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Phase 2 Trial of Baxdrostat for Treatment-Resistant Hypertension

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ABSTRACT

BACKGROUND

Aldosterone synthase controls the synthesis of aldosterone and has been a pharmacologic target for the treatment of hypertension for several decades. Selective inhibition of aldosterone synthase is essential but difficult to achieve because cortisol synthesis is catalyzed by another enzyme that shares 93% sequence similarity with aldosterone synthase. In preclinical and phase 1 studies, baxdrostat had 100:1 selectivity for enzyme inhibition, and baxdrostat at several dose levels reduced plasma aldosterone levels but not cortisol levels.

METHODS

In this multicenter, placebo-controlled trial, we randomly assigned patients who had treatment-resistant hypertension, with blood pressure of 130/80 mm Hg or higher, and who were receiving stable doses of at least three antihypertensive agents, including a diuretic, to receive baxdrostat (0.5 mg, 1 mg, or 2 mg) once daily for 12 weeks or placebo. The primary end point was the change in systolic blood pressure from baseline to week 12 in each baxdrostat group as compared with the placebo group.

RESULTS

A total of 248 patients completed the trial. Dose-dependent changes in systolic blood pressure of –20.3 mm Hg, –17.5 mm Hg, –12.1 mm Hg, and –9.4 mm Hg were observed in the 2-mg, 1-mg, 0.5-mg, and placebo groups, respectively. The difference in the change in systolic blood pressure between the 2-mg group and the placebo group was –11.0 mm Hg (95% confidence interval [CI], –16.4 to –5.5; P<0.001), and the difference in this change between the 1-mg group and the placebo group was –8.1 mm Hg (95% CI, –13.5 to –2.8; P=0.003). No deaths occurred during the trial, no serious adverse events were attributed by the investigators to baxdrostat, and there were no instances of adrenocortical insufficiency. Baxdrostat-related increases in the potassium level to 6.0 mmol per liter or greater occurred in 2 patients, but these increases did not recur after withdrawal and reinitiation of the drug.

CONCLUSIONS

Patients with treatment-resistant hypertension who received baxdrostat had dose-related reductions in blood pressure. (Funded by CinCor Pharma; BrigHTN ClinicalTrials.gov number, NCT04519658.)

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Elevated blood pressure, the leading global risk factor for cardiovascular disease, stroke, disability, and death, affects an estimated 1.4 billion persons worldwide.[1] In the United States, approximately 10% of persons with hypertension (10 to 12 million persons) have treatment-resistant hypertension, which is defined as elevated blood pressure despite concurrent use of at least three antihypertensive drugs of different classes, including a diuretic.[2] Persons with treatment-resistant hypertension have a substantially increased risk of cardiovascular and renal adverse events.[3,4]

Patients with treatment-resistant hypertension are often prescribed at least four antihypertensive agents,[5] with a goal (in the United States) of an in-office systolic blood pressure of less than 130 mm Hg and diastolic blood pressure of 80 mm Hg or less.[2,6,7] Current guidelines recommend the addition of spironolactone, a mineralocorticoid receptor antagonist, as a fourth-line agent despite common, dose-limiting adverse effects.[6] A total of 40 to 50% of patients with hypertension remain inadequately treated,[8] and yet no new class of antihypertensive medication has been approved since 2007.[9]

Aldosterone synthase inhibitors target a likely cause of treatment resistance by suppressing hormone synthesis rather than by blocking the mineralocorticoid receptor. Preclinical and phase 1 studies have shown that baxdrostat has high selectivity (selectivity ratio, 100:1) for aldosterone synthase as compared with the enzyme required for cortisol synthesis, 11β-hydroxylase, which shares 93% sequence similarity with aldosterone synthase.[10] In the current trial, we examined the efficacy and safety of baxdrostat in patients with treatment-resistant hypertension.

METHODS

TRIAL DESIGN AND POPULATION

BrigHTN, a multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging trial, had an adaptive design. The trial enrolled men and women who were 18 years of age or older, were receiving stable doses of at least three antihypertensive medications (one of which was a diuretic), and had a mean blood pressure of at least 130/80 mm Hg while seated. Blood pressure was determined as the average of three measurements obtained with the use of an automated in-office blood-pressure monitor.

