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Research: Treatment

Alirocumab safety in people with and without diabetes mellitus: pooled data from 14 ODYSSEY trials

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Abstract

Aim To evaluate the safety of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor alirocumab according to diabetes mellitus status.

Methods Safety data from 14 trials (8–104-week durations) were analysed by treatment (alirocumab or placebo/ezetimibe control) and diabetes status (yes/no, defined by medical history). Adverse event data were assessed using descriptive statistics and Cox models.

Results Of the 5234 trial participants, 1554 (29.7%) had diabetes. Overall, treatment-emergent adverse events were similar in the alirocumab and control groups, except for more frequent local injection site reactions with alirocumab. Fewer people with diabetes experienced local injection site reactions [alirocumab, 3.5%, control, 2.9%; hazard ratio 1.24 (95% CI 0.68–2.25)] than those without diabetes [alirocumab, 7.5%; control, 4.9%; hazard ratio 1.51 (95% CI 1.13–2.01)]. Those with diabetes reported a greater number of serious adverse events (alirocumab, 19.4%; control, 19.7%) than those without diabetes (alirocumab, 14.5%; control, 13.5%). In people with diabetes, major adverse cardiac events occurred in 2.7% of alirocumab-treated people [control, 3.3%; hazard ratio 0.74 (95% CI 0.41–1.35)]; in those without diabetes, 1.8% of alirocumab-treated people had major adverse cardiac events [control, 1.7%; hazard ratio 0.95 (95% CI 0.56–1.62)]. Overall, no increase in HbA_{1c} or fasting plasma glucose vs control treatment groups was observed, regardless of diabetes status.

Conclusion This pooled analysis across 14 trials demonstrated similar safety for alirocumab vs control treatment, irrespective of diabetes status, except for more frequent local injection site reactions with alirocumab. People with diabetes reported fewer local injection site reactions than those without diabetes.

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Introduction

People with Type 1 or Type 2 diabetes mellitus and elevated LDL cholesterol are at increased risk of cardiovascular disease [1]. Alirocumab is a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9) that is approved in over 60 countries [2], including the USA and countries in the European Union, for the management of people with heterozygous familial hypercholesterolaemia or clinical atherosclerotic cardiovascular disease (in the USA), or primary hypercholesterolaemia (in the European Union) and with elevated LDL cholesterol levels on maximally tolerated doses of statins and/or other lipid-lowering therapies, including ezetimibe [3,4]. In phase 3 ODYSSEY clinical studies, alirocumab significantly reduced LDL cholesterol levels from baseline at week 24 in people with hypercholesterolaemia, both alone and in combination

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What's new?

- People with diabetes are at high cardiovascular risk and may require additional lipid-lowering beyond statins. PCSK9 inhibitors provide additional LDL cholesterol reductions, but their safety has not been fully evaluated by diabetes status.
- Our pooled analysis of 14 phase 2/3 trials is the largest safety assessment of the PCSK9 inhibitor alirocumab in terms of study participant numbers (n = 5234), comparing those with vs without diabetes at baseline over 8–104 weeks of treatment.
- Our findings show comparable safety for alirocumab vs control, irrespective of diabetes status, except for more frequent local injection site reactions with alirocumab; people with diabetes reported fewer local injection site reactions than those without. No clinically significant changes in glycaemic variables (fasting plasma glucose and HbA_{1c}) were observed in people with or without diabetes, regardless of treatment with alirocumab or control.

with maximally tolerated statin, with or without other lipid-lowering therapies [5–13].

In sub-analyses by diabetes status in phase 3 ODYSSEY trials, the LDL cholesterol-lowering efficacy of alirocumab from baseline to week 24 was generally similar in people with and without diabetes [14,15]. The efficacy of alirocumab in those with diabetes has subsequently been confirmed vs placebo in insulin-treated people with Type 1 and Type 2 diabetes in the phase 3b ODYSSEY DM-INSULIN trial (NCT02585778) [16] and vs usual care in people with Type 2 diabetes and mixed dyslipidaemia in the phase 3b/4 ODYSSEY DM-DYSLIPIDEMIA study (NCT02642159) [17].

The safety results for alirocumab in people with diabetes were similar to those for the control groups in the above-mentioned sub-analyses and clinical trials [14–17]. These findings are consistent with the overall safety profile of alirocumab in a pooled analysis of 14 ODYSSEY trials, the largest safety assessment of alirocumab in terms of study participant numbers (n = 5234) [18]. The pooled safety analysis focused on adverse events (AEs) of special interest categories that were predefined based on identified, potential and theoretical risks for the new PCSK9 inhibitor drug class [18]. Results indicated a higher incidence of local injection site reactions in individuals who had received alirocumab vs the control groups, with a similar incidence of musculoskeletal, neurological, neurocognitive, ophthalmological and hepatic events, and AEs related to diabetes/diabetes complications, between alirocumab and control groups [18]. However, findings from a recent Mendelian randomization study, which showed an association between PCSK9 genetic variants that mimic the effects of PCSK9 inhibitors and an increased risk of diabetes, have raised new concerns about the safety of PCSK9 inhibitor therapy in people with diabetes [19]. To provide additional evidence regarding these concerns, we evaluated the safety of alirocumab according to diabetes status using the same pool of 14 ODYSSEY trials mentioned above.

