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Open-label therapy with alirocumab in patients with heterozygous familial hypercholesterolemia: Results from three years of treatment☆

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ABSTRACT

Background: PCSK9 inhibition with alirocumab significantly reduced LDL-C levels in trials of up to 78 weeks' duration in patients with heterozygous familial hypercholesterolemia (HeFH). We report results from 3 years of an ongoing open-label treatment extension (NCT01576484) to a 12-week double-blind trial in HeFH patients (NCT01266876).

Methods: Patients who completed the parent study and were receiving stable daily statin ± ezetimibe could enter the open-label extension, where they received alirocumab 150 mg every 2 weeks (Q2W) subcutaneously (n = 58). The primary endpoint was safety (treatment-emergent adverse events, TEAEs). Efficacy endpoints included the percentage change in LDL-C from baseline at Week 24. Safety and efficacy data were available up to Weeks 156 and 148, respectively.

Results: Mean baseline LDL-C was 150.7 mg/dL (3.9 mmol/L), despite all patients being on a statin (76% on high-intensity statin; 72% also receiving ezetimibe). Over 156 weeks, 54 (93.1%) patients experienced a TEAE, 12 (20.7%) experienced a serious TEAE, and two (3.4%) discontinued due to a TEAE. Injection site reactions occurred in 21 (36.2%) patients. Mean (SD) reduction in LDL-C from baseline to Week 24 was 65.4 (21.1)%, with reductions maintained through 148 weeks (Week 148 reduction: 56.0 [23.8]%). Mean apolipoprotein B reduction was 50.9% and median lipoprotein (a) reduction was 22.5% at Week 24 (46.1% and 25.6% at Week 148, respectively).

Conclusions: Open-label treatment for 3 years with alirocumab 150 mg Q2W, administered with background statin ± ezetimibe, was generally well-tolerated and had a safety profile comparable with that seen in the overall alirocumab clinical trial program. Alirocumab provided significant, sustained LDL-C reductions.

1. Introduction

Heterozygous familial hypercholesterolemia (HeFH) is one of the most common genetic disorders, with an estimated prevalence of one in every 200 to 500 individuals [1,2]. HeFH is associated with elevated levels of low-density lipoprotein cholesterol (LDL-C) and increased life-long risk of premature cardiovascular disease (CVD) [1,2]. HeFH is usually diagnosed clinically on the basis of lipid profile, physical findings, and family history, although genetic testing may also be performed, with mutations in genes for *LDLR*, *APOB* and *PCSK9* being associated with the FH phenotype [1–3].

Current recommended treatment for HeFH is high-dose statin therapy in combination with other lipid-lowering therapies (LLTs) such as ezetimibe [1–3]. European guidelines recommend LDL-C goals of

Abbreviations: AE, adverse event; Apo, apolipoprotein; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); LLT, lipid-lowering therapy; MedDRA, Medical Dictionary for Regulatory Activities; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; Q4W, every 4 weeks; SD, standard deviation; TEAE, treatment-emergent adverse event.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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<1.8 mmol/L (70 mg/dL) for patients with HeFH who have established coronary heart disease (CHD), and <2.6 mmol/L (100 mg/dL) in those without CHD [4]. The National Lipid Association recommends LDL-C < 100 mg/dL or ≤50% reduction [3]. However, it is recognized that, due to their high baseline LDL-C, many patients with HeFH will not reach these goals even with the currently available maximally tolerated statin therapy and other LLTs such as ezetimibe [1,2,5,6].

Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) with alirocumab, a fully human monoclonal antibody, significantly reduced LDL-C and other atherogenic lipids in patients with HeFH in trials with double-blind periods of up to 78 weeks [7,8]. In Phase 3 trials including patients with HeFH not at LDL-C goal on study entry, most patients (>70%) achieved risk-based LDL-C goals of <70 or <100 mg/dL with alirocumab added to maximally tolerated statin and other LLTs [7]. Frequencies of treatment-emergent adverse events (TEAEs) with alirocumab treatment were generally similar to those observed with placebo controls in the trials [7,8]. However, due to the chronic nature of HeFH, studies of even longer duration are required to evaluate the efficacy and safety of this new drug.

We report here safety and efficacy results from over 3 years of open-label treatment with alirocumab in patients with HeFH. These results are from an ongoing open-label extension study (NCT01576484) of a previous double-blind 12-week study [8].

2. Methods

2.1. Overview of parent study

Methods for the parent study have been described previously [8]. Briefly, the study was conducted in the USA and Canada and included men and women with a clinical diagnosis of HeFH (≥8 points on the World Health Organization criteria) who were receiving stable statin dose (with or without ezetimibe) and who had LDL-C of ≥100 mg/dL (2.6 mmol/L) at screening. Patients were randomized to 12 weeks of double-blind treatment with placebo or one of four alirocumab doses (Fig. 1). Alirocumab and placebo were administered subcutaneously. Of 77 patients randomized, 76 completed the parent study.

