Treatment Effects of Alirocumab as an Add-On to Maximally Tolerated Dose of Statin in Patients with Heterozygous Familial Hypercholesterolemia and/or Atherosclerotic Cardiovascular Disease

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Background

- Patients with atherosclerotic cardiovascular disease (ASCVD) and heterozygous familial hypercholesterolemia (HeFH) are at high cardiovascular risk.[1]
- Despite receiving maximally tolerated statin therapy, many have inadequately controlled levels of low-density lipoprotein cholesterol (LDL-C).[1,2]
- Alirocumab is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of patients with HeFH or ASCVD who require additional LDL-C reduction.[3,4]
- We present the efficacy and safety results of alirocumab in patients with ASCVD and/or HeFH on a maximally tolerated dose of statin, with or without other lipid-lowering therapies (LLTs), pooled from five placebo-controlled ODYSSEY Phase 3 studies.

Methods

- The five trials (52–78 weeks) enrolled patients with or without ASCVD whose LDL-C levels were not adequately controlled with a maximally tolerated stable daily dose of statin, with or without other LLTs.[5–8]
  - All patients were analyzed by ASCVD status (n=3499). Patients pooled from FH I, FH II, HIGH FH, LONG TERM, and COMBO I were grouped based on presence (n=2449) or absence (n=1050) of ASCVD.
  - Patients with HeFH (n=1257) were analyzed by ASCVD status. HeFH patients with (n=575) or without (n=682) ASCVD were pooled from all the trials except COMBO I, where recruited patients did not have HeFH.
- Maximally tolerated statin was defined as rosuvastatin 20 or 40 mg, atorvastatin 40 or 80 mg, or simvastatin 80 mg. Lower doses could be used e.g. in the case of intolerance or local practice.
- ASCVD was defined as atherosclerotic coronary heart disease (CHD), ischemic stroke, or peripheral arterial disease (PAD).[9]
- Patients received alirocumab at 75 mg every 2 weeks (Q2W), with possible increase to 150 mg Q2W at Week 12 depending on LDL-C values at Week 8 (FH I, FH II, COMBO I), or at 150 mg Q2W only (HIGH FH, LONG TERM).
- Efficacy endpoints included LDL-C percent change from baseline to Week 24 by alirocumab dose analyzed using an intention-to-treat (ITT) approach that included all data regardless of adherence to treatment.
- Percent change from baseline to Week 24 in LDL-C, apolipoprotein (Apo) B and non-high density lipoprotein cholesterol (non-HDL-C) were presented as least-squares (LS) mean values, calculated from a mixed-effect model with repeated measures to account for missing data, as previously described.[10]
- Triglycerides and lipoprotein(a) [Lp(a)] (non-normally distributed data) were assessed using robust regression to account for missing data.

Results

Baseline

- Baseline characteristics were similar between the alirocumab and placebo groups (Table 1).
  - In patients with ASCVD, the proportions with CHD, ischemic stroke or PAD were comparable between treatment arms.
  - Baseline lipid levels were comparable between treatment arms in each of the patient subgroups analyzed.
  - The most common reasons for not receiving high-dose statins were muscle symptoms and/or increased creatine kinase (6.3–16.1% of patients across the groups) and regional practice/local labeling (4.9–23.2% across the groups).

Table 1. Baseline characteristics and lipid parameters in patients with or without ASCVD and/or HeFH patients (randomized population)

