Pooled Safety Analysis of Hypertension Events in Phase 3 Trials of Obicetrapib

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BACKGROUND

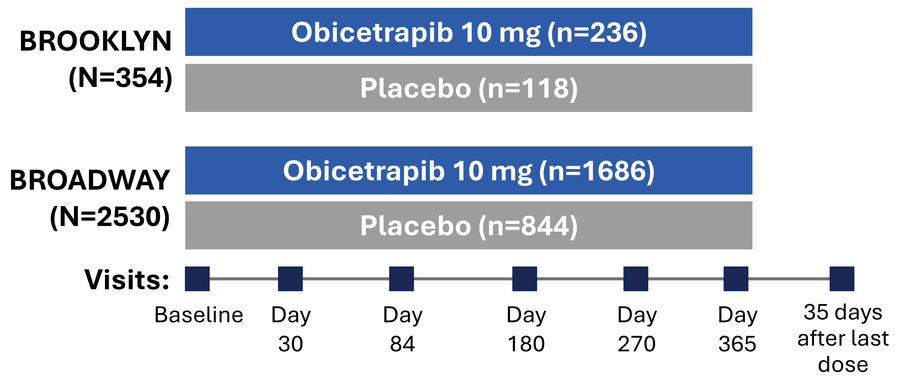
- Obicetrapib, a novel, potent cholesteryl ester transfer protein (CETP) inhibitor, has demonstrated promising low-density lipoprotein cholesterol (LDL-C) lowering and a favorable safety profile in phase 3 trials to date[1-4]
- An earlier generation CETP inhibitor had unanticipated off-target effects on aldosterone that led to increased blood pressure (BP)[5]
- Although phase 1 and 2 trials for obicetrapib have indicated no changes in BP, serum electrolytes, or aldosterone, a comprehensive evaluation of blood pressure parameters across later-stage clinical trials is needed[6]

OBJECTIVE

- To assess changes in BP among obicetrapib-treated participants compared with placebo in a pooled safety dataset from phase 3 trials

METHODS

- A pooled analysis of the phase 3 trials BROOKLYN (NCT05425745) and BROADWAY (NCT05142722) that included patients treated for 1 year with obicetrapib assessed:
  - Prespecified endpoints: systolic BP ≥160 mm Hg, ≥180 mm Hg, and increases ≥20 mm Hg from baseline at scheduled visits (up to 12 months and 35 days post treatment)
  - Changes in antihypertensive medication use
  - TEAEs and events of special interest
- A dedicated, prespecified 24-hour ambulatory BP substudy within the BROADWAY trial analyzed a subpopulation of patients (n=229)



Patient characteristics[2,3]

- Adults with atherosclerotic cardiovascular disease (ASCVD) and/or heterozygous familial hypercholesterolemia (HeFH)
- Maximally tolerated lipid-lowering therapy (LLT)
- Baseline LDL-C not adequately controlled

Patients were excluded if they had uncontrolled, severe hypertension, defined as either systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg before randomization

RESULTS

- The pooled analysis included 2880 participants; baseline characteristics were well balanced between groups **(Table 1)**
- Obicetrapib demonstrated no clinically meaningful change in BP at day 84 **(Figure 1)** or 24-hour ambulatory BP at day 270 **(Figure 2)**
- Across treatment visits, the proportion of patients with systolic BP ≥160 mm Hg remained low in the obicetrapib vs placebo groups **(Table 2)**
- Incidence of **systolic BP ≥180 mm Hg was ≤0.4%** in both arms at all timepoints
  - **Shifts in systolic BP ≥20 mm Hg from baseline occurred in 3.6% to 7.3% of participants across all time points**, with similar rates between obicetrapib and placebo
- Changes in hypertensive medication due to BP events were infrequent and comparable between obicetrapib and placebo **(3.9% vs. 3.1%, respectively)**
- Initiation of new antihypertensive therapy in participants not on BP medications at baseline was rare and similar between groups **(1.3% for obicetrapib and 3.4% for placebo)**
- TEAEs, study drug-related TEAEs, serious TEAEs, events of special interest, and discontinuations due to adverse events occurred at similar rates between obicetrapib and placebo, consistent with the safety profile observed in the individual trials **(Table 3** and **Table 4)**

