Consistent Low-Density Lipoprotein Cholesterol Lowering Efficacy of Alirocumab in High and Very-High Cardiovascular Risk Patients with Low-Density Lipoprotein Cholesterol >100/70 mg/dL at Baseline

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Background

- Patients with uncontrolled low-density lipoprotein cholesterol (LDL-C) despite maximally tolerated statins may require additional non-statin lipid-lowering therapy to reduce their risk of atherosclerotic cardiovascular disease (ASCVD).[1,2]
  - The American College of Cardiology (ACC) expert consensus decision pathway allows for treatment with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors such as alirocumab in certain patients, including those with heterozygous familial hypercholesterolemia (HeFH) or ASCVD without comorbidities and LDL-C >100 mg/dL, and those with ASCVD and comorbidities or HeFH and LDL-C >70 mg/dL, who are receiving maximally tolerated statin therapy.[2]
- In the ODYSSEY studies, alirocumab significantly reduced LDL-C in patients with hyperlipidemia.[3–9]
- This pooled analysis examined the efficacy and safety of alirocumab among a subgroup of patients from the ODYSSEY studies, estimated to be at high or very-high risk of ASCVD events (according to definitions from a systematic review[10]), with baseline LDL-C >100 or >70 mg/dL on statin (mostly maximally tolerated statin) with or without other lipid-lowering therapies.

Methods

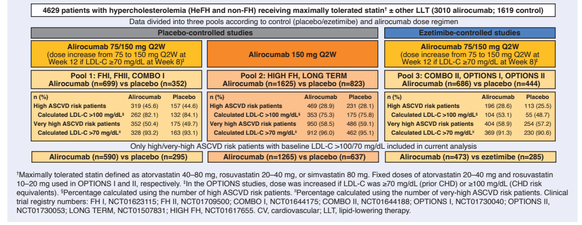
- This analysis used pooled data from eight Phase 3 ODYSSEY trials (Figure 1).[3–9]
  - Patients received alirocumab or control (placebo or ezetimibe) for 24–104 weeks, with statin ± other lipid-lowering therapies. Statin was at maximally tolerated dose in all trials except OPTIONS I&II (Figure 1).
  - In six of the trials, alirocumab 75 mg every 2 weeks (Q2W) was increased to 150 mg Q2W at Week 12 if at Week 8 LDL-C levels were ≥70/100 mg/dL, depending on cardiovascular risk (OPTIONS I&II), or if LDL-C levels were ≥70 mg/dL (COMBO I&II and FH I&II).
  - The LONG TERM and HIGH FH trials used alirocumab 150 mg Q2W throughout.
  - Only patients with baseline LDL-C >100 mg/dL (high or very-high ASCVD risk) or >70 mg/dL (very-high ASCVD risk only) were included in this analysis.

Definitions of high and very-high ASCVD risk

- Estimated level of ASCVD risk was assigned to the selected ODYSSEY patients based on new methods developed in a systematic review by Robinson et al (2016),[10] in which patients classified into ACC expert consensus decision pathway groups[2] were assigned a group-specific estimated level of risk of (new or recurring) ASCVD events (ASCVD risk), according to published ASCVD event rates in statin monotherapy arms from randomized cardiovascular outcomes trials, or cardiovascular disease (CVD) event rates in cohort studies.[10] Accordingly, patients were placed in the "high" or "very-high" ASCVD risk category if their extrapolated 10-year ASCVD risk was 20% to <30% or ≥30%, respectively.
  - According to the value of their extrapolated risk, the following patients were categorized as 'high ASCVD risk': a) CVD without diabetes or chronic kidney disease (CKD), b) CVD in a single vascular bed (coronary heart disease [CHD], ischemic stroke or peripheral arterial disease [PAD]), or c) primary prevention HeFH.
  - According to the value of their extrapolated risk, the following patients were categorized as 'very-high ASCVD risk': with CVD and one of the following: a) diabetes; b) moderate CKD; c) HeFH; d) PAD or stroke; e) poorly controlled risk factors (systolic blood pressure >140 mmHg or smoker), and patients with recent acute coronary syndrome (acute myocardial infarction or unstable angina within 1 year). These ASCVD risk definitions differ from those used in the ODYSSEY program, described elsewhere.[3–9]

- Baseline and efficacy data were pooled according to control group and alirocumab dose (Figure 1). Efficacy analyses at Week 24 were performed in the intention-to-treat (ITT) population (regardless of treatment discontinuation) using a mixed model for repeated measures to handle missing values. Safety data were pooled according to control group.