2.2. Open-label extension

All patients who successfully completed the parent study were eligible for the open-label extension study if they provided signed, informed consent. Patients had to be on a stable daily statin regimen for at least 3 weeks prior to screening. Other LLTs were allowed provided that they were also on a stable regimen for at least 3 weeks (6 weeks for fenofibrate; other fibrates were not allowed). Exclusion criteria were as for the parent study [8].

In this extension study, all patients received open-label alirocumab 150 mg every 2 weeks (Q2W), administered subcutaneously as a 1-mL injection. Patients or their caregivers received training to administer injections at home. Adjustment of dose from 150 mg was not allowed according to the protocol, although investigators were allowed to skip doses in the case of two consecutive LDL-C values <25 mg/dL (0.65 mmol/L), e.g., the drug could be given every 4 weeks (Q4W) instead of Q2W. It was also possible for the investigator to adjust the patient's background lipid-lowering medication to optimize LDL-C levels. The open-label study was planned to remain open until product approval, or up to 4 years, or until the program was halted. The study protocol was approved by the appropriate Independent Review Board/Ethics Committee. All investigators conducted the study in accordance with ethical guidelines based on the Declaration of Helsinki, and with the ICH guidelines for Good Clinical Practice and applicable regulatory requirements.

2.3. Endpoints

The primary aim of the trial was to assess the long-term safety and tolerability of alirocumab in patients with HeFH. Secondary aims included the long-term assessment of alirocumab efficacy in reducing LDL-C, and effects on other lipid parameters.

The pre-specified primary endpoint was the assessment of TEAEs in the open-label extension from baseline up to the last dose of study drug + 10 weeks. Safety data are reported for all patients for the duration of their treatment. CV events were adjudicated. As well as standard Medical Dictionary of Regulatory Activities (MedDRA) preferred terms, TEAEs were also assessed in categories of special interest (i.e., those potentially relevant to the new drug class or mode of administration), including injection site reactions, general allergic events, neurological events, and neurocognitive disorders. The categories

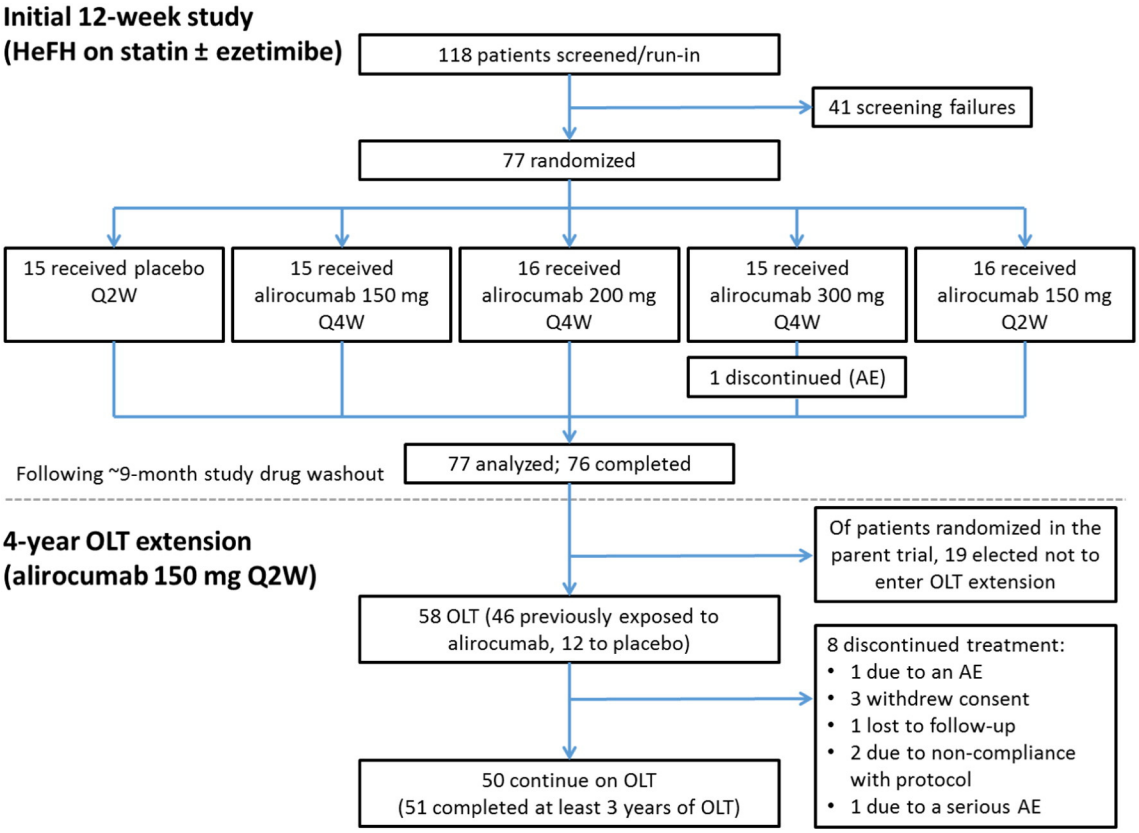

Fig. 1. Patient disposition. AE, adverse event, HeFH, heterozygous familial hypercholesterolemia, OLT, open-label treatment, Q2W, every 2 weeks, Q4W, every 4 weeks.

were not specified in the protocol for this study but were pre-specified for the alirocumab Phase 3 ODYSSEY trials [7,9].

