# Alirocumab Reduces Major Adverse Cardiovascular Events in Individuals with Atherosclerotic Cardiovascular Disease: A Post-Hoc Analysis of ODYSSEY LONG TERM

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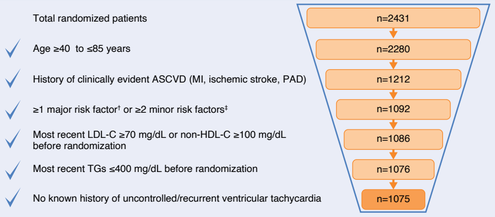
## Background

- Individuals with elevated low-density lipoprotein cholesterol (LDL-C) and atherosclerotic cardiovascular disease (ASCVD) are at increased risk for recurrent cardiovascular events.[1,2]
- The American College of Cardiology expert consensus writing committee suggests considering proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in patients with ASCVD or history of untreated LDL-C ≥190 mg/dL who might benefit from additional LDL-C-lowering.[3]
- The 78-week ODYSSEY LONG TERM study demonstrated a 61.0% reduction in LDL-C with the PCSK9 inhibitor alirocumab 150 mg every 2 weeks (Q2W) as add-on therapy to maximally tolerated statin ± other lipid-lowering therapies in high-risk individuals with or without ASCVD (placebo: 0.8% increase).[4]
  - A *post-hoc* analysis of LONG TERM showed a reduced rate of major adverse cardiovascular events (MACE; death from coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) in the alirocumab group (27 of 1550 patients [1.7%]) versus placebo (26 of 788 patients [3.3%]; hazard ratio [HR]: 0.52; 95% confidence interval [CI]: 0.31–0.90).
- In this analysis, we present data on the efficacy and safety of alirocumab versus placebo among the subgroup of individuals with ASCVD, plus at least one additional risk factor as shown in Figure 1, from the ODYSSEY LONG TERM study.

## Methods

- In this *post-hoc* analysis, a subset of individuals with ASCVD from LONG TERM (NCT01507831) was defined according to the inclusion criteria presented in Figure 1.
  - LDL-C percent reductions and occurrence of MACE were assessed for all individuals in this patient subset, both with and without heterozygous familial hypercholesterolemia (HeFH).
  - A Cox proportional hazards model was used to compare rates of MACE between alirocumab and placebo.
  - Baseline and overall safety data were assessed for all subjects.

**Figure 1.** Summary of inclusion criteria for this *post-hoc* subgroup analysis




†Including diabetes type 1 or 2, age ≥65 years at randomization, MI or non-hemorrhagic stroke within 6 months of screening, additional history of MI or stroke, daily smoking, history of PAD if selected by history of MI, or stroke. ‡Including history of non-MI related coronary revascularization, residual CAD with ≥40% stenosis in ≥2 large vessels, most recent HDL-C <40 mg/dL for men and <50 mg/dL for women before randomization, most recent hsCRP >2 mg/L before randomization, metabolic syndrome, most recent LDL-C ≥130 mg/dL, or non-HDL-C ≥160 mg/dL before randomization. CAD, coronary arterial disease; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; MI, myocardial infarction; PAD, peripheral artery disease; TGs, triglycerides.

## Results

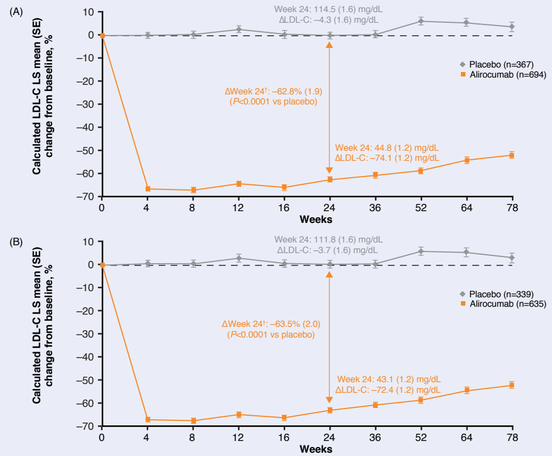
- Among this subgroup of participants with ASCVD, baseline characteristics were similar in the alirocumab (n=702) and placebo (n=373) groups (Table 1).
  - 8.4% and 7.5% of subjects had HeFH in the alirocumab and placebo groups, respectively.
  - All patients received statin therapy, including 45.9% and 49.6% receiving high-intensity statin, and 10.4% and 11.8% received ezetimibe at baseline in the alirocumab and placebo groups, respectively.
  - The mean LDL-C levels were 118.2 mg/dL and 119.9 mg/dL in the alirocumab and placebo groups, respectively.
- LDL-C reductions with alirocumab 150 mg Q2W were observed from Week 4 and sustained for up to 78 weeks in all subjects with ASCVD (Figure 2).
  - From Weeks 4 to 78, alirocumab reduced LDL-C levels by 62.1–79.2 mg/dL in the total ASCVD subgroup population and 60.4–77.5 mg/dL in those with ASCVD without HeFH.

