) was a multinational study that enrolled patients with moderate–to–very high CVD risk who had LDL-C concentrations ≥70 mg/dL (very high CVD risk) or LDL-C ≥100 mg/dL (high or moderate CVD risk), despite receiving maximally tolerated statin doses, patients with moderate–to–very high CVD risk and statin intolerance, and patients with moderate CVD risk who did not receive statin therapy. The CHOICE I study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and applicable amendments and the International Conference on Harmonization guidelines for Good Clinical Practice. For each participating study site, institutional review board or independent ethics committee approval of the protocol was obtained. All patients provided written informed consent and were aged ≥18 years.

Patients were randomized in a 4:2:1 ratio to alirocumab 300 mg Q4W, placebo, or alirocumab 75 mg Q2W and received treatment for 24 weeks. For both alirocumab groups, the dose was adjusted to 150 mg Q2W in a blinded manner at Week 12 if LDL-C concentrations at Week 8 were ≥70 mg/dL or ≥100 mg/dL (depending on CVD risk), or if LDL-C reduction was <30% from baseline to Week 8.

All patients receiving statins were on maximally tolerated statin therapy (atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg [or lower doses with an investigator-documented justification]).

As defined previously, statin intolerance is defined as the inability to tolerate at least 2 statins because of unexplained skeletal muscle–related symptoms.[13]

Endpoints and laboratory assessments

Blood samples were collected before study administration; lipid measurements and laboratory tests were assessed by a central laboratory. LDL-C concentrations were calculated using the Friedewald formula: LDL-C = total cholesterol – high-density lipoprotein cholesterol – (triglycerides/5). For alirocumab, free PCSK9 concentration, and total PCSK9 concentration, blood samples were collected predose at baseline, Week 12, and weekly from Weeks 20 to 24.

The current pharmacokinetic/pharmacodynamic analysis paid specific attention to the alirocumab 300 mg Q4W treatment regimen. It provides a comparison between individuals receiving statin and those on no statin, as well as by alirocumab dose adjustment status.

Total alirocumab, consisting of alirocumab both free and bound to PCSK9, was quantified with a specific validated enzyme-linked immunosorbent assay that had adequate sensitivity to assess the pharmacokinetics over time as well as good within-run and between-run accuracy (>90%) and precision (≤10%) (Regeneron Pharmaceuticals, Inc., Tarrytown, NY). The lower limit of quantification (LLOQ) was 78 ng/mL in the undiluted serum sample. Pharmacokinetic parameters were calculated using noncompartmental methods and included concentrations of alirocumab (C_{trough}: assessed 8–21 days after previous study drug injection and area under curve $[AUC]_{0–T}$, calculated by linear trapezoidal methods).

The concentrations of free PCSK9 or total PCSK9 (representing all PCSK9 in the circulation, whether free or bound to alirocumab or other proteins) were assessed with a specific validated enzyme-linked immunosorbent assay (Regeneron Pharmaceuticals, Inc). The LLOQ was 156 ng/mL for total PCSK9 and 31.2 ng/mL for free PCSK9 in undiluted serum. For the determination of mean concentrations, individual concentrations below the LLOQ were set to zero (0). When graphed in semilog, a value of LLOQ/2 was imputed.

Treatment-emergent adverse events were defined as any adverse events that developed, worsened, or became serious during the period from the first to the last study drug injection plus 70 days.

Statistical analysis

Analyses of alirocumab, PCSK9, and LDL-C concentrations over time were assessed descriptively. LDL-C data were assessed in the intent-to-treat population, which included all randomized patients with an LDL-C measurement at baseline and at least 1 of the postrandomization points within 1 of the analysis windows up to Week 24, regardless of treatment adherence. The analyses for pharmacokinetics were performed on all randomized and treated patients (safety population) in each of the 2 alirocumab randomized groups who had at least 1 evaluable blood sample after the first dose of the study drug (pharmacokinetic population). The pharmacokinetic/pharmacodynamic analysis set included patients who had at least 1 nonmissing target (free or total PCSK9) concentration or LDL-C concentration, as appropriate, after the first dose of the study drug (placebo treatment excluded). For assessment of the impact of PCSK9 on LDL-C reductions, least-squares mean LDL-C and standard error were taken from a mixed-effect model with repeated measures analysis.

The safety analysis included all patients randomized for CHOICE I who received at least 1 dose or part of a dose of the study drug (safety population). Safety data were analyzed by descriptive statistics. Safety data included a pool of alirocumab-treated CHOICE I participants (300 mg Q4W and 75 mg Q2W) in accordance with statin use.

Table 1 Baseline characteristics in patients receiving statins and those receiving no statin, regardless of treatment allocation (randomized population)

Parameter	Patients receiving statins (n = 547)	Patients not receiving statins (n = 256)
Age, years, mean (SD)	61.5 (9.8)	59.3 (10.6)
Male, n (%)	342 (62.5)	120 (46.9)
BMI, kg/m^2, mean (SD)	31.1 (6.0)	31.1 (5.9)
HeFH, n (%)	44 (8.0)	3 (1.2)
CVD risk, n (%)		
Very high	361 (66.0)	60 (23.4)
High	109 (19.9)	45 (17.6)
Moderate	77 (14.1)	151 (59.0)
Any LLT other than statin, n (%)	199 (36.4)	112 (43.8)
Ezetimibe	74 (13.5)	24 (9.4)
Nutraceuticals*	98 (17.9)	74 (28.9)
LDL-C, mg/dL, mean (SD)	112.7 (34.5)	142.1 (33.8)

BMI, body mass index; CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; SD, standard deviation.

*Nutraceuticals included omega-3 fatty acids, phytosterols, and policosanol.

Results

Patients

In total, 803 patients were randomized: 547 patients (68.1%) were receiving a background statin and 256 patients (31.9%) were not on a statin. Among patients receiving a statin vs not on a statin, there was a higher proportion who were male (62.5% vs 46.9%) and of very high CVD risk vs medium or high CVD risk (66.0% vs 23.4%); baseline mean LDL-C values were lower for patients receiving a statin vs no statin (112.7 vs 142.1 mg/dL; Table 1).