Pre-specified efficacy endpoints included the percent change in LDL-C, apolipoprotein (apo) B, non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol, HDL-C, apo A1, lipoprotein (a) (Lp[a]), and triglycerides from baseline to Week 24, and the proportion of patients reaching LDL-C goals at Week 24 of <70 mg/dL (1.8 mmol/L) in case of prior myocardial infarction (MI)/stroke, or <100 mg/dL (2.6 mmol/L) without prior MI/stroke. Percent changes in lipids from baseline to the latest time point with available data are also reported. Blood samples for lipid analysis were obtained at baseline and weeks 2, 4, 8, 12, 16, and 24, and subsequently at approximately 12-week intervals. Laboratory analysis methods have been previously described [7,8].

For patients with LDL-C levels <25 mg/dL (0.65 mmol/L) at two consecutive laboratory assessments during the study, the investigator reviewed the patient data and decided whether to continue, discontinue or temporary discontinue study treatment.

Anti-drug antibodies (ADAs) to alirocumab were assessed at regular intervals using a validated immunoassay by Regeneron Pharmaceuticals, Inc. (Tarrytown, NY, USA). A positive ADA response was described as "persistent" if it was detected on consecutive samples. The ADA assay incorporated false-positive rates recommended by published guidelines as reported previously [7].

2.4. Statistical analysis

Safety data were analyzed by descriptive statistics. As safety was the primary endpoint, formal statistical analysis of efficacy variables was not planned. However, a post hoc analysis of efficacy data was conducted, comparing the LDL-C value at each time point to baseline using a one-sample *t*-test.

3. Results

3.1. Patients

Nine months separated the end of the parent study and the start of the open-label extension. During this 9-month period, patients were not receiving alirocumab. In total, 58 patients (75% of those who completed the parent study) entered the extension study; of these, 51 (87.9%) received open-label treatment for up to 156 weeks (3 years). Seven patients (12.1%) discontinued before Week 156 and a further one patient discontinued after Week 156, for a total of eight patients (13.8%) who discontinued (Fig. 1). Of patients who discontinued, one patient discontinued due to an AE of epigastric discomfort after 28 weeks of exposure to alirocumab (this AE was not considered related to study treatment); three patients decided not to continue the study (withdrew consent); one patient was lost to follow-up; two patients had poor compliance to study protocol; and one patient discontinued due to a serious TEAE (behavioral and psychiatric symptoms of dementia, not considered related to study treatment) after 180 weeks. Safety data are reported up to Week 156, as this was the latest time point with data available for all continuing patients. The latest efficacy assessment completed by all patients continuing to receive treatment was at Week 148.

The mean baseline LDL-C level was 150.7 mg/dL (3.9 mmol/L), despite all patients being on a statin, 76% of whom were receiving a high-intensity statin (atorvastatin 40 to 80 mg daily, rosuvastatin 20 to 40 mg daily, or simvastatin 80 mg daily); furthermore, 72% were also receiving ezetimibe (Table 1).

3.2. Safety

Following 156 weeks of open-label treatment with alirocumab, 54 (93.1%) of patients experienced a TEAE, 12 (20.7%) experienced a serious TEAE, and two patients (3.4%) discontinued due to a TEAE (Table 2). There were no deaths. Two patients (3.4%) had an adjudicated cardiovascular event (both coronary revascularization procedures; Table 2).

With regards to TEAEs of special interest, TEAEs categorized as injection site reactions occurred in 21 (36.2%) of patients (Table 2). The majority of injection site reactions were of mild severity and none led to study treatment discontinuation. TEAEs categorized as allergic events occurred in six (10.3%) patients, none of which were considered related to alirocumab. Five (8.6%) patients reported TEAEs categorized as neurologic disorders (Table 2). Three patients (5.2%) reported TEAEs related to neurocognitive disorders (Table 2). None of the neurological or neurocognitive TEAEs were considered by the Investigator to be related to alirocumab treatment. One patient discontinued the study following a neurocognitive TEAE (amnesia). Further details on these TEAEs are shown in the online Supplemental Table.