Key exclusion criteria were a mean seated systolic blood pressure of at least 180 mm Hg or a diastolic blood pressure of at least 110 mm Hg, an estimated glomerular filtration rate (GFR) of less than 45 ml per minute per 1.73 m^2 of body-surface area, and uncontrolled diabetes. To be eligible for the trial, patients who had been receiving a mineralocorticoid receptor antagonist or a potassium-sparing diuretic were required to discontinue these agents for a total of 4 weeks before randomization. Complete inclusion and exclusion criteria are provided in the Supplementary Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The trial registration was submitted to ClinicalTrials.gov on August 17, 2020. Although the first patient in our trial underwent screening before that date, no patients were enrolled before the trial registration was submitted or accepted. After a screening period of up to 8 weeks, eligible patients entered a 2-week, single-blind run-in period to determine whether medication adherence was a factor in not attaining their blood-pressure goal. Patients with at least 70% adherence (determined on the basis of pill counts) to each antihypertensive medication and placebo during the run-in period and a seated blood pressure of at least 130/80 mm Hg were randomly assigned to receive either 0.5 mg, 1 mg, or 2 mg of baxdrostat or matching placebo. The doses of baxdrostat were selected on the basis of decreases in aldosterone levels that had been measured in our previous multiple-ascending-dose study.[11] After randomization, clinical visits were conducted on days 3, 8, 15, 22, 43, 64, and 85 (the last day of the treatment period), and a follow-up telephone call occurred 1 week after the last dose (Fig. S1 in the Supplementary Appendix). Additional details regarding the trial design are provided in the Supplementary Appendix.

BrigHTN was conducted primarily at community-based practices in the United States, as well as at a small number of academic hospital–based practices. The trial was designed by CinCor Pharma, CinRx Pharma, and external scientific advisers and funded by CinCor Pharma. Data were collected and analyzed by authors employed by Medpace and CinCor Pharma, who vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org. The first draft of the manuscript was written by the first and last au-

thors. A professional writer paid by the sponsor assisted the authors in the preparation of the manuscript. All the authors made the decision to submit the manuscript for publication.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Council for Harmonisation. All the clinical sites that participated in the trial obtained approval from an institutional review board at the site that was authorized to approve studies involving humans, and all patients provided written informed consent before enrollment in the trial. An independent data monitoring committee performed a formal unblinded interim analysis when approximately 200 patients had completed the 12-week treatment period. Details regarding the interim analysis are provided in the Supplementary Appendix.

END POINTS

The primary efficacy end point was the change in the mean seated systolic blood pressure from baseline to the end of the 12-week treatment period in each baxdrostat group as compared with the placebo group. The secondary end points were the change from baseline in the mean seated diastolic blood pressure and the percentage of patients with a seated blood pressure of less than 130/80 mm Hg at the end of the 12-week treatment period. No adjustments were made for multiplicity in the analysis of the secondary outcomes; hence, the confidence intervals should not be used in place of hypothesis tests.

The safety end points included adverse events, vital signs, and the results of laboratory tests, electrocardiography, and physical examinations. Prespecified adverse events of special interest were hyperkalemia, hyponatremia, and hypotension warranting clinical intervention. Patients with potassium levels between 5.5 and 5.9 mmol per liter were contacted and asked to return for a repeat electrolyte measurement as soon as feasible, but they continued to receive baxdrostat or placebo. In contrast, patients with potassium levels between 6.0 and 6.4 mmol per liter were directed to discontinue baxdrostat or placebo and return for reevaluation as soon as feasible.

Exploratory pharmacokinetic and pharmacodynamic analyses were performed to assess the levels of plasma baxdrostat, serum and urinary aldosterone, and serum cortisol as well as plasma renin activity. Details are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

We estimated that a sample of 77 patients in each group would provide the trial with at least 80% power to detect a difference in the mean (±SD) seated systolic blood pressure of 5±11 mm Hg after the 12-week treatment period between each of the three baxdrostat groups and the placebo group at a two-sided significance level of 0.05. This estimate was based on the assumption of a 13% early withdrawal rate, and an initial enrollment of 348 patients (87 per trial group) was planned. To prevent imbalance between the trial groups, patients were stratified according to their baseline systolic blood pressure (<145 mm Hg or ≥145 mm Hg) and their baseline estimated GFR (<60 ml per minute per 1.73 m^2 or ≥60 ml per minute per 1.73 m^2).

The primary efficacy analysis compared the change in the mean seated systolic blood pressure from baseline to the end of the treatment period between each baxdrostat group and the placebo group in the modified intention-to-treat population (patients who received at least one dose of baxdrostat or placebo and had a baseline value for the systolic blood-pressure assessment). We used linear regression for a repeated-measures model and an unstructured covariance matrix, and we assumed that missing blood-pressure values were missing at random. The model used change from baseline as the dependent variable and included fixed effects for treatment, visit, and treatment-by-visit interaction, including covariates of the baseline systolic blood pressure and estimated GFR. Restricted maximum likelihood estimation was used with an unstructured covariance matrix and the Kenward–Roger approximation for degrees of freedom. To preserve the overall alpha level for the primary end point, a fixed-sequence testing procedure was performed with the highest-dose group comparison tested first.

The secondary efficacy end point of change from baseline in diastolic blood pressure was analyzed with the use of linear regression for a repeated-measures model like that used in the primary efficacy analysis. A sensitivity analysis was performed for missing data for the primary end point, with the use of a control-based pattern imputation model and the assumption that the data were not missing at random.

