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Long-term treatment adherence to the proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab in 6 ODYSSEY Phase III clinical studies with treatment duration of 1 to 2 years

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KEYWORDS:
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Low-density lipoprotein cholesterol;
Proprotein convertase subtilisin/kexin type 9 inhibitor

BACKGROUND: Nonadherence to cardiovascular medications, including daily, oral statin therapy, negatively impacts outcomes in patients requiring low-density lipoprotein cholesterol (LDL-C)-lowering therapy. The proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab also reduces LDL-C, but has a different mode of administration (subcutaneous injection).

OBJECTIVE: The objective of the study was to assess long-term adherence to alirocumab 75 or 150 mg, given every 2 weeks, in phase III trials of patients with sub-optimally controlled hypercholesterolemia.

METHODS: Data were pooled from 6 ODYSSEY trials (n = 4212) with double-blind treatment durations of 52 to 104 weeks. Adherence was reported as percentage of days receiving injections according to dosing schedule and categorized into 100% adherence, below-planned dosing, above-planned dosing, and both below- and above-planned dosing. Overall adherence was calculated as 100 − (percentage of days with below-planned dosing + percentage of days with above-planned dosing). Safety of alirocumab and effect on LDL-C levels were also evaluated.

RESULTS: Adherence was analyzed for 4197 patients (n = 2786 alirocumab; n = 1411 control). Mean overall adherence was high (alirocumab 98.0%; control 97.8%). Among patients receiving alirocumab, 45.7% were 100% adherent, 20.4% had below-planned dosing, 2.9% had above-planned dosing, and 31.1% had both below- and above-planned dosing. Mean percentage reduction in LDL-C

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(baseline to Week 52) was 45.8% to 61.9%, depending on alirocumab dose, and was comparable across adherence categories. Treatment-emergent adverse events leading to alirocumab discontinuation were infrequent and included myalgia and injection-site reactions (<1% each).

CONCLUSIONS: Alirocumab injections were associated with a high level of adherence over ≥1 year. Infrequent below- or above-planned dosing had minimal impact on LDL-C reductions.

Introduction

Statin-based treatment constitutes the standard first-line therapy for reducing low-density lipoprotein cholesterol (LDL-C) levels and mitigating the risk of atherosclerotic cardiovascular (CV) events.[1,2] However, despite statin treatment, a large proportion of patients do not achieve sufficient reduction in LDL-C levels. A number of these patients may be at high CV risk, such as patients with a history of myocardial infarction or stroke, have very high baseline LDL-C levels, such as patients with heterozygous familial hypercholesterolemia (HeFH), or have statin intolerance.[3–5] Nonadherence to statin therapy is also relatively common, particularly in real-world settings where, compared with clinical trials, patients may be followed less rigorously.[2,6–11] In clinical trials, adherence to statins has been reported to be 79% to 90% at 1 year and 78% at 4 years.[12,13] In contrast, in a cohort study conducted using 4 separate population-based administrative data sources, 2-year adherence rates with statin therapy were only 40.1% in patients with acute coronary syndromes, 36.1% in patients with coronary artery disease, and 25.4% in the primary prevention setting.[8] A separate retrospective cohort study of 229,918 patients reported that the proportion of days covered with statin therapy was 45% in primary prevention groups and 59% in secondary-prevention groups; in both groups, adherence reduced over time, with ≥75% of patients discontinuing statin therapy by 2 years from the index date.[7] A meta-analysis of CV therapy adherence data from 20 studies demonstrated overall adherence rates to CV therapies of 57% after a median of 24 months.[10] Adherence to statin therapy was 57% and 76% in the primary and secondary prevention settings, respectively.[10] Nonadherence has an adverse effect on patient outcomes and is associated with increased healthcare costs, morbidity, hospital readmissions, and mortality.[2,14]

Alirocumab (Praluent; Sanofi, and Regeneron Pharmaceuticals, Inc) is a fully human monoclonal antibody that binds to and inhibits proprotein convertase subtilisin/kexin type 9 (PCSK9), preventing degradation of LDL receptors. This increases the number of LDL receptors on hepatocytes and promotes the removal of LDL-C from the circulation, thus lowering LDL-C levels.[15,16] Clinical trials of alirocumab, as a monotherapy or in combination with statins (with or without other lipid-lowering therapies [LLTs]), have demonstrated reductions in LDL-C of up to 61%.[17–19] Alirocumab received Food and Drug Administration approval in the United States in July 2015 as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical atherosclerotic CV disease (CVD) who require additional LDL-C lowering.[20] It was also approved in Europe in September 2015 for use in adults with primary hypercholesterolemia or mixed dyslipidemia, as an adjunct to diet either in combination with maximally tolerated statin with or without other LLTs for those unable to reach LDL-C goals, or as a monotherapy with or without other LLTs for those who are statin intolerant or for whom a statin is contraindicated.[21]

