ORIGINAL ARTICLE

Efficacy and Safety of Baxdrostat in Uncontrolled and Resistant Hypertension

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ABSTRACT

BACKGROUND

Aldosterone dysregulation plays an important pathogenic role in hard-to-control hypertension. In several studies, baxdrostat, an aldosterone synthase inhibitor, reduced the seated systolic blood pressure of patients with uncontrolled or resistant hypertension.

METHODS

In this phase 3, multinational, double-blind, randomized, placebo-controlled trial, we recruited patients with a seated systolic blood pressure of between 140 mm Hg and less than 170 mm Hg despite the receipt of stable treatment with two antihypertensive medications (uncontrolled hypertension) or three or more such medications (resistant hypertension), including a diuretic. After a 2-week placebo run-in period, we randomly assigned patients with a seated systolic blood pressure of 135 mm Hg or more in a 1:1:1 ratio to receive baxdrostat at a dose of 1 mg, baxdrostat at a dose of 2 mg, or placebo once daily for 12 weeks. The primary end point was the change in seated systolic blood pressure from baseline to week 12.

RESULTS

A total of 796 patients underwent randomization and 794 received 1-mg baxdrostat (264 patients), 2-mg baxdrostat (266 patients), or placebo (264 patients) in addition to background therapy. At 12 weeks, the change from baseline in the least-squares mean seated systolic blood pressure was –14.5 mm Hg (95% confidence interval [CI], –16.5 to –12.5) with 1-mg baxdrostat, –15.7 mm Hg (95% CI, –17.6 to –13.7) with 2-mg baxdrostat, and –5.8 mm Hg (95% CI, –7.9 to –3.8) with placebo. The estimated difference from placebo (placebo-corrected difference) was –8.7 mm Hg (95% CI, –11.5 to –5.8) with 1-mg baxdrostat and –9.8 mm Hg (95% CI, –12.6 to –7.0) with 2-mg baxdrostat ($P<0.001$ for both comparisons). A potassium level of more than 6.0 mmol per liter was reported in 6 patients (2.3%) with 1-mg baxdrostat, in 8 patients (3.0%) with 2-mg baxdrostat, and in 1 patient (0.4%) with placebo.

CONCLUSIONS

Among patients with uncontrolled or resistant hypertension, the addition of baxdrostat to background therapy resulted in a significantly lower seated systolic blood pressure at 12 weeks than placebo. (Funded by AstraZeneca and others; BaxHTN ClinicalTrials.gov number, NCT06034743.)

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This article was published on August 30, 2025, at NEJM.org.

DOI: 10.1056/NEJMoa2507109

Inappropriately elevated aldosterone production relative to patient sodium status is a key driver of hard-to-control (uncontrolled or resistant) hypertension and hypertension-mediated organ damage.[1-6] Mineralocorticoid receptor antagonists (MRAs) can block the mineralocorticoid receptor–mediated pathophysiological effects of aldosterone but are underused because of dose-dependent adverse effects.[7-9] Moreover, MRAs induce dose-related counter-regulatory increases in renin and circulating aldosterone levels that may stimulate MR-independent effects of aldosterone.[10-12]

An alternative therapeutic approach is direct inhibition of aldosterone synthase, which catalyzes the final three steps in aldosterone biosynthesis.[11] Baxdrostat is a highly selective, potent aldosterone synthase inhibitor with a plasma half-life of approximately 30 hours, which allows for once-daily administration.[13,14] In the 12-week, phase 2 BrigHTN trial involving patients with resistant hypertension, baxdrostat reduced seated in-office systolic blood pressure as compared with placebo.[15] However, in a phase 2 trial (HALO) involving patients with uncontrolled hypertension, baxdrostat did not show a between-group difference in the change from baseline to week 8 in seated systolic blood pressure as compared with placebo.[16] In a more recent small study involving patients with primary aldosteronism, baxdrostat substantially reduced seated systolic blood pressure.[17] Here, we report the results of a longer-term, phase 3 trial — BaxHTN (A Study to Investigate the Efficacy and Safety of Baxdrostat in Participants with Uncontrolled Hypertension on Two or More Medications, Including Participants with Resistant Hypertension) — to assess the efficacy and safety of baxdrostat in a broader population of patients with hard-to-control hypertension.

Methods

Trial Design and Oversight

The design of this multicenter, randomized, double-blind, placebo-controlled trial has been described previously.[18] Patients were enrolled at 214 clinical sites across multiple countries, as listed in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trial was designed by an executive committee and representatives of the funder, AstraZeneca. Patients with hypertension were involved in the trial design, and the trial was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference for Harmonisation Good Clinical Practice guidelines, and applicable laws and regulations. The protocol (available at NEJM.org) was approved by the local institutional review board or ethics committee for each site. All the patients provided written informed consent before enrollment.

Data were collected and analyzed by representatives of AstraZeneca. The statistical analysis was performed and independently verified by two separate teams at AstraZeneca to ensure accuracy. All the authors had access to the data and the analyses, reviewed and edited the manuscript, and agreed with the decision to submit the manuscript for publication. The last author wrote the first draft of the manuscript and vouches for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. Medical writing support was provided and funded by AstraZeneca.

