Alirocumab Efficacy and Safety in Patients with Hypercholesterolemia with or without Clinical Atherosclerotic Cardiovascular Disease: Pooled Analysis of 10 ODYSSEY Randomized Trials

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Background

- Randomized clinical trials have demonstrated that treatment with statins reduce low-density lipoprotein cholesterol (LDL-C) and cardiovascular risk, and are considered the standard first-line treatment for hypercholesterolemia.[1] However, some patients are intolerant to statins or are unable to reach desired LDL-C levels on statins or other traditional lipid-lowering therapies (LLTs).[2,3]
- Alirocumab is a fully human proprotein convertase subtilisin/kexin type 9 (PCSK9) antibody.
- The alirocumab ODYSSEY Phase 3 clinical trial program recruited patients with hypercholesterolemia, approximately 70% of whom had atherosclerotic cardiovascular disease (ASCVD).[4] Patients with or without ASCVD may have differences in their responses to drug therapy or a different adverse event profile because of the types and doses of background therapy or underlying disease characteristics. Therefore, this analysis evaluated the lipid-lowering effect and safety of alirocumab among patients with or without ASCVD pooled from 10 ODYSSEY trials.

Methods

- Data were pooled from 10 randomized studies (24 to 104 weeks) with a total of 4983 patients with hypercholesterolemia.
- ASCVD was defined as coronary heart disease (CHD), ischemic stroke/transient ischemic attack, or peripheral arterial disease (PAD), all of presumed atherosclerotic origin.

Table 1. Summary of ODYSSEY studies and key inclusion requirements

Pool 1: ALI 150 vs PBO (with statins)[†]		
LONG TERM (78 weeks) **Entry criteria:** **HeFH or non-FH + LDL-C ≥70 mg/dL** ALI 150 mg: n=1553 PBO: n=788		**HIGH FH (78 weeks)** **Entry criteria:** **HeFH + LDL-C ≥160 mg/dL** ALI 150 mg: n=72 PBO: n=35
Pool 2: ALI 75/150 vs PBO (with statins)[†]		
FH I (78 weeks) **HeFH** ALI 75/150 mg: n=323 PBO: n=163	**FH II (78 weeks)** **HeFH** ALI 75/150 mg: n=167 PBO: n=82	**COMBO I (52 weeks)** **Non-FH** ALI 75/150 mg: n=209 PBO: n=107
LDL-C entry criteria for Pool 2 studies: ≥70 mg/dL (with ASCVD), ≥100 mg/dL (without ASCVD)		
Pool 3: ALI 75/150 vs EZE (with statins)[†]		
OPTIONS I (24 weeks) **HeFH or non-FH** ALI 75/150 mg: n=104 EZE: n=102	**OPTIONS II (24 weeks)** **HeFH or non-FH** ALI 75/150 mg: n=103 EZE: n=101	**COMBO II (104 weeks)** **Non-FH** ALI 75/150 mg: n=479 EZE: n=241
LDL-C entry criteria for Pool 3 studies: ≥70 mg/dL (with ASCVD), ≥100 mg/dL (without ASCVD)		
Pool 4: ALI 75/150 vs EZE (without statins)[†]		
MONO (24 weeks) **Entry criteria:** **Non-FH[‡] + LDL-C ≥100 and <190 mg/dL** ALI 75/150 mg: n=52 EZE: n=51		**ALTERNATIVE (24 weeks)** **Entry criteria:** **HeFH or non-FH with statin intolerance** LDL-C ≥70 mg/dL (with ASCVD) or ≥100 mg/dL (without ASCVD) ALI 75/150 mg: n=126 EZE: n=125