Alirocumab is administered on a bi-weekly (Q2W) dosing schedule by subcutaneous injections using a prefilled pen or syringe for self-injection.[20,21] However, many patients requiring LLT may not be experienced with self-injected medication as, until recently, the only injectable LLT available was mipomersen (Kynamro; Kastle Therapeutics), an antisense oligonucleotide targeting apolipoprotein B, licensed in the United States for the treatment of homozygous familial hypercholesterolemia (HoFH),[22] a rare condition that affects approximately 1 in 300,000 individuals.[23] Now, however, there are 2 injectable anti-PCSK9 monoclonal antibodies available; in addition to alirocumab, evolocumab (Repatha; Amgen) was approved by the Food and Drug Administration in 2015 as an adjunct to diet and maximally tolerated statins in patients with HeFH or atherosclerotic CVD who require additional LDL-C-lowering or in addition to other LLTs in patients with HoFH who require further LDL-C reduction.[9,24] Similarly, evolocumab is also approved in Europe for treating patients with primary hypercholesterolemia or mixed dyslipidemia 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, and in patients with HoFH in combination with other LLTs.[25] Because self-injectable PCSK9 inhibitors such as alirocumab are a new concept in patients with hypercholesterolemia, there is a possibility for potential concerns with regard to patient adherence impacting on treatment outcomes.[26] In a study of patient and physician perspectives on the use of alirocumab, both physicians and patients responded positively to use of an injectable device, suggesting that alirocumab treatment by either prefilled pen or syringe

would not deter its use in patients requiring additional LLT.[27] However, long-term adherence to self-injected alirocumab has not been rigorously assessed.

In this analysis, data from 6 studies within the ODYSSEY Phase III program were used to explore treatment adherence to alirocumab over a period of at least 1 year.

Methods

Studies and patients

Adherence to alirocumab injections was evaluated over a period of 1 to 2 years using pooled data from 6 Phase III, randomized, double-blind, controlled ODYSSEY trials (FH I [NCT01623115], FH II [NCT01709500], HIGH FH [NCT01617655], COMBO I [NCT01644175], COMBO II [NCT01644188], and LONG TERM [NCT01507831]; Fig. 1). Study designs and results of the individual trials have been reported previously.[17,19,28–31] In short, FH I, FH II, and HIGH FH evaluated alirocumab in patients with HeFH,[28,29] whereas COMBO I and COMBO II investigated alirocumab in patients with high CV risk.[19,30] LONG TERM assessed alirocumab in patients with HeFH or those at high CV risk.[17] With the exception of COMBO II, which included ezetimibe as an active comparator, all trials were placebo-controlled. Patients were followed for at least 52 weeks (COMBO I: 52 weeks; COMBO II: 104 weeks; all other studies: 78 weeks; Fig. 1).

All 6 trials enrolled patients with sub-optimally controlled hypercholesterolemia who had been receiving maximally tolerated, potent statin therapy for at least 4 weeks before study entry. The use of nonstatin LLTs was permitted in all studies except COMBO II. FH I, FH II, COMBO I, and COMBO II included patients who had baseline LDL-C levels ≥70 mg/dL (1.8 mmol/L) and established CVD, or those with LDL-C ≥100 mg/dL (2.59 mmol/L) at baseline without a history of documented CVD or coronary heart disease risk equivalents. HIGH FH enrolled patients with baseline LDL-C levels ≥160 mg/dL (4.1 mmol/L) and LONG TERM enrolled patients with baseline LDL-C levels ≥70 mg/dL (1.8 mmol/L).

In the FH I, FH II, COMBO I, and COMBO II studies, the starting dose of alirocumab was 75 mg Q2W. A dose increase