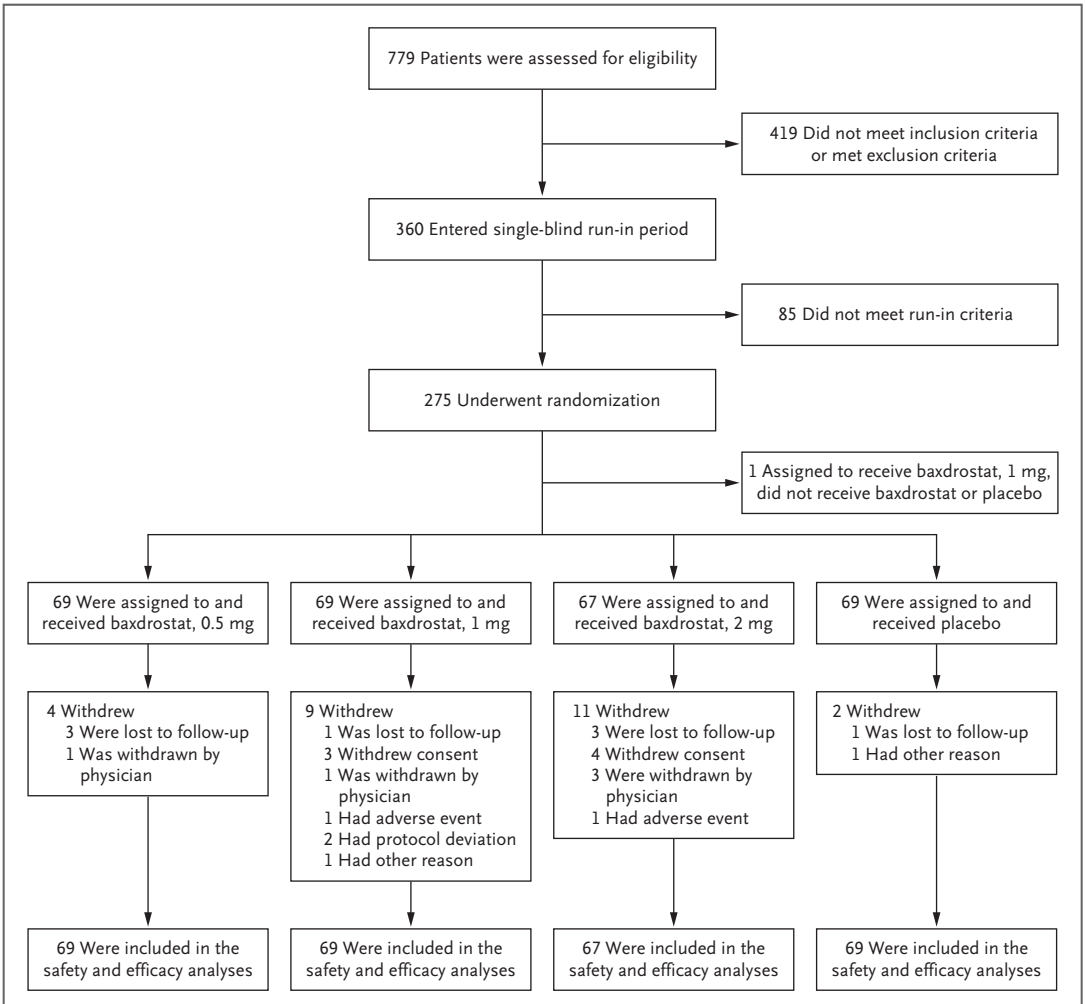


Figure 1. Screening, Randomization, and Follow-up.

Patients who received at least one dose of baxdrostat or placebo and who had a baseline systolic blood-pressure measurement were included in the modified intention-to-treat population. The efficacy analyses were based on the intention-to-treat approach. The primary reasons for trial discontinuation were withdrawal of consent and loss to follow-up. A total of 248 patients completed the 12-week treatment period.

RESULTS

PATIENT CHARACTERISTICS

A total of 779 patients underwent screening, and 360 were included in the placebo run-in period. A total of 275 patients were randomly assigned to receive once-daily baxdrostat at a dose of 0.5 mg (69 patients), 1 mg (70 patients), or 2 mg (67 patients), or placebo (69 patients). One patient who was randomly assigned to receive baxdrostat in the 1-mg group never received the drug, so the modified intention-to-treat population included 274 patients (Fig. 1). The trial groups were similar with respect to demographic and clinical characteristics at baseline. The trial population was predominantly White (70%). Black patients constituted a higher percentage of patients in the trial (28%) than their proportionate representation in the U.S. population (Table S1). The trial included a sizable percentage of patients who identified as Hispanic (43%) and a small percentage who identified as Asian (2%) (Table 1).

