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REVIEW ARTICLE

Clinical Pharmacokinetics and Pharmacodynamics of Baxdrostat

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Abstract

Patients with hypertension are at an increased risk of cardiovascular disease and death. Resistant hypertension, or hypertension that is unsuccessfully treated with multiple antihypertensive medications, further exacerbates the complications and negative outcomes for patients. A new pathway, via aldosterone synthesis inhibition, is currently being studied as a method to reduce blood pressure values in patients who are currently taking other antihypertensive medications. This review presents and discusses the current pharmacokinetic, pharmacodynamic, and clinical and scientific evidence pertaining to baxdrostat, a novel aldosterone synthase inhibitor.

Key Points

Baxdrostat offers a novel pathway for treatment of hypertension in addition to other agents.

The mechanism of action targets the rate limiting step in aldosterone synthesis ultimately leading to decreased blood pressure values.

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1 Background

Hypertension (HTN) is one of the most widely prevalent chronic diseases that is reported to affect 45.4% of the US population over the age of 18 years, with a staggering prevalence of 51% among men and 39.7% among women [1]. In isolation, HTN itself is generally asymptomatic but serves as the major risk factor for developing cardiovascular disease (CVD) and is second only to cigarette smoking as a preventable cause of death for any reason [2]. The American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines define stage 1 HTN as an average systolic blood pressure (SBP) of 130–139 mm Hg or average diastolic blood pressure (DBP) 80–89 mm Hg and stage 2 HTN as an average SBP of 140 mm Hg or average DBP of 90 mm Hg [3]. Any adult with an SBP above 130 mm Hg has a twofold increase in CVD risk compared to adults with normal BP [4]. There persists a continuous graded relationship between BP and cardiovascular risks across all age groups, with earlier onset HTN being associated with both higher cardiovascular mortality in addition to end-organ damage [5]

Current treatment modalities for HTN include both lifestyle modifications, involving dietary changes and exercise, and pharmacological treatment across 15 different drug classes. First-line therapy for new onset HTN of under 140 mm Hg is lifestyle modifications which may include weight loss, a diet that is low in sodium and high in potassium, physical activity, and cessation or reduction of alcohol consumption [6]. If target BP goals are not reached or if the individual is diagnosed as having an elevated atherosclerotic

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CVD risk, medications are the next option [6]. Resistant HTN is defined as HTN that fails to reach the target BP with use of the maximum tolerated dose of at least three of the clinical mainstays including thiazides, calcium channel blockers, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers alongside a diuretic. This form of HTN has become a substantial issue to tackle as HTN and obesity have become more pervasive throughout society with an estimated 9–12% of adult patients in the USA with HTN are classified as having resistant HTN [7]. There are multiple factors that contribute to resistant HTN ranging from kidney disease, excess alcohol intake, and drug-induced causes with excess dietary salt being the principal driver in 90% of patients [8]. Once a proper diagnosis of resistant HTN has been made after ruling out causes of "pseudoresistance," such as improper measurements, inadequate dosages, or combinations and poor patient adherence, healthcare providers can begin to consider a new medication or treatment modality to add to their patient's HTN regimen.

Currently, the fourth-line therapy for HTN are the mineralocorticoid receptor antagonists, such as spironolactone, which shows a strong benefit of reducing BP by 22/10 mm Hg in patients with resistant HTN [9]. This does not come without side effects as spironolactone can cause hyperkalemia, gynecomastia, and renal insufficiency owing to off-target blockade of steroid receptors [9]. A new option currently under investigation is baxdrostat, an aldosterone synthase inhibitor (ASI), being investigated to treat resistant HTN.

