Alirocumab Safety in Individuals with and without Diabetes Mellitus: Pooled Data from 14 ODYSSEY Trials

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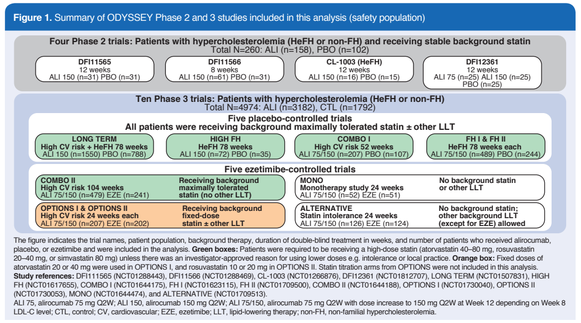
Background

- Individuals with diabetes mellitus (DM) and elevated low-density lipoprotein cholesterol (LDL-C) 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 more than 40 countries for the management of high-risk patients with elevated LDL-C levels despite maximally tolerated doses of statins and/or other lipid-lowering therapies including ezetimibe.[2]
- As demonstrated in the ODYSSEY clinical studies, alirocumab significantly reduces LDL-C levels (by 43–61% from baseline at Week 24 in Phase 3 trials)[3] in patients with hypercholesterolemia, both alone and in combination with maximally tolerated statin with or without other lipid-lowering therapies, and is generally well tolerated.[2,3]
- In a sub-analysis by DM status in the five placebo-controlled Phase 3 ODYSSEY trials,[4] LDL-C reductions from baseline at Week 24 on alirocumab 75/150 mg every 2 weeks (Q2W) were greater in individuals without DM (–43.4% with DM vs –49.8% without DM), likely due to a higher proportion of those without DM receiving a dose increase at Week 12; however, LDL-C reductions on alirocumab 150 mg Q2W throughout the study were similar regardless of DM status (–59.7% with DM vs –60.7% without DM at Week 24).[4] Also, in the 104-week ezetimibe-controlled COMBO II study,[5] LDL-C reductions from baseline at Week 24 on alirocumab 75/150 mg Q2W were comparable regardless of DM status (–49.1% with DM vs –51.2% without DM), and LDL-C reductions were maintained over 104 weeks.[5]
- A previous pooled safety analysis from 14 ODYSSEY trials (four Phase 2 and 10 Phase 3, including 5234 patients) demonstrated that alirocumab has a safety profile comparable with placebo or ezetimibe.[3]
- In this analysis using the same pool of 14 ODYSSEY trials, we evaluated the safety of alirocumab according to DM status.

Methods

- The safety of alirocumab versus control (placebo or ezetimibe) was analyzed in individuals with hypercholesterolemia with type 1 or type 2 DM versus those without DM in 14 double-blind, randomized Phase 2 and 3 ODYSSEY trials (8 to 104 weeks' duration; Figure 1), pooled according to DM status at baseline.
- Type 1 or type 2 DM was defined by medical history.
- Alirocumab dose was 150 mg Q2W in LONG TERM and HIGH FH; in the other eight Phase 3 studies, alirocumab dose was increased from 75 to 150 mg Q2W at Week 12 if pre-specified LDL-C levels were not achieved at Week 8 (Figure 1).
  - Patients were on background maximally tolerated statin in the five Phase 3 placebo-controlled studies and COMBO II, and on fixed statin doses in OPTIONS I and II; patients were not on background statin in ALTERNATIVE and MONO.
- Phase 2 studies evaluated a range of alirocumab doses on stable background statin; this safety analysis included only the 75 and 150 mg Q2W doses.

