Impact of the Cholesteryl Ester Transfer Protein Inhibitor, Obicetrapib, on Lipoprotein(a) Levels: Pooled Data From Phase 3 Clinical Trials

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Background

- Obicetrapib is a potent oral cholesteryl ester transfer protein (CETP) inhibitor developed primarily to lower low-density lipoprotein cholesterol (LDL-C) levels[1]
- Early studies suggest that obicetrapib also lowers lipoprotein(a) [Lp(a)][1]
- Studies have not required patients to have high Lp(a) levels; accordingly, more than 50% had baseline Lp(a) levels in the normal range[2,3]
- Although Lp(a)-lowering agents are in development, they are injectable, will likely be expensive, and are being studied (and will likely be used) in patients with very high Lp(a) levels (≥150 nmol/L)[4]
  - A high proportion of the at-risk population has moderate Lp(a) elevations (50 to <150 nmol/L)[5]
- We sought to determine whether obicetrapib can be an effective agent in the setting of Lp(a) elevations between 50 and <150 nmol/L

Objective

- To evaluate the effect of obicetrapib on Lp(a) levels in patients with baseline Lp(a) >50 nmol/L

Methods

- BROOKLYN (NCT05425745), BROADWAY (NCT05142722), and TANDEM (NCT06005597) were phase 3, randomized, double-blind, placebo-controlled trials evaluating the effect of obicetrapib 10 mg as an adjunct to maximally tolerated lipid-lowering therapy (LLT)
- A pooled analysis of LDL-C and Lp(a) measurements at day 84 in 2538 patients treated with obicetrapib in BROOKLYN, BROADWAY, and TANDEM was conducted
  - Median differences in placebo-adjusted percentage and absolute changes in LDL-C and Lp(a) were evaluated from baseline to day 84 using Hodges-Lehman analyses

Results

- At baseline across pooled patients (N=2538), LDL-C was 92 mg/dL and Lp(a) was 42.7 nmol/L
- LDL-C was reduced by 37.4% across all pooled patients, with an absolute reduction of 35 mg/dL (**Table 1**)
- In patients with baseline Lp(a) levels ≥50 nmol/L and <150 nmol/L, obicetrapib reduced Lp(a) by 44.8% and in absolute terms by 37.4 nmol/L (**Table 2**)
- Patients with baseline Lp(a) ≥150 nmol/L had Lp(a) percentage reductions less than the <150 nmol/L group, but the absolute reductions were similar in both groups (-33.1 nmol/L vs -37.4 nmol/L, respectively) (**Figure 1**)

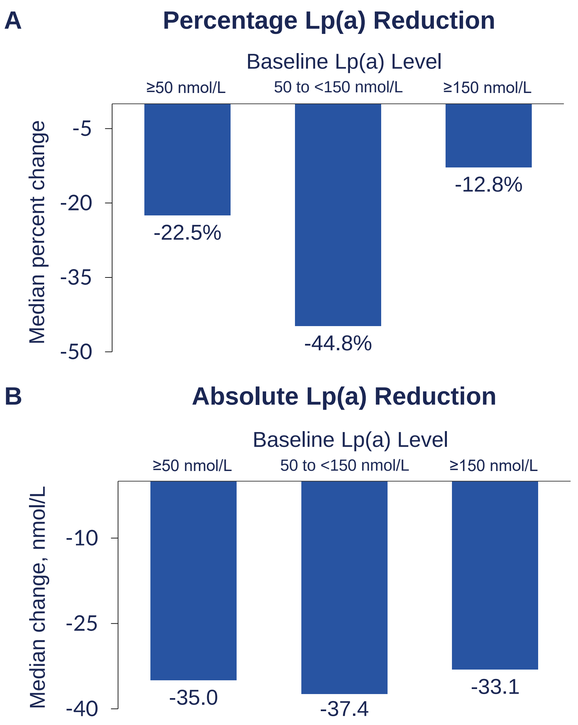
Table 1. LDL-C levels at baseline and percent and absolute changes in LDL-C levels at day 84

