Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: Design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial

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BACKGROUND: Statin intolerance has been a major limitation in the use of statins, especially at higher doses. New effective treatments are needed for lowering low-density lipoprotein cholesterol (LDL-C) in patients who cannot tolerate daily statin doses.

OBJECTIVE: ODYSSEY ALTERNATIVE (NCT01709513) evaluates efficacy and safety of alirocumab, a fully human proprotein convertase subtilisin/kexin type 9 monoclonal antibody, in patients with well-documented statin intolerance and moderate to very high cardiovascular risk.

METHODS: This is a phase 3, multicenter, randomized, double-blind, double-dummy study in statin-intolerant patients. Intolerance was defined as inability to take at least 2 different statins because of muscle-related adverse events (AEs), 1 at the lowest approved starting dose. Patients first received single-blind subcutaneous and oral placebo for 4 weeks, and were withdrawn if they developed muscle-related AEs after the placebo treatment. Continuing patients were randomized (2:2:1 ratio) to alirocumab 75 mg self-administered via single 1 mL prefilled pen every 2 weeks or ezetimibe 10 mg/day or atorvastatin 20 mg/day (statin rechallenge), for 24 weeks. Alirocumab dose was increased to 150 mg every 2 weeks (also 1 mL) at week 12 depending on week 8 LDL-C level. The primary endpoint is percent change in LDL-C from baseline to week 24 by intent-to-treat analysis. Muscle-related AEs were assessed by spontaneous patient reports and clinic queries.

RESULTS: A total of 314 patients have been randomized.

CONCLUSIONS: This is the first and only study of a new class of LDL-C–lowering agents in patients selected with a rigorously documented intolerance to statins, using a placebo run-in and statin control arm.

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Statins are the most effective medications presently available to reduce low-density lipoprotein cholesterol (LDL-C; expected reductions of 30%–50%) and thereby reduce cardiovascular (CV) risk. However, statin intolerance, broadly defined as the inability to tolerate statin therapy, usually because of muscle adverse events (AEs), has been a major limitation in the use of statins. Yet currently, there are no non-statin drugs that lower LDL-C as effectively as statins, and many of the statin alternatives are poorly tolerated.

Many patients in clinical practice (approximately 10%–25%) are not able to tolerate statins either at all or at a dose sufficient to effectively lower their LDL-C to recommended goal levels. Approximately 13% of both statin- and placebo-treated patients reported muscle complaints in randomized controlled statin trials; however, this does not provide a reliable indication of prevalence because most of these trials excluded patients with a history, or increased risk, of statin intolerance. Furthermore, there has been substantial variability in how statin intolerance has been assessed across these studies. Well-controlled, randomized trials in statin-intolerant patients are lacking, although the Effect of Statin Medications on Muscle Performance study reported that more subjects receiving atorvastatin 80 mg daily experienced muscle symptoms compared with placebo (9.4% vs 4.6%).

Alirocumab is a fully human monoclonal antibody that specifically binds to proprotein convertase subtilisin/kexin type 9. In 3 phase 2 studies, it was shown to reduce LDL-C by approximately 40 to 70% when administered as a 50- to 150-mg dose every 2 weeks (Q2W) on top of background statin therapy (compared with reductions of 5%–10% with placebo) and was well-tolerated, with self-limiting, mild injection site reactions as the most common AE. In the 2 phase 2 studies on stable background statin therapy, muscle disorders were reported in 6% of patients who received alirocumab 50 to 150 mg Q2W (n = 108) and 7% of placebo patients (n = 46). In the other phase 2 study (n = 30 or 31 per arm), patients were randomized to increase their background atorvastatin dose from 10 to 80 mg/day plus either placebo or alirocumab, or remain on atorvastatin 10 mg/day plus alirocumab; 17 to 19% of patients who received atorvastatin 80 mg experienced a muscle-related AE, compared with 6% who remained on atorvastatin 10 mg (with concomitant alirocumab). In a phase 3 study, a decrease in LDL-C of 54% (on-treatment) was reported at week 24 when alirocumab 75 mg Q2W was given as monotherapy (n = 51; dose could be increased to 150 mg Q2W at week 12 based on LDL-C), compared with a 17% reduction with ezetimibe (n = 50). In this monotherapy study, a similar proportion of AEs were reported with alirocumab (69% of patients) and ezetimibe (78% of patients), with muscle-related AEs reported in 4% of patients in both treatment arms. These results demonstrate the efficacy of alirocumab when administered as either combination therapy or monotherapy, the latter being relevant for patients with statin-intolerance.