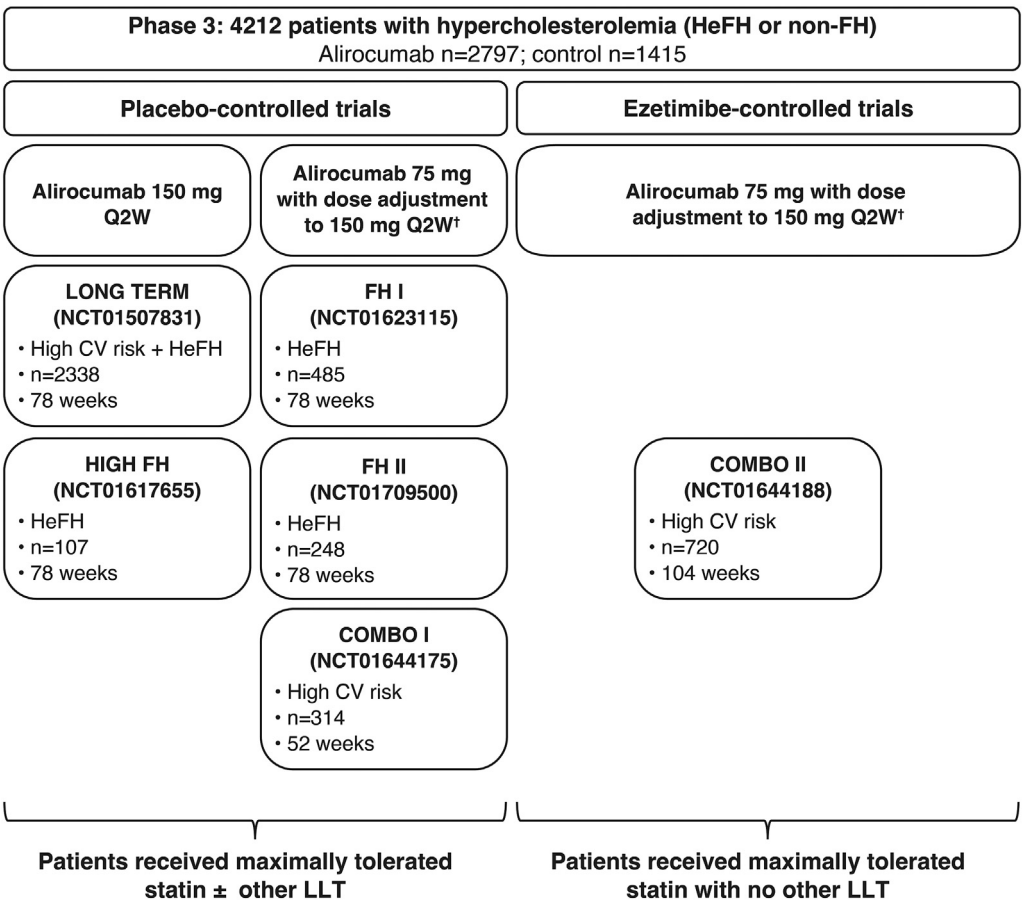


Figure 1 ODYSSEY Phase III studies and patient populations included in this analysis (randomized and treated population). Clinicaltrials.gov identifiers: NCT01507831 (LONG TERM); NCT01617655 (HIGH FH); NCT01623115 (FH I); NCT01709500 (FH II); NCT01644175 (COMBO I); NCT01644188 (COMBO II). †Alirocumab dose could be increased from 75 mg Q2W to 150 mg Q2W at Week 12 depending on Week 8 LDL-C level. n: randomized and treated patients. CV, cardiovascular; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Q2W, every 2 weeks.

to 150 mg Q2W occurred at Week 12 if, at Week 8, patients had LDL-C levels ≥70 mg/dL (1.8 mmol/L). Patients in LONG TERM and HIGH FH received alirocumab 150 mg Q2W throughout the study. Alirocumab was administered subcutaneously using a 1 mL prefilled pen, except for LONG TERM, which used a prefilled syringe. Patients either self-injected alirocumab or designated another person to assist them with the injections, if desired. Self-injection training using placebo was performed during the screening period. Those in the control groups received placebo injections subcutaneously to match the alirocumab Q2W injection schedule. In COMBO II, ezetimibe was given orally, at a daily dose of 10 mg, with or without food; patients in the alirocumab arm received oral placebo for ezetimibe to maintain the blinded nature of the trial.

The studies were performed in accordance with the ethical principles in the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice, and appropriate local or regulatory requirements. Informed consent was obtained from all patients included in these studies.

Endpoints

Treatment adherence

Patient adherence to treatment with alirocumab or control agents was based on information recorded by the patient in a specified patient diary. For each injection received, patients were required to record the date and time of the injection and treatment kit number. These data were then entered into electronic case report forms (eCRFs) at the study sites; the study monitor cross-checked the consistency between information recorded in the eCRFs against that recorded in patient diaries and against the number of returned unused syringes of a corresponding kit.

Adherence to injections was reported as the percentage of days that patients received injections according to the dosing schedule. Patients' adherence levels to injections were divided into 4 categories: 100% adherent, those with below-planned dosing, those with above-planned dosing, and those with both below- and above-planned dosing. In the case of below-planned dosing, this was defined as the number of days with no injection administered within the previous 17 days divided by the duration of treatment-injection exposure in days. For above-planned dosing, this was defined as the number of days with >1 injection administered within the previous 11 days divided by the duration of treatment-injection exposure in days. Overall adherence was calculated for each patient as 100 − (percentage of days with below-planned dosing + percentage of days with above-planned dosing). Evaluations of injection adherence levels took into account the fact that injections were given Q2W ± 3 days, as defined in the study protocols.

Adherence to ezetimibe and placebo capsules in the ezetimibe-controlled COMBO II trial was also based on information documented in patient dosing diaries. Information from these diaries, including capsule kit number, was logged into the eCRFs at study sites and cross-checked against the returned kits. Adherence to capsules was measured as the number of capsules taken multiplied by 100 divided by (the last capsule intake date − the first capsule intake date + 1). Good adherence to capsules was defined as having taken ≥80% of capsules at the scheduled time; poor adherence to capsules was defined as having taken <80% of capsules at the scheduled time.

LDL-C measurements

In the present analysis, the effect of alirocumab on LDL-C level was evaluated by calculating the percentage change from baseline to Week 52 in calculated LDL-C. Blood samples were collected in the morning after a 10-hour overnight fast and before administration of the study drug. LDL-C concentrations were calculated using the Friedewald formula.

Safety assessments

Safety was monitored continuously throughout the 6 studies. Treatment-emergent adverse events (TEAEs) were defined as adverse events, which, irrespective of relationship to study drug, developed, worsened, or became serious during the period from the first to the last dose of study treatment plus 70 days. In COMBO II, the first treatment administration of the investigative medicinal product was either a capsule or an injection, whichever came first.

Statistical considerations

Adherence and safety data were analyzed using the safety population (randomized and treated) and were summarized using descriptive statistics. The percentage change from baseline to Week 52 in calculated LDL-C was analyzed using the modified intent-to-treat population, defined as all randomized patients who took at least 1 or part of a dose of the study drug and had an evaluable primary efficacy endpoint during the efficacy treatment period (on-treatment approach). Missing data at Week 52 were imputed using the last value on-treatment.

Results

Patient disposition and baseline characteristics

Across the 6 studies, 4212 patients were randomized and treated: 2797 in the alirocumab arms and 1415 in the control arms. Two pools were considered based on the control arms in the trials: the placebo-controlled pool and the ezetimibe-controlled pool (Fig. 1). Pooled baseline characteristics are shown in Table 1. Mean age ranged from 58.6 to 61.7 years and mean body mass index was

Table 1 Baseline patient characteristics (randomized and treated population)—placebo- and ezetimibe-controlled pools

Characteristic	Placebo-controlled trials		Ezetimibe-controlled trial	
	Alirocumab (n = 2318)	Placebo (n = 1174)	Alirocumab (n = 479)	Ezetimibe (n = 241)
Mean age (SD), y	58.6 (11.6)	58.8 (11.3)	61.7 (9.4)	61.3 (9.2)
Males, n (%)	1413 (61.0)	711 (60.6)	360 (75.2)	170 (70.5)
Race, White, n (%)	2136 (92.1)	1071 (91.2)	404 (84.3)	206 (85.5)
Mean BMI (SD), kg/m^2	30.1 (5.6)	30.4 (5.6)	30.0 (5.4)	30.3 (5.1)
HeFH, n (%)	837 (36.1)	418 (35.6)	0	0
Diabetes, n (%)	698 (30.1)	356 (30.3)	148 (30.9)	77 (32.0)
ASCVD, n (%)	1611 (69.5)	834 (71.0)	461 (96.2)	224 (92.9)

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; HeFH, heterozygous familial hypercholesterolemia; SD, standard deviation.
Pooled data from the 6 phase III ODYSSEY trials (FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM) are shown.