Figure 1. Pooling strategy and patient disposition (randomized population)



†Maximally tolerated statin defined as atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg. Fixed doses of atorvastatin 20–40 mg and rosuvastatin 10–20 mg used in OPTIONS I and II, respectively. ‡In the OPTIONS studies, dose was increased if LDL-C was ≥70 mg/dL (prior CHD) or ≥100 mg/dL (CHD risk equivalents). §Percentage calculated using the number of high ASCVD risk patients. ¶Percentage calculated using the number of very-high ASCVD risk patients. Clinical trial registry numbers: FH I, NCT01623115; FH II, NCT01709500; COMBO I, NCT01644175; COMBO II, NCT01644188; OPTIONS I, NCT01730040; OPTIONS II, NCT01730053; LONG TERM, NCT01507831; HIGH FH, NCT01617655. CV, cardiovascular; LLT, lipid-lowering therapy.

Results

Baseline characteristics

- In total, 3545 high and very-high ASCVD risk patients with baseline LDL-C >100 mg/dL or >70 mg/dL were included in the analysis (Figure 1). Baseline characteristics are shown in Table 1.

Table 1. Baseline characteristics of high/very high ASCVD risk patients with baseline LDL-C >100/70 mg/dL

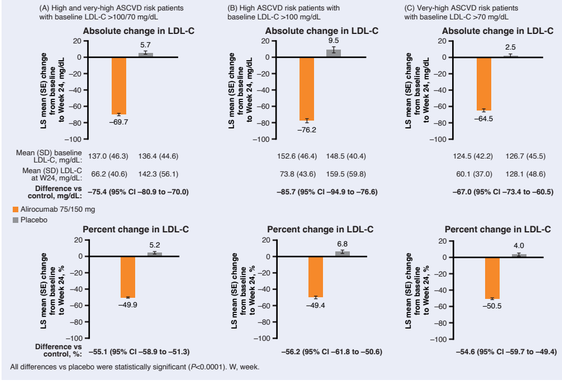
	Pool 1 (FHI & II, COMBO I)		Pool 2 (HIGH FH, LONG TERM)		Pool 3 (COMBO II, OPTIONS I & II)	
	Alirocumab 75/150 mg (n=590)	Placebo (n=295)	Alirocumab 150 mg (n=1265)	Placebo (n=637)	Alirocumab 75/150 mg (n=473)	Ezetimibe (n=285)
Age, years, mean (SD)	54.9 (13.0)	54.4 (12.5)	59.9 (10.9)	60.0 (10.4)	61.6 (9.8)	61.8 (10.2)
Male, n (%)	337 (57.1)	179 (60.7)	803 (63.5)	399 (62.6)	344 (72.7)	192 (67.4)
BMI, kg/m^2, mean (SD)	29.7 (5.3)	29.6 (5.6)	29.8 (5.6)	29.9 (4.9)	30.0 (5.5)	30.6 (5.5)
HeFH, n (%)	456 (77.3)	234 (79.3)	332 (26.2)	166 (26.1)	26 (5.5)	18 (6.3)
High-intensity statin,† n (%)	468 (79.3)	242 (82.0)	644 (50.9)	331 (52.0)	246 (52.0)	124 (43.5)
Non-statin LLT,‡ n (%)	353 (59.8)	189 (64.1)	381 (30.1)	198 (31.1)	46 (9.7)	27 (9.5)
No prior CVD	244 (41.4)	123 (41.7)	180 (14.2)	75 (11.8)	15 (3.2)	13 (4.6)
Prior CVD	346 (58.6)	172 (58.3)	1085 (85.8)	562 (88.2)	458 (96.8)	272 (95.4)
History of CHD§	320 (92.5)	166 (96.5)	958 (88.3)	506 (90.0)	427 (93.2)	256 (94.1)
History of ischemic stroke or TIA§	36 (10.4)	10 (5.8)	149 (13.7)	67 (11.9)	47 (10.3)	26 (9.6)
History of PAD§	55 (15.9)	25 (14.5)	165 (15.2)	89 (15.8)	58 (12.7)	35 (12.9)
≥1 comorbidity¶	250 (72.3)	122 (70.9)	876 (80.7)	463 (82.4)	399 (87.1)	237 (87.1)

†High-intensity statin defined as atorvastatin 40–80 mg daily, rosuvastatin 20–40 mg daily, or simvastatin 80 mg daily. ‡In combination with statins or without statins; not including ezetimibe for Pool 3. §Calculated as a percentage of patients with prior CVD. ¶Hypertension, diabetes, or moderate CKD.
BMI, body mass index; SD, standard deviation; TIA, transient ischemic attack.

