# Impact of Obicetrapib on Major Adverse Cardiovascular Events: A Pooled Analysis of Phase 3 Clinical Trials

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## Background

- Cholesteryl ester transfer protein (CETP) plays a pivotal role in lipid metabolism[1-5]
- Genomic studies and post hoc analyses of clinical trials demonstrated that the cardiovascular (CV) protection associated with low CETP activity results from lower levels of low-density lipoprotein cholesterol (LDL-C) and not increased levels of high-density lipoprotein cholesterol (HDL-C)[6-10]
- Early CETP inhibitor programs focused on HDL-C raising and failed to consistently demonstrate a reduction in CV events[7,8,11]
- Obicetrapib is a highly selective CETP inhibitor which is well-tolerated, lowers levels of LDL-C, apolipoprotein B (ApoB) and lipoprotein (a) (Lp[a]), and raises HDL-C when administered on top of maximally tolerated lipid-lowering therapy (LLT) in studies of high-risk patients with either heterozygous familial hypercholesterolemia (HeFH) or atherosclerotic cardiovascular disease (ASCVD)[12-15]
- The effects of obicetrapib on major adverse cardiovascular events (MACE) have not been investigated

## Objective

- To investigate the rate of CV events in patients treated with obicetrapib compared with placebo in a pooled analysis of 2 large phase 3 lipid-lowering trials over 12 months of treatment in high CV risk cohorts

## 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
  - BROOKLYN included 354 adult participants with HeFH with fasting LDL-C ≥70 mg/dL and triglycerides <400 mg/dL
  - BROADWAY included 2530 adult participants with HeFH and/or ASCVD and LDL-C ≥100 mg/dL or LDL-C ≥55 mg/dL with risk factors
- A pooled analysis of both clinical trials was performed as they involved administration of obicetrapib or placebo for 12 months
  - Potential CV events were adjudicated by a central committee who were blinded to the treatment status of the patients
  - Treatment groups were compared via proportional hazards modes, and the relationship between treatment effects and time since randomization was determined through post hoc models
  - The association between achieved levels of lipids and lipoproteins with the rate of MACE was investigated using restricted cubic spline models

**Figure 1.** Median percent changes in lipid and lipoprotein levels

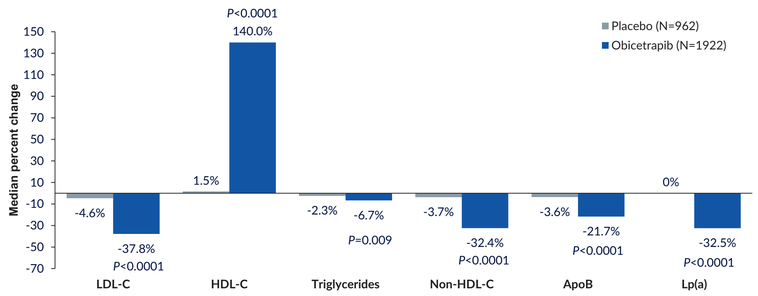



**Table 1.** Baseline clinical characteristics

| Parameter | Placebo (N=962) | Obicetrapib (N=1922) |
|---|---|---|
| Median age (years) | 65.0 | 66.0 |
| Females (%) | 35.9 | 36.3 |
| White race (%) | 78.7 | 76.0 |
| Body mass index (kg/m$^2$) | 28.9 | 28.7 |
| ASCVD (%) | 82.4 | 82.5 |
| HeFH (%) | 27.0 | 26.9 |
| Diabetes (%) | 37.6 | 34.9 |
| Hypertension (%) | 78.4 | 76.5 |
| Current smoker (%) | 20.5 | 20.9 |

**Table 2.** Concomitant medications and median baseline lipids

| Parameter | Placebo (N=962) | Obicetrapib (N=1922) |
|---|---|---|
| Statins (%) | 91.6 | 90.6 |
| HIS (%) | 68.7 | 69.6 |
| Ezetimibe (%) | 29.0 | 30.2 |
| PCSK9 inhibitor (%) | 6.1 | 4.9 |
| LDL-C (mg/dL) | 92.0 | 93.0 |
| HDL-C (mg/dL) | 48.0 | 48.0 |
| Triglycerides (mg/dL) | 127.0 | 122.0 |
| Non-HDL-C (mg/dL) | 116.0 | 116.0 |
| ApoB (mg/dL) | 88.0 | 88.0 |
| Lp(a) (nmol/L) | 40.0 | 40.5 |

