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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

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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

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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.

Table 1
Baseline characteristics of individuals with T2DM[a] from LONG TERM by MDL[b] status (randomized population).

n (%), unless otherwise specified	+MDL (n = 403)		−MDL (n = 409)	
	Alirocumab (n = 270)	Placebo (n = 133)	Alirocumab (n = 274)	Placebo (n = 135)
Age, years, mean (SD)	61.9 (9.1)	60.0 (9.6)	62.1 (9.7)	62.0 (10.5)
Male	158 (58.5)	76 (57.1)	158 (57.7)	62 (45.9)
Race, white	241 (89.3)	111 (83.5)	222 (81.0)	115 (85.2)
BMI, kg/m^2, mean (SD)	32.5 (6.0)	33.3 (5.9)	31.6 (6.3)	32.3 (5.5)
HbA1c, %, mean (SD)	7.1 (1.2)	7.1 (1.2)	6.8 (1.1)	7.0 (1.2)
FPG, mg/dL, mean (SD)	145.0 (47.3)	144.1 (45.4)	130.1 (39.9)	135.8 (45.7)
Median (Q1:Q3) duration of T2DM, years	6.7 (3.2:11.9)	5.4 (2.7:10.9)	7.6 (3.7:12.6)	7.2 (2.6:11.7)
HeFH	15 (5.6)	9 (6.8)	22 (8.0)	11 (8.1)
ASCVD	170 (63.0)	83 (62.4)	170 (62.0)	84 (62.2)
High-intensity statin[c]	101 (37.4)	51 (38.3)	111 (40.5)	51 (37.8)
Receiving LLTs (other than statin and nutraceuticals)	75 (27.8)	38 (28.6)	60 (21.9)	26 (19.3)
Most common LLTs				
Ezetimibe	13 (4.8)	16 (12.0)	23 (8.4)	10 (7.4)
Fenofibrate	32 (11.9)	15 (11.3)	17 (6.2)	4 (3.0)
Fish oil	7 (2.6)	3 (2.3)	2 (0.7)	3 (2.2)
≥1 antidiabetic drug	228 (84.4)	111 (83.5)	231 (84.3)	109 (80.7)
Baseline lipids, mean (SD) unless otherwise specified				
LDL-C (calculated), mg/dL [mmol/L]	122.1 (35.5) [3.164 (0.920)]	127.7 (39.0) [3.307 (1.010)]	110.9 (35.9) [2.871 (0.931)]	107.7 (31.3) [2.790 (0.811)]
LDL-C (measured), mg/dL [mmol/L]	116.9 (30.1) [3.028 (0.779)]	119.9 (34.9) [3.106 (0.904)]	108.0 (35.4) [2.798 (0.916)]	103.3 (29.0) [2.677 (0.751)]
Non-HDL-C, mg/dL [mmol/L]	168.4 (40.6) [4.362 (1.051)]	171.8 (42.4) [4.450 (1.099)]	133.7 (34.9) [3.462 (0.905)]	129.3 (32.1) [3.350 (0.832)]
HDL-C, mg/dL [mmol/L]	45.1 (8.6) [1.168 (0.224)]	45.2 (9.9) [1.171 (0.256)]	51.2 (12.6) [1.326 (0.326)]	51.6 (12.7) [1.336 (0.329)]
TGs, mg/dL, median (Q1:Q3)	209.8 (177.0:252.2)	208.0 (170.0:254.0)	112.2 (87.6:131.9)	109.0 (84.1:131.9)
Lp(a), mg/dL, median (Q1:Q3)	17.4 (4.8:49.0)	14.5 (4.4:53.4)	19.8 (6.3:49.8)	17.8 (6.5:62.4)
ApoB, mg/dL	112.9 (25.5)	113.1 (25.6)	90.8 (21.1)	88.1 (20.7)
ApoA1, mg/dL	144.9 (22.6)	143.8 (24.6)	147.1 (25.5)	148.0 (27.2)
TRL-C, mg/dL (LDL-C calculated)	46.3 (18.1)	44.2 (12.1)	22.8 (8.9)	21.6 (6.0)
TRL-C, mg/dL (LDL-C measured)	50.6 (24.8)	51.9 (24.6)	25.5 (11.7)	26.0 (11.5)

LDL-C calculated via Friedewald method or measured via beta quantification.
Apo, apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; Lp(a), lipoprotein (a); MDL, mixed dyslipidaemia; SD, standard deviation; T2DM, type 2 diabetes mellitus; TGs, triglycerides; TRL-C, TG-rich lipoprotein cholesterol.
[a] Individuals with T2DM as recorded in medical history; type 1 diabetes was an exclusion factor.
[b] MDL defined as baseline TGs ≥150 mg/dL and LDL-C ≥70 mg/dL.
[c] Rosuvastatin 20–40 mg, atorvastatin 40–80 mg, or simvastatin 80 mg daily.