1.1 Mechanism of Action

Baxdrostat is a selective, competitive inhibitor of aldosterone synthase, an enzyme that performs the rate-limiting step of aldosterone synthesis [10]. Aldosterone plays a vital role in the regulation of sodium transport and sodium-potassium linked transport across all epithelial structures via binding to steroid receptors and modulating genetic expression of these transporters. Inhibition of synthesis of aldosterone leads to a reduction in the reabsorption of sodium and secretion of potassium, and this in turn leads to a decrease in chronic blood volume ultimately resulting in decreased BP values [11]. Baxdrostat in comparison to others in the ASI family, has a 100:1 selectivity for enzyme inhibition of only aldosterone synthase without affecting an enzyme that shares 93% sequence similarity used in the synthesis of cortisol [10, 12]. Baxdrostat's novel structure and binding affinity allows it to decrease BP without causing the concomitant increase in cortisol levels as seen with other ASIs. This allows baxdrostat to be used for dose dependent reductions in BP without running the resultant risk of adrenocortical insufficiency, thus lessening the adverse risk profile previously seen with the ASI drug class. Aldosterone inhibition with baxdrostat has the additional ability to potentially decrease overall endothelial dysfunction owing to the reduction in BP decreasing the amount of endothelin-1 produced. This effect ultimately leads to more vasorelaxation and endothelial nitric oxide synthesis [13].

1.2 Preclinical Pharmacology and Pharmacokinetics

Once orally administered, baxdrostat undergoes rapid absorption with a median T_{max} seen within 1.5 h of dosing and an average half-life between 30 and 42 h [14]. Freeman et al. conducted a study showing that the apparent volume of distribution for baxdrostat ranges from 100 to 185 L, indicating extensive tissue penetration outside of the vascular compartment [10]. Baxdrostat is primarily metabolized by the liver [14]. Its primary metabolite, CIN-107-M, is found in much lower concentrations and does not substantially contribute to the effects of baxdrostat [10]. Baxdrostat is renally excreted, however, it was shown that renal impairment has no significant effect on maximum achieved concentration of drug (C_{max}), area under the curve (AUC), half-life, apparent plasma clearance, or renal clearance [14].

Owing to baxdrostat's mechanism of action and renal elimination, another study by Freeman et al. was designed to evaluate for potential interactions and pharmacokinetic implications associated with concomitant medications, namely metformin, as many patients diagnosed with HTN may have the additional diagnosis of type 2 diabetes, and thus be treated with metformin. This phase I, open-label, crossover study included 27 healthy adults who were randomized to receive 1000 mg metformin alone and 1000 mg metformin with 10 mg baxdrostat in a crossover manner. Study results showed a consistent pharmacokinetic profile for metformin when administered alone and with baxdrostat. On the basis of the C_{max} and AUC values for metformin alone and metformin with baxdrostat falling within the range to claim bioequivalence, it was determined that a pharmacokinetic drug–drug interaction did not exist between the two treatments. Additionally, pharmacokinetic parameters of baxdrostat confirmed study validity with a C_{max} of 118.9 $\pm$ 25.6 ng/mL, T_{max} of 1.7 $\pm$ 0.8 h, and terminal elimination rate constant of .033 $\pm$ 0.008 L/h [15]. Additional information on preclinical studies is provided in Table 1.

2 Clinical Studies

A phase II dose-ranging study, BrigHTN, evaluated multiple dose strengths of baxdrostat in participants with resistant HTN. In total, 275 participants were randomized to receive oral baxdrostat of 0.5 mg, 1 mg, or 2 mg or placebo once daily. Participants were included if they were on a stable regimen of at least three antihypertensives, including a

Table 1 Key results of selected preclinical PK/PD studies

Study details	Study population	Results
Freeman et al. [10]	• Healthy volunteers	• T_{max} within 4 h of dosing • Mean $t_{1/2}$ of 26–31 h • C_{max} and AUC_{0-24} increased proportionally with increasing doses • Dose-dependent reductions of plasma aldosterone observed at doses of at least 1.5 mg • Modest increase in 11-deoxycorticosterone • Dose-dependent increases of corticosterone levels observed • No effect on plasma cortisol, 11-deoxycortisol, or urine free cortisol • Mild increases in BUN and creatinine • Mild reduction is glomerular filtration rate • Dose-dependent decreases in plasma sodium • Dose-dependent increases in potassium levels • No dose-related trends in seated heart rate or blood pressure
Bogman et al. [24]	• Cynomolgus monkeys	• Aldosterone production decreased • No change in cortisol levels