Methods

Study design

The purpose of the present analysis was to evaluate the safety of alirocumab vs control (placebo or ezetimibe) in people with hypercholesterolaemia with Type 1 or Type 2 diabetes vs those without diabetes. Type 1 or Type 2 diabetes at baseline was defined according to medical history. Individual trial participant data from 14 double-blind, randomized clinical trials (four phase 2 trials [20–23] and 10 phase 3 trials [5–13]) were analysed in four pools according to diabetes status at baseline (yes/no), and according to whether participants were randomized to receive alirocumab or control.

This analysis uses a similar design to the previously published overall safety analysis of 14 alirocumab trials [18], results from which were included in the licensing application for alirocumab to the regulators. Details of trials included in the present analysis and the study design of the present analysis have been published previously [18]. Briefly, double-blind treatment durations of the trials were 8–104 weeks. Alirocumab dose and background statin use varied according to each trial. In eight phase 3 trials, the starting dose of alirocumab was 75 mg every 2 weeks, and was increased to 150 mg every 2 weeks at week 12 if prespecified LDL cholesterol levels were not achieved at week 8. Two phase 3 trials used the 150-mg dose every 2 weeks throughout. Phase 2 studies evaluated a range of alirocumab doses vs placebo on stable background statin; this safety analysis included only individuals who had received the approved 75-mg and 150-mg doses every 2 weeks. All study protocols of individual trials were approved by the appropriate institutional review boards, and all study participants provided informed written consent.

Safety assessments

All AEs were recorded by the investigators, regardless of seriousness or potential relationship to alirocumab, and were coded using the Medical Dictionary of Regulatory Activities version 18.0. AEs were defined as treatment-emergent AEs (TEAEs) if they developed, worsened or became serious during the period between the first and last dose of study treatment, plus 10 weeks to account for the potential prolonged effect of alirocumab.

An AE of special interest was an AE (serious or non-serious) that needed to be proactively monitored, documented and managed in the prespecified manner described in the study

protocols. If the investigator thought it necessary, participants were referred to a specialist for further testing. Categories for AEs of special interest were defined based on identified, potential and theoretical risks for the new drug class. The following AEs of special interest were prespecified in the phase 3 study protocols [18]: local injection site reactions; general allergic events; neurological events; and ophthalmological events. Other prespecified categories of interest, including TEAEs related to hepatic disorders, neurocognitive disorders and diabetes, were analysed in the same way as the other AEs of special interest, but were not specifically defined as AEs of special interest in the protocols. In this analysis, the definitions used for AEs of special interest in phase 3 trials were applied to the data from the phase 2 trials.

Major adverse cardiac events (MACE), defined as coronary heart disease death, non-fatal myocardial infarction, fatal or non-fatal ischaemic stroke, or unstable angina requiring hospitalization, were adjudicated by a central Clinical Events Committee. MACE were adjudicated only in phase 3 trials.

Laboratory values, including fasting plasma glucose (FPG) and fasting HbA_{1c} levels over time, were assessed by a central laboratory, as previously described [18].

Statistical analyses

The safety population was defined as all randomized people who received at least one full or partial dose of study treatment.

Any TEAE that was not prespecified but occurred commonly (by preferred term in ≥5% in any treatment group), AEs of special interest categories and MACE confirmed by adjudication were analysed using a predefined approach, including incidence and event rate per 100 person-years in each treatment group (calculated as number of people with an event divided by total person-years up to the first event or the end of the TEAE follow-up period). To assess the consistency of treatment effect across studies, hazard ratios (HRs) and 95% CIs were calculated for AEs of special interest and adjudicated MACE using a Cox model that included the treatment group for each study. In addition, the study-by-treatment interaction was tested in a separate Cox model including the study, treatment and the study-by-treatment interaction. Other TEAEs were summarized using descriptive statistics.

To assess potential differences in glycaemic variables for alirocumab vs control, mixed-effect model repeat measurement was used, assuming heterogeneous Toeplitz covariance structure [24] (HbA_{1c}) or unstructured covariance structure (FPG).

Results

Baseline characteristics

Among 5234 study participants analysed, 1554 (29.7%) had diabetes, of whom 1524 (98.1%) had Type 2 diabetes, 28 (1.8%) had Type 1 diabetes and two (0.1%) had diabetes for which the type was not specified. At baseline, mean (SD) HbA_{1c} levels in those with diabetes were 52 (11) mmol/mol [6.9 (1.1)%] and 52 (12) mmol/mol [6.9 (1.1)%] for the alirocumab and control groups, respectively, vs 38 (4) mmol/mol [5.7 (0.4)%] and 38 (5) mmol/mol [5.7 (0.4)%], respectively, for those without diabetes (Table 1). Baseline mean (SD) FPG levels in the alirocumab and control groups, respectively, were 7.5 (2.3) mmol/l (135.1 [41.3] mg/dl) and 7.5 (2.4) mmol/l (135.9 [43.9] mg/dl) in those with diabetes, vs 5.5 (0.7) mmol/l (99.2 [13.1] mg/dl) and 5.5 (0.8) mmol/l (98.8 [13.8] mg/dl) in those without diabetes (Table 1). Overall, 23.5% of those with diabetes were on insulin.

