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A phase III randomized trial evaluating alirocumab 300 mg every 4 weeks as monotherapy or add-on to statin: ODYSSEY CHOICE I

Eli M. Roth [a, *], Patrick M. Moriarty [b], Jean Bergeron [c], Gisle Langslet [d], Garen Manvelian [e], Jian Zhao [f], Marie T. Baccara-Dinet [g], Daniel J. Rader [h], for the ODYSSEY CHOICE I investigators

[a] The Sterling Research Group, 2230 Auburn Avenue, Cincinnati, OH 45219, USA
[b] Department of Internal Medicine, Division of Clinical Pharmacology, University of Kansas Medical Center, Kansas City, KS, USA
[c] Clinique des Maladies Lipidiques, Department of Medicine, Centre Hospitalier Universitaire de Québec – Université Laval Québec, Canada
[d] Lipid Clinic, Oslo University Hospital, Oslo, Norway
[e] Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA
[f] Regeneron Pharmaceuticals, Inc., Basking Ridge, NJ, USA
[g] Sanofi, Montpellier, France
[h] Department of Medicine, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, PA, USA

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ABSTRACT

Background and aims: In previous phase III studies, the PCSK9 monoclonal antibody alirocumab was administered at doses of 75 or 150 mg every 2 weeks (Q2W). CHOICE I (NCT01926782) evaluated 300 mg every 4 weeks (Q4W) in patients on either maximally tolerated statin or no statin, both ± other lipid-lowering therapies.

Methods: CHOICE I included patients with hypercholesterolemia at moderate-to-very-high cardiovascular risk. Patients were randomized to alirocumab 300 mg Q4W, 75 mg Q2W (calibrator arm), or placebo for 48 weeks, with dose adjustment for either alirocumab arm to 150 mg Q2W at Week (W) 12 if at W8 LDL-C levels were >70/100 mg/dL (1.8/2.6 mmol/L) depending on cardiovascular risk or LDL-C reduction was <30% from baseline. Co-primary endpoints were percent LDL-C change from baseline to W24, and to time-averaged LDL-C over W21–24.

Results: Approximately two-thirds of randomized patients were receiving statins. At W12, 14.7% (no statin) and 19.3% (statin) of patients receiving alirocumab 300 mg Q4W required dose adjustment. At W24, significant LDL-C reductions from baseline were observed with alirocumab 300 mg Q4W: mean differences were −52.7% (no statin; placebo: −0.3%) and −58.8% (statin; placebo: −0.1%). Average LDL-C reductions from baseline to W21–24 were also significantly greater with alirocumab 300 mg Q4W *vs.* placebo in patients not receiving (−56.9% *vs.* −1.6%) and receiving statin (−65.8% *vs.* −0.8%). Treatment-emergent adverse event rates ranged from 61.1 to 75.0% (placebo) and 71.5 to 78.1% (alirocumab 300 mg Q4W).

Conclusions: Alirocumab 300 mg Q4W is a viable additional treatment option in patients requiring LDL-C-lowering.

1. Introduction

Alirocumab is a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), a key regulator of the low-density lipoprotein (LDL) receptor and ultimately LDL cholesterol (LDL-C) levels. In prior phase III studies, using a dosing regimen of 75 mg every 2 weeks (Q2W) (with possible dose adjustment to 150 mg Q2W) added to background statin with or without other lipid-lowering therapies (LLTs) or as monotherapy, alirocumab reduced LDL-C levels by 44–54% [1–3]. Alirocumab 150 mg Q2W reduced LDL-C levels by 61% on background statin ± other LLTs [4]. Beneficial effects were also seen on other atherogenic lipid parameters, including non-high-density

* Corresponding author.
E-mail address: eroth@sterlingresearch.org (E.M. Roth).

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lipoprotein cholesterol (non-HDL-C), apolipoprotein (Apo) B, and lipoprotein (a) [Lp(a)] [1–4]. For some patients a dosing regimen of alirocumab every 4 weeks (Q4W) might be a preferred option.

The magnitude and duration of LDL-C reductions with alirocumab are related to dose and its rate of elimination following administration [5–7]. Alirocumab elimination occurs through nonspecific mechanisms as well as specific mechanisms related to its binding to PCSK9 in a process known as target-mediated clearance [8]. Statins are known to increase PCSK9 levels [9,10] and, when co-administered with alirocumab, appear to reduce alirocumab's duration of effect via enhanced target-mediated clearance in the setting of Q4W dosing [8]. In contrast, fenofibrate and ezetimibe were associated with only limited impact on alirocumab duration of effect [11].

In a phase II study of patients with heterozygous familial hypercholesterolemia receiving stable statin, LDL-C reductions on alirocumab were not fully maintained over the dosing interval in all statin-treated patients. Although alirocumab 150 mg Q4W reduced LDL-C levels from baseline by 61% at Week 10 (2 weeks post-alirocumab dose), the mean reduction at Week 12 was 28.9% (4 weeks post-alirocumab dose) [5], suggesting that this dosing strategy may not be appropriate for those receiving concomitant statin. The effectiveness of this dose of alirocumab (150 mg Q4W) in patients with hypercholesterolemia who are not receiving statin therapy has been investigated further in the ODYSSEY CHOICE II study [12].