diuretic, and had a seated SBP of at least 130 mm Hg and DBP of at least 80 mm Hg. Participants were excluded from the study if they were less than 70% compliant with their antihypertensive medication treatment regimen, were using a beta blocker for any primary indication other than HTN, or had a seated SBP 180 mm Hg or above and DBP 110 mm Hg or above. Additional inclusion and exclusion criteria are provided in Table 2. At week 12, baxdrostat produced dose-dependent changes in the least-squares mean SBP and the primary endpoint was met for both the 1 mg and 2 mg doses of baxdrostat with statistically significant decreases in SBP in these two groups compared with placebo (-20.3 ± 2.1 mmHg for the baxdrostat 2 mg group $P < 0.001$ and -17.5 ± 2.0 mmHg for the 1 mg group $P = 0.003$ compared with -9.4 mmHg for placebo). The group receiving baxdrostat at 0.5 mg daily showed a least-squares mean decrease in SBP of -12.1 ± 1.9 mm Hg, though not statistically significant compared with placebo. Additional measures were collected—diastolic blood pressure (DBP), changes in aldosterone levels, changes in serum cortisol levels, and changes in plasma renin activity. Changes in DBP appeared to be dose dependent with decreases of 8.6 mmHg, 11.8 mmHg, and 14.3 mmHg for baxdrostat 0.5 mg, 1 mg, and 2 mg, respectively compared with 9.2 mmHg decrease in the placebo group. There was also a sustained dose-dependent decrease in serum aldosterone levels from baseline through the end of the study while serum cortisol levels were not reduced in any baxdrostat group throughout. Ultimately, the study was terminated early, at the prespecified interim analysis, owing to meeting the criteria for overwhelming efficacy [12].

HALO, an 8-week, phase II study included 249 participants with uncontrolled HTN. Participants were included if they had a mean seated SBP $\geq$ 140 mmHg (or $\geq$ 130 mmHg if also presenting with diabetes) and currently taking a stable regimen of up to two antihypertensive medications [16]. Participants were excluded if they had a mean seated SBP 180 mm Hg or above, had chronic atrial fibrillation or had uncontrolled diabetes. Participants were randomized 1:1:1:1 to receive oral baxdrostat once daily at strengths of 0.5 mg, 1 mg, or 2 mg, or placebo. The primary outcome was the change from baseline in mean seated SBP, which produced similar results across each treatment group with a least squares mean reduction of 17.0 mmHg, 16.0 mmHg, and 19.8 mmHg for baxdrostat 0.5 mg, 1 mg, and 2 mg, respectively, compared with a reduction of 16.6 mmHg with placebo [17, 18]. The change from baseline in mean seated DBP was -5.8 mmHg, -5.0 mmHg, and -5.4 mmHg for baxdrostat at 0.5 mg, 1 mg, and 2 mg, respectively, compared with -5.9 mmHg with placebo, which also showed no statistically significant change across treatment groups [18]. It was noted that the placebo effect of this study was larger than anticipated and some study sites had low study medication adherence. It is possible that these factors contributed to the absence of significant reductions in BP with baxdrostat use for this population [16]. An open-label extension study including participants from the HALO study will continue

Table 2 Summary of inclusion and exclusion criteria for selected baxdrostat clinical studies