30.0 to 30.4 kg/m^2. The proportion of patients with HeFH was comparable among patients receiving alirocumab and those receiving placebo. There were no patients with HeFH recruited in COMBO II, which formed the ezetimibe-controlled pool (Table 1). The proportion of patients with diabetes at baseline was similar between alirocumab and control groups, ranging from 30.1% to 32.0%. Almost all (>92%) patients in the COMBO II trial had atherosclerotic CVD, compared with 69.5% and 71% in alirocumab and placebo arms, respectively, in pooled placebo-controlled studies.

Adherence

Treatment adherence data were available for 4197 of the 4212 patients, of whom 2786 received alirocumab injections and 1411 received placebo injections. Treatment adherence was high, with a mean overall adherence of 98.0% in the alirocumab arm and 97.8% in the control arm (Table 2). Within individual studies, overall mean treatment adherence ranged from 97.6% to 98.3% among the alirocumab arms and from 96.9% to 99.1% in control arms (Fig. 2). Almost half of patients receiving alirocumab (45.7%) or control (44.5%) were 100% adherent to their treatment regimen (Table 2). A comparable proportion of patients in the alirocumab and control groups experienced below-planned dosing only (20.4% vs 23.0%), above-planned dosing only (2.9% vs 3.3%), and both below- and above-planned dosing (31.1% vs 29.3%; Table 2). Adherence to ezetimibe or placebo capsules (COMBO II study only) was also high, with a mean of 96.8% in the alirocumab group and 97.6% in the ezetimibe group (Table 3).

To determine whether adherence to alirocumab or placebo injections were driven by variations in patient characteristics, baseline characteristics were evaluated according to the 4 treatment adherence categories. In all 4 categories, baseline characteristics were comparable between alirocumab and control groups (Table 4). Mean baseline LDL-C values varied from 119.7 mg/dL (3.1 mmol/L) to 132.5 mg/dL (3.43 mmol/L) in the different groups.

Effect on LDL-C

The percentage change from baseline to Week 52 in calculated LDL-C in alirocumab-treated patients only (ie, excluding the control arms) was evaluated according to the 4 treatment adherence categories and alirocumab initial

Table 2 Overall treatment adherence to alirocumab or placebo injections (randomized and treated population with evaluable compliance), calculated as 100 − (percentage of days with below-planned dosing + percentage of days with above-planned dosing)

Adherence parameter	Alirocumab, n = 2786	Control, n = 1411
Mean (SD) overall treatment adherence, %	98.0 (4.4)	97.8 (4.9)
Median overall treatment adherence, %	99.6	99.6
Min–max, %	44–100	46–100
Categories of treatment adherence, n (%)		
100% adherence	1272 (45.7)	628 (44.5)
Only below-planned dosing	567 (20.4)	324 (23.0)
Only above-planned dosing	81 (2.9)	46 (3.3)
Both below- and above-planned dosing	866 (31.1)	413 (29.3)

SD, standard deviation.
Pooled data from the 6 phase III ODYSSEY trials (FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM) are shown.

