Pooled On Treatment, Lipid Lowering Efficacy of the CETP Inhibitor Obicetrapib in Phase III Trials

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BACKGROUND

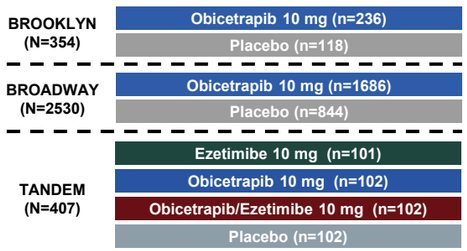
- Obicetrapib is a potent, selective CETP inhibitor in development for patients with HeFH or ASCVD[1]
- Prior phase 3 studies have consistently shown that obicetrapib, alone or in combination with ezetimibe, lowers LDL-C, non-HDL-C, and ApoB while markedly raising HDL-C[2-4]
- Because adherence can vary among clinical trial participants, reported lipid changes may not fully reflect the treatment effect specifically in patients who remain on therapy
- Evaluating patients who are pharmacologically confirmed to have maintained appropriate exposure to treatment may help reduce adherence-related variability and better characterize the magnitude of obicetrapib's lipid-lowering effects

OBJECTIVE

- To quantify the on-treatment lipid-lowering effectiveness of obicetrapib and the obicetrapib–ezetimibe FDC on top of maximum-tolerated LLT by evaluating a pooled pharmacokinetic-confirmed on-treatment ASCVD or HeFH population across three phase 3 trials

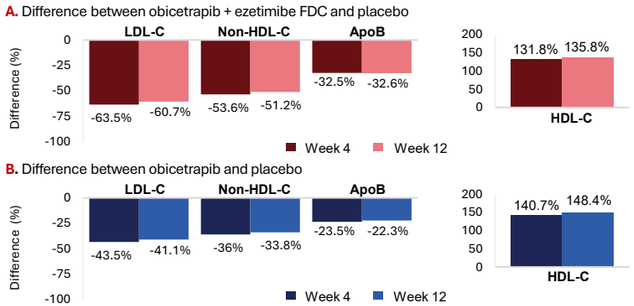
METHODS

- 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 LLT



- To be included, patients were required to have PK-confirmed on-treatment status (obicetrapib >100 ng/mL) and complete baseline, week 4, and week 12 labs
- Lipids were directly measured except LDL-C, which used the Martin-Hopkins equation
- Outcomes are reported as difference in LS mean percentage change versus placebo
- LDL-C goal attainment was assessed at <70 mg/dL and <55 mg/dL per the 2022 ACC Expert Consensus Pathway

Figure 1: LS Mean Percentage Change in Lipid Biomarkers vs Placebo at Weeks 4 and 12



P<0.0001 for every TANDEM FDC and obicetrapib vs placebo comparison, at both week 4 and week 12. Means reflect adjustment for baseline lipid levels.

Figure 2: Waterfall Plots Showing Distribution of Individual LDL-C % Change in the Treatment Groups

