ORIGINAL ARTICLE

Lorundrostat Efficacy and Safety in Patients with Uncontrolled Hypertension

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ABSTRACT

BACKGROUND

Aldosterone dysregulation contributes to hypertension. Lorundrostat is an aldosterone synthase inhibitor, but data on its efficacy and safety in patients with hypertension are limited.

METHODS

In this multicenter, double-blind, randomized, placebo-controlled trial, we assigned participants who were receiving two to five antihypertensive medications and had a blood-pressure measurement of 140/90 mm Hg or higher obtained during an office visit to undergo a standardized antihypertensive regimen for 3 weeks. Subsequently, participants with an average 24-hour ambulatory blood pressure of 130/80 mm Hg or higher were assigned to receive placebo, lorundrostat at a stable dose of 50 mg daily (the stable-dose group), or lorundrostat at a starting dose of 50 mg daily, with an increase to 100 mg daily if systolic blood pressure was 130 mm Hg or higher after 4 weeks (the dose-adjustment group). The primary end point was the change in 24-hour average systolic blood pressure from baseline to week 12, assessed as the least-squares mean difference from placebo (the placebo-adjusted change) in each lorundrostat group. A key secondary end point was the change in 24-hour average systolic blood pressure from baseline to week 4, assessed as the placebo-adjusted change in the combined lorundrostat groups.

RESULTS

A total of 285 participants underwent randomization; 94 were assigned to the stable-dose group, 96 to the dose-adjustment group, and 95 to the placebo group. The mean age was 60 years, and 150 participants (53%) were Black. After 12 weeks, the least-squares mean change in 24-hour average systolic blood pressure was –15.4 mm Hg in the stable-dose group, –13.9 mm Hg in the dose-adjustment group, and –7.4 mm Hg in the placebo group. The placebo-adjusted change in blood pressure was –7.9 mm Hg (97.5% confidence interval [CI], –13.3 to –2.6) in the stable-dose group and –6.5 mm Hg (97.5% CI, –11.8 to –1.2) in the dose-adjustment group. The placebo-adjusted change in 24-hour average systolic blood pressure from baseline to week 4 in the combined lorundrostat groups was –5.3 mm Hg (95% CI, –8.4 to –2.3). A potassium level above 6.0 mmol per liter occurred in 5 participants (5%) in the stable-dose group, 7 participants (7%) in the dose-adjustment group, and no participants in the placebo group.

CONCLUSIONS

Lorundrostat was associated with greater reductions in 24-hour average blood pressure than placebo in participants with uncontrolled and treatment-resistant hypertension. (Funded by Mineralys Therapeutics; Advance-HTN ClinicalTrials.gov number, NCT05769608.)

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*A complete list of the Advance-HTN investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Uncontrolled hypertension remains a leading cause of cardiovascular complications and death from cardiovascular disease.[1] Despite the use of multidrug regimens, reaching recommended blood-pressure targets remains elusive for many patients.[2] Among patients with uncontrolled, treatment-resistant hypertension, aldosterone dysregulation is increasingly recognized as a driver of persistent blood-pressure elevation.[3,4] Aldosterone promotes sodium retention, volume expansion, and vascular remodeling, all of which contribute to sustained hypertension and end-organ damage.[5] Current therapeutic approaches targeting aldosterone, such as mineralocorticoid receptor antagonists, have limitations — among them, compensatory increases in serum aldosterone levels, off-target effects, and concerns about acceptability to patients.[6] Lorundrostat, a highly selective aldosterone synthase inhibitor, may be an effective therapy through direct targeting of aldosterone biosynthesis. By inhibiting aldosterone production while sparing other adrenal steroid pathways, lorundrostat may offer better efficacy and have fewer adverse effects than existing approved therapies. We examined the efficacy and safety of lorundrostat in participants who had uncontrolled and treatment-resistant hypertension while receiving standardized background antihypertensive medication.

Methods

Trial Design and Oversight

The Advance-HTN trial was designed by Mineralys Therapeutics and the Cleveland Clinic Coordinating Center for Clinical Research (C5Research) and funded by Mineralys Therapeutics. 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. A central review board or a site-specific review board approved the trial, and all participants provided written informed consent. An independent data and safety monitoring committee provided oversight of participant safety. Data were collected by Caidya, a contract research organization. Cytel and the second author performed the statistical analyses, and C5Research independently confirmed the analyses. The first author wrote the first draft of the manuscript. The first and second authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol, available with the full text of this article at NEJM.org. All the authors agreed with the decision to submit the manuscript for publication.

