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Original article

Efficacy and safety of alirocumab in insulin-treated patients with type 1 or type 2 diabetes and high cardiovascular risk: Rationale and design of the ODYSSEY DM–INSULIN trial

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ARTICLE INFO

Article history:

Received 30 November 2016

Accepted 1st January 2017

Available online xxx

Keywords:

Alirocumab

Diabetes

Insulin

LDL-C

ODYSSEY

PCSK9

ABSTRACT

Aims. – The coadministration of alirocumab, a PCSK9 inhibitor for treatment of hypercholesterolaemia, and insulin in diabetes mellitus (DM) requires further study. Described here is the rationale behind a phase-IIIb study designed to characterize the efficacy and safety of alirocumab in insulin-treated patients with type 1 (T1) or type 2 (T2) DM with hypercholesterolaemia and high cardiovascular (CV) risk.

Methods. – ODYSSEY DM–INSULIN (NCT02585778) is a randomized, double-blind, placebo-controlled, multicentre study that planned to enrol around 400 T2 and up to 100 T1 insulin-treated DM patients. Participants had low-density lipoprotein cholesterol (LDL-C) levels at screening ≥ 70 mg/dL (1.81 mmol/L) with stable maximum tolerated statin therapy or were statin-intolerant, and taking (or not) other lipid-lowering therapy; they also had established CV disease or at least one additional CV risk factor. Eligible patients were randomized 2:1 to 24 weeks of alirocumab 75 mg every 2 weeks (Q2W) or a placebo. Alirocumab-treated patients with LDL-C ≥ 70 mg/dL at week 8 underwent a blinded dose increase to 150 mg Q2W at week 12. Primary endpoints were the difference between treatment arms in percentage change of calculated LDL-C from baseline to week 24, and alirocumab safety.

Results. – This is an ongoing clinical trial, with 76 T1 and 441 T2 DM patients enrolled; results are expected in mid-2017.

Conclusion. – The ODYSSEY DM–INSULIN study will provide information on the efficacy and safety of alirocumab in insulin-treated individuals with T1 or T2 DM who are at high CV risk and have hypercholesterolaemia not adequately controlled by the maximum tolerated statin therapy.

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Abbreviations: AE, adverse event; Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; HDL-C, high-density lipoprotein cholesterol; I-TAQ, Injection-Treatment Acceptance Questionnaire; ITT, intention-to-treat; LDL-C, low-density lipoprotein cholesterol; LDL-P, LDL particle; LLT, lipid-lowering therapy; Lp(a), lipoprotein(a); MI, myocardial infarction; mITT, modified intention-to-treat; MMRM, mixed-effects model with repeated measures; PAD, peripheral arterial disease; PCSK9, proprotein convertase subtilisin/kexin type 9; Q2W, every 2 weeks; TG, triglyceride; T1, type 1; T2, type 2; UA, unstable angina.

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<http://dx.doi.org/10.1016/j.diabet.2017.01.004>

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Please cite this article in press as: Cariou B, et al. Efficacy and safety of alirocumab in insulin-treated patients with type 1 or type 2 diabetes and high cardiovascular risk: Rationale and design of the ODYSSEY DM–INSULIN trial. *Diabetes Metab* (2017), <http://dx.doi.org/10.1016/j.diabet.2017.01.004>

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with type 1 (T1) or type 2 (T2) diabetes mellitus (DM) [1–3], and insulin-treated patients have an even higher CV risk [4]. Furthermore, the presence of comorbid DM among those who have atherosclerotic CVD (ASCVD) significantly increases the risk of CV events [4,5].

As in the general population, dyslipidaemia is a risk factor for CVD in both T1DM and T2DM [2,6]. The development of dyslipidaemia is associated with insulin resistance that precedes the development of T2DM; once hyperglycaemia is present, increased hepatic free fatty acid influx and synthesis, driven by concomitant loss of insulin sensitivity and glycaemic control, cause dyslipidaemia to deteriorate further [1,7]. Although T2DM is usually characterized by elevated non-high-density lipoprotein cholesterol (non-HDL-C) and triglyceride (TG) levels, along with low HDL-C, elevation in low-density lipoprotein cholesterol (LDL-C) can be variable and rather modest [7]. Nonetheless, small, dense LDL particles are increased, along with other qualitative lipid changes: LDL is more likely to be glycated and oxidized, and HDL undergoes increased catabolism [8]. As a result, two scenarios probably contribute to increased CV risk in T2DM:

- increased TG levels result in increased levels of intermediate-density lipoprotein (IDL) and very low-density lipoprotein (VLDL) remnants, which are atherogenic [8];
- whether smaller LDL particles (LDL-P) are more atherogenic on an individual level remains to be fully elucidated; however, a shift to smaller LDL-P at any given level of LDL-C is associated with a greater number of LDL particles and thereby an increased atherogenic risk.

