CETP Inhibition With Obicetrapib Preserved Kidney Function in Patients at High Cardiovascular Risk: Results From the BROADWAY Trial

Updated Analysis to Include Post Hoc Pooled Results From the BROADWAY and BROOKLYN Trials

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Background

- Cardiovascular disease (CVD) is a leading cause of mortality in patients with chronic kidney disease (CKD), particularly those with severe renal dysfunction[1,2]
- Low levels of high-density lipoprotein cholesterol (HDL-C) in patients with CKD is associated with adverse cardiovascular and renal outcomes (**Figure 1A**)[3,4]
- Cholesteryl ester transfer protein (CETP) inhibition raises HDL-C and may restore its function in renal protection (**Figure 1B**)[5]

Objective

- To inform the clinical potential of the use of the CETP inhibitor obicetrapib in patients with diminished renal function

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 lipid-lowering therapy (LLT) over 1 year
  - BROOKLYN included 354 adult participants with heterozygous familial hypercholesterolemia (HeFH) with fasting low-density lipoprotein cholesterol (LDL-C) ≥70 mg/dL and triglycerides <400 mg/dL
  - BROADWAY included 2530 adult participants with HeFH and/or atherosclerotic cardiovascular disease (ASCVD) and LDL-C ≥100 mg/dL or LDL-C ≥55 mg/dL with risk factors
- Fasting lipoprotein lipids and laboratory investigations, including those for estimated glomerular filtration rate (eGFR)—calculated with the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula—were measured, and adverse events, events of special interest (including renal abnormalities), and concomitant medication use were assessed
- A pooled analysis of both clinical trials was performed and included all randomized participants with at least 1 postbaseline eGFR assessment (n=2832) or at least 1 postbaseline urine albumin-to-creatinine ratio (UACR) measurement (n=1897) (**Figure 1B**)
- Treatment comparisons of the annualized change in eGFR and the annualized percent change in UACR were performed using repeated measures mixed effects models with random intercept, unstructured covariance matrices and terms for baseline value, treatment assignment, study, time, and the interaction between treatment assignment and time

Results

- Baseline characteristics are shown in **Table 1.** Baseline demographics, blood pressure, and concomitant medications (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, sodium-glucose cotransporter 2 inhibitors) were well-balanced in BROADWAY and BROOKLYN and remained stable throughout the trials
- The pooled treatment comparisons of the annualized change in eGFR and annualized percent change in UACR are shown in **Figure 1C and 2**
  - Obicetrapib had a slower annualized decline in eGFR compared with placebo, and when eGFR assessments after the last dose of study drug were excluded in an on-treatment analysis, there was an even larger difference
  - There was no significant difference observed between groups in annualized changes in UACR
  - There were no obvious differences in events of special interest related to liver and kidney function, new diabetes or worsening glycemic control, macular degeneration, or cardiovascular events
- Waterfall plots demonstrating individual-level eGFR change at 1 year for obicetrapib and placebo are shown in **Figure 3**
  - There was no evidence of heterogeneity in treatment effects by baseline eGFR <60 mL/min/1.73 m^2 vs ≥60 mL/min/1.73 m^2 for placebo ($P_{interaction}$=0.44) or obicetrapib ($P_{interaction}$=0.56)
- A spline analysis of time-weighted achieved HDL-C vs renal events demonstrated a strong association between higher achieved HDL-C and lower renal event risk (spline nominal *P*<0.0001), independent of baseline HDL-C and eGFR (**Figure 1C and 4**)
- Participants receiving obicetrapib compared with placebo had nominally fewer composite renal events (36/1888 [1.9%] vs 28/944 [3.0%]), including fewer cardiovascular deaths, fewer cases of eGFR <15 mL/min/1.73 m^2, and fewer cases of ≥40% decline in eGFR

Figure 1. CETP Inhibition With Obicetrapib: Potential Renoprotection via Increased HDL