The ODYSSEY ALTERNATIVE study (NCT01709513) compares the efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients. The definition of statin intolerance centers on myalgia, as this is considered to be the primary side effect limiting statin use. Intolerance is further reaffirmed in a novel study design by: 1) the use of a placebo run-in period, during which patients developing muscle events will be excluded, and 2) the inclusion of a blinded statin rechallenge arm of atorvastatin 20 mg/day in parallel to the blinded ezetimibe and alirocumab arms. These important controls were lacking from previous anti-PCSK9 trials in statin intolerant patients. Hence, this will be the first study of a new class of LDL-C lowering agents to prospectively and rigorously identify statin intolerant patients. The study allows for the alirocumab dose to be increased depending on pre-specified LDL-C levels. ALTERNATIVE is part of the ODYSSEY Phase 3 clinical trial program, which consists of 14 global trials that involve more than 23,500 patients from more than 2000 study centers, as well as a large 18,000 patient CV outcome trial. The program is designed to further assess the efficacy and safety of alirocumab in a range of clinical settings and patient groups.

Methods

ODYSSEY ALTERNATIVE is a randomized, double-blind, double-dummy, active-controlled, parallel-group study conducted in 67 sites across the United States, Canada, Austria, France, Italy, Israel, Norway, and the United Kingdom. The study was conducted in compliance with the principles of the Declaration of Helsinki and according to the International Conference on Harmonisation guidelines for Good Clinical Practice. The protocols were reviewed and approved by the institutional review board of each participating center. A progress report was sent to the relevant ethics committees at least annually, as was a summary of the outcome at the end of the trial. All participants were required to provide written informed consent.

Patients

Patients were eligible to participate if they were aged ≥18 years (or legal age of majority), had a documented history of statin intolerance, and were of moderate, high, or very high CV risk. Statin intolerance is defined in this study as the inability to tolerate at least 2 different statins because of unexplained skeletal muscle-related symptoms, such as pain, aches, weakness, or cramping that began or increased during statin therapy and returned to baseline when statin therapy was discontinued. For each patient to meet this definition, one of the statins that was discontinued had to have been at the lowest approved daily starting dose (ie, rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, pitavastatin 2 mg); the other statin was at any dose.
Risk was defined as shown in Table 1. Patients at very high CV risk were eligible with a calculated serum LDL-C ≥70 mg/dL (1.81 mmol/L), whereas those at high or moderate CV risk were eligible with a calculated serum LDL-C ≥100 mg/dL (2.59 mmol/L) at screening. Patients with heterozygous familial hypercholesterolemia were classified as high-risk regardless of their Systematic Coronary Risk Evaluation (SCORE). Diagnosis of heterozygous familial hypercholesterolemia in this study was made by genotyping or, if genotyping was not available, by clinical criteria (investigators could choose to use the Simon Broome19 or the World Health Organization/Dutch Lipid Network20 criteria).

Patients had not taken a statin at or above the lowest approved daily dose within 4 weeks before the screening visit. However, patients must have been receiving a stable dose of other lipid-lowering therapy, including ezetimibe, a bile acid sequestrant, nicotinic acid, omega-3 fatty acids (≥1000 mg daily), or fenofibrate, for at least 4 weeks before screening (6 weeks for fenofibrate). Patients receiving fibrates other than fenofibrate within 6 weeks of screening were excluded. Fibrates such as gemfibrozil can inhibit the metabolism of statins, thus potentially increasing the risk of muscle-related side effects; this class of drugs (apart from fenofibrate) was therefore not allowed in this study. Fenofibrate does not alter statin pharmacokinetics and thus was allowed.

Only patients who demonstrated intolerance to statins while on an alternate dosing statin regimen (eg, 1–3 times weekly) instead of a daily statin regimen were still considered as statin-intolerant to a daily dosing regimen and, therefore, eligible to enroll in the study if their cumulative weekly statin dose was no more than 7 times the lowest dose and the criteria outlined previously were met. Patients who experienced unexplained skeletal muscle-related AEs during the single-blind placebo run-in or at randomization were excluded. A partial list of exclusion criteria is given in Supplementary Table 1.