**Figure 2.** Incidence of the composite of coronary heart disease death, myocardial infarction, ischemic stroke, or coronary revascularization

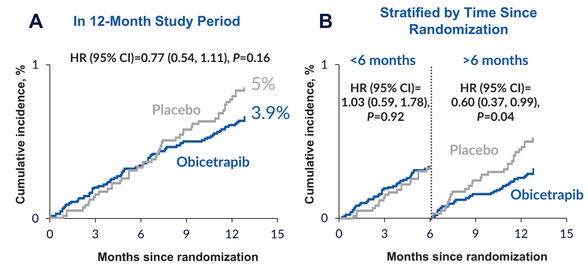



**Figure 3.** Incidence of the composite of coronary heart disease death, myocardial infarction, or coronary revascularization

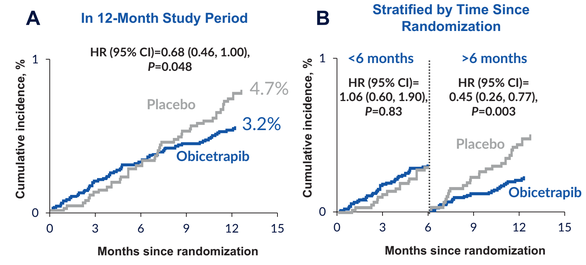
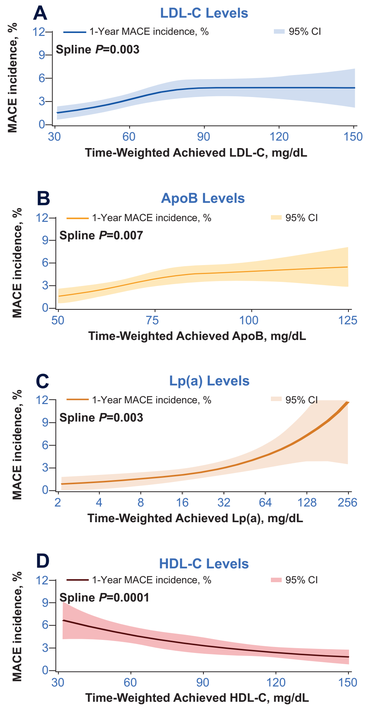



**Figure 4.** Achieved levels of LDL-C, ApoB, Lp(a), and HDL-C and MACE rates




## Results

- Baseline and clinical characteristics, including concomitant medications and lipid levels, are shown in **Tables 1** and **2**
- Treatment with obicetrapib produced greater reductions in LDL-C (-37.8% vs -4.6%), ApoB (-21.7% vs -3.6%), and Lp(a) (-32.5% vs 0%) and greater increases in HDL-C (+140.0% vs +1.5%) compared with placebo (**Figure 1**)
- The rate of coronary heart disease death, myocardial infarction, ischemic stroke, or coronary revascularization was lower with obicetrapib (3.9% vs 5.0%; HR: 0.77; 95% CI: 0.54–1.11; *P*=0.16), with a risk reduction in the second 6 months (HR: 0.60; 95% CI: 0.37–0.99; *P*=0.04) (**Figure 2**)
- The rate of coronary heart disease death, myocardial infarction or coronary revascularization was lower with obicetrapib (3.2% vs 4.7%; HR: 0.68; 95% CI: 0.46–1.00; *P*=0.048), with a risk reduction in the second 6 months (HR: 0.45; 95% CI: 0.26–0.77; *P*=0.003) (**Figure 3**)
- CV event rates were directly associated with achieved levels of LDL-C, ApoB, and Lp(a) and inversely associated with HDL-C levels (**Figure 4**)

## Conclusions

- **Treatment of high CV risk patients with obicetrapib resulted in a reduction in coronary events, which became evident beyond 6 months of treatment**
- **Achieved levels of LDL-C, ApoB, Lp(a), and HDL-C were associated with the ongoing risk of CV events**
- **This highlights the potential for obicetrapib to be a useful adjunctive therapy to lower CV risk**
- **The ultimate impact of obicetrapib on CV events is being evaluated in the ongoing PREVAIL trial of over 9000 patients**[16]

## Acknowledgements

**These data have been previously presented as a Late Breaker oral presentation at the European Society of Cardiology (ESC) 2025 Scientific Sessions, on Monday, September 1, 2025.**

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