Patients with T1DM under good glycaemic control often have a 'supernormal' lipid profile, and subcutaneous administration of insulin is known to increase lipoprotein lipase activity and, as a consequence, the turnover of VLDL particles [5]. However, there may be potentially atherogenic changes in the composition of both HDL and LDL particles [5]. Recent evidence has also suggested that components of metabolic syndrome (MetS) are often present in adults with T1DM [9]. Under conditions of poor glycaemic control or declining renal function, T1DM may also be accompanied by dyslipidaemia with a lipid profile that resembles what is seen in T2DM [1].

Several studies and meta-analyses have shown that lowering LDL-C by statins has led to significant reductions in CV events in those with DM [10–12], with further CV risk reduction associated with additional LDL-C-lowering by concomitant ezetimibe [13]. Guidelines generally recommend an LDL-C goal of < 70 mg/dL (1.81 mmol/L) and/or a reduction of $\geq 50\%$ from baseline in patients with T1DM or T2DM considered to be at high or very-high CV risk [5,14,15]. However, even with the currently available treatments, many patients with DM continue to have persistent lipid abnormalities [16–18] and are therefore exposed to a residual risk of CV events.

Alirocumab, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), is approved in several regions, including the US, Europe and Japan, for the management of patients with hypercholesterolaemia on maximum tolerated doses of statin. In phase-III clinical studies, alirocumab reduced LDL-C by up to 61% in patients treated with statins [19]. Significant reductions in apolipoprotein (Apo) B, non-HDL-C and lipoprotein(a) [Lp(a)], trends for TG reduction, and modest increases in HDL-C and ApoA-I were also observed. It is hoped that these robust lipid changes will translate into significant reductions in CV events, as the preliminary results were promising [19]. Indeed, the

ongoing ODYSSEY OUTCOMES study (NCT01663402) is evaluating the effect of alirocumab on major CV events in $\geq 18,000$ patients 4–52 weeks post-acute coronary syndrome, including a significant number with DM [20].

There is conflicting evidence regarding the possible association of PCSK9 with alterations of glucose homeostasis. The CODAM study [21] found that plasma levels of PCSK9 do not differ between those with recently diagnosed T2DM, normal glucose metabolism and impaired glucose metabolism. In contrast, the ILLUMINATE study [22] found that plasma PCSK9 levels were elevated in patients with DM compared with those without DM, with a significant association between PCSK9 levels and LDL-C, TGs, glucose, insulin and homeostasis model assessment of insulin resistance (HOMA-IR) scores. In addition, a study evaluating the impact of a short-term high-calorie, high-fructose diet showed that plasma PCSK9 levels were increased with this diet independently of cholesterol synthesis, and associated with insulin resistance, hepatic steatosis and TG levels [23]. Thus, the potential interaction between PCSK9 inhibitors and exogenously administered insulin is of considerable interest.

Based on currently available data, there is no evidence of any effect of alirocumab on glycaemia after a maximum follow-up of 78 weeks [24]. Nevertheless, despite no safety signals to date, the safety of the coadministration of a biological agent (insulin) with a monoclonal antibody (alirocumab) warrants further study. Of the 5296 participants in the phase-III ODYSSEY programme, around one-third had DM, and 28% of those DM patients receiving alirocumab were insulin-treated (8% of the overall alirocumab-treated population). In these phase-III studies, 56% of the insulin-treated patients received alirocumab at a starting dose of 150 mg every 2 weeks (Q2W). However, as a 75 mg Q2W dose is expected to be sufficient for most patients with DM, given their relatively lower elevations in LDL-C, the present study is using a starting dose of 75 mg Q2W, with an increase to 150 mg Q2W if LDL-C goals are not achieved. Given the high CV risk in DM patients who require insulin treatment, it is important to collect sufficient efficacy and safety data for alirocumab in such patients to inform clinical practice.

The present report describes the design of a placebo-controlled study – ODYSSEY DM–INSULIN – initiated to further characterize the efficacy and safety of alirocumab in insulin-treated patients with T1DM or T2DM who are at high CV risk and have failed to reach LDL-C goals despite maximum tolerated statin doses, with or without other lipid-lowering therapy (LLT).