### Study design

The study consisted of 5 to 6 periods (Fig. 1). Patients were asked to follow a stable diet equivalent to the National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes diet21 during the study. Patients receiving bile acid sequestrants, nicotinic acid, fenofibrate, or omega-3 fatty acids before screening could continue these medications, but ezetimibe, statins, red yeast rice, or fibrates other than fenofibrate were not allowed during the study. After screening, patients entered a 2-week washout of ezetimibe, statins (for patients taking a nonapproved dose or regimen), and red yeast rice. However, patients were not permitted to receive fibrates (other than fenofibrate) within 6 weeks of screening, and any patients receiving fibrates during this time were excluded. Fibrates such as gemfibrozil can inhibit the metabolism of statins, thus potentially increasing the risk of muscle-related side effects; this class of drugs (apart from fenofibrate) was therefore not allowed in this study. Fenofibrate does not alter statin pharmacokinetics and thus was allowed.

Only patients who were blinded to treatment during the 4-week, single-blind placebo run-in period when all patients received subcutaneous (SC) placebo injection Q2W as well as daily oral placebo. At the end of the single-blind run-in, patients were randomized to receive either alirocumab 75 mg SC Q2W and daily oral placebo, alirocumab SC placebo Q2W and daily oral ezetimibe 10 mg, or alirocumab SC placebo Q2W and daily oral atorvastatin 20 mg (Fig. 1) using a 2:2:1permuted-block randomization. Hence, each treatment arm received an injection (alirocumab or placebo) and an oral dosage form (single placebo capsule representing both ezetimibe and...
atorvastatin, ezetimibe 10 mg or atorvastatin 20 mg). Oral placebo, ezetimibe, and atorvastatin were overencapsulated to look identical. Randomization was stratified according to whether there was documented history of either myocardial infarction or ischemic stroke. Alirocumab and its placebo were administered subcutaneously by a prefilled pen capable of delivering the drug product or placebo in a 1-mL volume. Patients could self-inject or designate another person to assist them. At the first scheduled visit of the single-blind placebo run-in period, the patient or designated person was trained to use the prefilled pen, and the injection was performed on site.

The alirocumab dose was automatically up-titrated from 75 mg to 150 mg Q2W in a double-blinded fashion at week 12 of the double-blind treatment period, depending on a patient’s baseline CV risk and LDL-C level at week 8. The dose was increased for patients at very high CV risk if their week 8 LDL-C level was ≥70 mg/dL (1.81 mmol/L), and for those at high or moderate CV risk if their week 8 LDL-C level was ≥100 mg/dL (2.59 mmol/L).

At the end of the 24-week, double-blind treatment period, patients could choose to enter an open-label period that was followed by an 8-week off-treatment follow-up period. Patients who opted not to enter the open-label period entered an 8-week follow-up period. Patients who enrolled in the open-label extension underwent assessment at week 24, the end of the double-blind period (Fig. 1B). Those entering the open-label extension are receiving alirocumab 75 mg SC Q2W starting at week 24 of the double-blind period and continuing for approximately 3 years. The alirocumab dose was increased from 75 mg to 150 mg Q2W at week 36 of the open-label extension based on the LDL-C level at week 32 and the judgment of the investigator.

Figure 1  Study design of (A) the main part of the ODYSSEY ALTERNATIVE study and (B) the open-label extension. Time points for lipid assessments are indicated by vertical arrows under the schematics. *Eligible patients can opt to participate in a 196-week open-label treatment period. ATV, atorvastatin; CV, cardiovascular; EZE, ezetimibe; LDL-C, low-density lipoprotein cholesterol; NCEP-ATP III TLC, National Cholesterol Education Program Adult Treatment Panel III Therapeutic Lifestyle Changes; OLE, open-label extension; PO, orally; Q2W, every 2 weeks; QD, daily; R, randomization; RYR, red yeast rice; SC, subcutaneously; W, week.
Endpoints and assessments

The primary efficacy endpoint is the percent change in LDL-C from baseline to week 24, by intent-to-treat (ITT) analysis. Secondary endpoints include the change from baseline to 24 weeks using on-treatment LDL-C values, and in other atherogenic lipoproteins (Supplementary Table 2). Efficacy endpoints will be determined for the alirocumab vs ezetimibe arms only; the atorvastatin arm will only be included in the safety analysis.

Lipid parameters will be assessed at 0, 4, 8, 12, 16, and 24 weeks of the double-blind period and every 4 weeks during the open-label extension up to week 36, then at week 52 and every 12 weeks thereafter (Fig. 1B). Lipid parameters will be analyzed by a central laboratory. LDL-C will be calculated using the Friedewald formula at screening and all time points during the double-blind period. LDL-C will also be measured via beta quantification at weeks 0 and 24 of the double-blind period and if a patient’s triglycerides exceed 400 mg/dL (4.52 mmol/L) at any time point.