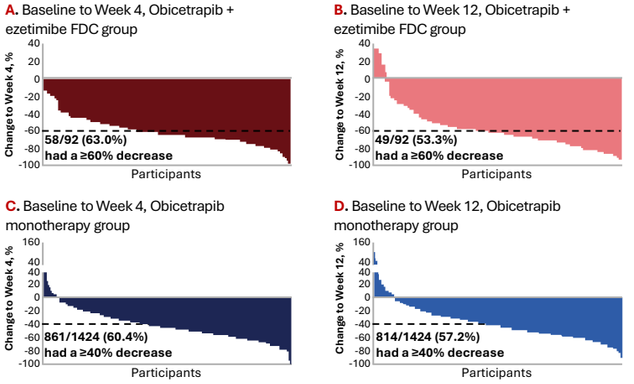


Figure 3: LDL-C Goal Attainment at Week 12

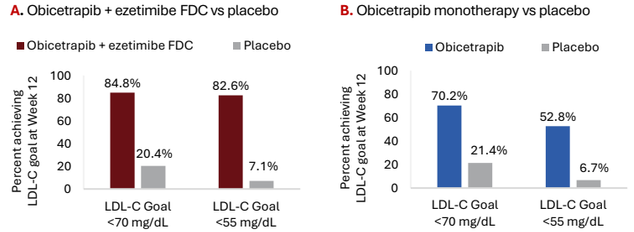


Table 1: Baseline Characteristics

	Obicetrapib + Ezetimibe FDC vs Placebo From TANDEM			Obicetrapib Monotherapy vs Placebo From Pooled Phase 3 Trials		
	FDC (n=92)	Placebo (n=98)	*P* value	Obicetrapib (n=1424)	Placebo (n=1015)	*P* value
Age, years*	68 (64, 73)	68 (62, 72)	0.40	66 (59, 72)	66 (58, 72)	0.41
Female†	48 (52.2)	48 (49.0)	0.66	499 (35.0)	377 (37.1)	0.29
Study†						
BROADWAY	-	-	--	1146 (80.5)	803 (79.1)	0.0022
BROOKLYN	-	-		191 (13.4)	114 (11.2)	
TANDEM	92 (100)	98 (100)		87 (6.1)	98 (9.7)	
Baseline statin†						
High dose	70 (76.1)	74 (75.5)	0.99	969 (68.0)	704 (69.4)	0.79
Low or moderate dose	14 (15.2)	15 (15.3)		305 (21.4)	209 (20.6)	
None	8 (8.7)	9 (9.2)		150 (10.5)	102 (10.0)	
History of ASCVD†	65 (70.7)	61 (62.2)	0.22	1165 (81.8)	815 (80.3)	0.35
BMI,* kg/m^2	32.1 (27.3, 36.3)	29.9 (26.7, 35.6)	0.34	28.8 (25.7, 32.9)	29.0 (26.0, 32.8)	0.33
eGFR,* ml/min/1.73m^2	81 (65, 92)	85 (73, 97)	0.08	88 (72, 98)	88 (74, 98)	0.25
hsCRP,* mg/L	2.4 (0.9, 4.4)	1.9 (0.8, 4.6)	0.82	1.3 (0.6, 3.3)	1.4 (0.6, 3.4)	0.07
Baseline lipids‡						
LDL-C, mg/dL	95.5 (89.7, 101.4)	92.7 (87.0, 98.3)	0.49	101.0 (98.9, 103.0)	102.3 (99.9, 104.7)	0.42
Non–HDL-C, mg/dL	120.8 (113.9, 127.6)	116.0 (109.4, 122.7)	0.33	125.0 (122.7, 127.3)	126.8 (124.1, 129.6)	0.30
HDL-C, mg/dL	48.3 (45.2, 51.4)	50.0 (47.0, 53.0)	0.45	49.9 (49.1, 50.7)	49.7 (48.8, 50.6)	0.77
ApoB, mg/dL	87.8 (83.5, 92.0)	85.7 (81.5, 89.8)	0.49	91.8 (90.4, 93.2)	92.6 (91.0, 94.3)	0.43

Note: Participants are from the MITT OT population from each study with available baseline, week 4, and week 12 Martin-Hopkins LDL-C; Obicetrapib participants also needed obicetrapib concentration ≥100 ng/mL at week 12. *Median (Q1, Q3). †n (%). ‡LS mean (95% CI).
BMI, body mass index; eGFR, estimated glomerular filtration rate; hsCRP, high-sensitivity C-reactive protein.

Table 2: Safety Population Data Table

	Obicetrapib + Ezetimibe FDC vs Placebo From TANDEM		Obicetrapib Monotherapy vs Placebo From Pooled Phase 3 Trials	
	FDC (n=92)	Placebo (n=98)	Obicetrapib (n=1424)	Placebo (n=1015)
Any TEAE	46 (50.0)	36 (36.7)	884 (62.1)	611 (60.2)
Any TEAE by severity				
Mild	24 (26.1)	16 (16.3)	435 (30.5)	285 (28.1)
Moderate	21 (22.8)	18 (18.4)	361 (25.4)	254 (25.0)
Severe	1 (1.1)	2 (2.0)	88 (6.2)	72 (7.1)
Any study drug–related TEAE	2 (2.2)	4 (4.1)	42 (2.9)	47 (4.6)
Any study drug–related TEAE by severity				
Mild	2 (2.2)	2 (2.0)	29 (2.0)	30 (3.0)
Moderate	0	2 (2.0)	12 (0.8)	17 (1.7)
Severe	0	0	1 (0.1)	0
Any TEAE leading to discontinuation	1 (1.1)	3 (3.1)	28 (2.0)	42 (4.1)
Any TEAE leading to death	0	0	13 (0.9)	12 (1.2)
Any serious TEAE	1 (1.1)	2 (2.0)	158 (11.1)	118 (11.6)
Any study drug–related serious TEAE	0	0	0	0

Note: Values in table are n (%)