Material and methods

Study design

ODYSSEY DM–INSULIN (ClinicalTrials.gov identifier: NCT02585778) is a phase-IIIb randomized double-blind, placebo-controlled, parallel-group multicentre trial being conducted in Europe and the US. It is evaluating the efficacy and safety of alirocumab in insulin-treated DM patients at high CV risk with hypercholesterolaemia not adequately controlled with the maximum tolerated LLT (Fig. 1). The study planned for a population of approximately 500 subjects, comprising 400 with T2DM and up to 100 with T1DM. Randomization began in November 2015 and ended in August 2016.

The study is being performed in accordance with the ethical principles outlined at the 18th World Medical Assembly (WMA) in Helsinki (1964), and all the relevant amendments laid down by the WMA and International Conference on Harmonization guidelines for Good Clinical Practice (GCP). Institutional review board or independent ethics committee approval of the protocol and informed consent forms were obtained from each study site

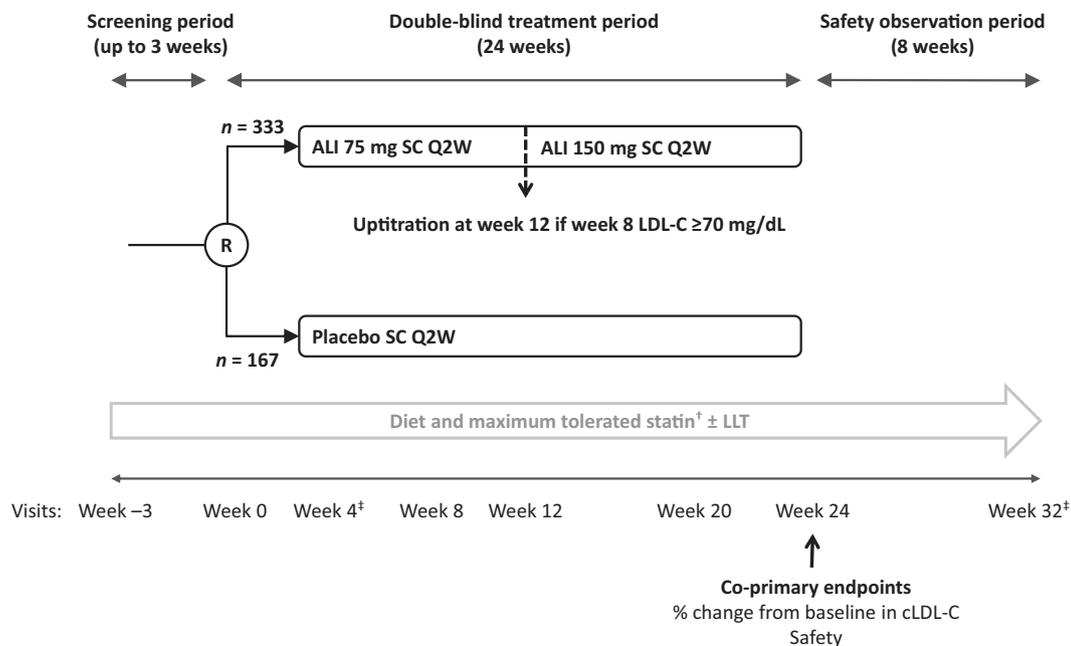


Fig. 1. Design of the ongoing ODYSSEY DM-INSULIN trial. [†] No statin if statin-intolerant; [‡] phone-call 'visits'. ALI: alirocumab; cLDL-C: calculated LDL-C; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy; R, randomization; SC: subcutaneous; Q2W: every 2 weeks.

(see supplementary materials associated with this article online), and written informed consent was obtained from all study participants.

Study population

The main inclusion and exclusion criteria are listed in Table 1; the full inclusion and exclusion criteria can be found in Appendix B (see supplementary materials associated with this article online).