**Table 1.** Baseline characteristics of individuals with ASCVD from LONG TERM (randomized population)

| | LONG TERM sub-group analysis (n=1075) | |
|---|---|---|
| | Placebo (n=373) | Alirocumab (n=702) |
| Age, years, mean (SD) | 63.0 (9.5) | 62.5 (9.3) |
| Gender, male, n (%) | 249 (66.8) | 489 (69.7) |
| Hypertension, n (%) | 311 (83.4) | 546 (77.8) |
| Diabetes, n (%) | 137 (36.7) | 230 (32.8) |
| Current smoker, n (%) | 91 (24.4) | 187 (26.6) |
| History of MI, n (%) | 272 (72.9) | 514 (73.2) |
| History of ischemic stroke, n (%) | 74 (19.8) | 151 (21.5) |
| History of PAD, n (%) | 93 (24.9) | 152 (21.7) |
| Individuals with HeFH, n (%) | 28 (7.5) | 59 (8.4) |
| Statin, n (%) | 373 (100) | 702 (100) |
| High intensity | 185 (49.6) | 322 (45.9) |
| Moderate intensity | 122 (32.7) | 254 (36.2) |
| Low intensity | 66 (17.7) | 126 (17.9) |
| Ezetimibe, n (%) | 44 (11.8) | 73 (10.4) |
| LDL-C, mg/dL, mean (SD) | 119.9 (39.1) | 118.2 (35.9) |
| Total cholesterol, mg/dL, mean (SD) | 199.1 (45.4) | 197.0 (40.6) |
| HDL-C, mg/dL, mean (SD) | 48.7 (12.0) | 49.1 (12.1) |
| TGs, mg/dL, median (Q1:Q3) | 134.5 (101.8:185.0) | 133.6 (95.6:181.4) |

SD, standard deviation.

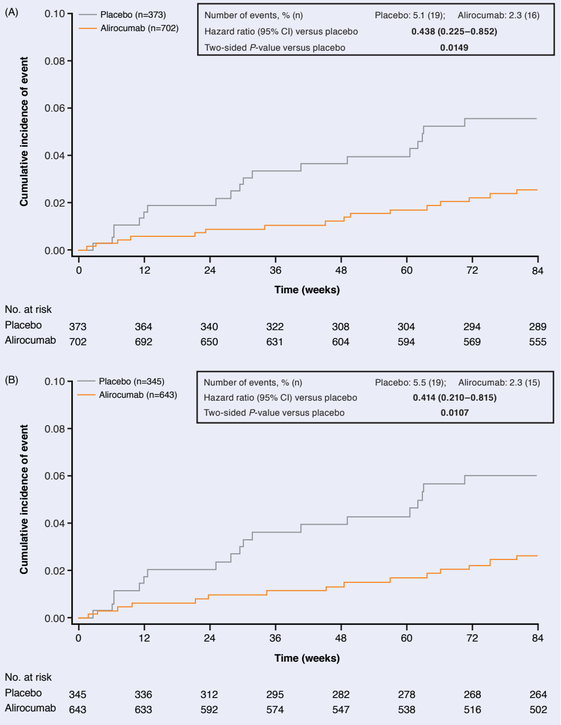
**Figure 2.** Percent change in calculated LDL-C over time: LONG TERM *post-hoc* analysis of individuals with ASCVD (A) with and without HeFH, and (B) without HeFH (intention-to-treat population)




For Week 24, values of absolute LDL-C levels and absolute reduction (ΔLDL-C) for alirocumab and placebo groups are presented on the graphs.
†Percent change in calculated LDL-C from baseline to Week 24 for alirocumab versus placebo. Least-squares (LS) means and standard errors (SE) taken from a mixed-effect model with repeated measures analysis.