Trial Population and Procedures

We conducted this phase 2b, multicenter, prospective, double-blind, randomized, placebo-controlled trial at 103 sites within the United States. The trial enrolled adults 18 years of age or older who were receiving stable doses of two to five antihypertensive medications and had a systolic blood pressure between 140 and 180 mm Hg and a diastolic blood pressure between 65 and 110 mm Hg — or a diastolic blood pressure between 90 and 110 mm Hg, regardless of systolic blood pressure — as measured with an automated device during an office visit (office blood pressure). Key exclusion criteria were an estimated glomerular filtration rate (eGFR) of less than 45 ml per minute per 1.73 m^2 of body-surface area, a serum potassium level above 5.0 mmol per liter, and a serum sodium level of less than 135 mmol per liter. Full inclusion and exclusion criteria are provided in the protocol.

Eligible participants discontinued their antihypertensive medications, and a standardized regimen was initiated. Participants taking two antihypertensive medications at enrollment were assigned to receive olmesartan once daily at a dose of 40 mg, along with indapamide at a dose of 2.5 mg or hydrochlorothiazide at a dose of 25 mg. For participants taking three to five antihypertensive medications at enrollment, amlodipine at a dose of 10 mg daily was also included in the standardized regimen. A lower dose of olmesartan (20 mg), amlodipine (5 mg), or both was allowed at the discretion of local investigators.

After 3 weeks of the standardized regimen with a concomitant single-blind run-in period in which all participants also received placebo, blood-pressure monitoring over 24 hours under ambulatory conditions was performed. Participants in whom blood pressure remained uncontrolled (defined as a 24-hour average systolic blood pressure between 130 and 180 mm Hg or a 24-hour average diastolic blood pressure of >80 mm Hg) were randomly assigned in a 1:1:1 ratio to receive daily doses of placebo (the placebo group), 50 mg of lorundrostat daily for 12 weeks (the stable-dose group), or 50 mg of lorundrostat daily for at least 4 weeks, with an increase to 100 mg daily for the remaining 8 weeks if office systolic blood pressure was 130 mm Hg or higher at week 4 and

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other biomarker criteria were met (a serum potassium level of less than 4.8 mmol per liter, a serum sodium level above 135 mmol per liter, an eGFR above 45 ml per minute per 1.73 m^2, and a reduction in the eGFR of less than 25% since randomization) (the dose-adjustment group). Randomization was stratified according to the number of medications in the standardized regimen (two or three). Ambulatory blood-pressure monitoring over 24 hours was performed at randomization, week 4, and week 12. After the 24-hour ambulatory monitoring at week 12, a subgroup of participants entered a 4-week washout period. Additional details of the trial design and blood-pressure measurement are provided in Figure S1 and elsewhere in the Supplementary Appendix, available at NEJM.org.

END POINTS

The primary efficacy end point was the change in 24-hour average systolic blood pressure from baseline (randomization) to week 12, assessed as the least-squares mean difference from placebo (the placebo-adjusted change) in each lorundrostat group. The first key secondary end point was the change in 24-hour average systolic blood pressure from baseline to week 4, assessed as the placebo-adjusted change in the combined lorundrostat groups. Other key secondary end points included a 24-hour average systolic blood pressure below 125 mm Hg at week 4; the change in office systolic blood pressure from baseline to week 12, assessed among participants who began taking 100 mg of lorundrostat daily at week 4; and the change in 24-hour average systolic blood pressure at week 4 according to obesity status and according to the number of antihypertensive medications in the standardized regimen. Key safety end points were prespecified adverse events of special interest, including hyperkalemia, hyponatremia, hypercortisolism, hypocortisolism, reduction in kidney function, symptomatic hypotension, and severely elevated blood pressure that led to modification of the lorundrostat dose.

STATISTICAL ANALYSIS

All participants who underwent randomization, received at least one dose of lorundrostat or placebo, and attended at least one trial visit after randomization were included in analyses conducted with the use of an analysis of covariance (ANCOVA) model with categorical factors for the assigned trial group, the number of medications in the standardized regimen, the interaction between the trial regimen and the standardized regimen, and the baseline 24-hour average systolic blood pressure as covariates. The Kenward–Roger adjustment for degrees of freedom was used. Results for each treatment dose were tested at a two-sided significance level of 0.025 to control for multiplicity. The primary estimand followed the treatment policy approach, which uses data collected from all participants regardless of the occurrence of intercurrent events, such as drug discontinuation due to an adverse event. Data that were missing because of discontinuation of lorundrostat or placebo due to adverse events were considered missing not at random and were multiply imputed with the use of the treatment policy approach.[7] Such imputation uses nonmissing data for participants with intercurrent events. For the one participant who died, we imputed missing data by applying a distribution of the worst 5% of observations across all trial groups to assign a poor outcome value. Remaining missing data were considered missing at random and were imputed according to the data distribution in the group to which the participant in question had been assigned. A graphical testing approach was used to control for multiplicity for the key secondary efficacy end points (Fig. S2), and results of sensitivity analyses of the primary end point are shown in Table S1. Confidence intervals for all secondary end points were adjusted for multiplicity.