Table 1
Main ODYSSEY DM-INSULIN inclusion and exclusion criteria.

| Inclusion criteria |
|---------------------------------------------------------------------------------------------------------------------------------|
| Age ≥ 18 years |
| T1 ^a or T2 DM (≥ 1 year) |
| HbA _{1c} < 10% |
| Insulin use |
| Stable maximum tolerated statin therapy (≥ 4 weeks) with or without other LLT |
| LDL-C ≥ 70 mg/dL (1.81 mmol/L) |
| ASCVD (includes CHD ^b , documented PAD, ischaemic stroke) and/or at least one additional CV risk factor ^c |
| Exclusion criteria |
| eGFR < 15 mL/min/1.73 m ² |
| BMI > 45 kg/m ² or weight variation > 5 kg within 2 months |
| TGs > 400 mg/dL (4.52 mmol/L) |
| Insulin treatment duration < 6 months or regimen/dose change within past 3 months ^d |
| Renal replacement therapy or planned renal replacement therapy |

T1: type 1; T2: type 2; DM: diabetes mellitus; HbA_{1c}: glycated haemoglobin; LLT: lipid-lowering therapy; LDL-C: low-density lipoprotein cholesterol; ASCVD: atherosclerotic cardiovascular disease; PAD: peripheral artery disease; CV: cardiovascular; eGFR: estimated glomerular filtration rate; BMI: body mass index; TGs: triglycerides.

^a Diagnosed before age 30 years and treated with multiple daily injection regimen/basal-prandial insulin regimen or insulin-pump regimen within 6 months of diagnosis, with C-peptide < 0.2 pmol/mL at screening.

^b History of acute myocardial infarction (MI), silent MI, unstable angina (UA), coronary revascularization procedure or clinically significant coronary heart disease (CHD) diagnosed by invasive or non-invasive testing.

^c Hypertension, current smoker, age ≥ 45 years (men) or ≥ 55 years (women), history of micro-/macroalbuminuria or diabetic retinopathy, family history of premature CHD, low levels of high-density lipoprotein cholesterol (HDL-C) or documented chronic kidney disease (CKD).

^d Or unstable treatment with other antihyperglycaemic agents (within past 3 months).

All eligible patients had insulin-treated T1DM or T2DM, and had failed to reach their LDL-C goals [< 70 mg/dL (1.81 mmol/L)] despite taking stable maximum tolerated doses of statin with or without other LLT. Participants also had established ASCVD [including coronary heart disease (CHD), peripheral arterial disease (PAD) and ischaemic stroke] and/or at least one additional CV risk factor. The maximum tolerated dose of statin is the largest registered dose/regimen tolerated by the patient, based on the investigator's judgment (see Appendix B for further details). Those with documented statin intolerance (and so not taking statin therapy) were also eligible for inclusion. Participants were required to have been taking insulin therapy for at least 6 months, with a stable regimen for the past 3 months; those who were anticipated to require changes in insulin type, frequency or mode of injection during the study period were excluded.

Study procedures

Patients were assessed for eligibility during a screening period of up to 3 weeks, followed by randomization to one of two treatment arms for a 24-week treatment period. After completing the treatment period, participants enter an 8-week safety observation period (Fig. 1). Participants must remain on a stable diet for glucose and lipid management, and receive a stable dose/regimen of statin and/or other LLT throughout the study. Treatment for DM should be in accordance with local/regional standards of care. On-site patient assessments are scheduled at regular intervals between randomization (week 0) and weeks 8, 12, 20 and 24 (end-of-treatment visit) during the double-blind treatment period, with additional phone calls scheduled for weeks 4 and 32.

Eligible patients were randomized to double-blind treatment at a ratio of 2:1 (alirocumab:placebo), with stratification by DM type. At randomization, treatment kit numbers were allocated according to a centralized treatment allocation system (either an interactive voice-response or web-response system, depending on the study site). Study participants, principal investigators and study-site personnel are blinded to all randomization assignments throughout the duration of the study. To maintain the blind, all planned

lipid analyses collected after randomization are masked. However, for safety reasons, the investigators are made aware if TG levels are ≥ 500 mg/dL (5.65 mmol/L).

The study drug (alirocumab or placebo) is administered as a 1-mL solution subcutaneously Q2W via a prefilled pen device. Those randomized to alicumab receive a starting dose of 75 mg Q2W for 12 weeks, with a blinded dose increase to 150 mg Q2W at week 12 if, at the week 8 visit, LDL-C is ≥ 70 mg/dL (1.81 mmol/L), whereas alicumab-treated patients with LDL-C < 70 mg/dL (1.81 mmol/L) at week 8 continue with 75 mg Q2W until the end of the treatment period. Those randomized to placebo remain on the placebo throughout the 24-week treatment period, although every participant receives a new study-drug supply at the week 12 visit to maintain the blind. All participants continue to receive a stable maximum tolerated statin dose (or no statin if statin-intolerant) throughout the study.