[†]Statins were at maximally tolerated dose in all studies in Pool 1 and 2, and in COMBO II. Patients received atorvastatin 20 or 40 mg in OPTIONS I and rosuvastatin 10 or 20 mg in OPTIONS II. Other non-statin background LLT were allowed in all studies except COMBO II and MONO.
[‡]10-year risk of fatal cardiovascular events of ≥1% and <5% based on the European Society of Cardiology Systematic Coronary Risk Evaluation; history of CHD or HeFH were exclusion criteria for MONO.
Clinical trial identifiers: HIGH FH, NCT01617655; LONG TERM, NCT01507831; FH I, NCT01623115; FHII, NCT01709500; COMBO I, NCT01644175; COMBO II, NCT01644188; OPTIONS I, NCT01730040; OPTIONS II, NCT01730053; MONO, NCT01644474; ALTERNATIVE, NCT01709513
ALI, alirocumab; EZE, ezetimibe; FH, familial hypercholesterolemia; PBO, placebo.

- The studies included patients with a history of ASCVD and/or other cardiovascular risk factors (e.g. heterozygous familial hypercholesterolemia [HeFH]), with LDL-C inadequately controlled on their existing treatment (statin/other LLT/diet).
- Efficacy and safety data were compared in patients with or without ASCVD at baseline, in four pools based on alirocumab dosage, control (placebo or ezetimibe), and whether background statin was received (see Table 1 for a summary of studies by pool number).
- Two studies (Pool 1) used a dosage of 150 mg every 2 weeks (Q2W) throughout. Eight studies (Pools 2–4) were initiated with alirocumab at 75 mg Q2W and the dosage was subsequently increased to 150 mg Q2W at Week 12 if Week 8 LDL-C was ≥70 mg/dL (or if Week 8 LDL-C was ≥70 mg/dL in patients with ASCVD and ≥100 mg/dL in patients without ASCVD in ALTERNATIVE and OPTIONS I and II).
- In this pooled analysis, the percentage change from baseline in calculated LDL-C was assessed at Week 24 using intention-to-treat analysis (ITT), reflecting the primary endpoint for each study.
- Goal achievement was defined as proportion of patients reaching calculated LDL-C <70 mg/dL or <100 mg/dL, for those with and without prior ASCVD, respectively, at Week 24.

Results

- Baseline characteristics were balanced between alirocumab and control groups across the subgroups (Tables 2 and 3). There was a trend for higher baseline LDL-C values in patients without ASCVD, which may reflect that fewer of those patients were receiving high-intensity statins and a higher proportion had HeFH compared with patients with ASCVD.
- The alirocumab dosage was increased from 75 to 150 mg Q2W at Week 12 in 23.6% of patients with ASCVD and 37.6% of those without ASCVD in the eight studies that allowed for a dosage increase.