Efficacy

- Pool of alirocumab 75/150 mg versus placebo at Week 24:
  - Similar absolute and percent reductions from baseline in LDL-C compared with the overall analysis were observed when subgroups of patients at high ASCVD risk with baseline LDL-C >100 mg/dL and very-high ASCVD risk with baseline LDL-C >70 mg/dL were analyzed separately (Figure 2).

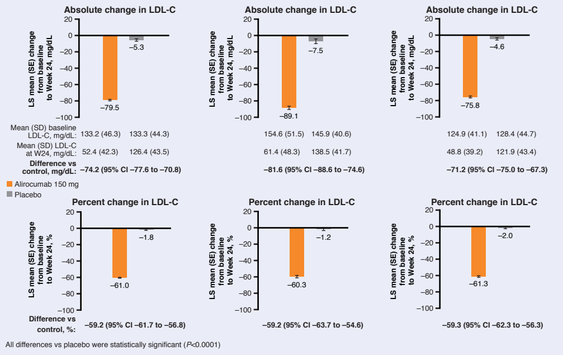
Figure 2. Alirocumab 75/150 mg vs placebo: Absolute and percent change in calculated LDL-C from baseline to Week 24 in high/very high ASCVD risk patients with baseline LDL-C >100/70 mg/dL (ITT analysis)



All differences vs placebo were statistically significant (P<0.0001). W, week.

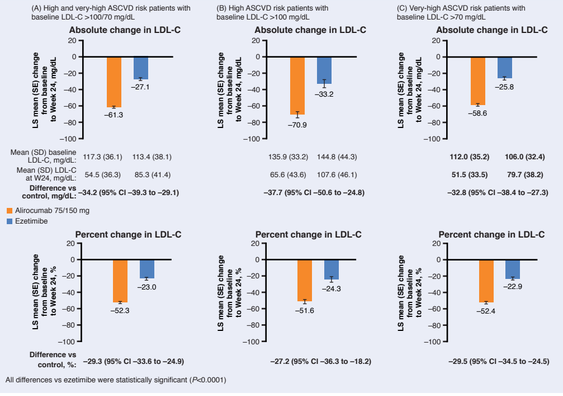
- Pool of alirocumab 150 mg versus placebo at Week 24:
  - Absolute and percent LDL-C reductions were similar to the overall analysis in the separate analyses of high and very-high ASCVD risk patients (Figure 3).
- Pool of alirocumab 75/150 mg versus ezetimibe at Week 24:
  - Absolute and percent LDL-C reductions were similar to the overall analysis in the separate analyses of patients at high and very-high ASCVD risk (Figure 4).

Figure 3. Alirocumab 150 mg vs placebo: Absolute and percent change in calculated LDL-C from baseline to Week 24 in high/very high ASCVD risk patients with baseline LDL-C >100/70 mg/dL (ITT analysis)



All differences vs placebo were statistically significant (P<0.0001)

Figure 4. Alirocumab 75/150 mg Q2W vs ezetimibe: Absolute and percent change in calculated LDL-C from baseline to Week 24 in high/very high ASCVD risk patients with baseline LDL-C >100/70 mg/dL (ITT analysis)



All differences vs ezetimibe were statistically significant (P<0.0001)

Safety

- The incidence of treatment-emergent adverse events (TEAEs) was comparable across groups, with 77.5% of alirocumab-treated patients and 77.6% of placebo-treated patients in the placebo-controlled study pool, and 68.1% and 65.1% of alirocumab- and ezetimibe-treated patients in the ezetimibe-controlled study pool, respectively, reporting TEAEs (Table 2).
- Injection-site reactions occurred in 7.9% of patients in the alirocumab group versus 5.3% in the control group in the placebo-controlled study pool; corresponding values for the ezetimibe-controlled study pool were 2.7% and 1.1%.