Endpoints and assessments

The primary objectives of the study are:

- to demonstrate the superiority of alicumab compared with a placebo in the reduction of calculated LDL-C after 24 weeks of treatment;
- to evaluate the safety and tolerability of alicumab.

Study endpoints are summarized in Table 2. The primary efficacy endpoint is the difference between treatment arms by percentage change in calculated LDL-C from baseline to week 24, using all values regardless of adherence [the intention-to-treat (ITT) approach]. Safety is assessed throughout the study by reports of adverse events (AEs), product complaints, laboratory analyses and measurements of vital signs (Table 2 and Appendix C, see supplementary materials associated with this article online).

Secondary efficacy endpoints include the effect of alicumab vs placebo on other lipid parameters at weeks 12 and 24 including, for the first time in a phase-III study of alicumab, the endpoints of LDL-P number and size, and plasma ApoC-III concentrations. Endpoints related to DM focus on changes from baseline in indices of glucose homeostasis (HbA_{1c} and fasting plasma glucose), total daily insulin dose and the number of glucose-lowering agents. Treatment acceptability is assessed at weeks 8 and 24 in those who self-inject, using a 22-item validated patient-reported Injection-Treatment Acceptance Questionnaire (I-TAQ) [25]. Specifically, the I-TAQ assesses four domains of treatment acceptability: perceived efficacy (i.e. patient's perception of whether the treatment is working); acceptance of side effects; injection self-efficacy (i.e. patient's ability to perform the task); and injection convenience. The I-TAQ also has three summarizing questions that measure overall acceptability. Anti-alicumab antibodies are measured at the time of randomization and at weeks 12 and 24.

Statistical design and analysis

Sample size determination

A sample size of 69 participants (46 alicumab, 23 placebo) per strata (T1DM or T2DM) should provide 90% power to detect a difference in a mean percentage change in LDL-C of 30% between alicumab and placebo, with a randomization ratio of 2:1 and a 0.05 two-sided significance level, assuming a common standard deviation of 35%. However, to obtain even greater power for the evaluation of safety as a co-primary endpoint, the sample size was increased to around 500 participants (roughly 400 with T2DM and up to 100 with T1DM). Final sample sizes of 333 taking alicumab and 167 taking placebo are expected to provide an 80% power to detect AEs with an odds ratio for

Table 2
ODYSSEY DM-INSULIN study endpoints.

| |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i>Primary efficacy endpoint</i> |
| Change (%) from baseline in calculated LDL-C at week 24 (ITT) |
| <i>Safety (co-primary endpoint)</i> |
| Adverse events (AEs) |
| Treatment-emergent adverse events (TEAEs) |
| Serious TEAEs |
| TEAEs leading to permanent treatment discontinuation |
| AEs of special interest (see Appendix C) |
| Deaths |
| Clinical laboratory data |
| Vital signs |
| Product complaints |
| <i>Key secondary efficacy endpoints</i> |
| Change (%) from baseline in |
| Calculated LDL-C at week 24 (mITT) |
| Measured LDL-C at week 24 (ITT) |
| Calculated LDL-C at week 12 (ITT) |
| Measured LDL-C at week 12 (ITT) |
| Non-HDL-C at week 24 (ITT) |
| Apolipoprotein B (ApoB) at week 24 (ITT) |
| Total cholesterol (TC) at week 24 (ITT) |
| Patients (%) at week 24 with |
| Calculated LDL-C < 70 mg/dL (mITT) |
| Calculated LDL-C < 50 mg/dL (mITT) |
| Non-HDL-C < 100 mg/dL (mITT) |
| Non-HDL-C < 80 mg/dL (mITT) |
| Change (%) from baseline at week 24 in |
| Lp(a) (ITT) |
| HDL-C (ITT) |
| Triglyceride (TG; ITT) |
| LDL particle number (ITT) |
| LDL particle size (ITT) |
| <i>Diabetes-related endpoints</i> |
| Absolute change from baseline to weeks 12 and 24 in |
| HbA _{1c} (ITT, mITT) |
| Fasting plasma glucose (FPG; ITT, mITT) |
| Total daily insulin dose (ITT, mITT) |
| Number of glucose-lowering agents (ITT, mITT) |
| <i>Other efficacy endpoints</i> |
| Change (%) from baseline in |
| Calculated LDL-C at week 12 (mITT) |
| Measured LDL-C at weeks 12 and 24 (mITT) |
| Non-HDL-C, ApoB, TC, Lp(a), HDL-C, TG, LDL particle number and size at weeks 12 (mITT, ITT) and 24 (mITT) |
| TGRL, ApoA-I, ApoC-III at weeks 12 and 24 (mITT, ITT) |
| Patients (%) with |
| Calculated LDL-C < 50 mg/dL and < 70 mg/dL at weeks 12 (mITT, ITT) and 24 (ITT) |
| $\geq 50\%$ reduction from baseline in calculated LDL-C at weeks 12 and 24 (ITT) |
| Non-HDL-C < 80 mg/dL and < 100 mg/dL at weeks 12 (mITT, ITT) and 24 (ITT) |
| ApoB < 80 mg/dL at weeks 12 and 24 (mITT, ITT) |
| Calculated LDL-C < 50 mg/dL and < 70 mg/dL at weeks 12 and 24 according to baseline HbA _{1c} ($< \text{or} \geq 8\%$; and $< \text{or} >$ median; mITT, ITT) |
| Absolute change from baseline in |
| ApoB/ApoA-I |
| TC/HDL-C ratio at weeks 12 and 24 (mITT, ITT) |
| <i>Patient-reported outcome</i> |
| Treatment acceptability (I-TAQ) at weeks 8 and 24 (mITT) |
| <i>Other endpoints</i> |
| Anti-alicumab antibodies |