The executive committee had professional-services agreements applicable to their role in the trial design, conduct, data analysis, and confidential information. This agreement also supported the right of the executive committee to publish the results of the trial and use confidential information in connection with the performance of the services. Representatives of AstraZeneca retained the right to review the manuscript for up to 60 days to confirm accuracy, safeguard confidential information, and manage information relevant to patents.

Eligible Patients and Run-in Period

The trial enrolled men and women who were at least 18 years of age and who had hard-to-control hypertension, which was defined as a mean seated systolic blood pressure of 140 mm Hg to less than 170 mm Hg, as measured during an office visit, despite treatment with maximally tolerated doses of either two antihypertensive medications (for uncontrolled hypertension) or three or more such medications (for resistant hypertension), including a diuretic, for at least 4 weeks before screening. Full inclusion and exclusion criteria are provided in the Supplementary Appendix.

After a 2-week single-blind run-in period in which patients received placebo in addition to their stable background medications, those who

had a seated systolic blood pressure of 135 mm Hg or more and had good adherence to background antihypertensive therapy (as assessed by direct observation and ≥80% adherence according to pill count) underwent randomization. Details regarding this evaluation are provided in the Supplementary Appendix.

COHORTS AND SEQUENTIAL PARTS OF TRIAL

The trial consisted of four sequential parts conducted over a total duration of 52 weeks (Fig. S1 in the Supplementary Appendix). The patients were divided into two cohorts on the basis of the time of randomization. The first 450 randomly assigned patients were included in cohort 1 and participated in all four parts of the trial. All the patients who were randomly assigned thereafter were included in cohort 2 and participated in only the first two parts of the trial. This design ensured sufficient power for the analysis of the primary end point (at the end of part 1) and reduced the number of patients who would be unnecessarily exposed to a second period of placebo administration during the randomized-withdrawal phase of the trial (part 3).

Part 1 was a 12-week, double-blind, randomized, placebo-controlled period and formed the basis of the primary end point reported here. The patients were randomly assigned in a 1:1:1 ratio to receive 1 mg of baxdrostat, 2 mg of baxdrostat, or placebo once daily. Randomization was stratified according to the hypertension status (uncontrolled or resistant hypertension) and seated systolic blood pressure (<145 mm Hg or ≥145 mm Hg) at baseline.

Part 2 (weeks 12 to 24) was a 12-week, open-label phase that was designed to collect safety data and that served as a run-in to part 3. The patients who had received 2-mg baxdrostat in part 1 continued treatment, whereas those who had received 1-mg baxdrostat or placebo underwent a second randomization to receive 2-mg baxdrostat or standard-of-care treatment (in a 4:1 or 1:4 ratio, respectively). Incorporation of the standard-of-care group provided a comparator for longer-term safety monitoring for the phases of the trial that did not include placebo.

Part 3 (weeks 24 to 32) was an 8-week, double-blind, randomized-withdrawal phase. Patients who were receiving 2-mg baxdrostat in part 2 underwent a third randomization (in a 2:1 ratio) to receive 2-mg baxdrostat or placebo.

Part 4 (weeks 32 to 52) is an ongoing 20-week, open-label phase to collect additional safety data regarding 2-mg baxdrostat. At the time of the trial data-cutoff date, the two randomized, controlled parts of the trial (parts 1 and 3) were complete, and the results are reported here. At that time, several patients in cohort 2 (who participated in only the first two parts of the trial) were still participating in the first open-label phase of the trial (part 2).

All the patients continued to receive their background antihypertensive therapy throughout the trial. During double-blind periods, background therapy had to remain unchanged unless the seated systolic blood pressure exceeded 170 mm Hg or the seated diastolic blood pressure exceeded 105 mm Hg, in which case rescue therapy could be added at the investigator's discretion. During the open-label phases, adjustments to background antihypertensive therapy were permitted at the investigator's discretion. However, the use of MRAs or potassium-sparing diuretics was permitted only in the standard-of-care group.

During part 1, the patients were evaluated at monthly visits before ingestion of baxdrostat or placebo on the date of the visit. Data were recorded regarding the seated systolic blood pressure and diastolic blood pressure (Microlife WatchBP Office 2G), vital signs, medication list, and adverse events. Blood samples were obtained to monitor levels of serum creatinine, sodium, aldosterone, and plasma renin activity, along with levels of baxdrostat. All the samples were measured at a central laboratory in a blinded manner; serum potassium was measured at both local and central laboratories. In total, investigators at 34 trial sites elected to undertake 24-hour ambulatory blood-pressure measurements at baseline and at week 12. Additional details are provided in the Supplementary Appendix.

END POINTS

The primary efficacy end point was the change in the seated systolic blood pressure from baseline to week 12, as assessed for each baxdrostat group as compared with placebo. The secondary end points were the change in the seated systolic blood pressure from week 24 to week 32 (after the randomized withdrawal of baxdrostat among patients who received open-label 2-mg baxdrostat daily for 12 weeks during part 2 [weeks 12 to 24] and then were randomly assigned to receive 2-mg

baxdrostat or placebo for 8 weeks), the change in seated systolic blood pressure from baseline to week 12 in the resistant-hypertension subpopulation, the change in the seated diastolic blood pressure from baseline to week 12, and a seated systolic blood pressure of less than 130 mm Hg at week 12. Exploratory end points included the change in the ambulatory 24-hour and night-time average systolic blood pressure from baseline to week 12, serum aldosterone levels, and plasma renin activity.