The first patient underwent screening on July 30, 2020, and the last patient visit occurred on June 14, 2022. A total of 248 patients (90%) com-

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

Characteristic	Placebo (N=69)	Baxdrostat, 0.5 mg (N=69)	Baxdrostat, 1 mg (N=70)	Baxdrostat, 2 mg (N=67)
Age				
Mean — yr	63.8±10.8	61.5±10.3	62.7±10.1	61.2±10.8
<65 yr — no. (%)	32 (46)	39 (56)	39 (56)	41 (61)
≥65 yr — no. (%)	37 (54)	30 (43)	31 (44)	26 (39)
Male sex — no. (%)	42 (61)	36 (52)	37 (53)	38 (57)
Race or ethnic group — no. (%)†				
White	51 (74)	45 (65)	48 (69)	47 (70)
Black	16 (23)	22 (32)	20 (29)	19 (28)
Asian	2 (3)	1 (1)	2 (3)	1 (1)
American Indian or Alaska Native	0	1 (1)	0	0
Hispanic or Latinx	30 (43)	33 (48)	23 (33)	32 (48)
Body-mass index‡	32.1±5.3	33.2±5.3	31.9±5.2	33.3±5.1
Seated blood pressure — mm Hg				
Systolic	148.9±12.4	147.6±12.5	147.7±13.1	147.3±11.8
Diastolic	88.2±6.1	87.6±7.7	87.7±6.0	88.2±7.1
Estimated glomerular filtration rate				
Mean — ml/min/1.73 m^2	85.5±17.5	81.0±20.4	83.2±20.6	85.2±19.4
<60 ml/min/1.73 m^2 — no. (%)	6 (9)	14 (20)	11 (16)	8 (12)
≥60 ml/min/1.73 m^2 — no. (%)	63 (91)	55 (80)	59 (84)	59 (88)
Diabetes — no. (%)				
Yes	28 (41)	26 (38)	20 (29)	31 (46)
No	41 (59)	43 (62)	50 (71)	36 (54)
Sodium level — mmol/liter	139±3	139±2	138±3	140±2
Potassium level — mmol/liter	4.2±0.5	4.3±0.4	4.0±0.4	4.1±0.4
Creatinine level — mg/dl	0.9±0.2	1.0±0.3	0.9±0.3	0.9±0.3
Background antihypertensive drug — no. (%)				
Diuretic	69 (100)	69 (100)	70 (100)	67 (100)
Beta-blocker	47 (68)	44 (64)	41 (59)	35 (52)
Calcium-channel blocker	47 (68)	44 (64)	49 (70)	47 (70)
ACE inhibitor or ARB	63 (91)	64 (93)	65 (93)	64 (96)
General antihypertensive drug	9 (13)	8 (12)	11 (16)	8 (12)

* Plus–minus values are means ±SD. Baseline characteristics are shown for the intention-to-treat population (all the patients who underwent randomization). Percentages may not total 100 because of rounding. To convert the values for sodium to milligrams, multiply by 23, to convert the values for potassium to milligrams, multiply by 39, and to convert the values for creatinine to micromoles per liter, multiply by 88.4. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.
† Race or ethnic group was reported by the patient.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

pleted the 12-week treatment period (Fig. 1). The most common reasons for trial discontinuation were withdrawal of consent (7 patients) and loss to follow-up (8 patients). Although discontinuations were not shown to be related to adverse events, adverse events initially occurred at a higher frequency in the 1-mg and 2-mg dose groups than in the 0.5-mg and placebo groups (Tables S2 and S3). Fewer losses to follow-up occurred in the latter half of the trial, potentially