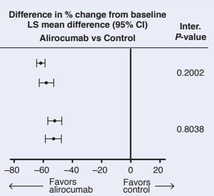
	With ASCVD		Without ASCVD		HeFH with ASCVD		HeFH without ASCVD	
	Alirocumab (n=1615)	Placebo (n=834)	Alirocumab (n=709)	Placebo (n=341)	Alirocumab (n=370)	Placebo (n=205)	Alirocumab (n=468)	Placebo (n=214)
Age, years, mean (SD)	61.3 (9.9)	61.3 (9.6)	52.6 (13.0)	52.7 (13.0)	56.9 (10.7)	57.4 (9.6)	49.2 (12.7)	48.5 (12.4)
Males, n (%)	1073 (66.4)	552 (66.2)	342 (48.2)	160 (46.9)	227 (61.4)	123 (60.0)	224 (47.9)	105 (49.1)
Race, White, n (%)	1499 (92.8)	780 (93.5)	640 (90.3)	292 (85.6)	349 (94.3)	192 (93.7)	447 (95.5)	196 (91.6)
BMI, kg/m^2, mean (SD)	30.1 (5.4)	30.3 (5.4)	30.0 (6.0)	30.5 (6.2)	29.2 (4.8)	30.0 (5.2)	28.8 (5.1)	28.4 (4.9)
Diabetes, n (%)	440 (27.2)	223 (26.7)	261 (36.8)	133 (39.0)	46 (12.4)	37 (18.0)	40 (8.5)	18 (8.4)
ASCVD, n (%)	1615 (100.0)	834 (100.0)	0	0	370 (100.0)	205 (100.0)	0	0
HeFH, n (%)	370 (22.9)	205 (24.6)	468 (66.0)	214 (62.8)	370 (100.0)	205 (100.0)	468 (100.0)	214 (100.0)
High statin intensity, n (%)	910 (56.3)	492 (59.0)	417 (58.8)	190 (55.7)	324 (87.6)	177 (86.3)	339 (72.4)	159 (74.3)
Moderate statin intensity, n (%)	471 (29.2)	227 (27.2)	179 (25.2)	87 (25.5)	26 (7.0)	17 (8.3)	84 (17.9)	32 (15.0)
Ezetimibe and other LLTs other than statin, n (%)	589 (36.5)	318 (38.1)	293 (41.3)	143 (41.9)	244 (65.9)	145 (70.7)	256 (54.7)	119 (55.6)
LDL-C, mg/dL, mean (SD)	120.1 (41.3)	122.8 (44.5)	142.1 (53.1)	136.5 (44.0)	148.1 (53.0)	151.0 (57.1)	155.9 (55.5)	148.3 (44.9)

High-intensity statin therapy was defined as taking atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg at randomization.
Moderate-intensity statin therapy was defined as taking atorvastatin 20–<40 mg, rosuvastatin 10–<20 mg, or simvastatin 40–<80 mg at randomization.

Efficacy

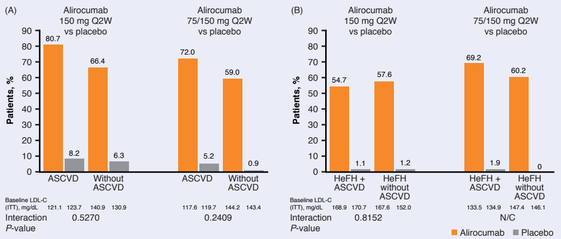
- LDL-C reduction from baseline at Week 24 ranged from 46.8% to 51.3% with alirocumab 75/150 mg and 54.1% to 61.8% with alirocumab 150 mg in the patient subgroups analyzed and was sustained for 52–78 weeks. There was no difference in alirocumab efficacy based on ASCVD and/or HeFH status (interaction *P*-value >0.05 for all, Figure 1).
- There was no difference in percentage of patients achieving LDL-C goal based on their ASCVD and/or HeFH status (interaction *P*-value >0.05 for all, Figure 2).

Figure 1. Percent change from baseline in calculated LDL-C at Week 24 (ITT analysis): (A) subgroup analysis by ASCVD status and (B) subgroup analysis of HeFH patients by ASCVD status



Panel A includes both HeFH and non-FH patients from LONG TERM and HIGH FH (alirocumab 150 mg Q2W) and FH I, FH II, and COMBO I (alirocumab 75/150 mg Q2W). Panel B includes only HeFH patients from LONG TERM and HIGH FH (alirocumab 150 mg Q2W) and FH I and FH II (alirocumab 75/150 mg Q2W). Alirocumab 75/150 mg Q2W = patients received alirocumab 75 mg Q2W with possible dose increase at Week 12 depending on LDL-C values at Week 8. FH, familial hypercholesterolemia.

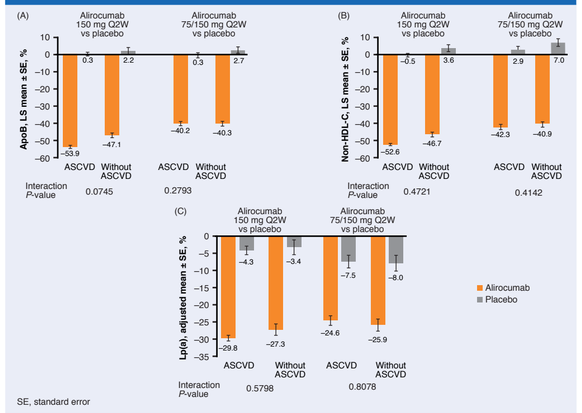
Figure 2. Proportion of patients achieving LDL-C <70 mg/dL at Week 24 based on (A) ASCVD and (B) HeFH with or without ASCVD (ITT analysis logistic regression with multiple imputation)



N/C, not computable. Note: Multiple imputation method is used to address missing values in the ITT population. Combined estimate for proportion of patients was obtained by averaging all the imputed proportions of patients reaching the level of interest. For HeFH patients with or without ASCVD, it is not possible to provide an interaction *P*-value since there is a quasi-complete separation of the data that prevents fitting the statistical model of logistic regression used for the analysis.