LDL-C: low-density lipoprotein cholesterol; ITT: intention-to-treat; mITT: modified intention-to-treat; HDL-C: high-density lipoprotein cholesterol; Lp(a): lipoprotein(a); HbA_{1c}: glycated haemoglobin; TGRL: triglyceride-rich lipoproteins; I-TAQ: Injection-Treatment Acceptance Questionnaire.

alicumab vs placebo equal to 3 for an incidence in the control group $\geq 5\%$.

Primary analyses

The primary efficacy analysis population is the ITT population, defined as all of the randomized participants with a calculated LDL-C value at baseline and at least one value within one of the analysis windows up to week 24, regardless of treatment adherence.

Separate analyses will be performed for patients with T1DM and T2DM, with an overall analysis of all participants for some efficacy endpoints.

The percentage change in calculated LDL-C from baseline to week 24 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach to account for any missing data, using all available post-baseline data within the analysis windows (weeks 8–24). The model will also include fixed categorical effects of treatment group, time point and treatment-by-time interaction, as well as the continuous fixed covariates of baseline LDL-C value and baseline value-by-time point interaction. Alirocumab will be compared with placebo, and the 95% confidence interval (CI) of the difference calculated.

Safety analyses will be descriptive and based on the safety population (all randomized participants receiving at least one dose or part of a dose of the study treatment), and performed separately overall and by DM type. The safety analysis will focus on the treatment-emergent adverse event (TEAE) period, defined as the time from the first double-blind dose to the last double-blind dose of study treatment plus 70 days (10 weeks).

Secondary analyses

A hierarchical procedure (key secondary endpoints only) will be used to control the type-I error and handle multiple endpoints. If the primary efficacy endpoint analysis is significant at an alpha level of 5%, then secondary endpoints will be tested sequentially in the order in which they are presented in Table 2. Secondary efficacy endpoints will be analyzed in the ITT and/or 'on treatment' (modified ITT [mITT]) population, defined as all randomized participants who took at least one (or part) dose of double-blind treatment, and had both baseline and at least one calculated LDL-C value during the treatment-efficacy period (i.e. up to 21 days after the last injection) within one of the analysis windows up to week 24.

Continuous secondary endpoints anticipated to have a normal distribution will be analyzed using the same MMRM as for the primary endpoint, with continuous fixed covariates of corresponding baseline value and baseline value-by-time point interaction. Continuous secondary endpoints anticipated to have a non-normal distribution will be analyzed using a multiple imputation approach for handling missing values followed by robust regression. Binary secondary endpoints will be analyzed using a multiple imputation approach for handling missing values followed by logistic regression. The Mann-Whitney test will be used to compare changes from baseline between treatment groups by I-TAQ scores. Anti-drug antibodies will be correlated with safety and efficacy endpoints. Descriptive analyses will be performed for all DM-related endpoints.

Results

Recruitment was completed in August 2016, and the clinical trial is currently ongoing. In total, 517 participants have been randomized from 10 countries (Austria, Belgium, France, Germany, Italy, The Netherlands, Spain, Switzerland, UK and US) for a total number of 76 patients with T1DM and 441 patients with T2DM. Results of the 24-week treatment period are expected to be available in mid-2017.