Safety end points included adverse events, vital signs, laboratory tests, and adjudicated major adverse cardiovascular events. Adverse events of special interest (i.e., those that needed medical intervention) included hyperkalemia (serum potassium level, >5.0 mmol per liter), hyponatremia (serum sodium level, <135 mmol per liter), and hypotension requiring medical intervention. An independent data monitoring committee performed regular reviews of the trial data.

STATISTICAL ANALYSIS

The full analysis and safety analysis populations consisted of all the patients who had undergone randomization and received at least one dose of baxdrostat or placebo (modified intention-to-treat population). An analysis of the change in the seated systolic blood pressure during the 8-week randomized-withdrawal period (part 3, from week 24 to week 32) consisted of all the patients in the full analysis population during that period.

The primary comparison was performed by means of analysis of covariance, with treatment and hypertension status (uncontrolled or resistant) as factors and the baseline seated systolic blood pressure as a covariate. All blood-pressure measurements were included, regardless of the discontinuation of baxdrostat or placebo or the need for rescue therapy. A hierarchical multiple-testing procedure was used to control for the familywise type I error at a two-sided alpha level of 0.05 between the primary and secondary end points.

We estimated that the enrollment of 720 patients would provide the trial with a power of 98% to detect a mean (±SD) difference of 6±15 mm Hg for the change from baseline in the seated systolic blood pressure at week 12 in favor of baxdrostat as compared with placebo according to a two-sample t-test with a two-sided significance level of 0.025. Additional details regarding the analysis plan, procedures for handling missing data and multiplicity analyses, sensitivity analyses, and subgroup analyses are provided in the Supplementary Appendix.

Continuous variables are expressed as means (±SD) and medians (interquartile range), and categorical variables as frequency (percent). Between-group differences are expressed as least-squares means and 95% confidence intervals. All statistical analyses were performed with SAS software (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PATIENTS

From November 2023 through February 2025, a total of 2591 patients were screened and 1109 were included in the placebo run-in period; 796 underwent randomization, and 794 received treatment (modified intention-to-treat population) with 1-mg baxdrostat (264 patients), 2-mg baxdrostat (266 patients), or placebo (264 patients) (Fig. S2). Screening failure was most commonly the result of findings outside the blood-pressure criteria for inclusion. A total of 66 patients (8.3%) discontinued treatment during the 12-week double-blind period (part 1). The full analysis population included 794 patients. Of these patients, 754 (95.0%) were found to have adhered to the treatment regimen at least 80% of the time according to the tablet count in part 1.

The clinical characteristics of the patients at baseline were similar across the trial groups (Table 1 and Table S1). The trial population was broadly representative of patients with uncontrolled or resistant hypertension (Table S2). The mean blood pressure at baseline was 149/87 mm Hg across groups. The background antihypertensive medications were similar at baseline and week 12 (Tables S1 and S3). During part 1, rescue medication was used by 3 patients (1%) in the 1-mg baxdrostat group, by 3 patients (1%) in the 2-mg baxdrostat group, and by 7 patients (3%) in the placebo group. The imputation of missing data for the primary analysis was performed for 13 patients (5%) in the 1-mg baxdrostat group, 16 patients (6%) in the 2-mg baxdrostat group, and 18 patients (7%) in the placebo group (Table S4).

PRIMARY END POINT

At week 12 (end of part 1), treatment with baxdrostat at doses of 1 mg and 2 mg resulted in a change from baseline in the least-squares mean seated systolic blood pressure of –14.5 mm Hg (95% confidence interval [CI], –16.5 to –12.5) and

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Baxdrostat, 1 mg (N=264)	Baxdrostat, 2 mg (N=266)	Placebo (N=264)
Age — yr	59.8±11.8	61.8±11.7	61.9±11.6
Male sex — no. (%)	169 (64.0)	163 (61.3)	162 (61.4)
Race or ethnic group — no. (%)†			
White	165 (62.5)	168 (63.2)	167 (63.3)
Black	23 (8.7)	21 (7.9)	15 (5.7)
Asian	65 (24.6)	72 (27.1)	72 (27.3)
Other	10 (3.8)	2 (0.8)	8 (3.0)
Hispanic or Latino	27 (10.2)	39 (14.7)	38 (14.4)
Missing data	1 (0.4)	3 (1.1)	2 (0.8)
Seated blood pressure — mm Hg			
Systolic	149.7±10.1	149.1±9.1	149.0±8.7
Diastolic	88.0±10.5	85.8±10.5	85.8±10.5
Body-mass index‡	31.5±6.4	31.2±6.2	31.1±6.0
Estimated glomerular filtration rate — ml/min/1.73 m^2§	86.6±18.5	84.3±17.9	84.1±18.0
Diabetes — no. (%)	83 (31.4)	110 (41.4)	110 (41.7)
Serum sodium — mmol/liter			
Mean	139.9±2.6	139.8±2.5	139.6±2.5
Median (IQR)	140 (138–141)	140 (138–141)	140 (138–141)
Serum potassium — mmol/liter			
Mean	4.2±0.4	4.2±0.4	4.2±0.5
Median (IQR)	4.2 (3.9–4.4)	4.2 (3.9–4.5)	4.2 (3.9–4.5)
Hypertension — no. (%)¶			
Uncontrolled	77 (29.2)	67 (25.2)	71 (26.9)
Resistant	187 (70.8)	199 (74.8)	193 (73.1)

