ODYSSEY OUTCOMES was not designed to explore the safety and ASCVD efficacy at the lowest possible targeted LDL-C level that would achieve the greatest benefit

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Despite High Baseline Values, Alirocumab, Reached Very Low Atherogenic Cholesterol Levels, in Phase 3 ODYSSEY Trials

- Pooled data, post-hoc analysis of 10 double-blind trials of the PCSK9 alirocumab, involving 4974 patients (3182 taking alirocumab, 618 taking ezetimibe 1174 taking placebo,); 8 trials with background statin
- Despite statin ± ezetimibe, atherogenic cholesterol markers at baseline were above normal; LDL-C was ~126 mg/dL, non-HDL-C ~156 mg/dL and Apo B ~104 mg/dL
- Alirocumab 75/150 mg administered every 2 wks vs. control, for 24-104 wks for total of 6,699 patient-yrs of follow-up
- Alirocumab use, with/without ezetimibe, resulted in 48-55% lower LDL-C (mean ~60 mg/dL), 40-47% lower non-HDL-C (mean ~86 mg/dL) and 36-46% lower ApoB (mean ~60 mg/dL)
- The relationship between average on-treatment lipid levels and percent reductions in lipids from baseline were correlated with 4-point MACE (coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or unstable angina requiring hospitalization) in multivariable analyses
- The adjusted 4-point MACE rate by average achieved LDL-C during treatment showed a nearly linear continuous 24% lower event rate per 39 mg/dL between-group decrease in LDL-C [HR 0.76 (0.63 to 0.91)]
- The continuous relationship (p=0.0025 for trend) was noted at least down to 25 mg/dL LDL-C level and similar results were noted as low as Non-HDL-C of 50 mg/dL Apo B of 40 mg/dL

ODYSSEY OUTCOMES was not Designed to Explore Safety and ASCVD Efficacy at Lowest Possible Targeted LDL-C Level to Achieve Greatest Benefit

- While pooled analyses clearly demonstrated safety[2] and practicability of reducing atherogenic cholesterol markers to very low levels, i.e. LDL-C, 25 mg/dL; ApoB, 40 mg/dL; and non-HDL-C, 50 mg/dL[3]
  - ODYSSEY Outcomes[1] included 18,924 patients at 1,315 sites in 57 countries who had recent ACS within the previous 12 mos
- After 2-16 wks of intensive/maximally tolerated statin therapy (atorvastatin or rosuvastatin), eligible patients had residual LDL-C levels ≥70 mg/dL, non–HDL-C ≥100 mg/dL or apolipoprotein B ≥80 mg/dL
  - 29% of patients had diabetes
  - Patients randomized to either subcutaneous injections of alirocumab 75 mg every 2 wks (n=9,462) or placebo (n=9,462)

What was Different About ODYSSEY OUTCOMES?

- ODYSSEY Outcomes, was not designed to target LDL-C to a lowest goal, but rather to narrow, limited goal range (25 to 50 mg/dL)[4]
  - To maximize number of patients in the specific goal range, up-titration or down titration blinded dose titration algorithms were in place for targeted LDL-C
  - Alirocumab was up-titrated from every 2 wk-dosing of 75 mg -150 mg in patients with higher LDL-C ≥50 mg/dL
  - Alirocumab was down titrated in patients with consistent (2 consecutive LDL-C values) LDL-C levels <25 mg/dL with blinded dose tapering of 150 mg dose to 75 mg or blinded permanent discontinuation, switched to placebo, if <15 mg/dL
- The blinded switch to placebo occurred for 730 (7.7%) within alirocumab-allocated group
  - Number (%) dose-tapered from 150 - 75 mg is not reported

What was Different about ODYSSEY OUTCOMES? Potential Rationale

- These maneuvers should result in
  - Widened between-group LDL-C difference in patient group allocated to alirocumab at the highest LDL and
  - Narrowed between-group LDL-C difference in those achieving the lowest in-trial LDL-C levels

- Such differences would be expected to skew ASCVD benefits favorably for those with higher baseline LDL-C and unfavorably for those with lower baseline LDL-C

- Of interest, premature treatment discontinuation occurred for an additional 1,343 (14.2%) of alirocumab-allocated group, which could have reduced the ITT between group differences

ODYSSEY OUTCOMES: Key Results

- ↓LDL-C in alirocumab vs. placebo at 4 mos was 37.6 mg/dl vs. 93.3 mg/dl, (62.7% reduction); at 48 mos. 53.3 mg/dL vs. 101.4 mg/dl (54.7% reduction) [1]
- After median 2.8 yrs-F/U, LDL-C levels: 53.3 mg/dL (alirocumab) and 101.4 mg/dL placebo; absolute ↓54.7%
- ↑LDL-C over time in ITT analysis due to premature discontinuation of tx, ↓dose or substitution of placebo for alirocumab under blinded conditions, and attenuation of intensity of statin treatment
- At 2.8-yr median F/U duration, primary 5-point MACE was significantly lower in alirocumab group (9.5%) vs placebo (11.1%); 15% RRR
- Non-fatal MI, fatal & non-fatal stroke, any CVD event, any CHD event, major CHD event, and all-cause death, were significantly reduced by 14%, 27%, 13%, 12%, 12% and 15%, respectively
- 3-point MACE (CV death, non-fatal MI or non-fatal stroke) was not prespecified but could be estimated from Table 2, Schwartz GG et al 2018], for alirocumab up to 10.3% and placebo group up to 12.1%, (RRR ~15%)
- Placebo group extrapolated 10-year risk 3-point MACE of 43% is consistent with extreme risk

ODYSSEY OUTCOMES: A Prespecified Post Hoc Analysis

- Prespecified post hoc analysis by baseline LDL-C level: Patients with LDL-C ≥100 mg/dL experienced reductions in all endpoints
- ↓24% in MACE translated to absolute risk reduction (ARR) of 3.4%
  - ↓ CHD death 28% (ARR 0.9%)
  - ↓ CV death 31% (ARR 1.3 %)
  - ↓ all-cause death 28% (ARR 1.7%)
- Baseline LDL-C in ODYSSEY OUTCOMES: 92 mg/dL, 34 mg/dL lower than baseline (126 mg/dL) of its pooled phase 3 studies that reached LDL-C levels 25 mg/dL

Summary and Conclusions

- Despite high baseline values, the PCSK9 inhibitor, Alirocumab, reached very low atherogenic cholesterol levels in its ODYSSEY Phase 3 studies
- However, ODYSSEY Outcomes was not designed or prespecified to evaluate a targeted LDL-C goal at the lowest possible level, but rather the narrow limited 25-50 mg/dL goal range,[4]
- At 2.8-yr median F/U duration, the primary 5-point MACE was significantly lower in alirocumab group (9.5%) vs. placebo group (11.1%); 15% RRR
- Non-fatal MI, fatal & non-fatal stroke, any CVD event, any CHD event, major CHD event, and all-cause death, were significantly reduced by 14%, 27%, 13%, 12%, 12% and 15%, respectively
- Prespecified post hoc analysis by baseline LDL-C level, patients with LDL-C ≥100 mg/dL experienced reductions in all endpoints
- Post-hoc subgroup or subset analyses may reveal information regarding lowest CV event rates among patients achieving LDL-C goal <30 mg/dL
- Future analyses may add to current guidance for clinical decision-making supplied already by very low LDL-C levels (<30 mg/dL) reached by high-intensity statin IVUS trials, by ezetimibe in IMPROVE-IT, by the PCSK9 inhibitor, evolocumab, in its IVUS study, GLAGOV, and the level 1A FOURIER CVOT

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