Table 2 Baseline LDL-C, free PCSK9 concentrations, and alirocumab dose adjustment status at Week 12 (safety population*)

	Alirocumab 300 mg Q4W cohort (N = 419)	
Parameter	No dose adjustment	Dose adjustment
All patients		
Patients, n/N (%)	344/419 (82.1)	75/419 (17.9)
Very high CVD risk	165/221 (74.7)	56/221 (25.3)
High CVD risk	72/79 (91.1)	7/79 (8.9)
Moderate CVD risk	107/119 (89.9)	12/119 (10.1)
Mean (SD) baseline LDL-C, mg/dL	120.8 (34.4)	136.4 (47.4)
Mean (SD) baseline free PCSK9, ng/mL	275 (109)	308 (118)
Patients not on statin		
Patients, n/N (%)	110/129 (85.3)	19/129 (14.7)
Very high CVD risk	20/31 (64.5)	11/31 (35.4)
High CVD risk	17/19 (89.5)	2/19 (10.5)
Moderate CVD risk	73/79 (92.4)	6/79 (7.6)
Mean (SD) baseline LDL-C, mg/dL	143.6 (29.6)	174.3 (49.4)
Mean (SD) baseline free PCSK9, ng/mL	202 (79.3)	211 (65.3)
Patients on statin		
Patients, n/N (%)	234/290 (80.7)	56/290 (19.3)
Very high CVD risk	145/190 (76.3)	45/190 (23.7)
High CVD risk	55/60 (91.7)	5/60 (8.3)
Moderate CVD risk	34/40 (85.0)	6/40 (15.0)
Mean (SD) baseline LDL-C, mg/dL	110.0 (31.1)	123.5 (39.5)
Mean (SD) baseline free PCSK9, ng/mL	310 (105)	340 (114)

CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; Q4W, every 4 wk; SD, standard deviation.

*Patients with at least 1 alirocumab injection from Week 12.

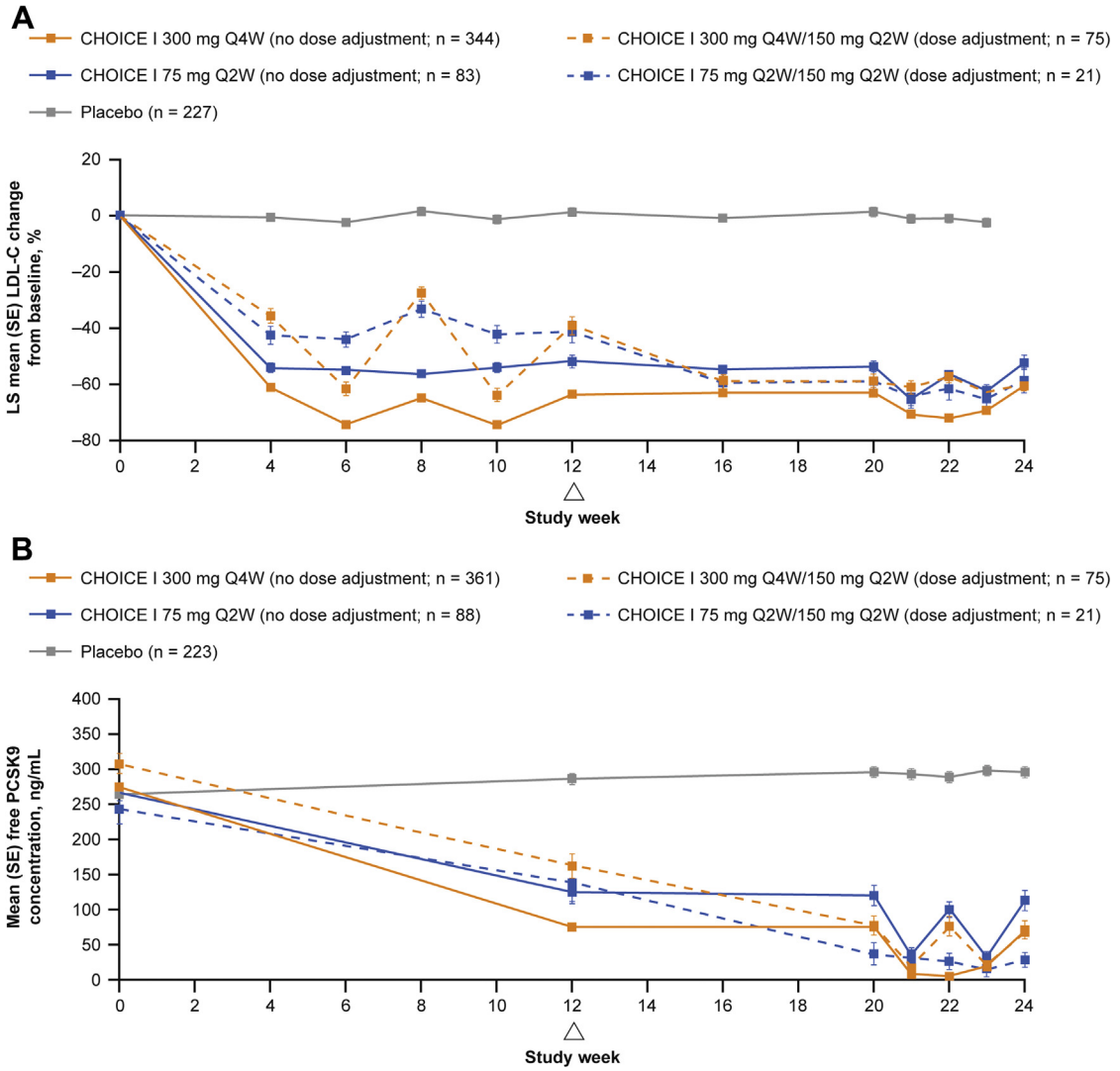


Figure 1 Mean (SE) (A) LDL-C, (B) free PSCK9, (C) total PCSK9 concentrations, and (D) alirocumab concentrations in accordance with dose adjustment status for all patients regardless of statin therapy (pharmacokinetic population*) *LDL-C data assessed in the intention-to-treat population. LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error.

Changes in LDL-C, PCSK9, and alirocumab concentrations in accordance with dose-adjustment status (irrespective of statin use)

Overall, most patients (344/419, 82.1%) starting on the 300 mg Q4W dose regimen achieved the study-defined LDL-C goals at Week 8 and did not need dose adjustment at Week 12. A higher proportion of patients at very high CVD risk required dose adjustment as LDL-C was ≥70 mg/dL or reduced by <30% at Week 8 (56/221, 25.3%) compared with patients at moderate-to-high CVD risk who had dose adjustment if LDL-C was ≥100 mg/dL or reduced by <30% at Week 8 (12/119, 10.1%; Table 2). Baseline LDL-C concentrations were 120.8 vs 136.4 mg/dL, respectively, for patients who remained on 300 mg Q4W vs those who had their dose adjusted from 300 mg Q4W (Table 2).