Baseline characteristics, including age, BMI and mean baseline lipid levels, were similar in the alirocumab and control groups within the pools of people with and without diabetes (Table 1). Generally, compared to those without diabetes, people with diabetes were slightly older, and had higher BMI and more hypertension, and lower LDL cholesterol and higher triglyceride levels (Table 1). Heterozygous familial hypercholesterolaemia and chronic kidney disease were only reported in the phase 3 studies; in this population, 9.6% of people with diabetes had heterozygous familial hypercholesterolaemia (vs 34.5% without diabetes), and 15.0% of people with diabetes had chronic kidney disease (vs 7.2% without diabetes). Overall, 63.3% of those with diabetes had atherosclerotic cardiovascular disease (vs 69.3% without diabetes), and 44.4% of those with diabetes were on high-intensity statins (vs 55.3% without diabetes). The duration of total exposure to alirocumab was 62.4 weeks for people with diabetes, and 63.6 weeks for those without diabetes (vs 58.4 weeks for control for both diabetes subgroups).

Safety

The overall incidences of TEAEs, serious AEs, deaths and discontinuations were similar in the alirocumab and control groups (Table 2). Overall, serious AE incidence was higher in people with diabetes (alirocumab, 19.4%; control, 19.7%) vs those without diabetes [alirocumab, 14.5%; control, 13.5%; $P < 0.0001$ (Table 2)]; however, no pattern was observed in terms of individual specific serious AE frequency, and no difference in incidence was observed in alirocumab-treated people vs controls.

As shown in Fig. 1, the most commonly reported TEAEs by preferred term in people with and without diabetes were nasopharyngitis (diabetes: alirocumab, 9.2%, control, 8.1%; non-diabetes: alirocumab, 11.1%, control, 10.7%) and upper respiratory tract infection (diabetes: alirocumab, 7.2%, control, 9.0%; non-diabetes: alirocumab, 6.6%, control, 6.5%). TEAEs that occurred with preferred term ≥5% in any treatment group by primary system organ class and preferred term, stratified by diabetes status, are shown in Table S1.

The incidence rates of AEs of special interest are shown in Fig. 2. A significantly higher incidence of local injection site reactions was seen with alirocumab vs control in people without diabetes [alirocumab, 7.5%, control, 4.9%; HR 1.51 (95% CI 1.13–2.01)]. The incidence of local injection site reactions was lower in people with diabetes, with no significant differences between treatment arms [alirocumab, 3.5%, control, 2.9%; HR 1.24 (95% CI 0.68–2.25)]. In those with diabetes, rates of local injection site reactions in people receiving concomitant injectable therapies at baseline were 2.0% [8/397 participants; alirocumab, 1.9% (5/265 participants); control, 2.3% (3/132 participants)] vs 3.7% in those not receiving concomitant injectable therapies at baseline [43/1157 participants; alirocumab, 4.1% (30/731 participants); control, 3.1% (13/426 participants)]. Most local injection site reactions were mild in intensity (Fig. 3). Other AEs of special interest generally occurred at similar rates in the alirocumab and control groups in both diabetes and non-diabetes subgroups (Fig. 2). Further details of AEs of special interest, including specific events in ≥0.5% of study participants, stratified by diabetes status, are shown in Table S2.

Adjudicated MACE (in phase 3 trials only) were reported in 2.7% of alirocumab-treated people with diabetes [3.3% of

Table 1 Baseline characteristics according to baseline diabetes status in the pool of 14 phase 2/3 trials (safety population)

	People with diabetes *N* = 1554		People without diabetes *N* = 3680	
	Control *n* = 558	Alirocumab *n* = 996	Control *n* = 1336	Alirocumab *n* = 2344
Age, years	61.7 (9.6)	62.1 (9.5)	58.9 (11.2)	58.3 (11.6)
Male, *n* (%)	313 (56.1)	587 (58.9)	837 (62.6)	1476 (63.0)
BMI, kg/m^2	32.8 (6.0)	32.3 (6.4)	29.0 (5.0)	29.0 (5.1)
Atherosclerotic cardiovascular disease*, *n* (%)	346 (62.0)	637 (64.0)	912 (68.3)	1640 (70.0)
Chronic kidney disease†, *n*/*N* (%)	79/546 (14.5)	149/979 (15.2)	80/1246 (6.4)	170/2203 (7.7)
Heterozygous familial hypercholesterolemia†, *n*/*N* (%)	57/546 (10.4)	90/979 (9.2)	404/1246 (32.4)	787/2203 (35.7)
Hypertension, *n* (%)	492 (88.2)	887 (89.1)	766 (57.3)	1324 (56.5)
Statins, *n* (%)	524 (93.9)	941 (94.5)	1117 (83.6)	2079 (88.7)
High-intensity statins‡, *n* (%)	239 (45.7)	451 (47.9)	720 (64.7)	1315 (63.3)
Any other lipid-lowering therapy, *n* (%)	127 (22.8)	231 (23.2)	443 (33.2)	770 (32.8)
Anti-hyperglycaemic agent, *n* (%)	459 (82.3)	828 (83.1)	0	0
Injectable anti-hyperglycaemic, *n* (%)	132 (23.7)	265 (26.6)	0	0
Insulin, *n* (%)	123 (22.0)	242 (24.3)	0	0
LDL cholesterol				
mmol/l	3.0 (1.1)	3.0 (1.0)	3.4 (1.3)	3.4 (1.3)
mg/dl	115.9 (41.8)	115.7 (37.9)	130.6 (50.3)	130.0 (49.8)
Non-HDL cholesterol				
mmol/l	3.8 (1.2)	3.9 (1.1)	4.1 (1.4)	4.1 (1.4)
mg/dl	148.3 (47.9)	149.3 (43.9)	159.0 (55.3)	157.5 (53.5)
Triglycerides, median (Q1:Q3)				
mmol/l	1.6 (1.2:2.3)	1.7 (1.2:2.3)	1.4 (1.0:2.0)	1.4 (1.0:1.9)
mg/dl	144.0 (107.1:201.0)	147.0 (108.0:207.0)	122.1 (89.4:175.0)	120.0 (87.6:167.3)
HDL cholesterol				
mmol/l	1.2 (0.3)	1.2 (0.3)	1.3 (0.4)	1.3 (0.4)
mg/dl	47.4 (12.3)	46.9 (11.9)	51.0 (13.8)	51.3 (14.2)
FPG				
mmol/l	7.5 (2.4)	7.5 (2.3)	5.5 (0.8)	5.5 (0.7)
mg/dl	135.9 (43.9)	135.1 (41.3)	98.8 (13.8)	99.2 (13.1)
HbA_{1c}				
mmol/mol	52 (12)	52 (11)	38 (5)	38 (4)
%	6.9 (1.1)	6.9 (1.1)	5.7 (0.4)	5.7 (0.4)
Duration of diabetes, years	9.1 (8.7)	9.3 (8.4)	0	0
Duration of total exposure to study treatment, weeks	58.4 (31.1)	62.4 (29.2)	58.4 (31.3)	63.6 (30.0)

