Safety of Obicetrapib: An Integrated Pooled Phase III Safety Analysis

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Background

- Obicetrapib is a potent, selective cholesteryl ester transfer protein (CETP) inhibitor that lowers low-density lipoprotein cholesterol (LDL-C) and raises high-density lipoprotein cholesterol[1,2]
- Earlier CETP inhibitors were limited by safety concerns[3]
- Although prior studies have demonstrated efficacy and general tolerability, a comprehensive evaluation of the safety profile of obicetrapib across later-stage clinical trials is needed[2]

Objective

- To comprehensively investigate the safety of obicetrapib compared with placebo in a pooled dataset of two phase III clinical trials

Methods

A pooled analysis of 2 phase 3 trials (NCT05425745 and NCT05142722) of patients treated for 1 year with obicetrapib assessed its impact on

- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious adverse events (TESAEs)
- TEAEs leading to drug discontinuation
- Events of special interest

Patient characteristics:

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

BROOKLYN (N=354)
- Obicetrapib 10 mg (n=236)
- Placebo (n=118)

BROADWAY (N=2530)
- Obicetrapib 10 mg (n=1686)
- Placebo (n=844)

The safety analysis population included all randomized patients who received at least one dose of study drug

CETP Inhibition With Obicetrapib: Safe and Well Tolerated

Obicetrapib was well tolerated among patients with high cardiovascular (CV) risk

- **Similar frequency of overall TEAEs** between obicetrapib and placebo groups; TEAEs were mostly **mild or moderate**
- **Treatment discontinuation occurred in fewer participants** in the obicetrapib vs placebo group

Events of special interest were either similar to placebo or occurred less frequently with obicetrapib

- Comparable **blood pressure–related outcomes**
- No difference in abnormal **liver- or muscle-related endpoints**
- Fewer rates of **new-onset diabetes mellitus (NODM) or worsening glycemic control**
- Numerically fewer **estimated glomerular filtration rate (eGFR) decline events**
- No increased risk of **macular degeneration**

Results

- A total of 2880 participants are included in the safety analysis set
- Baseline characteristics were well-balanced between patients treated with obicetrapib or placebo (**Table 1**)
- TEAEs occurred in 62% of placebo-treated participants and 60.2% of obicetrapib-treated participants (Risk Ratio [RR] 0.97 [0.91, 1.03], **Table 2**)
- Events of special interest (identified based on nonclinical or previous clinical findings with obicetrapib, known effects with other LLTs, and events related to previous CETP inhibitors) are summarized in **Table 3**
- Deaths were infrequent and comparable between groups, with 14 (1.5%) in the placebo arm and 22 (1.1%) in the obicetrapib arm (RR 0.79, Confidence Interval [CI] 0.40-1.53)
  - CV deaths occurred in 8 (0.8%) placebo-treated participants and 12 (0.6%) obicetrapib-treated participants, with no significant difference versus placebo (Hazard Ratio [HR] 0.74; 95% CI 0.30–1.82)
  - Coronary heart disease deaths were similarly rare; 7 (0.7%) on placebo and 9 (0.5%) on obicetrapib—with no statistical separation between groups (HR 0.63; 95% CI 0.24–1.70)
- One TESAE, an episode of aggravated heart failure, was reported but deemed unrelated to study drug
- Reasons for treatment discontinuation and early study discontinuation are individually listed in **Table 4**
- Obicetrapib demonstrated no clinically meaningful differences in blood pressure versus placebo

Table 1. Baseline clinical characteristics and medication use

Parameter	Placebo (N=961)	Obicetrapib (N=1919)
Age – years ± 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 ± 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. 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 3. Events of special interest and changes in vital signs

	Placebo (N=961)	Obicetrapib (N=1919)	Risk Ratio (95% CI)
Events of special interest			
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3x upper limit of normal (ULN)	8 (0.8)	10 (0.5)	0.63 (0.25, 1.58)
Bilirubin > 2x ULN	6 (0.6)	2 (0.1)	0.17 (0.03, 0.83)
Creatine kinase > 5x 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/1.73m² 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
AEs suggestive of heart failure*			
Cardiac failure	0	3 (0.2)	N/A
Cardiac failure congestive	1 (0.1)	2 (0.1)	1.00 (0.09, 11.0)
Cardiac failure chronic	1 (0.1)	0	N/A
Changes in vital signs from baseline to day 84			
Heart rate – beats/min	0.40	-0.22	-0.62 (-1.25, 0)†
Systolic blood pressure – mmHg	-0.46	-0.11	0.35 (-0.62, 1.33)†
Diastolic blood pressure – mmHg	-0.16	-0.22	-0.06 (-0.67, 0.55)†

**Not a prespecified AE of special interest.*

†Difference in means (95% CI).

Table 4. Discontinuations

	Placebo (N=961)	Obicetrapib (N=1919)
Discontinued treatment	122 (12.7%)	205 (10.7%)
AE	50 (5.2%)	76 (4.0%)
Subject decision	37 (3.8%)	61 (3.2%)
Lost to follow-up	13 (1.4%)	31 (1.6%)
Withdrawal of consent	9 (0.9%)	10 (0.5%)
Death	8 (0.8%)	10 (0.5%)
Physician decision	2 (0.2)	4 (0.2%)
Pregnancy	0 (0.0%)	1 (0.1%)
Other	3 (0.3%)	12 (0.6%)
Discontinued study early	57 (5.9%)	96 (5.0%)
Lost to follow-up	17 (1.8%)	38 (2.0%)
Withdrawal of consent	20 (2.1%)	23 (1.2%)
Death	13 (1.4%)	20 (1.0%)
AE	0 (0.0%)	1 (0.1%)
Physician decision	0 (0.0%)	1 (0.1%)
Other	7 (0.7%)	13 (0.7%)

Conclusion

- **Overall TEAEs, study drug–related TEAEs, serious TEAEs, and discontinuations due to adverse events occurred at similar frequencies between obicetrapib and placebo, consistent with the safety profile observed in the individual trials**
- **This analysis supports the safety and tolerability of obicetrapib in patients with high cardiovascular risk**

Clinical Relevance

- **If confirmed in larger and adequately powered trials, the safety of obicetrapib relative to hepatic, kidney, muscle, and glycemic events may favorably differentiate it from other available LLTs**

Affiliations and Disclosures: AJN: Victoria Heart Institute. Monash University Clayton AU: COI: AstraZeneca, Amgen, Eli Lilly, Novartis, Novo Nordisk, Sanofi. SJN: AstraZeneca, NewAmsterdam, Amgen, Eli Lilly, Esperion, Novartis, Merck, Takeda, Sanofi-Regeneron, CSL, Daiichi-Sankyo, Silence ; SJN: Victoria Heart Institute. Monash University: AstraZeneca, NewAmsterdam, Amgen, Eli Lilly, Esperion, Novartis, Merck, Takeda, Sanofi-Regeneron, CSL, Daiichi-Sankyo, Silence.JJPK, MD, DK, NO, DLW, AH, MHD, employees of NewAmsterdam Pharma and hold stocks or options

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