There were few instances of elevated levels of creatine kinase or hepatic transaminases (Table 3). There were no meaningful changes in mean levels of either glycated hemoglobin (HbA1C) or glucose from baseline to Week 148 (Table 3). Some patients reported increases in glucose levels during the study (Table 3); however, these changes were transitory.

Fourteen patients (24.1%) had two consecutive LDL-C values <25 mg/dL (0.65 mmol/L) during treatment with alirocumab 150 mg Q2W. Furthermore, five patients (8.6%) had two consecutive LDL-C values <15 mg/dL (0.39 mmol/L). For six of the 14 patients with LDL-C < 25 mg/dL, the investigator decided to temporarily stop alirocumab treatment as a safety precaution. One (7.1%) of the 14 patients with two consecutive LDL-C values <25 mg/dL withdrew from the study (patient withdrew consent). None of the five patients with consecutive LDL-C < 15 mg/dL had their dose changed and all continued treatment (due to no safety concern in the judgment of the investigator). Neurological TEAEs occurred in three patients whose LDL-C levels were <25 mg/dL before the event, and in two patients who did not have LDL-C < 25 mg/dL. Neurocognitive TEAEs occurred in one patient who previously had LDL-C < 25 mg/dL, and in two patients who did not have LDL-C < 25 mg/dL.

Immunogenicity was examined over the entire course of the treatment period using highly sensitive assays that generated the recommended false positive rate to ensure any ADA response was detected. The incidence of treatment-emergent ADAs was low and the vast majority (94.8%) of patients did not exhibit any ADA response. Three patients exhibited positive responses in the ADA assay that were either persistent, positive for neutralizing antibodies (i.e. ADA with potential to inhibit binding of alirocumab to PCSK9), or only positive at the last time point analyzed. A persistent ADA assay response was reported in one patient who had a low-level pre-existing reactivity in the ADA assay, with a low titer ADA assay response maintained through the study (to Week 172). One patient had a transient, low-titer assay response at a single time point (Week 12) which was positive

Table 1
Baseline characteristics and lipid parameters of patients entering the open-label treatment extension*.

	Alirocumab 150 mg Q2W (n = 58)
Age, years, mean (SD)	54.4 (9.4)
Gender, male, n (%)	38 (65.5)
Race, White, n (%)	55 (94.8)
Body mass index, kg/m^2, mean (SD)	29.3 (4.1)
History of CAD, n (%)	27 (46.6)
Diabetes mellitus, n (%)	3 (5.2)
Statin therapy, n (%)	58 (100)
High-intensity statin†	44 (75.9)
Ezetimibe use, n (%)	42 (72.4)
Baseline lipid parameters, mean (SD)	
Calculated LDL-C, mg/dL [mmol/L]	150.7 (40.4) [3.9 (1.0)]
Apo B, mg/dL	121.4 (24.0)
Non-HDL-C, mg/dL [mmol/L]	175.8 (42.6) [4.6 (1.1)]
Total cholesterol, mg/dL [mmol/L]	227.8 (45.6) [5.9 (1.2)]
Lipoprotein(a), mg/dL	40.0 (5.0: 104.0)‡
Triglycerides, mg/dL [mmol/L]	113.0 (87.0: 160.0) [1.3 (1.0: 1.8)]‡
HDL-C, mg/dL [mmol/L]	51.9 (15.3) [1.3 (0.4)]
Apo A1, mg/dL	147.7 (24.0)

Apo, apolipoprotein; CAD, coronary artery disease; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

* Baseline values defined as the last available value collected in the current study before the first dose of the open-label treatment.

† Defined as atorvastatin 40–80 mg daily, rosuvastatin 20–40 mg daily, or simvastatin 80 mg daily.

‡ Median (Q1:Q3).

Table 2
Safety: TEAEs during open-label treatment with alirocumab 150 mg Q2W*.

