Obicetrapib Demonstrates Significant Reductions of Lp(a) on Top of High-Intensity Statins

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Background

- Lipoprotein(a) [Lp(a)] transports cholesterol and oxidized phospholipids in the blood and comprises two major proteins, apolipoprotein(a) and apolipoprotein B.
- Elevated Lp(a) leads to increased atherosclerotic cardiovascular disease risk (1).
- There are currently no pharmacological therapies specifically approved for reducing Lp(a), although several are being investigated (2-4).
- Previous cholesteryl ester transfer protein (CETP) inhibitors, including anacetrapib and evacetrapib, reduced Lp(a) by up to ~40% (2, 5, 6).
- Most of the approved low-density lipoprotein cholesterol (LDL-C) lowering agents have relatively modest effects on Lp(a) or, as for statins, do not reduce Lp(a) (2-4).
- The newest, selective CETP inhibitor, obicetrapib, has been shown to substantially lower Lp(a), as well as reduce LDL-C, apolipoprotein B, and LDL particles, and increase high-density lipoprotein cholesterol and apolipoprotein A1 (7-9).

Objective

- A pooled analysis of two Phase II trials of obicetrapib was undertaken to further examine its effects on Lp(a).

Study Designs

Randomized Study of Obicetrapib as an Adjunct to Statin Therapy (ROSE) (8):

- N=120 participants taking 40 or 80 mg/d atorvastatin or 20 or 40 mg/d rosuvastatin for at least 8 weeks prior to screening
- Placebo or 5 or 10 mg obicetrapib daily for 8 weeks on top of statin
- Lp(a) was measured at baseline and end of treatment using Tina-quant® Lipoprotein(a) on a Roche c502 analyzer (10)
- Participants included men and women 18–75 years of age with a fasting LDL-C >70 mg/dL

Study to Evaluate the Effect of Obicetrapib in Combination With Ezetimibe as an Adjunct to High-Intensity Statin Therapy (ROSE2) (9):

- N=119 participants taking 40 or 80 mg/d atorvastatin or 20 or 40 mg/d rosuvastatin for at least 8 weeks prior to screening
- Placebo, 10 mg obicetrapib, or 10 mg obicetrapib plus 10 mg ezetimibe daily for 12 weeks on top of statin
- Lp(a) was measured at baseline and end of treatment with the University of California San Diego isoform independent assay using monoclonal antibody LPA-KIV9 (11)
- Participants included men and women 18–75 years of age with a fasting LDL-C >70 mg/dL

Results

Table 1. Lp(a) concentrations at baseline and percent changes from baseline to end-of-treatment in ROSE, ROSE2, and pooled (8, 9)

ROSE	Placebo (n=40)	Obicetrapib 5 mg (n=40)	Obicetrapib 10 mg (n=40)
Lp(a)			
Baseline, nmol/L			
Median (min, max)	45.3 (2.9, 410)	89.4 (2.8, 354)	29.9 (2.8, 354)
Week 8 change, %[1]			
Median (min, max)	4.00 (-29.6, 45.5)	-33.8 (-84.6, 93.8)	-56.5 (-85.7, 18.3)
P-value vs. placebo[2]		<0.0001	<0.0001

ROSE2	Placebo (n=24)	Obicetrapib 10 mg (n=24)	Obicetrapib 10 mg + Ezetimibe 10 mg (n=31)
Lp(a)			
Baseline, nmol/L			
Median (min, max)	37.8 (0.9, 396)	44.0 (0.8, 372)	27.6 (0.2, 480)
Week 12 change, %			
Median (min, max)	2.3 (-67.9, 145)	-47.2 (-97.5, 215)	-40.2 (-92.4, 702)
P-value vs. placebo[3]		<0.001	<0.008