Safety

An important safety consideration is the number of withdrawals because of AEs (particularly muscle-related AEs), which will help to characterize the statin-intolerant population in this study. The study was designed to randomize a sufficient number of patients to ensure that at least 1 withdrawal from an AE in the ezetimibe arm can be detected (see Statistical Design and Analysis). Muscle-related AEs are being assessed by both patient self-reports and AE query at each clinic visit. The study treatments will be discontinued permanently if the patient, after counseling by the site study staff, is convinced that prior statin-related muscle symptoms have been reproduced and that his or her symptoms may be unduly prolonged by continuing treatment. If muscle symptoms are tolerable, study treatment can be continued. Patients who prematurely discontinue the study treatment during the double-blind treatment period will remain in the study and undergo all remaining scheduled visits and safety assessments. Within 5 days of study drug discontinuation, the patient will undergo an end-of-treatment assessments visit. Subsequent visits will follow the original planned study schedule until the end of study.

In this study of patients who are intolerant to statins, certain AEs commonly associated with statins, including muscle-related AEs (including myositis) and liver function–related abnormalities (elevated alanine aminotransferase levels), will be classed as AEs of special interest, and will be monitored closely, documented, and managed in a prespecified manner (whether serious or nonserious). Myositis is here defined as myalgia (muscle-related AEs) with creatine phosphokinase elevation between >3 times and ≤10 times the upper limit of normal, with the creatine phosphokinase elevation occurring within 2 weeks of the onset of muscle symptoms.

General safety is being assessed as treatment-emergent AEs (TEAEs), blood biochemistry, hematology, urinalysis abnormalities, vital signs, electrocardiogram, and development of anti-alirocumab antibodies at the time points given previously for the lipid assessments. Injection site reactions will be closely monitored as AEs of special interest. TEAEs are defined as AEs that develop or worsen during treatment, regardless of their possible relationship to the study drug. The TEAE period is the time from first dose of study treatment to 70 days after the last injection, because residual alirocumab effects are expected up until this time.

Safety laboratory parameters will be analyzed by a central laboratory, and anti-alirocumab antibodies will be determined by the Regeneron Clinical Bioanalysis Group (Regeneron Pharmaceuticals Inc, Tarrytown, NY, USA) using a validated nonquantitative, titer-based bridging immunoassay.

Statistical design and analysis

A sample size of 42 patients in the alirocumab and ezetimibe treatment groups was calculated to provide 95% power to detect a difference of 20% between alirocumab and ezetimibe in mean percent change from baseline to week 24 in LDL-C, using a 2-sided t-test. This assumes a common standard deviation of 25% based on a previous alirocumab trial.

With the sample size consideration for the safety profile, the overall study sample size during the double-blind treatment period will be 250 patients, allocating 100 patients to each of the alirocumab and ezetimibe treatment arms, and 50 patients to the statin treatment arm. Based on withdrawal events occurring in approximately 3.3% of patients in the general hypercholesterolemic population taking ezetimibe, it was calculated that 100 patients in each treatment arm (alirocumab and ezetimibe) will give a 96% probability of recording at least 1 withdrawal because of an AE. If the withdrawal rate in this statin-intolerant population occurs at a rate that is actually higher than 3.3%, 100 patients per treatment arm will provide an even stronger ability to provide an estimate of the withdrawal rate.

The primary efficacy endpoint will be evaluated in the ITT population. The ITT population will include all randomized patients with calculated LDL-C value at baseline and at least 1 calculated LDL-C value within 1 of the analysis windows up to week 24. Missing data will be accounted for using a mixed-effect model with repeated measures approach. For the ITT analysis, all available measurements at planned time points from weeks 4 to 24, regardless of status on- or off-treatment, will be used (Supplementary Methods). An analysis of the primary endpoint that assesses the consistency of the treatment effect across prespecified subgroups will be evaluated. Statistical significance of the primary parameter at the 0.05 alpha level is required before drawing inferential conclusions about the first key secondary parameter. A hierarchical
testing procedure will be used to control type I error and handle multiplicity for analyzing the key secondary endpoints, which will be tested sequentially in the order given in Supplementary Table 2. Analysis of the secondary endpoints is described in the Supplementary Methods.