LDL-C reductions in accordance with dose adjustment status, irrespective of background statin therapy, are shown in Figure 1A. Before Week 12, there were large peak-to-trough fluctuations in LDL-C reductions in the group who had their 300 mg Q4W dose changed to 150 mg Q2W (ie, their LDL-C percent reductions were 61.5% and 27.5% at Weeks 6 and 8, respectively); however, after dose adjustment, these fluctuations were diminished and were leveled out by Weeks 20 to 24 (LDL-C reductions of 57.2–63.0% and achieved concentrations of 52.4–59.3 mg/dL). By contrast, the group that remained on 300 mg Q4W did not show such large fluctuations before Week 12 (LDL-C reductions of 74.1% and 64.8% at Weeks 6 and 8, respectively) and demonstrated similar LDL-C

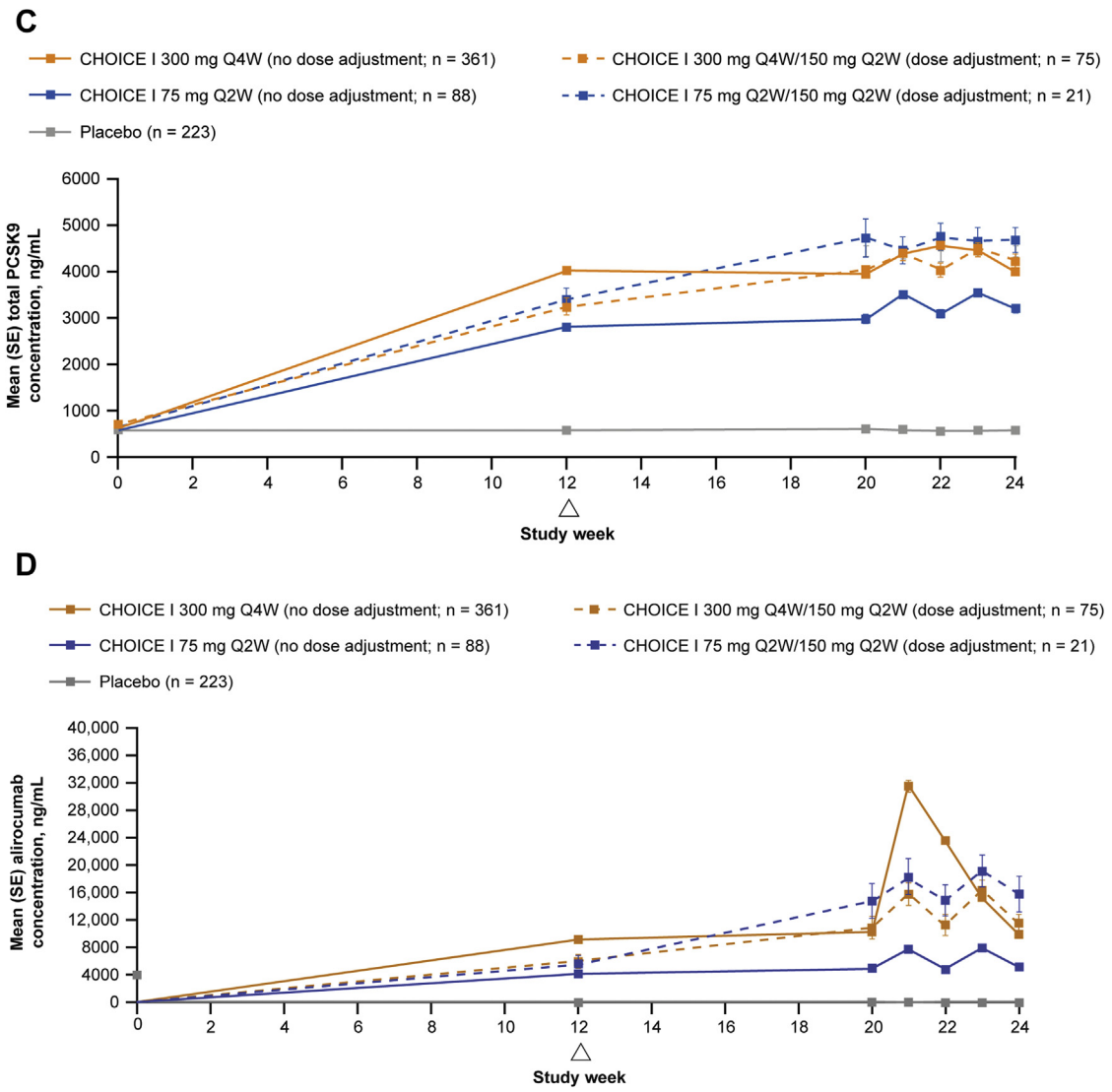


Figure 1 (*continued*).

reductions over Weeks 20 to 24 compared with the group who had their dose adjusted from 300 mg Q4W (LDL-C reductions of 60.5%–71.9% and achieved concentrations of 35.6–47.8 mg/dL).

Among patients receiving alirocumab 300 mg Q4W who did not have dose adjustment, mean free PCSK9 concentrations fell from 275 to 74.9 ng/mL at Week 12; mean free PCSK9 concentrations fell from 308 to 162 ng/mL in patients who received dose adjustment to 150 mg Q2W (Fig. 1B). Between Weeks 20 and 24, the changes in free PCSK9 showed a similar pattern to changes in LDL-C; mean free PCSK9 concentrations reached a nadir of 76.3 ng/mL in patients who remained on 300 mg Q4W and fluctuated from 17.2 to 77.3 ng/mL in the group who had their dose adjusted from 300 mg Q4W. Reductions in free PCSK9 were accompanied by increases in mean total PCSK9 concentrations (representing all PCSK9 in the circulation, both free and bound to alirocumab) in all groups (Fig. 1C).

