Efficacy of Olpasiran by Apolipoprotein(a) Isoform Size: Insights from the OCEAN(a)-DOSE Trial

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Background

- **Lipoprotein (a)** [Lp(a)] is a presumed risk factor for atherosclerotic cardiovascular disease (ASCVD).
- The apolipoprotein(a) [apo(a)] component of Lp(a) can vary markedly in size due to a variable # of **Kringle IV-2** [KIV-2] repeats.
- An inverse correlation has been described between the # of KIV-2 repeats and Lp(a) concentration.
- **Olpasiran** is a small interfering RNA that prevents translation of the apo(a) transcript in the hepatocyte.
- In phase 2 testing, higher doses of olpasiran were shown to **reduce Lp(a) levels by >95%.**

Objective

- To assess the relationship between **apo(a) isoform size and response to lowering of Lp(a) with olpasiran** through RNA interference of apo(a) expression.

Patient and Methods

- OCEAN(a)-DOSE was a randomized, placebo-controlled, phase 2 trial that evaluated 4 active doses of olpasiran (10 mg Q12W, 75 mg Q12W, 225 mg Q12W, 225 mg Q24W) in patients with ASCVD and Lp(a) >150 nmol/L.
- With a BioRad Submarine gel electrophoresis and immunoblotting assay, the # of KIV-2 repeats and the relative expression of each patient's apo(a) isoform was determined (dominant defined as most expressed).
- The placebo-adjusted least-square means (LSM) percent change in Lp(a) from baseline to week 36 with olpasiran was examined as a function of number of KIV-2 repeats on the dominant isoform.

Results

- A total of 270 patients had apo(a) isoform and Lp(a) available at baseline and W36.
- At baseline, the median Lp(a) [IQR] concentration was 260.2 [197.9–358.5] nmol/L.
- Higher KIV-2 repeat number tended to be associated with lower Lp(a) concentration in this population who all had elevated baseline Lp(a) concentration (Fig 1).
- At week 36, the placebo-adjusted LSM percent change from baseline in Lp(a) with olpasiran was consistent irrespective of baseline KIV-2 repeat number (Fig 2; Table 1)

Tab 1. Placebo-adjusted LSM % change in Lp(a) from baseline to W36 with olpasiran by # of KIV-2 copies (dominant isoform)

	Baseline #KIV			
Olpasiran	<16 n=60	16-18 n=193	>18 n=27	**P int**
10 mg Q12W	-67.5	-67.2	-84.2	0.55
75 mg Q12W	-96.9	-95.6	-103.6	
225 mg Q12W	-100.9	-99.1	-104.6	
225 mg Q24W	-102.5	-97.5	-107.6	

- No significant change was observed over time in the percent expression of the dominant apo(a) isoform with olpasiran vs. placebo (mean change from baseline to week 36 [±SD]: +1.1 [±9.8] % with olpasiran and +2.1 [±12.8] % with placebo, p = 0.65; Fig 3).

Fig 1. Baseline Lp(a) concentration by # of KIV-2 copies (dominant isoform)

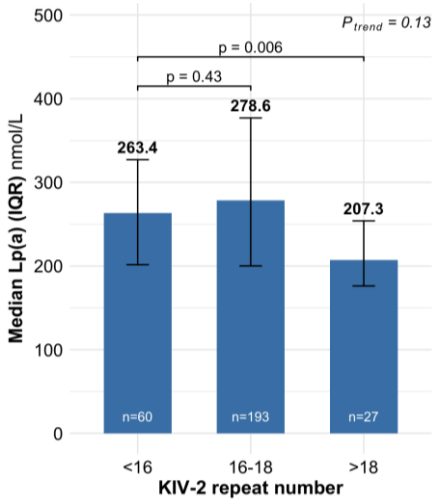


Fig 2. Lp(a) % reduction with olpasiran from baseline to week 36 by # of KIV-2 copies (dominant isoform)

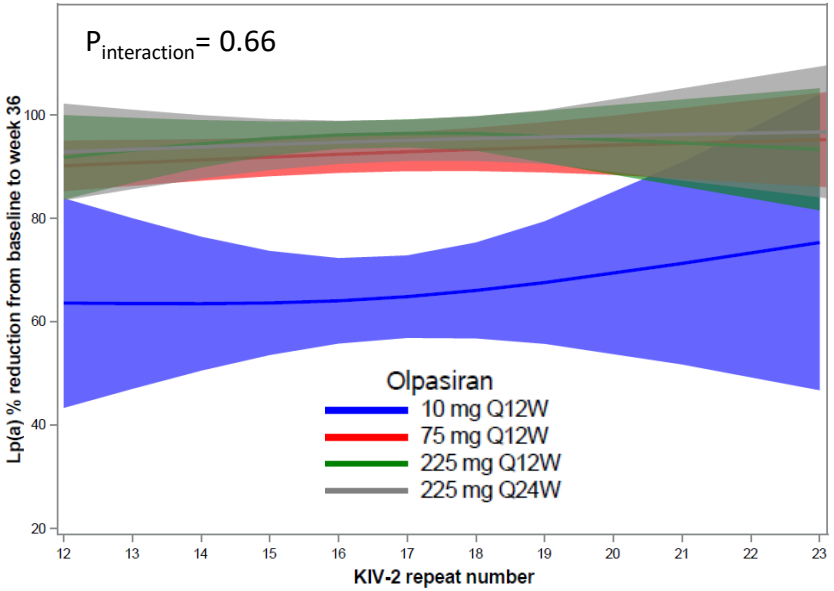
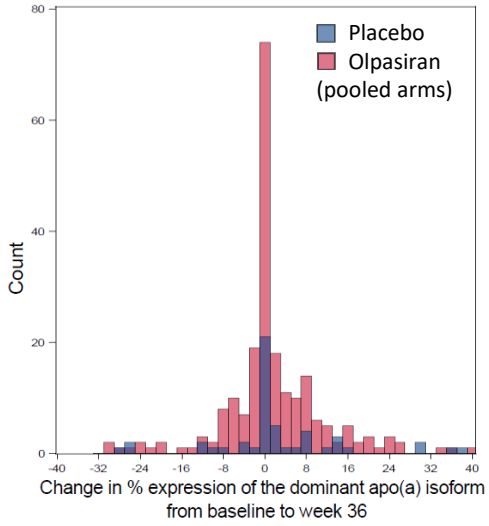


Fig 3. Dominant apo(a) isoform % expression change from BL to W36



Conclusions

- In patients with ASCVD and elevated Lp(a), olpasiran reduces Lp(a) irrespective of apo(a) isoform size and appears to affect both dominant and non-dominant isoforms equally.

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