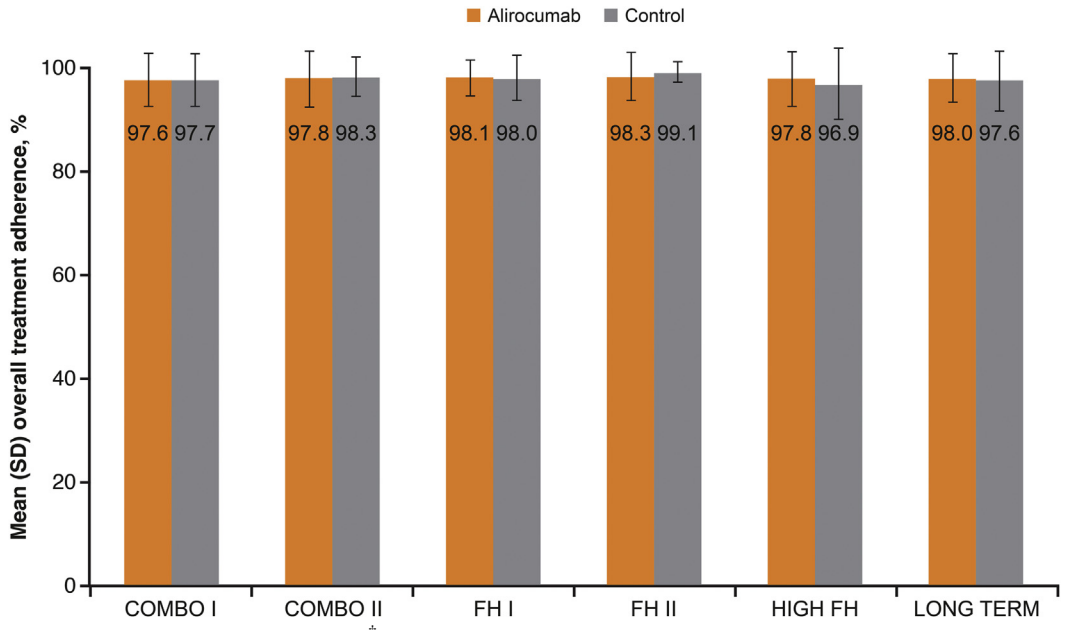


Figure 2 Mean (SD) overall treatment adherence[†] (to alirocumab or placebo injections) in individual studies (randomized and treated population). Clinicaltrials.gov identifiers: NCT01507831 (LONG TERM); NCT01617655 (HIGH FH); NCT01623115 (FH I); NCT01709500 (FH II); NCT01644175 (COMBO I); NCT01644188 (COMBO II). [†]Overall treatment adherence was calculated as 100 − (percentage of days with below-planned dosing + percentage of days with above-planned dosing). SD, standard deviation.

dose, using an on-treatment approach (on-treatment LDL-C values). A total of 2738 patients in the alirocumab arm had data for LDL-C during the on-treatment period. The mean percentage change from baseline to Week 52 in calculated LDL-C ranged from −45.8% to −61.9% and was broadly comparable across all 4 treatment adherence categories (Fig. 3). A total of 1148 patients were initiated on alirocumab 75 mg Q2W, whereas 1590 patients were initiated on alirocumab 150 mg Q2W (LONG TERM and HIGH FH). Of those initiated on 75 mg alirocumab Q2W, 25.1% to 30.6% received dose increase to 150 mg alirocumab Q2W at Week 12 (Fig. 3). For each adherence category, the mean percentage reduction in calculated LDL-C was slightly greater for those receiving alirocumab 150 mg Q2W vs those starting on 75 mg Q2W (with possible increase to 150 mg Q2W; Fig. 3).

Safety analyses

All 4212 patients were included in the safety analysis. Pooled safety data from the 6 studies are shown in Tables 5–7. The rates of TEAEs, treatment-emergent serious adverse events, and TEAEs leading to discontinuations or deaths were generally comparable between alirocumab and control arms (Table 5). The most common TEAE leading to treatment discontinuation in the alirocumab group was myalgia, occurring in 6 (0.3%) and 3 (0.6%) patients in the placebo- and ezetimibe-controlled pools, respectively (Table 6). Within the control groups, myalgia was also the most common TEAE leading to discontinuation in the ezetimibe group (2 patients [0.8%]); whereas back pain was the most common TEAE leading to treatment discontinuation in the placebo group (4 patients [0.3%]). There were no cases of myalgia leading to

Table 3 Overall treatment adherence to ezetimibe or placebo capsules in the COMBO II study (randomized and treated population with evaluable compliance), calculated as 100 × the number of capsules taken/(last capsule intake date − first capsule intake date + 1)

Adherence parameter	Placebo capsule for ezetimibe, n = 479	Ezetimibe, n = 241
Number of patients with available data	472	237
Mean (SD) overall treatment adherence, %	96.8 (8.7)	97.6 (5.7)
Median overall treatment adherence, %	99.6	99.4
Min–max, %	1–135	47–115
Categories of treatment adherence, n (%)		
Poor adherence (patients with <80% adherence)	18 (3.8)	4 (1.7)
Good adherence (patients with ≥80% adherence)	454 (96.2)	233 (98.3)

SD, standard deviation.
Data from the ezetimibe-controlled COMBO II study is shown.

Table 4 Baseline patient characteristics (randomized and treated population) according to treatment adherence category

Characteristic	100% adherence		Below-planned dosing		Above-planned dosing		Both below- and above-planned dosing	
	Alirocumab (n = 1272)	Control (n = 628)	Alirocumab (n = 567)	Control (n = 324)	Alirocumab (n = 81)	Control (n = 46)	Alirocumab (n = 866)	Control (n = 413)
Mean age (SD), y	59.8 (10.6)	59.5 (11.2)	59.5 (11.8)	59.7 (10.7)	59.6 (10.3)	60.5 (11.6)	58.1 (11.9)	58.5 (11.0)
Males, n (%)	806 (63.4)	386 (61.5)	355 (62.6)	205 (63.3)	48 (59.3)	25 (54.3)	556 (64.2)	261 (63.2)
Race, White, n (%)	1170 (92.0)	571 (90.9)	508 (89.6)	291 (89.8)	73 (90.1)	41 (89.1)	779 (90.0)	370 (89.6)
Mean BMI (SD), kg/m^2	30.1 (5.6)	30.2 (5.7)	30.3 (5.6)	30.9 (5.7)	30.3 (5.0)	29.0 (4.5)	29.8 (5.5)	30.2 (5.3)
HeFH, n (%)	355 (27.9)	182 (29.0)	145 (25.6)	82 (25.3)	30 (37.0)	15 (32.6)	298 (34.4)	139 (33.7)
Diabetes, n (%)	390 (30.7)	188 (29.9)	184 (32.5)	117 (36.1)	23 (28.4)	15 (32.6)	248 (28.6)	112 (27.1)
ASCVD, n (%)	959 (75.4)	477 (76.0)	430 (75.8)	247 (76.2)	56 (69.1)	29 (63.0)	621 (71.7)	302 (73.1)
Mean baseline LDL-C (SD), mg/dL	122.7 (44.8)	123.7 (47.0)	123.9 (48.5)	119.7 (39.9)	124.0 (42.1)	132.5 (42.9)	124.9 (44.3)	123.5 (42.3)

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; SD, standard deviation.
Pooled data from the 6 phase III ODYSSEY trials (FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM) are shown.

