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Efficacy of alirocumab in high cardiovascular risk populations with or without heterozygous familial hypercholesterolemia: Pooled analysis of eight ODYSSEY Phase 3 clinical program trials

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ABSTRACT

Objectives: Despite maximally tolerated statin therapy, many patients with high cardiovascular risk, with or without heterozygous familial hypercholesterolemia may require additional low-density lipoprotein cholesterol (LDL-C) reduction. We report pooled alirocumab (ALI) efficacy and safety data from eight Phase 3 trials in 4629 hypercholesterolemia patients, receiving background statin therapy.
Material and methods: Studies were pooled by ALI dose and control: ALI 75/150 mg every 2 weeks (Q2W; dose increased to 150 mg Q2W at Week 12 based on Week 8 LDL-C) versus ezetimibe (EZE; Pool 1) or placebo (PBO; Pool 2), and ALI 150 mg Q2W versus PBO (Pool 3).
Results: Mean baseline LDL-C was 109 vs. 105 mg/dL (Pool 1), 129 vs. 130 mg/dL (Pool 2) and 126 vs. 125 mg/dL (Pool 3). ALI 75/150 mg Q2W reduced LDL-C by 48.9% (vs. −19.3% EZE) and 48.6% (vs. +4.2% PBO) from baseline to Week 24, and ALI 150 mg Q2W reduced LDL-C by 60.4% (vs. +0.5% PBO; all $p < 0.0001$). LDL-C reductions were sustained to Week 104. Risk-based LDL-C goals (<70 mg/dL or <100 mg/dL) were achieved by 78.0%, 75.2%, and 79.0% (Pool 1–3) of ALI-treated patients (vs. 52.4%, 6.4%, and 8.4%, respectively, for controls) at Week 24. Consistent reductions were observed in apolipoprotein B, non-high-density lipoprotein cholesterol, and lipoprotein (a) ($p < 0.0001$ vs. control). Common adverse events in ALI-treated patients were nasopharyngitis, injection-site reactions, upper respiratory tract infections, and influenza.
Conclusions: Alirocumab treatment significantly reduced LDL-C in high cardiovascular risk patients, enabling most to achieve risk-based LDL-C goals.

1. Introduction

Elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for developing and worsening of atherosclerotic cardiovascular disease (ASCVD) [1]. LDL-C reduction is particularly important in people defined as having a high risk of CV events, including those with familial dyslipidemia, severe hypertension, diabetes mellitus, moderate chronic kidney disease (CKD) or a calculated SCORE risk of fatal CV disease of ≥5% [2,3]. However, many of these patients do not reach LDL-C targets, despite receiving maximally tolerated statin therapy [1,3,4].

Although LDL-C remains the primary focus of lipid-lowering therapy (LLT), other lipoproteins, such as non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein (apo) B, are also recognized as important risk factors. In fact, it has been proposed that these may more accurately reflect the level of circulating atherogenic lipoprotein than LDL-C (calculated using the Friedewald equation) [4]. Lipoprotein(a) [Lp(a)] is an apo B-containing atherogenic lipoprotein that predicts CV risk and is associated with aortic valvular disease independently of LDL-C; it is recognized that statin therapy has little, if any, effect on this parameter.

Alirocumab (a monoclonal antibody that binds to and inhibits proprotein convertase subtilisin/kexin type 9, preventing low-density lipoprotein receptor degradation and thereby increasing LDL-C clearance) has been approved for the treatment of hypercholesterolemia in

Abbreviations: Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); Q2W, every 2 weeks; TEAE, treatment-emergent adverse event.

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the USA and the European Union as an adjunct to diet and maximally tolerated statin therapy [5,6]. In the USA, alirocumab is indicated for use in adults with HeFH or clinical ASCVD who require additional lowering of LDL-C [6]; in Europe, approval includes adults with primary hypercholesterolemia (HeFH and non-familial) or mixed dyslipidemia, with or without other LLTs, in patients unable to reach LDL-C goals with maximum tolerated statin. In Europe, the indication also specifically permits the use of alirocumab as monotherapy or combination therapy with other LLTs in statin-intolerant patients, or for those where statins are contraindicated [5].