Using a higher dose of 300 mg Q4W (*vs.* 150 mg Q4W), a greater reduction of 42.5% was maintained at Week 12 in patients with heterozygous familial hypercholesterolemia receiving statin therapy, suggesting that this dose could be an option for some patients both with and without concomitant statin [5]. Furthermore, in a separate phase II study including patients with baseline LDL-C levels of ≥100 mg/dL (2.6 mmol/L) receiving stable atorvastatin 10–40 mg daily, LDL-C reductions of 43.2% with alirocumab 200 mg Q4W and 47.7% with alirocumab 300 mg Q4W were achieved [6].

The objective of the phase III ODYSSEY CHOICE I study (NCT01926782) was to determine the efficacy, long-term safety, and tolerability of a potential starting dose regimen of alirocumab 300 mg Q4W (with dose adjustment depending on individual patient response) either as add-on to maximally tolerated doses of statin (with or without other LLTs) or when used without statin. This study used alirocumab 75 mg Q2W as a calibrator arm.

2. Materials and methods

ODYSSEY CHOICE I was a randomized, double-blind, placebo-controlled, phase 3 multinational study which enrolled 803 patients from 105 study sites from the USA ($n = 63$), Canada ($n = 7$), Hungary ($n = 6$), the United Kingdom ($n = 10$), Bulgaria ($n = 5$), Israel ($n = 5$), Slovakia ($n = 6$), and Norway ($n = 3$). The study was initiated on October 24, 2013 (first patient screened), with the first patient randomized on November 4, 2013 and the last patient randomized on May 12, 2014. The study was conducted in accordance with the ethical principles in the Declaration of Helsinki and applicable amendments, and the International Conference on Harmonization for Good Clinical Practice guidelines. The protocol was approved by the relevant institutional review board or independent ethics committee, and all participating patients provided written informed consent.

2.1. Patients

The study included adult patients (aged >18 years) who did not have adequately controlled hypercholesterolemia, with (a) moderate-to-very-high cardiovascular disease (CVD) risk and receiving the maximally tolerated dose of statin, (b) moderate-to-very-high CVD risk and with statin-associated muscle symptoms (defined in protocol as muscle-related statin intolerance), or (c) moderate CVD risk and not receiving statin. Enrollment was stratified so that approximately two-thirds of the randomized patients were receiving concomitant statin therapy, with enrollment of patients receiving statins and with moderate CVD risk capped at 25% of the statin subgroup.

Patients receiving concomitant statin were to receive stable daily doses (for at least 4 weeks) of rosuvastatin 20–40 mg, atorvastatin 40–80 mg, or simvastatin 80 mg (which must have been at a stable dose for ≥1 year), or maximally tolerated dose of one of these three statins. Background treatment with LLTs other than statins was allowed for all patients, provided they had been on a stable dose for at least 4 weeks (6 weeks for fenofibrate) prior to study entry, excluding statins (other than atorvastatin, rosuvastatin, or simvastatin), fibrates other than fenofibrate, and red yeast rice products. A list of exclusion criteria is given in Supplementary Table 1. Patients were required to follow a stable diet equivalent to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) Therapeutic Lifestyle Changes diet from screening to end of study [13].

Baseline LDL-C level was required to be ≥70 mg/dL (1.8 mmol/L) if the patient was considered at very high CVD risk or ≥100 mg/dL (2.6 mmol/L) if the patient was considered at high or moderate CVD risk, with these levels based on the NCEP ATP III guidelines available when the study was initiated [13]. In addition, the population of patients who were not on statin therapy was restricted to patients who were at moderate CVD risk with LDL-C ≥100 mg/dL (1.8 mmol/L) and <160 mg/dL (4.1 mmol/L) at screening. Patients considered statin intolerant were required to have LDL-C ≥70/100 mg/dL (1.8/2.6 mmol/L; depending on cardiovascular risk) and <160 mg/dL (4.1 mmol/L) if not on any non-statin LLT; however, there was no upper LDL-C limit for patients who were statin intolerant and receiving clinically appropriate LLT, as they were already on best standard of care.

Very-high, high, and moderate CVD risk were defined according to previously defined methods [14]. Very-high CVD risk was defined as documented coronary heart disease (CHD) or CHD risk equivalents (ischemic stroke, transient ischemic attack, carotid artery occlusion >50% without symptoms, carotid endarterectomy or carotid artery stent procedure, peripheral arterial disease, abdominal aortic aneurysm, renal artery stenosis, renal artery stent procedure, or type 1 or type 2 diabetes mellitus with target organ damage). High CVD risk was defined as no CHD/CVD but with a Systematic Coronary Risk Evaluation (SCORE) [15] 10-year fatal CVD risk ≥5%, moderate chronic kidney disease, type 1 or type 2 diabetes mellitus without target organ damage, or heterozygous familial hypercholesterolemia (by genetic or clinical criteria). Moderate CVD risk was defined as a SCORE of between ≥1 and <5%. Statin-associated muscle symptoms were defined as per a previous study in the protocol as statin intolerance, and included the inability to tolerate at least two statins: one statin at the lowest daily starting dose and another statin at any dose, due to skeletal muscle-related symptoms [14].

2.2. Study procedures

The study comprised a 3-week screening period, followed by 48 weeks of double-blind treatment and 8 weeks of follow-up (off-treatment). Patients were randomized using a permuted block design in a 4:2:1 ratio to receive alirocumab 300 mg Q4W, placebo, or alirocumab 75 mg Q2W (Fig. 1). Each treatment was administered subcutaneously as 2 × 1 mL injections (placebo or alirocumab) by pre-filled syringe. To maintain the blind, all patients

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