Table 2. Baseline characteristics

		Pool 1 (n=2448)		Pool 2 (n=1051)		Pool 3 (n=1130)		Pool 4 (n=354)	
	ASCVD status	**ALI**	**PBO**	**ALI**	**PBO**	**ALI**	**EZE**	**ALI**	**EZE**
ASCVD status, n	With	1219	634	396	200	580	353	71	58
	Without	406	189	303	152	106	91	107	118
Age, years, mean (SD)	With	61.6 (9.6)	61.6 (9.5)	60.4 (10.8)	60.2 (9.9)	62.1 (9.4)	62.6 (9.7)	67.2 (8.5)	65.2 (9.2)
	Without	55.1 (12.6)	55.5 (12.5)	49.3 (12.8)	49.3 (12.9)	58.9 (10.5)	60.8 (9.2)	60.4 (6.7)	60.2 (8.6)
Males, n (%)	With	824 (67.6)	415 (65.5)	249 (62.9)	137 (68.5)	431 (74.3)	252 (71.4)	47 (66.2)	38 (65.5)
	Without	194 (47.8)	81 (42.9)	148 (48.8)	79 (52.0)	52 (49.1)	42 (46.2)	51 (47.7)	56 (47.5)
Race, White, n (%)	With	1146 (94.0)	600 (94.6)	353 (89.1)	180 (90.0)	497 (85.7)	307 (87.0)	69 (97.2)	54 (93.1)
	Without	359 (88.4)	160 (84.7)	281 (92.7)	132 (86.8)	85 (80.2)	78 (85.7)	94 (87.9)	109 (92.4)
BMI, kg/m^2, mean (SD)	With	30.0 (5.4)	30.1 (5.1)	30.4 (5.5)	30.8 (6.2)	30.0 (5.4)	30.5 (5.3)	29.9 (5.8)	28.7(4.6)
	Without	30.5 (6.4)	31.5 (6.4)	29.4 (5.4)	29.2 (5.7)	32.2 (7.8)	31.3 (6.6)	29.6 (6.8)	28.2 (5.8)
HeFH, n (%)	With	153 (12.6)	92 (14.5)	217 (54.8)	113 (56.5)	10 (1.7)	5 (1.4)	5 (7.0)	6 (10.3)
	Without	195 (48.0)	82 (43.4)	273 (90.1)	132 (86.8)	16 (15.1)	13 (14.3)	9 (8.4)	19 (16.1)
Diabetes, n (%)	With	347 (28.5)	177 (27.9)	93 (23.5)	46 (23.0)	176 (30.3)	112 (31.7)	23 (32.4)	12 (20.7)
	Without	221 (54.4)	108 (57.1)	40 (13.2)	25 (16.4)	68 (64.2)	55 (60.4)	16 (15.0)	13 (11.0)
High-intensity statin,[†] n (%)	With	596 (48.9)	327 (51.6)	314 (79.3)	165 (82.5)	389 (67.1)	225 (63.7)	0	0
	Without	189 (46.6)	73 (38.6)	228 (75.2)	117 (77.0)	41 (38.7)	40 (44.0)	0	0
LDL-C mg/dL at baseline, mean (SD)	With	121.0 (40.7)	123.6 (44.1)	117.4 (43.0)	120.4 (45.7)	108.1 (35.6)	102.4 (34.6)	180.0 (52.4)	174.2 (63.4)
	Without	140.5 (56.4)	130.9 (45.1)	144.2 (48.5)	143.3 (41.6)	116.8 (34.4)	115.1 (40.6)	174.2 (75.0)	178.9 (67.5)

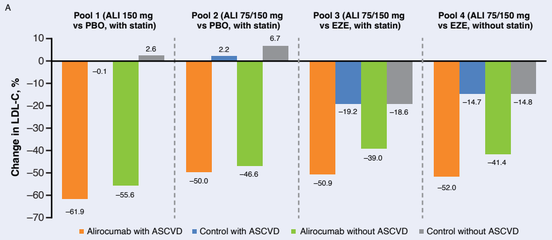
Pool 1 = alirocumab 150 mg versus placebo (LONG TERM + HIGH FH); Pool 2 = alirocumab 75/150 mg versus placebo (FH I, FH II, COMBO I); Pool 3 = alirocumab 75/150 mg versus ezetimibe (COMBO II, OPTIONS I, OPTIONS II); Pool 4 = alirocumab 75/150 mg versus ezetimibe (MONO, ALTERNATIVE; without background statin).
BMI, body mass index; SD, standard deviation.
[†]High-intensity statin = atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg daily.

Table 3. Medical history: Details of cardiovascular events in patients with history of ASCVD

	Pool 1 (n=1853)		Pool 2 (n=596)		Pool 3 (n=933)		Pool 4 (n=129)	
n (%)	**ALI (n=1219)**	**PBO (n=634)**	**ALI (n=396)**	**PBO (n=200)**	**ALI (n=580)**	**EZE (n=353)**	**ALI (n=71)**	**EZE (n=58)**
CHD	1085 (89.0)	574 (90.5)	369 (93.2)	192 (96.0)	547 (94.3)	336 (95.2)	64 (90.1)	54 (93.1)
Acute coronary syndrome	734 (60.2)	394 (62.1)	246 (62.1)	134 (67.0)	402 (69.3)	241 (68.3)	31 (43.7)	27 (46.6)
Coronary revascularization procedure	725 (59.5)	382 (60.3)	281 (71.0)	140 (70.0)	410 (70.7)	253 (71.7)	45 (63.4)	38 (65.5)
Other clinically significant CHD	470 (38.6)	243 (38.3)	152 (38.4)	79 (39.5)	270 (46.6)	177 (50.1)	40 (56.3)	29 (50.0)
PAD	80 (6.6)	43 (6.8)	17 (4.3)	13 (6.5)	32 (5.5)	17 (4.8)	1 (1.4)	2 (3.4)
Ischemic stroke	160 (13.1)	76 (12.0)	39 (9.8)	10 (5.0)	55 (9.5)	31 (8.8)	4 (5.6)	5 (8.6)