- Kaplan-Meier estimates for the time to first event were significantly lower for the alirocumab group versus placebo in subjects with ASCVD from LONG TERM (Figure 3).
  - Treatment-emergent MACE occurred in 2.3% (alirocumab) versus 5.1% (placebo) of all individuals with ASCVD, and in 2.3% (alirocumab) versus 5.5% (placebo) of those with ASCVD without HeFH.
  - For all participants with ASCVD, the HR versus placebo was 0.438 (95% CI 0.225–0.852) and for those with ASCVD without HeFH, the HR versus placebo was 0.414 (95% CI 0.210–0.815).
  - In all individuals with ASCVD, a 26.5% reduction in MACE (95% CI 6.8–42.0%; *P*=0.0109) was observed for each 38.6 mg/dL decrease in LDL-C during the treatment period.
  - In individuals with ASCVD and without HeFH there was a 33.7% reduction in MACE, with 95% CI of 14.4–48.6% (*P*=0.0016) for each 38.6 mg/dL decrease in LDL-C during the treatment period.

**Figure 3.** Kaplan-Meier cumulative incidence curve for time to first event in individuals with ASCVD (A) with and without HeFH, and (B) without HeFH (safety population)




- Overall safety was similar in the alirocumab and placebo groups, with 81.8% and 81.5% of participants with ASCVD experiencing treatment-emergent adverse events (TEAEs), respectively (Table 2).

**Table 2.** Summary of overall safety parameters in individuals with ASCVD from LONG TERM (safety population)

| | LONG TERM subgroup analysis (n=1075) | |
|---|---|---|
| n (%) | Placebo (n=373) | Alirocumab (n=702) |
| TEAEs | 304 (81.5) | 574 (81.8) |
| Treatment-emergent SAEs | 87 (23.3) | 158 (22.5) |
| TEAEs leading to death | 5 (1.3) | 2 (0.3) |
| TEAEs leading to treatment discontinuation | 29 (7.8) | 50 (7.1) |
| TEAEs occurring in ≥5% of individuals by preferred term | | |
| Nasopharyngitis | 44 (11.8) | 102 (14.5) |
| Upper respiratory tract infection | 30 (8.0) | 49 (7.0) |
| Back pain | 26 (7.0) | 35 (5.0) |
| Diarrhea | 25 (6.7) | 42 (6.0) |
| Urinary tract infection | 24 (6.4) | 41 (5.8) |
| Pain in extremity | 21 (5.6) | 26 (3.7) |
| Fall | 21 (5.6) | 24 (3.4) |
| Myalgia | 9 (2.4) | 38 (5.4) |
| Bronchitis | 19 (5.1) | 34 (4.8) |

SAE, serious adverse event

## Conclusions

- In a subset of individuals with ASCVD from the ODYSSEY LONG TERM study who received maximally tolerated statin, alirocumab substantially reduced LDL-C levels and the risk of MACE versus placebo (absolute reduction of 56% in MACE [with a 74.1 mg/dL LDL-C reduction at Week 24 in the alirocumab group] and a 26.5% reduction in MACE for each 38.6 mg/dL decrease); similar findings were observed in individuals without HeFH.
  - In comparison, the Cholesterol Treatment Trialists' meta-analysis (N=90,056) observed a 21% reduction in major cardiovascular events per 39 mg/dL reduction in LDL-C from statins.[5]
- Alirocumab was generally well tolerated in this patient subgroup.
- These findings from this *post-hoc* analysis are consistent with findings from the overall LONG TERM patient population, and support the "LDL-C hypothesis" that excess LDL-C is a causal factor in ASCVD development.[6]

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**William J Sasiela:** was an employee and stockholder of Regeneron Pharmaceuticals, Inc. at the time of this analysis.
**Tu Nguyen:** employee and stockholder in Sanofi.
**Jonas Mandel:** contractor for Sanofi.
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