Figure 1. Changes in BP from baseline to Day 84

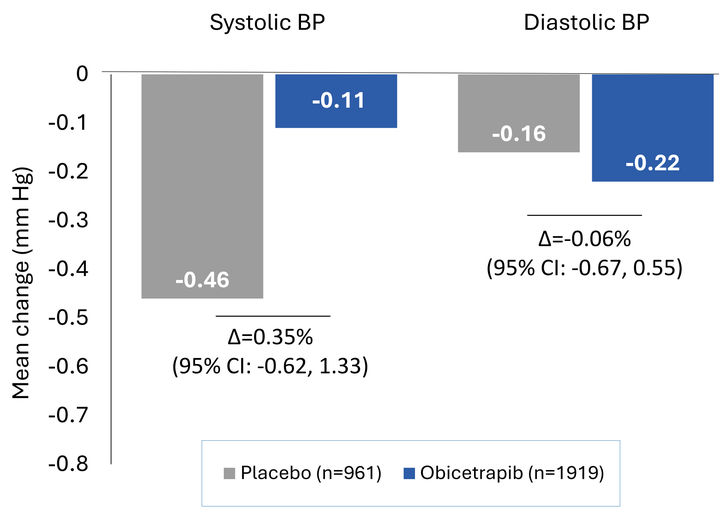


Figure 2. Ambulatory BP measurements

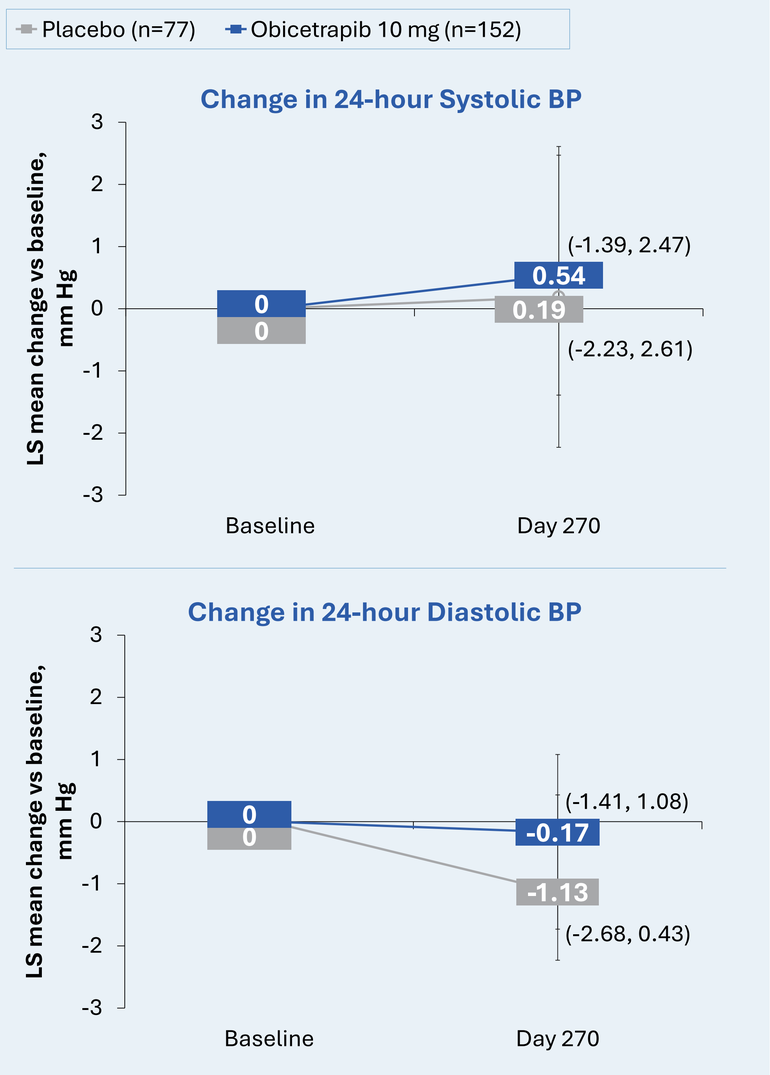


Table 1. Baseline clinical characteristics and medication use

Parameter	Placebo (N=961)	Obicetrapib (N=1919)
Age, years – mean ± SD	64.2±10.2	64.4±10.6
Females – n (%)	345 (35.9)	696 (36.3)
Race – n (%)		
White	757 (78.8)	1458 (76.0)
Asian	150 (15.6)	317 (16.5)
Black	42 (4.4)	115 (6.0)
Body Mass Index, kg/m² – mean ± SD	29.7±5.8	29.4±5.4
Diabetes – n (%)	362 (37.7)	669 (34.9)
Hypertension – n (%)	754 (78.4)	1471 (76.5)
Current Smoker – n (%)	197 (20.5)	402 (20.9)
ASCVD – n (%)	788 (82)	1573 (82)
Coronary artery disease	631 (65.7)	1297 (67.6)
Cerebrovascular disease	164 (17.1)	357 (18.6)
Peripheral artery disease	34 (3.5)	99 (5.2)
HeFH – n (%)		
Definite	175 (18.2)	337 (17.6)
Possible	84 (8.7)	167 (8.7)
LLT – n (%)		
Statins	880 (91.6)	1741 (90.7)
High-intensity statins	661 (68.8)	1337 (69.7)
Ezetimibe	278 (28.9)	579 (30.2)
PCSK9 inhibitors	59 (6.1)	94 (4.9)