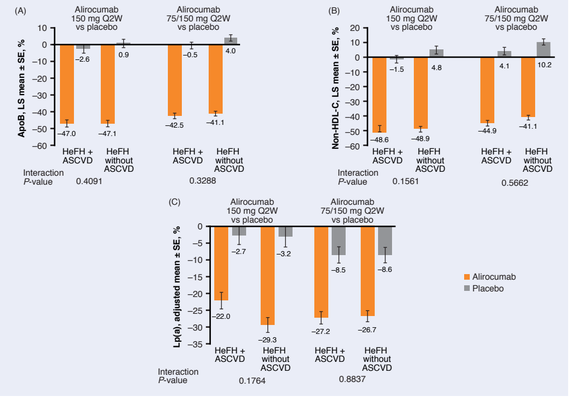
- Significant mean percent changes from baseline up to Week 24 in ApoB, non-HDL-C, and Lp(a) were observed at both doses of alirocumab versus placebo and did not differ based on ASCVD and/or HeFH status (interaction *P*-value >0.05 for all, Figures 3 and 4).
- Alirocumab treatment in patients based on ASCVD and/or HeFH status resulted in similar reductions in triglyceride levels and ranged from 7–15.7% (*P*s≤0.006 vs control; interaction *P*-value >0.05 for all).

Figure 3. Mean percent change from baseline up to Week 24 in (A) ApoB, (B) non-HDL-C, and (C) Lp(a) based on ASCVD status



SE, standard error

Figure 4. Mean percent change from baseline up to Week 24 in (A) ApoB, (B) non-HDL-C, and (C) Lp(a), based on HeFH status



Safety

- In the overall patient pool from the five trials (i.e. not grouped by ASCVD or HeFH status), overall rates of treatment-emergent adverse events (TEAEs) were 79.9% with alirocumab versus 81.3% with placebo, serious adverse events (SAEs) were 16.6% versus 17.2%, deaths were 0.7% versus 1.1%, and discontinuations were 6.2% versus 5.7%, respectively.
- TEAEs occurring more frequently (≥5.0%) with alirocumab versus placebo were nasopharyngitis (12.6% vs 12.1%), influenza (6.3% vs 5.4%), diarrhea (5.3% vs 4.9%), and injection-site reaction (7.2% vs 5.3%).
- Overall, alirocumab and placebo showed similar safety profiles in all patient subgroups analyzed based on ASCVD and/or HeFH status, except for a higher rate of injection-site reactions with alirocumab compared with placebo (Table 2).

Table 2. Safety data in patients based on ASCVD and HeFH status (safety population)

	With ASCVD		Without ASCVD		HeFH with ASCVD		HeFH without ASCVD	
n (%)	Alirocumab (n=1611)	Placebo (n=834)	Alirocumab (n=707)	Placebo (n=340)	Alirocumab (n=370)	Placebo (n=205)	Alirocumab (n=467)	Placebo (n=213)
TEAEs	1299 (80.6)	671 (80.5)	552 (78.1)	283 (83.2)	305 (82.4)	171 (83.4)	369 (79.0)	176 (82.6)
Treatment-emergent SAEs	321 (19.9)	168 (20.1)	64 (9.1)	34 (10.0)	76 (20.5)	38 (18.5)	38 (8.1)	17 (8.0)
TEAEs leading to death	13 (0.8)	12 (1.4)	3 (0.4)	1 (0.3)	5 (1.4)	2 (1.0)	2 (0.4)	0
TEAEs leading to discontinuation	105 (6.5)	52 (6.2)	39 (5.5)	15 (4.4)	15 (4.1)	8 (3.9)	18 (3.9)	7 (3.3)
Injection site reaction	105 (6.5)	36 (4.3)	62 (8.8)	26 (7.6)	36 (9.7)	13 (6.3)	59 (12.6)	23 (10.8)

Conclusions

- Alirocumab treatment for 52–78 weeks resulted in significant and substantial LDL-C-lowering in high-risk patients with ASCVD and/or HeFH who required further reduction in LDL-C despite maximally tolerated doses of statin therapy with or without other LLT.
- Whether this translates into a greater benefit in relation to cardiovascular events is being evaluated in ODYSSEY OUTCOMES (~18,000 patients with recent acute coronary syndrome).

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