Study name	Inclusion criteria	Exclusion criteria
BrigHTN [12]	• On a stable regimen of ≥ 3 antihypertensive agents (one of which is a diuretic) • At least 70% compliant to their anti-hypertensive medication regimen • Seated BP ≥ 130/80 mmHg	• Seated SBP ≥ 180 mmHg or DBP ≥ 110 mmHg • BMI > 40 kg/m^2 • Documented eGFR < 45 mL/min/1.73 m^2 • Documented New York Heart Association stage III or IV chronic HF • Documented eGFR < 45 mL/min/1.73 m^2 • Use of a beta blocker for any primary indication other than systemic HTN
HALO [15–18]	• On a stable regimen of background antihypertensive agent(s) • Has mean seated SBP ≥ 140 mmHg or ≥ 130 mmHg if diabetic	• Has a mean seated SBP ≥180 mmHg • BMI >50 kg/m^2 • Documented estimated eGFR <30 mL/min/1.73 m^2 • Documented New York Heart Association stage III or IV chronic HF • Chronic permanent atrial fibrillation • Uncontrolled diabetes with glycated hemoglobin > 10%
BaxHTN [20]	• Mean seated SBP on AOBPM ≥ 140 mmHg and < 170 mmHg • uHTN subpopulation: have a stable regimen of two antihypertensive medications, from different therapeutic classes (at least one must be a diuretic), at maximum tolerated dose OR rHTN subpopulation: have a stable regimen of ≥ 3 antihypertensive medications, from different therapeutic classes (at least one must be a diuretic), at maximum tolerated dose • eGFR ≥ 45 mL/min/1.73 m^2	• Mean sitting SBP on attended AOBPM ≥ 170 mmHg • Mean seated DBP on attended AOBPM ≥ 110 mmHg • Serum sodium level < 135 mmol/L • Has the following known secondary causes of HTN: renal artery stenosis, uncontrolled or untreated hyperthyroidism, uncontrolled or untreated hypothyroidism, pheochromocytoma, Cushing's syndrome, aortic coarctation • New York Heart Association functional HF IV • Persistent atrial fibrillation
Bax24 [21]	• Mean seated SBP on AOBPM of ≥ 140 mmHg and < 170 mmHg at Screening. • Have a stable regimen of ≥ 3 antihypertensive medications, from different therapeutic classes (at least one should be a diuretic), at maximum tolerated dose • Beta blockers used to treat other conditions (i.e., migraine, HF, coronary artery disease) • Have eGFR ≥ 45 mL/min/1.73 m^2	• Mean seated SBP on AOBPM ≥ 170 mmHg • Mean seated DBP on AOBPM ≥ 110 mmHg • Serum sodium level < 135 mmol/L • Participant has the following known secondary causes of HTN: renal artery stenosis, uncontrolled or untreated hyperthyroidism, uncontrolled or untreated hypothyroidism, pheochromocytoma, Cushing's syndrome, aortic coarctation. • New York Heart Association functional HF class IV • Persistent atrial fibrillation
A Phase iii study to investigate the efficacy and safety of baxdrostat in combination with dapagliflozin on CKD progression in participants with CKD and high blood pressure [22]	• CKD and eGFR ≥ 30 and < 90 mL/min/1.73 m^2 • Urine albumin creatinine ratio > 200 mg/g (22.6 mg/mmol) and < 5000 mg/g (565 mg/mmol) • History of HTN and a SBP ≥ 130 mmHg	• SBP > 180 mmHg, or DBP > 110 mmHg • Known hyperkaliemia, defined as potassium of ≥ 5.5 mmol/L within 3 months • Serum sodium < 135 mmol/L • Type 1 diabetes mellitus or uncontrolled type 2 diabetes mellitus with glycated hemoglobin > 10.5% (> 91 mmol/mol) • New York Heart Association functional HF class IV • Stroke, transient ischemic cerebral attack, valve implantation or valve replacement, carotid surgery or carotid angioplasty, acute coronary syndrome, or hospitalization for worsening HF

AOBPM, automated office blood pressure measurement; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HF, heart failure; HTN, hypertension; SBP, systolic blood pressure

to evaluate effectiveness and long-term safety of baxdrostat up to 52 weeks [19].