FPG, fasting plasma glucose.
Values are mean (SD), unless otherwise specified.
*Atherosclerotic coronary heart disease, ischaemic stroke or peripheral arterial disease. †*n*/*N* = number of people in phase 3 studies only.
‡High-intensity statins were defined as atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg or simvastatin 80 mg daily.
Study references: phase 2 trials [DFI111565 (NCT01288443), DFI11566 (NCT01288469), CL-1003 (NCT01266876), DFI12361 (NCT01812707)]; phase 3 trials [LONG TERM (NCT01507831), HIGH FH (NCT01617655), COMBO I (NCT01644175), FH I (NCT01623115), FH II (NCT01709500), COMBO II (NCT01644188), OPTIONS I (NCT01730040), OPTIONS II (NCT01730053), MONO (NCT01644474), and ALTERNATIVE (NCT01709513)].

controls; HR 0.74 (95% CI 0.41–1.35)], and in 1.8% of alirocumab-treated people without diabetes [1.7% of controls; HR 0.95 (95% CI 0.56–1.62); Fig. 2].

Overall, no changes in median HbA_{1c} and FPG measurements were observed over time for up to 104 weeks with alirocumab, regardless of diabetes status (Fig. 4). There were no differences in least squares mean HbA_{1c} and FPG for alirocumab vs control (*P* values comparing alirocumab and control by diabetes status at each time >0.05), except for one timepoint showing a small but significant difference for alirocumab vs control [week 12 least squares mean HbA_{1c} in people without diabetes:

Table 2 Safety characteristics according to diabetes status at baseline in the pool of 14 phase 2/3 trials (safety population).

	People with diabetes *N* = 1554		People without diabetes *N* = 3680	
n (%)	Control *n* = 558	Alirocumab *n* = 996	Control *n* = 1336	Alirocumab *n* = 2344
TEAEs	431 (77.2)	781 (78.4)	1030 (77.1)	1818 (77.6)
Serious TEAEs	110 (19.7)	193 (19.4)	181 (13.5)	341 (14.5)
TEAEs leading to death	7 (1.3)	9 (0.9)	15 (1.1)	13 (0.6)
TEAEs leading to discontinuation	43 (7.7)	87 (8.7)	94 (7.0)	145 (6.2)

AE, adverse event; TEAE, treatment-emergent adverse event.

TEAEs in ≥5% of individuals	Study Population	*n/N* (%) Control	*n/N* (%) Alirocumab	Proportion (%) of individuals ● Control ▲ Alirocumab	Rate per 100-patient-years (control vs alirocumab)†
Upper respiratory tract infection	DM	50/558 (9.0)	72/996 (7.2)		7.6 vs 5.7
	Non-DM	87/1336 (6.5)	155/2344 (6.6)		5.5 vs 5.2
Nasopharyngitis	DM	45/558 (8.1)	92/996 (9.2)		6.8 vs 7.4
	Non-DM	143/1336 (10.7)	261/2344 (11.1)		9.3 vs 9.0
Bronchitis	DM	36/558 (6.5)	44/996 (4.4)		5.4 vs 3.4
	Non-DM	42/1336 (3.1)	95/2344 (4.1)		2.6 vs 3.1
Arthralgia	DM	33/558 (5.9)	37/996 (3.7)		4.9 vs 2.8
	Non-DM	72/1336 (5.4)	124/2344 (5.3)		4.5 vs 4.1
Urinary tract infection	DM	32/558 (5.7)	60/996 (6.0)		4.7 vs 4.7
	Non-DM	58/1336 (4.3)	90/2344 (3.8)		3.6 vs 2.9
Influenza	DM	28/588 (5.0)	53/996 (5.3)		4.1 vs 4.1
	Non-DM	58/1336 (4.3)	131/2344 (5.6)		3.6 vs 4.3
Diarrhoea	DM	23/558 (4.1)	40/996 (4.0)		3.3 vs 3.1
	Non-DM	59/1336 (4.4)	118/2344 (5.0)		3.6 vs 3.9
Back pain	DM	26/558 (4.7)	45/996 (4.5)		3.8 vs 3.5
	Non-DM	71/1336 (5.3)	114/2344 (4.9)		4.4 vs 3.7
Myalgia	DM	23/558 (4.1)	34/996 (3.4)		3.3 vs 2.6
	Non-DM	72/1336 (5.4)	140/2344 (6.0)		4.5 vs 4.6
Headache	DM	22/558 (3.9)	42/996 (4.2)		3.2 vs 3.2
	Non-DM	69/1336 (5.2)	127/2344 (5.4)		4.3 vs 4.2