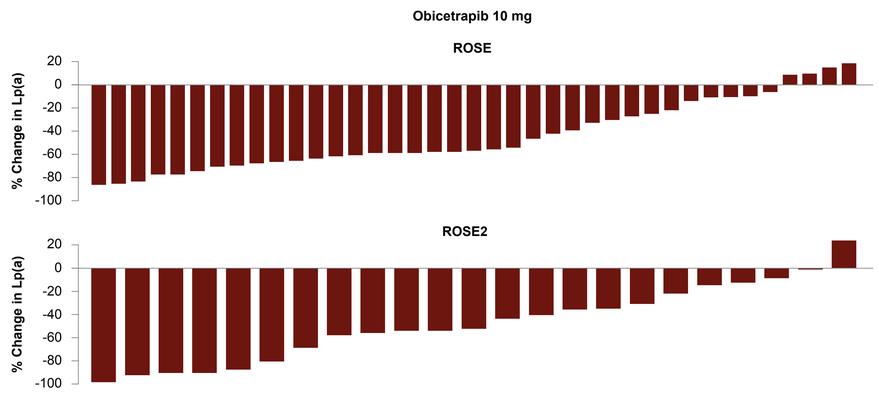
Pooled	Placebo (n=63)	Obicetrapib 10 mg (n=64)
Lp(a)		
Baseline, nmol/L		
Median (min, max)	44.8 (0.9, 410)	31.1 (0.8, 435)
End of Treatment change, %		
Median (min, max)	4.0 (-67.9, 145)	-53.1 (-97.5, 215)
P-value vs. placebo[3]		<0.001
Median placebo-corrected response		-57.1

[1] n=39 for placebo, n=38 for obicetrapib 5 mg.

[2] P-values are from a mixed measures repeated model with treatment, visit, and treatment-by-visit as factors and the baseline value as a covariate.

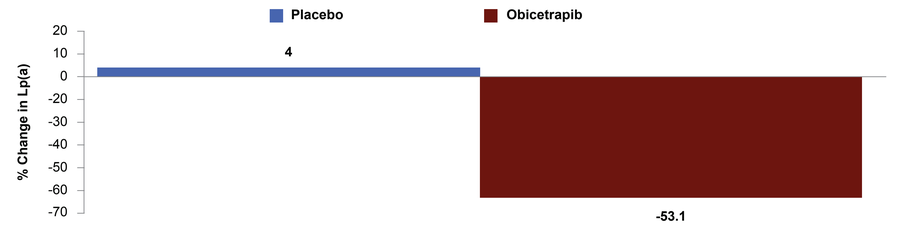
[3] P-values are from an analysis of covariance model that included the rank of percent change values as the dependent value, treatment as a fixed effect, and the rank of the baseline value as a covariate. A ranked analysis was performed because the assumption of normality of residuals was violated.

Figure 1. Waterfall plots of Lp(a) responses[1] to obicetrapib 10 mg on top of high-density statin in ROSE and ROSE2 (8, 9)



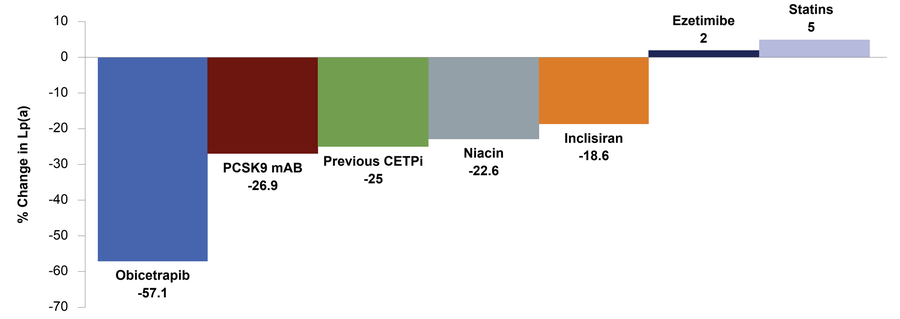
[1] % change from baseline to end of treatment, which was week 8 in ROSE and week 12 in ROSE2.

Figure 2. Median pooled Lp(a) responses[1] to placebo and 10 mg obicetrapib monotherapy administered on top of high-density statin in ROSE and ROSE2 (n=127) (8, 9)



[1] % change from baseline to end of treatment, which was week 8 in ROSE and week 12 in ROSE2.

Figure 3. Lp(a) response with obicetrapib compared with previous CETP inhibitors and approved LDL-C lowering agents



Conclusions

Obicetrapib 10 mg on top of high-intensity statin significantly lowered Lp(a) by 57% vs. placebo in a pooled analysis of two Phase II trials of participants with dyslipidemia, which is a substantially greater reduction than has been reported for other CETP inhibitors and other available LDL-C-lowering agents.

Abbreviations

CETP, cholesteryl ester transfer protein; CETPi, cholesteryl ester transfer protein inhibitor; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); max, maximum; min, minimum; PCSK9 mAb, monoclonal antibody to proprotein convertase subtilisin kexin type 9; ROSE, Randomized Study of Obicetrapib as an Adjunct to Statin Therapy; ROSE2, Study to Evaluate the Effect of Obicetrapib in Combination with Ezetimibe as an Adjunct to High-Intensity Statin Therapy

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