BaxHTN is an ongoing phase III, randomized, double-blinded, placebo-controlled study that is examining once daily oral baxdrostat's ability to reduce resistant elevated SBP. Approximately 720 adult participants diagnosed with uncontrolled or resistant HTN will be randomized to receive baxdrostat at 1 mg, 2 mg, or placebo once daily. The primary outcome is change in seated SBP from baseline to week 12. The study will also evaluate the number of participants able to achieve SBP < 130 mmHg. Ultimately, results of this study are expected to be complete in October 2025 and further the investigation and placement of baxdrostat in the pipeline of resistant HTN management [20].

Currently underway is Bax24, a phase III study comparing oral, once daily baxdrostat of 2 mg to placebo. The study includes 212 adults with resistant HTN (defined here as unmet BP target despite utilizing at least three antihypertensive medication classes including a diuretic) to evaluate baxdrostat's ability to reduce their ambulatory SBP. Participants were included if they met criteria of a seated SBP of ≥ 140 mmHg and <170 mmHg at screening, eGFR ≥ 45, and serum potassium ≥ 3.5 and < 5 mmol/L. The primary outcome is expected to showcase the effects of the change from baseline ambulatory SBP at week 12. Results are expected in April 2025 [21].

Another phase III study aims to assess progression of CKD with baxdrostat in combination with dapagliflozin compared with dapagliflozin alone in participants with CKD and HTN. The study will include approximately 2500 participants with CKD and eGFR ≥ 30 and < 90 mL/min/1.73 m^2, urine albumin creatinine ratio between 20 and 5000 mg/g, and HTN with SBP ≥ 130 mmHg. The study is expected to be complete in December 2027 [22]. Table 3 summarizes the completed and ongoing clinical studies for baxdrostat.

2.1 Safety

In the BrigHTN study, a total of 232 adverse events were reported with a greater percentage of patients experiencing adverse events in the baxdrostat 1 mg and 2 mg groups compared with the baxdrostat 0.5 mg group and placebo group (52%, 48%, 35%, and 41%, respectively). The most commonly reported adverse events were urinary tract infections, hyperkalemia, headache, and fatigue. The majority of the adverse events reported were mild in severity and were unrelated to the study medication. Of note, urosepsis occurred in one patient, which accounted for 6 of the 18 serious adverse events reported by ten participants, though none of the serious adverse events were related to study medication [12]. Prespecified adverse events of particular interest were hyperkalemia, hyponatremia (too much water, low amount of sodium electrolyte), and hypotension. A total of ten of these adverse events occurred in eight participants. Three participants experienced hyperkalemia, with potassium levels between 6.0 and 6.3 mmol/L, prompting temporary discontinuation of baxdrostat. No occurrences of adrenocortical insufficiency were noted [12].

Adverse event information from the HALO study has not yet been reported. Dr. Bhatt presented preliminary findings of hyperkalemia to be 0%, 1.6%, 5.0%, and 1.6% for baxdrostat 0.5 mg, 1 mg, 2 mg, and placebo, respectively. Additionally, it was noted that the 2 mg dose of baxdrostat significantly increased plasma renin activity and all three baxdrostat doses (0.5 mg, 1 mg, and 2 mg) reduced serum aldosterone [16].