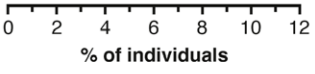


FIGURE 1 Treatment-emergent adverse events (TEAEs) in ≥5% of people with and without diabetes in the pool of 14 phase 2/3 trials (safety population). *n/N* = number of study participants with at least one event. †Number of people with an event per person-year, calculated as number of people with an event divided by total person-years. For people with an event, number of person-years is calculated up to the date of the first event; for those without an event, it corresponds to the length of the TEAE period. DM, diabetes mellitus.

TEAEs of special interest	Study population	*n/N* (%) Control	*n/N* (%) Alirocumab	Proportion (%) of individuals ▲ Alirocumab ● Placebo	Rate per 100-patient-years (control vs alirocumab)†	HR vs control (95% CI)‡
LISRs	DM	16/558 (2.9)	35/996 (3.5)		2.3 vs 2.7	1.24 (0.68 to 2.25)
	Non-DM	65/1336 (4.9)	175/2344 (7.5)		4.1 vs 5.9	1.51 (1.13 to 2.01)
Neurocognitive disorders	DM	10/558 (1.8)	13/996 (1.3)		1.4 vs 1.0	0.75 (0.33 to 1.73)
	Non-DM	7/1336 (0.5)	19/2344 (0.8)		0.4 vs 0.6	1.57 (0.65 to 3.76)
Neurological events	DM	22/558 (3.9)	35/996 (3.5)		3.2 vs 2.7	0.85 (0.50 to 1.45)
	Non-DM	49/1336 (3.7)	99/2344 (4.2)		3.0 vs 3.2	1.14 (0.81 to 1.61)
Hepatic disorders	DM	20/558 (3.6)	25/996 (2.5)		2.9 vs 1.9	0.69 (0.38 to 1.24)
	Non-DM	25/1336 (1.9)	70/2344 (3.0)		1.5 vs 2.3	1.49 (0.94 to 2.36)
General allergic events	DM	42/558 (7.5)	80/996 (8.0)		6.3 vs 6.3	1.00 (0.69 to 1.46)
	Non-DM	101/1336 (7.6)	224/2344 (9.6)		6.4 vs 7.6	1.23 (0.97 to 1.55)
Ophthalmologic events	DM	11/558 (2.0)	25/996 (2.5)		1.6 vs 1.9	1.21 (0.59 to 2.46)
	Non-DM	14/1336 (1.0)	39/2344 (1.7)		0.8 vs 1.3	1.42 (0.77 to 2.62)
DM or diabetic complications	DM	58/558 (10.4)	105/996 (10.5)		8.8 vs 8.5	0.95 (0.69 to 1.32)
	Non-DM	33/1336 (2.5)	47/2344 (2.0)		2.0 vs 1.5	0.73 (0.46 to 1.13)
Adjudicated MACE§	DM	18/546 (3.3)	26/979 (2.7)		2.6 vs 2.0	0.74 (0.41 to 1.35)
	Non-DM	21/1246 (1.7)	39/2203 (1.8)		1.3 vs 1.3	0.95 (0.56 to 1.62)

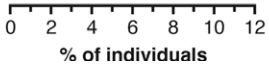


FIGURE 2 Adverse events of special interest according to diabetes status at baseline in the pool of 14 phase 2/3 trials (safety population). †Calculated as number of people with an event divided by total person-years. For people with an event, the number of person-years is calculated up to the date of the first event; for those without an event, it corresponds to the length of the treatment-emergent adverse event (TEAE) period. ‡Calculated using a Cox model stratified on the study. §Major adverse cardiac events (MACE) were defined as coronary heart disease death, non-fatal myocardial infarction, ischaemic stroke or unstable angina requiring hospitalization, and were adjudicated by a central Clinical Events Committee only in phase 3 trials. Local injection site reactions (LISRs) were selected using an electronic case report form-specific tick box on the adverse event page in phase 3 studies and phase 2 study DFI12361, selected using Medical Dictionary of Regulatory Activities (MedDRA) high-level term 'injection site reaction' in the other phase 2 studies. Neurocognitive disorder: events selected using a custom MedDRA query, based on the five following high-level group terms: deliria (including confusion); cognitive and attention disorders and disturbances; dementia and amnestic conditions; disturbances in thinking and perception; and mental impairment disorders. Neurological events: standardized MedDRA queries 'demyelination' (broad and narrow), 'peripheral neuropathy' (broad and narrow), and 'Guillain–Barre syndrome' (broad and narrow), excluding the following preferred terms: 'acute respiratory distress syndrome', 'asthenia', 'respiratory arrest' and 'respiratory failure'. Hepatic disorder: standardized MedDRA query 'hepatic disorder'. General allergic events: selected using a custom MedDRA query with standardized MedDRA query 'hypersensitivity' (broad and narrow), excluding the following preferred terms linked to LISRs: ('infusion site dermatitis', 'infusion site hypersensitivity', 'infusion site rash', 'infusion site urticaria,' 'injection site dermatitis', 'injection site hypersensitivity', 'injection site rash', 'injection site urticaria' and 'vasculitis'. Ophthalmologic events: standardized MedDRA queries 'optic nerve disorders' (broad and narrow), 'retinal disorders' (narrow) and 'corneal disorders' (narrow). Diabetes or diabetic complications: high-level group term 'diabetes complications', high-level term 'diabetes mellitus' and high-level term 'carbohydrate tolerance analyses (including diabetes)', excluding preferred term 'blood glucose decreased'. In study participants with diabetes at baseline, terms such as 'diabetes mellitus' indicate a worsening of the condition or loss of glycaemic control. DM, diabetes mellitus; HR, hazard ratio; TEAE, treatment-emergent adverse event.