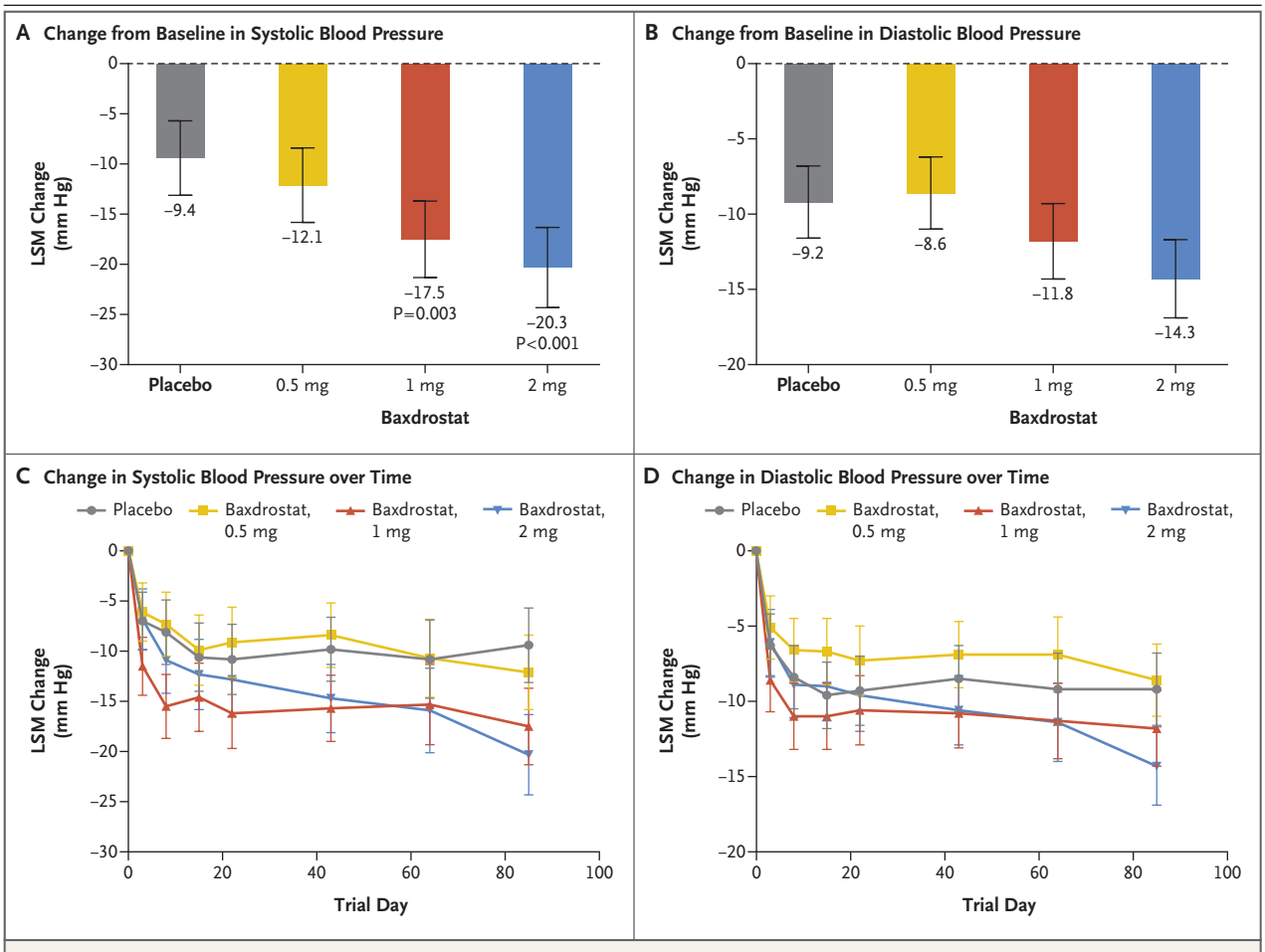


Figure 2. Dose-Dependent Decreases in Blood Pressure in Patients with Treatment-Resistant Hypertension Who Received Baxdrostat.

Shown are the changes from baseline in the least-squares mean (LSM) seated systolic blood pressure (Panel A) and diastolic blood pressure (Panel B) according to the dose of baxdrostat. The changes in systolic blood pressure (Panel C) and diastolic blood pressure (Panel D) according to the trial day are also shown. The baseline measurement was the measurement at randomization. Restricted maximum likelihood estimation was used with an unstructured covariance matrix and the Kenward–Roger approximation for degrees of freedom (Panels C and D). P values are shown for significant changes in blood pressure between the baxdrostat and placebo groups. I bars indicate 95% confidence intervals.

because of improved coronavirus disease 2019 protocols and immunization, and these losses were evenly distributed among the trial groups.[12-15]

The use of background medication was similar among the trial groups. All the patients received a diuretic, 91 to 96% received an angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker, and 64 to 70% received a calcium-channel blocker (Table 1 and Table S4).

PRIMARY END POINT

After the prespecified interim analysis, the trial was stopped early because the independent data monitoring committee concluded that the trial had met the criteria for overwhelming efficacy. At week 12, baxdrostat was associated with dose-dependent changes in the least-squares mean (±SE) systolic blood pressure of –20.3±2.1 mm Hg, –17.5±2.0 mm Hg, and –12.1±1.9 mm Hg at the 2-mg, 1-mg, and 0.5-mg doses, respectively (Fig. 2). As compared with the change in systolic blood pressure of –9.4 mm Hg in the placebo group, there were significantly greater decreases in systolic blood pressure in the 2-mg baxdrostat group (difference between the 2-mg group and the placebo group, –11.0 mm Hg; 95% confidence interval [CI], –16.4 to –5.5; P<0.001) and in the 1-mg baxdrostat group (difference

between the 1-mg group and the placebo group, −8.1 mm Hg; 95% CI, −13.5 to −2.8; P=0.003), but these decreases were not significantly greater with the 0.5-mg dose. The results of the per-protocol analysis are presented in Table S5, and the results of the sensitivity analysis for missing data are shown in Table S6.

SECONDARY END POINTS

At the 2-mg dose, baxdrostat reduced diastolic blood pressure by 14.3±1.31 mm Hg. The difference in the change in diastolic blood pressure between the baxdrostat 2-mg group and the placebo group was −5.2 mm Hg (95% CI, −8.7 to −1.6) (Fig. 2).

EXPLORATORY END POINTS

Pharmacokinetic Measures

Plasma levels of baxdrostat increased proportionately with increasing doses and reached a maximum plasma level in less than 4 hours. Details of this analysis are presented in Figure S2 and Table S7.