* Plus–minus values are means ±SD. Baseline characteristics are shown for the full analysis population (all the patients who underwent randomization and received at least one dose of baxdrostat or placebo). Percentages may not total 100 because of rounding. To convert the values for potassium to milligrams per deciliter, divide by 0.2558. IQR denotes interquartile range.

† Race and ethnic group were reported by the patients. Data were missing for patients for whom information regarding race was not available.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The estimated glomerular filtration rate was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation as described by Inker et al.[19]

¶ Data are based on information collected in the medication case-report form.

–15.7 mm Hg (95% CI, –17.6 to –13.7), respectively, as compared with a change of –5.8 mm Hg (95% CI, –7.9 to –3.8) with placebo (Fig. 1 and Table S5). The estimated treatment difference relative to placebo was –8.7 mm Hg (95% CI, –11.5 to –5.8; P<0.001) for 1-mg baxdrostat and –9.8 mm Hg (95% CI, –12.6 to –7.0; P<0.001) for 2-mg baxdrostat (Table 2). Sensitivity analyses produced similar results (Table S6). Treatment effects for the change in the seated systolic blood pressure from baseline to week 12 according to prespecified subgroups are presented in Figure 2 and Figure S3.

SECONDARY END POINTS

At the start of the 8-week randomized-withdrawal period (part 3, week 24 to week 32), the mean seated systolic blood pressure among patients who had been randomly assigned to receive 2-mg baxdrostat or placebo was 133 mm Hg. The change in the least-squares mean seated systolic blood pressure during the randomized-with-

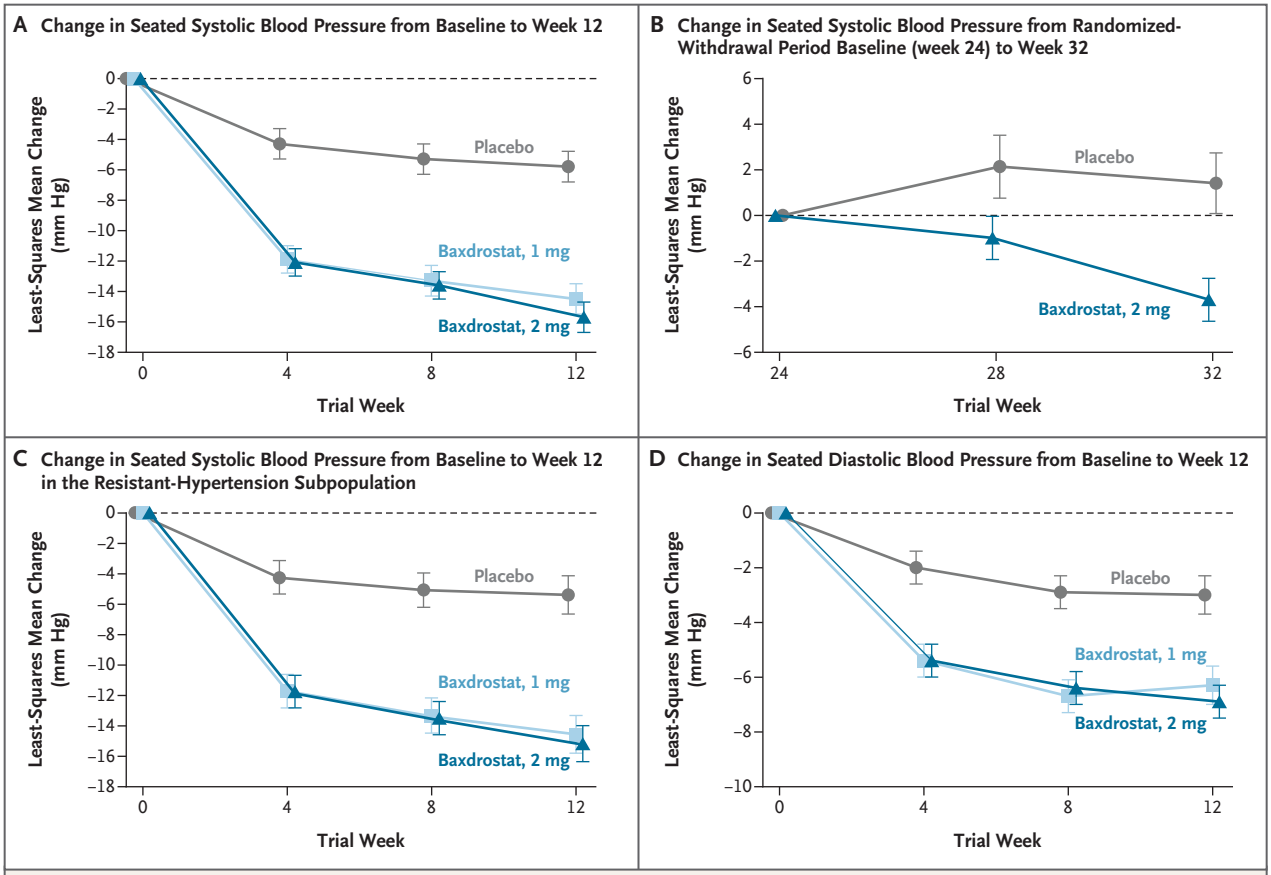

Figure 1. Change in Blood Pressure in Patients with Uncontrolled or Resistant Hypertension.