At Week 12, mean alirocumab concentrations were ~50% higher in the group who remained on 300 mg Q4W than those in the group who had the dose adjustment from 300 mg Q4W (9190 vs 6010 ng/mL; Fig. 1D). Between Weeks 20 and 24, mean alirocumab concentrations ranged from 9910 to 31,500 ng/mL in the group who remained on 300 mg Q4W, with a peak in alirocumab concentrations at Week 21; alirocumab concentrations varied from 10,900 to 16,400 ng/mL between Weeks 20 and 24 in patients who received dose adjustment from 300 mg Q4W. Alirocumab AUC concentrations for Weeks 20 and 24 are shown in Table 3.

Changes in LDL-C, PCSK9, and alirocumab concentrations in accordance with dose-adjustment status and use of statin

Among patients assigned to alirocumab 300 mg Q4W, 290/419 (69.2%) were receiving a statin; 80.7% vs 85.3%

Table 3 AUC_{W20-24} in accordance with initial alirocumab treatment, dose adjustment status, and statin use (pharmacokinetic population)

Statin use	AUC_{W20-24}, mg*d/L	75 mg Q2W (no dose adjustment)	150 mg Q2W (adjusted from 75 mg Q2W)	300 mg Q4W (no dose adjustment)	150 mg Q2W (adjusted from 300 mg Q4W)
All (statin + no statin)	n	66	19	286	65
	Mean (SD)	189 (107)	463 (290)	578 (325)	390 (340)
	Median, Q1:Q3	158 (120:236)	422 (199:592)	499 (352:703)	279 (194:489)
Statin	n	46	13	198	50
	Mean (SD)	172 (104)	449 (298)	518 (301)	336 (211)
	Median, Q1:Q3	133 (109:205)	343 (199:592)	451 (328:632)	248 (192:471)
No statin	n	20	6	88	15
	Mean (SD)	227 (105)	494 (297)	711 (338)	517 (572)
	Median, Q1:Q3	225 (161:265)	488 (223:586)	668 (465:909)	378 (197:715)

AUC_{W20-24}, area under the alirocumab concentration-time curve from weeks 20 to 24; Q2W, every 2 wk; Q4W, every 4 wk; SD, standard deviation.

of those receiving vs not receiving a statin achieved LDL-C goals and remained on alirocumab 300 mg Q4W without dose adjustment (Table 2). Baseline mean LDL-C concentrations in patients with no dose adjustment vs dose adjustment were 110.0 vs 123.5 mg/dL (patients on statin) and 143.6 vs 174.3 mg/dL (patients not on statin). Baseline mean free PCSK9 concentrations were higher among patients receiving a statin vs no statin, both for patients who remained on 300 mg Q4W (310 vs 202 ng/mL) and those who had their dose adjusted (340 vs 211 ng/mL; Table 2).

Before Week 12, patients receiving a statin who went on to have dose adjustment from 300 mg Q4W showed larger fluctuations in LDL-C (eg, reductions of 65.0% and 24.3% at weeks 6 and 8, respectively) than patients who had dose adjustment but were not on a statin (reductions of 51.7% and 37.4% at weeks 6 and 8, respectively; Fig. 2A, B). These fluctuations were reduced after dose adjustment from 300 mg Q4W (LDL-C percent reductions over weeks 20 to 24 of 58.5%–65.4% and 51.9%–56.3% for patients with or without statin treatment, respectively). Percentage LDL-C reductions over weeks 20 to 24 were greater or similar for patients who remained on alirocumab 300 mg Q4W (62.0%–75.3% and 57.4%–65.0% for patients with or without a statin, respectively) compared with the groups who had their dose adjusted from 300 mg Q4W to 150 mg Q2W (LDL-C reductions noted above) as well as the group who had the dose increased from 75 mg to 150 mg Q2W (LDL-C reductions over weeks 20 to 24 of 62.9%–69.6% and 48.7%–55.7% for patients with and without statin treatment, respectively).

By Week 12, mean free PCSK9 concentrations were higher among patients receiving a statin vs no statin, both for patients who remained on 300 mg Q4W (98.6 vs 25.7 ng/mL) and those who had their dose adjusted to 150 mg Q2W (191 vs 79.9 ng/mL). After dose adjustment from 300 mg Q4W to 150 mg Q2W, mean free PCSK9 concentrations fell by approximately 2- to 4-fold; Week 20 to 24 mean free PCSK9 concentrations were 21.4–94.3 ng/mL for patients receiving a statin and 3.36–25.1 ng/mL for patients not on a statin (Fig. 2C, D). For patients who remained on alirocumab 300 mg Q4W, mean free PCSK9 values for Weeks 20 to 24 ranged from 4.25 to 98.3 ng/mL (receiving statin) and 5.3 to 24.8 ng/mL (no statin), with a nadir observed at Weeks 21 to 22 (Fig. 2C, D). Mean total PCSK9 concentrations were greater at Week 12 in patients who remained on alirocumab 300 mg Q4W than those in patients who had dose adjustment, irrespective of statin use (Fig. 2E, F). Total PCSK9 concentrations for Weeks 20 to 24 were similar in patients who remained on alirocumab 300 mg Q4W or had the dose adjustment (Fig. 2E, F).

For patients remaining on alirocumab 300 mg Q4W, mean alirocumab concentrations at Week 12 were lower in patients receiving a statin vs no statin (7620 vs 12,400 ng/mL); between Weeks 20 and 24, alirocumab concentrations ranged from 8040 to 29,000 ng/mL (receiving statin) and 14,200 to 37,000 ng/mL (no statin; Fig. 2G, H). Mean