Pharmacodynamic Measures

The use of baxdrostat led to a sustained dose-dependent decrease in serum aldosterone levels (Fig. 3). The least-squares mean differences in changes in aldosterone levels at the end of the trial between the baxdrostat groups and the placebo group ranged from −3.0 ng per deciliter (95% CI, −4.3 to −1.7) (−83.2 pmol per liter; 95% CI, −119.3 to −47.2) at the 0.5-mg dose to −4.9 ng per deciliter (95% CI, −6.3 to −3.5) (−135.9 pmol per liter; 95% CI, −174.8 to −97.1) at the 2-mg dose. The 24-hour urinary aldosterone levels decreased with all three dose levels of baxdrostat (Fig. 3); the changes in the urinary aldosterone level (normalized for urinary creatinine excretion) from baseline to the end of the trial were −187 ng of aldosterone (95% CI, −254 to −119) per gram of creatinine with the 0.5-mg dose, −180 ng of aldosterone (95% CI, −250 to −110) per gram of creatinine with the 1-mg dose, and −273 ng of aldosterone (95% CI, −342 to −204) per gram of creatinine with the 2-mg dose. In patients in the placebo group, the urinary aldosterone level increased by 6 ng of aldosterone (95% CI, −55 to 67) per gram of creatinine.

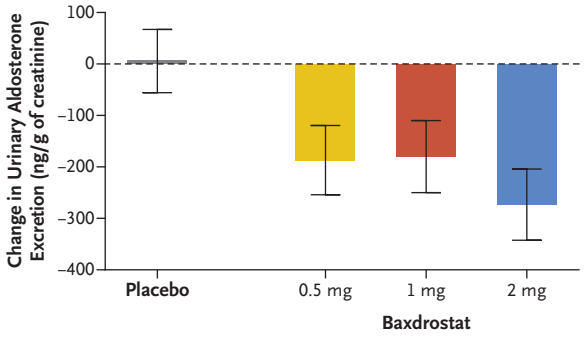
The least-squares mean change in plasma renin activity from baseline to the end of the trial was higher by 13.8 ng per milliliter per hour (95% CI, 9.6 to 17.9) in the 2-mg baxdrostat group than in the placebo group (Fig. 3). Serum cortisol levels were not reduced in any of the baxdrostat groups throughout the trial, and there were no significant differences between the baxdrostat groups and the placebo group in the least-squares mean change in these levels at week 12. At the highest dose level of baxdrostat, the least-squares mean change in the serum cortisol level from baseline to the end of the trial was 1.91 μg per deciliter (95% CI, 0.70 to 3.12) (52.7 nmol per liter; 95% CI, 19.3 to 86.1) (Fig. 3).

SAFETY

No deaths occurred during the trial, and baxdrostat had an acceptable side-effect profile overall. A total of 232 adverse events occurred during the treatment period in 120 patients (44%) (Table 2). A higher percentage of patients in the 1-mg group (52%) and 2-mg group (48%) had adverse events than those in the 0.5-mg group (35%) or the placebo group (41%). Adverse events that occurred in 5% or more patients in any of the trial groups were urinary tract infections, hyperkalemia, headache, and fatigue. Most adverse events (62%) were mild, and 89% were deemed by the investigators to be unrelated to baxdrostat or placebo. A total of 18 serious adverse events occurred in 10 patients; 6 occurred in a patient with urosepsis. None of the serious adverse events were deemed by the investigators to be related to baxdrostat or placebo. There were no instances of adrenocortical insufficiency.

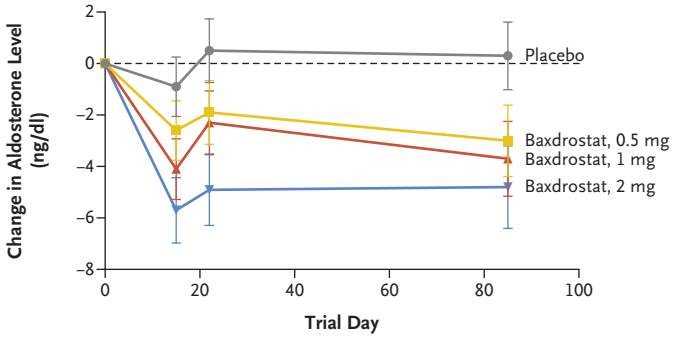
A total of 10 adverse events of special interest occurred in eight patients. These events, which were prespecified as adverse events of special interest because they warranted clinical intervention, included one case of hypotension, three cases of hyponatremia, and six cases of hyperkalemia. Three of the cases of hyperkalemia, which occurred in three patients, led to potassium levels ranging from 6.0 to 6.3 mmol per liter. At a potassium level of 6.0 mmol per liter, the protocol mandated temporary discontinuation of baxdrostat or placebo. One of these patients was the patient with urosepsis who discontinued the trial because of multiple serious adverse events that were deemed by the investigators before unblinding of the trial-group assignments to be unrelated to baxdrostat or placebo. The other two patients resumed baxdrostat

