Use of High-Intensity Statin Therapy Post-Acute Coronary Syndrome in the Ongoing ODYSSEY OUTCOMES Trial of Alirocumab, a Proprotein Convertase Subtilisin/Kexin Type 9 Monoclonal Antibody, versus Placebo: Interim Baseline Data

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Background

- Despite intensive statin therapy after acute coronary syndromes (ACS), risk for recurrent cardiovascular (CV) events remains high and related to low-density lipoprotein cholesterol (LDL-C) levels
- The ODYSSEY OUTCOMES trial tests the hypothesis that alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9) that produces substantial and sustained LDL-C reductions, improves CV outcomes after ACS

Methods

- **Study population:** At 1,297 participating sites in 57 countries, 18,536 patients have been randomized 4-52 weeks after ACS to biweekly treatment with alirocumab or matching placebo. All have recent ACS and higher than desirable lipid levels (LDL-C≥70 mg/dL [1.81 mmol/L], non-high-density lipoprotein [HDL-C]≥100 mg/dL [2.59 mmol/L], or apolipoprotein B [apoB]≥80 mg/dL [0.8 g/L]) despite atorvastatin 40-80 mg/day, rosuvastatin 20-40 mg/day, or maximum prudent and tolerated dose of one of these statins ± other lipid modifying therapy
- **Key exclusion criteria**: Uncontrolled hypertension, New York Heart Association (NYHA) congestive heart failure class III-IV or left ventricular ejection fraction (LVEF)<25%, history of hemorrhagic stroke, fasting triglycerides >400 mg/dL (4.52 mmol/L), hepatitis, estimated glomerular filtration rate <30 mL/min/1.73m^2
- **Treatment assignment:** Initial randomization to alirocumab 75 mg subcutaneously (SC) every 2 weeks or placebo
  - *Uptitration:* If LDL-C remains ≥50 mg/dL (1.29 mmol/L) at Month 1, patients are blindly uptitrated to alirocumab 150 mg SC every 2 weeks or ongoing placebo
  - *Downtitration:* If 2 consecutive direct measurements of LDL-C are <25 mg/dL (0.65 mmol/L), patients are monitored by an independent, blinded safety physician. If alirocumab dose is 150 mg, it is downtitrated blindly to 75 mg SC every 2 weeks. If 2 consecutive measurements of LDL-C are <15 mg/dL (0.39 mmol/L) on alirocumab dose 75 mg, treatment is blindly changed to placebo for the remainder of the study
- **Primary outcome: T**ime to first occurrence of coronary heart disease death, non-fatal MI, ischemic stroke, or hospitalization for unstable angina

Methods (Continued)

- **Follow-up:** Until the later of 1613 primary endpoints or 2 years from last patient randomized (except in China). With an assumed event rate of 11.4% at 4 years in the placebo group and 15% risk reduction with alirocumab, 1-sided p=0.025 and 1% loss to follow-up, 18,000 patients provide 90% power

Results

- Randomization began in November 2012 and was completed in November 2015, except in China where it is ongoing
- At randomization, high intensity statin (atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily) was used in 89%; of those, 94% remained on high-intensity at 12 months
- Median (IQR) baseline LDL-C was 87 (73-104) mg/dL (2.25 [1.89-2.69] mmol/L)

Table 1. Selected Baseline Characteristics

Interim Data (randomization ongoing in China)	Patients randomized (N=18,536)
Age, years - Median (interquartile range [IQR])	58 (52-65)
Male sex, n (%)	13873 (75)
Region, n (%)	
North America/South America	2871 (15)/2588 (14)
Western Europe/Eastern Europe	4172 (23)/5437 (29)
Asia/Rest of World	1905 (10)/1560 (9)
Body Mass Index (BMI), kg/m^2 – Median (IQR)	28 (25-31)
Cardiovascular (CV) risk factors, n (%)	
History of hypertension	11877 (64)
History of diabetes mellitus	4501 (24)
Current cigarette smoker	4449 (24)
CV history prior to index event, n (%)	
Myocardial infarction	3652 (20)
Coronary revascularization (PCI and/or CABG)	3719 (20)
Ischemic stroke	484 (3)
Peripheral artery disease	719 (4)
Index ACS – Type and Procedures, n (%)	
Time, index ACS to randomization (median, months)	2.6
STEMI/NSTEMI/Unstable Angina	6329 (34)/ 9027 (49)/3152 (17)
Percutaneous coronary intervention (PCI)	12362 (67)
Coronary artery bypass graft surgery (CABG)	1018 (6)

Table 2. Selected Treatments and Lipid Values at Randomization

Selected therapy at randomization, n (%)	N=18,536
Acetylsalicylic acid (ASA; Aspirin™)	17649 (95)
P2Y$_{12}$ antagonist	16111 (87)
Beta-blocker	15600 (84)
Angiotensin Converting Enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)	14354 (77)
Lipid Modifying Therapy, n (%)	
Statin >3 months before index ACS	6064 (33)
Statin (atorvastatin or rosuvastatin, any intensity) at randomization	18036 (97)
Statin (high-intensity=atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day)	16565 (89)
Ezetimibe at randomization	545 (3)
Fasting Lipid values at randomization, mg/dL [mmol/L] – Median (IQR)	
Low-density lipoprotein-cholesterol (LDL-C)	87 (73-104) [2.25 (1.89-2.69)]
Non-high-density lipoprotein-cholesterol (Non-HDL-C)	115 (99-137) [2.97 (2.56-3.54)]
Apolipoprotein-B (Apo-B)	79 (69-93) [0.79 (0.69-0.93)]
High-density lipoprotein-cholesterol (HDL-C)	43 (36-50) [1.11 (0.93-1.29)]
Triglycerides	129 (94-182) [1.46 (1.06-2.05)]

Conclusion

- ODYSSEY OUTCOMES has randomized a high-risk population with recent ACS on intensive statin and guideline-based therapy and will determine whether the addition of PCSK9 antibody alirocumab reduces major CV events

Reference: Schwartz GG, Bessac L, Berdan LG, Bhatt DL, Bittner V, Diaz R, Goodman SG, Hanotin C, Harrington RA, Jukema JW, Mahaffey KW, Moryusef A, Pordy R, Roe MT, Rorick T, Sasiela WJ, Shirodaria C, Szarek M, Tamby JF, Tricoci P, White H, Zeiher A, Steg PG. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomes following acute coronary syndromes: Rationale and design of the ODYSSEY Outcomes trial. *Am Heart J* 2014;168:682-689.e1

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