3. Results

3.1. Study participant characteristics

A total of 2341 participants were randomized in the LONG TERM study, of whom 812 had T2DM (544 alirocumab-treated and 268 placebo recipients) and were included in this analysis; 403 had MDL and 409 did not.

Baseline characteristics (Table 1) were well balanced between the alirocumab and placebo cohorts with T2DM and with and

Table 2
Percentage change from baseline in lipid parameters at Week 24 in individuals with T2DM by MDL status (ITT population).

	+MDL		-MDL		
	Alirocumab (n = 264)	Placebo (n = 131)	Alirocumab (n = 270)	Placebo (n = 133)	Interaction *p*-value
LDL-C[a] (calculated)	−62.6 (2.0)	−6.0 (2.7)	−56.1 (1.9)	5.6 (2.7)	
% difference *vs.* placebo[b]	−56.6 (−50.1 to −63.1)		−61.6 (−55.3 to −68.0)		0.0842
LDL-C[b] (measured)	−56.0 (2.0)	−0.5 (2.8)	−53.9 (1.9)	11.6 (2.7)	
% difference *vs.* placebo[b]	−55.6 (−49.0 to −62.2)		−65.5 (−59.1 to −71.9)		0.6679
Non-HDL-C[a]	−49.2 (1.7)	−4.2 (2.4)	−47.8 (1.7)	5.5 (2.4)	
% difference *vs.* placebo[b]	−45.0 (−39.4 to −50.6)		−53.3 (−47.8 to −58.9)		0.0528
Apo B[a]	−50.2 (1.8)	−3.2 (2.5)	−49.1 (1.8)	6.5 (2.5)	
% difference *vs.* placebo[b]	−47.0 (−41.0 to −52.9)		−55.6 (−49.8 to −61.4)		0.7935
HDL-C[b]	4.1 (0.9)	−1.3 (1.3)	1.1 (0.9)	−0.1 (1.2)	
% difference *vs.* placebo[b]	5.5 (8.4–2.5)		1.2 (4.1 to −1.7)		0.5970
TGs[c]	−17.4 (2.3)	−1.5 (3.1)	−12.7 (2.3)	10.0 (3.2)	
% difference *vs.* placebo[d]	−15.9 (−23.2 to −8.7)		−22.7 (−29.8 to −15.7)		0.1861
Lp(a)[c]	−29.9 (1.9)	−0.2 (2.8)	−27.9 (1.9)	−3.3 (2.7)	
% difference *vs.* placebo[d]	−29.8 (−36.3 to −23.2)		−24.6 (−31.0 to −18.2)		0.2695
TRL-C[a] (calculated LDL-C)	−11.8 (2.9)	4.9 (3.8)	−4.2 (2.7)	12.8 (3.8)	
% difference *vs.* placebo[b]	−16.7 (−7.8 to −25.6)		−17.0 (−8.4 to −25.7)		0.2145
TRL-C[a] (measured LDL-C)	−16.1 (6.9)	11.3 (9.6)	−16.8 (6.8)	−8.7 (9.4)	
% difference *vs.* placebo[b]	−27.4 (−5.2 to −49.5)		−8.2 (13.4 to −29.7)		0.9479

ITT analysis. Interaction *p*-values test for treatment effect of MDL, comparing the difference (alirocumab *vs.* placebo) in % reduction for individuals with *versus* without MDL.
[a] LS mean (SE).
[b] LS mean (95% CI).
[c] Adjusted mean (SE).
[d] Adjusted mean (95% CI).

without MDL. An exception was the higher frequency of HeFH in the alirocumab and placebo groups without MDL (8.0 and 8.1%, respectively) compared with the corresponding groups with MDL (5.6 and 6.8%, respectively).

Baseline lipids reflected expected differences between the cohorts with and without MDL. Compared with the alirocumab and placebo groups without MDL, LDL-C, non-HDL-C, apo B, and TG levels were higher in the treatment groups with MDL, and HDL-C levels were lower, while Lp(a) levels were similar between the two groups. Additionally, fenofibrate use was greater among individuals with than without MDL.

