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Efficacy and safety of alirocumab in individuals with type 2 diabetes mellitus with or without mixed dyslipidaemia: Analysis of the ODYSSEY LONG TERM trial

Marja-Riitta Taskinen [a, *], Stefano Del Prato [b], Maja Bujas-Bobanovic [c], Michael J. Louie [d], Alexia Letierce [e], Desmond Thompson [d], Helen M. Colhoun [f]

[a] Cardiovascular Research Unit, Diabetes and Obesity Research Program, University of Helsinki, Helsinki, Finland
[b] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[c] Sanofi, Paris, France
[d] Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA
[e] Sanofi, Chilly-Mazarin, France
[f] University of Edinburgh, Edinburgh, UK

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ABSTRACT

Background and aims: Alirocumab, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9, significantly reduces low-density lipoprotein cholesterol (LDL-C). We evaluated the efficacy and safety of alirocumab in individuals with type 2 diabetes mellitus (T2DM) with *versus* without mixed dyslipidaemia (MDL, defined as baseline LDL-C ≥70 mg/dL [1.8 mmol/L] and triglycerides ≥150 mg/dL [1.7 mmol/L]).

Methods: Data from 812 individuals with T2DM, from the placebo-controlled, 78-week, Phase 3 ODYSSEY LONG TERM trial of alirocumab 150 mg every 2 weeks (Q2W), on a background of maximally tolerated statins ± other lipid-lowering therapies, were pooled according to MDL status. Efficacy endpoints included percentage change from baseline to Week 24 in calculated LDL-C and other lipids/lipoproteins.

Results: In individuals with T2DM who received alirocumab 150 mg Q2W, mean LDL-C changes from baseline to Week 24 were −62.6% (*vs.* −6.0% with placebo) in those with MDL and −56.1% (*vs.* 5.6%) in those without MDL, with no significant between-group difference (p-interaction = 0.0842). Risk-based LDL-C goals (<70 [1.8 mmol/L] or <100 mg/dL [2.6 mmol/L]) were achieved by 69.1% and 72.4% of alirocumab-treated individuals with and without MDL, respectively. Mean reductions in non-high-density lipoprotein cholesterol (49.2% and 47.8%) and apolipoprotein B (50.2% and 49.1%) with alirocumab were also similar in those with and without MDL, respectively. Treatment-emergent adverse event rates were comparable between alirocumab-treated individuals with T2DM, with and without MDL.

Conclusions: Reductions in LDL-C and other lipids with alirocumab, as well as safety and tolerability, were comparable between individuals with T2DM and with *versus* without MDL.

1. Introduction

Individuals with type 2 diabetes mellitus (T2DM) are at high risk of cardiovascular disease (CVD) [1,2]. T2DM is often associated with mixed dyslipidaemia (MDL), characterized by elevated levels of triglycerides (TGs) and non-high-density lipoprotein cholesterol (non-HDL-C), which further increase CVD risk [1,3,4]. The increased CVD risk is primarily due to elevations in TG-rich lipoprotein (TRL) remnant particles and small dense low-density lipoproteins (LDLs), which constitute an atherogenic lipid profile, accompanied by elevated apolipoprotein (apo) B levels as a result of the increased number of apo B-containing particles [1,5,6].

Guidelines from the European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) [1], American Diabetes

* Corresponding author. University of Helsinki, Research Programs Unit, Diabetes and Obesity Research Program, Biomedicum 1, Haartmaninkatu 8, 00290, Helsinki, Finland.
E-mail address: marja-riitta.taskinen@helsinki.fi (M.-R. Taskinen).

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Association [2], and the American College of Cardiology/American Heart Association [7] specify moderate- to high-intensity statin therapy for the management of lipid levels in individuals with diabetes and atherosclerotic cardiovascular disease (ASCVD) or those at increased ASCVD risk. Recommendations from the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) [8] and the National Lipid Association [9] specify LDL cholesterol (LDL-C) goals for individuals at high or very-high ASCVD risk, including those with diabetes; in the recent AACE/ACE guidelines, special consideration is given to individuals with diabetes in a new "extreme" cardiovascular risk category [10]. Despite such guidance, the literature regarding statin use often reports underutilization and suboptimal lipid levels in high-risk individuals with diabetes [11–13]. Although LDL-C is generally considered to be the primary target for ASCVD risk reduction, in a background of MDL, non-HDL-C and apo B levels are important to assess as they correlate more closely with the number of atherogenic particles (and therefore cardiovascular risk) than LDL-C calculated by the Friedewald formula [9].

The 78-week Phase 3 ODYSSEY LONG TERM randomized trial was conducted in 2341 high-risk individuals, including 35% (n = 812) with T2DM. Addition of alirocumab (a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 [PCSK9]) to background maximally tolerated statin (MTS) therapy significantly reduced LDL-C levels by 62% relative to placebo [14]. Subgroup analyses of alirocumab treatment in individuals with T2DM and MDL have not been reported; estimates of treatment effects on lipid parameters such as non-HDL-C and apo B in this population may be important from a clinical perspective, as individuals with T2DM and MDL represent a high CVD risk group who may benefit from additional reduction in lipids beyond that provided by statin therapy. Due to the typical lipid profile in MDL (elevated TGs, non-HDL-C, and apo B particles, reduced HDL-C) it is possible that there may be differential effects of alirocumab on lipid parameters (LDL-C, non-HDL-C, and apo B) in individuals with MDL compared with those without MDL. Therefore, we feel that it is important to provide information on the efficacy and safety of alirocumab in the MDL population, to support clinicians in their treatment decisions.