The estimated sample size for the trial was 261 participants, who would be randomly assigned in a 1:1:1 ratio to one of the three trial groups (approximately 87 per group). We calculated that this sample size, which was based on the primary efficacy end point and the comparison of each lorundrostat dosing strategy with placebo, would provide the trial with 90% power at a two-sided alpha level of 0.05 to detect a placebo-adjusted change in 24-hour average systolic blood pressure of 7 mm Hg from randomization to week 12, with a common standard deviation of 14 mm Hg.

RESULTS

PARTICIPANT CHARACTERISTICS

From March 2023 until October 2024, a total of 2617 participants were screened, and 926 were given the standardized regimen during the placebo run-in period (Fig. S3). In all, 285 participants underwent randomization, and 282 received at

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least one dose of lorundrostat or placebo and attended at least one trial visit after randomization — 94 in the stable-dose group, 94 in the dose-adjustment group, and 94 in the placebo group. Baseline characteristics were broadly similar among the trial groups, although more participants with diabetes were assigned to the dose-adjustment group than to the other groups (Table 1). The mean age of the participants was 60 years, 172 (60%) were men, and 150 (53%) were Black. The trial population was representative of the population with uncontrolled and treatment-resistant hypertension in the United States (Table S2). At randomization, the standardized regimen included two drugs in 179 participants (63%) and three drugs in all other participants. A total of 174 participants (61%) were given indapamide, rather than hydrochlorothiazide, as the diuretic component of the standardized regimen. Among the 94 participants assigned to the dose-adjustment group who received at least one dose of lorundrostat and attended at least one trial visit after randomization, 19 (20%) had their dose increased to 100 mg at week 4. A total of 262 participants completed ambulatory blood-pressure monitoring at week 4, and 241 participants completed the monitoring at week 12.

PRIMARY END POINT

Results for the primary end point are reported in Table 2. Twelve weeks after randomization, the least-squares mean change in 24-hour average systolic blood pressure was –15.4 mm Hg (97.5% confidence interval [CI], –19.0 to –11.8) in the stable-dose group, –13.9 mm Hg (97.5% CI, –17.6 to –10.3) in the dose-adjustment group, and –7.4 mm Hg (97.5% CI, –11.4 to –3.4) in the placebo group (Fig. 1). The placebo-adjusted change in systolic blood pressure was –7.9 mm Hg (97.5% CI, –13.3 to –2.6; P=0.001) in the stable-dose group and –6.5 mm Hg (97.5% CI, –11.8 to –1.2; P=0.006) in the dose-adjustment group.

SECONDARY AND EXPLORATORY END POINTS

Four weeks after randomization, the placebo-adjusted change in 24-hour average systolic blood pressure was –5.3 mm Hg (95% CI, –8.4 to –2.3; P<0.001) among the 188 participants receiving lorundrostat (Table 2). The percentage of participants with a systolic blood pressure below 125 mm Hg at 4 weeks was higher with lorundrostat than with placebo (41% vs. 18%; odds ratio, 3.3; 98.75% CI, 1.4 to 7.8; P<0.001). Among the participants who received the increased dose of 100 mg of lorundrostat daily after week 4, the mean change in office blood pressure from baseline to week 12 was –17.5 mm Hg (99.58% CI, –30.3 to –4.7; P<0.001). The placebo-adjusted reduction in blood pressure at 4 weeks was greater among participants who were taking two standardized antihypertensive medications than among those who were taking three antihypertensive medications (Fig. S4). There was no evidence that the efficacy of lorundrostat as compared with placebo differed according to body-mass index (BMI). The results of the adjustment for multiplicity with the use of a graphical testing strategy are reported in Table S4.

In an exploratory analysis, the least-squares mean reduction in blood pressure was similar among Black and White participants (Fig. S5). Additional biomarker changes are reported in Table S5.