Figure 1. Summary of ODYSSEY Phase 2 and 3 studies included in this analysis (safety population)



The figure indicates the trial names, patient population, background therapy, duration of double-blind treatment in weeks, and number of patients who received alirocumab, placebo, or ezetimibe and were included in the analysis. **Green boxes:** Patients were required to be receiving a high-dose statin (atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg) unless there was an investigator-approved reason for using lower doses e.g. intolerance or local practice. **Orange box:** Fixed doses of atorvastatin 20 or 40 mg were used in OPTIONS I; and rosuvastatin 10 or 20 mg in OPTIONS II. Statin titration arms from OPTIONS were not included in this analysis. **Study references:** DFI11565 (NCT01288443), DFI11566 (NCT01288469), CL-1003 (NCT01266876), DFI12361 (NCT01812707), 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).
ALI 75, alirocumab 75 mg Q2W; ALI 150, alirocumab 150 mg Q2W; ALI 75/150, alirocumab 75 mg Q2W with dose increase to 150 mg Q2W at Week 12 depending on Week 8 LDL-C level; CTL, control; CV, cardiovascular; EZE, ezetimibe; LLT, lipid-lowering therapy; non-FH, non-familial hypercholesterolemia.

- Treatment-emergent adverse events (TEAEs) were defined as events occurring from the first dose of study treatment to the last dose (plus 70 days to account for the prolonged effect of alirocumab).[3]
- Categories for TEAEs of special interest were defined based on potential theoretical risks for the new drug class.[3]
- Cardiovascular events were adjudicated in the Phase 3 trials. Laboratory values were assessed by a central lab.[3]

Results

Baseline characteristics

- Of 5234 patients analyzed, 1554 (29.7%) had DM, of which 1524 (98.1%) had type 2 DM, 28 (1.8%) had type 1 DM, and two (0.1%) had DM of unspecified type.
- Baseline characteristics, including age, body mass index (BMI), and mean baseline lipid levels, were comparable between alirocumab and control groups within the pools of individuals with and without DM (Table 1).
- Generally, individuals with DM were older, and had higher BMI, lower LDL-C, and higher TGs than individuals without DM (Table 1).
- Overall, 9.6% of individuals with DM (vs 34.5% without) had heterozygous familial hypercholesterolemia (HeFH), and 44.4% of those with DM (vs 54.6% without) were on high-dose statin; 15.0% of individuals with DM (vs 7.2% without) had chronic kidney disease (CKD).

Table 1. Baseline characteristics according to DM status at baseline in the pool of 14 Phase 2/3 trials (safety population)

	Individuals with DM (n=1554)		Individuals without DM (n=3680)	
Mean (SD), unless otherwise specified	**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)
ASCVD, n (%)	346 (62.0)	637 (64.0)	912 (68.3)	1640 (70.0)
CKD, n/N[†] (%)	79/546 (14.5)	149/979 (15.2)	80/1246 (6.4)	170/2203 (7.7)
HeFH, n/N[†] (%)	57/546 (10.4)	90/979 (9.2)	404/1246 (32.4)	787/2203 (35.7)
Statin, n (%)	523 (93.7)	941 (94.5)	1098 (82.2)	2063 (88.0)
High-dose statin,[‡] n (%)	239 (42.8)	451 (45.3)	707 (52.9)	1304 (55.6)
Any other LLT, n (%)	127 (22.8)	231 (23.2)	443 (33.2)	770 (32.8)
Anti-hyperglycemic agent, n (%)	459 (82.3)	828 (83.1)	0	0
Injectable anti-hyperglycemic, n (%)	132 (23.7)	265 (26.6)	0	0
Insulin, n (%)	123 (22.0)	242 (24.3)	0	0
LDL-C, mg/dL	115.9 (41.8)	115.7 (37.9)	130.6 (50.3)	130.0 (49.8)
Non-HDL-C, mg/dL	148.3 (47.9)	149.3 (43.9)	159.0 (55.3)	157.5 (53.5)
TGs, mg/dL, median (Q1 :Q3)	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-C, mg/dL	47.4 (12.3)	46.9 (11.9)	51.0 (13.8)	51.3 (14.2)
FPG, mg/dL [mmol/L]	135.9 (43.9) [7.54 (2.44)]	135.1 (41.3) [7.50 (2.29)]	98.8 (13.8) [5.48 (0.77)]	99.2 (13.1) [5.51 (0.73)]
HbA_{1c}, %	6.9 (1.1)	6.9 (1.1)	5.7 (0.4)	5.7 (0.4)
Duration of DM, 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)