Here, we present a pooled analysis of alirocumab efficacy and safety data from eight ODYSSEY Phase 3 clinical trials of up to 104 weeks in high-risk patients (including people with HeFH, and people with established CVD, or risk equivalents). Each trial was conducted in individuals on background statin therapy. In six of the eight studies, individuals received maximally tolerated statins (accounting for 91% of the total number of individuals included in the pooled dataset), while in the other two studies a fixed dose of background statin was used, either atorvastatin 20–40 mg or rosuvastatin 10–20 mg. In all the individual trials, alirocumab treatment at a dose of 75 or 150 mg every 2 weeks (Q2W) resulted in a significant reduction in LDL-C versus controls in patients at high CV risk with or without HeFH [7–13]. For the pooled analysis, we report on the effects of alirocumab treatment on LDL-C and other lipid parameters, including non-HDL-C, apo B, and Lp(a).

2. Methods

2.1. Study designs and pooling strategy

This analysis includes data from eight Phase 3 randomized, double-blind, controlled trials (Fig. 1). Methods of the individual trials have been reported previously [8,9,11–14]. Patients were randomized to either alirocumab or control in a 2:1 ratio (1:1 ratio in the OPTIONS I and II studies) and received double-blind study treatment for 24–104 weeks.

For the purposes of the present analysis, efficacy data were analyzed in three pools according to the alirocumab dose and control used in each individual trial. Three trials compared alirocumab 75/150 mg Q2W versus ezetimibe (Pool 1, n = 1130), three trials compared alirocumab 75/150 mg Q2W versus placebo (Pool 2, n = 1051), and two trials compared alirocumab 150 mg Q2W versus placebo (Pool 3, n = 2448) (Fig. 1). In Pools 1 and 2, the alirocumab dose was increased in a blinded fashion from 75 to 150 mg Q2W at Week 12 if Week 8 LDL-C level was ≥70 mg/dL (or ≥70 or ≥100 mg/dL, depending on CV risk, in the OPTIONS I and II studies). Safety data were analyzed in two pools according to control group.

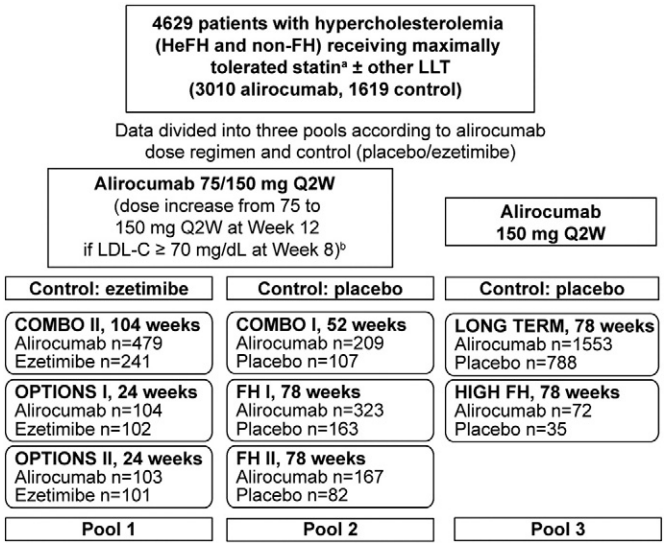

Fig. 1. Pooling strategy. For purposes of this analysis, efficacy data were analyzed in three pools according to alirocumab dose (75/150 mg or 150 mg Q2W) and control (ezetimibe or placebo). For safety analysis, Pool 2 and Pool 3 were combined. n values refer to the number of patients in the randomized study populations. [a] Maximally tolerated statin was defined as atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg. Fixed doses of atorvastatin 20–40 mg and rosuvastatin 10–20 mg were used in OPTIONS I and II, respectively. [b] In the OPTIONS studies, dose was increased if LDL-C was ≥70 mg/dL (prior CHD) or ≥100 mg/dL (CHD risk equivalents). CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolemia; FH, familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Q2W, every 2 weeks. Clinicaltrials.gov identifiers: COMBO II, NCT01644188; OPTIONS I, NCT01730040; OPTIONS II, NCT01730053; FH I, NCT01623115; FH II, NCT01709500; COMBO I, NCT01644175; LONG TERM, NCT01507831; HIGH FH, NCT01617655.