SAFETY

One participant in the dose-adjustment group died during the trial; that death was due to arteriosclerosis and was deemed to be unrelated to the trial drug by the site investigator and medical monitor. Intercurrent events for each trial group are noted in Table S3. Serious adverse events occurred in 16 participants, and the events were deemed to be related to the trial drug in 3 of these participants (2 in the stable-dose group and 1 in the dose-adjustment group) (Table 3). A maximum observed serum potassium level between 5.6 and 6.0 mmol per liter occurred in 6 participants (6%) in the stable-dose group, 10 (11%) in the dose-adjustment group, and 3 (3%) in the placebo group. A potassium level above 6.0 mmol per liter occurred in 5 participants (5%) in the stable-dose group, 7 (7%) in the dose-adjustment group, and no participants in the placebo group. The incidence of hyperkalemia confirmed by per-protocol repeat measurement to exclude factitious hyperkalemia (a condition in which the serum potassium level appears to be elevated because of an artifact introduced into the blood sample during collection or processing) is reported in Table S6. Among participants with a potassium level above 6.0 mmol per liter, the mean (±SD) eGFR calculated with the use of cystatin C at randomization was 58.3±22.4 ml per minute per 1.73 m^2.

After 12 weeks of treatment, the mean eGFR

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

Characteristic	Placebo (N=95)	Lorundrostat, Stable Dose (N=94)	Lorundrostat, Dose Adjustment (N=96)
Age — yr	59.1±10.5	61.3±9.6	60.9±10.2
Male sex — no. (%)	62 (65)	56 (60)	54 (56)
Body-mass index†	32.2±4.8	31.2±4.6	32.4±5.4
Race or ethnic group — no. (%)‡			
Black	44 (46)	50 (53)	56 (58)
White	41 (43)	39 (41)	35 (36)
Other	10 (11)	5 (5)	5 (5)
Hispanic or Latino	15 (16)	13 (14)	9 (9)
Office BP at screening — mm Hg§			
Systolic	155.1±12.7	153.2±11.7	152.4±12.2
Diastolic	90.7±9.9	88.4±9.0	88.6±9.1
Office BP at randomization — mm Hg§			
Systolic	141.7±14.0	141.8±14.4	143.5±12.8
Diastolic	85.5±10.3	84.3±9.4	85.6±10.2
24-Hr average ambulatory BP at randomization — mm Hg			
Systolic	141.1±9.3	140.5±11.3	141.4±11.5
Diastolic	86.8±8.8	85.5±8.9	86.5±9.4
eGFR at screening¶			
Mean — ml/min/1.73 m^2	79.6±17.4	80.6±18.4	83.0±18.5
<60 ml/min/1.73 m^2 — no. (%)	12 (13)	13 (14)	15 (16)
≥60 ml/min/1.73 m^2 — no. (%)	83 (87)	81 (86)	81 (84)
eGFR at randomization¶			
Mean — ml/min/1.73 m^2	73.6±18.0	76.6±17.8	76.4±19.4
<60 ml/min/1.73 m^2 — no. (%)	20 (21)	17 (18)	19 (20)
≥60 ml/min/1.73 m^2 — no. (%)	75 (79)	77 (82)	76 (79)
Coexisting conditions — no. (%)			
Diabetes mellitus	34 (36)	39 (41)	46 (48)
Lipid disorder‖	55 (58)	44 (47)	46 (48)
Obstructive sleep apnea	8 (8)	3 (3)	7 (7)
Concomitant antihypertensive medications at randomization — no. (%)			
Three-drug standardized regimen	34 (36)	35 (37)	37 (39)
Two-drug standardized regimen	61 (64)	59 (63)	59 (61)

* Plus–minus values are means ±SD. Baseline characteristics are shown for the intention-to-treat population, which includes all participants who underwent randomization, regardless of whether they received a dose of placebo or lorundrostat. Participants in the stable-dose group were assigned to receive 50 mg of lorundrostat daily for 12 weeks, and those in the dose-adjustment group were assigned to receive 50 mg of lorundrostat daily for 4 weeks followed by 50 or 100 mg daily for 8 weeks according to the blood-pressure (BP) measurement at week 4.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Race and ethnic group were reported by participants.
§ Office BP was obtained with the use of an automated device during an office visit.
¶ The estimated glomerular filtration rates (eGFRs) shown were calculated with the use of the serum creatinine level.
‖ Lipid disorders included dyslipidemia, hypercholesterolemia, hyperlipidemia, and hypertriglyceridemia.