The line graphs show the time course for least-squares mean changes from baseline in the seated systolic blood pressure up to week 12 (Panel A), the change from the randomized-withdrawal baseline (week 24) in the seated systolic blood pressure up to week 32 (Panel B), the change from baseline in the seated systolic blood pressure up to week 12 in the resistant-hypertension subpopulation (Panel C), and the change from baseline in the seated diastolic blood pressure up to week 12 (Panel D). I bars on the line graphs indicate standard errors.

drawal period was –3.7 mm Hg (95% CI, –5.5 to –1.9) with 2-mg baxdrostat and +1.4 mm Hg (95% CI, –1.2 to 4.0) with placebo (estimated difference, –5.1 mm Hg; 95% CI, –8.3 to –1.9; P=0.002) (Fig. 1, Table 2, and Table S5).

In the resistant-hypertension subpopulation, the least-squares mean estimated placebo-corrected difference in the change in the seated systolic blood pressure at week 12 was –9.1 mm Hg (95% CI, –12.6 to –5.7; P<0.001) with 1-mg baxdrostat and –9.8 mm Hg (95% CI, –13.1 to –6.4; P<0.001) with 2-mg baxdrostat. For the seated diastolic blood pressure, the least-squares mean estimated placebo-corrected difference at week 12 was –3.3 mm Hg (95% CI, –5.2 to –1.4; P=0.001) with 1-mg baxdrostat and –3.9 mm Hg (95% CI, –5.7 to –2.0; P<0.001) with 2-mg baxdrostat.

The percentage of patients with a controlled seated systolic blood pressure (<130 mm Hg) at week 12 was 39.4% with 1-mg baxdrostat, 40.0% with 2-mg baxdrostat, and 18.7% with placebo (odds ratios for blood-pressure control, 2.9 for both 1-mg and 2-mg doses of baxdrostat; P<0.001 for both comparisons) (Table S5).

EXPLORATORY END POINTS

Data regarding the exploratory end points, including ambulatory blood pressure, serum aldosterone levels, plasma renin activity, and pharmacokinetic analysis of baxdrostat drug levels, are provided in Figures S4, S5, and S6 and in Table S7.

SAFETY

During part 1, one death occurred in the placebo group. Serious adverse events occurred in 5 pa-

Table 2. Changes in Blood Pressure, According to Hierarchical Order.*

End Point	Baxdrostat, 1 mg	Baxdrostat, 2 mg	Placebo
Primary end point: change in seated SBP from baseline to 12 wk†			
No. of patients	264	266	263
Least-squares mean placebo-corrected difference (95% CI) — mm Hg	–8.7 (–11.5 to –5.8)	–9.8 (–12.6 to –7.0)	—
P value	<0.001	<0.001	—
Secondary end points			
Change in seated SBP during randomized-withdrawal period: wk 24 to 32‡			
No. of patients	NA	172	85
Least-squares mean placebo-corrected difference (95% CI) — mm Hg	NA	–5.1 (–8.3 to –1.9)	—
P value	NA	0.002	—
Change from baseline in seated SBP up to wk 12 in the resistant-hypertension subpopulation§			
No. of patients	187	199	192
Least-squares mean placebo-corrected difference (95% CI) — mm Hg	–9.1 (–12.6 to –5.7)	–9.8 (–13.1 to –6.4)	—
P value	<0.001	<0.001	—
Change from baseline in seated diastolic blood pressure up to wk 12¶			
No. of patients	264	266	263
Least-squares mean placebo-corrected difference (95% CI) — mm Hg	–3.3 (–5.2 to –1.4)	–3.9 (–5.7 to –2.0)	—
P value	0.001	<0.001	—

* NA denotes not applicable, and SBP systolic blood pressure.
† This analysis was performed on the full analysis population with the use of an analysis of covariance (ANCOVA) model with treatment and hypertension at baseline (uncontrolled or resistant hypertension) as factors and the baseline seated SBP as a covariate.
‡ This analysis was performed in the randomized-withdrawal population as a prespecified analysis of the 2-mg baxdrostat group as compared with the placebo group with the use of an ANCOVA model with treatment and hypertension at baseline (uncontrolled or resistant hypertension) as factors and the baseline (week 24) seated SBP during the randomized-withdrawal period as a covariate.
§ This analysis was performed in the full analysis population with the use of an ANCOVA model with treatment as a factor and the baseline seated SBP as a covariate. Only patients with resistant hypertension at baseline were included in this analysis.
¶ This analysis was performed in the full analysis population with the use of an ANCOVA model with treatment and hypertension at baseline (uncontrolled or resistant hypertension) as factors and the baseline seated diastolic blood pressure as a covariate.

tients (1.9%) with 1-mg baxdrostat, in 9 patients (3.4%) with 2-mg baxdrostat, and in 7 patients (2.7%) with placebo (Table 3 and Table S8). Adverse events occurred in 125 patients (47.3%) with 1-mg baxdrostat, in 119 patients (44.7%) with 2-mg baxdrostat, and in 109 patients (41.3%) with placebo (Table 3). Most adverse events were mild; the most common events were hyperkalemia, hyponatremia, hypotension, muscle spasms, and dizziness (Table 3 and Table S9). No cases of adrenal insufficiency were reported.

