

Optimal Dose Identification of Baxdrostat as an Antihypertensive Agent: A Secondary Analysis Using Sigmoid Emax Modeling, Parametric Bootstrap, and Monte Carlo Simulation

Abdulaziz Alzahrani, MCP, PhD*

ABSTRACT

To characterize the dose–response relationship of baxdrostat using Sigmoid Emax modeling, quantify parameter uncertainty via parametric bootstrap ($n=5,000$) and Monte Carlo simulation ($n=10,000$), assess risk of bias using Cochrane RoB 2, rate evidence certainty with GRADE, and evaluate conclusion robustness across seven pre-specified sensitivity scenarios. This analysis is exploratory, not confirmatory. Pre-registered secondary analysis of aggregate data from published randomized controlled trials. PRISMA 2020 reporting guidelines followed. Multi-centre Phase II (BrigHTN, NEJM 2023) and Phase III (BaxHTN, NEJM 2025) randomized controlled trials; 24-hour ambulatory blood pressure monitoring substudy (Bax24, AHA 2025). Placebo-adjusted Δ SBP data from four dose levels (0, 0.5, 1, 2 mg) were pooled. A Sigmoid Emax model was fitted using nonlinear least squares with a biologically constrained Hill coefficient ($n=2.0$, supported by prior CYP11B2 pharmacodynamic literature). Parametric bootstrap resampling ($n=5,000$) from published standard errors generated 95% confidence intervals. Monte Carlo simulation ($n=10,000$; $\sigma=15$ mmHg per BaxHTN protocol; 264 patients/arm) estimated dose-specific outcome probabilities. Sensitivity analyses spanning Hill coefficient values of 1.0–2.5 and σ values of 12–18 mmHg were performed to assess the impact of key modelling assumptions. Bootstrap estimates: $E_{max} = -12.51$ mmHg (95% CI: -17.23 to -8.87); $ED_{50} = 0.873$ mg (95% CI: 0.591 – 1.268 mg). The 1 mg dose achieved 56.2% (95% CI: 44.1–67.7%) of E_{max} . Monte Carlo results at 1 mg: mean Δ SBP = -7.01 mmHg (95% CI: -8.45 to -5.51); $P(\Delta$ SBP ≥ 10 mmHg) = 42.1%; $P(\text{SBP} < 130 \text{ mmHg}) = 28.2\%$. Incremental Δ SBP of 2 mg over 1 mg: 3.37 mmHg (95% CI: 1.65–5.60). eGFR decline $\geq 30\%$: 15.6% (2 mg), 12.6% (1 mg), 1.5% (placebo). Sensitivity analysis: robust in 5/7 scenarios. BaxHTN: Low Risk of bias (RoB 2). Primary efficacy and safety outcomes: GRADE HIGH certainty. Baxdrostat 1 mg once daily is the pharmacodynamically optimal antihypertensive dose in this exploratory model-based analysis, achieving ~56% of E_{max} with a more favorable renal safety profile than 2 mg. Dose escalation to 2 mg is warranted only in resistant hypertension with documented aldosterone excess and preserved renal function (eGFR ≥ 60 ml/min/1.73 m²), with mandatory eGFR and potassium monitoring. These findings require validation using individual patient data.

Keywords: baxdrostat; aldosterone synthase inhibitor; CYP11B2; sigmoid Emax model; Monte Carlo simulation; hypertension; dose optimization; pharmacometrics; bootstrap; GRADE

Bahrain Med Bull 2026; 48 (3): 3596 - 3607

* Department of Pharmacology and Toxicology, Faculty of Pharmacy
Al-Baha University, Al-Baha, Saudi Arabia. ORCID: 0000-0003-3918-40140
Email: Alzahraniar@bu.edu.sa