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Table 2. Blood-Pressure Changes with Lorundrostat.*

End Point	Stable Dose (N=94)	Dose Adjustment (N=94)	Any Dose (N=188)†	With 2-Drug Standardized Regimen (N=117)‡	With 3-Drug Standardized Regimen (N=71)§	With Dose Increase at Week 4 (N=19)¶
Primary end point						
Placebo-adjusted change in 24-hr average ambulatory systolic BP at week 12 (97.5% CI) — mm Hg‖	−7.9 (−13.3 to −2.6)	−6.5 (−11.8 to −1.2)	—	—	—	—
P value	0.001	0.006	—	—	—	—
Key secondary end points						
Placebo adjusted change in 24-hr average ambulatory systolic BP at week 4 (98.75% CI) — mm Hg‖	—	—	−5.3 (−8.4 to −2.3)**	−6.1 (−10.8 to −1.4)	−4.6 (−10.6 to 1.5)	—
P value	—	—	<0.001	0.001	0.06	—
Mean change in office systolic BP at week 12 (99.58% CI) — mm Hg	—	—	—	—	—	−17.5 (−30.3 to −4.7)
P value	—	—	—	—	—	<0.001

* Data for participants who received at least one dose of the trial product and attended at least one trial visit after randomization are shown. Data from 24-hour ambulatory BP monitoring that were missing owing to treatment discontinuation due to adverse events were considered missing not at random and were multiply imputed according to the treatment policy imputation approach, incorporating data from participants who discontinued lorundrostat or placebo but remained in the trial to impute missing data for other participants who dropped out of the trial. Missing data for the one participant who died were imputed to assign a poor outcome value by applying a distribution of the worst 5% of observations across all trial groups. Remaining missing data were considered missing at random and were imputed according to the distribution of data in the trial group to which the participant in question was assigned. At week 4, a total of 262 participants had 24-hour ambulatory BP data available, and at week 12, a total of 241 participants had 24-hour ambulatory BP data available. CI denotes confidence interval.

† All participants assigned to a lorundrostat group (either the group receiving 50 mg daily for 12 weeks [stable-dose group] or the group receiving 50 mg for 4 weeks and then either 50 mg or 100 mg for 8 weeks [dose-adjustment group]) are included.

‡ The placebo group included 60 participants receiving two drugs in the standardized antihypertensive regimen in addition to placebo.

§ The placebo group included 34 participants receiving three drugs in the standardized antihypertensive regimen in addition to placebo.

¶ Participants in the dose-adjustment group received a dose increase from 50 mg daily to 100 mg daily at week 4 if all the following criteria were met: office systolic BP was 130 mm Hg or higher, the serum potassium level was less than 4.8 mmol per liter, the serum sodium level was greater than 135 mmol per liter, the eGFR was greater than 45 ml per minute per 1.73 m^2, and the reduction in the eGFR since randomization was less than 25%.

‖ Values shown are the least-squares mean difference from placebo. The placebo group included 94 participants.

** The 95% confidence interval is provided.

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calculated with the use of cystatin C had decreased by 13% in the stable-dose group, 15% in the dose-adjustment group, and 3% in the placebo group. A subgroup of 151 participants (54%) underwent a 4-week washout period after the 12-week trial regimen. After this washout period, the eGFR remained the same among participants who had received placebo but increased among those who received lorundrostat. Changes in selected safety biomarkers over time are shown in Figure 2.

DISCUSSION

Lorundrostat at a dose of 50 mg daily led to a placebo-adjusted reduction of 7.9 mm Hg in 24-hour average systolic blood pressure among adults with uncontrolled hypertension after 12 weeks of treatment. A strategy of adjusting the dose of lorundrostat from 50 mg to 100 mg in participants with systolic blood pressure of 130 mm Hg or higher after receiving the 50-mg dose for 4 weeks resulted in a placebo-adjusted mean reduction of 6.5 mm Hg. The observed efficacy reinforces the concept that aldosterone plays an important role in the pathogenesis of hypertension.[8] The safety profile of lorundrostat appeared to be acceptable, with adverse events consistent with the known effects of targeting the renin–angiotensin–aldosterone system — an increased risk of hyperkalemia and hyponatremia and decreases in the eGFR.

Two important characteristics of this trial were the use of a standardized antihypertensive regimen and the use of ambulatory blood-pressure monitoring to assess treatment effects, features that distinguish this trial from other trials of aldosterone synthase inhibitors. Inadequate medication doses and the "white coat effect" may result in hypertension being falsely classified as treatment resistant.[9] With a standardized medication regimen and ambulatory blood-pressure monitoring, a large percentage of participants who were screened were not eligible for randomization because blood-pressure control had been achieved. Recent trials of ultrasound renal denervation and aprocitentan also used a standardized antihypertensive regimen and rigorous blood-pressure measurement.[10,11] In those trials, many enrolled participants also did not meet criteria for randomization because the blood pressure was too low for inclusion.[12]

The fact that only participants with confirmed uncontrolled and treatment-resistant hypertension were able to undergo randomization probably contributed to the high proportion of Black partici-