- Alirocumab treatment resulted in greater percentage reductions in LDL-C compared with control in both patients with and without ASCVD in each pool (Figure 1). Minor differences were seen between the subgroups, in particular Pools 3 and 4, but this was at the limit of significance and nevertheless substantial reductions are seen.

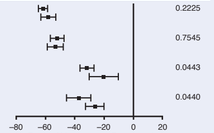
Figure 1. (A) Percent change from baseline in calculated LDL-C at Week 24 by treatment pool and ASCVD status and (B) statistical analysis by treatment pool comparing patients with and without ASCVD (ITT analysis)



Interaction *P*-values: Pool 1, 0.2225; Pool 2, 0.7545; Pool 3, 0.0443; Pool 4, 0.0440.

B

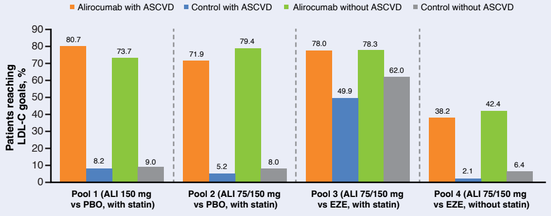
Study pool	Subgroup	N	% change from baseline LS mean (SE) Control	ALI	Difference in % change from baseline LS mean difference (95% CI ALI - control	Inter. *P*-value
Pool 1: ALI 150 mg vs PBO (with statins)	ASCVD	1827	−0.1 (1.2)	−61.9 (0.8)		0.2225
	No ASCVD	589	2.6 (2.1)	−55.6 (1.5)		
Pool 2: ALI 75/150 mg vs PBO (with statins)	ASCVD	590	2.2 (2.0)	−50.0 (1.4)		0.7545
	No ASCVD	453	6.7 (2.3)	−46.6 (1.7)		
Pool 3: ALI 75/150 mg vs EZE (with statins)	ASCVD	914	−19.2 (1.9)	−50.9 (1.5)		0.0443
	No ASCVD	191	−18.6 (3.9)	−39.0 (3.7)		
Pool 4: ALI 75/150 mg vs EZE (without statins)	ASCVD	126	−14.7 (3.4)	−52.0 (3.0)		0.0440
	No ASCVD	225	−14.8 (2.3)	−41.4 (2.4)		



CI, confidence interval; LS, least squares; SE, standard error. LS means and SE taken from mixed-effect model with repeated measures analysis.

- A greater proportion of alirocumab-treated patients achieved risk-based LDL-C goals compared with controls (Figure 2).
- Goal achievement in Pool 4 was lower than the others (Figure 2); in this pool (including mostly statin intolerant patients from the ALTERNATIVE study), patients were not receiving background statin therapy and had higher baseline LDL-C than the other pools. However, percentage reductions in LDL-C were comparable with the other pools (Figure 1).

Figure 2. Percentage of patients reaching risk-based LDL-C goals at Week 24 (ITT population)



All interaction *P*-values were >0.05.

- Incidence of treatment-emergent adverse events (TEAEs) and TEAEs resulting in discontinuation of study treatment were similar to control groups regardless of clinical ASCVD status (Table 4). Alirocumab had a similar safety profile in patients with and without ASCVD as reflected by TEAEs occurring with a frequency ≥5%.