		All patients (n = 58)
Patients with any TEAE		54 (93.1)
Patients with any serious TEAE		12 (20.7)
Patients with TEAEs leading to permanent treatment discontinuation		2 (3.4)
Patients with any TEAE leading to death		0
Adjudicated CV events		2 (3.4)
TEAEs occurring in ≥5% of patients†		
System organ class‡	Preferred term‡	
Infections and infestations	Upper respiratory tract infection	14 (24.1)
	Nasopharyngitis	12 (20.7)
	Bronchitis	11 (19.0)
	Urinary tract infection	7 (12.1)
	Influenza	6 (10.3)
	Gastroenteritis	6 (10.3)
	Sinusitis	5 (8.6)
	Conjunctivitis	3 (5.2)
	Tooth infection	3 (5.2)
	Ear infection	3 (5.2)
Blood and lymphatic system disorders	Anemia	3 (5.2)
Immune system disorders	Seasonal allergy	3 (5.2)
Psychiatric disorders	Anxiety	5 (8.6)
Nervous system disorders	Headache	11 (19.0)
	Dizziness	5 (8.6)
	Carpal tunnel syndrome	3 (5.2)
Vascular disorders	Hypertension	4 (6.9)
Respiratory, thoracic, and mediastinal disorders	Cough	6 (10.3)
	Oropharyngeal pain	3 (5.2)
Gastrointestinal disorders	Diarrhea	8 (13.8)
	Gastroesophageal reflux disease	4 (6.9)
	Nausea	4 (6.9)
	Vomiting	4 (6.9)
	Abdominal pain	3 (5.2)
Skin and subcutaneous tissue disorders	Urticaria	4 (6.9)
Musculoskeletal and connective tissue disorders	Arthralgia	11 (19.0)
	Myalgia	9 (15.5)
	Back pain	8 (13.8)
	Osteoarthritis	5 (8.6)
	Pain in extremity	5 (8.6)
	Tendonitis	3 (5.2)
	Neck pain	3 (5.2)
General disorders and administration site conditions	Injection-site bruising	11 (19.0)
	Injection site hemorrhage	7 (12.1)
	Fatigue	5 (8.6)
	Injection-site pain	5 (8.6)
	Injection-site mass	3 (5.2)
	Injection-site discoloration†	2 (3.4)
	Injection-site erythema†	2 (3.4)
	Injection-site swelling†	2 (3.4)
	Injection-site induration†	1 (1.7)
	Injection-site pruritus†	1 (1.7)
	Injection-site urticaria†	1 (1.7)
Injury, poisoning and procedural complications	Ligament sprain	5 (8.6)
	Procedural pain	3 (5.2)
Safety events of interest§		
Injection site reactions		21 (36.2)
Allergic events		6 (10.3)
Neurological events		5 (8.6)
Hypoaesthesia		2 (3.4)
Paraesthesia		2 (3.4)
Neuralgia		1 (1.7)
Neurocognitive events‖		3 (5.2)
Disturbance in attention		2 (3.4)
Amnesia		1 (1.7)
Memory impairment		1 (1.7)

MedDRA, Medical Dictionary for Regulatory Activities.
TEAE, treatment-emergent adverse event.
* Safety analyses are reported for the duration of the study, with all patients who have treatment ongoing having completed to at least 156 weeks (3 years) of open-label therapy.
† Although reported by <5%, injection site reactions are of special interest given that alirocumab is an injectable medication and these events are reported accordingly.
‡ MedDRA.
§ Categories based on standardized MedDRA queries.
‖ Although three patients reported neurocognitive events, one patient reported two different events coming under this category.

in the neutralizing antibodies assay. Finally, one patient exhibited a single low-titer assay response at the last available assessment. No pattern was observed in relation to positive ADA assay responses in these patients and either incidence of TEAEs or reductions in LDL-C.

3.3. Lipids and lipoproteins

LDL-C was reduced from a mean (SD) baseline level of 150.7 (40.4) mg/dL [3.9 (1.1) mmol/L] to 54.5 (40.5) mg/dL [1.4 (1.0) mmol/L] at Week 24, an absolute reduction of 98.9 (37.9) mg/dL [2.6 (1.0) mmol/L] and a mean percentage reduction of 65.4 (21.1)% (Fig. 2; Table 4). LDL-C reductions were sustained from Weeks 4 through 148 ($P < 0.05$ versus baseline at each time point; Fig. 2). At Week 148, the mean achieved LDL-C level was 65.9 (35.5) mg/dL [1.7 (0.9) mmol/L] (Fig. 2A), a mean (SD) percentage reduction of 56.0 (23.8)% from baseline (Table 4).

At Week 24, 51 of 55 patients (92.7%) who were receiving treatment achieved pre-defined treatment goals of LDL-C < 70 mg/dL (1.8 mmol/L) or <100 mg/dL (2.6 mmol/L) depending on risk. At Week 148, 78.4% achieved their pre-defined LDL-C goal (Fig. 2A).

At Week 24, the mean level of apo B fell by 50.9%, non-HDL-C by 55.7%, and median level of Lp(a) by 22.5%, versus baseline ($P < 0.0001$), with reductions sustained from Week 4 onwards (Table 4; absolute levels over time in Fig. 3A–C). At Week 24, HDL-C and apo A1 levels were increased by 6.2% and 4.9%, respectively, versus baseline (both $P < 0.05$;

Table 3
Laboratory parameters of interest.