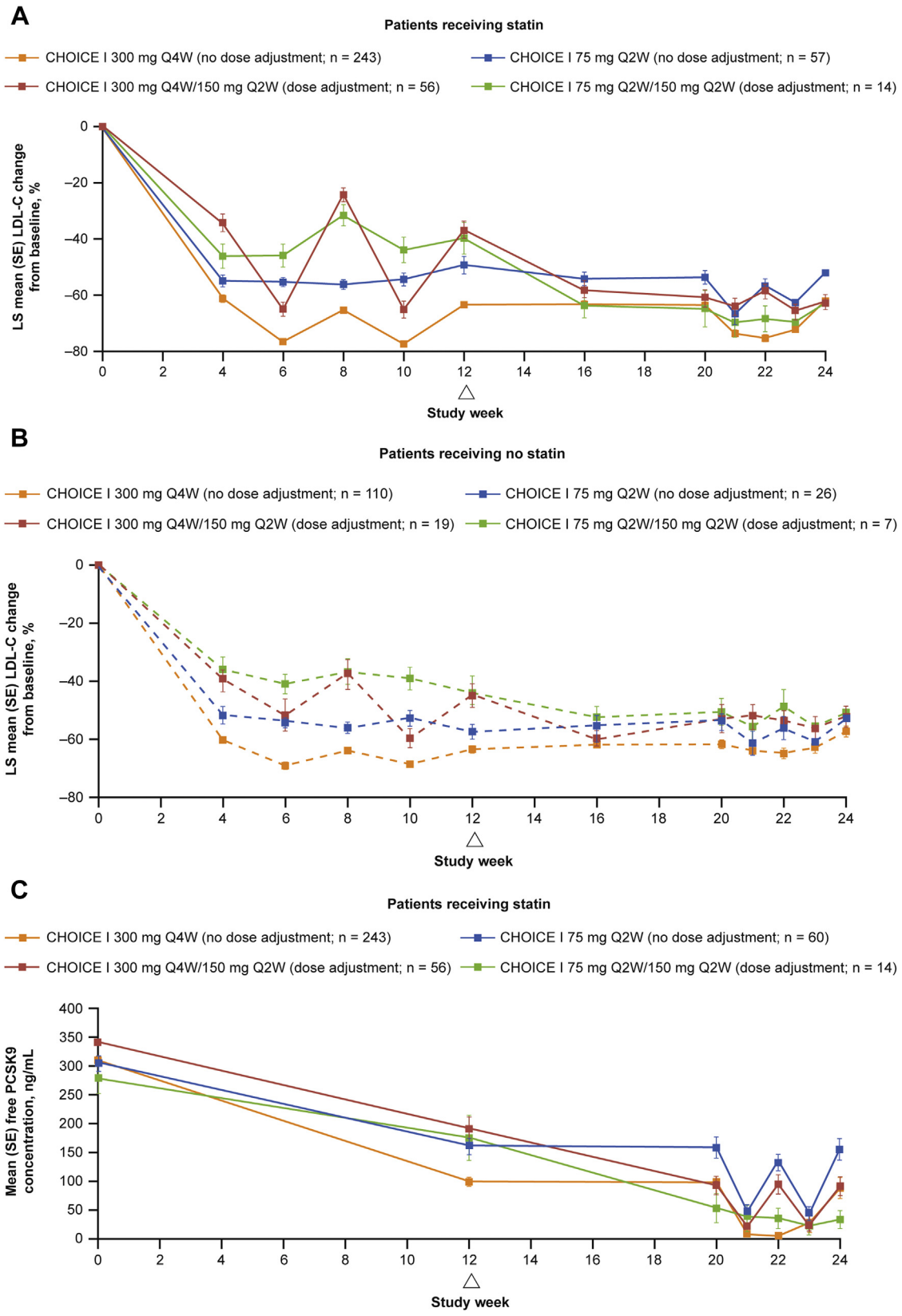
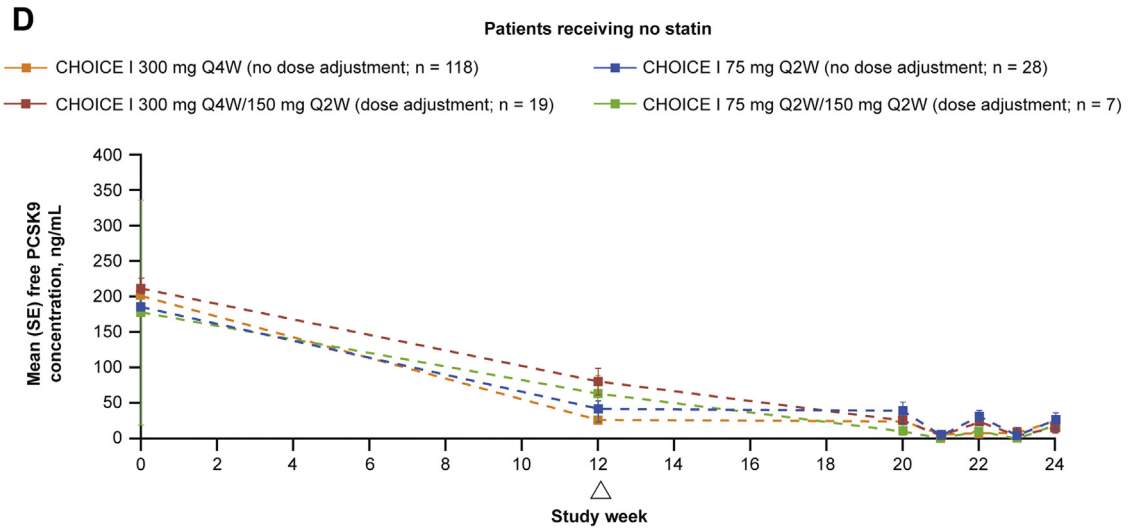
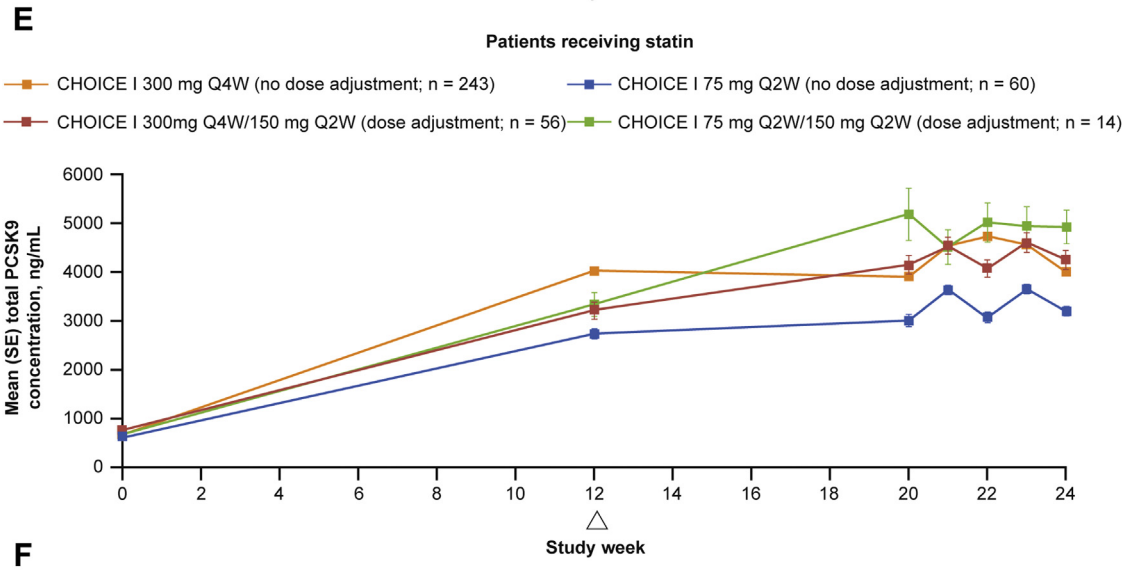