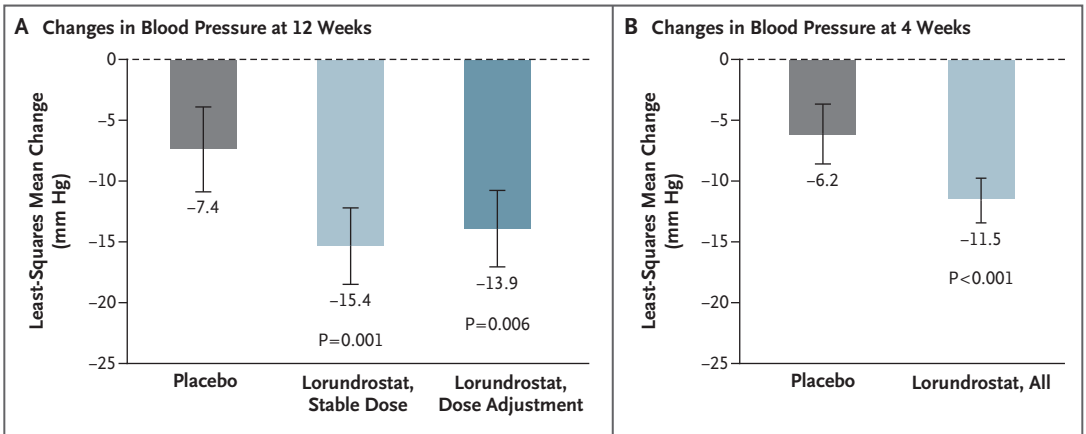

Figure 1. Changes in Blood Pressure among Trial Participants with Uncontrolled and Treatment-Resistant Hypertension.

Shown are the least-squares mean changes from baseline (randomization) in the 24-hour average ambulatory systolic blood pressure at 12 weeks (Panel A) and 4 weeks (Panel B). The baseline 24-hour average systolic blood pressure was 141.1 mm Hg in the placebo group, 140.5 mm Hg in the group assigned to receive 50 mg of lorundrostat daily for 12 weeks (the stable-dose group), and 141.4 mm Hg in the group assigned to receive 50 mg of lorundrostat daily for 4 weeks followed by 50 or 100 mg daily for 8 weeks (the dose-adjustment group). The P values shown are for the comparison with the placebo group. I bars indicate the 97.5% confidence interval in Panel A and the 95% confidence interval in Panel B.

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Table 3. Adverse Events during the Trial.*

Event	Placebo (N=95)	Lorundrostat, Stable Dose (N=94)	Lorundrostat, Dose Adjustment (N=95)
		number (percent)	
Any adverse event†	46 (48)	61 (65)	64 (67)
Mild	19 (20)	29 (31)	25 (26)
Moderate	24 (25)	27 (29)	29 (31)
Severe	3 (3)	5 (5)	10 (11)
Any serious adverse event	2 (2)	6 (6)	8 (8)
Any serious adverse event related to the trial product	0	2 (2)	1 (1)
Death	0	0	1 (1) ‡
Adverse events of special interest			
Any adverse event of special interest†	15 (16)	23 (24)	30 (32)
Symptomatic hypotension	3 (3)	8 (9)	8 (8)
Severely elevated blood pressure§	4 (4)	1 (1)	3 (3)
Hyperkalemia leading to dose modification¶	0	5 (5)	8 (8)
Hyponatremia leading to dose modification‖	6 (6)	8 (9)	10 (11)
Hypercortisolism leading to dose modification**	0	0	0
Hypocortisolism leading to discontinuation of trial product††	0	0	0
Reduction in eGFR leading to dose modification‡‡	3 (3)	3 (3)	7 (7)
Overdose§§	0	1 (1)	1 (1)

* All participants who underwent randomization, with the exception of one participant who refused treatment, were included in the safety analysis. Data for adverse events that emerged during the 12-week trial period are shown.

† Affected participants were counted once per event category.

‡ The one death that occurred during the trial was deemed to be unrelated to the trial drug by the site investigator and medical monitor.

§ Severely elevated blood pressure was defined as office systolic blood pressure above 180 mm Hg or office diastolic blood pressure above 110 mm Hg as measured with an automated device.

¶ Hyperkalemia was defined as a serum potassium level above 5.5 mmol per liter.

‖ A serum sodium measurement between 130 and 135 mmol per liter was mandated to be repeated. If on repeat measurement the level remained between 130 and 135 mmol per liter, the decision to continue the current dose or decrease the dose was made at the discretion of the medical monitor and local investigator. A serum sodium measurement of less than 130 mmol per liter was also mandated to be repeated. If on repeat measurement the level was 135 mmol per liter or higher, the dose was reduced; if serum sodium was less than 135 mmol per liter, the trial product was withheld.