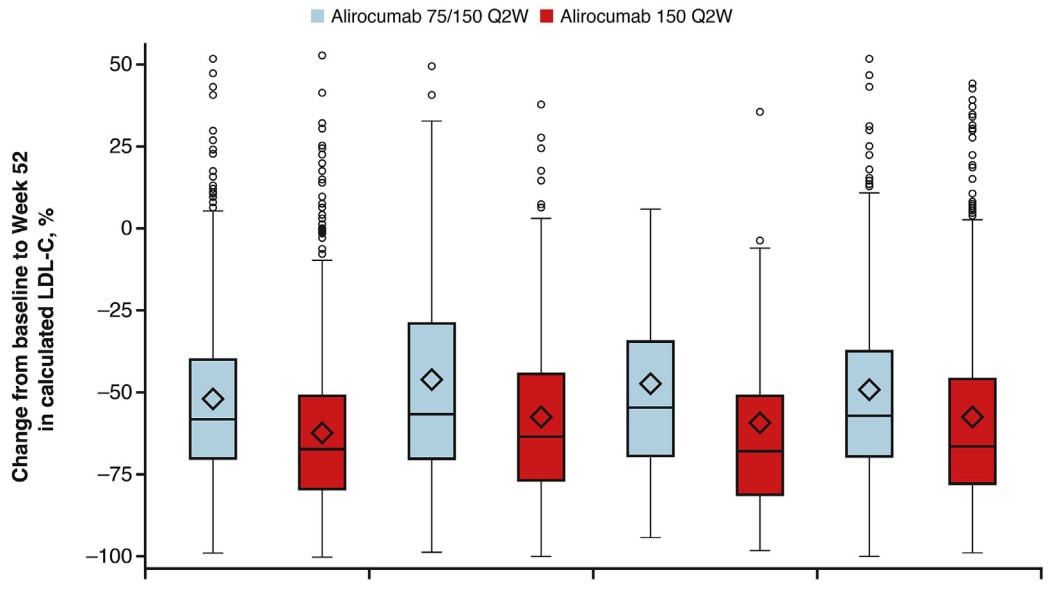
treatment discontinuation in the placebo group (Table 6). Injection site reactions led to treatment discontinuation in a small number of patients: 4 (0.2%; placebo-controlled pool) and 2 (0.4%; ezetimibe-controlled pool) patients in the alirocumab group vs 3 patients (0.3%) in the placebo group and 1 (0.4%) in the ezetimibe group (Table 6). The rates of TEAEs were also similar among the different treatment adherence categories, ranging from 77.9% (100% adherence) to 84.7% (below-planned dosing) in alirocumab arms and 73.9% (above-planned dosing) to 84.9% (below-planned dosing) in control arms (Table 7). In the 100% adherence group, 9.7% of patients receiving alirocumab discontinued treatment due to TEAEs, compared with 8.6% in the above-planned dosing group, 5.5% in the below-planned dosing group, and 2.9% in the both above- and below-planned dosing group (Table 7). The proportion of TEAEs leading to treatment discontinuation was comparable between alirocumab and control groups for patients in the 100% adherence group (9.7% vs 8.3%, respectively) and those with below-planned dosing (5.5% vs 4.6%, respectively; Table 7).

Discussion

Injectable biologics and medications are becoming increasingly common in the primary care setting, beyond their use in diabetes management, for the treatment of chronic illnesses.[32,33] Although they represent an important step in the management of chronic diseases, the high cost of biologics and diverse administration methods may negatively impact treatment adherence.[33] As therapeutic outcomes are linked to adequate treatment adherence, understanding adherence to biologics over the long term is therefore important to ensuring optimal outcomes for patients.[32]

In the CV setting, it is widely accepted that global adherence to oral CV medications is generally suboptimal and that this has an adverse influence on patient outcomes.[10,14] In a meta-analysis based on incidence rates in the European Union population, the relative risks of developing CVD in patients with good (≥80%) vs bad (<80%) adherence were 0.85 for statins and 0.81 for antihypertensive medications.[14] The relative risks of all-cause mortality were 0.55 and 0.71 for good adherence to statins and antihypertensive agents.[14] It is therefore reasonable to infer that a considerable proportion of CVD events may be caused by suboptimal adherence to oral CV therapies. As injectable biologics penetrate the CV field, adherence to such agents, in addition to their proven efficacy, is likely to play a pivotal role in determining whether CV outcomes can be enhanced.

In this analysis from 6 Phase III ODYSSEY trials, adherence to treatment with subcutaneous, injectable alirocumab or placebo over a period of ≥1 year was high, with an overall adherence rate of ~98% in both alirocumab and control groups. Within individual studies, adherence rates ranged from 97.6% to 98.3% among the alirocumab treatment groups. Adherence rates for control



	100% adherent		Below-planned		Above-planned		Both	
Alirocumab dose	75/150 mg†	150 mg	75/150 mg†	150 mg	75/150 mg†	150 mg	75/150 mg†	150 mg
N	522	705	221	344	36	45	369	496
Patients with alirocumab dose increase,%	25.1	N/A	29.9	N/A	30.6	N/A	27.4	N/A
Mean percent change in calculated LDL-C (SD)	−51.7 (28.3)	−61.9 (26.5)	−45.8 (35.7)	−57.0 (27.3)	−47.8 (40.1)	−59.0 (29.1)	−49.5 (30.6)	−57.3 (31.0)
Median	−57.9	−67.3	−56.7	−63.4	−54.5	−67.9	−56.6	−66.4

