Determinants of Short Term Lp(a) Variability in Phase 3 Obicetrapib Trials

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BACKGROUND

- In phase 3 studies, treatment with the cholesteryl ester transfer protein (CETP) inhibitor, obicetrapib, reduced Lp(a) in participants with a range of elevated Lp(a) concentrations below those studied in phase 3 trials of RNA-targeted Lp(a)-lowering therapies[1,2]
  - Across pooled analyses, obicetrapib produced 43.3% to 44.8% placebo-adjusted reductions and 36.3 to 37.4 nmol/L absolute reductions in Lp(a) in patients with baseline Lp(a) 50 to <150 nmol/L and at intermediate Lp(a) risk[1,2]
- Although repeated Lp(a) testing is generally viewed as unnecessary due to the genetically determined nature of levels, there are limited data on the variability in Lp(a) measurements over time, which might impact the ability to identify individuals who might benefit from Lp(a) lowering with obicetrapib and, therefore, justify repeated testing

PURPOSE

- To document predictors of short-term variability in Lp(a) assessments among patients in the placebo arms of phase 3 studies of obicetrapib

METHODS

- BROOKLYN (NCT05425745) and BROADWAY (NCT05142722) were phase 3, randomized, double-blind, placebo-controlled trials evaluating the effect of obicetrapib as an adjunct to maximally tolerated lipid-lowering therapy (LLT) in adults with ASCVD and/or heterozygous familial hypercholesterolemia (HeFH)
- In 920 placebo-arm participants across both trials (median baseline Lp(a) 38.6 nmol/L), Lp(a) was measured at randomization and week 12 using a particle-enhanced turbidimetric assay at Medpace Reference Laboratories
  - A Bland-Altman plot was used to summarize the variability of the assessments **(Figure 1)**
  - A Sankey diagram was used to illustrate the number of participants shifting between Lp(a) ranges **(Figure 2)**
  - Logistic regression models identified characteristics that were related to having a week 12 value ≥50 to <150 nmol/L at baseline and separately among those ≥150 nmol/L at baseline; relationships were summarized by odds ratios (OR) with associated 95% confidence intervals (CIs) and p-values

Figure 1: Bland-Altman Plot of Lp(a) Measurements at Baseline and Week 12 Among Patients in the Placebo Arms

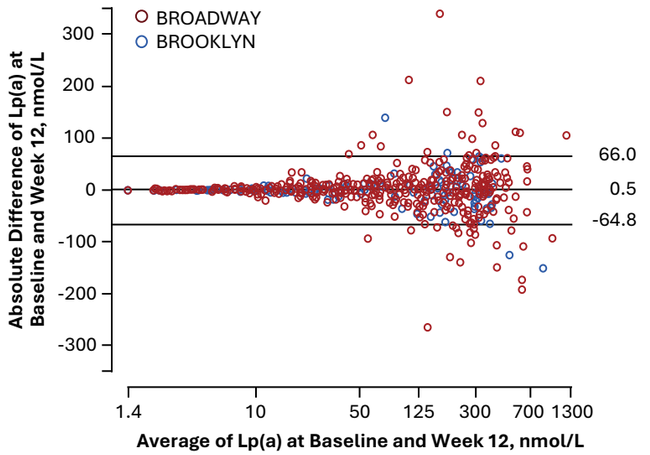
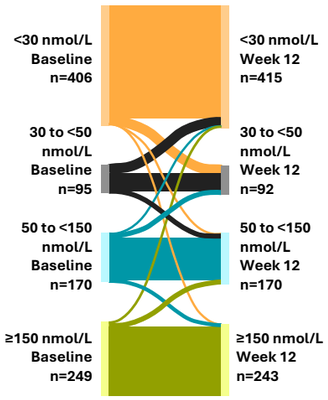


Figure 2: Transitions Between Ranges of Lp(a) at Baseline and Week 12 Among Patients in the Placebo Arms*