An on-treatment analysis or modified ITT will also be conducted as the first secondary endpoint, and will include all randomized and treated patients with a baseline and at least one LDL-C measurement at 4 to 24 weeks of treatment as long as the LDL-C samples are obtained while the patient is receiving the study treatment, including an additional time period after last study treatment administration for residual treatment effect. This endpoint is reflective of the ability of a therapy to lower LDL-C. For the on-treatment analysis (modified ITT), all available measurements from weeks 4 to 24 within the on-treatment time window will be used in the mixed-effect model with repeated measures. The safety analysis will include randomized and treated patients. Safety data will be analyzed using descriptive statistics. Safety and efficacy in the open-label extension will be assessed in all patients who receive at least 1 dose of open-label alirocumab. Statistical analyses will be conducted using SAS version 9.2 or higher (SAS Institute Inc., Cary, NC).

Results

The trial is being conducted across 8 countries. Between November 21, 2012, and October 4, 2013, 314 patients were randomized. This is an ongoing clinical trial with the double-blind period expected to complete in mid-2014. Full details of baseline characteristics, patient disposition, and efficacy and safety results will be available in the future.

Discussion

Muscle complaints are the most common symptom limiting statin use. In patients for whom daily statin dosing is no longer a treatment option, non-statin therapies are available but only provide approximately a 15 to 20% reduction in LDL-C, compared with the 30 to 50% reductions expected with daily regimens of statins such as atorvastatin 10–80 mg, rosuvastatin 5–40 mg, or simvastatin 20–40 mg. Intermittent (non-daily) statin dosing has been reported to provide LDL-C reductions varying from 12% to 38%; however, these data are based on results from observational studies. In a small, randomized controlled crossover study in 17 patients with previous statin intolerance, once-weekly dosing with rosuvastatin 5 mg reduced LDL-C by 12.2% vs 0.4% with placebo; myalgia leading to discontinuation was experienced by 20% of patients while receiving rosuvastatin compared with 12% of placebo patients. Two studies of the PCSK9 inhibitor evolocumab have been reported in statin-intolerant patients; however, both studies lacked both a placebo run-in period, to exclude patients with non-statin related muscle events, and a statin control arm. Large, well-controlled randomized trials of cholesterol-lowering drugs in patients who are intolerant to statins have yet to be conducted. One difficulty is that defining and selecting a truly statin-intolerant population is challenging. The study described in this report rigorously defines a statin-intolerant population of patients to investigate a novel LDL-C-lowering therapy.

The specific criteria for statin intolerance used in the study described in this report are based on discussions with experts, regulatory agencies, and investigators during development of the study protocol. The definition used is also in agreement with published guidance. The described study includes a 4-week run-in period in which patients will only receive single-blind placebo. Patients reporting muscle symptoms during this period will not be randomized, because those symptoms will be assumed to be non-statintolerated. This is to help to mitigate the impact of patients with non-statin-induced muscle issues on the study. Also in the described study, patients will receive atorvastatin 20 mg/day if randomized to the statin rechallenge arm to provide further evidence that the patient population is statin intolerant. The 20-mg dose of atorvastatin was chosen after discussion with experts, who were of the opinion that it represents a dose that would elicit muscle symptoms upon rechallenge, but would not preclude patients from enrolling. Although the statin rechallenge arm will likely be associated with an increased risk of muscle-related AEs, it was determined by regulators to be an essential control for this study to define the appropriate patient population. In addition, the 3-year open-label extension is designed to provide further efficacy and safety information on alirocumab in this particular population.

Treating hypercholesterolemia in patients who are intolerant to statins can be difficult because there are few effective alternative treatments. Ezetimibe was chosen as a comparator in the present study because it is a recommended option for statin-intolerant patients from its favorable safety profile. Ezetimibe reduces LDL-C levels by 15 to 20% and, in the absence of statins, requires other agents to produce the magnitude of LDL-C reduction attained with statins. These additional agents, such as niacin and bile acid sequestrants, cause additional (albeit non-muscle-related) symptoms, which make their use difficult. At the same time, the magnitude of LDL-C reduction with statin treatment is not correlated with increased rates of muscle complaints, although the risk of myopathy is increased for very high doses of some statins. For example, high doses (80 mg) of simvastatin are no longer recommended by the Food and Drug Administration because of concerns over an increased risk of myopathy. Clearly, there is a need to develop additional cholesterol-lowering therapies for patients with statin intolerance. Alirocumab may have the potential to meet this need, because it reduces LDL-C levels by approximately 50% when used as monotherapy, and has so far shown a safety profile comparable with ezetimibe or placebo.
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Supplementary data

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