** Hypercortisolism was defined as a morning serum cortisol level above 35 μg per deciliter (966 nmol per liter), confirmed by measurement of 24-hour urinary free cortisol. All participants were monitored for signs and symptoms of hypercortisolism throughout the trial. Scheduled measurements of 24-hour urinary free cortisol were taken at randomization and at week 12.

†† All participants were monitored for signs and symptoms of hypocortisolism throughout the trial. Serum specimens for the measurement of morning serum cortisol levels were obtained at every scheduled trial visit from randomization to week 12. Asymptomatic participants with a level of less than 3 μg per deciliter (83 nmol per liter) were mandated to undergo corticotropin stimulation testing. Participants with a level of less than 10 μg per deciliter (276 nmol per liter) accompanied by a sign or symptom of adrenal insufficiency were also mandated to undergo corticotropin stimulation testing.

‡‡ The decision to modify a dose was made by the site investigator after discussion with the medical monitor if the eGFR decreased by more than 25% from the value at randomization or if the eGFR was less than 30 ml per minute per 1.73 m^2.

§§ Any dose of trial drug that exceeded 200 mg within a 24-hour period or more than two doses of any component of the standardized antihypertensive regimen within an 18-hour period was considered an overdose.

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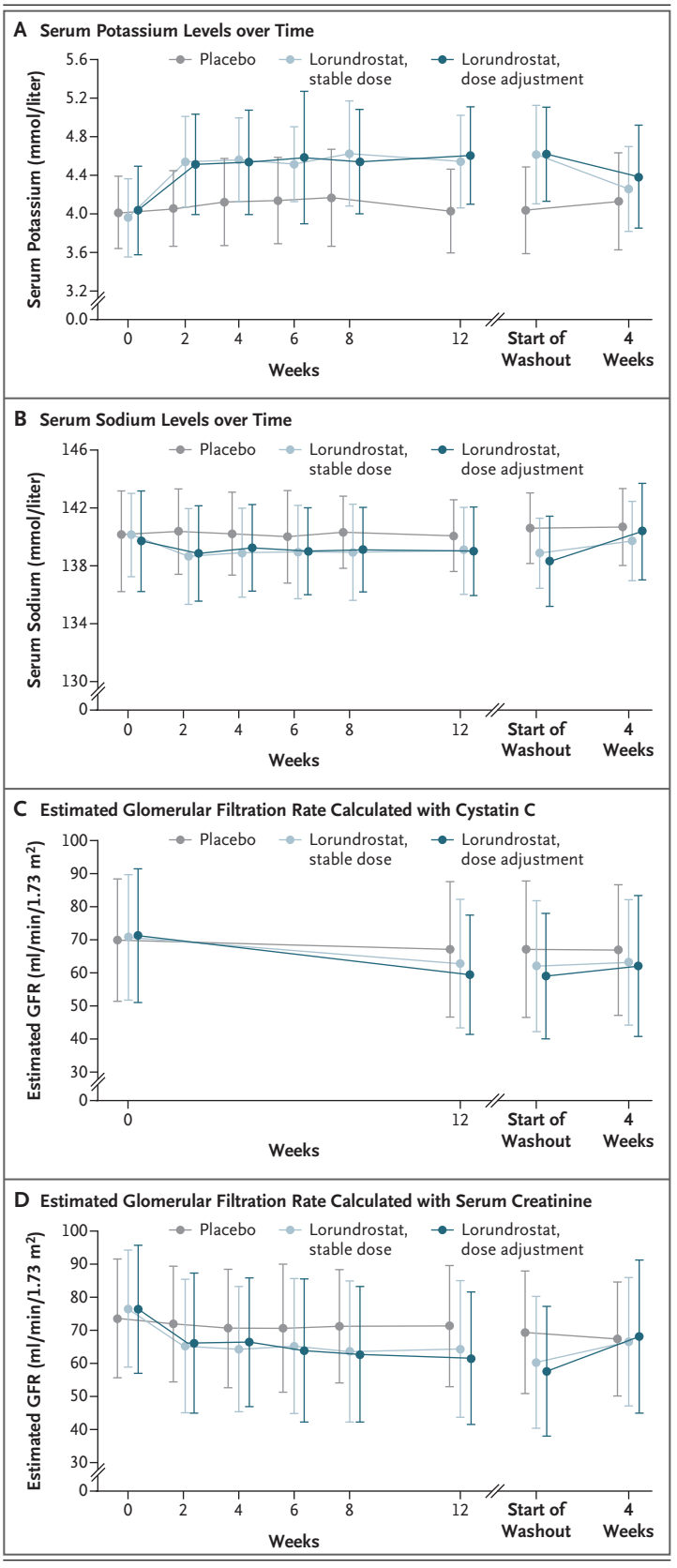
Figure 2. Effect of Lorundrostat on Safety Biomarkers.