38.0 (alirocumab) and 38.3 (control); P=0.0338 (Figs S1 and S2)].

Discussion

The present pooled safety analysis across 14 phase 2 and three ODYSSEY trials of treatment duration ranging from 8 to 104 weeks showed that, irrespective of diabetes status, alirocumab safety was similar to that of control. The exception was the higher rates of local injection site reactions (the majority of which were mild in nature) with alirocumab treatment vs control in those with and without diabetes. These findings are consistent with previous findings in the overall ODYSSEY study population [18]. Similar overall safety findings were also demonstrated in insulin-treated participants with diabetes in the DM-INSULIN study [16] and in those with Type 2 diabetes and mixed dyslipidaemia in the DM-DYSLIPIDEMIA study (both 24 weeks' treatment duration) [17]. Additionally, similar safety results were shown with evolocumab, another PCSK9 inhibitor, in

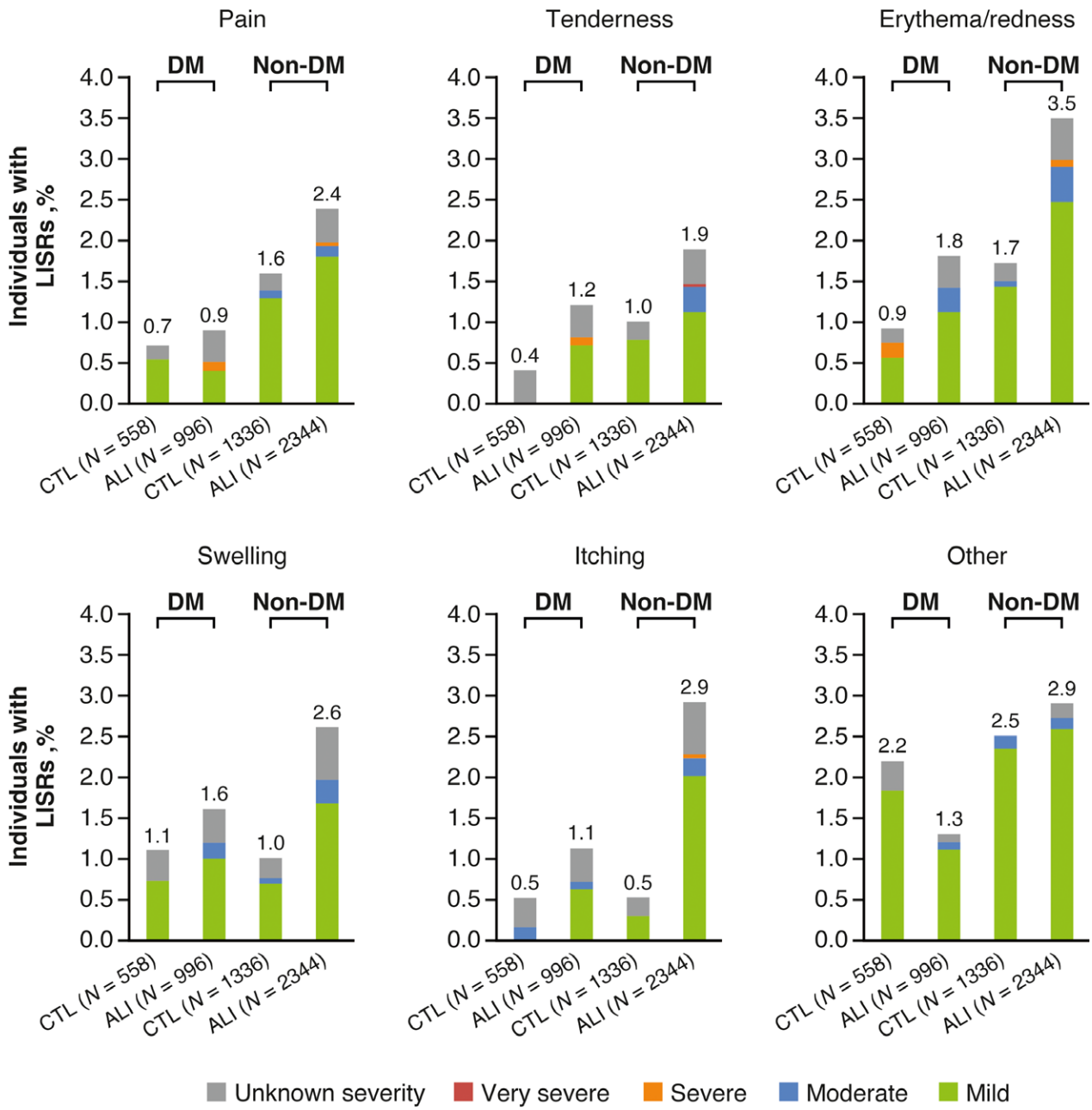
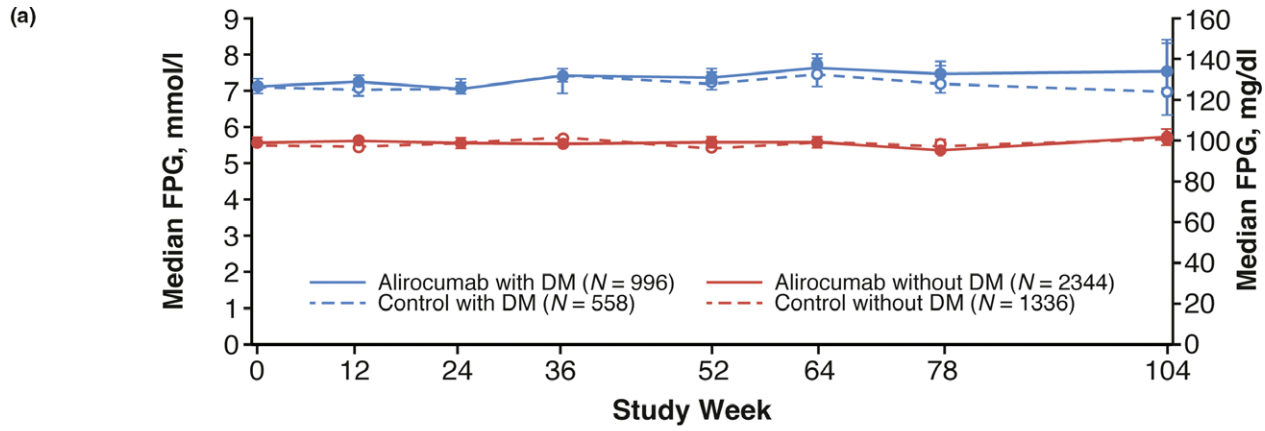
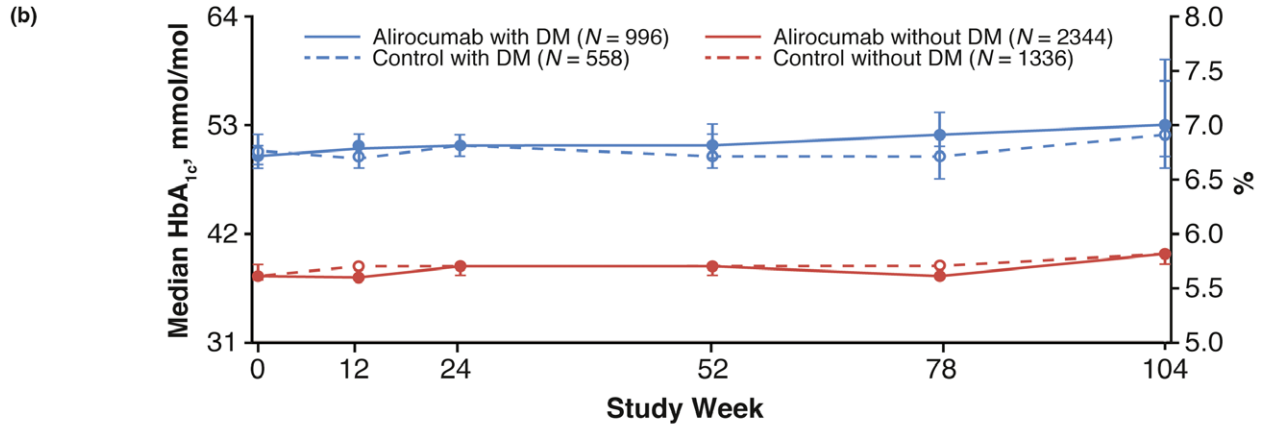