A 24-Hr Urinary Aldosterone Normalized for Creatinine



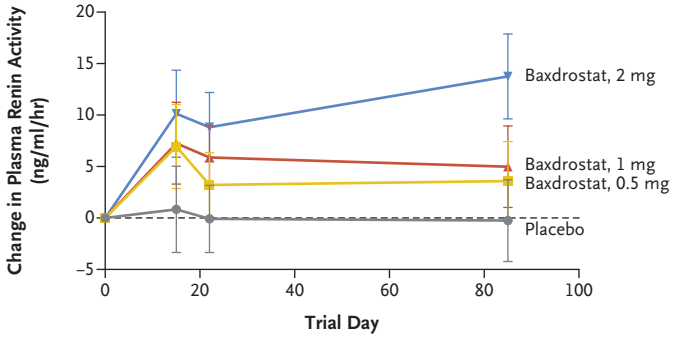
	Mean (±SD) Baseline 24-Hr Urinary Aldosterone Level
	ng/g
Placebo	364±228
Baxdrostat, 0.5 mg	437±264
Baxdrostat, 1 mg	398±233
Baxdrostat, 2 mg	431±399

B Serum Aldosterone



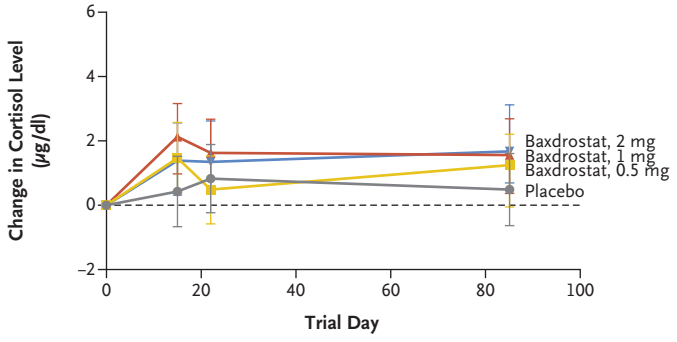
	Mean (±SD) Baseline Serum Aldosterone Level
	ng/dl
Placebo	6.7±4.8
Baxdrostat, 0.5 mg	6.9±4.2
Baxdrostat, 1 mg	7.9±5.8
Baxdrostat, 2 mg	8.4±5.5

C Plasma Renin Activity



	Mean (±SD) Baseline Plasma Renin Activity
	ng/ml/hr
Placebo	4.5±6.7
Baxdrostat, 0.5 mg	3.1±5.2
Baxdrostat, 1 mg	5.2±10.8
Baxdrostat, 2 mg	6.7±10.4

D Serum Total Cortisol



	Mean (±SD) Baseline Serum Total Cortisol Level
	μg/dl
Placebo	8.9±3.6
Baxdrostat, 0.5 mg	9.6±4.0
Baxdrostat, 1 mg	9.7±4.1
Baxdrostat, 2 mg	10.3±4.0

Figure 3 (facing page). Effects of Baxdrostat on Pharmacodynamic Measures.

Shown are the changes from baseline in the LSM values for urinary aldosterone normalized for urinary creatinine excretion (Panel A), serum aldosterone (Panel B), plasma renin activity (Panel C), and serum total cortisol (Panel D). The baseline measurement was the measurement at randomization. Reported urinary aldosterone levels that were below the assay lower limit of quantification (<3 ng per deciliter) were imputed to be one half this lower limit (1.5 ng per deciliter). Reported serum aldosterone levels that were below the assay lower limit of quantification (<1 ng per deciliter) were imputed to be one half this lower limit (0.5 ng per deciliter). Values censored owing to dilution error and other missing values were excluded. To convert the values for cortisol to nanomoles per liter, multiply by 27.6. To convert the values for aldosterone to picomoles per liter, multiply by 27.74. I bars indicate 95% confidence intervals.

2 days and 6 days after it was discontinued and completed the trial with normal potassium levels. The other three patients with hyperkalemia had potassium levels between 5.5 and 5.9 mmol per liter on at least two consecutive occasions, and baxdrostat was discontinued. Two of these three patients resumed baxdrostat and also completed the trial with normal potassium levels while receiving baxdrostat. The third patient in this group did not resume baxdrostat. Hyperkalemia was not correlated with the estimated GFR at screening. As shown in Table S8, which provides data on additional vital signs, no meaningful change in body weight occurred in any of the trial groups. Results of additional safety analyses are presented in Table S9.

DISCUSSION

Our trial showed substantial decreases in blood pressure when patients with treatment-resistant hypertension who were receiving stable doses of at least three antihypertensive medications also received the selective aldosterone synthase inhibitor baxdrostat. The reduction in blood pressure was associated with a decrease in the plasma aldosterone level and a compensatory increase in plasma renin activity, without a reduction in the cortisol level. Baxdrostat generally had an acceptable side-effect profile, and none of the patients discontinued the trial because of hyperkalemia.

Treatment-resistant hypertension is associat-

Table 2. Adverse Events That Occurred during the Treatment Period.