Table 2. Safety summary in high/very high ASCVD risk patients with baseline LDL-C >100/70 mg/dL (safety population)

	Pool of placebo-controlled studies		Pool of ezetimibe-controlled studies	
n (%)	Alirocumab (n=1849)	Placebo (n=931)	Alirocumab (n=473)	Ezetimibe (n=284)
Any TEAE	1433 (77.5)	722 (77.6)	322 (68.1)	185 (65.1)
Any treatment emergent SAE	282 (15.3)	150 (16.1)	74 (15.6)	47 (16.5)
Any TEAE leading to death	11 (0.6)	10 (1.1)	2 (0.4)	6 (2.1)
Any TEAE leading to permanent treatment discontinuation	98 (5.3)	47 (5.0)	29 (6.1)	19 (6.7)
TEAEs occurring in ≥5% patients†				
Nasopharyngitis	214 (11.6)	107 (11.5)	19 (4.0)	12 (4.2)
Injection-site reaction	146 (7.9)	49 (5.3)	13 (2.7)	3 (1.1)
Upper respiratory tract infection	124 (6.7)	66 (7.1)	27 (5.7)	15 (5.3)
Influenza	120 (6.5)	51 (5.5)	15 (3.2)	8 (2.8)
Headache	90 (4.9)	51 (5.5)	16 (3.4)	11 (3.9)
Diarrhea	93 (5.0)	40 (4.3)	9 (1.9)	6 (2.1)
Arthralgia	82 (4.4)	52 (5.6)	17 (3.6)	8 (2.8)
Back pain	80 (4.3)	52 (5.6)	13 (2.7)	7 (2.5)
Accidental overdose	21 (1.1)	11 (1.2)	27 (5.7)	16 (5.6)

†Only events with a frequency of at least 5% in at least one treatment group are shown for each pool. SAE, serious adverse event.

Conclusions

- Improvements in LDL-C observed with alirocumab were consistent in subgroups of high and very-high ASCVD risk patients with baseline LDL-C >100 or >70 mg/dL, and were similar to those seen in the overall ODYSSEY study population.[3–9]
- In a recent meta-analysis of LDL-C lowering drugs, including PCSK9 monoclonal antibodies, ezetimibe, and statins, each 1 mmol/L (39 mg/dL) reduction in LDL-C was associated with a 23% reduction in major CVD events.[11]
- The safety profile of alirocumab observed in these patients was also similar to that seen in the overall studies.[3–9] These findings support the benefits of alirocumab in high and very-high ASCVD risk patients with baseline LDL-C >100 or >70 mg/dL.

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Acknowledgements

This study was funded by Sanofi and Regeneron Pharmaceuticals, Inc. Medical writing support and typesetting was provided by Prime, Knutsford, UK, funded by Sanofi and Regeneron Pharmaceuticals, Inc.

Disclosures

Jennifer G Robinson: Consultant fees/honoraria from Akcea/Ionis, Amgen, Eli Lilly and Company, Esperion, Merck & Co., Pfizer, Sanofi, Regeneron Pharmaceuticals Inc.; research grants from Amarin, Amgen, AstraZeneca, Eli Lilly and Company, ESAI, Esperion, GlaxoSmithKline, Merck, Pfizer, Regeneron Pharmaceuticals Inc., Sanofi-Aventis, Takeda. **François Schiele:** Consultant fees/honoraria from Amgen, AstraZeneca, Merck & Co., Pfizer, Sanofi; research grants from Amgen, AstraZeneca, Eli Lilly and Company, Merck, Pfizer, Sanofi-Aventis. **Ulrich Laufs:** Consultant fees/honoraria from Amgen, MSD, Sanofi. **Maddalena Lettino:** Consultant fees/honoraria from AstraZeneca, BMS, Boehringer, Bayer, Pfizer, Sanofi, Aspen, Eli Lilly, Daiichi Sankyo. **Velichka Valcheva:** Employee of and stockholder in Sanofi. **Sophie Guillonneau:** Employee of and stockholder in Sanofi. **Şerban R Iorga:** Employee of and stockholder in Regeneron Pharmaceuticals, Inc. **Nadège Narcisse:** Employee of Keyrus Biopharma, contracted to Sanofi. **Keith A A Fox:** Consultant fees and advisory board member for Sanofi and Regeneron. Outside the scope of this work, consultant fees and advisory board member for Bayer/Janssen and AstraZeneca.

Poster presented at the American College of Cardiology 66th Annual Scientific Session, March 17–19 2017, Washington, DC, USA