Changes in laboratory parameters, n (%)	All patients (n = 58)
Albumin ≤25 g/L	0
Creatine kinase >3× ULN and ≤10× ULN	6 (10.3)
Creatine kinase >10× ULN	0
High sensitivity C-reactive protein >2× ULN or >10 mg/L (if ULN not provided)	17 (29.3)
Alanine aminotransferase >3× ULN and ≤5 ULN	0
Alanine aminotransferase >5× and ≤10× ULN	1 (1.7)
Aspartate aminotransferase >3× ULN and ≤5 ULN	0
Aspartate aminotransferase >5× and ≤10× ULN	1 (1.7)
Bilirubin >1.5× ULN	6 (10.3)
Bilirubin >2× ULN	3 (5.2)
Bilirubin >2× ULN and alanine aminotransferase >3× ULN	0
Glycemic parameters	
HbA1C, baseline, mean (SD), %	5.8 (0.4)
HbA1C, change from baseline at Week 148, mean (SD), %	0.1 (0.3)
Glucose, baseline, mean (SD), mmol/L [mg/dL]	5.6 (0.6) [100.0 (10.8)]
Glucose, change from baseline at Week 148, mean (SD), mmol/L [mg/dL]	0.2 (0.8) [3.6 (14.3)]
Glucose ≤3.9 mmol/L [70.3 mg/dL] and <LLN, n	0
Glucose ≥11.1 mmol/L [200 mg/dL] (unfasted), ≥7.0 mmol/L [126 mg/dL] (fasted), n (%)	10 (17.2)

HbA1c, glycated hemoglobin LLN, lower limit of normal;
ULN, upper limit of normal.

Table 4; HDL-C levels over time in Fig. 3D). Median triglyceride levels fell by 13.9% at Week 24 (Table 4; levels over time in Fig. 3E).

4. Discussion

Patients in this study had HeFH and a mean baseline LDL-C level of 151 mg/dL (3.9 mmol/L) despite treatment with high-dose statin (and ezetimibe use in 72% of patients). These patients were therefore in need of further LDL-C reduction. Addition of open-label alirocumab 150 mg Q2W to the patient's existing LLT resulted in a sustained mean LDL-C reduction of ~60% from baseline over the course of the study. The percentage reduction in LDL-C from baseline to Week 148 (56%) was somewhat lower than that seen at Week 24 (65%). This could be due to several reasons, including patient drop-outs, adjustment of alirocumab dosing regimen from Q2W to Q4W in some patients, and adjustment of background lipid medication in some patients. However, at Week 148, the mean LDL-C was 65.9 mg/dL [1.7 mmol/L], an absolute mean (SD) reduction from baseline of 85.6 (40.5) mg/dL [2.2 (1.0) mmol/L], and ~80% of patients had achieved their LDL-C goal. These reductions are comparable with those observed in Phase 3 double-blind trials of alirocumab in patients with HeFH [7]. Alirocumab also resulted in substantial sustained decreases in Lp(a) over 148 weeks, similar to reductions observed previously [9,10]. Elevated Lp(a) is an independent risk factor for CVD [10]; however, the clinical implications of reducing Lp(a) and the precise mechanism of alirocumab effect on Lp(a) have yet to be fully determined.

Table 4
Percentage reductions from baseline in lipid efficacy parameters at Week 24 (primary analysis) and Week 148 (latest available efficacy assessment for all patients continuing to receive treatment).

	Alirocumab 150 mg Q2W (N = 58)	
Percentage reduction from baseline[†]	Week 24 (n = 55)	Week 148 (n = 51)
LDL-C	−65.4 (21.1)**	−56.0 (23.8)**
Absolute levels, mg/dL [mmol/L]	54.5 (40.5) [1.4 (1.0)]	65.9 (35.5) [1.7 (0.9)]
Apo B	−50.9 (18.4)**	−46.1 (20.6)**
Non-HDL-C	−55.7 (21.0)**	−48.7 (23.3)**
Lp(a)	−22.5 (−50.0: −7.9)**	−25.6 (−42.5: −8.1)**
Triglycerides	−13.9 (−29.5: 15.4)	−15.1 (−33.3: 6.8)
HDL-C	6.2 (15.9)*	3.6 (17.7)
Apo A1	4.9 (11.2)*	5.6 (13.0)**

Apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); Q2W, every 2 weeks.
† Values are mean (SD) except for Lp(a) and triglycerides, for which median (interquartile range) are shown.
* $P < 0.05$
** $P < 0.0001$ vs. baseline.

Open-label treatment over 3 years with alirocumab 150 mg Q2W had a safety profile comparable with that seen in a pooled analysis of 14 randomized, double-blind, Phase 2 and 3 clinical trials of alirocumab including over 5000 patients [11]. The most common type of TEAEs in this open-label study were injection site reactions, which were mostly mild and did not result in treatment discontinuation. Alirocumab