Shown are the trajectories of the mean serum potassium level (Panel A), mean serum sodium level (Panel B), and mean estimated glomerular filtration rate (eGFR) calculated with cystatin C (Panel C) and serum creatinine (Panel D) from randomization through the 12-week treatment period and 4 weeks of washout. A subgroup of 151 participants (55 in the placebo group and 48 in each lorundrostat group) participated in the washout period and had samples collected for the analysis of biomarkers at the beginning and end of the washout. I bars indicate the standard deviation. Values are offset for readability.



pants. A disproportionate burden of treatment-resistant hypertension exists among Black adults in the United States, and mortality from hypertension and its associated diseases among Black adults is 4 to 5 times as high as that among White adults.[13,14] Yet Black adults are underrepresented in trials of antihypertensive drugs, and their participation in such trials decreased between the years 2010 and 2020.[15] Although the higher prevalence of uncontrolled hypertension among Black adults is multifactorial, new aldosterone-directed therapies may prove beneficial in this population. Recent data from the Jackson Heart Study confirmed the association of higher levels of serum aldosterone and lower plasma renin activity with increased ambulatory blood pressure among Black patients.[16,17]

In an initial dose-finding trial of lorundrostat, participants taking 100 mg had no greater reduction in blood pressure than those taking 50 mg.[18] The results of the present trial support this observation and suggest that maximal blood-pressure reduction is achieved with a daily dose of 50 mg of lorundrostat, and that the risk of adverse events is lower with this dose. Although the previous dose-finding trial showed greater blood-pressure reduction among participants with obesity than among those without obesity, the present trial did not show a correlation between blood-pressure reduction with lorundrostat and baseline BMI. Hyperkalemia was more common with lorundrostat than with placebo, and its incidence was probably exacerbated by concomitant use of an angiotensin-receptor blocker. A decline in eGFR was expected and is commonly observed when treatment with renin–angiotensin–aldosterone system antagonists is initiated. Such declines are related to the lowering of intraglomerular pressure and often signify a therapeutic effect rather

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than harm.[19] The decline in the eGFR among participants in the current trial reflects both the effects of lorundrostat and the efficacy of the standardized regimen administered for 3 weeks before randomization. The full extent of the decline in eGFR attributed to the standardized regimen was probably not reached before randomization, given the further 3% decrease at week 12 among participants who received placebo. This possibility is corroborated by the larger-than-expected reduction in ambulatory blood pressure in the placebo group. Cystatin C, in addition to serum creatinine, was used to calculate the eGFR during the trial because conventional measures of renal function based on increases in serum creatinine may be confounded by competitive inhibition of the multidrug and toxin extrusion 1 (MATE1) renal transporter shared by creatinine and lorundrostat. Therefore, some increase in creatinine without alteration of the eGFR is anticipated during lorundrostat treatment, as would similarly occur with cimetidine or trimethoprim.[20] The effect of lorundrostat on renal function needs further evaluation and is being studied in the phase 3 Launch-HTN trial (ClinicalTrials.gov number, NCT06153693).

Baxdrostat, an alternative aldosterone synthase inhibitor, was associated with placebo-adjusted decreases between 8.1 and 11.0 mm Hg in office systolic blood pressure in patients with apparent treatment-resistant hypertension.[21] Aldosterone synthase inhibition may address the aldosterone breakthrough that occurs with long-term use of angiotensin-converting–enzyme inhibitors or angiotensin-receptor blockers and is a risk factor for the progression of renal and cardiovascular diseases.[22] Aldosterone synthase inhibitors thus hold promise for the treatment of heart failure and chronic kidney disease.[23] Trials of another aldosterone synthase inhibitor, vicadrostat, in which cardiovascular and kidney outcomes are being evaluated are ongoing.[24]

This trial has certain limitations, including the relatively short duration (12 weeks). The effects of lorundrostat administration over a longer period are expected to be assessed in an ongoing, open-label extension trial (NCT05968430). Additional limitations include a lack of direct comparison between lorundrostat and alternative antihypertensive medications, including mineralocorticoid receptor antagonists.

In this trial, aldosterone synthase inhibition with lorundrostat effectively lowered blood pressure in patients with uncontrolled and treatment-resistant hypertension.

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