3.2. Efficacy

In individuals with T2DM, alirocumab treatment resulted in significant changes (based on 95% confidence interval) in calculated and measured LDL-C levels *versus* placebo at Week 24. Overall, there were no significant differences in LDL-C reductions between alirocumab-treated individuals with and without MDL (interaction *p*-values >0.05; Table 2). Reductions in LDL-C were observed as early as Week 4 onwards. Mean achieved LDL-C levels were lower with alirocumab 150 mg Q2W than placebo over 78 weeks and were similar for individuals with and without MDL (Fig. 1).

Percentage change from baseline to Week 24 in other lipid parameters is shown in Table 2. Non-HDL-C, apo B, TGs, Lp(a) and TRL-C levels were reduced from baseline in alirocumab-treated individuals at Week 24 with no significant difference based on MDL status (all interaction *p*-values >0.05; Table 2). HDL-C levels were slightly increased with alirocumab, regardless of MDL status (interaction *p*-value = 0.5970).

Regardless of MDL status, compared with placebo, a greater proportion of alirocumab-treated individuals achieved risk-based LDL-C goals (<70 mg/dL and <100 mg/dL for individuals at very-high and high cardiovascular risk, respectively), non-HDL-C <100 mg/dL goal, and risk-based apo B goals (<80 mg/dL and <100 mg/dL for individuals at very-high and high cardiovascular risk, respectively) (Fig. 2).

3.3. Safety

Mean exposure to treatment was similar (~61 weeks) between groups (alirocumab and placebo, both with and without MDL). Overall rates of TEAEs, treatment-emergent serious AEs, and discontinuations due to AEs were similar in the alirocumab and placebo groups, regardless of MDL status (Table 3). The most frequent TEAEs in individuals with T2DM with or without MDL were nasopharyngitis, upper respiratory tract infection, urinary tract infection, and bronchitis. The frequency of local injection-site reactions was similar, regardless of MDL status (with or without), between the alirocumab (2.2% and 4.8%) and placebo (3.0% and 3.7%) groups, as was the proportion of individuals who experienced a major

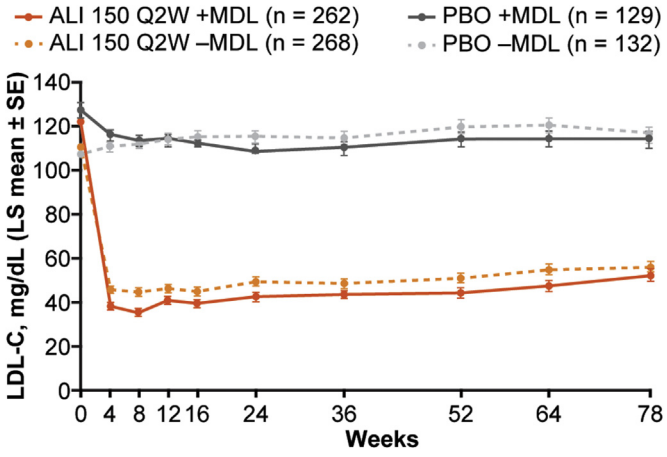

Fig. 1. Mean calculated LDL-C levels over time in alirocumab and placebo recipients with T2DM by MDL status (modified intention-to-treat analysis).
LS means and SEs taken from mixed-effect model with repeated measures analysis. ALI, alirocumab; LDL-C, low-density lipoprotein cholesterol; LS, least squares; MDL, mixed dyslipidaemia; PBO, placebo; Q2W, every 2 weeks, SE, standard error; T2DM, type 2 diabetes mellitus.