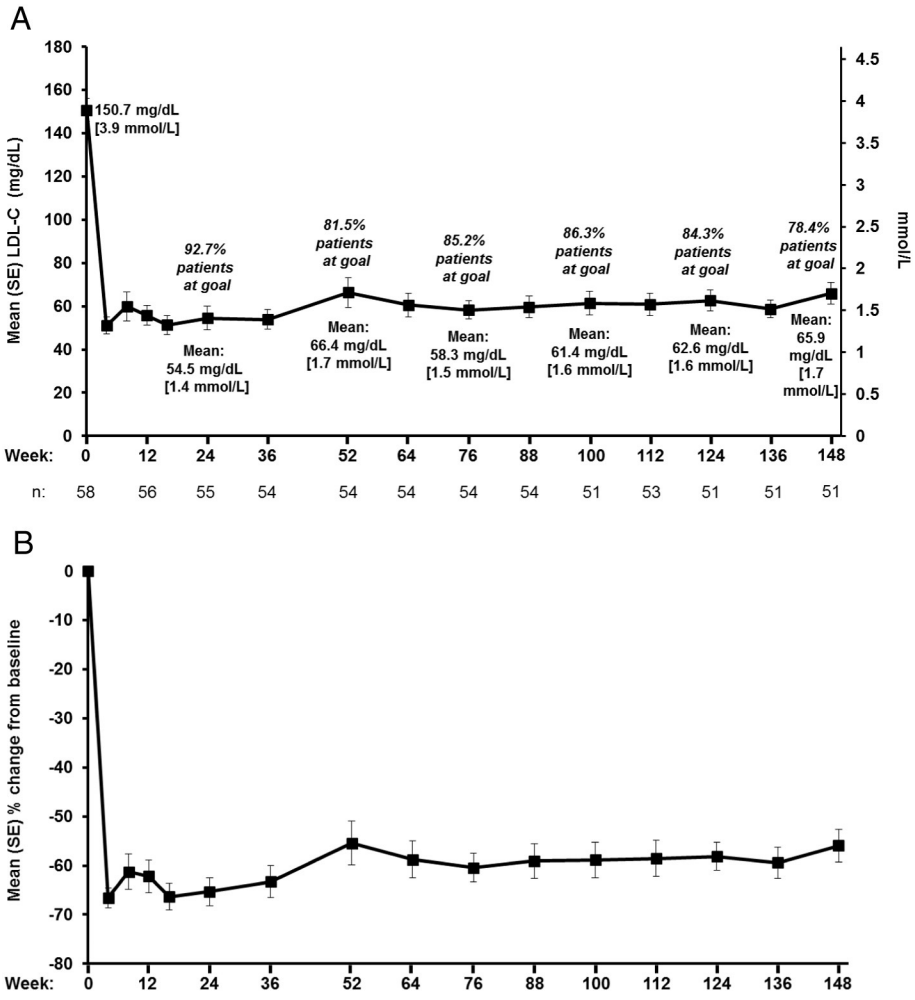

Fig. 2. Absolute LDL-C levels over time and achievement of (A) risk-based LDL-C goals and (B) LDL-C percentage change from baseline.