3 Discussion

Owing to the differing results seen between the BrigHTN and HALO studies, data from future studies will be imperative in determining if baxdrostat has a significant place in therapy for patients with resistant HTN. The results from the BrigHTN study were promising; the highest dose of baxdrostat in this study, 2 mg, was superior to placebo in reducing BP at 12 weeks in participants with treatment-resistant HTN with a change in mean SBP of −20.3 ± 2.1 mmHg [16]. Alternatively, results from the HALO study did not show statistical significance with the same promising BP lowering effects. For the same 2 mg of baxdrostat, the HALO study reported a change in mean SBP of 19.8 mmHg. While BP lowering was still achieved with baxdrostat, it has been noted that the placebo effect in the HALO study was quite large and there may have been lower rates of adherence with baxdrostat at some study sites [16]. Participants in the BrigHTN study were required to be taking at least three antihypertensive medications while those in the HALO study were only required to be taking at least two antihypertensive medications. Population differences between the two studies may have also contributed to the difference in results. Participants in BrigHTN had more highly elevated SBP at baseline and were inclusive of participants with eGFR values of less than 45 mL/min/1.73 m^2 whereas in the HALO study, participants with eGFR values below 30 mL/min/1.73 m^2 were excluded [23]. Finally, the HALO study was only 8 weeks in length compared with BrigHTN's 12-week duration. Future studies with an increased duration may provide more substantial results. Results from BrigHTN show promising data regarding baxdrostat's safety; data from the open-label extension of the HALO study should provide more information. Bax24 (NCT06168409; $n = 212$) and BaxHTN (NCT06034743; $n = 720$), both phase III studies expected to be complete in 2025, will provide much anticipated data regarding the safety and efficacy of baxdrostat.

Table 3 Summary of completed and ongoing clinical studies

Study name	Phase	Duration	Population Size (*n*)	Comparator	Primary outcome measure	Results
BrigHTN [12]	II	12 weeks	275	Baxdrostat 0.5 mg versus baxdrostat 1 mg versus baxdrostat 2 mg versus placebo	Change from baseline in mean seated SBP	Baxdrostat 0.5 mg: −12.1 ± 1.9 mm Hg, baxdrostat 1 mg: −17.5 ± 2.0 mmHg, baxdrostat 2 mg: −20.3 ± 2.1 mmHg, placebo: −9.4 mmHg
HALO [15–17]	II	8 weeks	249	Baxdrostat 0.5 mg versus baxdrostat 1 mg versus baxdrostat 2 mg versus placebo	Change from baseline in mean seated SBP	Baxdrostat 0.5 mg: 17.0 mmHg, baxdrostat 1 mg: 16.0 mmHg, baxdrostat 2 mg: 19.8 mmHg, placebo: 16.6 mmHg
BaxHTN [20]	III	12 weeks	~720	Baxdrostat 2 mg versus placebo	Change from baseline in seated SBP	Planned completion October 2025
Bax24 [21]	III	12 weeks	212	Baxdrostat 2 mg versus placebo	Change from baseline in ambulatory 24-h average SBP	Planned completion April 2025
A phase III study to investigate the efficacy and safety of baxdrostat in combination with dapagliflozin on CKD progression in participants with CKD and high blood pressure [22]	III	24 months	~2500	Baxdrostat + dapagliflozin versus dapagliflozin	Change from baseline in eGFR to post treatment	Planned completion December 2027

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure

4 Conclusions

Baxdrostat is the first competitive inhibitor of aldosterone synthase for the treatment of resistant HTN. Patients who are currently taking multiple antihypertensive medications and continue to have elevated BP values may benefit from this additional treatment option. To date, studies have shown baxdrostat to be effective in BP lowering with a tolerable safety profile. Future studies will give information on the long-term effectiveness of baxdrostat in addition to other potential treatment indications.

Declarations

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Conflict of Interest J.H., D.O., A.K., Andrea.A., Andrew.A., J.B., Y.A., D.S., W.D., M.B., and R.F.G. declare that they have no potential conflicts of interest that might be relevant to the contents of this manuscript.

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Code Availability Not applicable.

Data Availability Statement Data sharing are not applicable to this article as no datasets were generated.

Authors' Contributions J.H. was involved in supervision, data curation, analysis, reviewing, editing, and writing; D.O. was involved in data curation, analysis, and writing; A.K. was involved in data curation, analysis, and writing; Andrea.A. was involved in data curation, writing, and analysis; Andrew.A. was involved in data curation, analysis, and writing; J.B. was involved in reviewing and editing; Y.A. was involved in reviewing and editing; D.S. was involved in reviewing and editing; W.D. was involved in reviewing and editing; M.B. was involved in reviewing and editing; R.F.G. was involved in the conceptualization, project administration, reviewing, and editing.

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