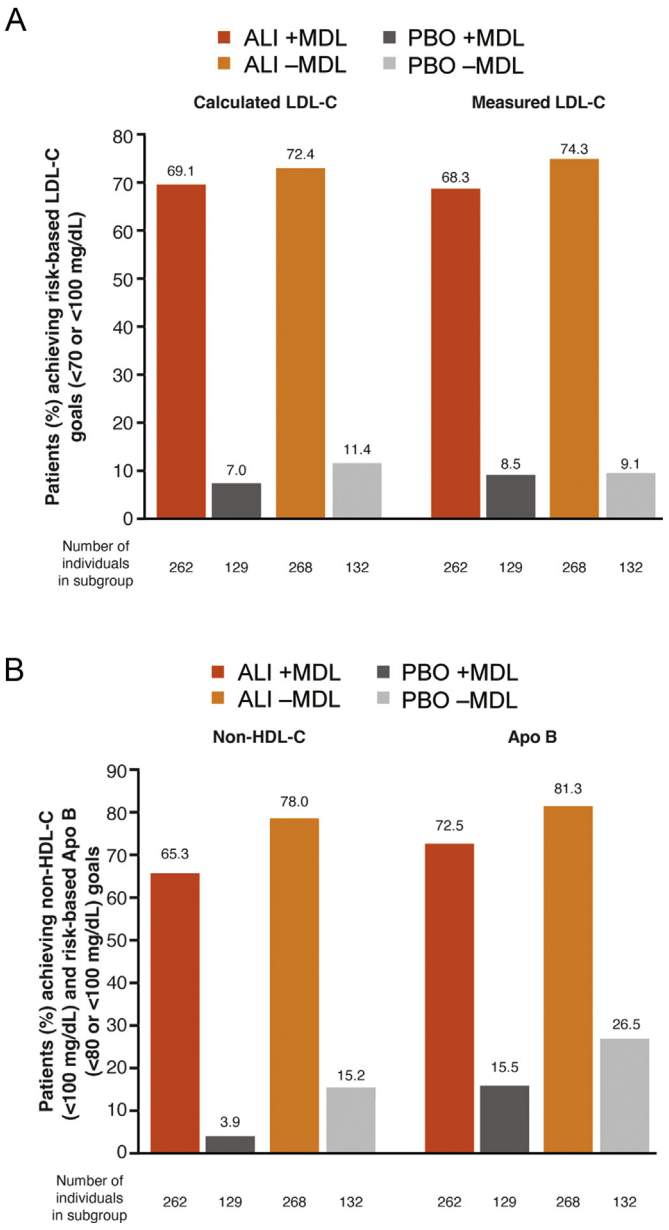

Fig. 2. Proportion of alirocumab and placebo recipients with T2DM[a] achieving (A) LDL-C,[b] and (B) non-HDL-C[c] and apo B[d] goals at Week 24 by MDL status (modified intention-to-treat analysis).
[a] As recorded in medical history; type 1 diabetes was an exclusion factor. [b] LDL-C goal: <70 mg/dL and <100 mg/dL for individuals at very-high and high cardiovascular risk, respectively. [c] Non-HDL-C goal: <100 mg/dL [d] Apo B goal: <80 mg/dL and <100 mg/dL for individuals at very-high and high cardiovascular risk, respectively. ALI, alirocumab; apo, apolipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDL, mixed dyslipidaemia; PBO, placebo; T2DM, type 2 diabetes mellitus.

Table 3
Safety data by MDL status (safety T2DM population).

n (%)	+MDL		−MDL	
	Alirocumab (n = 269)	Placebo (n = 133)	Alirocumab (n = 272)	Placebo (n = 135)
TEAEs[a]	211 (78.4)	109 (82.0)	228 (83.8)	114 (84.4)
Treatment-emergent SAEs	55 (20.4)	34 (25.6)	57 (21.0)	34 (25.2)
TEAEs leading to death	2 (0.7)	1 (0.8)	3 (1.1)	1 (0.7)
TEAEs leading to discontinuation	26 (9.7)	8 (6.0)	20 (7.4)	5 (3.7)
Adverse events of special interest				
Local injection-site reactions	6 (2.2)	4 (3.0)	13 (4.8)	5 (3.7)
Major adverse CV events[b]	8 (3.0)	6 (4.5)	6 (2.2)	5 (3.7)
TEAEs by preferred term in ≥ 5% of individuals in any group				
Nasopharyngitis	28 (10.4)	14 (10.5)	38 (14.0)	15 (11.1)
Upper respiratory tract infection	17 (6.3)	12 (9.0)	24 (8.8)	18 (13.3)
Bronchitis	17 (6.3)	12 (9.0)	12 (4.4)	10 (7.4)
Urinary tract infection	15 (5.6)	7 (5.3)	22 (8.1)	13 (9.6)
Fall	13 (4.8)	4 (3.0)	11 (4.0)	9 (6.7)
Influenza	10 (3.7)	11 (8.3)	20 (7.4)	7 (5.2)
Osteoarthritis	9 (3.3)	9 (6.8)	10 (3.7)	6 (4.4)
Diarrhoea	9 (3.3)	7 (5.3)	14 (5.1)	8 (5.9)
Headache	7 (2.6)	6 (4.5)	18 (6.6)	5 (3.7)
Fatigue	7 (2.6)	4 (3.0)	7 (2.6)	8 (5.9)
Muscle spasms	7 (2.6)	3 (2.3)	7 (2.6)	7 (5.2)
Nausea	6 (2.2)	7 (5.3)	10 (3.7)	4 (3.0)