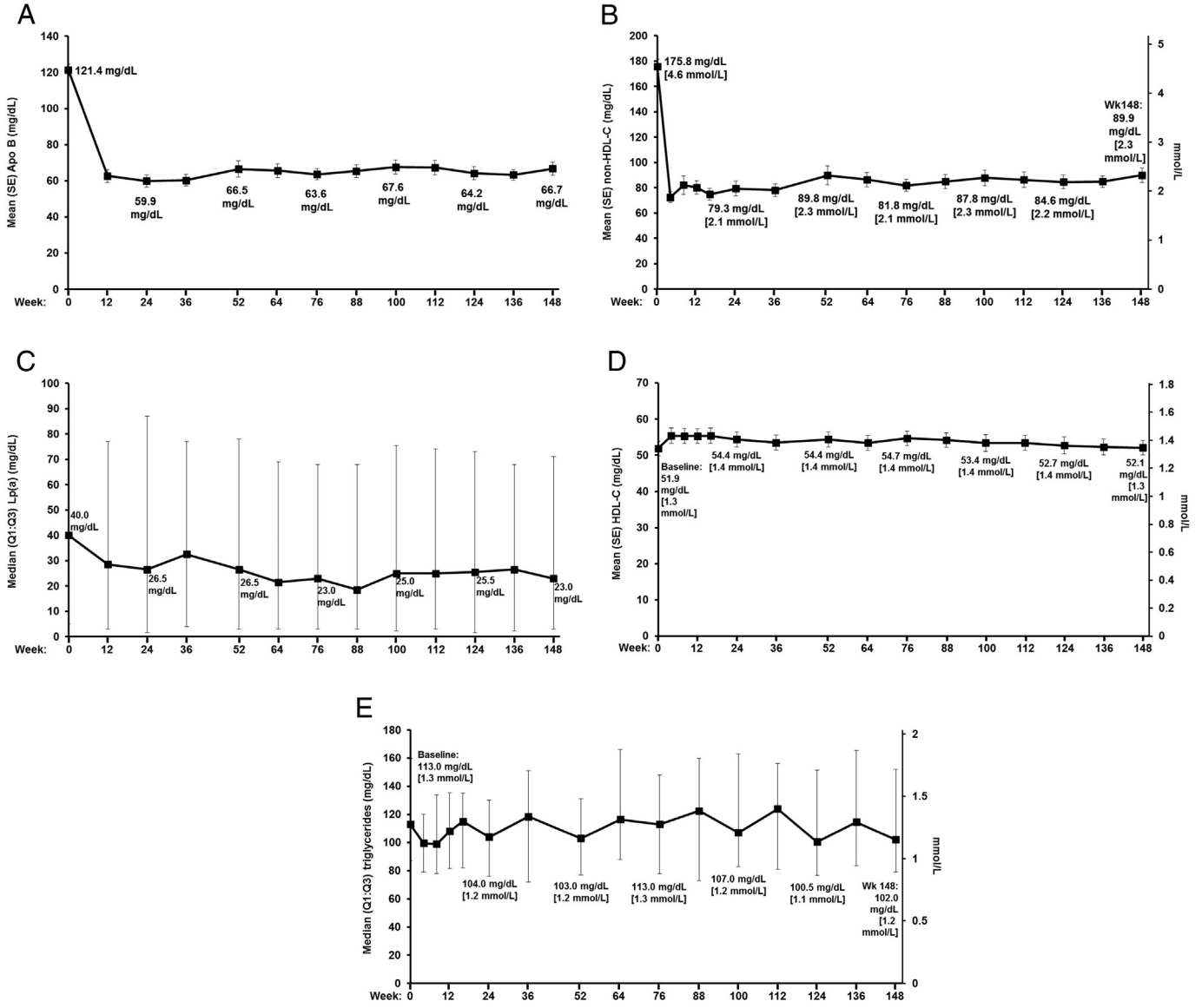

Fig. 3. Levels of other lipids and lipoproteins over time: (A) apo B, (B) non-HDL-C, (C) Lp(a), (D) HDL-C, and (E) triglycerides. Values shown on the charts are rounded to one decimal place.

treatment was associated with a higher rate of injection site reactions compared with controls in double-blind trials [11]. Neurological and neurocognitive events reported in this open-label study were not considered to be related to alirocumab treatment. In double-blind trials, no increase in neurological or neurocognitive events was associated with alirocumab [11]. Treatment with statins has been associated with an increased incidence of diabetes mellitus [12]. In the present study, alirocumab did not meaningfully impact glycemic parameters (HbA1C and glucose), in agreement with results reported from across the alirocumab clinical trial program [12]. No pattern was observed in relation to the ADA responses (n = 3) and either incidence of TEAEs or reductions in LDL-C. No specific safety concerns were identified in patients who reached LDL-C values <25 mg/dL (<0.65 mmol/L) or <15 mg/dL (<0.39 mmol/L); similarly, no safety signals were identified in patients with LDL-C < 25 mg/dL in the ODYSSEY LONG TERM trial [9].

Patients with HeFH typically have LDL-C levels of 200–500 mg/dL (5.2–12.9 mmol/L) prior to treatment, far above the optimal level of <100 mg/dL (<2.6 mmol/L) for adults (or <70 mg/dL [1.8 mmol/L] in those with pre-existing CV disease). Although there had been continued improvement in LDL-C levels in patients with HeFH since the advent of statins, development of more potent statins, and addition of ezetimibe, the majority of these patients were still not achieving sufficient reduction in LDL-C levels (~80% were not at goal in recent studies [5, 6]). There has therefore been great interest in using PCSK9 inhibitors for treatment of HeFH. However, understanding the long-term safety and efficacy of PCSK9 inhibitors is important for this lifelong condition. Data from this study represent the longest exposure to date with alirocumab in patients with HeFH.

Limitations of this study include the potential bias introduced by having an open-label treatment. Over a 3-year follow-up period, a higher overall rate of AEs may be expected; however, the lack of a comparative control and relatively low patient numbers limit the interpretation of results. Studies with a longer duration of exposure to alirocumab are required to provide further reassurance about incidence of neurological and neurocognitive events. The ongoing ODYSSEY OUTCOMES trial (involving over 18,000 patients) is evaluating the effect of alirocumab on CV events and will also provide further information on long-term safety [13].

5. Conclusion

In patients with HeFH who were receiving stable background statin with or without ezetimibe, treatment with open-label alirocumab 150 mg Q2W for 3 years was well-tolerated, with no evidence of specific

safety signals including in those patients with LDL-C < 25 mg/dL. Alirocumab treatment resulted in significant, sustained reductions in LDL-C of approximately 60% and allowed achievement of LDL-C goals previously unobtainable in these patients with statins and other current lipid-lowering therapies. Substantial reductions in Lp(a), an independent cardiovascular risk factor, were also observed.

Supplementary data to this article can be found online at doi:10.1016/j.ijcard.2016.11.046.

Disclosures

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