Figure 2 Mean (SE) LDL-C (A, statin; B, no statin), free PSCK9 (C, statin; D, no statin), total PCSK9 (E, statin; F, no statin), and alirocumab (G, statin; H, no statin) concentrations in accordance with dose adjustment status for alirocumab-treated patients receiving statin and no statin (pharmacokinetic population*) *LDL-C data assessed in the intention-to-treat population. LDL-C, low-density lipoprotein cholesterol; LS, least squares; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; Q4W, every 4 weeks; SE, standard error.





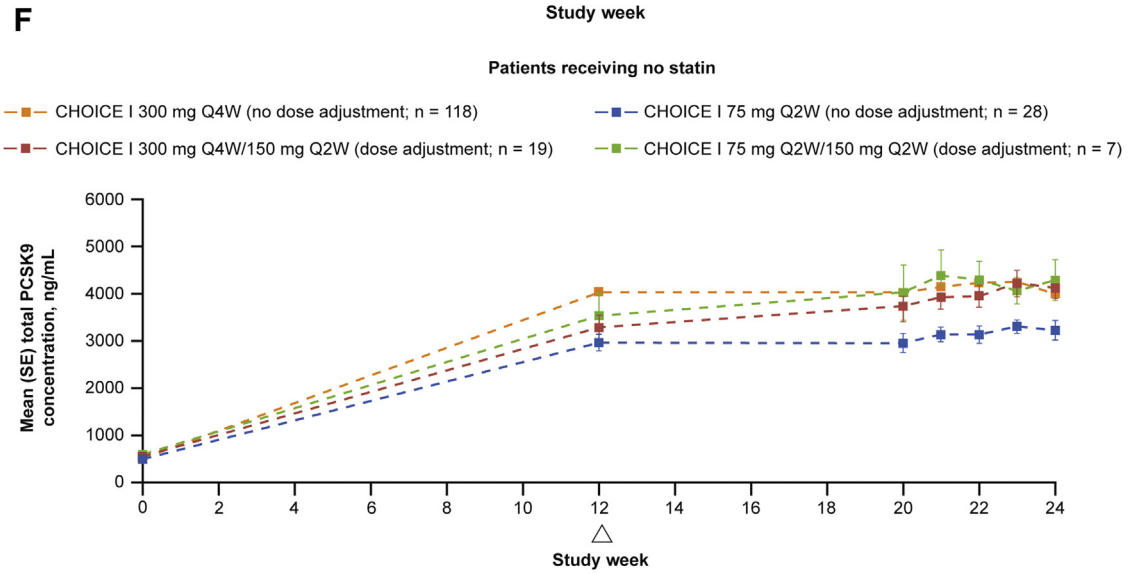


Figure 2 (*continued*).

alirocumab concentrations at Week 12 for patients who received dose adjustment from 300 mg Q4W were 4580 ng/mL (receiving statin) and 10,100 ng/mL (no statin); mean alirocumab concentrations were 8570–14,100 ng/mL (statin) and 17,200–23,000 ng/mL (no statin) between weeks 20–24 (Fig. 2G, H). Patients receiving a statin had an