Discussion

Newly approved drugs, such as alirocumab, are likely to be administered to patients with the highest CV risk, including those with ASCVD and insulin-treated DM. Acquiring sufficient efficacy and safety data for the DM subgroup is of considerable importance to inform evidence-based clinical practice. The ODYSSEY

DM-INSULIN study has been designed specifically to investigate the efficacy and safety of alirocumab in insulin-treated DM patients at high CV risk whose LDL-C levels are inadequately controlled despite maximum tolerated statin therapy. Findings from this study will supplement the data available from a large number of DM patients from the phase-III ODYSSEY clinical-development programme, which showed that significant LDL-C reductions and improvements in non-HDL-C, ApoB, Lp(a), HDL-C and TG levels can be achieved with alirocumab irrespective of DM status [26].

In addition to 440 insulin-treated participants with T2DM, the study has recruited 77 patients with T1DM, whose inclusion is important as randomized controlled data on LLT in such a population are limited. Moreover, specific evaluations of safety in those with T1DM and T2DM are important in the context of concomitant insulin injections with a monoclonal antibody. A pooled analysis of data from 3499 participants in five placebo-controlled phase-III trials of alirocumab (COMBO I, FH I and II, HIGH FH and LONG TERM) indicated that TEAEs arise overall at a similar frequency to alirocumab in those with or without DM [26], but only a relatively small proportion of these patients were taking concomitant insulin.

In analyses of both pooled data and individual studies, fewer injection-site reactions were reported in patients with than without DM. This may be a consequence of patients with DM being more accustomed to receiving injectable medications and/or performing blood glucose monitoring. The present ongoing study should provide more information on injection-site reactions in this population, while also exploring treatment acceptability by administration of the I-TAQ, a patient-reported outcome questionnaire specifically developed to investigate perspectives on treatment with LLTs requiring subcutaneous injections [25]. Based on previous data, most participants and physicians consider the alirocumab prefilled pen easy to use, and patients have shown a willingness to self-inject [27]. Furthermore, high rates of treatment adherence (approximately 98%) were reported in phase-III studies with alirocumab [19,28,29]. The ODYSSEY DM-INSULIN trial will also provide useful information on the use of alirocumab in subjects already familiar with self-injection, but for whom data are limited regarding treatment with alirocumab from previous phase-III studies.

The effect of alirocumab on LDL-P number and size is of interest, as patients with T2DM are known to have a higher proportion of small, dense LDL particles than people without DM [8]. Hypertriglyceridaemia, commonly seen in T2DM, leads to the preferential formation of small, dense LDL by stimulation of cholesteryl ester transfer protein. These small, dense LDL particles are more susceptible to glycation or oxidation, decreasing their affinity for the LDL receptor and, thus, contributing to reduced LDL catabolism [8]. Alirocumab has previously been shown to significantly reduce LDL-C, LDL-P, VLDL-P and chylomicron concentrations in a phase-II study of patients with hypercholesterolaemia (but without DM) on stable statin therapy [30].

Among other secondary lipid parameters, the percentage change in plasma ApoC-III levels is also being examined. This is the first time this endpoint has been incorporated into a phase-III alirocumab trial. ApoC-III, an important regulator of TG levels, has been shown to be an independent CV risk factor in patients with DM [31]. ApoC-III genetic deficiencies are associated with low TG levels and a reduced risk of CHD [32]. In a post-hoc analysis of three phase-II trials, alirocumab reduced plasma ApoC-III levels by 14.5–19.1% in patients with LDL-C \geq 100 mg/dL (2.59 mmol/L) on stable statin therapy [33]. However, the effect may be a consequence of increased clearance and/or reduced production of VLDL particles rather than an impact on ApoC-III synthesis.

Understanding the impact of alirocumab on glycaemic control is also of interest, particularly in light of the apparent increased risk of DM associated with statin therapy [34,35]. In addition, significant correlations between PCSK9 levels and glucose and insulin levels, as well as the HOMA-IR, have recently been reported [22]. Moreover, recombinant PCSK9 has been shown to regulate expression of the LDL receptor in isolated pancreatic islets as well as in the liver [36]. However, the function of PCSK9 in pancreatic beta cells remains a matter of debate [37]. To further explore this, glycaemic-related endpoints have been incorporated into the design of ODYSSEY DM-INSULIN. It is notable that alirocumab had no impact on glycaemia compared with either placebo or ezetimibe in pooled analyses of patients without diabetes at baseline from 10 phase-III ODYSSEY studies of up to 18 months' duration [24].