Table 4. TEAEs (safety population)

	Patients with ASCVD				Patients without ASCVD			
	Placebo-controlled pool (n=2455)		EZE-controlled pool (n=1060)		Placebo-controlled pool (n=1047)		EZE-controlled pool (n=422)	
n (%)	**ALI (n=1611)**	**PBO (n=834)**	**ALI (n=651)**	**EZE (n=409)**	**ALI (n=707)**	**PBO (n=340)**	**ALI (n=213)**	**EZE (n=209)**
TEAEs	1299 (80.6)	671 (80.5)	510 (78.3)	315 (77.0)	552 (78.1)	283 (83.2)	147 (69.0)	142 (67.9)
Treatment-emergent SAEs	321 (19.9)	168 (20.1)	137 (21.0)	79 (19.3)	64 (9.1)	34 (10.0)	10 (4.7)	7 (3.3)
TEAEs leading to discontinuation	105 (6.5)	52 (6.2)	59 (9.1)	47 (11.5)	39 (5.5)	15 (4.4)	25 (11.7)	19 (9.1)
TEAEs leading to death	13 (0.8)	12 (1.4)	6 (0.9)	9 (2.2)	3 (0.4)	1 (0.3)	0	0
TEAEs ≥5%								
Nasopharyngitis	207 (12.8)	93 (11.2)	34 (5.2)	19 (4.6)	84 (11.9)	49 (14.4)	18 (8.5)	22 (10.5)
Upper respiratory tract infection	121 (7.5)	71 (8.5)	48 (7.4)	28 (6.8)	41 (5.8)	23 (6.8)	14 (6.6)	12 (5.7)
Injection-site reaction	105 (6.5)	36 (4.3)	18 (2.8)	6 (1.5)	62 (8.8)	26 (7.6)	7 (3.3)	7 (3.3)
Diarrhea	88 (5.5)	42 (5.0)	19 (2.9)	12 (2.9)	35 (5.0)	15 (4.4)	11 (5.2)	9 (4.3)
Arthralgia	87 (5.4)	51 (6.1)	32 (4.9)	19 (4.6)	31 (4.4)	25 (7.4)	10 (4.7)	7 (3.3)
Urinary tract infection	85 (5.3)	42 (5.0)	14 (2.2)	14 (3.4)	43 (6.1)	23 (6.8)	7 (3.3)	11 (5.3)
Influenza	84 (5.2)	34 (4.1)	24 (3.7)	19 (4.6)	63 (8.9)	29 (8.5)	13 (6.1)	4 (1.9)
Myalgia	83 (5.2)	29 (3.5)	41 (6.3)	29 (7.1)	28 (4.0)	17 (5.0)	21 (9.9)	19 (9.1)
Back pain	80 (5.0)	50 (6.0)	27 (4.1)	17 (4.2)	43 (6.1)	20 (5.9)	6 (2.8)	9 (4.3)
Bronchitis	78 (4.8)	40 (4.8)	23 (3.5)	15 (3.7)	34 (4.8)	18 (5.3)	3 (1.4)	5 (2.4)
Headache	76 (4.7)	40 (4.8)	30 (4.6)	16 (3.9)	43 (6.1)	24 (7.1)	13 (6.1)	8 (3.8)
Hypertension	66 (4.1)	34 (4.1)	38 (5.8)	19 (4.6)	20 (2.8)	12 (3.5)	4 (1.9)	9 (4.3)
Dizziness	56 (3.5)	36 (4.3)	32 (4.9)	24 (5.9)	25 (3.5)	13 (3.8)	4 (1.9)	6 (2.9)
Accidental overdose	21 (1.3)	11 (1.3)	47 (7.2)	20 (4.9)	9 (1.3)	6 (1.8)	7 (3.3)	4 (1.9)

SAE, serious adverse event.

Conclusions

- Following alirocumab treatment, patients with or without clinical ASCVD achieved greater reductions in LDL-C levels and greater LDL-C goal achievement compared with placebo or ezetimibe.
- Minor differences in efficacy were observed between some subgroups; however, substantial LDL-C reductions were seen in all groups regardless of ASCVD status
- Alirocumab was generally well tolerated with no differences in safety profile between patients with and without ASCVD.

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