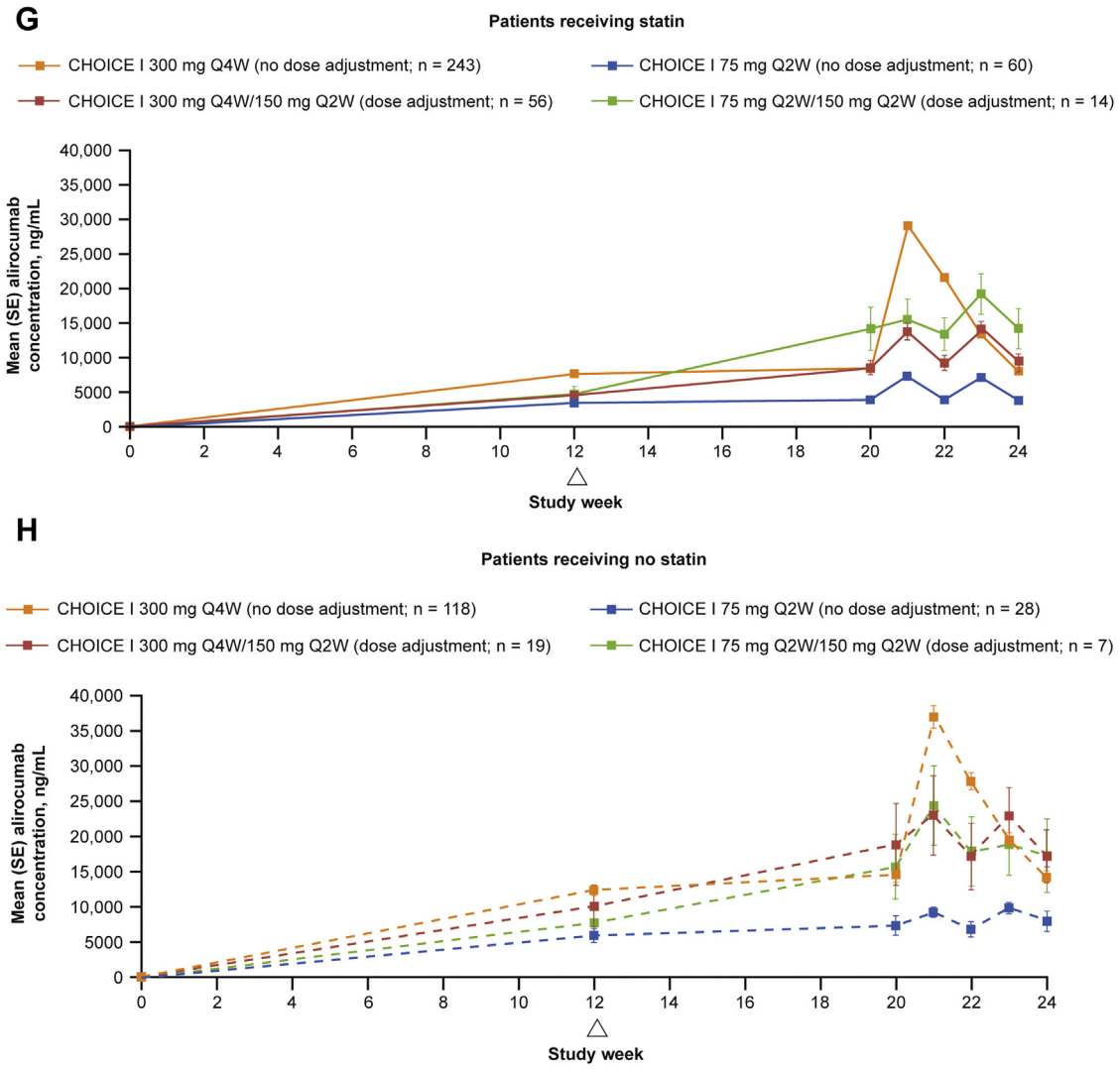


Figure 2 (*continued*).

approximately 25% lower Week 20 to 24 alirocumab AUC concentration vs patients not receiving a statin (Table 3). Regardless of statin use, Week 20 to 24 alirocumab AUC concentrations were lower in patients who had the dose adjustment from 300 mg Q4W than those in patients who remained on 300 mg Q4W (Table 3), despite the same total monthly dose of alirocumab, suggesting a higher degree of alirocumab clearance in the group who had the dose adjusted.

Efficacy of alirocumab 300 mg Q4W/possible dose adjustment to 150 mg Q2W in accordance with baseline PCSK9 concentrations

Alirocumab efficacy (assessed as the difference in LDL-C percent reduction from baseline to Week 24 between alirocumab 300 mg Q4W/possible dose adjustment to 150 mg Q2W vs placebo) was consistent between patients with baseline total or free PCSK9 concentrations at/above or below the median, both for patients receiving and not receiving a statin (Fig. 3).

Safety analysis

A summary of safety data for alirocumab and placebo in accordance with statin usage is shown in Table 4. Overall, safety results were consistent between patients receiving a statin or not. There was a higher frequency of injection-site reactions and headache with alirocumab vs placebo.

Discussion

Monoclonal antibodies are subject to target-mediated clearance, where clearance of the antibody (in this case alirocumab) and therefore duration of the pharmacodynamic effect (LDL-C reduction) is dictated by concentrations of the target (PCSK9) and influenced by factors that

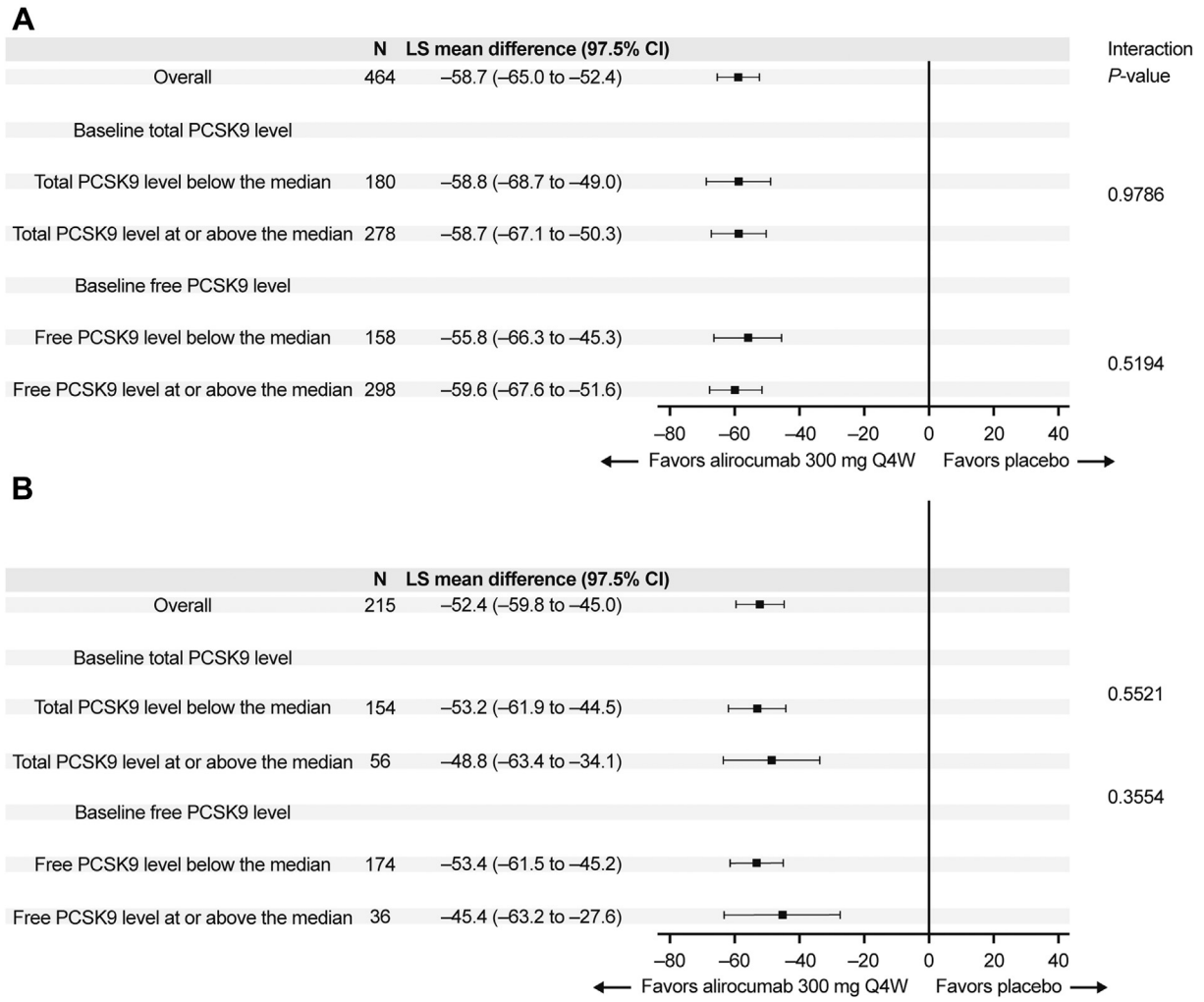


Figure 3 Difference in LDL-C percent reductions from baseline to Week 24 for alirocumab 300 mg Q4W vs placebo in accordance with baseline free and total PCSK9 levels and (A) concomitant statin use or (B) no background statin use (intention-to-treat population). CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; LS, least squares; PCSK9, proprotein convertase subtilisin/kexin type 9; Q4W, every 4 weeks.