CV, cardiovascular; MDL, mixed dyslipidaemia; SAE, serious adverse event; TEAE, treatment-emergent adverse event; T2DM, type 2 diabetes mellitus.
[a] Any adverse event that developed, worsened, or became serious during the period from first to last injection +70 days.
[b] Adjudicated CV events, including the following categories: death due to coronary heart disease, non-fatal myocardial infarction, ischemic stroke, unstable angina requiring hospitalization.

adverse cardiovascular event with alirocumab (3.0% and 2.2%) and placebo (4.5% and 3.7%) in the subgroups with and without MDL, respectively. Additionally, mean FPG and HbA1c levels remained constant up to Week 78 with alirocumab and placebo, regardless of MDL status (Supplementary Fig. 1), with mean FPG levels ranging from 130.1–157.7 mg/dL (alirocumab ± MDL) and 135.8–156.5 mg/dL (placebo ± MDL), and HbA1c levels ranging from 6.8–7.3% (alirocumab ± MDL) and 7.0–7.2% (placebo ± MDL).

4. Discussion

In individuals with T2DM at high risk of CVD, and with elevated LDL-C despite receiving MTS with or without other LLTs, alirocumab treatment for up to 78 weeks resulted in significant LDL-C reductions regardless of whether or not they had MDL. Although LDL-C is the primary treatment target for reducing CVD risk, non-HDL-C and apo B have been shown to be more predictive, particularly in individuals with diabetes and MDL [21–23]. Importantly, our analysis showed significant reductions in non-HDL-C (49.2%) and apo B (50.2%) with alirocumab in individuals with MDL, and that most of these individuals achieved non-HDL-C (65.3%) and apo B (72.5%) goals; results were similar in individuals without MDL. Alirocumab treatment resulted in moderate reductions in TGs (17.4% in MDL and 12.7% in non-MDL), in agreement with previous results [24–26].

Overall, the lipid-lowering efficacy and safety of alirocumab are similar in this cohort of individuals with T2DM with or without MDL, and are aligned with results reported previously for the overall ODYSSEY trial populations [14,27,28]. Results are also in agreement with prior reports indicating consistent efficacy and safety findings with alirocumab treatment in various patient groups, such as those with and without chronic kidney disease [29], prior cardiovascular events [30], or diabetes [31]. Consistent results were also seen in two dedicated, prospective 24-week ODYSSEY trials in individuals with diabetes receiving the 75 mg Q2W dose of alirocumab (with possible dose increase to 150 mg Q2W): in DM-INSULIN, alirocumab reduced LDL-C by 49.0% and 47.4% among insulin-treated individuals with T2DM with or without MDL, respectively [26], and in DM-DYSLIPIDEMIA, in which all participants had T2DM with MDL, LDL-C was reduced by 47.3% with alirocumab [25]. As reported previously for other ODYSSEY studies [24], moderate reductions in TGs were observed with alirocumab treatment in these trials (5.7% in DM-INSULIN [26] and 13% in DM-DYSLIPIDEMIA [25]). Consistent reductions in LDL-C, non-HDL-C, and apo B have also been shown in subjects with mixed hyperlipidaemia, regardless of elevated TGs, treated with evolocumab, another PCSK9 inhibitor [32].

Moderate-to high-intensity statin therapy is recommended for the management of lipid levels in individuals with diabetes, for those either at increased risk of or with existing ASCVD [1,7,33]. However, in the study population of individuals with T2DM with or without MDL in this analysis, among whom 62% had ASCVD, the use of high-intensity statin was relatively low (37–41%). This may be attributed to resistance from physicians in prescribing high-intensity statins in individuals with diabetes [34]. However, the incremental benefit from doubling the statin dose is only a 4–7% further reduction in LDL-C [35]. For individuals who require a greater reduction in LDL-C, the addition of a PCSK9 inhibitor (providing approximately 60% additional LDL-C reduction) [14,36] is more likely to achieve treatment goals than doubling the statin dose.