FIGURE 3 Comparison of local injection site reactions (LISRs) according to diabetes status at baseline in the pool of 14 phase 2/3 trials (safety population). The category of LISRs included those judged to be related to the injection of study treatment by the investigator and not attributable to another injectable agent. If the investigator or study participant recognized any LISRs and/or signs of local intolerability at the injection site, this was to be treated and followed up as per the investigator's medical judgement, and recorded on a special case report form. Local injection site reactions were graded by severity and characterized by related signs and symptoms such as (but not limited to) redness and pain. Drug reactions and/or LISRs considered to be allergic (or that had an allergic component) were reported under the category of general allergic events. Adverse events with cutaneous involvement and with obvious allergic origin or LISRs that expanded/worsened were to be evaluated by a dermatologist as soon as possible [18]. ALI, alirocumab; CTL, control; DM, diabetes mellitus.

diabetes sub-analyses of the evolocumab PROFICIO studies [25,26] including the cardiovascular outcomes FOURIER trial [27]. The lower rates of local injection site reactions that were observed in people with diabetes compared with people without diabetes, were previously seen in the diabetes sub-analyses of five placebo-controlled phase 3 trials (52–78 weeks' treatment duration) and the ezetimibe-controlled COMBO II trial (104 weeks' treatment duration) [14,15]. This difference may simply be attributable to a greater familiarity with injectable therapies and/or fingerstick blood glucose testing in people with diabetes compared with those without; in the present analysis, ~25% of study participants



n	Week 0	Week 12	Week 24	Week 36	Week 52	Week 64	Week 78	Week 104
Alirocumab with DM	996	895	848	720	685	475	406	103
Control with DM	558	495	451	357	341	252	227	51
Alirocumab without DM	2342	2112	1920	1695	1648	1253	1123	257
Control without DM	1334	1211	1086	854	829	637	576	121



n	Week 0	Week 12	Week 24	Week 52	Week 78	Week 104
Alirocumab with DM	990	618	859	691	410	100
Control with DM	556	340	455	345	227	49
Alirocumab without DM	2315	1159	1929	1652	1125	252
Control without DM	1322	695	1088	827	577	116