Serum potassium levels of more than 6.0 mmol per liter were recorded in a central laboratory in 6 of 262 patients (2.3%) with 1-mg baxdrostat, in 8 of 263 patients (3.0%) with 2-mg baxdrostat, and in 1 of 262 patients (0.4%) with placebo (Table 3 and Table S10). Of these values, 3 (1.1%) each in the 1-mg and 2-mg baxdrostat groups were confirmed to be more than 6.0 mmol per liter, as measured by a local laboratory on the same day (Table S11). Hyperkalemia (potassium level, >5.5 mmol per liter) occurred in 16 of 262

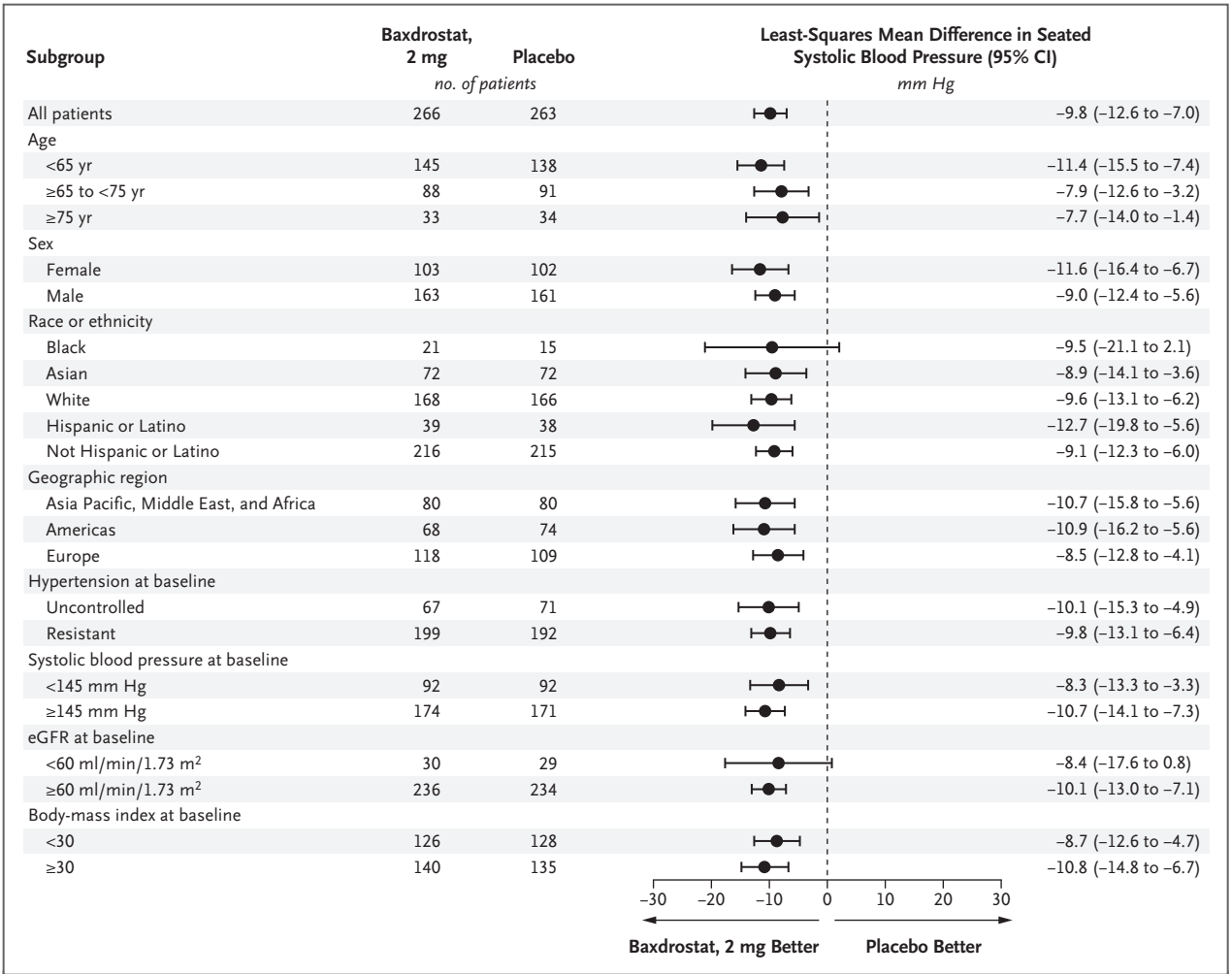

Figure 2. Change from Baseline in Seated Systolic Blood Pressure at Week 12 for the Comparison between 2-mg Baxdrostat and Placebo, According to Subgroup.