Event	Placebo (N=69)		Baxdrostat, 0.5 mg (N=69)		Baxdrostat, 1 mg (N=69)		Baxdrostat, 2 mg (N=67)	
	No. of Patients with Event (%)	No. of Events	No. of Patients with Event (%)	No. of Events	No. of Patients with Event (%)	No. of Events	No. of Patients with Event (%)	No. of Events
Any serious adverse event*	2 (3)	3	0	0	2 (3)	3	6 (9)	12
Any adverse event	28 (41)	50	24 (35)	38	36 (52)	77	32 (48)	67
Adverse event of special interest†	0	0	1 (1)	1	5 (7)	6	2 (3)	3
Hyponatremia	0	0	0	0	2 (3)	2	1 (2)	1
Hypotension	0	0	0	0	1 (1)	1	0	0
Potassium level ≥6.0 mmol/liter	0	0	0	0	2 (3)	2	1 (2)	1
Potassium level between 5.5 and 5.9 mmol/liter on at least two consecutive occasions‡	0	0	1 (1)	1	2 (3)	2	1 (2)	1

* No serious adverse events were deemed by the investigators to be related to baxdrostat.
† Elevated potassium levels were adverse events of special interest if they warranted clinical intervention.
‡ One patient had a potassium level between 5.5 and 5.9 mmol per liter as well as a potassium level of 6.0 mmol per liter or higher, and these measurements were counted as the same event; thus, a total of six patients with hyperkalemia had an adverse event of special interest.

ed with high cardiovascular risk,[16] but this classification provokes skepticism regarding the frequency with which poor medication adherence accounts for the condition.[17,18] Although nonadherence may be a contributor, there is mounting evidence that in adherent patients, treatment-resistant hypertension is a subtype of hypertension that has a poor response to conventional drugs because of its pathogenesis. The results of the Prevention and Treatment of Hypertension with Algorithm-based Therapy–2 (PATHWAY-2) trial, combined with inferences from its three mechanistic substudies, provide support for the hypothesis that treatment-resistant hypertension is associated with autonomous aldosterone production, which could account for the finding in that trial that a mineralocorticoid receptor antagonist (spironolactone) had superior efficacy in reducing blood pressure as compared with multiple other antihypertensive agents.[19,20] Our trial, which adds to the evidence that aldosterone appears to be a driver of treatment resistance, showed dose-related reductions in both blood pressure and indexes of aldosterone secretion. We did not compare baxdrostat with alternative drugs. A meta-analysis involving 11,000 participants from 42 trials showed that in patients who received currently licensed drugs (angiotensin-converting–enzyme inhibitors, calcium-channel blockers, or diuretics) in addition to previous therapy, systolic blood pressure was a mean of 7 to 8 mm Hg lower than that in those who received placebo.[21]

The main limitations of spironolactone with respect to side effects — gynecomastia in men and menstrual irregularities and postmenopausal bleeding in women — are due to the off-target blockade of multiple steroid hormone receptors by spironolactone. In addition, the risk of inducing hyperkalemia with spironolactone, as shown in a large epidemiologic study involving patients with heart failure, has contributed to a decrease in its use for other medical conditions.[22]

An alternative strategy to mineralocorticoid receptor blockade is to lower aldosterone levels through inhibition of aldosterone synthase. However, the development of such a drug has been thwarted by the 93% sequence similarity between aldosterone synthase and the final enzyme required for cortisol synthesis, 11β-hydroxylase.[23,24] The first aldosterone synthase inhibitor to enter clinical development, LCI-699 (osilodrostat), was associated with off-target inhibition of cortisol synthesis and was ultimately repurposed to treat excess cortisol states rather than hypertension.[25] The selective action of baxdrostat may avert the risk of inducing adrenal insufficiency and the loss of blood-pressure–lowering efficacy that can result from the accumulation of mineralocorticoid receptor–activating steroid precursors seen with first-generation aldosterone synthase inhibitors.[25,26] These advantages will need to be confirmed in phase 3 trials involving more patients over a longer period.

Similar caution applies to our findings regarding potassium. Mild hyperkalemia is common in patients taking approved renin–angiotensin–aldosterone system inhibitors.[26] In our trial, few patients who received baxdrostat had recurrent hyperkalemia, and the cases of elevated potassium levels resolved quickly, without dose modification or intervention other than routine dietary advice.

The limitations of the present phase 2 dose-ranging trial include the fact that it was not designed to test the benefits and risks of aldosterone synthase inhibition beyond 12 weeks, nor to compare aldosterone synthase inhibition with alternative antihypertensive agents. The selection of patients with an estimated GFR greater than 45 ml per minute reduced the likelihood of hyperkalemia, and planned longer-term studies may determine whether the incidences of hyperkalemia and other adverse events differ from those reported for currently licensed drugs. The inclusion of patients with at least 70% adherence (assessed on the basis of pill counts) was based on the PATHWAY-2 trial, in which high adherence was confirmed in a subgroup of patients by means of urinary drug analysis.[20] Excluded patients might have had a lower response to baxdrostat.

In our trial, aldosterone synthase inhibition with baxdrostat led to substantial reductions in systolic and diastolic blood pressure in patients with treatment-resistant hypertension.

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