Mediation Analysis on LDL-C and Lp(a) From Pooled BROADWAY and BROOKLYN MACE Data

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Background

- In phase 3 studies, treatment with the cholesteryl ester transfer protein (CETP) inhibitor obicetrapib on top of maximally tolerated lipid-lowering therapy (LLT) significantly reduced low-density lipoprotein cholesterol (LDL-C) by up to 36.3% and lipoprotein (a) [Lp(a)] by up to 56.2%[1-3]
- In a pooled analysis of 2 phase 3 studies, 123 patients (4.3%) experienced at least 1 cardiovascular event during the 12-month period, and treatment with obicetrapib was associated with a reduction in major adverse cardiovascular events (MACE)[4]
- The extent to which these lipoprotein reductions contribute to the effect of obicetrapib on MACE has not previously been studied

Objective

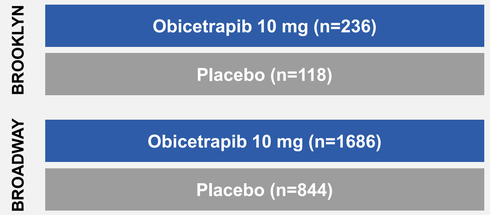
- To characterize the extent to which LDL-C and Lp(a) reductions contribute the effect of obicetrapib on MACE

Methods

- BROOKLYN (NCT05425745) and BROADWAY (NCT05142722) were phase 3, randomized, double-blind, placebo-controlled trials evaluating the effect of obicetrapib 10 mg as an adjunct to maximally tolerated LLT

Patient characteristics:

- Adults with ASCVD and/or HeFH
- Maximally tolerated LLT
- Baseline LDL-C not adequately controlled



ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia.

- A mediation analysis was performed using pooled data from the BROADWAY and BROOKLYN studies, where 2884 participants with ASCVD or HeFH and elevated LDL-C despite maximally tolerated statins were randomized to treatment with obicetrapib 10mg or placebo daily for 12 months
  - Time-weighted achieved concentrations in LDL-C and log-transformed Lp(a) were related to MACE risk in proportional hazard models that also included treatment assignment
  - The time-weighted concentration for each participant was a single value calculated as the area under the curve (AUC) using all available values before the participant's event date or date of right censoring for the event divided by the number of days from baseline to the last value
  - The AUC was calculated using the linear trapezoidal rule accounting for the number of days from baseline for each assessment

Results

- Baseline characteristics are shown in **Table 1**
- Obicetrapib produced greater reductions in LDL-C (-34.0 vs -4.0 mg/dL, -37.8% vs -4.6%) and Lp(a) (-9.8 vs 0 nmol/L, -32.5% vs 0%) compared with placebo
- Obicetrapib reduced MACE (coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or coronary revascularization) by 23% (hazard ratio [HR]: 0.77; 95% confidence interval [CI]: 0.54-1.11; *P*=0.16) (**Figure 1**)
- LDL-C and Lp(a) were significant individual mediators of MACE and jointly mediated 84.5% of the effect of obicetrapib on MACE (**Figure 2**)

Table 1. Baseline clinical characteristics

Parameter	Placebo (N=962)	Obicetrapib (N=1922)	Total
Mean age (years)	65.0	66.0	65.7
Female (%)	35.9	36.3	36.2
White race (%)	78.7	76.0	76.9
Body mass index (kg/m^2)	28.9	28.7	28.8
ASCVD (%)	82.4	82.5	82.5
HeFH (%)	27.0	26.9	26.9
Diabetes (%)	37.6	34.9	35.8
Hypertension (%)	78.4	76.5	77.1
Current smoker (%)	20.5	20.9	20.8

Figure 1: Pooled incidence of MACE (composite of coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or coronary revascularization) in 12-month study period

HR (95% CI)=0.77 (0.54, 1.11), *P*=0.16

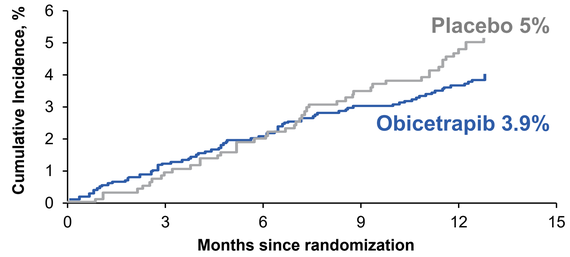
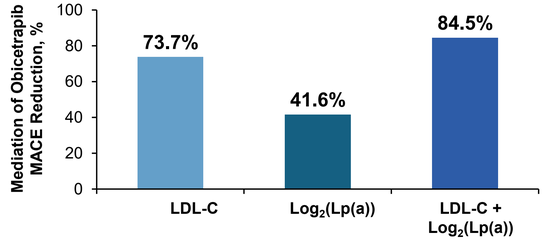


Figure 2: Individual and joint percent mediation of MACE reduction by obicetrapib vs placebo in the BROADWAY and BROOKLYN studies



MACE included coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, and total coronary revascularizations.

Conclusions

- **The MACE benefit observed in BROOKLYN and BROADWAY was primarily attributable to LDL-C reductions, with Lp(a) also being an important mediator**
- **The remaining treatment effect may be due to additional effects of obicetrapib related to MACE**

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Affiliations and Disclosures: Michael Szarek: State University of New York Downstate School of Public Health, New York, United States of America, serves as a consultant or research support (or both) from Amarin, Lexicon, New Amsterdam, Novartis, Regeneron, Sanofi, Silence, and Tourmaline. KR: *Imperial College, London, United Kingdom* COI:Amgen, Amarin, Sanofi, Daiichi-Sankyo, and Ultragenyx to Imperial College London; CConsultant for Novartis, Daiichi-Sankyo, Kowa, Esperion, Novo Nordisk, MSD, Eli Lilly, Silence Therapeutics, AstraZeneca, New Amsterdam Pharma, Bayer, Beren Therapeutics, Cleerly, EmendoBio, Scribe, Nodthera, Crispr, Vaxxinity, and Sanofi; Lecture fees from Novartis, Boehringer Ingelheim, AstraZeneca, Novo Nordisk, Viatris, Amarin, Sanofi, Amgen, Esperion, Daiichi-Sankyo, DK, AH, JJPK, and MHD, NewAmsterdam Pharma, Naarden, The Netherlands: Employees & Shareholders of NewAmsterdam Pharma. SN: Victoria Heart Institute. Monash University: Victoria Heart Institute. Monash University: AstraZeneca, NewAmsterdam, Amgen, Eli Lilly, Esperion, Novartis, Merck, Takeda, Sanofi-Regeneron, CSL, Daiichi-Sankyo, Silence. AstraZeneca, NewAmsterdam, Amgen, Eli Lilly, Esperion, Novartis, Merck, Takeda, Sanofi-Regeneron, CSL, Daiichi-Sankyo, Silence.

1. Nicholls SJ et al. *Nat Med.* 2026;32(3):1052-1060. **2.** Nicholls SJ et al. *N Engl J Med.* 2025;393(1):51-61. **3.** Sarraju A et al. *Lancet.* 2025;405(10491):1757-1768. **4.** Nicholls SJ et al. *J Am Coll Cardiol.* 2025;86(14):1046-1056.