The forest plot shows the least-squares mean difference between patients in the 2-mg baxdrostat group and the placebo group regarding the change from baseline in the seated systolic blood pressure at week 12. The analysis was performed within each subgroup category with the use of an ANCOVA (analysis of covariance) model, with treatment and baseline hypertension (uncontrolled or resistant) as factors and the seated systolic blood pressure at baseline as a covariate. For the baseline hypertension subgroup analysis, the baseline hypertension factor was removed from the ANCOVA models for uncontrolled and resistant hypertension categories. Missing data were handled by means of multiple imputation. Circles denote point estimates. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. The body-mass index is the weight in kilograms divided by the square of the height in meters. The abbreviation eGFR denotes estimated glomerular filtration rate.

patients (6.1%) with 1-mg baxdrostat, in 29 of 261 patients (11.1%) with 2-mg baxdrostat, and in 1 of 260 patients (0.4%) with placebo (Table 3). Clinical intervention because of hyperkalemia (an adverse event of special interest) was reported in 7 of 264 patients (2.7%) with 1-mg baxdrostat, in 21 of 266 patients (7.9%) with 2-mg baxdrostat, and in no patients with placebo (Table 3).

Hyponatremia (sodium level, <135 mmol per liter) was reported in 49 of 256 patients (19.1%) with 1-mg baxdrostat, in 59 of 259 patients (22.8%) with 2-mg of baxdrostat, and in 18 of 256 patients (7.0%) with placebo; sodium levels of less than 132 mmol per liter — a lower range that could trigger potential clinical concern — occurred in 15 of 261 patients (5.7%) with 1-mg baxdrostat, in 21 of 263 patients (8.0%) with 2-mg baxdrostat, and in 3 of 261 patients (1.1%) with placebo up to week 12 (Table S10). However, few of these events required medical intervention (in 2 of 264 [0.8%] with 1-mg baxdro-

Table 3. Adverse Events during the 12-Week Double-Blind Treatment Period.

Adverse Events	Baxdrostat, 1 mg (N = 264)	Baxdrostat, 2 mg (N = 266)	Placebo (N = 264)
Any serious adverse event — no. (%)*	5 (1.9)	9 (3.4)	7 (2.7)
Death — no. (%)	0	0	1 (0.4)
Any adverse event — no. (%)	125 (47.3)	119 (44.7)	109 (41.3)
Moderate or severe event	27 (10.2)	37 (13.9)	23 (8.7)
Severe event	3 (1.1)	7 (2.6)	5 (1.9)
Adverse event leading to discontinuation — no. (%)			
Any	7 (2.7)	12 (4.5)	5 (1.9)
Hyperkalemia	2 (0.8)	4 (1.5)	0
Adverse event of special interest — no. (%)†			
Hyperkalemia	7 (2.7)	21 (7.9)	0
Hyponatremia	2 (0.8)	6 (2.3)	1 (0.4)
Hypotension	5 (1.9)	6 (2.3)	2 (0.8)
Serum potassium — no./total no. (%)‡			
>5.5 mmol/liter	16/262 (6.1)	29/261 (11.1)	1/260 (0.4)
>6.0 mmol/liter	6/262 (2.3)	8/263 (3.0)	1/262 (0.4)
>6.5 mmol/liter	5/262 (1.9)	1/263 (0.4)	1/263 (0.4)

* One case of hyperkalemia in the 1-mg baxdrostat group and two cases of hyponatremia (one each in the 1-mg baxdrostat group and the 2-mg baxdrostat group) were deemed by the investigator to be possibly related to baxdrostat. A complete list of clinical chemistry abnormalities according to prespecified criteria up to week 12 is provided in Table S10 in the Supplementary Appendix.

† Adverse events of special interest are those that required medical intervention.

‡ Denominators include patients who did not already fulfill the specific criteria in each row at baseline. For patients with no missing postbaseline values but a missing baseline value, the baseline value was assumed to have not fulfilled the criterion in the specific row.

stat, 6 of 266 [2.3%] with 2-mg baxdrostat, and 1 of 264 [0.4%] with placebo) (Table 3).

Changes in serum levels of potassium and sodium with baxdrostat occurred predominantly in the first 2 weeks and remained stable thereafter (Figs. S7 and S8). No changes were observed with placebo.

The mean change in the estimated glomerular filtration rate (eGFR) from baseline to week 12 was –7.0±12.8 ml per minute per 1.73 m^2 of body-surface area with 1-mg baxdrostat, –6.9±12.4 ml per minute per 1.73 m^2 with 2-mg baxdrostat, and –0.1±8.6 ml per minute per 1.73 m^2 with placebo (Fig. S9). A change of 30% or more in the eGFR occurred during treatment in 12.6% of the patients with 1-mg baxdrostat, in 15.6% with 2-mg baxdrostat, and in 1.5% with placebo; a change of 50% or more in the eGFR occurred in 1.5%, 1.1%, and 0.4% of the patients, respectively (Table S10). During the randomized-withdrawal period (part 3), the eGFR remained stable in the patients receiving 2-mg baxdrostat and returned toward baseline levels in the placebo group (Fig. S9). Two investigator-defined events of acute kidney injury were reported: one in the placebo group (0.4%) and one in the 2-mg baxdrostat group (0.4%).