Baseline	Week 12
<30 nmol/L: n=406	<30 nmol/L: n=380
	30 to <50 nmol/L: n=23
	50 to <150 nmol/L: n=2
	≥150 nmol/L: n=1
30 to <50 nmol/L: n=95	<30 nmol/L: n=27
	30 to <50 nmol/L: n=57
	50 to <150 nmol/L: n=11
	≥150 nmol/L: n=0
50 to <150 nmol/L: n=170	<30 nmol/L: n=6
	30 to <50 nmol/L: n=12
	50 to <150 nmol/L: n=142
	≥150 nmol/L: n=10
≥150 nmol/L: n=249	<30 nmol/L: n=2
	30 to <50 nmol/L: n=0
	50 to <150 nmol/L: n=15
	≥150 nmol/L: n=232

*The numbers within the plot represent the number of participants within each range at each timepoint. The table provides the number of participants with category shifts at each timepoint.

Table. Predictors of Shift in Lp(a) from Baseline to the 50 to <150 nmol/L Range at Week 12 For Patients in the Placebo Arms

Characteristics	Participants >LLQ to <50 nmol/L at Baseline (n=451)		Participants ≥150 nmol/L at Baseline (n=247)	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Baseline				
Lp(a), per nmol/L increment	1.14 (1.07, 1.20)	<0.0001	0.96 (0.94, 0.98)	0.0004
Age, per year increment	0.99 (0.94, 1.05)	0.77	0.99 (0.95, 1.04)	0.80
Female Sex	1.42 (0.46, 4.42)	0.55	0.43 (0.13, 1.40)	0.16
Black or African American race	6.00 (0.67, 53.79)	0.11	0.97 (0.12, 7.81)	0.97
HeFH	0.46 (0.10, 2.11)	0.32	0.41 (0.09, 1.88)	0.25
ASCVD	2.48 (0.32, 19.34)	0.39	1.35 (0.29, 6.23)	0.70
History of diabetes	0.99 (0.32, 3.06)	0.98	1.05 (0.35, 3.17)	0.94
High intensity statin	1.65 (0.45, 6.09)	0.45	1.27 (0.35, 4.67)	0.72
PCSK9 inhibitor	1.38 (0.17, 11.02)	0.76	0.90 (0.11, 7.29)	0.92
Body mass index, per kg/m^2 increment	1.04 (0.95, 1.14)	0.45	1.04 (0.97, 1.12)	0.23
LDL-C, per mg/dL increment	1.00 (0.98, 1.01)	0.64	0.99 (0.98, 1.01)	0.35
HDL-C, per mg/dL increment	0.98 (0.94, 1.02)	0.31	0.95 (0.91, 0.99)	0.0250
ApoB, per mg/dL increment	1.01 (0.99, 1.02)	0.59	0.99 (0.96, 1.01)	0.28
Triglyceride, per mg/dL increment	1.01 (1.00, 1.01)	0.0134	1.00 (0.99, 1.01)	0.90
eGFR per mL/min/1.73m^2 increment	0.99 (0.96, 1.03)	0.74	1.00 (0.97, 1.02)	0.76
HbA1c, per percent increment	1.07 (0.66, 1.74)	0.79	0.72 (0.36, 1.45)	0.36
Log$_2$(hsCRP), per log$_2$ mg/L increment	1.04 (0.75, 1.45)	0.81	0.95 (0.70, 1.29)	0.73
Change from Baseline to Week 12				
LDL-C, per mg/dL increment	1.01 (0.99, 1.03)	0.39	0.99 (0.98, 1.01)	0.30
HDL-C, per mg/dL increment	1.01 (0.96, 1.06)	0.80	1.04 (1.00, 1.08)	0.0376
ApoB, per mg/dL increment	0.99 (0.96, 1.02)	0.53	0.99 (0.97, 1.02)	0.43
Triglyceride, per mg/dL increment	0.99 (0.99, 1.00)	0.0104	1.00 (0.99, 1.00)	0.27
eGFR per mL/min/1.73 m^2 increment	1.03 (0.96, 1.10)	0.49	1.04 (0.97, 1.11)	0.27

ApoB, apolipoprotein B; eGFR, estimated glomerular filtration rate; HbA1c; hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; LLQ, lower limit of quantification; PCSK9, proprotein convertase subtilisin/kexin type 9.