In this analysis of the ODYSSEY LONG TERM trial, we assessed the efficacy (main outcome parameters: LDL-C, non-HDL-C, and apo B) and safety of alirocumab, on a background of MTS therapy, in the high-risk subgroup of individuals with T2DM, with *versus* without MDL. MDL was defined as TGs ≥150 mg/dL (1.7 mmol/L), levels associated with increased CVD risk [15], and LDL-C levels ≥70 mg/dL (1.8 mmol/L) at baseline. This analysis for the first time assessed the efficacy and safety of alirocumab *versus* placebo in groups of individuals with T2DM and with or without MDL, over 78 weeks of treatment.

2. Patients and methods

2.1. Study participants

This *post-hoc* analysis included data from individuals with T2DM from LONG TERM (NCT01507831) [14]. T2DM was diagnosed based on medical history. LONG TERM recruited individuals with hypercholesterolaemia who were on MTS therapy plus or minus other lipid-lowering therapies (LLTs) but who had LDL-C levels above pre-specified goals. MTS therapy was defined as atorvastatin 40–80 mg, rosuvastatin, 20–40 mg, or simvastatin 80 mg daily (or lower doses with an investigator-approved reason for using a lower dose, e.g., intolerance). LONG TERM recruited individuals with heterozygous familial hypercholesterolemia (HeFH) or non-familial hypercholesterolemia at high cardiovascular risk. Exclusion criteria included fasting TGs >400 mg/dL (4.5 mmol/L).

Randomization was 2:1 to alirocumab 150 mg Q2W or placebo, administered subcutaneously, for a double-blind period of up to 78 weeks. Study participants continued to receive their stable MTS dose plus other baseline LLTs (if used) for the duration of the trial.

2.2. Efficacy and safety analysis

Efficacy and safety data were compared between individuals with T2DM (defined based on medical history) with and without MDL. MDL was defined in this analysis as TGs ≥150 mg/dL (1.7 mmol/L) and LDL-C ≥70 mg/dL (1.8 mmol/L) at baseline. Efficacy endpoints included the percentage change from baseline to Week 24 in calculated LDL-C and other lipids, and changes in LDL-C over time up to 18 months. Lipid levels were determined by a central laboratory using standardized methods. In the primary study, LDL-C levels were calculated using the Friedewald equation [16] at all time points. LDL-C was also determined via beta-quantification at baseline and at Week 24, and was determined by beta-quantification (rather than calculation) if TG levels were >400 mg/dL (4.5 mmol/L); however, LDL-C values derived by beta-quantification were not included in the analysis of calculated LDL-C. LDL-C determined by beta-quantification was included as a sensitivity analysis (termed 'measured LDL-C').

Secondary efficacy endpoints included the percentage change from baseline to Week 24 in non-HDL-C (calculated by subtracting HDL-C from total cholesterol), apo B, HDL-C, TGs, lipoprotein (a) (Lp [a]), and TRL cholesterol (TRL-C). TRL-C was calculated by subtracting HDL-C and calculated LDL-C from total cholesterol, as per the method of Nordestgaard et al. (2007) [17]. Achievement of lipid goals was assessed based on thresholds given in the ESC/EAS guidelines: calculated LDL-C <70 mg/dL and <100 mg/dL for individuals at very-high and high cardiovascular risk, respectively, non-HDL-C <100 mg/dL, and apo <80 mg/dL and <100 mg/dL for individuals at very-high and high cardiovascular risk, respectively [1].

Safety assessments included reporting of treatment-emergent adverse events (TEAEs), defined as any event that developed, worsened, or became serious during the period from first to last study drug injection plus 70 days. The safety population included all randomized individuals with T2DM who received at least one full or partial dose of study treatment. Adverse events (AEs) of special interest included local injection-site reactions and adjudicated major adverse cardiovascular events, as previously described [14,18,19]. Changes over time in glycaemic parameters, glycated haemoglobin (HbA1c), and fasting plasma glucose (FPG) were also assessed.

2.3. Statistical analysis

For statistical analyses, the percentage changes from baseline in LDL-C, non-HDL-C, apo B, and HDL-C were analysed using a mixed-effect model with repeated measures as previously described [14,20]. TGs and Lp(a) were analysed by multiple imputation to handle missing data, followed by robust regression. The intention-to-treat (ITT) population was used for efficacy analyses, which included all data irrespective of adherence to study treatment. Achievement of lipid goals was analysed by multiple imputation to account for missing data, followed by logistic regression using on-treatment analysis and was assessed in the modified ITT population (including only on-treatment lipid data). Interaction *p*-values (comparing the difference in percentage change from baseline with alirocumab vs placebo, in individuals with and without MDL) were derived using the same models as for the primary analyses, and are provided for descriptive purposes only. Safety data were analysed by descriptive statistics.