DISCUSSION

In patients with uncontrolled or resistant hypertension, the addition of 1-mg or 2-mg daily doses of baxdrostat to background antihypertensive medication led to differences relative to placebo in the seated systolic blood pressure of –8.7 mm Hg and –9.8 mm Hg, respectively, after 12 weeks of treatment. In our trial, we enrolled patients with hard-to-control blood pressure despite the receipt of multiple antihypertensive medications. Changes in blood pressure were similar in prespecified subgroups, which suggests an important role for dysregulated aldosterone in the pathophysiology

of both uncontrolled and resistant hypertension, along with a potentially broader population of patients with hypertension.[5] We noted reduced levels of aldosterone and increased levels of plasma renin activity that may suggest that baxdrostat may induce further urine sodium excretion in patients who are already being treated with diuretics, although this finding was not subject to hypothesis testing. We speculate that these changes may indicate that despite inhibition of the renin–angiotensin system, an aldosterone breakthrough may be contributing to the pathophysiology of hard-to-control blood pressure.

Previous studies have shown that reductions of 5 to 10 mm Hg in systolic blood pressure are associated with a reduced risk of cardiovascular disease and death.[20,21] The blood-pressure–lowering effects of baxdrostat in the current trial were consistent with those reported for lorundrostat, another aldosterone synthase inhibitor.[22,23] In a phase 3 trial involving patients with uncontrolled or resistant hypertension, patients who received lorundrostat had a difference relative to the placebo group in the seated systolic blood pressure of –9.1 mm Hg (95% CI, –13.3 to –4.9) at week 6 (the primary end point).[22]

Our trial provides additional data, including the effect of a randomized treatment withdrawal. At the start of the randomized-withdrawal period (part 3), the mean seated systolic blood pressure was 133 mm Hg in patients who were subsequently randomly assigned to receive 2 mg of baxdrostat or placebo. During the next 8 weeks (weeks 24 to 32), the change in the seated systolic blood pressure was –3.7 mm Hg (95% CI, –5.5 to –1.9) in the baxdrostat group. In the placebo group of the 8-week randomized-withdrawal period, the change in seated systolic blood pressure was only +1.4 mm Hg (95% CI, –1.2 to 4.0), despite the expected clearance of baxdrostat from the blood by 1 week.[14] Moreover, serum aldosterone levels and plasma renin activity did not fully return to baseline levels. We speculate that the slow offset of the effect of baxdrostat on blood pressure was consistent with its mechanism of action on sodium homeostasis.[13] Other possible mechanisms include inhibition or reversal of the deleterious effects of aldosterone on the vasculature and sympathetic nervous system activity.[12,24]

In our trial, the 12-week safety data with baxdrostat were generally consistent with the findings of clinical trials of lorundrostat.[22,23] The percentage of patients with serious adverse events was low and similar across treatment groups. Hyperkalemia and hyponatremia occurred more frequently in the baxdrostat groups than in the placebo group, but the incidence of hyperkalemia leading to discontinuation was low, as was the incidence of potassium measurements of more than 6.0 mmol per liter (Tables S10 and S11).

The mean change of –7.0 ml per minute per 1.73 m^2 in the eGFR from baseline to week 12 that was observed in patients treated with either dose of baxdrostat occurred early. During the randomized-withdrawal period (part 3), the eGFR returned toward baseline levels in the placebo group. These findings are consistent with functional eGFR changes caused by the effect of blood-pressure lowering on renal perfusion.[25]

Our trial has certain limitations. Ambulatory blood pressure was measured in only a small number of patients. However, ambulatory blood pressure is being measured in the ongoing 12-week Bax24 trial (ClinicalTrials.gov number, NCT06168409).[18] The percentages of female and Black patients with hypertension who were enrolled in the trial were lower than the percentages observed in the real world, although the percentage of Black patients was greater in North America (36%) than in the total trial population (7%) (Table S2). Otherwise, the characteristics of the patients were largely aligned with those of patients with uncontrolled and resistant hypertension, and global recruitment was well balanced. Finally, medication adherence was not measured directly by objective methods throughout the trial. However, the plasma levels of baxdrostat that were measured during the trial indicate good adherence to baxdrostat, with 10% or less below the lower limit of quantification (Table S7).

We found that in a broad population of patients with uncontrolled or resistant hypertension, the addition of baxdrostat to background antihypertensive therapy resulted in a reduction in the seated systolic blood pressure at 12 weeks as compared with placebo.

Supported by AstraZeneca. Bryan Williams is supported by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients who participated in our trial, along with the clinical trial personnel and research teams; George Bakris, M.D. (deceased), who provided substantial support as part of our trial steering committee before and during the trial; and Jane Murphy, Ph.D., and Mary Sayers, M.Sc., of Ashfield MedComms, an Inizio Company, for providing medical writing and editing support for an earlier version of the manuscript under the direction and guidance of the authors.

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