Figure 3 Alirocumab-induced percentage change in LDL-C from baseline to Week 52 according to treatment adherence category and starting dose regimen (modified ITT population). Pooled data from patients treated in the alirocumab arm of 6 phase III ODYSSEY trials (FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM) are shown. Patients received alirocumab 150 mg Q2W in LONG TERM and HIGH FH studies, whereas patients in the remaining studies received an initial alirocumab dose of 75 mg Q2W with the possibility of dose increase to 150 mg Q2W at week 12 based on LDL-C at Week 8. Boxplots were based on calculated LDL-C values during the on-treatment period (modified ITT population). Missing data at Week 52 imputed using last value on-treatment. The central line within a given box represents the median, and the mean is denoted by the diamond. The lower and upper boundaries of the box represent the lower (Q1) and upper (Q3) quartiles. The ends of the "whiskers" signify Q1 − 1.5 interquartile range and Q3 + 1.5 interquartile range. The small circles above each box denote the outliers (>Q3 + 1.5 interquartile range). †Patients received an initial dose of 75 mg Q2W alirocumab, which was increased in an automated manner to 150 mg Q2W at Week 12 depending on LDL-C levels at Week 8. N: number of patients with adherence nonmissing and at least 1 nonmissing LDL-C value during the on-treatment period. ITT, intent-to-treat; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; SD, standard deviation.

were similar, ranging from 96.9% to 99.1%. Treatment adherence to oral ezetimibe and placebo capsules (COMBO II study) was also high, with 98.3% and 96.2% of patients, respectively, having adherence rates of at least 80%.

Adherence to therapy may be influenced by patient-related factors.[34] In the context of hypercholesterolemia, patients who have previously experienced a CV event might be expected to be more adherent to alirocumab than those who have not. Similarly, patients with diabetes, who may be familiar with injectable medications, or those with HeFH, who have a heightened awareness of their disease and the implications of treatment, could be expected to be more adherent than the overall population. In the present analysis, baseline characteristics were generally comparable among patients who had 100% adherence, below-planned dosing only, above-planned dosing only, and both below- and above-planned dosing. Although patients with diabetes, HeFH, or atherosclerotic CVD were well represented in this analysis, the proportion of patients with these indications was generally similar between the 100% adherent group and the above- and/or below-planned dosing groups. Very few patients had above-planned dosing. Further assessment of the impact of patient-related factors on treatment adherence, for example by comparing adherence in patients with HeFH or diabetes vs those without these conditions in a real-world setting, is required to fully understand whether adherence to alirocumab differs among patient subgroups.

Practical considerations with respect to injectable biologics, such as willingness to self-inject or availability of a

Table 5 Overall safety summary (randomized and treated population)—global pool

n (%)	Alirocumab (n = 2797)	Control (n = 1415)
TEAEs	2242 (80.2)	1152 (81.4)
Treatment-emergent SAEs	509 (18.2)	262 (18.5)
TEAEs leading to death	22 (0.8)	19 (1.3)
TEAEs leading to treatment discontinuation	188 (6.7)	86 (6.1)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Pooled data from the 6 phase III ODYSSEY trials (FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM).

caregiver, may also influence adherence rates.[35] For example, adherence to self-injections appears to be greater than injection by a caregiver or healthcare professional, and subcutaneous injections with auto-injectors or pen devices are generally favored over needle and syringe administration.[32,36] Dosing schedules also play an important role in treatment adherence. It has been suggested that prolonged intervals between doses, such as Q2W dosing with alirocumab, may minimize the burden on patients and enhance adherence.[35] Another PCSK9 inhibitor, evolocumab, is approved with both Q2W and once-monthly dosing schedules,[24] and clinical trial data suggest that alirocumab may also be dosed on a monthly basis.[37,38] However, whether monthly administration of either alirocumab or evolocumab translates into improved adherence vs Q2W administration over the long term remains to be seen.

A key limitation of this analysis is that it was based on randomized controlled trials, which are typically associated with high levels of treatment adherence.[2] The findings presented here may therefore not accurately reflect alirocumab adherence patterns in everyday clinical practice. Indeed, adherence to statins reported in clinical trials is greater than that observed in real-world settings (78%–90% vs 44%–57%, respectively).[11,12] In the Collaborative Atorvastatin Diabetes Study, in which patients with type II diabetes but no history of CVD were randomized to receive atorvastatin or placebo, 90% of patients allocated to the atorvastatin group were taking atorvastatin (and/or another statin) after 1 year, and 87% were taking atorvastatin (and/or another statin) at 2 years (85% of patients on average were taking atorvastatin and/or another statin over a 4-year period).[12] In a cluster randomized sub-study of the Atorvastatin in Factorial with Omega EE90 Risk Reduction in Diabetes trial, adherence to atorvastatin over 1 year was ~79%.[13] An average statin adherence rate of 85% was also demonstrated over a 5-year period in patients with diabetes from the large, randomized controlled Heart Protection Study.[11] In contrast, based on data from the Finnish FinDM database, the average adherence rate to statins over ~3 years in patients with type II diabetes in the real-world setting was reported to be 57%.[11] Similarly, in a retrospective cohort study using the Saskatchewan Drug Plan and Extended Benefits database in Canada, adherence to statins was 52% in the first year and 44% by the third year.[39] Real-world data on adherence to ezetimibe capsules are limited; however, 1 retrospective study investigating oral LLTs, including the combination of ezetimibe and simvastatin, in a managed care setting demonstrated that mean proportion of days covered fell below the threshold for adherence (80%) even within the first 3 months of therapy.[40] This contrasts with the >80% to 97% adherence rates observed with ezetimibe plus statin therapy at within the first 3 months of treatment in clinical trials.[41,42] The introduction of injectable agents for asymptomatic conditions, such as hypercholesterolemia, has been met with uncertainties regarding patients' willingness to self-inject and maintain the injection schedule over the long term compared with taking oral drugs on a daily basis. Results from this and a previous study[27] suggest that acceptance of and adherence to injectable alirocumab is high in clinical trials. However, they also raise the question of how