[†]n/N = number of individuals in Phase 3 studies only. [‡]High-dose statins defined as atorvastatin 40 to 80 mg, rosuvastatin 20 to 40 mg, or simvastatin 80 mg daily.
ASCVD, atherosclerotic cardiovascular disease; SD, standard deviation; TGs, triglycerides.

Safety

- The overall incidences of TEAEs, serious adverse events (SAEs), deaths, and discontinuations (Table 2) were comparable between the alirocumab and control groups.

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

	Individuals with DM (n=1554)		Individuals without DM (n=3680)	
	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)
Treatment emergent SAEs	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)

All AEs were recorded by the investigators, regardless of seriousness or potential relationship to alirocumab, and were coded using Medical Dictionary of Regulatory Activities version 18.0. AEs were defined as TEAEs if they developed, worsened, or became serious during the period between first and last dose of study treatment plus 10 weeks.
SAEs were defined as any untoward medical occurrence that at any dose: resulted in death, was life-threatening (patient was at risk of death at the time of the event), required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or was a congenital anomaly/birth defect.

- Overall SAE incidence was 19.7% (control) and 19.4% (alirocumab) in individuals with DM versus 13.5% (control) and 14.5% (alirocumab) in those without DM (Table 2); however, no pattern was observed in terms of individual specific SAE frequency and no difference was observed in alirocumab versus controls.
- The most commonly occurring TEAEs in both individuals with and without DM were nasopharyngitis and upper respiratory tract infection (Figure 2).

Figure 2. TEAEs in ≥5% of individuals with and without DM pooled from 14 Phase 2/3 trials (safety population)

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
Diarrhea	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
Backpain	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

0 2 4 6 8 10 12
% of individuals

n = number of patients with at least one event.
[†]Number of patients with an event per patient-year, calculated as number of patients with an event divided by total patient-years. For patients with an event, number of patient-years is calculated up to date of the first event; for patients without event, it corresponds to the length of the TEAE period.

- Incidence of TEAEs of special interest was similar between alirocumab and control groups, except for a higher incidence of local injection-site reactions (LISRs) with alirocumab (Figure 3).
- LISRs occurred in 3.5% of alirocumab-treated individuals with DM versus 7.5% of those without DM (Figure 3). Most LISRs were mild in intensity (Figure 4).
- Skeletal muscle events were seen in 18.5% (control) and 13.6% (alirocumab) of individuals with DM versus 16.8% (control) and 18.1% (alirocumab) of those without DM.
- Major adverse cardiac events (MACEs) were reported in 2.7% of individuals with DM on alirocumab (vs 3.3% on control), and in 1.8% of individuals without DM on alirocumab (vs 1.7% on control) (Figure 3).

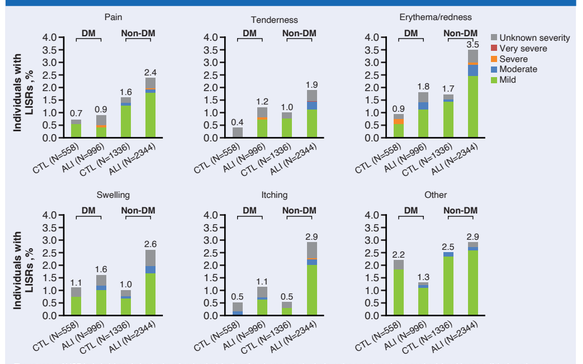
Figure 3. TEAEs of special interest according to DM status at baseline in the pool of 14 Phase 2/3 trials (safety population)