FIGURE 4 Median (a) fasting plasma glucose (FPG) and (b) HbA_{1c} over time in people with and without diabetes in the pool of 14 phase 2/3 trials (safety population). Error bars indicate 95% CI values. Approximate values of FPG in mmol/l and HbA_{1c} in mmol/mol are shown on the left-hand *y*-axis in panels (a) and (b), respectively. For HbA_{1c}, the following formula was used to convert % to mmol/mol units: HbA_{1c} in mmol/mol = 10.93* (HbA_{1c} in %) – 23.5. DM, diabetes mellitus.

in the diabetes group were receiving injectable antihyperglycaemic drugs. Other AEs of special interest generally occurred at similar rates between alirocumab and control in both the diabetes and non-diabetes subgroups.

Consistent with previous results that did not find an association between alirocumab treatment and impaired glycaemic control [14,15,17,28,29], including at very-low LDL cholesterol levels of <25 or <15 mg/dl (<0.6 or <.4 mmol/l) [30], the present pooled safety analysis showed that alirocumab did not affect FPG and HbA_{1c} levels over time for up to 104 weeks of treatment in people with and without diabetes. Analyses of evolocumab PROFICIO trials with 48–52 weeks of follow-up and the diabetes sub-analysis of the FOURIER trial with 168 weeks of follow-up also did not show changes in FPG or HbA_{1c} levels with evolocumab treatment [25,27,31].

Adjudicated MACE rates from the present analysis are similar to the rates seen in the *post hoc* analysis of the ODYSSEY LONG TERM trial (alirocumab, 1.7% vs placebo, 3.3%) [10]. As expected, and consistent with results

from the FOURIER diabetes sub-analysis [27], MACE rates were higher in those with diabetes (compared with people without diabetes), which is consistent with their expected higher baseline cardiovascular risk.

This safety assessment by diabetes status was conducted in the largest dataset for alirocumab available to date (N = 5234), representing a more robust and heterogenous study population than the populations assessed in previous sub-analyses of alirocumab by diabetes status, such as the *post hoc* analysis of the COMBO II study (n = 720) [15] and the pooled analysis of five placebo-controlled ODYSSEY trials (n = 3499) [14]. Nevertheless, these data are limited by the overall study durations, and by differences among the studies pooled (such as durations and populations). Although the studies included in the present analysis had follow-up durations of up to 2 years, a longer-term effect of PCSK9 inhibition on glycaemic control cannot be excluded, and studies of longer duration are required. The present analysis included people with Type 1 and Type 2 diabetes, who may differ in their demographic and clinical characteristics, although the proportion of people with Type 1 diabetes included was small (1.8% of the overall diabetes population). Furthermore, the studies included in this analysis were not designed to determine the effect of alirocumab on cardiovascular events. Such data will be provided by the long-term cardiovascular outcomes trial for alirocumab (ODYSSEY OUTCOMES; NCT01663402) in 18 924 study participants (~29% of whom had diabetes) randomized 1–12 months after acute coronary syndrome, with a median follow-up of 2.8 years; the primary results for the OUTCOMES trial are now available (Steg et al., American College of Cardiology 2018; unpublished). Data on diabetes and prediabetes variables (reported by investigators and determined by serial HbA_{1c} and FPG measurements) from OUTCOMES are expected to be reported at a later date.

In conclusion, the present pooled analysis across 14 phase 2 and three trials of 8 to 104 weeks' duration showed that the safety of alirocumab was similar to that of control treatment, irrespective of diabetes status. The exception was the higher rates of local injection site reactions with alirocumab vs control treatment, generally mild in intensity, which were lower in those with vs those without diabetes.

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Competing interests

The authors report the following: L.A.L.: personal fees from Esperion, and grants and personal fees from Amgen, AstraZeneca, Kowa, The Medicines Company, Merck, Regeneron Pharmaceuticals, Inc. and Sanofi, outside the submitted work; F.J.T.: speaker's bureau and consultant/advisory board fees from AstraZeneca, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Janssen Pharmaceuticals, Merck Sharpe & Dohme, Novartis Pharmaceuticals Co., Novo Nordisk, Sanofi and Regeneron Pharmaceuticals, Inc.; D.G.K.: served as a consultant for Regeneron Pharmaceuticals, Inc. and Sanofi; M.B.-B. and A.L.: employees of and shareholders in Sanofi. J.M.: contractor for Sanofi; R.S.: employee of and shareholder in Regeneron Pharmaceuticals, Inc.; and P.H.J.: Chief Science Officer for the National Lipid Association and consultant/on advisory panels for Amgen, Merck, Sanofi and Regeneron Pharmaceuticals, Inc.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. HbA_{1c} over time in people with (A and B) and without diabetes mellitus (C and D) according to treatment status (safety population).

Figure S2. Fasting plasma glucose over time in people with (A and B) and without diabetes mellitus (C and D) according to treatment status (safety population).

Table S1. Treatment-emergent adverse events that occurred with preferred term ≥5% in any treatment group by primary system organ class and preferred term, by diabetes status (safety population).

Table S2. Further details on adverse events of special interest, including specific events in ≥0.5% of participants (safety population).