Table 2. Incidence of systolic BP ≥160 mm Hg (%)

Timepoint	Placebo (N=961)	Obicetrapib (N=1919)
Baseline	0.3	0.2
Day 30	1.6	1.7
Day 84	1.9	2.0
Day 180	2.3	3.3
Day 270	1.8	3.1
Day 365	2.2	2.6
35 days after last dose	1.8	2.5

Table 3. TEAEs

	Placebo (N=961)	Obicetrapib (N=1919)	Risk Ratio (95% CI)
Any TEAEs	596 (62.0)	1156 (60.2)	0.97 (0.91, 1.03)
Any TEAEs by severity			
Mild	275 (28.6)	565 (29.4)	1.02 (0.91, 1.16)
Moderate	245 (25.5)	465 (24.2)	0.95 (0.83, 1.09)
Severe	76 (7.9)	126 (6.6)	0.83 (0.63, 1.09)
Any study drug-related TEAEs	47 (4.9)	86 (4.5)	0.92 (0.65, 1.30)
Any study drug-related TEAEs by severity			
Mild	30 (3.1)	56 (2.9)	0.93 (0.61, 1.45)
Moderate	17 (1.8)	28 (1.5)	0.82 (0.45, 1.50)
Severe	0 (0.0)	2 (0.1)	N/A
Any TEAEs leading to discontinuation	51 (5.3)	78 (4.1)	0.77 (0.54, 1.08)
Any TEAEs leading to death	14 (1.5)	22 (1.1)	0.79 (0.40, 1.53)
Any TESAEs	125 (13.0)	224 (11.7)	0.90 (0.73, 1.10)
Any study drug-related TESAEs	0 (0.0)	1 (0.1)	N/A
Any treatment-emergent nonserious AEs	577 (60.1)	1104 (57.5)	0.96 (0.90, 1.02)

Table 4. Events of special interest

	Placebo (N=961)	Obicetrapib (N=1919)	Risk Ratio (95% CI)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3× upper limit of normal (ULN)	8 (0.8)	10 (0.5)	0.63 (0.25, 1.58)
Bilirubin >2× ULN	6 (0.6)	2 (0.1)	0.17 (0.03, 0.83)
Creatine kinase >5× ULN	7 (0.7)	8 (0.4)	0.57 (0.21, 1.57)
NODM or worsening of glycemic control	361 (37.6)	631 (32.9)	0.88 (0.79, 0.97)
eGFR <30 mL/min/1.73 m² or ≥25% decrease in eGFR from baseline	84 (8.7)	129 (6.7)	0.77 (0.59, 1.00)
Increase of serum creatinine ≥0.3 mg/dL from baseline	70 (7.3)	96 (5.0)	0.69 (0.51, 0.93)
Macular degeneration	0 (0.0)	1 (0.1)	N/A

CONCLUSIONS

- **In pooled phase 3 analyses, metrics associated with BP increases were comparable between obicetrapib and placebo**
- **Rates of systolic BP elevations (≥160 mm Hg, ≥180 mm Hg, or ≥20 mm Hg from baseline) and antihypertensive medication changes were low and balanced across treatment arms**
- **These findings support the favorable cardiovascular safety profile of obicetrapib for patients with dyslipidemia**

AFFILIATIONS AND DISCLOSURES

AN: Victoria Heart Institute. Monash University Clayton AU: COI: AstraZeneca, Amgen, Eli Lilly, Novartis, Novo Nordisk, Sanofi; KR: *Imperial College, London, United Kingdom* COI: Amgen, Amarin, Sanofi, Daiichi-Sankyo, and Ultragenyx to Imperial College London; Consultant 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; MD, DK, AH, and JK: Employee & Shareholders of NewAmsterdam Pharma; SN: Victoria Heart Institute. Monash University: AstraZeneca, NewAmsterdam, Amgen, Eli Lilly, Esperion, Novartis, Merck, Takeda, Sanofi-Regeneron, CSL, Daiichi-Sankyo, Silence.

1. Ford J et al. *Br J Clin Pharmacol*. 2014;78(3):498-508. **2.** Nicholls SJ et al. *Nat Med*. 2026;32(3):1052-1060. **3.** Nicholls SJ et al. *N Engl J Med*. 2025;393(1):51-61.
4. Sarraju A et al. *Lancet*. 2025;405(10491):1757-1768. **5.** Nicholls SJ et al. *Curr Opin Lipidol*. 2022;33(6):319-325. **6.** Kastelein JJP et al. *Curr Atheroscler Rep*. 2024;26(2):35-44.

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