2.2. Patients

The FH I, FH II, and HIGH FH studies exclusively recruited patients with HeFH and who were therefore at high CV risk. COMBO I and II recruited non-FH patients at high CV risk (established CHD/CVD or CHD risk equivalents [e.g. CKD or diabetes mellitus with other risk factors]). The other studies recruited both HeFH patients and non-FH patients at high CV risk (as above plus people without documented CHD or CVD but with a 10-year risk of fatal CVD ≥5% [SCORE] in the OPTIONS studies). For study entry, LDL-C at screening had to be ≥70 or 100 mg/dL, depending on CV risk (except in LONG TERM, where LDL-C was ≥70 mg/dL for all patients, and in HIGH FH, where LDL-C had to be ≥160 mg/dL). Eligibility also required all patients to be receiving maximally tolerated statin, with or without other LLT, which was continued throughout the study as background therapy. Exceptions were the OPTIONS I and II trials, which used fixed doses of atorvastatin 20–40 mg and rosuvastatin 10–20 mg, respectively, and COMBO II, in which no other LLT was allowed. Maximally tolerated statin was defined as atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg (lower doses were allowed with an investigator-approved reason, e.g. intolerance). All studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and applicable amendments laid down by the World Medical Assemblies, and the International Conference Harmonization guidelines for Good Clinical Practice. For each participating study site, institutional review board or independent ethics committee approval of the protocols was ascertained and written informed consent was obtained from all patients.

2.3. Endpoints and statistical analysis

Efficacy endpoints included the percentage change in LDL-C (calculated using the Friedewald formula), apo B, non-HDL-C, Lp(a), triglycerides, HDL-C, and apo A1 from baseline to Week 12 (before possible dose increase) and Week 24 (primary endpoint in each individual study), and the proportion of patients achieving risk-based LDL-C goals. Data were analyzed using an intention-to-treat approach, including all lipid data regardless of adherence to treatment. An analysis using only on-treatment data was also performed. Least-squares mean lipid values were calculated from a mixed-effects model with repeated measures to account for missing data, as described previously [15]. Adjusted means were calculated for Lp(a) and triglycerides, with missing values calculated by multiple imputation followed by robust regression. Combined estimates were calculated for LDL-C goal achievement, with missing data accounted for by multiple imputation followed by logistic regression. Safety was assessed via reporting of treatment-emergent adverse events (TEAEs) and laboratory values. Adverse events were classed as TEAEs if they were reported from the first dose of study treatment up to the last dose plus 70 days. Descriptive statistics only were used for safety analyses (no formal statistics were planned in the study protocols).

3. Results

3.1. Patients

In total, this analysis included 4629 patients (1130 in Pool 1, 1051 in Pool 2, and 2448 in Pool 3). Demographic and baseline characteristics were similar for the alirocumab and control groups within the study pools (Table 1). More patients were male than female, and the majority of patients were white. A history of ASCVD was reported for the majority of patients; Pool 1, 84.5% alirocumab versus 79.5% control; Pool 2, 56.5% versus 56.8%; Pool 3, 75.0% versus 77.0%, and a history of diabetes was reported in 35.4% versus 37.4% in Pool 1, 18.9% versus 20.2% in Pool 2, and 34.7% versus 34.5% in Pool 3, respectively (Table 1). Pool 2 had the lowest proportion of patients with diabetes or ASCVD, and this pool had the highest baseline LDL-C values (Table 1). A greater proportion of patients in Pool 2 had HeFH (69.9%) as the FH I and FH II studies exclusively recruited patients with this condition (Table 1). Lower rates of ASCVD, diabetes and higher LDL-C are all reflections of the enrichment in FH patients. Most patients were receiving maximally tolerated statin therapy (91%). In Pool 1, 11% of alirocumab-treated individuals were also receiving additional LLT at study entry (vs. 12% control group) compared with 57% and 28% of alirocumab-treated individuals in Pools 2 and 3 (vs. 62% and 28% in respective control groups).