RESULTS

- Among 920 participants, median (interquartile range) Lp(a) concentrations were 38.6 (11.9, 161.7) nmol/L at baseline and 38.4 (10.9, 156.2) nmol/L at week 12
- A Bland-Altman analysis demonstrated that the overall bias was small (0.6 nmol/L), but 95% limits of agreement were relatively wide (-64.8 to 66.0 nmol/L; **Figure 1**)
  - Although the assessments were strongly correlated (Spearman r=0.96), variability increased with average Lp(a) concentration
- While the proportion of participants in each Lp(a) range was relatively stable at each timepoint, meaningful fractions of participants changed categories (**Figure 2**)
- Linear regression models indicated that baseline Lp(a) explained a meaningful proportion of the variance between the baseline and week 12 assessments (**Table**)

CONCLUSIONS

- Short-term Lp(a) measurements in the BROADWAY and BROOKLYN placebo cohorts were highly correlated but showed wide limits of agreement, with variability increasing at higher concentrations and baseline Lp(a) emerging as the strongest predictor of fluctuation
- A notable subset of participants shifted from <50 nmol/L or ≥150 nmol/L at baseline to Lp(a) 50 to 150 nmol/L over 12 weeks, suggesting that repeated Lp(a) testing may help identify additional candidates who could benefit from obicetrapib if Lp(a) lowering proves clinically beneficial

AFFILIATIONS: MS: University of Colorado School of Medicine. KR: Imperial College London School of Public Health. DC, EW, AH, MD, JJPK, and MHD: NewAmsterdam Pharma. SN: Victorian Heart Institute. **DISCLOSURES**: MS: Receives salary support from CPC, a non-profit academic research organization affiliated with the University of Colorado, consultant or research support (or both) from Amarin, Lexicon, NewAmsterdam Pharma, Novartis, Regeneron, Sanofi, Silence, and Tourmaline. KKR: advisory boards, steering committees, or as a consultant or speaker for Abbott Pharmaceuticals, Amarin Pharma Inc., Amgen, AstraZeneca, Bayer Healthcare, Boehringer Ingelheim, Cleerly, CRISPR Therapeutics, CSL Behring, Dr. Reddy's, Eli Lilly, Esperion Therapeutics, Kowa, MacLeods Pharmaceuticals, Mankind, Menarini International, NewAmsterdam Pharma, Nodthera, Novartis, Novo Nordisk, Pfizer, Sanofi, Silence Therapeutics, Vaxxinity, and Viatris. He reports roles related to trial leadership, oversight, or design for Eli Lilly, Esperion Therapeutics, Kowa, NewAmsterdam Pharma, Nodthera, and Scribe Therapeutics and also holds stock options in NewAmsterdam Pharma, PEMI31, and Scribe Therapeutics. DK, DC, EW, AH, MD, JJPK, MHD: employees and/or shareholders of NewAmsterdam Pharma. SN: Advisor, Consultant and Steering Committee related activities for AstraZeneca, NewAmsterdam Pharma, Amgen, Eli Lilly, Esperion, Novartis, Merck, Takeda, Sanofi-Regeneron, CSL, Daiichi-Sankyo, Silence.

1. Nicholls SJ et al. *J Clin Lipidol.* 2025;19(3S):e99-e100. **2.** Nicholls SJ et al. *Eur Heart J.* 2026;ehag399. doi:10.1093/eurheartj/ehag399

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