TEAEs of special interest	Study population	n/N (%) Control	n/N (%) Alirocumab	Proportion (%) of individuals ● Control ▲ Alirocumab	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 to1.24)
	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)

0 2 4 6 8 10 12 14 16 18 20

[†]Calculated as number of patients with an event divided by total patient-years. For patients with an event, the number of patient-years is calculated up to the date of the first event; for patients without an event, it corresponds to the length of the TEAE period. Only calculated for TEAEs of special interest. [‡]Calculated using a Cox model stratified on the study. The following AEs of special interest were pre-specified in the Phase 3 study protocols: LISRs, general allergic events, neurological events, hepatic disorders, and ophthalmologic events. Other pre-defined categories including TEAEs related to neurocognitive disorders and DM were analyzed in the same way as the other AEs of interest, but 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 data from the Phase 2 trials. Other AEs of special interest, including neurologic, ophthalmologic, and hepatic disorders (as well as alanine aminotransferase increase), were also collected using special electronic case report forms. Patients were referred to a specialist for further testing if the investigator thought it necessary. Neurocognitive events included those related to memory impairment, disorientation, and confusion.[§]The "Diabetes mellitus or diabetic complications" category was defined as follows: HLGT "Diabetes Complications." HLT "Diabetes Mellitus," and HLT "Carbohydrate tolerance analyses (including diabetes)" excluding PT "Blood glucose decreased." In patients with diabetes at baseline, terms such as "diabetes mellitus" include a worsening of the condition or loss of glycemic control. MACEs were defined as coronary heart disease death, non-fatal myocardial infarction, ischemic stroke, or unstable angina requiring hospitalization, and were adjudicated by a central Clinical Events Committee. MACEs were adjudicated only in Phase 3 trials.
HLGT, high-level group term; HLT, high-level term; NC, not calculated (not AE of special interest); PT, preferred term.

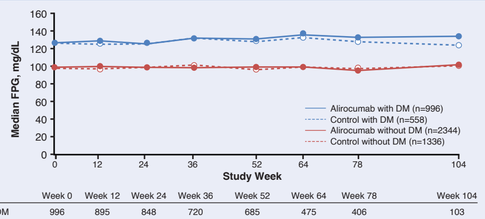
Figure 4. Comparison of LISRs according to DM status at baseline in the pool of 14 Phase 2/3 trials (safety population)



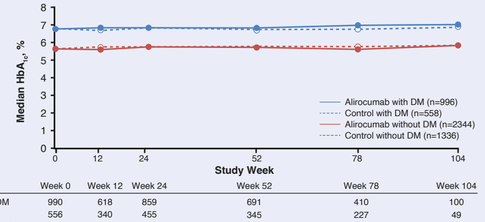
The category of LISR included those judged to be related to the injection of study treatment by the investigator and not due to another injectable agent. If the investigator or patient recognized any LISRs and/or signs of local intolerability at the injection site, this was to be treated and followed up as per the investigator's medical judgement and recorded on a special case report form. LISRs were graded by severity and were 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 have an allergic component) were reported under the category of general allergic events. AEs with cutaneous involvement and with obvious allergic origin or LISRs that expanded/worsened were to be evaluated by a dermatologist as soon as possible.[3]

- No changes in mean HbA_{1c} and FPG measurements were observed over time with alirocumab, regardless of diabetes status (Figure 5).

Figure 5. Median (A) FPG (mg/dL) and (B) HbA_{1c} (%) over time in individuals with and without DM in the pool of 14 Phase 2/3 trials (safety population)



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

Conclusions

- This pooled analysis across 14 Phase 2 and 3 trials of 8 to 104 weeks' duration demonstrated that alirocumab safety was comparable to control irrespective of DM status.
- The exception was the higher rates of LISRs with alirocumab treatment versus control, generally mild in intensity and consistent with previous findings,[3,4] which were seen in those without DM but not in those with DM.

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