Table 6 TEAEs leading to treatment discontinuation in ≥0.4% of alirocumab-treated patients in any pool (randomized and treated population)—placebo- and ezetimibe-controlled pools

	Placebo-controlled pool		Ezetimibe-controlled pool	
n (%)	Alirocumab (n = 2318)	Placebo (n = 1174)	Alirocumab (n = 479)	Ezetimibe (n = 241)
Myalgia	6 (0.3)	0	3 (0.6)	2 (0.8)
Dizziness	2 (<0.1)	3 (0.3)	2 (0.4)	1 (0.4)
Ischemic stroke*	2 (<0.1)	0	2 (0.4)	0
Vision blurred	1 (<0.1)	0	2 (0.4)	0
Diarrhea	3 (0.1)	1 (<0.1)	2 (0.4)	0
Back pain	1 (<0.1)	4 (0.3)	2 (0.4)	1 (0.4)
Renal cyst	0	1 (<0.1)	2 (0.4)	0
Injection site reaction	4 (0.2)	3 (0.3)	2 (0.4)	1 (0.4)
Increased transaminases	1 (<0.1)	0	2 (0.4)	0

TEAE, treatment-emergent adverse event.

Pooled data from the 6 phase III ODYSSEY trials (FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM).

*Only 1 event in the ezetimibe-controlled pool was considered related to study treatment.

Table 7 Overall TEAEs and TEAEs leading to treatment discontinuation in alirocumab-treated patients, according to treatment adherence categories (randomized and treated population)

n (%)	100% adherence		Below-planned dosing		Above-planned dosing		Both below- and above-planned dosing	
	Alirocumab (n = 1272)	Control (n = 628)	Alirocumab (n = 567)	Control (n = 324)	Alirocumab (n = 81)	Control (n = 46)	Alirocumab (n = 866)	Control (n = 413)
TEAEs	991 (77.9)	494 (78.7)	480 (84.7)	275 (84.9)	68 (84.0)	34 (73.9)	697 (80.5)	345 (83.5)
Treatment-emergent SAEs	205 (16.1)	97 (15.4)	119 (21.0)	79 (24.4)	12 (14.8)	7 (15.2)	170 (19.6)	78 (18.9)
TEAEs leading to death	11 (0.9)	10 (1.6)	4 (0.7)	5 (1.5)	0	0	5 (0.6)	3 (0.7)
TEAEs leading to discontinuation	123 (9.7)	52 (8.3)	31 (5.5)	15 (4.6)	7 (8.6)	1 (2.2)	25 (2.9)	18 (4.4)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Pooled data from the 6 phase III ODYSSEY trials (FH I, FH II, HIGH FH, COMBO I, COMBO II, and LONG TERM).

adherence to a therapy requiring Q2W injections (26 injections per year) and adequate refrigeration compares with that of an oral drug that is given daily (365 administrations per year) and does not require refrigeration in the real-world setting.

Open-label extension studies, such as ODYSSEY OLE (NCT01954394), are ongoing. In these studies, patients will have the opportunity to observe the impact of their treatment, which may consequently impact adherence levels. The results of these studies may therefore provide further insight into long-term adherence to alirocumab in a setting that is closer to clinical practice than randomized controlled trials. In addition, although treatment adherence was high over a period of 1 to 2 years in a relatively large patient population in this analysis, it remains to be seen whether treatment adherence levels remain high over a period of follow-up longer than 2 years and in larger patient populations. Adherence to alirocumab injections will be further assessed in a large, ongoing CV outcomes study (ODYSSEY OUTCOMES) of approximately 18,000 patients randomized to either alirocumab or placebo with a planned follow-up period of $\geq$2 years.[43]

Mean percentage changes from baseline to Week 52 in LDL-C were not markedly different in patients who had 100% adherence, below-planned dosing only, above-planned dosing only, or both below- and above-planned dosing. As the endpoint in the studies included in this analysis was mean percentage change in LDL-C over time, individual changes in LDL-C levels calculated at a given patient visit are not represented here. Although the impact of above- or below-planned dosing of alirocumab on LDL-C levels at specific patient visits is currently unknown, the average percentage change in LDL-C was not significantly affected by above- or below-planned dosing. The average of LDL-C levels taken over several visits might provide a more balanced view of a patient's LDL-C levels in response to treatment than a single measurement taken at 1 visit, which could result in unnecessary dose adjustment. Deviations greater than $\pm$3 days from the dosing frequency of Q2W did not meaningfully affect the percentage of LDL-C reduction. For injectable medications, TEAEs are often highlighted as a reason for poor adherence and treatment discontinuation.[32,44,45] In this analysis, alirocumab was generally well tolerated and had a favorable safety profile, with few TEAEs leading to treatment discontinuation. Injection site reactions, which can be frequently observed with injectable medications, were generally mild in severity and led to treatment discontinuations in $<$1% of the study population.

Conclusions

In conclusion, the results presented here indicate that, in clinical trials, alirocumab injections, via self-injection or with the help of a caregiver, are associated with a high level of adherence over a period of at least 1 year, and that

infrequent below- or above-planned dosing had minimal impact on LDL-C reductions. This further supports the use of alirocumab 75 mg Q2W (with possible adjustment to 150 mg Q2W) and 150 mg Q2W over the long term to achieve clinically meaningful LDL-C reductions in patients with HeFH or high CV risk.

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