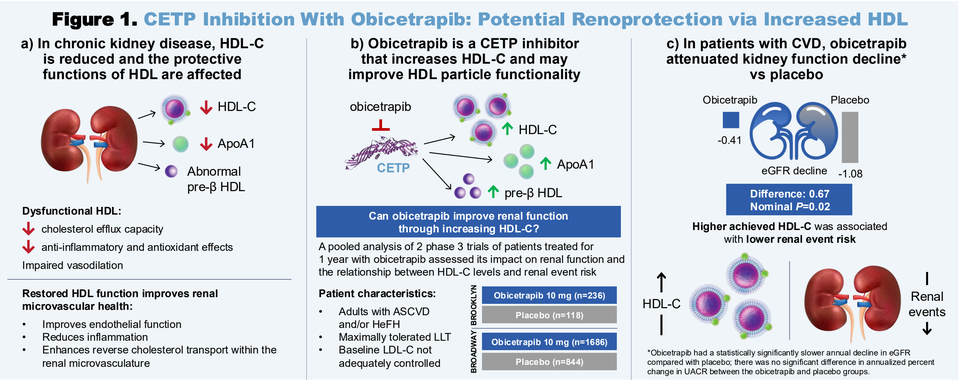


Table 1. Baseline clinical characteristics and medication use

Parameter	Obicetrapib (n=1888)	Placebo (n=944)
Age, years	64 (11)	64 (10)
Females, n (%)	680 (36.0)	337 (35.7)
White race, n (%)	1437 (76.1)	745 (78.9)
Body mass index, kg/m²	29.4 (5.3)	29.7 (5.7)
History of ASCVD, n (%)	1559 (82.6)	778 (82.4)
HeFH, n (%)	506 (26.8)	254 (26.9)
Diabetes, n (%)	658 (34.9)	355 (37.6)
Hypertension, n (%)	1448 (76.7)	738 (78.2)
eGFR, mL/min/1.73m²	85.1 (18.2)	85.7 (17.7)
HbA1c, %	6.2 (1.0)	6.2 (1.0)
LDL-C, mg/dL	101 (39)	101 (41)
HDL-C, mg/dL	50 (15)	50 (15)
ApoB, mg/dL	93 (27)	94 (28)
Triglyceride, mg/dL	122 (89, 170)	127 (91, 175)
hsCRP, mg/L	1.3 (0.6, 3.4)	1.4 (0.6, 3.2)
Medication use		
Statins, n (%)	1712 (90.7)	863 (91.4)
High-intensity statins, n (%)	1314 (69.6)	648 (68.6)
Ezetimibe, n (%)	573 (30.3)	274 (29.0)
PCSK9 inhibitor, n (%)	93 (4.9)	59 (6.3)

Continuous variables presented as mean (standard deviation) or median (quartile 1, quartile 3) and categorical variables as number (percentage).

Figure 2. Treatment comparison of annualized change in eGFR (mL/min/1.73 m^2 per year) and UACR (% change) in a pooled analysis of BROADWAY and BROOKLYN

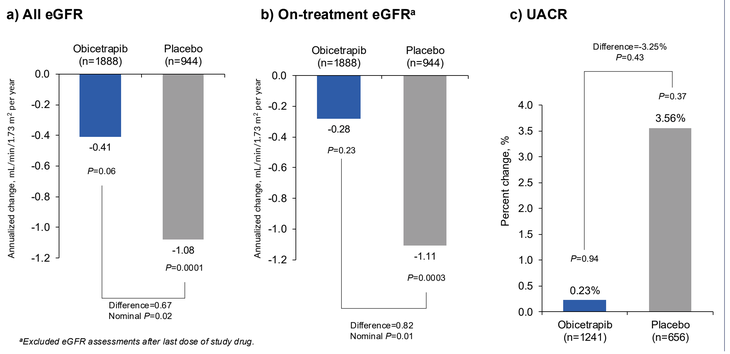


Figure 3. Predicted eGFR change at 1 year for patients treated with obicetrapib (a) and patients treated with placebo (b)

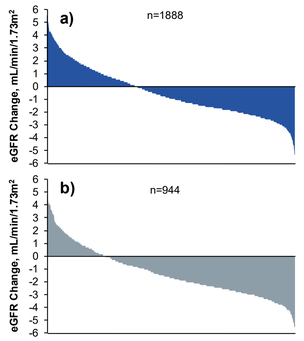
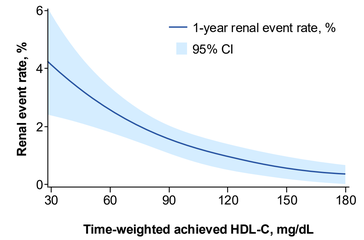


Figure 4. Spline of time-weighted achieved HDL-C vs the absolute risk of the renal event composite through 1 year in BROADWAY and BROOKLYN



Analysis included all intent-to-treat participants with at least 1 postbaseline eGFR assessment. Spline is restricted cubic with knots at the 33rd and 67th percentiles and spans the approximate 1st to 99th percentiles of time-weighted achieved HDL-C. There were 64 events among 2832 participants. Spline nominal *P*<0.0001 from proportional hazard model reflects adjustment for HDL-C, baseline eGFR, and study.

Conclusions

- **In patients at high cardiovascular risk, CETP inhibition with obicetrapib demonstrated signals of renal preservation, including significantly slower eGFR decline, fewer renal events, and a favorable trend in time-to-renal event analyses**
- **There was a strong association between higher achieved HDL-C and reduced renal risk, independent of baseline HDL-C and baseline eGFR**
- **These analyses reinforce the plausibility of CETP inhibition as a renoprotective mechanism that is potentially mediated through increased HDL, which would be expected to improve endothelial function, reduce inflammation, and enhance reverse cholesterol transport within the renal microvasculature[3,6]**

Clinical Relevance

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

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1. Thompson S, James M, Wiebe N, et al. Cause of death in patients with reduced kidney function. *J Am Soc Nephrol.* 2015;26(10):2504-2511. **2.** Hassan MB, Siddique S, Maheshwari SK, et al. Chronic kidney disease and cardiovascular risk: Pathophysiology and interventional approaches - systematic review. *Medicine (Baltimore).* 2025;104(49):e46189. **3.** Pavanello C, Ossoli A. HDL and chronic kidney disease. *Atheroscler Plus.* 2023;52:9-17. **4.** Navaneethan SD, Schold JD, Walther CP, et al. High-density lipoprotein cholesterol and causes of death in chronic kidney disease. *J Clin Lipidol.* 2018;12(4):1061-1071.e7 **5.** Schmidt AF, Hunt NB, Gordillo-Marañón M, et al. Cholesteryl ester transfer protein (CETP) as a drug target for cardiovascular disease. *Nat Commun.* 2021;12(1):5640. **6.** Rysz J, Gluba–Brzózka A, Rysz-Górzyńska M, Franczyk B. The role and function of HDL in patients with chronic kidney disease and the risk of cardiovascular disease. *Int J Mol Sci.* 2020;21(2):601.