Although statins reduce cardiovascular risk [33], they are associated with a small increased risk of T2DM. In addition, genetic studies suggest that PCSK9 loss of function mutations, although associated with reduced cardiovascular risk, are also associated with an increased risk of T2DM [37]. However, in trials to date, PCSK9 inhibitors have not shown effects on glycaemic control or increased incidence of developing diabetes [25,26,38–42]. In the ODYSSEY OUTCOMES trial (n = 18,924), after ~3 years of follow-up there was no increase in the frequency of diabetes worsening or diabetic complications in subjects with diabetes at baseline, and no increase in new onset diabetes in subjects without diabetes at baseline, with alirocumab *versus* placebo [43]. Similarly, in this analysis, FPG and HbA1c levels showed no notable changes with

alirocumab treatment in individuals with T2DM, with or without MDL.

The present *post-hoc* analysis is limited by the post-randomization nature of the study, sample sizes within each subgroup, and trial duration (78 weeks). Additionally, the LONG TERM trial excluded individuals with baseline TGs >400 mg/dL; hence, conclusions cannot be drawn about the effect of alirocumab in subjects with severe hypertriglyceridaemia.

To summarize, this sub-analysis based on data from a placebo-controlled, double-blind, randomized trial showed that in individuals with T2DM and high cardiovascular risk, alirocumab significantly reduced LDL-C and other atherogenic lipids and was generally well tolerated regardless of MDL status. Results align with those from prior studies, suggesting consistent efficacy and safety of alirocumab across a range of patient populations. Further insights into the efficacy and safety of alirocumab in individuals with T2DM and the impact on cardiovascular events in this high-risk population will come from the large ODYSSEY OUTCOMES study [44], primary results of which have been reported [43].

Conflicts of interest

Prof Taskinen has received research support from Amgen, Novo Nordisk, and Sanofi Aventis, and is a consultant for or has received honoraria from Amgen, AstraZeneca, Chiesi, Eli Lilly and Company, Merck Sharpe & Dohme, Novo Nordisk, and Sanofi Aventis.

Dr Del Prato has received research funding from AstraZeneca, Boehringer Ingelheim, Novartis Pharmaceuticals Co., and Merck Sharpe & Dohme; and is a consultant for or has received honoraria from AstraZeneca, Boehringer Ingelheim, Eli Lilly and Company, GlaxoSmithKline, Janssen Pharmaceuticals, Laboratoires Servier, Merck Sharpe & Dohme, Novartis Pharmaceuticals Co., Novo Nordisk, Sanofi, Servier, and Takeda Pharmaceuticals.

Dr Bujas-Bobanovic and Dr Letierce are employees of and shareholders in Sanofi.

Dr Louie is an employee of and shareholder in Regeneron Pharmaceuticals, Inc.

Dr Thompson is a consultant to Medical Affairs at Regeneron Pharmaceuticals, Inc.

Prof Colhoun has received research support, travel expenses, and honoraria from, and is also a member of the advisory panels and speakers' bureaus for Sanofi Aventis, Regeneron Pharmaceuticals, Inc., and Eli Lilly and Co.; is a member of the Advisory Panel and receives institutional fees from Novartis Pharmaceuticals; receives or has recently received research support from Roche Pharmaceuticals, Pfizer Inc., Boehringer Ingelheim and AstraZeneca LP; receives research support, travel expenses and is on the Steering Committee for Novo Nordisk; is a shareholder of Roche Pharmaceuticals and Bayer; and has received speaker fees from Pfizer, Inc.

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Author contributions

M-R Taskinen, S Del-Prato, M Bujas-Bobanovic, MJ Louie, and H Colhoun contributed to the study concept, data analysis and interpretation, and in drafting the manuscript. A Letierce and D Thompson were involved in statistical analysis and interpretation. All authors provided critical review of drafts and approved the final version for submission.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.atherosclerosis.2018.07.017.

Apo, apolipoprotein; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; ITT, intention-to-treat; MDL, mixed dyslipidaemia; LDL-C, low-density lipoprotein cholesterol; Lp(a); lipoprotein (a); LS, least squares; SE, standard error; T2DM, type 2 diabetes mellitus; TG, triglycerides; TRL-C, triglyceride-rich lipoprotein cholesterol.

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