affect target production (which may include use of statins and other lipid-lowering therapies such as ezetimibe and fenofibrate, as well as disease states including familial hypercholesterolemia, chronic kidney disease, and diabetes). In this analysis, we demonstrated that patients receiving a statin had higher free PCSK9 concentrations at baseline and during treatment. Alirocumab concentrations were also lower in patients receiving a statin, suggesting increased target-mediated clearance. However, alirocumab concentrations were also lower in patients who had the 300 mg Q4W dose adjusted to 150 mg Q2W, both among patients receiving a statin and those who did not. This suggests increased clearance of alirocumab among patients receiving the dose adjustment, regardless of statin use; other factors contributing to the increased alirocumab clearance and need for dose adjustment may include higher baseline LDL-C concentrations and more severe background disease (higher CVD risk).

Increased target-mediated clearance of alirocumab (and loss of duration of pharmacodynamic effect over the 4-week dosing interval) can explain the greater fluctuations in LDL-C observed over weeks 6 to 12 in patients receiving alirocumab 300 mg Q4W who required dose adjustment. Patients who had the 300 mg Q4W dose adjusted to 150 mg Q2W at Week 12 showed reduced fluctuations in LDL-C over weeks 20 to 24.

Most patients remained on 300 mg Q4W without dose adjustment (82.1%; statin-treated: 80.7%; no statin: 85.3%), and this dosing regimen was sufficient to produce adequate LDL-C reduction with minimal fluctuation in LDL-C concentrations for these patients. Mean LDL-C reductions were greater or similar over weeks 20 to 24 for patients who remained on 300 mg Q4W (both with and without concomitant statin) compared with those on 150 mg Q2W. Dose adjustment from 300 mg Q4W to 150 mg Q2W was more likely in patients with higher baseline LDL-C, higher CVD risk, or for patients on a statin.

The relationship between alirocumab, free PCSK9, and LDL-C concentrations observed in CHOICE I was consistent with observations from previous studies.[5,6] Results

Table 4 Safety summary in accordance with statin therapy status (safety population)

	Receiving statin (n = 547)		No statin (n = 255)	
n (%)	Alirocumab* (n = 390)	Placebo (n = 157)	Alirocumab* (n = 183)	Placebo (n = 72)
TEAEs	302 (77.4)	115 (73.2)	153 (83.6)	56 (77.8)
Treatment-emergent SAEs	43 (11.0)	23 (14.6)	23 (12.6)	10 (13.9)
TEAEs leading to discontinuation	21 (5.4)	13 (8.3)	17 (9.3)	4 (5.6)
TEAEs leading to death	0	0	2 (1.1)	1 (1.4)
TEAEs by preferred term occurring in ≥5% of patients in any group				
Injection-site reaction	47 (15.1)	10 (6.4)	29 (15.8)	6 (8.3)
Headache	15 (3.8)	9 (5.7)	20 (10.9)	4 (5.6)
Arthralgia	19 (4.9)	12 (7.6)	17 (9.3)	3 (4.2)
Sinusitis	16 (4.1)	4 (2.5)	16 (8.7)	7 (9.7)
Fatigue	10 (2.6)	9 (5.7)	12 (6.6)	2 (2.8)
Nasopharyngitis	37 (9.5)	14 (8.9)	12 (6.6)	4 (5.6)
Nausea	14 (3.6)	11 (7.0)	12 (6.6)	4 (5.6)
Pain in extremity	14 (3.6)	2 (1.3)	11 (6.0)	0
Bronchitis	16 (4.1)	7 (4.5)	10 (5.5)	5 (6.9)
Diarrhea	19 (4.9)	12 (7.6)	10 (5.5)	5 (6.9)
Upper respiratory tract infection	34 (8.7)	14 (8.9)	8 (4.4)	4 (5.6)
Urinary tract infection	27 (6.9)	6 (3.8)	8 (4.4)	4 (5.6)
Hypertension	13 (3.3)	6 (3.8)	7 (3.8)	6 (8.3)
Myalgia	12 (3.1)	4 (2.5)	7 (3.8)	4 (5.6)
Muscle spasms	8 (2.1)	10 (6.4)	6 (3.3)	3 (4.2)
Muscle strain	4 (1.0)	4 (2.5)	6 (3.3)	4 (5.6)
Back pain	28 (7.2)	9 (5.7)	5 (2.7)	5 (6.9)
Eye disorders	11 (2.8)	9 (5.7)	5 (2.7)	3 (4.2)
Contusion	10 (2.6)	8 (5.1)	4 (2.2)	2 (2.8)
Cough	13 (3.3)	9 (5.7)	3 (1.6)	1 (1.4)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Data from the CHOICE I study.
*Alirocumab data are a pool of patients who received 300/150 mg Q4W and 75/150 mg Q2W doses.

with the alirocumab 75 mg Q2W dose were consistent with those observed in the alirocumab phase 3 program.[14] The increased total PCSK9 concentrations after alirocumab administration likely reflect the longer half-life of the inactive alirocumab:PCSK9 complex.

The safety profile of alirocumab was similar between patients receiving and not receiving a statin and was consistent with previous safety reports for alirocumab.[15]

Results from this analysis were consistent with the known mode of action of alirocumab and provided further insight in terms of the relationship between alirocumab, PCSK9, and LDL-C and disease severity. Most patients, including those receiving concomitant statin therapy, should achieve adequate LDL-C reduction using the alirocumab 300 mg Q4W dose. The alirocumab 300 mg Q4W dose provides patients with a less frequent dosing regimen than Q2W dosing regimens, which may be more convenient for some patients and could lead to greater long-term adherence to treatment. Dose adjustment decisions should be based on achieved LDL-C and target levels; however, concomitant statin use and/or increased disease severity may explain a less-than-expected LDL-C response when alirocumab is dosed Q4W (because of increased PCSK9 production by the statin resulting in increased alirocumab clearance).

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