Association of Baseline Lipoprotein(a) and Percentage of Lipoprotein(a) Lowering with Olpasiran
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Background
• Data support a causal role for lipoprotein(a) [Lp(a)] in atherogenesis.
• Olpasiran is a siRNA that reduces Lp(a) by >95% at higher doses by preventing synthesis of apolipoprotein(a).
• It remains unknown whether the % reduction of Lp(a) with olpasiran differs depending on baseline Lp(a).

Methods
• OCEAN(a)-DOSE was a phase 2 dose-ranging study in 281 patients with established ASCVD and Lp(a) levels >150 nmol/L.
• Participants were randomly allocated to one of 4 doses of olpasiran [10 mg, 75 mg, 225 mg q12 wks or an exploratory dose of 225 mg every 24 wks or matching placebo] administered subcutaneously.
• The % Lp(a) reduction at week 36 on-treatment as a function of baseline Lp(a) was assessed using a generalized linear regression model (values log-transformed for achieved value analysis).

Results
• Median baseline Lp(a) concentration was 260 nmol/L (IQR 198-352 nmol/L); the distribution was skewed (Fig 1).
• For patients randomized to olpasiran, the placebo-adjusted percent reduction in Lp(a) was >95% when dosed 75mg or higher every 12 weeks.
• The placebo-adjusted mean percent reduction in Lp(a) with olpasiran was consistent across the range of baseline Lp(a) concentration at doses ≥75 mg q12 wks (Fig 2A).
• Since the relative percent reduction was similar, the absolute reduction in Lp(a) mean concentration was greater in those patients with higher baseline Lp(a) (Fig 2B).
• Olpasiran at doses ≥75 mg q12 wks achieved on average nearly undetectable concentrations of Lp(a) including in those patients with markedly elevated levels at baseline (Fig 3).

Conclusions
• Olpasiran markedly reduces Lp(a) concentration irrespective of baseline Lp(a) concentration
• As the clinical benefit is postulated to be related to the absolute reduction in Lp(a) levels, these findings provide relevant insights for phase 3 testing.