Conclusion

The ODYSSEY DM-INSULIN trial is an investigation dedicated to assessing the efficacy and safety of alirocumab in insulin-treated patients with either T1DM or T2DM at high CV risk and with hypercholesterolaemia not optimally managed despite maximum tolerated statin therapy. In addition, a second study (ODYSSEY DM-DYSLIPIDEMIA) will address the effects of alirocumab in patients with T2DM and mixed dyslipidaemia. Together, the findings of these two studies will provide valuable information on the efficacy and safety of alirocumab in DM patients at high CV risk to ultimately help to guide clinical decision-making beyond statin therapy.

Funding

This study is sponsored by Sanofi and Regeneron Pharmaceuticals, Inc.

Disclosure of interest

B.C. has received research funding and personal fees from Sanofi and Regeneron during the conduct of the study, research funding from Pfizer, and honoraria from Amgen, AstraZeneca, Pierre Fabre, Janssen, Eli Lilly and Company, MSD (Merck & Co.), Novo Nordisk, Sanofi and Takeda outside of this submitted work.

L.A.L. has received personal fees from Aegerion, grants and personal fees from Amgen, AstraZeneca, Eli Lilly and Company, Merck, Regeneron Pharmaceuticals, Inc. and Sanofi, and grants from The Medicines Company and Pfizer outside of this submitted work.

D.M.-W. has received speakers' bureau and consultant/advisory board fees from Amgen, AstraZeneca, Boehringer Ingelheim, MSD (Merck & Co.), Novartis, Novo Nordisk and Sanofi.

G.B. is an employee of IVIDATA, contracted to Sanofi.

A.L. is an employee of and shareholder in Sanofi.

H.M.C. has received grants, personal fees and non-financial support from Sanofi and Regeneron Pharmaceuticals, Inc. during the conduct of this study; grants, personal fees and non-financial support from Eli Lilly and Company; and grants from Roche Pharmaceuticals, Pfizer, Boehringer Ingelheim, AstraZeneca and Bayer outside of this submitted work.

S.D.P. has received research funding from Novartis Pharmaceuticals Co., MSD (Merck & Co.) and Novo Nordisk, and has been a consultant for or received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Janssen Pharmaceuticals, Laboratoires Servier, MSD (Merck & Co.), Novartis Pharmaceutical Co., Novo Nordisk, Sanofi-Aventis and Takeda Pharmaceuticals.

R.R.H. has received research funding from Eli Lilly and Company, Fuji Chemicals, Hitachi, Lexicon, Novo Nordisk, Pfizer

and Viacyte, and has been a consultant and advisory panel member for Alere Inc., AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Elcelyx, Intarcia, Ionis, Janssen/Johnson & Johnson and Sanofi-Aventis.

F.J.T. has received speakers' bureau and consultant/advisory board fees from AstraZeneca, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Janssen Pharmaceuticals, MSD (Merck & Co.), Novartis Pharmaceutical Co., Novo Nordisk and Sanofi-Aventis.

L.A. is an employee of and shareholder in Sanofi.

J.M. is an employee of and shareholder in Regeneron.

K.K.R. has received personal fees (data safety monitoring board) from AbbVie Inc., consultant fees/honoraria from Aegerion, Algorithm, Amgen, AstraZeneca, Boehringer Ingelheim, Cerenis, Eli Lilly and Company, Ionis Pharmaceuticals, Kowa, The Medicines Company, MSD (Merck & Co.), Novartis, Pfizer, Regeneron, Reservlogix, Sanofi and Takeda, and research grants from Kowa, Pfizer and Regeneron.

M.B.-B. is an employee of and shareholder in Sanofi.

Acknowledgments

The authors are grateful to the study investigators and committee members listed in [Appendix A](#).

Medical writing support was provided by Melanie Jones of Prime (Knutsford, Cheshire, UK), supported by Sanofi and Regeneron Pharmaceuticals, Inc. The following people from the study sponsors reviewed and provided editorial comments on the manuscript: Robert Pordy, Robert J. Sanchez and William J. Sasiela (all Regeneron). The authors were responsible for all content and editorial decisions, and received no honoraria related to the development/presentation of this publication.

The design and conduct of the study, as well as analyses of the study data and opinions, conclusions and interpretation of the data, are the responsibility of the authors.

Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at <http://dx.doi.org/10.1016/j.diabet.2017.01.004>.

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