Parameter	Pooled (n=2538)	BROADWAY (n=2041)	BROOKLYN (n=315)	TANDEM (n=182)
Baseline LDL-C (mg/dL)	92.0 (76.0, 120.0)	90.0 (74.0, 117.0)	111.0 (88.0, 144.0)	91.0 (75.0, 114.0)
Percent change LDL-C	-37.4 (-39.3, -35.5)	-36.6 (-38.7, -34.5)	-40.3 (-45.2, -35.4)	-40.7 (-47.5, -33.8)
Absolute change (mg/dL)	-35.0 (-37.0, -33.0)	-32.5 (-35.0, -30.0)	-45.5 (-52.0, -39.0)	-42.0 (-49.0, -35.0)

Table 2. Lp(a) levels at baseline and percent and absolute changes in Lp(a) levels at day 84 stratified by baseline Lp(a) level

Parameter	Pooled (n=2538)	BROADWAY (n=2041)	BROOKLYN (n=315)	TANDEM (n=182)
Baseline Lp(a)	42.7 (12.3, 171.4)	42.6 (12.2, 170.1)	45.0 (14.1, 178.5)	38.9 (11.2, 187.2)
Percent change Lp(a)				
Baseline Lp(a) ≥50 nmol/L	-22.5 (-25.7, -19.3)	-21.4 (-24.9, -18.0)	-29.2 (-39.8, -18.5)	-24.8 (-38.0, -11.6)
Baseline Lp(a) 50-<150 nmol/L	-44.8 (-50.7, -38.9)	-42.8 (-49.5, -36.1)	-52.2 (-70.6, -33.7)	-52.4 (-73.5, -31.3)
Baseline Lp(a) ≥150 nmol/L	-12.8 (-15.7, -9.9)	-12.6 (-15.9, -9.3)	-13.3 (-21.2, -5.3)	-12.6 (-25.9, 0.6)
Absolute change Lp(a) (nmol/L)				
Baseline Lp(a) ≥50 nmol/L	-35.0 (-39.6, -30.3)	-33.6 (-38.7, -28.4)	-39.8 (-53.8, -25.8)	-40.0 (-61.2, -18.7)
Baseline Lp(a) 50-<150 nmol/L	-37.4 (-42.0, -32.7)	-35.8 (-40.9, -30.7)	-43.5 (-60.4, -26.6)	-43.4 (-63.4, -23.4)
Baseline Lp(a) ≥150 nmol/L	-33.1 (-41.0, -25.2)	-31.7 (-40.7, -22.7)	-37.3 (-21.2, -5.3)	-35.2 (-76.0, 5.7)

Figure 1. Pooled A) percentage reductions and B) absolute reductions in Lp(a) stratified by baseline Lp(a) level



Conclusions

- **Across 3 phase 3 trials, obicetrapib, an oral CETP inhibitor, effectively reduced not only LDL-C, but also Lp(a), especially in those with moderately elevated Lp(a) levels**
- **These combined effects of obicetrapib on both LDL-C and Lp(a) have the potential to robustly lower cardiovascular risk in the majority of patients with ASCVD**

1. Kastelein JJP, Hsieh A, Dicklin MR, Ditmarsch M, Davidson MH. Obicetrapib: reversing the tide of CETP inhibitor disappointments. *Curr Atheroscler Rep.* 2024;26(2):35-44. doi:10.1007/s11883-023-01184-1 **2.** Nicholls SJ, Ditmarsch M, Kastelein JJ, et al. Lipid lowering effects of the CETP inhibitor obicetrapib in combination with high-intensity statins: a randomized phase 2 trial. *Nat Med.* 2022;28(8):1672-1678. doi:10.1038/s41591-022-01936-7 **3.** Hovingh GK, Kastelein JJ, van Deventer SJ, et al. Cholesterol ester transfer protein inhibition by TA-8995 in patients with mild dyslipidaemia (TULIP): a randomised, double-blind, placebo-controlled phase 2 trial. *Lancet.* 2015;386(9992):452-460. doi:10.1016/S0140-6736(15)60158-1 **4.** Sosnowska B, Surma S, Banach M. Targeted treatment against lipoprotein (a): the coming breakthrough in lipid lowering therapy. *Pharmaceuticals (Basel).* 2022;15(12):1573. doi:10.3390/ph15121573 **5.** Shapiro MD, Haddad TM, Weintraub HS, et al. Lipoprotein(a) levels in a population with clinical atherosclerotic cardiovascular disease in the United States: a subanalysis from the Lp(a)HERITAGE study. *J Clin Lipidol.* 2025;19(1):28-38. doi:10.1016/j.jacl.2024.11.007