Table 3: Events of Special Interest and Vital Signs

	Obicetrapib (n=1424)	Placebo (n=1015)	Risk Ratio (95 % CI)
AST or ALT >3x ULN	9 (0.6)	8 (0.8)	0.88 (0.53, 1.47)
Bilirubin >2x ULN	1 (0.1)	6 (0.6)	0.48 (0.36, 0.66)
Creatine kinase >5x ULN	6 (0.4)	7 (0.7)	0.77 (0.47, 1.28)
NODM or worsening glycemic control	472 (33.1)	383 (37.7)	0.89 (0.81, 0.98)
eGFR <30 ml/min/1.73m^2 or ≥25% decrease in eGFR from baseline	94 (6.6)	88 (8.7)	0.85 (0.73, 0.99)
Increase in serum creatinine ≥0.3 mg/dL from baseline	70 (4.9)	73 (7.2)	0.80 (0.68, 0.95)
Macular degeneration	1 (0.1)	0	--
			Difference (95% CI)
Change in vital signs to week 12:			
Heart rate, beats/min	-0.47 (-0.88, -0.05)	0.28 (-0.22, 0.77)	-0.75 (-1.39, -0.10)
Systolic BP, mmHg	0.05 (-0.61, 0.70)	-0.44 (-1.22, 0.34)	0.49 (-0.53, 1.51)
Diastolic BP, mmHg	-0.12 (-0.53, 0.28)	-0.10 (-0.58, 0.38)	-0.02 (-0.65, 0.61)

Note: values in table are n (%) or mean (95% CI).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CI, confidence interval; NODM, new onset diabetes mellitus; ULN, upper limit of normal.

RESULTS AND DISCUSSION

- The pooled analysis included 2,531 patients and baseline characteristics were well balanced **(Table 1)**
- Both obicetrapib + ezetimibe FDC and obicetrapib monotherapy produced statistically significant reductions in LDL-C, non-HDL-C, and ApoB and significant increases in HDL-C vs placebo at weeks 4 and 12 **(Figure 1)**
- Most obicetrapib + ezetimibe FDC patients achieved ≥60% LDL-C reduction from baseline and most obicetrapib monotherapy patients achieved ≥40% LDL-C reduction from baseline by week 4 and 12 **(Figure 2)**
- At week 12, LDL-C goal attainment was markedly higher with obicetrapib than with placebo: with the obicetrapib + ezetimibe FDC, 84.8% of patients reached LDL-C <70 mg/dL (vs 20.4%) and 82.6% reached <55 mg/dL (vs 7.1%); goal attainment was 70.2% and 52.8% with monotherapy (vs 21.4% and 6.7% with placebo, respectively) **(Figure 3)**
- TEAEs were generally moderate and transient and did not differ from placebo **(Table 2)**
- A significant reduction in events of special interest was observed for bilirubin increase, NODM, eGFR decline, and serum creatinine increase **(Table 3)**

CONCLUSIONS

- Obicetrapib, alone or in combination with ezetimibe, delivered clinically meaningful LDL-C lowering across a large pooled phase 3 population
  - Most patients reached guideline-recommended LDL-C goals, with the greatest attainment achieved using the obicetrapib + ezetimibe FDC
  - Rapid lipid-lowering was observed by Week 4 and sustained through Week 12
  - Both regimens also lowered non-HDL-C and ApoB and raised HDL-C, indicating broad improvement across the atherogenic lipoprotein profile
  - These once-daily oral options may help more patients reach LDL-C and other lipoprotein targets that remain difficult to achieve with current therapies
- Obicetrapib with or without ezetimibe was tolerable with no new safety signals observed

ApoB, apolipoprotein B; ASCVD, atherosclerotic cardiovascular disease; CETP, cholesteryl ester transfer protein; FDC, fixed-dose combination; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; LS, least-squares; PK, pharmacokinetic; TEAE, treatment-emergent adverse event.

AFFILIATIONS AND DISCLOSURES: Mathijs AC de Kleer, Jeremy Smart, Marc Ditmarsch, John JP Kastelein, Nancy Ortiz, Andrew Hsieh, and Michael H Davidson are employees and shareholders at NewAmsterdam Pharma and receive stock or stock options; 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; Kausik K Ray: 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; Stephen J Nicholls: Victoria Heart Institute. Monash University: AstraZeneca, NewAmsterdam, Amgen, Eli Lilly, Esperion, Novartis, Merck, Takeda, Sanofi-Regeneron, CSL, Daiichi-Sankyo, Silence.

1. Kastelein JJP et al. *Curr Atheroscler Rep*. 2024;26(2):35-44. **2.** Nicholls SJ et al. *N Engl J Med*. 2025;393(1):51-61. **3.** Nicholls SJ et al. *Nat Med*. 2026;32(3):1052-1060. **4.** Sarraju A et al. *Lancet*. 2025;405(10491):1757-1768.

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